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INBC 2017

International Conference on

NEUROLOGY *and* BRAIN DISORDERS

JUNE 26 TO JUNE 28
2017

Venue
Eurostars Rey Don Jaime
Av. de les Balears, 2, 46023
Valencia, Spain

Index

Welcome Message

Dear Attendees, Presenters, Organizing Committee and Distinguished Guests,

The invitation to write the welcome message is both an honour and a privilege. Therefore, I am very grateful to the Organizing Committee of INBC 2017. All of us are ever conscious of the need to maintain a balance between classical morphology of the neurological diseases, molecular and cellular neurobiology, new therapies, and new techniques of diagnosis. I am sure that INBC 2017 will fulfil this expectation. Furthermore, the presentations and discussion will provide provocative hypotheses and suggestions for new research directions: we will honestly say at the end of the Meeting to have learned much and to feel greatly enriched.

Let me conclude with a statement taken from David Hume's "A treatise of human nature (Book 1, part IV, section VI) (1740): " Thus we have finished our examination of the several systems of philosophy, both of the intellectual and natural world; and in our miscellaneous way of reasoning have been led into several topics; which will either illustrate and confirm some preceding part of this discourse, or prepare the way for our following opinions. 'This now time to return to a more close examination of our subject .....".

Giuseppe Scalabrino, M.D.

Former Professor of General Pathology
Faculty of Medicine and Surgery
University of Milan, Milano (ITALY)

Welcome Message

Dear Attendees, Presenters, Organizing Committee and Distinguished Guests,

I am delighted to be able to welcome you to this International Neurology and Brain Disorders Conference in the beautiful city of Valencia. This 2017 conference is a remarkable gathering of some of the doyens in the field of brain disease and am both humbled and honoured to play a small part. The scientific committee have worked tirelessly to present to you a unique opportunity to see and hear about the cutting-edge work being done in numerous fast moving fields. The brain is said to be the last untapped organ. This conference shows that the tap is not only opening but gushing with knowledge!

Pankaj Sharma

Professor of Neurology & Director, Institute of Cardiovascular Research,
Royal Holloway University of London.
Consultant Neurologist, Imperial College London NHS Healthcare Trust.

Keynote Speakers

Sergi Ferre
National Institute on
Drug Abuse (NID, NIH), USA

Marisela Morales
National Institute on Drug
Abuse (NID, NIH), USA

Giuseppe Scalabrino
University of Milan
Italy

Harry W.M. Steinbusch
Maastricht University, The
Netherlands

Pankaj Sharma
University of London
UK

Sapna Sharma
University of London
UK

Mira Rakacolli-Kapisyzi
President of Albanian Society
of Neurology, Albania

Henry Bakunts
International Medical Centre
”STROKE”, Armania

Special Talks

Steven Benvenisti
United States Civil Attorney
and Partner at Davis, USA

Robyn Tolhurst
Red Fern Communication
Australia

About Magnus Group

Magnus Group (MG) is initiated to meet a need or to pursue collective goals of scientific community, especially in exchanging the ideas which facilitates growth of research and development. We specialize in organizing conferences, meetings and workshops internationally to overcome the problem of good and direct communication between scientists, researchers working in same fields or in interdisciplinary research.

MG promotes open discussions and free exchange of ideas at the research frontiers mainly focusing on science field. Intense discussions and examination based on professional interests will be an added advantage for the scientists and helps them learn most advance aspects of their field.

It proves that these events provide a way for valuable means of disseminating information and ideas that cannot be achieved by usual channels of communications. To encourage an informal community atmosphere usually we select conference venues which are chosen partly for their scenic and often isolated nature. Suggestion from many scientists and their reviews on our conferences reflected us to continue organizing annual conferences globally.

About INBC 2017

"Magnus Group" takes the privilege to welcome you for the "International Neurology and Brain Disorders Conference" scheduled on June 26-28, 2017 at Valencia, Spain (INBC 2017).

INBC 2017 will provide a dedicated platform to peer researchers, young inspired scientists, academicians, and industrialists to meet, discuss and share the knowledge that's still more to be revealed in the field of Neurology and Brain Disorders. The series of talks, poster presentations, workshops, discussions and networking events will keep participants engaged in learning and making new connections at this conference.

Neuro Science Conferences 2017 welcomes you to join us for these 3 days of stimulating discussions, knowledge sharing and networking event at Valencia, Spain.

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DAY 1

Keynote Forum

International Conference on

Neurology and Brain Disorders

June 26-28, 2017 | Valencia, Spain

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Pre-coupling of Receptor Oligomers and Signaling Molecules. Challenging Classical Pharmacology

Sergi Ferre

National Institute on Drug Abuse (NID, NIH), USA

It has been the general assumption for several decades that the three elements of the most studied transmembrane cell signaling pathway, G protein-coupled receptors (GPCRs), G proteins and adenylyl cyclase (AC), are freely mobile molecules within the plasma membrane that interact by random collision ('collision coupling' mode). Two still controversial concepts are changing our classical views of GPCR physiology and pharmacology: pre-coupling and GPCR oligomerization. Pre-coupling implies that GPCRs, G proteins and the effectors are pre-coupled before receptor activation and that they do not dissociate upon activation. In addition, the phenomenon of GPCR homo- and heteromerization is becoming widely accepted. A GPCR homodimer and its cognate G protein provides a main functional symmetric unit and oligomeric entities can be viewed as multiples of dimers. A GPCR heterotetramer constituted by two molecularly different homodimers coupled to their cognate G protein and to AC seems to constitute a common structure of a GPCR heteromer. Our recent studies indicate that the canonical Gs-Gi interaction at the AC level is a specific property of the GPCR heterotetramer. In addition to the allosteric properties of ligands demonstrated when considering GPCR as putative monomeric entities, such as probe dependence and functional selectivity, GPCR heteromerization includes the possibility of allosteric interactions between different orthosteric ligands, wproviding utmost potential for drug development. The evidence for GPCR oligomerization and the elucidation of symmetrical minimal functional units of GPCR homomers and heteromers, promotes oligomerization and allosterism within GPCR oligomers as necessary elements in the research of GPCR physiology and pharmacology.

Audience Take away:

1.Classical concepts of GPCR physiology and pharmacology need to be revisited to include the concepts of 'pre-coupling' and 'GPCR oligomerization'

2.GPCR heteromers uncover a previously unforeseen vast number of new possible subpopulations of GPCR subtypes, with specific neuronal localizations and functions.

3.GPCR heteromers represent new targets for drug development, providing utmost potential in the discovery of more efficacious compounds for the treatment of neuropsychiatric disorders

Biography

Sergi Ferré is Senior Scientist at the National Institute on Drug Abuse. His research deals with the study of signaling complexes of G protein-coupled receptors (GPCRs), particularly those including different receptor units, GPCR heteromers. He is interested in the discovery of GPCR heteromers that can constitute therapeutic targets in neuropsychiatric disorders and in the role of GPCR heteromers determining functional differences of the products of gene polymorphisms associated with endophenotypes of neuropsychiatric disorders. His laboratory uses multiple approaches, from biophysical techniques in cell lines, to in vivo animal models, with combinations of intracranial electrical and optogenetic stimulation and in vivo microdialysis techniques.

Dorsal raphe dual serotonin-only and serotonin-glutamate neurons synapsing on VTA dopamine neurons drive dopamine release and reward

Marisela Morales

National Institute on Drug Abuse (NID, NIH), USA

Ventral tegmental area (VTA) dopamine neurons are theorized to play distinct roles in positive and negative reinforcement, decision-making, working memory, incentive salience, and aversion. This behavioral heterogeneity is reflected in part in the diverse phenotypic characteristics of VTA dopamine neurons and of the brain structures with which they are connected. The VTA receives a major innervation from the Dorsal Raphe (DR), which properties remain to be determined. By tracing studies, we found that within the total population of DR neurons innervating the VTA, a major population (≈46%) expresses the vesicular glutamate type 3, and a minor population (≈13%) expresses only serotonergic markers (serotonin-only neurons) or co-expresses serotonergic markers and VGluT3 (dual serotonin-VGluT3 neurons; ≈14%). By immunolabeling, we found that axon terminals from these three classes of DR neurons are present in the VTA with different proportions; axon terminals containing only VGluT3 (≈65%) are more abundant that than those containing only serotonergic markers (≈23%) or those co-expressing serotonergic markers and VGluT3 (≈12%). By electron microscopy, we found that within the VTA dopamine neurons are the major target of both VGluT3-only terminals and dual serotonin-VGluT3 terminals. The synapses establish between dopamine neurons and either VGluT3-terminals or dual serotonin-VGluT3 terminals are asymmetric (putative) excitatory synapses, suggesting that these two types of terminals are capable to release glutamate on VTA dopamine neurons. By optogenetics, we found that VTA photoactivation of VGluT3-fibers elicits AMPA-mediated excitatory currents in VTA dopamine neurons, promotes dopamine release in nucleus accumbens, reinforces instrumental behavior, and establishes conditioned place preference (CPP). VTA photoactivation of serotonin transporter (SERT) fibers promotes CPP, elicits excitatory currents on dopamine neurons, increases their firing rate, and evokes dopamine release in the nucleus accumbens. Dopamine release and CPP elicited by VTA SERT-fibers depend on local activation of AMPA- and serotonin type 3-receptors. By comparing CPP produced by VTA photoactivation of SERT-fibers or VGluT3-fibers, we found that the immediate rewarding effects mediated by SERT-inputs are less rewarding, but more resistant to extinction than those caused by VGluT3-inputs.

Our findings provide evidence for a glutamatergic DR →VTA pathway from both serotonergic-only and serotonergic-glutamatergic neurons that participate in reward processing. The discovery of this brain pathway opens new avenues to examine its participation in a variety of mental disorders related to motivation.

Biography

Marisela Morales is a Senior Investigator in the Intramural Research Program at the National Institute on Drug Abuse in the National Institutes of Health. She has been investigating the molecules, cells and neuronal pathways central to the neurobiology of drug addiction through use of anatomical, biochemical, cell biological and electrophysiological approaches. The primary questions to be addressed by her research include: (a) what is the brain circuitry through which addictive drugs have their habit-forming actions and (b) what neuro-adaptations of this circuitry accompany the transition from recreational to compulsive drug-taking.

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Special Session

International Conference on

Neurology and Brain Disorders

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Spring break: A true story of hope and determination

Steven Benvenisti

United States Civil Attorney and Partner at Davis, USA

Attorney Steven Benvenisti will share the captivating story of a famous case involving a college student who sustained severe traumatic brain injuries and catastrophic orthopedic injuries, resulting in his family being asked to consent his organ donation. "Spring Break" is a book about this true story, which is regularly featured on TV, the news media and has been presented at hundreds of international conferences. This book highlights the compelling role played of Rehabilitation in getting a patient to reach successes far beyond the expectations of Neurologists and related professionals.

Audience take away:

- The audience will benefit from the powerful perspective of the patient, their family and their rehabilitation professional providers.
- The thousands who have already seen this program presented by Steven Benvenisti have shared that they now have a much better understanding of how a brain injury or disorder impacts the patient and their family's lives. This program provides powerful and effective tools for the audience to utilize in enhancing their own personal and professional lives, as well as benefitting the lives of their patients and families.

Biography

Steven is a Partner at one of the largest personal injury law firms in the United States and is included on the list of the National Trial Lawyers "Top 100 Trial Lawyers". He is President of the Brain Injury Alliance and is a Director of Mothers Against Drunk Driving. Steven has received over 30 awards, including a US Congressional Citation, US House of Representatives Certificate of Special Congressional Recognition and "Citizen of the Year". Steven authored "Spring Break: A True Story of Hope and Determination" about a famous case he handled involving a severely brain injured college student. Spring Break credits the doctors, nurses and rehabilitation professionals for the wonderful work that they do in improving the lives of patients and their families.

He has been a keynote speaker at over 100 conferences and gladly donates 100% of his honoraria to charity.

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DAY 1

Speakers

International Conference on

Neurology and Brain Disorders

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Session on: Neurodegenerative disorders

Session Chair
Michel Baudry
Western University of Health Sciences, USA

Session Co-Chair
Serhiy Forostyak
Charles University, Czech Republic

Session Introduction

Title: Calpain-2: A new target for the prevention of neurodegeneration
Michel Baudry, Western University of Health Sciences, USA

Title: Mechanisms of cerebral hyperexcitability induction by antiviral acute phase response
Miranda N. Reed, Auburn University, USA

Title: Discovery of novel inhibitors of P300/CBP-associated factor (PCAF)
Stephen Wren, University of Oxford, UK

Title: Multiple Sclerosis, corpus callosum and bedside test
KHIN MAUNG BO, Northern Lincolnshire and Goole NHS Foundation Trust, UK

Title: Mutant Profilin1 transgenic mice recapitulate cardinal features of motor neuron disease
Mahmoud Kiaei, University of Arkansas for Medical Sciences, United States

Title: Upgraded prodromal diagnosis of parkinson's disease based on a search for biomarkers and a provocation test
Michael Ugrumov, Institute of Developmental Biology RAS, Russian Federation

Title: Neuropathology of neuronal intermediate filament inclusion disease (NIFID): Immunophenotypic and topographical analysis of the neuronal inclusions
Kimiko Inoue, Toneyama National Hospital, Japan

Title: Tamoxifen: Not only a breast cancer drug but also a putative neurodegenerative disorder treatment ?
Caroline Corbel, Institut de Recherche Dupuy de Lôme (IRDL), France

Title: The application of human mesenchymal stem cell for alzheimer's disease
Jong Wook Chang, Samsung Medical Center, Korea

Title: Isometric exercise training for managing vascular risk factors in mild cognitive impairment and alzheimer's disease
Nicole Hess, University of New England, Australia

Title: Perturbed stress granule dynamics in RNA-mediated neurodegenerative diseases
Udai Pandey, University of Pittsburgh Medical Center, USA

Title: Telomerase in brain and the beneficial effects of telomerase activators on brain ageing and neurodegeneration
Gabriele Saretzki, Newcastle University, UK

Title: SOD1- linked familial ALS with marked intrafamilial phenotypic variation. How do clinical features relate to pathology?
Shinji Ohara, Matsumoto Medical Center, Japan

Title: Parkin and p53 functional interplay in parkinson's disease and brain tumors physiopathology
Cristine Alves da Costa, Institut de Pharmacologie Moléculaire et Cellulaire, France

Title: Ethanol modulates gene expression in the brain by activating the heat shock pathway
Leonardo Pignataro, Columbia University-City University of New York-CSI, USA

Title: Misregulation of an activity-dependent splicing network as a common mechanism underlying autism spectrum disorders
Sabine Cordes, Lunenfeld-Tanenbaum Research Institute/Mt Sinai Hospital, Canada

Title: Targeting copper for the treatment of neurodegeneration
Jeffrey Liddell, University of Melbourne, Australia

Title: Continuous real-time monitoring of brain extracellular fluid using microamperometric sensors and their application in a humanized mouse model of Parkinson's disease
Niall Finnerty, Maynooth University, Ireland

Title: Alzheimer's disease and diabetes in context: Common surface receptors, adaptors and degenerative signals
Debashis Mukhopadhyay, Saha Institute of Nuclear Physics, India

Title: The kynurenine pathway in brain cells and its involvement in neuroinflammatory diseases
Gilles Guillemin, Macquarie University, Australia

Title: Low dose chronic prenatal alcohol exposure abolishes the pro-cognitive effects of angiotensin IV
Abigail Takyi, University of Brighton, UK

Calpain-2: A new target for the prevention of neurodegeneration

Michel Baudry*, GCBS and Xiaoning Bi, COMP.
Western University of Health Sciences, USA

Numerous reviews have discussed the role of calpain in neurodegeneration in general, and in stroke and Traumatic Brain Injury (TBI). Consequently, numerous studies have attempted to use calpain inhibitors to reduce neurodegeneration in both stroke and TBI. While some studies have reported some positive effects of calpain inhibitors in TBI, other studies have not confirmed these results. Recent studies concluded that even two blood-brain barrier- and cell-permeable calpain inhibitors, SNJ-1945 and MDL-28170, did not have sufficient efficacy or a practical therapeutic window in a model of controlled cortical impact (CCI). While those non-isoform selective calpain inhibitors were shown to inhibit overall calpain activation (without distinguishing which calpain isoform was targeted) following TBI, they failed to provide neuroprotection. Several reasons could account for the failure to develop clinical applications with such inhibitors, including their lack of specificity/potency/selectivity, and the incomplete knowledge regarding the functions of the major calpain isoforms in the brain, e.g., calpain-1 and calpain-2 (aka μ- and m-calpain). Work from our laboratory over the last 5 years has shown that calpain-1 and calpain-2 play opposite functions in both synaptic plasticity and neuroprotection/neurodegeneration. Thus, calpain-1 activation is required for theta burst stimulation-induced long-term potentiation (LTP), and is neuroprotective. On the other hand, calpain-2 activation limits the magnitude of LTP and is neurodegenerative. In addition, we found that ischemia-induced damage to retinal ganglion cells was exacerbated in calpain-1 knockout mice, indicating that calpain-1 inhibition is likely to counteract the potential beneficial effects of calpain-2 inhibition. These findings could explain the failure of the previous studies to convincingly demonstrate the role of calpain in neurodegeneration and the lack of clear efficacy of the previously tested calpain inhibitors, which did not discriminate between calpain-1 and calpain-2. We will review the evidence that supports the notion that calpain-2 is a good target for preventing neurodegeneration using our work with a mouse model of TBI. In addition, we will discuss a new link between calpain-2 activation and tau phosphorylation.

Mechanisms of cerebral hyperexcitability induction by antiviral acute phase response

Miranda Reed*, PhD, Auburn University; Holly Hunsberger, PhD, Auburn University, Gregory Konat, PhD, West Virginia University
Auburn University, USA.

A body of clinical evidence has demonstrated that viral infections in the periphery exacerbate neurodegenerative conditions, e.g., multiple sclerosis, Parkinson disease, Alzheimer Disease (AD), and seizures. For example, peripheral infections increase the propensity and severity of seizures in susceptible populations, and AD patients suffering from systemic infections develop symptoms earlier and exhibit greater cognitive impairments than patient with less infectious insults. Although experimental studies strongly indicate the initial response of the innate immune system to infection, i.e., the acute phase response (APR), as the primarily trigger, the underlying mechanisms have not been defined. In a quest to elucidate these mechanisms, we have shown that APR instigated by a viral mimic, polyinosinic-polycytidylic acid (PIC), elicits protracted hyperexcitability of cerebral networks by robustly increasing the levels of resting extracellular glutamate. These levels gradually return to baseline values within four days. While pre-synaptic potassium-evoked glutamate release is not affected, glutamate uptake is profoundly impaired and non-vesicular glutamate release is augmented, indicating functional alterations of astrocytes. Electrophysiological examination of hippocampal slices from PIC-challenged mice reveals a several fold increase in the basal synaptic transmission as compared to control slices. PIC challenge also increased the probability of pre-synaptic glutamate release as seen from a reduction of paired-pulse facilitation. Furthermore, twenty-four hours after PIC challenge, the mice feature an approximately 3-fold increase in cumulative seizure scores and 2-fold increase in the duration of status epilepticus induced by subcutaneous (s.c.) injection of 12 mg/kg of kainic acid. Seizure scores positively correlated with pre-seizure tonic glutamate. Moreover, seizures resulted in a profound (76%) elevation of extracellular glutamate in the CA1 of PIC-challenged but not saline-injected mice. Our results implicate the increase of extracellular glutamate as a mediator of seizure hypersusceptibility induced by peripheral viral challenge. Finally, our findings that similar alterations in glutamatergic functioning (i.e., increased extracellular levels and decreased glutamate uptake) are observed in mouse models of AD early suggests one possible mechanism by which peripheral infections accelerate the onset and progression of AD.

Audience take away:

The elucidation of underlying mechanisms by which peripheral infections increase hyperexcitability will vertically advance and expand understanding of the mechanistic link between viral infections in the periphery and the exacerbation of neurodegeneration, an important consideration given the number of neurodegenerative diseases in which increased glutamatergic signaling is observed. The proposed study is significant because it will provide a foundation for the development of innovative therapeutic strategies to attenuate or even prevent the progression of neurological deficits in patients afflicted with neurodegenerative disorders.

How will this help the audience in their job? Is this research that other faculty could use to expand their research or teaching? Does this provide a practical solution to a problem that could simplify or make a designer's job more efficient? Will it improve the accuracy of a design, or provide new information to assist in a design problem? List all other benefits.

In addition to the general knowledge, we will discuss a novel method to examine glutamatergic levels in awake, behaving animals. This methodology allows for correlation with behavioral tasks, allowing for more nuanced experimental questions.

Biography

Dr. Miranda N. Reed is an Associate Professor of Drug Discovery and Development at Auburn University. Trained in psychology, neuroscience, and neurology, her postdoctoral studies focused on the consequences of tau mislocalization into dendritic spines in the context of Alzheimer's disease at University of Minnesota under the direction of Karen Hsiao Ashe. Her current work focuses on alterations in glutamatergic functioning and the resultant consequences of these alterations in various neurodegenerative conditions, including Alzheimer's disease and seizures.

Discovery of novel inhibitors of P300/CBP-associated factor (PCAF)

Stephen P. Wren*, John B. Davis, Paul E. Brennan, Elena Di Daniel, Loukia Katsouri, Emma J. Murphy, Matthias T. Ehebauer, Katherine S. England, Oleg Fedorov; Sarah Dixon-Clarke Moses Moustakim, Isaac Kang, Stephane De Cesco, Peter G. K. Clark, Laura Trulli, Angel L. Fuentes de Arriba, Apirat Chaikuad, Jacqui Mendez-Johnson, Danette Daniels, Chun-Feng D. Hou, Yu-Hui Lin, John R. Walker, Raymond Hui, Hongbing Yang, Lucy Dorrell, Catherine M. Rogers, Octovia P. Monteiro, Kilian V. M. Huber, Stefan Knapp, Jag Heer, Darren J. Dixon, Sohaib Nizami and Stuart Grice
University of Oxford, UK

The Alzheimer's Research UK Oxford Drug Discovery Institute combines the deep disease knowledge and biology expertise of Oxford University with high quality, innovative drug discovery technologies and expertise to identify new ways of treating neurodegeneration. Our capabilities directed towards the creation of lead compounds for neurodegenerative targets will be presented along with our ability to progress successful candidates through the drug discovery pipeline towards commercialisation.

One of our projects involves the development of novel PCAF inhibitors with the aim to inhibit neuroinflammatory pathways in Alzheimer's disease through the modulation of histone acetylation of key inflammatory genes. PCAF inhibition is expected to decrease neuroinflammation by regulation of NF-kB acetylation. We will present our efforts to delineate which functional domain (histone acetyl transferase or bromodomain) of PCAF is most important to target for efficacy versus neuroinflammation.

Audience take away:

- The audience will become aware of the Alzheimer's Research UK Oxford Drug Discovery Institute's activities and focus.
- How the Structural Genomics Consortium, Oxford, is working together with the Alzheimer's Research UK Oxford Drug Discovery Institute to discover new PCAF inhibitors.
- The audience will be introduced to targeting neuroinflammation as a new modality for treatment of dementia.

Biography

Stephen Wren obtained his PhD in Organic Chemistry from Cambridge University. He is highly experienced in medicinal chemistry and has worked on a diverse set of biological targets over many disease areas in several organisations. For examples, he helped to lead the chemistry effort directed towards the identification of SMTC1100 (Summit's Duchenne Muscular Dystrophy drug), currently undergoing clinical evaluation. Direct experience of CNS research was gained when Stephen guided a team in support of a lead optimisation project for Lundbeck (during his time at Argenta Discovery). In this role, he acted as project leader for the discovery of novel glycine transporter 1 inhibitors for the treatment of schizophrenia. These studies resulted in the identification of a development candidate. Stephen joined Prof. Paul Brennan's Group at the Oxford Drug Discovery Institute in June 2015 to work on Alzheimer's drug discovery.

Multiple Sclerosis, corpus callosum and bedside test

KHIN MAUNG BO
Northern Lincolnshire & Goole NHS Foundation Trust, UK

Abstract: Demyelination affects highly myelinated structures like Corpus Callosum (CC). CC is unique in function that it connects right and left hemisphere. It synchronises bimanual or bipedal activities. Affecting CC can disturb synchrony between the two hemispheres will affect bimanual and bipedal tasks.

Methodology: Consecutive 70 Multiple Sclerosis patients from Outpatient clinics and Home visits were tests for bimanual hand function. Comparison of speed between rapid supination/pronation of left and right hand separately and then clapping of both hands supination/pronation of each hands alternatively. Patients has to do as fast as they could. Noticeable slowing of clapping was taken as a sign slowing down of conduction through CC. Exclusion criteria are upper limb power <3/5 MRC scale, Pain, visual impairment, intentional tremors, Stroke or cognitive impairment. Study period started from 01 09 2016.

Findings: 31 patients were excluded, 34 patients showed no noticeable difference, 2 patients were difficult to make conclusions and 3 patients showed definite slowing down in clapping.

Conclusion: It is possible to detect CC involvement by doing above bedside test. Positive patients will have difficulties in doing bimanual activities like mobility using two sticks, typing using keyboard, pushing wheel chair bimanually etc. etc. The magnitude of slowing down can be used as an indicator of the reference day (a good or a bad day). Clapping can also be used as an exercise for CC. It is difficult to test CC conduction speed electro physiologically. Sample size is not large enough and larger studies need to follow to validate the finding.

Audience Take away:

Audience will learn new easy bedside test for Corpus Callosum involvement in Multiple Sclerosis. It is very easy to do and even the patients can monitor by themselves the relative conduction speed of Corpus Callosum of a reference day. Progression of Corpus Callosum can be monitored as disease advances. The benefits of Disease Modifying Treatment on Corpus Callosum can be tested with this simple Bedside test. Clinical finding is more objective than Brain Scan findings. Researchers can correlate clinical findings and Brain Scan findings.

Biography

Dr Khin Bo is involved in NeuroRehabilitation over 20 years. He is also a Lecturer (Hon) in Hull and York Medical School teaching 4th Year Medical Students in CNS and Musculoskeletal Blocks. He is doing Botulinum Toxin injection in Spasticity, Dystonia and Involuntary Movement disorders over 15 years and done Poster presentations in International NeuroRehabilitation Conferences. He is also involved in using Functional Electrical Stimulation (FES) over 10 years and presented regularly in International FES Conferences. He is working on developing Hypertonic Hand Monitoring Scale.

The mechanism of mutant profilin1 neurotoxicity in ALS-mouse model (PFN1G118V Mice)

Duah AlkamMS, Daniel FilPhD., Ezra Feldman, Samuel G. Mackintosh PhD., Stephanie ByrumPhD., Alan TackettPhD. and Mahmoud Kiaei*PhD.
University of Arkansas for Medical Sciences (UAMS), USA.

Mutations in profilin1 (PFN1) have been shown to cause Amyotrophic Lateral Sclerosis (ALS) in human patients, however the molecular mechanisms responsible for this effect are unknown. To study profilin1 neurotoxicity and the mechanism of neurodegeneration, transgenic mice overexpressing mutant PFN1 could be highly advantageous. Therefore, recently we developed a much-needed novel mouse model for the neurodegenerative disease, ALS. These mice were generated by introducing a human mutant form of the actin-binding protein, PFN1. We utilized one of the characterized ALS-linked mutations in profilin1 (PFN1G118V) to generate transgenic mice which exhibit ALS pathology and phenotype (Fil et al., 2017). In an effort to understand the underlying mechanisms of PFN1G118V toxicity, we conducted a mass spectrometry analysis on the spinal cords of WT transgenic mice (PFN1WT) and mutant profilin1 mice (PFN1G118V). The mass spectrometry data revealed several promising proteins which could play a role in mediating the neurotoxic effects of PFN1G118V.

We will present our newly-developed ALS mouse model (PFN1G118V mice) and proteomic analyses to elucidate proteins involved in the ALS-causing mechanism of mutant profilin1. We show several promising proteins which, with further validation, may prove to play a role in the pathology of this neurodegenerative disease.

Audience take away:

- Mouse model development for neurodegenerative disease. A specific example of the new mouse model for motor neuron disease (PFN1G118V transgenic mouse model for Motor neuron disease)
- How to investigate to determine the mechanism of mutant protein causing neurodegeneration, e.g. profilin1 mutant toxicity.
- The value of proteomic as a tool in identifying molecules involved and novel target to investigate and therapeutic strategy development.
- will be able to acquire this new mouse model and apply the methodology of developing model for neurodegenerative diseases.

Biography

Dr. Mahmoud Kiaei is an Assistant Professor of Pharmacology and Toxicology at the University of Arkansas for Medical Sciences. He is an expert in animal model development to study motor neuron disease mechanism and identify the common interactive factors among neurodegenerative diseases, ALS, AD, PD and HD. He utilizes his extensive experience on pre-clinical studies to identify drug-able targets in neurodegenerative diseases, with the goal of developing efficacious therapy for them.

Upgraded prodromal diagnosis of Parkinson's disease based on a search for biomarkers and a provocation test

M. Ugrumov*, Professor, M.D., Ph.D., Institute of Developmental Biology RAS, Moscow, Russia
A. Kim, Ph.D., Institute of Developmental Biology RAS, Moscow, Russia
A. Kolacheva, Ph.D., Institute of Developmental Biology RAS, Moscow, Russia
V. Safandeev, Ph.D. student, Institute of Developmental Biology RAS, Moscow, Russia
Institute of Developmental Biology RAS, Moscow, Russia

Motor symptoms first appear in Parkinson's disease (PD) years after beginning of degradation of the nigrostriatal dopaminergic system at loss of threshold amount of dopamine (DA) in the striatum (70%), which explains low efficiency of treatment. Therefore, the development of preclinical diagnosis of PD is a high priority. Considering the systemic pathogenesis of PD, current methodology is based mainly on finding biomarkers, such as non-motor clinical symptoms and changes in body fluids (blood, CSF) and blood cells. A number of weak points makes this methodology doubtful: (i) there is no guarantee that biomarkers found in body fluids of patients at clinical stage are also characteristic of patients at preclinical stage; (ii) considering that individual biomarkers (non-motor symptoms, changes in body fluids) are semi-specific, it is necessary to use a battery of biomarkers; (iii) the diagnostic procedure should be too expensive for mass examinations. This methodology can be improved by additional searching biomarkers in animals at modeling preclinical PD. In fact, some biomarkers, detected in blood of patients were also present in mice at symptomatic stage (e.g., DOPAC, L-DOPA in plasma, D3 gene expression in lymphocytes). However, only few of them (e.g., L-DOPA, D3) were detected in presymptomatic mice, suggesting that only these markers are suitable for PD preclinical diagnosing. Importantly, the alternative approach - the provocative, or challenge test can be successfully used for specific preclinical diagnosis of chronic internal diseases. Provocative test is used to specifically and reversibly enhance latent failure of a defective organ to the threshold level, thereby causing a short-term appearance of specific symptoms. We have proven the validity of this methodology for the development of preclinical diagnosis of PD by systemic administration of a reversible inhibitor of dopamine synthesis to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated mice at the presymptomatic stage of parkinsonism.

Conclusion: We developed a novel methodology for preclinical diagnosing of PD, basing on a search for biomarkers in blood in patients and experimental models, and a provocation test

Audience take away:

Authors present a novel methodology that can be applied to various studies focusing on developing preclinical diagnosing of Parkinson's disease.

Biography

Professor Michael Ugrumov MD, PhD Head of Laboratory of neural and neuroendocrine regulations in the Institute of Developmental Biology RAS.

M. Ugrumov graduated from Moscow University Medical School (USSR), obtained PhD at the Institute of Evolutionary Physiology and Biochemistry RAS (Leningrad, USSR) and Professorship in Anatomy and Physiology at Institute of Developmental Biology RAS and in Radiology and Pharmacology at State Medical University (Moscow, Russia). Ugrumov was elected as a full member of the Russian Academy of Sciences, European Academy of Science and Arts, Serbian Academy of Sciences and Arts, French National Academy of Pharmacy and nominated as a visiting Professor in Japan (Tokushima University Medical School), US (SUNY Upstate Medical University, Syracuse, NY), France (University P. et M. Curie, Paris, University of Tours) and Germany (University of Ulm). Ugrumov is a chair of the scientific council on Neuroscience and Neurotechnologies at the Ministry of Education and Science of RF President of the Russian Society for Neurochemistry. Main interests: Developmental neurobiology and neuroendocrinology, Neurodegenerative diseases.

Neuropathology of neuronal intermediate filament inclusion disease (NIFID): Immunophenotypic and topographical analysis of the neuronal inclusions

Kimiko Inoue*, MD, Harutoshi Fujimura, MD, PhD and Kyoko Itoh, MD, PhD.
Toneyama National Hospital, Japan.

Neuronal intermediate filament inclusion disease (NIFID) is a rare neurodegenerative disorder which is a type of frontotemporal lobar degeneration (FTLD) with various clinical features including frontotemporal dementia and pyramidal and extrapyramidal signs occurring at a young age.

According to the latest pathological classification of FTLD, NIFID is categorized in the FTLD-FUS group because of the neuronal cytoplasmic inclusions (NCI) immunoreactive for fused in sarcoma protein (FUS). Several subtypes of NCI in NIFID brains were shown by immunohistochemical and electromicroscopic techniques; however, the maturation process and interaction of each subtype of NCI are still unknown. By immunohistochemical and semiquantitative analysis of NCI, we found that 1) cytoplasmic mislocalization and aggregation of FUS without nuclear FUS immunoreactivity appeared in the area without neuronal loss, 2) more than one NCI type can develop in a single neuron during the disease process, and 3) the frequency of another subtype of NCI without FUS immunoreactivity, hyaline conglomerate inclusions, was well correlated with neuronal loss in advanced lesions. These findings suggest that in the course of the disease, 1) cytoplasmic mislocalization and aggregation of FUS begin at onset or an early stage of the disease, 2) fibrous (hyaline conglomerate, made of intermediate filament) inclusion will be made in the neuron with cytoplasmic FUS aggregation, and 3) when neuronal degeneration progress, in the nearly end stage of suffered areas, surviving neurons will have recovered nuclear FUS immunoreactivity and some of them have FUS-negative hyaline conglomerate inclusions. The mechanisms and processes of FUS-associated neurodegeneration are not yet known. I will discuss relation between neuronal inclusions and neurodegeneration using the data of this study and review of the literature.

Biography

Dr. Kimiko Inoue graduated from Kobe university medical school in 1987. She is a neurologist, neuropathologist and director of rehabilitation at the Toneyama National Hospital. She has worked as a physician and neurologist for about 30 years. She has been investigating neuropathology since 2001, mainly in autopsied central nervous systems of patients with neurodegenerative disorders, by histochemical and immunohistochemical approaches.

Tamoxifen: Not only a breast cancer drug but also a putative neurodegenerative disorder treatment?

Caroline Corbel*, PhD, France; Bing Zhang, PhD, China; Annabelle Le Parc, PhD, France; Blandine Baratte, PhD, France; Pierre Colas, PhD, France; Cyril Couturier, PhD, France; Kenneth S. Kosik, MD, PhD, USA; Isabelle Landrieu, PhD, France; Veronique Le Tilly, PhD, France; Stephane Bach, PhD, France.
Institut de Recherche Dupuy de Lome (IRDL), Vannes, France

Cyclin-dependent kinase 5 (CDK5) is a multifunctional enzyme that plays numerous roles, notably in brain development. CDK5 is activated through its association with the specific activators, p35 and p39. Proteolytic procession of the N-terminal part of its activators has been linked to Alzheimer's disease and various other neuropathies. The interaction with the proteolytic cytoplasmic product p25, in comparison with the membrane protein p35, hyper-activates CDK5 and modifies its substrate phosphorylation state. In order to discover smallmolecule inhibitors of the interaction between CDK5 and p25, we have used a bioluminescence resonance energy transfer (BRET)-based screening assay. Among the 1,760 compounds screened, the generic drug tamoxifen has been identified. Tamoxifen is on the market for nearly 35 years and the most-prescribed medication to treat breast cancer. In this work, inhibition of the CDK5 activity by tamoxifen was notably validated by monitoring the phosphorylation state of one of its target prtein, tau, involved in neurodegenerative diseases. This could be explained by the fact that tamoxifen interacts with p25 to avoid the CDK5/p25 interaction. Such studies pave the way for treatments of tauopathies.

Audience take away:

- The protein kinase studied here is CDK5 (Cyclin Dependent Kinase 5). This protein is ubiquitously expressed and involved in many pathological processes such as neurodegenerative diseases and pancreatic, lung, prostate cancers… The specific inhibition of CDK5 is a new challenging prospect and the key to the development of therapeutic solutions.
- One of the techniques used is the BRET (Bioluminescence Resonance Energy Transfer)-based high through put screening assay, we developed for the first time in yeast, allowing the discovery of protein-protein interaction inhibitors. An important advantage of this method is the possibility to screen small molecules against non-preformed protein complexes.
- The experiments conducted are complementary: in silico, in vitro, in levuro and ex vivo studies have been performed and will be presented

Biography

Caroline Corbel is a post-doctoral researcher at IRDL, France, since 2013. She received her PhD in Biology from the University of Rennes1 in 2011, on the research of new anticancer agents acting by protein-protein interaction inhibition. From 2011 to 2013, she performed postdoctoral researches at the Neuroscience Research Institute, University of California, USA, in the team of Dr K. Kosik. She worked on the developmental attenuation of NMDA receptor subunit expression by microRNAs. Then, she joined the Pr O. Sire's team in Vannes to focus on CDK5, an attractive target to discover new therapeutic treatments: CDK5 kinase activity is implicated in neurodegenerative diseases and cancers.

The application of human mesenchymal stem cell for Alzheimer's disease

Jong Wook Chang
Samsung Medical Center, Korea

Various groups have presented findings that human mesenchymal stem cells (MSCs) have both immunomodulatory and trophic properties. MSCs tend to act indirectly at sites of injury or damage through the secretion of paracrine factors in vitro & in vivo. For example, our studies have been done using a transgenic Alzheimer's disease mouse model where intraparenchymal injections of MSCs resulted in the reduction of amyloid plaque levels, anti-apoptosis, activation of endogenous neural stem cell and also activate proteasome in neuron. In addition, efficient MSC delivery also is significant issue for human study. By possessing a broad range of functions, MSCs hold great potential in being used as a novel treatment for various diseases including neurodegenerative disorders.

Isometric exercise training for managing vascular risk factors in mild cognitive impairment and Alzheimer's disease

Nicole Catherine Lincoln Hess
University of New England, Australia

Pathological changes to the cerebral microvasculature precede and/or accompany vascular disorders such as hypertension, neurovascular disorders such as AD, and cognitive decline.Individuals with a history of vascular risk factors (VRF's) and vascular disease are considered high risk candidates for developing cognitive impairment in later life. Evidence suggests that vascular injury exacerbates the severity of dementia in AD and that the neurodegenerative process is heavily driven by vascular factors. Data from recent analyses suggests that isometric exercise training (IET) may improve vascular integrity and elicit blood pressure reductions in hypertensives greater than those seen with dynamic aerobic and resistance exercise. Unlike aerobic exercise, the effects of IET on cognitive performance have not been investigated. Supporting a proposition that IET performed by elderly individuals might promote healthy neural functioning and boost cognitive performance are the same principles that support the efficacy of remote ischemic conditioning (RIC) and physiological ischemic training (PIT).

Ischemic conditioning of a healthy limb to stimulate endogenous protective pathways to support and improve the healthy functioning of distant organs such as the kidneys, heart and the brain has been successfully demonstrated through blood restriction techniques such as remote ischemic conditioning (RIC) and physiological ischemic training (PIT). Originally ischemic conditioning was developed as a cardio protective technique for patients with cardiovascular arterial disease and myocardial ischemia, however, current research demonstrates that similar to the heart, the brain can also be conditioned with ischemia and hypoxia. RIC has been demonstrated to stimulate endogenous neuroprotectivepathways and increase cerebral blood flow. Mouse models of vascular cognitive impairment show that when compared to the control cohort, RIC resulted in less inflammation, less β-amyloid deposition, reduced white and grey matter damage, increased cerebral blood flow and improved cognition. Furthermore, RIC has also been implicated in enhancing neuroplasticity. PIT is a technique whereby skeletal muscle is subjected to intense contraction via isometric contraction or tourniquet in order to stimulate physiological ischemia. In clinical trials, PIT using isometric handgrip exercise performed by patients with coronary artery disease and a coronary artery occlusion significantly increased collateral blood flow in the myocardium. Unlike RIC, the efficacy of PIT to neural applications has not yet been investigated.

Most encouraging is the potential neuroprotective implications that ischemic training may offer those with mild cognitive impairment (MCI), AD, and vascular dementia. Whilst the protocols between RIC and PIT differ from each other and the extent of commonality of the signalling and protective mechanisms involved is still the subject of investigation, both of these techniques involve the activation of endogenous signalling and protective pathways and, according to recent literature, also appear to engage some shared mechanisms. Encouragingly RIC administered to patients aged 80 to 95 years old with intracranial atherosclerosis stenosis was found to be both safe and effective in stroke prevention and treatment and IET has been safely implemented among a cohort of hypertensive elderly women, 70 to 82 years old. Moreover, the principles that support the efficacy of RIC and PIT also support the feasibility of a hypothesis that IET performed by elderly individuals might promote healthy neural functioning and boost cognitive performance. It may be that IET might have the capacity to play an effective role in the management of VRF's at the MCI stage of AD and may prove to be a significant strategy in the prevention, attenuation or delay of progression to AD.

Biography

Dr Hess is an early career researcher having completed a PhD in science and psychology. She was awarded the Chancellors Doctoral Research Medal for this work. Previously, Dr Hess completed a degree in Psychology with honours.

Across the course of her PhD Dr Hess worked closely with elderly individuals with dementia. She has also both volunteered for and coordinated the activities of a dementia day respite program.

Dr Hess is now pursuing both clinical and research work in the field of neuropsychology, specifically, investigating the aging brain and the various cognitive pathways underpinning changes in the aging brain.

Perturbed stress granule dynamics in RNA-mediated neurodegenerative diseases

UdaiPandey
University of Pittsburgh Medical Center, USA

Amyotrophic lateral Sclerosis (ALS) is a debilitating disease involving the progressive loss of motor functions resulting in neuronal death. Recently, several genes have found the mutated in ALS and majority of these ALS-causative gene are involved in regulating RNA metabolism. FUS and TDP-43, DNA/RNA binding proteins with similar functions, are found to be mutated in both sporadic and familial forms of ALS.

Using a Drosophila model for FUS-associated ALS that was developed by our laboratory, we performed an unbiased genetic screen to identify modifiers of FUS toxicity. We discovered muscleblind (mbl), the Drosophila homolog of human muscleblind-like (MBNL), as a strong modifier of neurodegeneration. MBNL1 colocalizes in cytoplasmic stress granules in ALS patient cells carrying pathogenic mutations in FUS. Muscleblind-like proteins have been linked to several neurodegenerative diseases, and understanding how MBNL can modulate FUS toxicity in ALS will help to elucidate its role in other diseases, including myotonic dystrophy, Huntington's disease and spinocerebellar ataxia. We found that RNAi-mediated knockdown of Drosophila mbl rescues neurodegenerative phenotypes caused by ALS-associated mutant FUS in our model. Interestingly, overexpression of muscleblind strongly enhanced the FUS toxicity in vivo. We performed RNA sequencing using Drosophila brains expressing WT or mutant FUS with or without mbl to understand molecular mechanisms of mbl mediated suppression. Our RNA sequencing approach identified several genes whose expression is altered when FUS is overexpressed, and subsequently returned to almost normal following knockdown of endogenous mbl. Quantitative, reverse transcription, polymerase chain reaction (qPCR) confirmed expression changes of identified genes. Taken together, the results of these experiments not only provide new insights into the mechanisms by which mutant FUS is toxic in patients with ALS, but they will also have broader implications for other related neurodegenerative diseases.

Audience take away:

- The audience will learn about the molecular mechanisms of human motor neuron diseases such as ALS for which currently no cure available. Our currently work demonstrates the role of cytoplasmic stress granules in RNA-mediated neurodegeneration using mammalian neuronal and animal model systems.
- This presentation will help the audience in learning how to model human motor neuron diseases in different model systems, perform unbiased genetic screen and identify molecular pathways that regulate pathological symptoms associated with neurodegenerative diseases. These findings would enhance research, teaching and training skills of the audience.

Biography

Dr. Udai Pandey is an Associate Professor in the Department of Pediatrics, Human Genetics and Neurology at the University of Pittsburgh Medical Center. Dr. Pandey's laboratory is studying the molecular pathogenesis of amyotrophic lateral sclerosis (ALS) and other related motor neurons diseases. The Pandey lab developed mammalian neuronal and fly models of ALS that recapitulate several key pathological features of human disease such as neurodegeneration and behavioral defects. The Pandey lab is looking for genetic and small molecule modifiers of ALS in fly and mammalian neuronal models. He serves as an editorial board member for Scientific Reports, Plos One and American Journal of Neuroscience. He also serves as a reviewer for several scientific journals such as Nature Genetics, EMBO J, Human Molecular Genetics, Brain Research, Journal of Neuroscience, Plos Genetics etc. Dr. Pandey's laboratory has been supported by the National Institute of Health and the Robert Packard Center for ALS at Johns Hopkins.

Telomerase in brain and the beneficial effects of telomerase activators on brain ageing and neurodegeneration

Tengfei Wan, Alison Spilsbury (PhD), Rafal Czapiewski (PhD), Satomi Miwa (PhD), Gabriele Saretzki* (PhD)
Newcastle University, UK

I will give an overview about the enzyme telomerase and the non-canonical functions of the protein part TERT (Telomerase reverse transcriptase) with an emphasis of its beneficial effect within mitochondria which has been mainly analysed in cultured cell models in vitro.

I will then present the evidence of possible in vivo functions of TERT, focussing on brain and TERT's persisting presence in adult brain, predominantly in neurons. Then I will demonstrate results about the role of TERT protein in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). This includes published data on the possible protective role of the TERT protein in the hippocampus of AD brains, its mutual exclusion with tau protein as well as the experimental modelling of tau pathology using transduction of primary neurons with and without TERT protein expression (Spilsbury et al., 2015).

In the second part I will show results on the mitochondrial TERT localisation in mouse brain mitochondria under conditions of dietary restriction and rapamycin treatment from a recently published study (Miwa et al., 2016).

Finally, I will present our unpublished results on using 2 telomerase activators to boost TERT levels in the brains of old wild type mice and on a mouse model of PD where we performed various behaviour tests, analysed brain pathology and gene expression as well as mitochondrial generation of oxidative stress. Our results show that telomerase activators are able to counteract diminished brain function such as cognition, balance and motor skills during ageing and neurodegeneration. Thus, telomerase activators might form novel treatment options for neurodegenerative diseases such as PD and AD

Audience Take Away:

- The knowledge about a role of the telomerase/TERT protein in the brain is rather new and not widely disseminated in the field of brain research. Thus, the scientists and clinicians from various fields of brain research will get an update about this rather young field of research with a potential application to their own research field.

Biography

Gabriele Saretzki (PhD) is a cellular biology working in the areas of telomeres, telomerase, cellular senescence, ageing, mitochondria and oxidative stress. She was instrumental in establishing telomeres as a biomarker of oxidative stress and senescence/ageing. She has published around 77 papers to date and has focussed her research recently on the non-canonical functions of the telomerase protein TERT (telomerase reverse transcriptase) in mitochondria and the brain during ageing and in neurodegenerative diseases.

SOD1- linked familial ALS with marked intrafamilial phenotypic variation. How do clinical features relate to pathology?

Shinji Ohara* M.D., Yo-ichi Takei M.D., Akinori Nakamura M.D., Kenya Oguchi, M.D. Department of Neurology, Matsumoto Medical Center, Matsumoto, Japan, Hidemi Misawa Ph.D. Division of Pharmacology, Faculty of Pharmacy, Keio University, Tokyo, Japan, Yoshiaki Furukawa Ph.D, Department of Chemistry, Keio University, Tokyo, Japan.
Matsumoto Medical Center, Japan

Objective: Familial ALS with a mutation in the superoxide dismutase (SOD1) gene often shows marked intrafamilial phenotypic variation, although its pathologic background remains to be investigated.

Methods: Immunohistochemical studies were performed on postmortem brain and spinal cord from three patients (two brothers and a son) with C111Y mutation in SOD1 gene. The patients came from a family in which the rate of progression of the illness varied markedly over three generations. Two of them (father and son) presented with an ALS phenotype and both died at age 53, 1.2 and 4 years after the onset. One patient with a spinal muscular atrophy (SMA) phenotype died at age of 89 more than 50 years after the onset of his disease. Patients with an ALS phenotype died of respiratory failure without using mechanical ventilation, and the patient with SMA died of aspiration pneumonia.

Results: Pathologically, severe loss of lower motor neurons associated with marked gliosis was evident in the patient with an ALS phenotype with the shortest disease duration. In the other patient with ALS phenotype with more slowly progressive disease, the spinal anterior horn neurons were better preserved and were associated with the appearance of massive intracellular cytoplasmic neuronal inclusions and reactive astrocytes. In the patient with SMA phenotype, the loss of lower motor neurons was equivocal histologically, althoughneuronal loss was quantitatively demonstrable in the cervical segments where the symptoms began. There was no evidence of active neuronal degeneration or reactive gliosis. The posterior column was involved in only one patient with an ALS phenotype. Immunohistochemistry using an antibody against SOD1 oligomers revealed an accumulation of SOD1 aggregates in the motor neurons in all patients, although there were very few in the patient with SMA. Insoluble SOD1 aggregates could be detected by Western blot analysis of the spinal cord tissue sample from one patient with an ALS phenotype but not from the patient with an SMA phenotype. In one patient with ALS phenotype with longer survival, phosphorylated α-synuclein was often found co-localized with SOD1 in the lower motor neurons. All of the intracytoplasmic aggregates were TDP-43 negative.

Discussion: Our data clearly show significant pathologic difference among three patients from a single family despite the presence of identical SOD1 mutation. Phenotypic variability in SOD1-linked ALS may not only be genetically determined, but may also reflect the difference in the rate of disease progression which may reflect acquired factors or post-translational modification. Clinicopathological significance of co-aggregation of α-synuclein with SOD1 protein is unclear but may play an important role in producing phenotypic diversity.

Audience take away:

- understand occurrence of phenotypic variability in SOD1-linke ALS in a family with the same genetic mutation, and
- gain insight on the role of insoluble SOD1 aggregates in the formation of pathologic lesions, and
- may direct attention to the yet-to-be elucidated mechanism(s) of acquired factors which may prevent developing lesions in SOD1-linked ALS.

Biography

1980 Graduation from Tohoku University School of Medicine, Sendai, Japan
1986 Graduation from postdoctoral course (Neuropathology) at Brain Research Institute, Niigata University, Niigata Japan
1994 Completion of Neurology Residency Program at Department of Neurology, Washington University School of Medicine, St.Louis, MO, USA
1995 Department of Neurology, Shinshu University School of Medicine, Matsumoto, Japan
1996 Director, Department of Neurology, Chushin-Matsumoto Hospital, Matsumoto, Japan
2010 Vice Director, Matsumoto Medical Center, Matsumoto, Japan

Parkin and p53 functional interplay in Parkinson's disease and brain tumors physiopathology

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Institut de Pharmacologie Moleculaire et Cellulaire, France

PD is a complex age-associated neurodegenerative disorder characterized by a progressive loss of midbrain dopamine neurons in the substantia nigra. Although, mainly of sporadic origin, the identification and characterization of PD-associated gene products, strongly contributed to the delineation of the major physiological processes disrupted in sporadic PD. Thus, in early 90s the search of gene candidates associated to either autosomal dominant or recessive familial PD-forms, led to the identification of Parkin (PRKN) mutations as key triggers of most juvenile autosomal recessive (AR-JP) cases of PD. Thus, Parkin (Pk) has been shown to be an E3-ligase responsible for the physiological degradation by the proteasomal machinery of a considerable number of substrates. We recently established a new function of Pk as a transcription factor. We showed that Pk represses expression and activity of the pro-apoptotic tumor suppressor p53 independently of its E3-ligase function. Interestingly p53 is a key transcription factor involved in either neurodegenerative diseases due to its pro-apoptotic function or cancer due to its tumor suppressor properties. This led us to study the implication of parkin in glioma etiology. We have demonstrated that parkin expression is drastically reduced according to the grade in gliomas of distinct origins and that the reduction of parkin expression in human biopsies was associated to p53 inactivation by mutations. We show that endogenous and overexpressed p53 control parkin transcription ex-vivo and vivo. In conclusion, we delineated a functional interplay between parkin and p53 that allow their respective homeostasis in normal conditions suggesting that the dysfunction of this retro control may be at the origin of both Parkinson's disease and gliomas.

Biography

Dr. Cristine Alves da Costa is a neurobiologist and she received PhD Degree from the University of Sao Paulo USP, Brazil. She is a research director at INSERM and drives a team at the "Institute of Pharmacology Moleculaire et Cellulaire".

Her work has been recognized by various honors including the Scientific Prize of Excellence (PES) INSERM. Actually, she drives a team that works in the study of the implication of Parkinson's disease associated proteins in the origin of cell death in neurodegenerative disorders and tumor suppression. Her research interests include Parkinson's and Alzheimer's disease molecular and cell biology, apoptosis and p53. Moreover, she is also interested in the interplay between these two pathologies via common molecular denominators and the link between neurodegenerative disorders and human brain cancer.

Ethanol modulates gene expression in the brain by activating the heat shock pathway

Petr Protiva, Giuseppe Minniti, Leonardo Pignataro*
Columbia University-City University of New York-CSI, USA

Chronic alcohol drinking causes profound physiological adaptations, which lead to physical dependence and tolerance. Some of these adaptations result from a complex chain of events that occur in the brain, long before a state of alcohol dependence is reached. Studies performed in animal models demonstrated that brief exposure to alcohol modifies the expression of various genes. This modulation of gene expression seems to be the underlying molecular mechanism responsible for the alteration of the brain circuits that result in tolerance and dependence. Although many alcohol-responsive genes have been identified; little is known about the mechanism/s through which alcohol modulates their expression. The current research demonstrates that physiological concentrations of ethanol (10-60mM) alter gene expression through the activation the heat shock cascade and the transcription factor heat shock factor 1 (HSF1) in both cortical neurons and glial cells. More specifically, we revealed that the ethanol activation of HSF1 results in the translocation of this transcription factor into the nuclei of cortical neurons and glial cells. This transcriptionally active factor binds to a novel DNA cis-acting regulatory element, present in the alcohol-responsive genes; a sequence that we named the alcohol response element (ARE). Results from microarray analysis of cortical neurons revealed that alcohol-induced genes are involved in synaptic transmission, neurotransmitter release, presynaptic calcium sensing, synaptic vesicle docking, synapse formation and plasticity. Alterations of this set of genes in neurons can explain the physiological changes that occur in the brain of alcoholics. Other genes activated by alcohol in neurons included: ethanol metabolism, oxidoreductase activity, insulin-like growth factor signaling, acetyl-CoA, and lipid metabolism genes. Finally, the microarray analysis conducted in astrocytes indicated that ethanol increased the expression of glial-specific immune-response genes, as well as genes involved in transcription regulation, proliferation, and differentiation. These results suggest that ethanol activates the immune response and causes oxidative stress in the glia and it canprovide an explanation for the inflammatory cell damage typically observed in the brains of alcoholics.

Audience take away:

- The audience will gain a deeper understanding of the molecular adaptive mechanisms triggered by alcohol that lead to tolerance and dependence.
- This work can help identify pharmacological opportunities for novel therapeutics to treat patients at risk of developing alcohol dependence.
- This research will allow investigator and teachers to explain the physiological and psychological changes observed in alcoholic individuals.
- The genes indentified by microarray analysis can explain the massive brain cell loss observed in alcoholics. This can help investigators to identify targets for clinical invervetions in patients.

Biography

Dr. Pignataro completed his graduate studies at theUniversity of Buenos Aires in Argentina and University of Alberta in Canada. After finishing his Ph.D. in Neuroscience, he moved to Chicago to become a Postdoctoral Associate at Feinberg School of Medicine of Northwestern University where he studied the physiology of glutamate transporters in the retina. In 2004, he moved to NYC and joined the laboratory of Dr. Neil Harrison at Weill Cornell Medical College to study the alcohol-induced genomic mechanism of plasticity in the brain. In 2008, Dr. Pignataro moved to Columbia University as an Assistant Professor where he extended his work on the effects of alcohol on gene expression to the glia. He is currently and Assistant Professor at the City University of New York.

Misregulation of an activity-dependent splicing network as a common mechanism underlying autism spectrum disorders

Mathieu Quesnel-Vallieres, Zahra Dargaei, Manuel Irimia, Thomas Gonatopoulos-Pournatzis, Joanna Ip, Tim Sterne-Weiler, Mingkun Wu, Shinichi Nakagawa, Melanie A. Woodin, Benjamin J.Blencowe, and Sabine P. Cordes*
Lunenfeld-Tanenbaum Research Institute/Mt Sinai Hospital, Canada

A key challenge in understanding and ultimately treating autism is to identify common molecular mechanisms underlying this genetically heterogeneous disorder. Transcriptomic profiling of autistic brains has revealed correlated misregulation of the neuronal splicing regulator nSR100/SRRM4 and its target microexon splicing program in more than one-third of analyzed individuals. To investigate whether nSR100 misregulation is causally linked to autism, we generated mutant mice with reduced levels of this protein and its target splicing program. Remarkably, these mice display multiple hallmark features of autism, including altered social behaviors, synaptic density and signaling. Moreover, increased neuronal activity, which is often associated with autism, results in a rapid decrease in nSR100 and splicing of microexons that significantly overlap those misregulated in autistic brains. Collectively, our results provide evidence that misregulation of an nSR100-dependent splicing network controlled by changes in neuronal activity is causally linked to an important subset of autism cases.

Targeting copper for the treatment of neurodegeneration

Jeffrey Liddell
University of Melbourne, Australia

Copper is essential for normal brain function, but must be strictly regulated as either too much or too little copper leads to dysfunction. This is evident in many neurodegenerative diseases, most obviously in Wilson's disease and Menkes disease driven by copper overload and copper deficiency, respectively, but also in Alzheimer's disease, Parkinson's disease and motor neuron disease. The latter diseases involve a misregulation of copper resulting in cellular deficiency or insufficiency. We have developed a novel strategy for targeting neurodegeneration aimed at correcting copper homeostasis. Our preclinical work demonstrates that CuII(atsm), a copper delivery drug, alleviates symptoms and extends survival in multiple animal models of Parkinson's disease and motor neuron disease. This suggests that copper dysregulation may be driving neurodegeneration. On the basis of this work, CuII(atsm) is under investigation in a Phase I clinical trial in motor neuron disease patients (NCT02870634). However, the exact mechanism of action of CuII(atsm) is unclear. One robust feature of CuII(atsm) treatment evident in our preclinical work is the conspicuous attenuation of both oxidative stress and neuroinflammation. Consistent with these outcomes is the activation of Nrf2 signalling. Nrf2 is a transcription factor that regulates hundreds of antioxidant genes and is impaired in neurodegeneration. My work has found that CuII(atsm) activates neuroprotective Nrf2 signalling in vitro and in vivo models of motor neuron disease. Nrf2 is an attractive therapeutic target as its activation boosts the endogenous antioxidant and anti-inflammatory systems within cells. Indeed many studies have found that pharmacological or genetic activation of Nrf2 is protective in models of neurodegeneration, and is targeted by clinically-approved therapies. That a copper delivery drug activates Nrf2 and improves symptoms in models of neurodegeneration suggests that the Nrf2 insufficiency and resulting oxidative stress and neuroinflammation evident in neurodegeneration may be driven by copper dysregulation. Hence this provides a druggable disease-modifying therapeutic target.

Audience take away:

- Copper is an essential element for normal brain function. Compelling evidence demonstrates that copper is dysregulated in neurodegeneration, yet this is an often overlooked aspect of neurodegeneration. This presentation will provide the audience with critical insight and recognition of its importance.
- The audience will also gain an understanding of the importance and effectiveness of alleviating targeting inflammation and oxidative stress by targeting endogenous mechanisms.
- Finally, this presentation exhibits our exciting findings generated with a copper drug, showing that increasing copper is beneficial in neurodegeneration in contrast to the pervading view that increasing copper is detrimental.

Biography

Completing PhD in 2011, Dr Liddell is a basic scientist investigating the underlying mechanisms driving neurodegeneration and therapeutics targeting these mechanisms, with a focus on essential biometals and the therapeutic utility of their modulation. Emerging expert in the field, ~30 publications including PNAS, J Neurosci, HMG. H-index 16, 500 citations in last 5 years.Invited speaker at recent Gordon Research Conference 'Metals in Medicine'.

Continuous real-time monitoring of brain extracellular fluid sing microamperometric sensors and their application in a humanized mouse model of Parkinson's disease

Caroline Reid, PhD. Candidate, Chemistry Department, Maynooth University
Niall Finnerty*PhD., Research Fellow, Chemistry Department, MaynoothUniversity
Maynooth University, Ireland

In vivo amperometry is an electroanalytical technique whereby a sensitive and selective microelectrochemical sensor is implanted into a particular brain region for continuous real-time recordings of a particular neurochemical. A suitable potential is applied to the sensor surface, generating a faradaic current that is proportional to the concentration of the detected neurochemical. This presentation will discuss the in vitro development and characterization of an electrochemical sensor through to its subsequent in vivo characterization in the rodent brain and its eventual application in an animal model of disease. Current work is focusing on the ability of this technique to measure neurochemical transitions in a humanized mouse model of Parkinson's disease (PD). In summary, PD patient-derived induced pluripotent stem cells (iPSC) are differentiated into dopaminergic neurons and transplanted into the striatum of NOD SCID mice to facilitate anatomical integration over a couple of months. To date, there has been limited translation from existing animal models of PD to clinical neuroprotection in human populations. A large number of potentially neuroprotective compounds from a broad range of pharmacological groups have been identified in rodent and primate models, however, none have proven neuroprotective during clinical testing. The general consensus is that this disparity is mainly due to the aetiopathogenic diversity of PD and humanised models can potentially bridge the gap between standard pre-clinical animal models of PD and clinical translation. This humanised mouse model will facilitate unprecedented access to perform amperometric recordings within the microenvironment of transplanted PD human cells.

Audience take away:

- How to develop and characterize a sensitive and selective amperometric sensor in vivo.
- How to characterize an amperometric sensor in rodent brain extracellular fluid.
- The application of amperometry to measure from within transplanted PD human cells.
- Knowledge of work being performed by SysMedPD consortium on the development of a neuroprotective treatment to slow down the progression of PD.

Biography

Niall Finnerty is a Research Fellow at Maynooth University in Ireland who has over 13 years' experience in the development and characterisation of microelectrochemical sensors for neurochemical analysis. His research portfolio to date includes in vitro and in vivo investigations using microsensors for the real time measurement of nitric oxide, oxygen, hydrogen peroxide, superoxide and pH with applications in animal models of Parkinson's disease and schizophrenia. Furthermore, he spent four years investigating the translation of a tissue oxygen sensor from an early stage research tool into a commercial product suitable for clinical tissue monitoring. Currently, he is a principal investigator within the Horizon 2020 funded SysMedPD consortium, focusing on the continuous real time monitoring of reactive oxygen and nitrogen species in a humanized mouse model of Parkinson's disease.

Alzheimer's disease and diabetes in context: Common surface receptors, adaptors and degenerative signals

DebashisMukhopadhyay
Saha Institute of Nuclear Physics, India

Alzheimer's Disease (AD) and Type 2 Diabetes (T2D), two serious health problems with vastly different symptoms, share a complex and linked mechanism. The majority of the data suggests that diabetics, specifically T2D subjects, are at much higher risk of developing AD than normal subjects. We hypothesized that Receptor Tyrosine Kinases (RTKs) play important roles in establishing the linkage between these two diseases at the level of signal dissemination. Humans have 58 known RTKs having a similar molecular architecture with the evolutionarily conserved mechanism of activations and key components of the intracellular signalling pathways that they trigger. Results of the RTK array assay for both the disease conditions showed that two apparently unrelated proteins ALK and Ryk respond similarly upon exposure to pathological signals. Much is not known about the roles of these two RTKs in AD or T2D but at the downstream of both the signalling cascades, Grb2 emerged as a potential common adapter when either or both of ALK and Ryk received pathological signals akin to either T2D or AD and it was shown to take part in the restoration of homeostasis. Monitoring several cytoskeletal proteins at protein and transcript levels we could show that in degenerative conditions the integrity of the cytoskeleton network was largely compromised. Grb2 is naturally overexpressed in AD or T2D model systems, probably as a causality to reinforce cellular survival. While estimating the contributions of other concurrent effects owing to Grb2 overexpression affecting cytoskeletal integrity it was noted that an aggravated Grb2-NOX4 interaction might be instrumental. Overexpression of Grb2 in both the scenarios and the ubiquitous role played by it probably help retract cytoskeletal degradation by interfering with the signalling at different levels. It is premature to apprehend anything about the retroactive failure of the process, though.

Audience Take Away:

- The talk will pedagogically explain the relation between two apparently unrelated disease viz. Alzhiemer's Disease and Diabetes
- It would help clinicians to correlate cases of Diabetics developing Alzheimer's Disease
- This new concept and the evidence presented would definitely help teachers to design training in the fields of complex disorders.

Biography

With background training in Physics and Biophysics, Professor Mukhopadhyay obtained his Ph.D. in Protein Crystallography from the University of Calcutta. Upon completion he did Post-doctoral research in Structural Biology from The Scripps Research Institute, La Jolla, USA, followed by a second Post-doctoral stint in Neurobiology from the School of Medicine, UCSD, USA. After coming back to India he established his own laboratory in 2006, which contributed significantly in understanding the molecular players in Neurodegenerative disorders including Alzheimer's and Huntington's Disease, Spinal Cord Injury etc. Using confocal imaging, Proteomics and other tools his present focus lies on the interface of Neurodegeneration and Diabetes.

The kynurenine pathway in brain cells and its involvement in neuroinflammatory diseases

G.J. Guillemin
Macquarie University, Australia

The kynurenine pathway (KP) of tryptophan metabolism is one of the major regulatory mechanisms of the immune response. Activation of the KP is implicated in the pathogenesis of a wide range of neuro inflammatory diseases. Several pro-inflammatory mediators can activate indoleamine 2,3 dioxygenase (IDO-1) one of the first and regulatory enzymes of the KP. A prolonged activation of the KP leads to production and accumulation of several neuroactive metabolites including the potent excitotoxin quinolinic acid (QUIN). Every brain cell types appear to express differently the KP enzymes and producing different KP metabolites. Neurons, astrocytes, oligodendrocytes and brain microvascular endothelial cells produce neuroprotective compounds whereas activated microglia, pericytes, and infiltrating macrophages synthesize and release neurotoxic KP metabolites. Tumours use the KP to switch off the immune response and produce energy for proliferation. We have shown that the KP is activated and QUIN level in most of the major neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis…), brain cancers (glioblastoma, neuroblastoma…) and neuropsychiatric disorders (depression, suicidality, schizophrenia, autism…). This dynamic and complex interplay between KP metabolites from different brain and immune cells is directly involved in the global and progressive inflammatory response involved in the neuro pathogenesis of major brain diseases and tumours.

Low dose chronic prenatal alcohol exposure abolishes the pro-cognitive effects of angiotensin IV

S.Fidalgo, C.Skipper, A.Takyi*, A McIver, T Siligkardis, A Quadir, PR Gard
University of Brighton, UK

Foetal alcohol syndrome (FAS) is a condition that currently affects approximately 1% of babies born in Europe and North America. It is characterised by memory impairment, developmental delay and distinctive facial features. This research uses a Mouse Prenatal Alcohol Exposure (PAE) model to explore the effects of PAE on learning, memory and to explore the potentially beneficial effects of common drugs previously shown to have cognitive enhancing effects in both humans and animals.

60 mice (M=30 F=30) C57 Breeding harem of mice, were exposed to 5% ethanol throughout pregnancy. After weaning, the offspring received Losartan (10mg/kg) via their drinking water for eight weeks. At three months of age, learning and memory was assessed using the novel object recognition paradigm.

The results indicate that PAE caused a significant decrease in offspring body weight. Treatment with Losartan caused no growth impairment or renal damage. Novel object recognition indicated that PAE caused male offspring to spend significantly less time exploring the novel object than controls and that treatment with Losartan had the effect of improving awareness of the novel object both in the control and alcohol group; in addition to decreasing anxiety ($p \leq 0.05$). A significant opposite effect was noticed in the female alcohol progeny when compared to the male alcohol progeny ($p \leq 0.05$). Losartan in female alcohol progeny had no effect on anxiety. Overall, male control losartan spent more time exploring the novel object than male alcohol losartan ($p \leq 0.05$).

The results suggest that Losartan had no deleterious effects on the development of the animals, and was able to improve learning and memory in control animals without effect in PAE mice.

Audience take away

- Our mouse paper demonstrates that low-level, but chronic, alcohol intake during pregnancy has an effect on learning and memory without there being any obvious physical effects (e.g birth weight, gross anatomical changes).
- Importantly the study suggests that there are sex differences, which might reflect differences in rate of development, or some people suggest that oestrogens are protective. (This is illogical though because both male and female foetus is exposed to maternal oestrogens, more likely that androgens are deleterious).
- How might this change practice? It reinforces the message about no safe limit of alcohol.
- Our original hypothesis was that losartan may improve cognition in young children, as it does in adults. The mouse results suggests that this will not be the case.

Biography

Dr Abigail Takyi is a recently qualified medical doctor. She completed her medical training at the University of Leicester. She intercalated at the University of Brighton in BSc Pharmacogical Science. Her interest in Obstetrics and Gynaecology led her to work alongside Professor Paul Gard and Dr Sara Fidalgo looking at learning and memory; particularly the adverse effects of prenatal alcohol exposure on learning and memory in mice. This research is looking to identify the underlying biochemical disorders of foetal alcohol spectrum disorder to facilitate diagnosis and enable targeted treatment. She is also involved in widening participation into medicine at the Sixth Form College Solihull.

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DAY 2

Keynote Forum

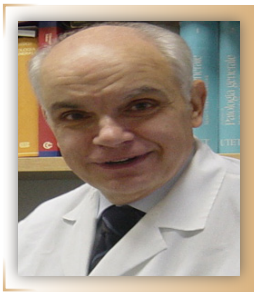
International Conference on

Neurology and Brain Disorders

June 26-28, 2017 | Valencia, Spain

INBC 2017

Cobalamin, normal prions, and epidermal growth factor. A three-cornered hat



Giuseppe Scalabrino
University of Milan, Italy

Cobalamin (Cbl), epidermal growth factor (EGF), and normal prions (PrPCs) are key molecules for myelin maintenance in the central (CNS) and peripheral nervous system (PNS). We have previously shown that Cbl deficiency causes an imbalance in some cytokines (e.g. tumour necrosis factor(TNF)-alpha and interleukin-6) and growth factors (e.g. EGF and nerve growth factor) in the CNS and PNS of the rat, and in serum and cerebrospinal fluid (CSF) of adult Cbl-deficient (Cbl-D) patients.More in detail, we demonstrated that the neurotrophic of Cbl in the CNS of Cbl-D rats is mediated by stimulation of the EGF synthesis in the CNS itself. It is conceivable that this imbalance triggers subsequent cellular events. We posited the working hypothesis that there may be a link between Cbl and PrPCs, and that this link is deranged in Cbl-D neuropathy because of the Cbl deficiency-induced imbalance in CNS and/or PNS cytokines and/or growth factors.

We demonstrated that:

(1) bothCbl and EGF up-regulate PrPC synthesis independently in rat spinal cord (SC)
(2) Cbl deficiency induces excess PrPC in rat SC and PNS, concomitantly with myelin damage and PNS electrophysiological abnormalities
(3) the SC increase is mediated by a local Cbl deficiency-induced excess of TNF-alpha
(4) intracerebroventricular (icv) treatment with anti-PrPCoctapeptide repeat region antibodies normalizes the ultrastructure of the Cbl-D rat SC and PNS myelins, and the PNS electrophysiological abnormalities, without modifying their Cbl-D status
(5) icvPrPC administration to otherwise normal rats causes SC and PNS myelin lesions and PNS electrophysiological abnormalities, similar to those of Cbl-D neuropathy, and increases in SC and liver TNF-alpha concentrations
(6) CSF and serum PrPC concentrations in adult Cbl-D patients are significantly higher than in the corresponding controls
(7) the concentrations significantly correlate with their CSF and serum Cbl concentrations; and
(8) no increases have been observed in PrPC levels of serum of patients with non-Cbl-D anemias, and CSF of patients with ALS or AD.

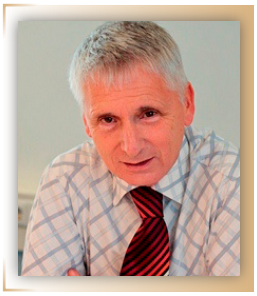
Therefore, we can conclude that:

(a) Cbl deficiency causes a vicious circle, because the Cbl deficiency-induced increase in SC and PNS TNF-alpha levels contributes to the local increase in PrPC levels and vice versa;
(b) we were the first to demonstrate that the experimental Cbl-D neuropathy is also caused by a local excess of PrPCs that do not show any apparent conformational change;
(c) our clinical data of Cbl-D patients and the myelinotoxic effects of exogeneous PrPCs appear to confirm this notion;
(d) all of the myelinotrophic agents (i.e. Cbl, EGF, and anti-TNF-alpha antibodies) markedly increased the PrPC-mRNA levels of the SC and duodenal mucosa (but not the liver) of the Cbl-D rats; and
(e) the myelinotrophic effect of Cbl takes many inter-related routes, and that of EGF may be both Cbl-independent and Cbl-dependent.

Biography

Dr. Giuseppe Scalabrino studied at the School of Medicine of the University of Milan and received his M.D. degree magna cum laude in 1968. Since 1969, Dr. Scalabrino has held a number of academic positions in the Institute of General Pathology of the Faculty of Medicine and Surgery. He was Associate Professor of General Pathology between 1971 and 1985; from 1986 till 2014 has been full Professor of General Pathology. Over the course of his distinguished career, Dr. Scalabrino has been involved as invited speaker in various professional conferences, mainly dealing with the role of polyamines in oncology and subsequently with the role of vitamin B12 (cobalamin) in mammalian central nervous system. Among Dr. Scalabrino's numerous honors is the International Award "Roentgen" from Italian Accademia dei Lincei in Rome, which he received for oncological research in 1983. Reviewer of International Scientific Journals and author of more than 100 scientific papers published in journals with impact factors. Dr. Scalabrino's studies of cobalamin neurotrophism have been mentioned in 12 american textbook of neurology, hematology, biochemistry, and vitaminology.

Epigenetic changes and brainstem dysfunction in neuropsychiatric disorders – AD/PD/Anx



Harry W.M. Steinbusch

Maastricht University Medical Center, The Netherlands

Despite the fundamental role of the brainstem in regulating vital functional abilities such as arousal, breathing, autonomic nervous system activity as well as regulating all higher cerebral functions via neurotransmitter projections systems originating in the brainstem, the role of the brainstem has received relatively little attention in most neuropsychiatric disorders. Besides the dorsal and median raphe nuclei complex comprising mainly serotonin-producing neurons, the brainstem also contains noradrenalin, dopamine and histamine-producing nuclei, i.e. resp. the locus coeruleus, the substantia nigra and the mamillary bodies. The brainstem is furthermore the relay station of afferent and efferent projections between the autonomic nervous system in the peripheral body and higher cerebral brain regions. The current presentation aims to review the neuroanatomy of the brainstem as well as the current status on findings, derived from a wide range of studies using molecular, cellular and imaging technologies, of brainstem involvement in neurodevelopmental (i.e. autism, schizophrenia) and neurodegenerative disorders (Alzheimer's and Parkinson's disease).

Over the past decades, the incidence of age-related, neurological and psychiatric disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), but also depression has considerably increased. Mood disorders are strongly related to the exposure to stress. The hippocampus and other forebrain structures are the apex of the stress hormone control mechanism and damage to them may be one way in which stress hormone secretion escapes from inhibitory control in depression. In turn, stress, probably through toxic effects of glucocorticoids, decreases neurogenesis and cell survival while antidepressants enhance these processes in experimental animals. Therefore, since treatment strategies are not yet available, primary prevention in these age-related and stress related neurological disorders is of importance. As mentioned before most of the focus on neurobiological questions on above mentioned disease are related to forebrain structures since they are often associated with cognitive dysfunction. The brainstem is a highly neglected brain area in neurodegenerative diseases, including Alzheimer's (AD) and Parkinson's (PD) disease and frontotemporal lobar degeneration. Likewise, despite a long-standing recognition of brainstem involvement, relatively few studies have addressed the exact mechanisms that underlie brainstem autonomic dysfunction. Improved insight in the cellular and molecular characteristics of brainstem function is pivotal to study the developmental origins. As brainstem dysfunction also poses health issues in several other, neurodegenerative, disorders (like AD and PD), progress in these neurological fields will benefit from scientific advancement in the current proposal as well. In the area of depression, several observations have been made in relation to changes in one particular brain structure: the Dorsal Raphe Nucleus (DRN). In addition dysfunction of the cerebellum is also observed in AD and associated with pulmonary deregulation. The DRN is also related in the circuit of stress regulated processes and cognitive events.

In order to gain more information about the underlying mechanisms that may govern the neurodegeneration, e.g. amyloid plaques, neurofibrillary tangles, and impaired synaptic transmission in AD, a rat dissociation culture model was established that allows mimicking certain aspects of our autopsy findings. We observed a similar phenomenon in brains from patients suffering from neurodegenerative disease since this also related to changes in BDNF levels. The ascending projections and multitransmitter nature of the DRN in particular and the brainstem in general stress its role as a key target for AD/PD research and autonomic dysfunction. It also points towards the increased importance and focus of the brainstem as key area in various neurodevelopmental and age-related diseases.

Biography

Dr. Harry W.M.Steinbusch is a Full Professor in Cellular Neuroscience & Director of the European Graduate School of Neuroscience, since 1996. He is Director for Institute Brain & Behavior & Mental Health and Neuroscience. He received his PhD from the Faculty of Medicine of the Catholic University, Nijmegen entitled: “Serotoninergic Neurons in the Central Nervous System of the Rat” in 1982.

His Research is focussing on the neuroanatomical, pharmacological, physiological and behavioral aspects of development and aging. Our general working hypothesis is that pre/ peri or postnatal stress can lead to depression and this by itself can be an early initiator of neurodegeneration. In addition, neurodegeneration and functional repair are studied in animal models and in human material obtained from patients. Topics are development, plasticity, brain aging and dementia, movement disorders, learning and memory. Research questions have primarily to do with the mechanism of changes in the nervous system in diseases and in development and aging. Participating disciplines are: Animal neuropsychology, genetics, neuroanatomy, neuropathology, neurochemistry, neuroimmunology, animal neuropsychology, molecular cell biology, neurophysiology, developmental neurobiology and neuropharmacology. He is an Editorial Board member & Reviewer for many Journals.

Stroke in South Asians

Pankaj Sharma

University of London,UK

Stroke is the third commonest cause of death in the West yet by the year 2050 the WHO predicts that 80% of its occurrence will lay between India and China. These two most globally populous nations are home to an aging people with increasing risk factors for all cardiovascular diseases. The UK is home to the largest South Asian population outside of India. This group present later with cardiovascular disease and are a greater burden to the National Health Service compared to their Caucasian counterparts.

We have created, to the best of our knowledge, the largest DNA biobank of stroke in South Asians having recruited affected patients and controls from site in the UK, India, Sri Lanka and the Middle East. We present the epidemiological findings of our data and compare and contrast our findings with those of Caucasians. This presentation is a prelude to the identification of genetic loci in stroke in South Asians.

Audience take away:

- Stroke is more common in the South Asian population who are at greater risk of cardiovascular disease
- Their management for such disease needs to be more aggressive compared to their Caucasian counterparts
- Stroke has a likely genetic component

Biography

Professor Pankaj Sharma is Director of the Institute of Cardiovascular Research, Royal Holloway University of London (ICR2UL). He was formally head of Imperial College Cerebrovascular Research Unit (ICCRU) at Imperial College London. He holds doctorates from both the Universities of Cambridge and London. He is Editor-in-Chief of the Journal of the Royal Society of Medicine Cardiovascular Disease, Hon. Medical Director of Different Strokes, a UK national charity which seeks to support young stroke victims, and President of the London Cardiovascular Society.

A former Dept of Health Senior Fellow, British Heart Foundation Clinician Scientist at Cambridge University and Fulbright Scholar at Harvard Medical School, he has a long standing interest in the genetics of hypertension, cardio- and cerebrovascular disease. He has published extensively in the field and is an internationally recognized authority on the genetic basis of stroke. In 2015 he was named the UKs top Asian doctor at the annual British Indian Awards.

Stroke in South Asians

Sapna Sharma

University of London, UK

Stroke is the third commonest cause of death in the West yet by the year 2050 the WHO predicts that 80% of its occurrence will lay between India and China. These two most globally populous nations are home to an aging people with increasing risk factors for all cardiovascular diseases. The UK is home to the largest South Asian population outside of India. This group present later with cardiovascular disease and are a greater burden to the National Health Service compared to their Caucasian counterparts.

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Audience take away:

- Stroke is more common in the South Asian population who are at greater risk of cardiovascular disease
- Their management for such disease needs to be more aggressive compared to their Caucasian counterparts
- Stroke has a likely genetic component

Biography

Dr Sapna Sharma is Senior Lecturer in Medicine at the University of London based within the Institute of Cardiovascular Research at Royal Holloway College. She graduated in medicine from Aberdeen University in the UK and undertook her research at Harvard Medical School on a Howard Hughes Scholarship. Her research led to the award of a doctorate from Aberdeen University

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Special Session

International Conference on

Neurology and Brain Disorders

June 26-28, 2017 | Valencia, Spain

INBC 2017

English for scientists – Getting published

Robyn Tolhurst

Red Fern Communication, Australia

This presentation will cover tried and tested techniques for writing and publishing scientific papers including:

- The scientists' toolkit
- Elements of writing a good paper
- Tips for overcoming writers' block
- Getting published – what editors look for in a manuscript
- Common writing mistakes
- Plagiarism and using online translation tools

Biography

Robyn Tolhurst is Managing Director of Red Fern Communication, based in Sydney Australia. She is an accomplished writer and editor for corporations and academic institutions, and is an international speaker on English in the fields of science and business for students and academics from non-English speaking backgrounds.

Robyn conducts professional development workshops for doctors and clinicians on doctor-patient communication.

Over the past 25 years, Robyn has been engaged as a trusted adviser, speechwriter and strategists for directors of some of the world's largest companies. She is a professional editor of scientific and academic manuscripts for students and universities throughout the world with a 100 per cent acceptance rate; and has mediatrained and promoted scientific discoveries for world re-known scientists.

As an advocate for the Arts, Robyn is a director of Australian Dance Vision. She was a member of the NSW mixed handball team that won the Australian National Championships in 2016 and were silver medallists in 2017.

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DAY 2

Speakers

International Conference on

Neurology and Brain Disorders

June 26-28, 2017 | Valencia, Spain

INBC 2017

Session on: Behavioral Neurology & Neuropsychiatry | Paediatric Neurology

Session Chair
Marisela Morales
National Institute on Drug Abuse (NID, NIH), USA

Session Co-Chair
Udai Pandey
University of Pittsburgh Medical Center, USA

Session Introduction

Title: Title: Disorders of consciousness: Basic and applied research
Medvedev Svyatoslav, N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences, Russian Federation

Title: Title: Microwave frequency electromagnetic fields (EMFs) produce widespread neuropsychiatric effects including depression
Martin L. Pall, Washington State University, USA

Title: Title: Involvement of the occipito-temporal pathway in delayed reaching: Data from a case of optic ataxia
Sergio Chieffi, Second University of Naples, Italy

Title: Title: Automatic analysis of spontaneous speech for detecting mild cognitive impairment: A screening tool?
Laura Calza, University of Bologna, Italy

Title: Title: The mGlu4 receptors as target for novel antipsychotic drugs; Interactions with other neurotransmitter systems
Andrzej Pilc, Polish Academy of Sciences, Poland

Title: Title: Sensory processing in autism spectrum disorders: literature review and perspective on the latest theories
Razvana Stanciu, Universite Libre de Bruxelles (ULB), Belgium

Title: Title: The magic and mystery of brain serotonin
Kathryn Commons, Children's Hospital Boston-Harvard Medical School, USA

Title: Title: Psychiatric pathology in somatically ill hospital patients: Implications of current data on consultation-liaison psychiatry
Caroline Lücke, Medical Campus University of Oldenburg, Germany

Title: Title: Changes in the orexin system in the rats expressing learned helplessness behaviors
Sabrina Wang, National Yang-Ming University, Taiwan

Title: Title: Cux1 enables inter-hemispheric connections of layer II-III neurons by regulating Kv1-dependent firing
Marta Nieto, Spanish National Research Council, Spain

Title: Title: Concurrent exercise training improves anthropometric measures in schizophrenic individuals by engaging epigenetic mechanism and inflammatory modulation
Viviane Rostirola Elsner, IPA Methodist University, Brazil

Title: Title: FDG PET, DAT SPECT and olfaction in rapid eye movement sleep behavior disorder
K.L. Leenders, University of Groningen, The Netherlands

Title: Title: Masgutova Neuro-Sensory-Motor Reflex Integration (MNRI)
Leah K. Light, Brainchild Institute, USA

Disorders of consciousness: Basic and applied research

Medvedev Svyatoslav
N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences, Russia

Analysis of clinical neurological and radiological data (MRI and FDG-PET) of patients with disorders of consciousness after coma (vegetative state, minimal consciousness state), obtained during the course of their treatment, has shown that a more prominent improvement of consciousness was observed when functional changes in the brain (glucose hypometabolism) prevail over structural pathology. Patients with corresponding functional and structural changes had minimum or lack of recovery. This phenomena might be explained if we consider disorder of consciousness as a stable pathological state (SPS), formed under the influence of the primary damaging factors (trauma, anoxia, etc.), and then "consolidated" and stabilized by further factors of damage developed during the course of disease of the brain (hydrocephalous, inflammatory, etc.). Correction of factors which stabilize the SPS contributes to its destabilization and improvement of consciousness. These ideas constitute the basis for the development of effective diagnostic and prognostic criteria and new approaches to treatment of disorders of consciousness.

We found that influence at «peripheral level» unexpectedly resulted in an improvement of consciousness: reduction of generalized spasticity at the level of muscles (with botulinum toxin therapy) resulted in the improvement of functional state of the brain (according to positron emission tomography and clinical data). Electrophysiological studies (EEG) showed that central effects of botulinum toxin therapy start immediately with the beginning of reduction of afferentation from the muscles. Taking into account the polyfunctionality of neurons, we offer a possible underlying physiological mechanism: blocking permanent neuromuscular transmission in spastic muscles reduces the abnormal afferent and efferent hyperactivity of motor and sensory neuronal circuits, and therefore liberates the functional neuronal brain networks for other activities, including maintenance of the higher functions.

Audience take away:

During this lecture, both basic mechanisms of the brain and the results of applied studies that were carried out based on this new knowledge will be discussed. These considerations and data are useful for a better understanding of the brain mechanisms. They may be used in designing of future research and in teaching.

Biography

Prof. Medvedev received his Ph.D. degree in Theoretical Physics from Lenigrad State University in 1972. His further research interests were devoted to the mechanisms of the human brain in both healthy and diseased states, with a special interest in brain functions inherent to humans: speech, emotions, creativity, etc. In 1988, he received his Dr.Sci degree in neurophysiology. In 1990, Prof. Medvedev organized and headed the Institute of the Human Brain of the Russian Academy of Sciences. In 1997, he was elected Corresponding Member of the Russian Academy of Sciences, and in 2016, Full Member of the Russian Academy of Sciences.

Microwave frequency electromagnetic fields (EMFs) produce widespread neuropsychiatric effects including depression

Martin L. Pall
Washington State University, USA

Non-thermal microwave/lower frequency electromagnetic fields (EMFs) act via voltage-gated calcium channel (VGCC) activation. Calcium channel blockers block EMF effects and several types of additional evidence confirm this mechanism. Low intensity microwave EMFs have been proposed to produce neuropsychiatric effects, sometimes called microwave syndrome, and the focus of this review is whether these are indeed well documented and consistent with the known mechanism(s) of action of such EMFs. VGCCs occur in very high densities throughout the nervous system and have near universal roles in release of neurotransmitters and neuroendocrine hormones. Soviet and Western literature shows that much of the impact of non-thermal microwave exposures in experimental animals occurs in the brain and peripheral nervous system, such that nervous system histology and function show diverse and substantial changes. These may be generated through roles of VGCC activation, producing excessive neurotransmitter/neuroendocrine release as well as oxidative/nitrosative stress and other responses.Excessive VGCC activity has been shown from genetic polymorphism studies to have roles in producing neuropsychiatric changes in humans. Two U.S. government reports from the 1970s to 1980s provide evidence for many neuropsychiatric effects of non-thermal microwave EMFs, based on occupational exposure studies. 18 more recent epidemiological studies, provide substantial evidence that microwave EMFs from cell/mobile phone base stations, excessive cell/mobile phone usage and from wireless smart meters can each produce similar patterns of neuropsychiatric effects, with several of these studies showing clear dose–response relationships. Lesser evidence from 6 additional studies suggests that short wave, radio station, occupational and digital TV antenna exposures may produce similar neuropsychi-atric effects. Among the more commonly reported changes are sleep disturbance/insomnia, headache, depression/depressive symptoms, fatigue/tiredness, dysesthesia, concentration/attention dysfunction,memory changes, dizziness, irritability, loss of appetite/body weight, restlessness/anxiety, nausea, skin burning/tingling/dermographism and EEG changes. In summary, then, the mechanism of action of microwave EMFs, the role of the VGCCs in the brain, the impact of non-thermal EMFs on the brain,extensive epidemiological studies performed over the past 50 years, and five criteria testing for causality, all collectively show that various non-thermal microwave EMF exposures produce diverse neuropsychiatric effects.

Involvement of the occipito-temporal pathway in delayed reaching: Data from a case of optic ataxia

Sergio Chieffi
Second University of Naples, Italy

Two functionally specialized cortical pathways of visual processing have been hypothesized: a dorsal (occipito-parietal) action-related and a ventral (occipito-temporal) perception-related pathway (Milner and Goodale, 1993, 2008). However, the ventral pathway would also contribute to actions directed to remembered target positions (Milner et al. 2003). In this theoretical framework, the present experiment aimed to study the performance of a patient, G.P., with bilateral lesion of the dorsal pathway. G.P. (33 years-old, right-handed woman) exhibited optic ataxia, bilateral concentricvisual field defect and neglect for the proximal and inferior hemispaces. MRI showed a bilateral lesion involving occipital lobes with extension to the adjacent posterior parietal lobes. Initially, G.P. performed a visual reaching task, in which she was asked to reach a target under visual control. Subsequently, G.P. and eight healthy controls performed a delayed reaching task. In this task, G.P. and controls saw the target, closed their eyes, and then, when the retention interval (2 s) had elapsed, reached the remembered target position. The target could be localized in the left or right hemispace, and the participants used their right or left hand. In visual reaching task, G.P. undershot visual targets in all conditions. In the delayed reaching task, G.P.'s distance errors differed from those of controls in all conditions, since she overshot whereas controls undershot target positions. The data of the present study are consistent with the hypothesis that the ventral pathway is involved in reaching of memorized target locations. We suggest that the damage of the dorsal pathway, associated with integrity of the ventral, produced a forward shifting of attention, as shown by G.P.'s proximal neglect. In turns, the forward attentional shifting, displacing in the same direction memorized target locations, produced G.P.'s overshot errors in delayed reaching.

Biography

Sergio Chieffi was born in Naples May 6, 1960. He graduated in Medicine and Surgery in 1984 and specialized in Neurology in 1988. In 1993 he obtained the PhD degree in Neuroscience. Sergio Chieffi became Researcher in Human Physiology in 1993 and Associate Professor of Human Physiology in 2001. Currently he teaches at the School of Medicine of the Second University of Naples. The main topics of his research are the study, in healthy normal and neurological patients, of reaching-grasping movement planning; distractor interference on visuo-motor performance; coding in spatial working memory of target location to be reached with hand movement.

Automatic analysis of spontaneous speech for detecting mild cognitive impairment: A screening tool?

Laura Calza*, Daniela Beltrami, Gloria Gagliardi, Rema Rossini Favretti, Fabio Tamburini, Enrico Ghidoni
University of Bologna, Italy

Due to increased life expectancy, the prevalence of cognitive decline related to neurodegenerative diseases and to non-neurological conditions is increasing in western countries. Thus, there is an increasing demand, from both social and healthcare systems, for instruments and strategies to recognize cognitive decline, and possibly distinguish the precursor of serious neurodegeneration from "benign senile forgetfulness" or the temporary consequences of illness or trauma. Moreover, novel approaches for the identification of "preclinical " or "pre-symptomatic" Alzheimer's disease and other dementia are a key issue in the field. Recent studies showed that discourse alterations may be one of the earliest signs of the pathology, frequently measurable years before other cognitive deficits become apparent. Traditional neuropsychological tests fail to identify these changes. In contrast, the analysis of spoken language productions by Natural language processing (NLP) techniques can ecologically pinpoint language modifications in potential patients. This interdisciplinary study aimed at using NLP to identify early linguistic signs of cognitive decline in the elderly. Methods: We enrolled 96 subjects (age range 50-75): 48 healthy controls and 48 impaired subjects: 16 subjects with single domain amnestic Mild Cognitive Impairment (a-MCI), 16 with multiple domain MCI (md-MCI) and 16 with early Dementia (eD). Each subject underwent a brief neuropsychological screening composed by MMSE, MoCA, GPCog, CDT and verbal fluency (phonemic and semantic). The spontaneous speech during three tasks (complex picture; a typical working day; the last remembered dream) was then recorded, transcribed and annotated at various linguistic levels. A multidimensional parameter computation was performed by a quantitative analysis of spoken texts, computing 67 rhythmic, acoustic, lexical, morpho-syntactic and syntactic features. Results: Neuropsychological tests showed significant differences between controls, md-MCI and eD subjects (p=…..), while they didn't differentiate between controls and a-MCI subjects (p=….). In the linguistic experiments, a number of features regarding lexical (p=…), acoustic (p=…) and syntactic aspects (p=…) were significant (using the Komolgorov-Smirnov test) in differentiating between all the considered subject groups. Conclusions: Linguistic features of spontaneous discourse transcribed and analyzed by LNP techniques show significant differences between controls and pathological states, and seems to be a promising approach for the identification of preclinical stages of dementia. Long duration follow up studies are needed to confirm this assumption.

Audience take away:

- Should we screen for cognitive decline and dementia?
- Should/could screening for "warning signs" of cognitive be performed in the primary care setting?
- Is spontaneous language a biomarker candidate for cognitive decline?

Biography

Laura Calza, MD, Endocrinologist

Professor of Embryology, Regenerative Medicine and Cognitive Sciences at University of Bologna

Director of the Health Sciences and Technologies - Interdepartmental Center for Industrial Research (HST-ICIR), University of Bologna

President of the Scientific and Technical board of the Montecatone Rehabilitation Institute for spine and brain injury

Scientific Advisor of the Life Science Platform, High Technology Network, Emilia Romagna Region

Scientific Director of IRET Foundation, Ozzano Emilia, Italy

Founder of TransMed Research srl, Ozzano Emilia, Italy

Scientific interests: neurobiology, with regard to neurodegenerative diseases (focus on Alzheimer disease and multiple sclerosis) and acute injuries (stroke, spinal cord injury and peripheral nerve injury); stem cells and nanostructured scaffolds for neural and myelin repair; stem cells for high content screening; dynamic imaging by confocal laser scan microscopy. Biomarker discovery in neurodegenerative diseases

The mGlu4 receptors as target for novel antipsychotic drugs; Interactions with other neurotransmitter systems

Joanna M Wieronska, Paulina Cieślik, Monika Wozniak, Krzysztof Tokarski, Magdalena Kusek, Krystyna Gołembiowska, Grzegorz Burnat and Andrzej Pilc*
Polish Academy of Sciences, Poland

The aim of our studies was to further investigate to antipsychotic potential of glutamate metabotropic receptor 4 (mGlu4) agonists and positive allosteric modulators (PAMs) as well as to investigate the interactions between mGlu4 receptor stimulators and 5-HT1A serotonin agonists in order to develop potential novel and efficacious ways to treat this devastating disease. The possibility that the mGlu4 receptors and 5-HT1A receptors may form dimers was also investigated. An orthosteric agonist of mGlu4 receptors was investigated in several rodent tests used to study antipsychotic-like activity of drugs, such as MK-801 and amphetamine-induced hyperactivity, DOI-induced head twitches, social interactions, modified forced swim test, and novel object recognition test. Interactions of mGlu4 receptor agonists with serotonergic system was also evaluated. Moreover the in vivo microdialysis, the electrophysiological studies were also conducted. The potential dimerization of mGlu4 and 5-HT1A receptors was also investigated. The mGlu4 receptororthostericagonist LSP4-2022was effective in all preclinical tests of schizophrenia applied. In subsequent experiments it was shown that the administration of subeffective doses of LSP4-2022 may be intensified with the administration of the ligands of the other receptors. The co-administration of sub-effective dose of the 5-HT1A agonist (R)-(S)-8-OH-DPAT revealed the activity of ineffective doses of LSP4-2022, while the 5-HT1A antagonist WAY100635 reversed LSP4-2022-induced effects on MK-801-induced hyperactivity, DOI-induced head twitches, MK-801-induced disruptions of social interactions and novel object recognition.

In the microdialysis studies MK-801 at a dose of 0.6 mg•kg−1 significantly increased cortical DA, 5-HT and Glu levels, reaching a maximal effect between 80 and 120 min after administration. LSP4-2022 reversed this effect and WAY100635 (5-HT1A antagonist) antagonized this LSP4-2022-induced effect. In the electrophysiological studies in slices from the mouse prefrontal cortex, LSP4-2022 reversed the DOI-induced changes in both the frequency and amplitude of the EPSCs, but the more robust effect on the frequency was observed. When mGlu4 and 5-HT1A receptor were co-expressed in the T-Rex 293 cells, the fluorescenceresonance energy transfer (FRET) studies revealed the close vicinity of both receptors. The experiments with the use of proximity ligation assay (PLA) conducted ona primary cultures of astrocytes or neurons have shown a positive PLA signal, which indicated that both receptors are placed in a close vicinity, which enables the potential dimerization of bot receptors. The efficacy shown by mGlu4 receptor activator in mechanistic and behavioral models of schizophrenia provides evidence for a potential role played by this receptor in the pathophysiology of this disease and suggests that mGlu4 receptor activators can become future antipsychotics.

Our results indicate that:

- Combined treatment based on the simultaneous stimulation of 5-HT1A and mGlu4 receptors may be considered as combinations active in psychosis
- Such combination may allow for lowering drug doses and achieving a greater efficacy.
- The study was supported by the National Science Centre grants No. 2012/6/06/A/NZ7/00014 (MAESTRO) given to A. Pilc.

Biography

Professor Andrzej Pilc, MD., PhD is now the Head of Neurobiology Department at the Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland. His main research interest is in the studies of the mechanism of action of antidepressant/anxiolytic/antipsychotic drugs including the involvement of mGlu or GABAB receptor ligands. He is a principal investigator in a number of grants, received several national awards and is one of the most frequently cited Polish pharmacologists.

Sensory processing in autism spectrum disorders: literature review and perspective on the latest theories

Razvana Stanciu*, MD; VeroniqueDelvenne, MD, PhD
UniversiteLibre de Bruxelles (ULB), Belgium

Background: Since the publication of the Diagnostic and Statistical Manual of mental disorders: DSM-5, sensory processing anomalies have for the first time been identified as diagnostic criteria in the international classification and thus been recognized as part of the core symptoms in autism spectrum disorders (ASDs). Their clinical relevance and their critical importance for the patients is underlined by numerous first-person accounts, and many recent studies have investigated their epidemiology as well as their behavioral and neurophysiological links with the other core symptoms of ASDs. In the past years, several explanatory models of autism have been developed in relation with the atypical sensory processing features found in these disorders.

Methods: In this presentation, we summarize the research data found in a systematic literature review about sensory anomalies in ASDs, with regard to epidemiology, clinical presentations, and neurophysiology. We then summarize the latest explanatory theories based on perception in autism, and discuss the implications of the recent data in relation with them, as well as the latest research directions.

Findings: Sensory anomalies in ASDs are characterized by the variability of their presentation and of their clinical impact, not only between individuals but also in time. At present the underlying physiological mechanisms and their relation with the other core symptoms in autism are not fully understood, but much progress has been made in the last years, as research focus on these anomalies has been increasing. Several models show interesting perspectives for explaining atypical sensory processing as well as other core symptoms in ASDs. Some could account for the complexity and clinical features variability of the autism spectrum, as well as provide indications for underlying neurological processes and even treatment possibilities.

Main ideas of the presentation:

- Sensory processing anomalies in autism are described and their clinical relevance is emphasized
- Their complexity is highlighted by the summarized literature results
- The latest and most promising explanatory theories of autism take these anomalies into account or even consider them at the origin of the peculiarities of the autistic functioning

Further research perspectives are examined in relation with these theories

Audience take away:

The audience will be familiarized with one of the main clinical issues in ASDs, that has until recently been very often ignored by many clinicians. This presentation is also an opportunity to exchange about an interesting topic in recent research on ASDs, and on the latest advances in the exploration of the aetiology of ASDs.

Biography

Dr Razvana Stanciu is a child psychiatrist, a researcher and a PhD candidate in child psychiatry at the Université Libre de Bruxelles (ULB). After she completed her medical studies at the ULB, she became mainly a hospital practitioner in child and adolescent psychiatry, but she also acquired a background in child neurology and adult psychiatry, and a training in systemic therapy. Her clinical interest led her to focus on autism spectrum disorders (ASDs). After being in charge for two years of a diagnostic centre for ASDs, she contributed to the creation of a day care facility for young children with ASDs. Her research work focuses on sensory aspects in ASDs and is mainly located at the Queen Fabiola Children Hospital in Brussels, Belgium.

The magic and mystery of brain serotonin

Kathryn G. Commons
Children's Hospital Boston-Harvard Medical School, USA

Serotonin neurotransmission has pervasive effects on behavior. While it is not responsible for any single behavior, serotonin helps shift between myriad of different behavioral repertoires and mood is perhaps related to our subjective experience of this shifting. It's unknown how serotonin neurons perform this function. A current theory in the field is that there are small subsets of serotonin neurons that are highly specialized to facilitate specific behaviors. However, the extent of specialization and the identity of functionally relevant units remain poorly resolved. Here we review current understanding of the organization of brain serotonin neurons and discuss how these networks could function at the systems level. While ascending serotonin neurons exhibit substantial diversity, they are organization into two major families. Feedback inhibitory networks regulate these networks and are likely particularly important for the etiology of psychopathology and designing treatment strategies. Experiments using rodents modeling the behavioral response to both chronic developmental and acute stress suggest some hypotheses for how serotonin neurotransmission could be involved in depression and how antidepressants could work to modify their action.

Audience take away:

- The serotonin system may be composed of many highly specialized subunits, although the extent of specialization remains controversial.
- Feedback inhibitory circuits may exist between functionally distinct groups of serotonin neurons.
- Disorders such as depression could be related to imbalances within the serotonin system rather then simply a serotonin deficit.

Biography

Dr. Kathryn G. Commons is an Associate Professor of Anesthesia at Harvard Medical School and Children's Hospital Boston. Trained in neuroscience at Cornell University Medical College, she performed postdoctoral studies at Rockefeller University and the University of Pennsylvania. She is a leader in basic neurobiology research aimed at understanding the form and function of serotonin in the vertebrate brain. Her work is relevant for understanding the contribution of serotonin to a wide range of disorders including depression, anxiety, obsessive compulsive disorder, drug addiction and autism.

Psychiatric pathology in somatically ill hospital patients: Implications of current data on consultation-liaison psychiatry

Caroline Lucke*, Jurgen M. Gschossmann, Alexandra Philipsen, Helge H.O. Muller
Medical Campus University of Oldenburg, Germany

Psychiatric comorbidities are very common in somatically ill hospital patients, yet the timely recognition and initiation of appropriate care is still insufficient in many clinical settings. Here, I will present data from a large prospective study on consultation-liaison psychiatry conducted in Germany, analyzing data of 890 patients who required psychiatric care during their hospital stay due to the development of comorbid psychiatric symptoms. The study provides up-to-date results on the distribution of psychopathology and psychiatric diagnoses in this population as well as pharmacological and urgent treatment requirements. Organic mental disorders play an important role in this context, most strikingly in the field of neurological disorders, where direct affection of the ZNS may induce a variety of psychiatric manifestations. In general, there are clear indications that a hospital stay constitutes a significant stressful life event, sufficient to trigger psychiatric pathology especially of the affective/anxiety spectrum, which was very common in our study population. Risk factors for such pathological stress reactions, i.e. the role of pre-existing psychiatric disorders are discussed. Furthermore, we present data on methodological aspects on the conduct of modern consultation-liaison services. The traditional "on-demand" model with individually requested consultations is compared to new, "quasi-liaison" approaches, combining regular routine consultation hours with appropriate emergency services. Our data indicate, that the on-demand approach may have advantages for acutely affected patients due to the short waiting time, while for patients with mild or beginning symptoms a service model with fixed consultation hours increases their chance of being referred to a psychiatric consultation in the first place. Such patients seem to be at risk of being overlooked until their psychiatric symptoms have reached a substantial clinical manifestation. This is supported by the fact that in our study population the rates of patients requiring extensive further psychiatric treatment of even referral to a psychiatric ward following the consultation were very high. Thus, better routine offers of early recognition and counselling of psychiatric problems in hospital patients are required. A "quasi-liaison" model as presented in our study may provide an effective and easy to implement way to improve care for such patients.

Audience Take Away:

- Audiences will receive an up-to-date overview on the spectrum of psychiatric diagnoses, characteristics and specific treatment requirements to be expected in the specific population of somatically-ill hospital patients.
- For audience working in a non-psychiatric clinical field, i.e. neurology, these insights can be helpful for easier identification of specific psychiatric symptomology in their patients and may encourage physicians to initiate psychiatric care early in the development of symptoms which may prevent further exacerbation.
- For audience working in the field of consultation-liaison psychiatry the here presented implications on the benefits of regular psychiatric consultation hours may provide new ideas and impulses for the improvement of consultation-liaison services in their specific area of work.

Biography

Caroline Lucke, MD, studied medicine at the University of Munster, Germany and completed her doctoral thesis at the Department of Neuroanatomy & Molecular Brain Research, Ruhr-University Bochum. After a research stay at the Institute of Neurology, UCL, UK, she worked as a Medical Advisor at Boehringer Ingelheim Pharma, Germany. Dr. Lucke then continued her clinical and academic career at the University Clinic Frankfurt am Main, Germany, where she worked in the group of Prof. U. Ziemann on basic research using transcranial magnetic stimulation. Since 2016 Dr. Lucke is a postdoctoral researcher at the Psychiatry Department of the University of Oldenburg, Germany (Prof. A. Philipsen). Her research interests include psychiatric epidemiology, adult ADHD and transcranical magnetic stimulation in psychiatry.

Changes in the orexin system in the rats expressing learned helplessness behaviors

Sabrina Wang*, Ph.D. and Chung-Wei Hsu, M.Sc
National Yang-Ming University, Taiwan

Orexins (also known as hypocretins) are two excitatory neuropeptides, including orexin-A (OX-A) and orexin B (OX-B), produced by a small population of neurons located in the lateral hypothalamus, the dorsomedial hypothalamus, and the perifornical hypothalamus. The orexin neurons have projection fields widely distributed throughout the central nervous system, including several brain regions implicated in mood disorders. Recent studies reveal that in addition to feeding and sleep regulation orexin system is also involved in the modulation of autonomic and neuroendocrine function, energy regulation, reward and stress responses, and attention. There is an especially dense projection of orexin-containing terminals in locus coeruleus and raphe nucleus, both areas are important for sleep regulation. Orexins also play a role in positively regulating cognitive processes of attention and memory. In addition, orexin system modulates HPA axis stress response by directly stimulating corticotropin-releasing hormone (CRH)-synthesizing neurons in the paraventricular nucleus of the hypothalamus. The broad physiological functions and its extensive interaction with dopamine, serotonin, and norepinephrine systems made orexin a potential player in neuropsychiatric disorders. Both preclinical and clinical studies suggest orexin system is been associated addiction and mood disorders, including depression and anxiety. In the present study we investigated the correlation of orexin system and depression-like behaviors using learned helplessness animal model of depression. We compared the number of orexin neurons among rats that displayed learned helplessness behaviors following inescapable electrical shocks (LH rats), rat that did not display LH behaviors (NoLH rats), and non-shocked control rats. We also examined orexin peptides and receptors in brain areas involved in major depression and serum OX-A and corticosterone concentrations. We found that in comparison to control rats the shocked rats all showed higher OX-A concentrations in the serum. However, the NoLH rats had significantly higher serum OX-A levels comparing to that of the LH rats. The NoLH rats also had significantly more OX-A neurons than LH rats while the LH rats had more OX-B neurons. Among the brain areas examined the orexin peptides and receptors also displayed different changes in the LH and NoLH rats. The detailed study of orexin-A and orexin-B peptide concentrations and receptor distributions in various brain areas involved in depression could facilitate our understanding of the role of orexin system in major depression and contribute to our basic knowledge of orexin neuropeptides, particularly on their antagonizing function proposed in past literatures.

Audience take away:

- Serum orexin A level does not always show positive correlation with the orexin A change in brain areas involved in major depression
- Orexin A neuron might play a role in depression resilience
- The rats that displayed LH behaviors has higher activation of hypothalamic OX-B neurons. The orexin B peptide seems correlate with depression-like behavior
- More and more evidences indicate orexin system is involved in major depression pathophysiology

Biography

Dr. Sabrina Wang is an Assistant Professor in the Institute of Anatomy and Cell Biology, National Yang-Ming University of Taiwan. She is a member of Research Collaborating Group for New insight, Strategy, and Evaluation the Treatment Refractory Depression Program (RECOGNISE). She received her Ph.D. degree from University of Toronto, Toronto, Canada. She worked at National Health Research Institute from 2005 to 2011 then joined National Yang-Ming University. In the past 10 years her research was focusing on the delineation of neuronal mechanisms that might serve as the underpinning for the development of major depression.

Cux1 enables inter-hemispheric connections of layer II-III neurons by regulating Kv1-dependent firing.

Fernanda M. Rodriguez-Tornos, Carlos G. Briz, Linnea A. Weiss, Alvaro Sebastian-Serrano, Saul Ares, Marta Navarrete, Laura Frangeul, Maria Galazo, Denis Jabaudon, Jose A. Esteban and Marta Nieto*Equalcontribution, Centro Nacional de Biotecnologia (CNB-CSIC),Darwin , Campus de Cantoblanco
Spanish National Research Council, Spain

Neuronal subtype specific transcription factors (TF) instruct key features of neuronal function and connectivity. Activity-dependent mechanisms also contribute to wiring and circuit assembly, but whether and how they relate to TF-directed neuronal differentiation is poorly investigated. Here we demonstrate that the TF Cux1 controls the formation of the layer II-III corpus callosum (CC) projections through the developmental transcriptional regulation of Kv1 voltage-dependent potassium channels and the resulting postnatal switch to a Kv1-dependent firing mode. Loss of Cux1 function led to a decrease in the expression of Kv1 transcripts, aberrant firing responses and selective loss of CC contralateral innervation. Firing and innervation were rescued by re-expression of Kv1 or postnatal reactivation of Cux1. Knocking-down Kv1 mimicked Cux1-mediated CC axonal loss. These findings reveal that activity-dependent processes are central bona fide components of neuronal TF-differentiation programs, and establish the importance of intrinsic firing modes in circuit assembly within the neocortex.

Audience take away:

- how the audience will be able to use what they learn?

1.New mechanisms of corpus callosum formation.

2.An understanding of how ion channels and excitability might be implicated in mental disorders.

3.The description of a window of plasticity in which callosal axons can be repaired can promote new therapeutic strategies targeting plasticity.

How will this help the audience in their job? Is this research that other faculty could use to expand their research or teaching? Does this provide a practical solution to a problem that could simplify or make a designer's job more efficient? Will it improve the accuracy of a design, or provide new information to assist in a design problem? List all other benefits.

Understanding the mechanisms of callosal formation and the plasticity of cerebral cortical circuits during development that I will describe will contribute to understand mental disorders. It can promote new ideas for therapeutic intervention.

Biography

Marta Nieto Lopez.
Date of birth: 03/03/1970.
Current Position: CSIC Group Leader. Spanish National Research Council.

EDUCATION

1988-1993. Bachelor in Chemistry. Universidad Complutense de Madrid.
1993-1998. PhD in Molecular Biology. Universidad Autonoma de Madrid.
06/2000-2004 Postdoctoral Neuroscience, Dept. of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School. Laboratory of Christopher A. Walsh, M.D.
1999– 06/2000 Postdoctoral IGBMC, Strasburgo, France. Laboratory of Dr. Francois Guillemot.
1993-1999Ph. D. Servicio de Immunologia. Hospital de la Princesa. UAM: Madrid. Laboratory of Dr Francisco Sanchez-Madrid.

The impact of physical exercise on the modulation of epigenetic and inflammatory markers in schizophrenic individuals

Viviane Rostirola Elsner*, Caroline Lavratti, Gilson Dorneles, Daniela Pochmann, Alessandra Peres, Andreia Bard, Lucas de Lima Schipper, Pedro Dal Lago, Luciane Wagner.
IPA Methodist University, Brazil

Approximately 1% of the world's population is affected by schizophrenia (SZ). Among possible factors, an imbalance on epigenetic machinery and inflammatory markers have been recognized in it´s physiopathogenesis and course. The patients with SZ usually adopts a sedentary lifestyle, which has been partially associated with the increase in obesity incidence rates, metabolic syndrome and type 2 diabetes. Interestingly, exercise has been considered an important additional therapeutic option for this population, promoting benefits to physical and mental health. Few studies have been pointed out that the positive effects of exercise in different populations engage the modulation of epigenetic and inflammatory markers. However, studies investigating this interaction in SZ patients are lack. Furthermore, the studies regarding the exercise impact on SZ generally use aerobic and/or resistance programs, while less attention have been devoted to concurrent protocols. Therefore, we aimed to evaluate the effect of a concurrent exercise protocol (CEP) on anthropometric parameters, global histone H4 acetylation levels and inflammatory markers (IL-4, IL-6 and IFN-γ) in peripheral blood of SZ patients at different time-points. This study was approved by the Centro Universitário Metodista-IPA Research Ethics Committee (no 1.243.680/2015). The participants (n=15) were submitted to the CEP during 90 days, 3 times a week/60 minutes-session. Blood samples were collected pre, 30, 60 and 90 days after the intervention began. The CEP significantly reduced body mass index and body mass. The CEP induced a remarkable histone H4 hypoacetylation status in all times evaluated when compared to the baseline period. A reduction in IL-6 levels during the 60 and 90 days compared to the baseline period was observed. Finally, diminished IFN-γ levels were found in the 90 days period compared to the baseline and 30 days after periods. These data suggest that the improvement in anthropometric measures following CEP is associated to the histone H4 hypoacetylation status and the reduction on anti-inflammatory cytokines.

This is the first evidence demonstrating the exercise effects on epigenetic modulation in SZ individuals. We believe that these preliminary findings will encourage future investigations with a larger sample, which could include a control group which could enable verify other issues such as the influence of gender and age on epigenetic machinery in response of exercise in patients with SZ.

Biography

Dr. Viviane Elsner has completed her PhD at the age of 28 years from Universidade Federal do Rio Grande do Sul, Brazil. Currently she has 31 years old and is professor/research in a Post Graduate Program and guides 8 master students. She coordinates the "Interdisciplinary Group of Study on Epigenetics Applied to Health and Disease" and their academic production primarily involves the line of research related to the effects of physical exercise on the modulation of epigenetic mechanisms in healthy subjects or patients with chronic diseases". She has published 14 papers in reputed journals in the last years.

FDG PET, DAT SPECT and olfaction in rapid eye movement sleep behavior disorder

Klaus L. Leenders*, MD, PhD; Sanne K. Meles, MD; David Vadasz, MD; Wolfgang H. Oertel MD, PhD
University of Groningen, The Netherlands

Objective: Idiopathic rapid eye movement sleep behavior disorder (iRBD) is a well-known risk factor for Parkinson's disease, and provides an opportunity to test biomarkers in the prodromal stage. Recently, expression of the Parkinson's disease related metabolic pattern (PDRP) was used to predict conversion from iRBD to Parkinson's disease. We compared PDRP expression in iRBD to striatal dopamine transporter (DAT) binding and olfaction.

Methods: PDRP expression z-scores were computed in 18F-FDG PET brain scans of 30 iRBD patients and 19 controls. PDRP z-scores were compared to z-scores in Parkinson's disease (n=14) and dementia with Lewy bodies (n=14). Based on prior research, a cut-off z-score of 1.8 was used to indicate 100% specificity for Parkinson's disease.

In 21/30 iRBD patients, DAT imaging with 123I-FP-CIT SPECT was performed. The relationship between pattern expression, DAT binding and olfactory function (Sniffin' Sticks test) was studied.

Results: PDRP expression was higher in iRBD compared to controls (P=0.003), but lower compared to Parkinson's disease. Seventeen iRBD patients (57%) had a z-score≥1.8. PDRP z-scores correlated to putamen DAT binding (r=-0.61, P=0.005). Loss of striatal DAT binding was observed in 9/21 patients (43%). Interestingly, of the 12 iRBD patients with a normally rated 123I-FP-CIT SPECT scan, 5 (42%) expressed the PDRP (z-score≥1.8). Olfactory dysfunction was observed in 23/26 iRBD subjects. There was no significant relationship between olfaction and PDRP z-scores or DAT binding.

Interpretation: The PDRP is a suitable biomarker for neurodegeneration in prodromal Parkinson's disease, and its expression may be detected before the nigrostriatal pathway is affected.

Biography

Prof Dr K.L. Leenders is a clinical neurologist who trained at the University of Amsterdam.From 1982 until 1988 he worked at the Hammersmith Hospital London as Senior Registrar and in the PET research program at the MRC Cyclotron Unit.

From 1989 until 1998 he was head of the movement disorder clinic of the Neurology Department at the Zurich University Hospital (Switzerland). At the same time he has been responsible for running a research program concerning movement disorders using PET radiotracer imaging techniques at the Paul Scherrer Institute, the national physics institute in Switzerland.

Masgutova Neuro-Sensory-Motor Reflex Integration (MNRI)

Leah K. Light
Brainchild Institute, USA

Dr. Leah Light, on behalf of the Svetlana Masgutova Educational Institute (SMEI), will discuss primary reflexes, which encompass our innate and subcortical, genetic motor intelligence that ultimately gives rise to more controlled physical activity, emotional and behavioral self-regulation, and higher levels of conscious thought and analytical thinking. Developmental sequelae that often result from poorly integrated primary reflexes will be reviewed and their negative impact on self-reliance, stress levels, and the ability to learn cohesively. Discussion of how MNRI® (Masgutova Neuro-Sensory-Motor Reflex Integration) uses specific strategies and techniques to connect the brain-body system by supporting maturation of neural pathways from the brainstem to the cortex will be described. Published articles and research outlining the benefits of using MNRI® with various populations including Down's Syndrome, Autism Spectrum Disorder, Post-Traumatic Stress Disorder, Cerebral Palsy, and Chronic Bronchitis will be discussed so as to show the far reaching benefits of this relatively simple yet profound neuro-sensory-motor approach that is shared with family members and caregivers for at-home use.

Audience Take Away:

Attendees of this session will learn about the functional purpose of primary reflexes and the role they play in laying the foundation for human development. They will also learn some simple techniques to identify children and adults with retained primary reflexes and when to refer to a specialist for primary reflex integration services. A few basic reflex integration techniques will be demonstrated for attendees to begin using with children suspected of having a Reflex Integration Disorder. Attendees will also learn about supporting research and studies that are currently underway by the Svetlana Masgutova Educational Institute to provide further validation for the use of the MNRI® program for a variety of neurological and health conditions.

Biography

Dr. Leah Light is owner and director of the Brainchild Institute. She completed her B.A. in Special Education and her Master of Science and Doctorate (Au.D.) degrees in Audiology. In addition, she completed a year of speech pathology studies. Dr. Light is a member and is certified by the American Speech-Language and Hearing Association (ASHA). She is also a member of AAA, FLASHA and FLAA. Having worked with almost every aspect of hearing impairment and deafness from newborns to the aged, Dr. Light has extensive clinical expertise in the diagnosis and treatment of hearing loss, vestibular dysfunction and other auditory related disorders. In addition, she has worked as an integral part of child development and patient management teams. Over the past 24 years, Dr. Light's focus has centered around neurodevelopmental audiology and Auditory Processing Disorders. In addition, Dr. Light is a certified Core Specialist and instructor in the Masgutova Method (MNRI®), a program for addressing retained primary reflexes, which are often at the root of impairments in communication, learning, behavior, and social skills. Dr. Light regularly attends conferences and workshops on (Central) Auditory Processing Disorders in addition to a variety of related areas to better understand the global impact of sensory, motor and neurological deficits on central auditory processing skills. As a neurodevelopmental specialist, she has participated as a speaker in events for numerous organizations including the American Academy of Audiology and the Florida Academy of Audiology. Furthermore, Dr. Light has written articles for local magazines and newspapers, and authored a chapter in the book, Auditory Processing Disorders: Assessment, Management, and Treatment.

Session on: Neurological Disorders and Stroke

Session Chair
Pankaj Sharma
University of London, UK

Session Co-Chair
Henry Bakunts
International Medical Centre "STROKE", Republic of Armenia

Session Introduction

Title: Novel stroke care delivery designs
Kenneth Gaines, Vanderbilt university, USA

Title: Blockade of NMDA receptors in the developing cortex and consequences on the autophagic death of migrating interneurons
Bruno Gonzalez, Inserm - U1245 Team NeoVasc, France

Title: Post-acute stroke rehabilitation
Raquel Sofia Marques Neves, Amana Healthcare Medical and Rehabilitation Hospital, UAE

Title: Areas of applications and the market of non-linear technologies for restoration and modulation of the dynamics of brain activity and behavior
Marina Vladimirovna Zueva, Moscow Helmholtz Research Institute of Eye Diseases, Russian Federation

Title: EEG data analysis for motor rehabilitation of stroke patients
Laehyun Kim, Korea Institute of Science and Technology, Korea

Title: Computer cognitive training in acute stroke
Prokopenko Semen, Krasnoyarsk State Medical University, Russian Federation

Title: Neuroprotective agents target molecular mechanisms of programmed cell death after traumatic brain injury
Luyang Tao, Soochow University, China

Title: Bilingualism: Cognitive assessment of post stroke patients in republic of tyva
Anna Bezdeneznykh, Krasnoyarsk State Medical University, Russian Federation

Title: The use of the infrascanner to prevent head injuries in combat sport
M.R. Graham, Llantarnam Health Care, UK

Title: Stem cells application for the therapy of neurological disorders
Serhiy Forostyak, Charles University, Czech Republic

Title: Healthy and successful pregnancy while receiving intrathecal ziconotide for arachnoiditis-related chronic pain
Gladstone C McDowell, Integrated Pain Solutions, USA

Title: Novel therapeutic strategies to improve t-PA therapy and promote recovery after stroke
Saema Ansar, Lund University, Sweden

Title: Selenium and alzheimer's disease: Facts and effects
Bárbara R. Cardoso, University of Sao Paulo, Brazil

Title: Urgent carotid endarterectomy after acute stroke
Hassan Ravari, Mashhad university of medical sciences, Iran

An integrated practice unit can address gaps in stroke care delivery to impact outcomes across the continuum of care

Kenneth Gaines*, MD, MBA, FAAN, FAHA, Patricia Commiskey, DrPH, MA
Vanderbilt University Medical Center, USA

As the 5th leading cause of death and adult disability in the United States (US), stroke care is complex, involving multiple mechanisms and high risk and cost.Even when initial acute events are managed successfully, patient risk remains high from complications and poor risk factor management that can lead to rehospitalization and stroke recurrence. Current US stroke care delivery is fragmented and well-engineered to foster both miscommunication and uncoordinated, inefficient care across poorly integrated nodes of care. These nodes of care have varying geographies, personnel, and focus, and even when initial acute strokes are managed successfully, patient risk remains high from in-hospital complications like pneumonia and urinary tract infections (UTI) and poor risk factor management post-discharge. Despite advances in care, current stroke care delivery models have not addressed these limitations in a comprehensive way across the continuum of care. However, an Integrated Practice Unit model has the potential to improve care coordination across each node of care and has the potential to decrease morbidity and mortality and encourage better risk factor management for stroke patients.

An innovative stroke care delivery model was implemented at Ochsner Medical Center (OMC) in New Orleans, Louisiana, US in 2012 that combined integrated technology and real-time care redesign across the care continuum. Supported by a Health Care Innovation Award (#1C1CMS331043) from the Centers for Medicare and Medicaid Services (CMS), this model utilized an Integrated Practice Unit design and combined in-hospital and outpatient, home-based components to follow stroke patients from symptom onset through 12-months post-discharge. This novel Integrated Stroke Practice Unit combined an in-hospital component (called Stroke Central) with a home-based, outpatient component (called Stroke Mobile). Post-discharge, stroke patients and their families were visited 12 times (once per month) at home to assess overall health and recovery, evaluate risk factors, and provide stroke and stroke-related comorbidity management, comprehensive risk/recovery/recurrence education, and caregiver/family support.

This presentation will describe the US stroke care infrastructure, including stroke care delivery models and systems in place and benefits and limitations of each. An Integrated Stroke Practice Unit (IPU) Model and an example of an Integrated Stroke Practice Unit (ISPU) implemented at a hospital in Louisiana will be described.

Audience take away:

This presentation will provide its audience with detailed background on the issues surrounding effective stroke care in the US, including an overview and pros and cons of a number of stroke delivery care models. It will highlight an example of an Integrated Stroke Practice Model, including design, implementation, and challenges experiences. Specifically, this presentation will meet the following objectives:

- The current state of stroke and existing stroke care infrastructure in the United States will be discussed and described.
- Existing stroke care delivery models and systems will be described, including benefits and limitations of each.
- An Integrated Practice Unit (IPU) Model will be detailed that shows how the IPU design fills existing stroke care delivery gaps.
- An example of an Integrated Stroke Practice Unit (ISPU) implemented at a hospital in Louisiana will be described in detail.

Biography

Dr. Kenneth Gaines is a Board-certified Neurologist/Vascular Neurologist with 40+ years' experience in stroke care and research. He has served as Site PI/Steering Committee member for 20+ randomized stroke trials, including SECORDS, an NIH-funded RO1 multicenter study of ethnic differences in stroke; Stroke Mobile, a NIH Office of Minority Health-funded study of home-based care delivery in the African American community; and a CDC-funded grant developing stroke telemedicine in rural Louisiana. Dr. Gaines designed and was PI of a CMS-funded Innovation Award to redesign stroke care delivery and is PI for C3FIT (Coordinated, Collaborative, Comprehensive, Family-based, Integrated, and Technology-enabled Care), a multidisciplinary, randomized comparative effectiveness trial testing an integrated delivery model from symptom onset through 12-months' post-stroke discharge at 18 US sites.

Blockade of NMDA receptors in the developing cortex and consequences on the autophagic death of migrating interneurons

Bruno J Gonzalez
Inserm - U1245 Team NeoVasc, France

In neonates, excitotoxicity is a major process involved in hypoxic-ischemic brain lesions, and several studies reported neuroprotective effects of NMDA antagonists. However, there is more and more evidence indicating that, in the developing brain, glutamate exerts trophic effects on migrating GABAergic interneurons and that NMDA antagonists would present neurodevelopmental side effects. Thus, characterizing the mechanisms leading to developmental impairments of NMDA antagonists would be therapeutically useful. Because macroautophagy is involved in the adaptive response to trophic deprivation, we investigated the impact of autophagy modulators on MK801-induced death of immature GABAergic interneurons. Using cortical slices from wild type and Gad67-GFP mice, we showed that blockade of the NMDA receptor resulted in an accumulation of autophagosomes due to the disruption of the autophagic flux. This effect preceded the activation of the mitochondrial apoptotic pathway, and the degeneration of immature GABAergic neurons present in the developing cortical layers II-IV. The autophagy inhibitor, 3-MA, prevented the apoptotic death of GABA interneurons whereas modulators of autophagy (3-MA, rapamycin) did not interfere with the anti-excitotoxic effect of MK801 observed in deep layers V and VI. In vivo, 3-MA blocked the rapid increase in caspase-3 cleavage induced by NMDA antagonists and prevented death of Gad67-GFP neurons in layers II-IV. Together, these data suggest that, in the developing cortex, blockade of theNMDA receptor in the developing cortex induces autophagy-mediated death of migrating cortical GABAergic interneurons. These results point out the risk of side effects regarding the use of some anesthetics such as ketamine when administered to preterm neonates. They also suggest that autophagy modulators would open new opportunities to prevent side effects of NMDA antagonists used for neuroprotection in the developing brain.

Post-Acute stroke rehabilitation

Raquel Sofia Marques Neves
Amana Healthcare Medical and Rehabilitation Hospital, UAE

Globally, life expectancy from birth increased from 61.7 years in 1980 to 71.8 years in 2015 (GBD, 2015). This means we live longer and we are more susceptible to acute and/or chronic disease. Ischaemic hearth disease and stroke are the leading two cases of premature death and according with Global Burden of Disease 2010 (Feigin et al, 2014) stroke continues to increase, with 16.9 million of people being affected by stroke annually. From these numbers, 5 million die and another 5 million are left permanently disabled (WHO, 2016) being the stroke the leading cause of disability.

An estimated 50 million stroke survivors worldwide currently cope with significant physical, cognitive and emotional deficits and 25% to 74% of these survivors require some assistance or they need fully assistance of caregivers for activity of daily living. (Miller, et al, 2010) Following a stroke an individual may experience cognitive, physical and psychological deficits. After the stroke, the first aim is to stabilize medical condition during the acute phase, and then to retrain the previously learnt tasks through actual trial and performance in the rehabilitation phase. Evidence shows that the earlier rehabilitation is commenced the better the outcome for the stroke survivor and this principles should be applied in the acute and post-acute settings. The main goal for stroke rehabilitation is to help stroke survivors relearning skills that are lost when part of the brain is damaged and to adjust him to this new condition.

Stroke rehabilitation is proactive, person-centered and goal-oriented process that should begin the first day after stroke. And the literature shows rehabilitation is not only related with physical recovery but also with reintegration of the person into the community and therefore the transition between hospital and community care.

A multidisciplinary team with a holistic, comprehensive and interactive approach should be in place to implement a stroke rehabilitation program as soon as possible, by setting realistic goals with the stroke survivor and family.

Audience take away:

- This knowledge can be use daily, during all phases of the stroke rehabilitation program.
- The knowledge acquired by all of participants will be useful on the floor with stroke patients. It is necessary for the healthcare provider to have knowledge regarding stroke rehabilitation. So it can be started since the acute phase.
- State of art will be provided, the audience will know what new is been done in stroke rehabilitation and how they can adjust to their reality.

Biography

Raquel Neves.Graduated in 2006 in Nursing School of Lisbon, Portugal.Completed her Master and Post-Specialization in Rehabilitation in 2013, Lisbon, Portugal.Working since 2006 with stroke patients in stroke wards. At the moment is the stroke coordinator in Amana Healthcare Hospital, Abu Dhabi, UAE.

Areas of applications and the market of non-linear technologies for restoration and modulation of the dynamics of brain activity and behavior

Zueva Marina Vladimirovna
Moscow Helmholtz Research Institute of Eye Diseases, Russia

The theory of 'Fractality of sensations' implies that the deficit of nonlinear complexity of the environment naturally leads to abnormal development and aging of the brain (Zueva M.V., 2015). The theory explains the need to restore the complex dynamics of the functional activity in retinal and brain diseases in various situations, which lead to simplification of the pattern of the oscillation activity and structure in CNS. The notions of the theory explain why a healthy brain is characterized by the fractal complexity of its structure and function, while pathological conditions are associated with their simplification. It follows from the theory that the use of fractal and other nonlinear regimes of sensory (photo, audio, etc.) stimulation can promote recovery of the neuronal circuits and activity in the visual system and the brain, including in neurodegenerative diseases and amblyopia by a reactivation of neuroplasticity. Note that even a brief opening of windows of increased plasticity of the adult brain, similar to the sensitive periods in the early development, could serve as a promising target for new therapeutic strategies, since in this time, the effectiveness of any (pharmacological and non-pharmacological) therapy should be improved.

We have a Patent for the Invention of the generator of fractal flickering, in which the sequence of flashes is time-invariant (Zueva MV Spiridonov IN, Semenova NA, Rezvykh S. Patent Russian Federation №0002549150 from 25.03.15). As well, we created a prototype of this device for testing, in which the self-similar pattern of flashes can be programmed with the adjustable complexity of dynamics. In a limited pilot study of effects of fractal visual stimulation on the electroretinogram of healthy rabbits, preliminary indicated that fractal flickers modulated the function of the rod system and the efficiency of synaptic transmission in the outer plexiform layer of the retina.

We believe that the complex nonlinear structure of stimuli should be regarded as a physiologically appropriate way to normalize the neuronal activity and cognitive function not only in pathology but also in healthy individuals in a variety of situations, where the development of innovative technologies can have not only a social but also a significant economic effect. Numerous studies have demonstrated that the normally functioning brain operates in a state of so-called "Self-organized criticality" to be ready to act at a critical point between order and randomness. Critical systems are associated with a fractal scaling and the presence of long-range correlations in space and time, as well as with the rapid changes in their configurations in response to external inputs. It can be expected that the use of non-linear techniques to restore physical and mental performance after heavy load and effects of stress factors, including in the sport, will help to restore the complex nonlinear dynamics of functional activity, maintaining a high level of criticality and improving the adaptive brain reserve.

Audience Take away:

- The prospective directions of scientific research and fields of future collaborations
- Areas of practical applications of innovative non-linear technologies
- The future market of non-linear technologies
- The real issues on creating user-friendly devices of various designs (such as a stimulator in the form of spectacles), suitable for industrial production.

Biography

Professor of Pathophysiology Marina Zueva graduated from the Lomonosov Moscow State University (Physiology of Higher Nervous Activity), received her Ph.D. and Dr. Biol. from Moscow Helmholtz Research Institute of Eye Diseases. Currently, she is the Head of the Division of Clinical Physiology of Vision at the Moscow Helmholtz Research Institute of Eye Diseases. Zueva is a member of International Society of Clinical Electrophysiology of Vision (ISCEV), European Association on Vision and Eye Research (EVER), European Society of Retina Specialists (EURETINA). She has published over ten peer-reviewed papers in English (over 86 in Russian) and presented over 65 topics at international conferences.

EEG data analysis for motor rehabilitation of stroke patients

Laehyun Kim
Korea Institute of Science and Technology, Korea

Stroke is the leading cause of adult neurological disabilities in most countries and typically damages particular regions of a patient's brain and results in functional impairments. The process underlying the recovery of impaired motor functions after stroke involves brain plasticity, in which motor rehabilitation therapy stimulates new neural connections and enhances cortical reorganization in order to recover normal motor function. Thus, EEG data from storke patients can reflect the brain damage and recovery during the rehabilitation. We have studied EEG data analysis for motor rehabilitation of stroke patients. Firstly, we proposed a novel method for monitoring cognitive engagement in stroke patients during motor rehabilitation. Active engagement reflects implicit motivation and can enhance motor recovery. Secondly, we found that brain activation differs according to lesion location. The hemispheric asymmetry and topographic characteristics of the beta band power patterns in the patients with stroke differed according to the location of the lesion, which suggested that EEG analyses of neurorehabilitation should be implemented according to lesion location. Finally, If an early predictor of motor functional outcome after stroke were available, stroke patients would receive more appropriate treatments for motor recovery. We performed a correlation analysis of the electroencephalography (EEG) signal patterns of nine subacute stroke patients and their motor recovery rates. In this study, EEG patterns in motor areas correlate with motor recovery after stroke and can be used as an early predictor of motor functional outcome.

Computer cognitive training in acute stroke

S. Prokopenko*, T. Dyaduk, A. Bezdenezhnykh, E. Mozheyko, I. Shvetsova.
Krasnoyarsk State Medical University, Russia

Introduction: The first in Russia computer complex of neuropsychological programs for cognitive rehabilitation was developed at the department of Neurology and medical rehabilitation of Krasnoyarsk State Medical University. It consists of some computer programs modules that are focused on training of different cognitive functions such as memory, attention, counting, etc. This method has shown effectiveness in patients with vascular cognitive impairments in earlyrecoveringperiodofstroke.

Objectives: To evaluate effectiveness of neuropsychological computer programs for correction cognitive impairments in patients in acute ischemic stroke.

Methods: The study was conducted in the local stroke center from 2010 till 2012. 144 patients met including criteria. All participants were randomized into four groups. Patients in groups 1 and 2 were examined after 2-5 days from beginning of stroke, and participants in groups 3 and 4 – 8-10 days after stroke. Apart from medical treatment, patients in the intervention groups (group 1 and group 3) had 10 daily training sessions of 20 min duration with neuropsychological computer programs. We assessed cognitive, neurological, affective states before and after training period. Patients in the group 3 were also examined in follow up.

Results: In the group 1 and the group 2 after training period we observed statistically significant improvements on all cognitive scales. Comparing the results after treatment between groups 1 and 2, we didn't find significant differences on MMSE ($p=0.853$), FAB ($p=0.06$), Clock drawing test (0.934), Phonetic and Semantic Speech tests ($p= 0.28$ and $p=0.87$).

Patients in the groups 3 and 4 were observed from 8-10 days after stroke. It was found that in 10 days of treatment (18-20 days after stroke onset) cognitive functions statistically improved on all cognitive scales: MMSE, FAB,CDT, Phonetic and Semantic Speech tests in both groups (3 and 4). Though better effects were achieved in the intervention group (group 3) comparing with the control group (group 4) on MMSE ($p<0.001$), FAB ($p<0.001$), Phonetic Speech test ($p=0.003$), Semantic Speech tests ($p<0.001$).

36 participants in the group 3 were examined in 6-8 months after the computer cognitive training. There were no statistically significant differences on MMSE, FAB, Clock drawing test, Speech tests in follow-up.

Conclusions: In the first 10-12 days of acute ischemic stroke period cognitive functions are restored spontaneously. It is probably connected with decreasing of brain edema and penumbra reperfusion.

The computer cognitive training in patients with cognitive impairments in acute ischemic stroke has shown the effectiveness starting from 8-10 days after stroke onset. The computer complex of neuropsychological programs can be recommended to this category of patients as an accessible and simple approach for early cognitive rehabilitation in stroke departments.

Improvements after computer cognitive correction in acute period of stroke were intact in recovery period during 6-8 months at least.

Discussions: Also we have a hypothesis that stimulation of sensor areas of brain, particularly, parietal occipital areas which provide optical spatial gnosis, can improve other cognitive domains, for example frontal subcortical deficit. A computer complex for stimulation visual-perceptual recognition was developed. It presents images of two- and three-dimensional objects frequently encountered in daily life, which can be turned in different planes. At the present time clinical studies is carrying out in group of post stroke patients.

Neuroprotective agents target molecular mechanisms of programmed cell death after traumatic brain injury

Xiping Chen, M.D., Ph.D., Cengliang Luo, Ph.D., and Luyang Tao*, M.D., Ph.D
Soochow University, China

The talk is to update the current state of knowledge in post-TBI pathophysiological mechanisms, mainly including programmed cell death mechanisms; mechanism-based preclinical pharmacological intervention used in animal models; to summarize their effects on cell death, inflammatory events, and prolonged motor and cognitive deficits; and further evaluate their potential success for clinical application. Many of the above mentioned mechanisms that may be important targets for limiting the consequences of TBI.

Audience take away:

- Post-TBI pathophysiological mechanisms;
- Mechanism-based preclinical pharmacological intervention used in animal models;
- Summarize the effects of the agents on cell death, inflammatory events, and prolonged motor and cognitive deficits; and further evaluate their potential success for clinical application.

Biography

Dr.Luyang Tao, Professor of Soochow University, Department of Forensic Medicine, China.

Research Interest:

- Forensic Medicine: clinical and pathological aspects
- Neuroscience: Mechanism of PCD after Neurotrauma / Intercerebral Hemorrhage
- Neuroimaging after brain injury

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Bilingualism: Cognitive assessment of post stroke patients in republic of tyva

Anna Bezdenezhnykh*, Semen Prokopenko, Tatyana Anay-ool, Elena Mozheyko, Marina Petrova
Krasnoyarsk State Medical University, Russia

Introduction: Bilingualism is an important issue in neuropsychological assessment worldwide and especially in Russia. Republic of Tyva is federal subject of Russia, where ethnic Tuvans speak both languages Russian and Tuvan. The aim is post stroke cognitive assessment of Tyva residents, depending on language of examination.

Methods: 185 people were divided into 4 groups. A group 1 consisted of healthy ethnic Tuvans. Post stroke ethnicTuvans were included in groups 2 and 3. In the group 2 cognitive assessment (MMSE, FAB, MoCA) was performed first in Russian language and then in Tuvan. In the group 3 the first examination was in Tuvan language and the second in Russian. A group 4 consisted of ethnic Russian residents of Tyva, they underwent only Russian cognitive assessment.

Results: In both Tuvan groups tests' scores in Tuvan language were statistically better comparing with scores of Russian language examination. Comparing results of Russian and Tuvan groups in Russian language there were higher scores in the Russian group. Though comparison of results in Russian group in Russian language and in Tuvan groups in Tuvan language did not show any differences. Comparing two Tuvan groups - group 2 and group 3 in Tuvan language it was found higher scores on FAB in group 2 where the second examination were in Tuvan.

Conclusion: Cognitive assessment of bilingual Tuvans has to be performed in native Tuvan language.

The use of the infrascanner to prevent head injuries in combat sport

M.R. Graham
Llantarnam Health Care, UK

Traumatic brain injuries (TBI) can be caused by a blow to the head, or sudden motions of the head, as in semi-contact or full contact sport and can result in death. The pathophysiology of TBI varies considerably depending on the location of the injury, within the brain and its severity. Severe injuries may lead to intracranial bleeds, large destruction of the brain tissue, and at worst death. The diagnosis of TBI is mainly based on a neurological examination of the patient and additionally using imaging radiology techniques such as computed axial tomography (CAT) or magnetic resonance imaging (MRI). The Glasgow Coma Scale (GCS) can be used to assess the severity of TBI on the basis of cognitive behaviour. A total score of 13–15 refers to mild TBI (mTBI), 9–12 to moderate TBI, and 3–8 to severe TBI. However, neurological examination by GCS has limitations and MRI and CAT scans are enormous pieces of equipment and not portable. Also, one CAT scan is equivalent to the electromagnetic radiation of 400 chest X-Rays. This concentration can be particularly harmful, to the traumatised brain.

The "Infrascanner" can provide field-based diagnosis and assist in the decision to evacuate an injured athlete to a hospital for immediate investigation and medical or surgical management, if required.

The "Infrascanner" can accurately detect intracranial haematomas using the unique light-absorbing properties of haemoglobin which is located within blood and the non-invasive, non-ionizing nature of Near Infrared (NIR) technology.

Enormous advantages of the "Infrascanner" for speed of diagnosis are:

• Portability (Weight: 400 grams)
• Patient measurement is completed within 2-3 minutes;
• It detects haematomas greater than 3.5 ml in volume;
• It detects haematomas up to 2.5 cm deep from the surface of the brain (or 3.5 cm from the skin)

Such technologically advanced equipment, should become mandatory in all boxing events, within a very short period. Failure to have the "Infrascanner" and personnel trained in its use will ultimately invalidate sporting licences and insurances and result in enormous medical negligence claims. Already in boxing, deaths from intracranial haemorrhages would have been prevented, if the "Infrascanner" had been present and be used as a diagnostic tool. Controlled Research Studies have already proven 80-100% sensitivity and 90-100% specificity.

Audience take away:

- Head injuries are a common occurrence as a result of combat sport.
- The resultant effect of a head injury can be a brain haemorrhage and catastrophic.
- The Infrascanner is a very sophisticated piece of equipment that is portable and capable of detecting small intracranial haemorrhages to permit urgent referral for tertiary medical assessment and so preventing further complications.

Biography

Chartered Forensic Scientist.

Scientific Legal Expert, Association of Personal Injury Lawyers;

Fellow of the Royal Society of Medicine;

Chartered Member of the Chartered Society of Forensic Sciences;

Fellow of the Institute of Clinical Researchers;

Fellow of British Association of Sport and Exercise Medicine;

Visiting Professor Ningbo University, Zhejiang, 315211, P.R. China;

MD, Llantarnam Research Academy; Llantarnam Health Care.

Stem cells application for the therapy of neurological disorders

SerhiyForostyak* M.D., Ph.D., Oksana Forostyak, M.D., Jessica Kwok, Ph.D., Prof. Dayanithi Govindan, Ph.D., Prof. James Fawcett, M.D., Ph.D. and Prof. Eva Sykova, M.D., Ph.D.
Charles University, Czech Republic

Diseases of the central nervous system (CNS) still remain among the most challenging pathologies known to mankind, having limited therapeutic possibilities and a very pessimistic prognosis. Stem cells technologies has passed a long and exciting way from the discovery, to preclinical and clinical applications. Here, will be discussed the data from preclinical and clinical research involving adult stem cells (bone marrow MSCs) and the latest results from our research focusing on the regenerative/neuroprotective properties of induced pluripotent stem cells (iPS). We will demonstrate an extracellular matrix (ECM) involvement into the pathogenesis of ALS and will show an important modulating influence of human MSCs and NP-iPS on the host ECM-related genes and proteins that could have a potential diagnostic and therapeutic application in patients. We will also present results of the study evaluating neuroprotective and neuroregenerative influence of human NP-iPS transplantation into the pre-/symptomatic SOD1-transgenic rats and will present a novel mechanisms of Ca2+ channels/receptors involvement in the differentiation of neural precursors' toward motorneurons.

Biography

2005 I have graduated (with honors) a Faculty of Medicine, Ternopil' State Medical University, Ukraine. 2005-2008 employed at the Department of Surgery as a resident-surgeon at the internship program General Surgery. 2008-2012 employed as a Ph.D-student at the 2nd Faculty of Medicine, Charles University in Prague and Institute of Experimental Medicine ASCR, Czech Republic. 2009-2010 Marie Curie Fellowship program CORTEX, under the Marie Curie Action of the FP 6. 2012 successfully defended a doctoral thesis and received a Ph.D. title in Neuroscience. 2012-2015 received a postdoctoral research fellowship in the project Development of Research Teams of IEM AS CR for the BIOCEV", at the IEM ASCR, v.v.i. and was granted a Postdoctoral research project at Department of Neuroscience, Charles University in Prague. During my postdoctoral studies attended a 6 months internship under the supervision of Professor James Fawcett in the John van Geest Centre for Brain Repair, University of Cambridge, UK. In 2014 FENS Young Investigator Training Programme (YITP) Fellowship at the Neuroscience Institute Cavalieri Ottolenghi (NICO), Turin, Italy. 2013 a laboratory visit with the training in the group of Professor Steven Badylak at McGowan Institute for Regenerative Medicine, University of Pittsburgh, USA. From 2015-present employed at the position of a Junior Research Scientist at the IEM ASCR, Czech Republic.

Healthy and successful pregnancy while receiving intrathecal ziconotide for arachnoiditis-related chronic pain

Gladstone McDowell
Integrated Pain Solutions, USA

Arachnoiditis-associated pain is notoriously treatment-resistant and may persist for many years. Despite treatment with varying combinations of drugs, patients are often left with a high pain burden. Many analgesics and medications used to treat such pain are contraindicated for use during pregnancy.

The use of high dose or prolonged oral, topical or intrathecal opioids may result in abnormalities of the hypothalamic-pituitary-gonadal axis in some patients. There is extensive literature documenting these adverse effects and the need for supplemental or hormone replacement therapy to counteract these effects. We have treated several young chronic pain patients with ziconotide intrathecal monotherapy or combination therapy using ziconotide as the base (primary drug in the programmer) drug with opioids, bupivacaine or baclofen. Ziconotide has been used as a bolus injection without any dangerous adverse effects. The drug does not have any cardiac or pulmonary adverse effects and has been used for bolus trials successfully in the outpatient setting.

A23 year old with arachnoiditis-associated pain (average 7/10, numeric rating scale) received a bolus trial of ziconotide (3-mcg in 1ml over 30 sec) by intrathecal (IT) injection, reducing her pain score to 3/10. She subsequently had a Synchromed II 20 ml IT pump implanted for ziconotide monotherapy infusion. The starting ziconotide dose was 1 mcg/day, which was titrated over 2 months to 2.5 mcg/d. After several miscarraiges she became pregnant and remained on IT Prialt.

A Personal Therapy Manager (PTM) was added, allowing an additional 0.2 mcg ziconotide bolus every eight hours for breakthrough pain (eventually increased to 0.25 mcg every 4 hours). The patient maintained an active lifestyle with a continuous ziconotide dose of 16.4 mcg/day with an average pain score of 4/10. Two years after implantation, the patient became pregnant but miscarried. She became pregnant again one year later while on a stable continuous ziconotide dose of 16.2 mcg/day (reduced to 14.98 mcg/day during pregnancy) with a PTM dose of 0.25 mcg every four hours.

There were no apparent adverse effects related to drug during pregnancy, and she delivered a healthy girl at 38 weeks via elective Caesarian section after prolonged labor. She remains stable on ziconotide 14.98 mcg/day with a PTM dose of 0.25 mcg every 4 hours.

Biography

Gladstone C McDowell II, MD, is the Founder and Medical Director of Integrated Pain Solutions, a multimodal private practice in Columbus, Ohio. Dr McDowell is a founding member and on the board of the Cancer Pain Research Consortium. He has held faculty appointments at US Patient Safety Congress meetings, National Press Club Safety Congress, The National Institute on Health Care Fraud, Cancer Pain Conference, Targeted Drug Delivery Conference, International Association for Study of Pain, and numerous US and European pain meetings. Dr McDowell was on the Polyanalgesic Consensus Conference (PACC) panels of 2007, 2012, and 2017 and the Neuromodulation Appropriateness Consensus Committee (NACC) panels of 2013 and 2016. Dr McDowell is the Chairman of the Steering Committee for the US PRIZM intrathecal registry.

Novel therapeutic strategies to improve t-PA therapy and promote recovery after stroke

SaemaAnsar
Lund University, Sweden

Each year 15 million people suffer from a stroke and it is the number one cause of disability worldwide and a major drain on health cost. The only available FDA-approved drug therapy for ischemic stroke today is tissue plasminogen activator (t-PA), which is used to dissolve the occluding clot. However, less than 10% of patients actually receive this therapy because of the very limited time-window in which t-PA can be safely administered. If t-PA is given later than 4.5 hours after stroke onset, the patient is at risk for a hemorrhagic transformation within the infarct. It is thought that metalloproteinases (MMPs) are the key culprit in causing hemorrhagic transformation. In this presentation a therapeutic approach which improve the safety of t-PA administration by blocking MMP-9 will be presented. Our results suggest that blocking MMP-9 is a promising adjuvant strategy to alleviate the detrimental side effects of delayed t-PA treatment. These results provide new insights into how we can improve the only FDA approved treatment for ischemic stroke.

Audience take away:

- Insight into how we can improve the only FDA approved drug

Biography

SaemaAnsar is an Associate Professor at Department of Clinical Science of Lund University Sweden. She completed her PhD at Lund University, Sweden in 2007. Afterwards she performed two postdoctoral trainings at Department of Neurology at Heidelberg University, Germany and at Glostrup Research Institute, Copenhagen University, Denmark. She has well-recognized expertise in the field of stroke, vascular research, physiology, pharmacology, drug delivery and advanced imaging technology such as MRI. She is teaching at the medical programme at the Medical Faculty at Lund University and has supervised more than 20 graduate and undergraduate students. She has published more than 25 papers in reputed journals.

Selenium and Alzheimer's disease: Facts and effects

Barbara R. Cardoso
The University of Melbourne, Australia

Oxidative stress has a central role in the pathogenesis of neurodegeneration. Thus deficient status of antioxidants is associated with cognitive decline and risk of dementia. Here, we show the association between selenium status in two different populations (Australian and Brazilian) and cognition, and discuss the possible variables implicit in the search for selenium-based biomarkers in Alzheimer's disease. Additionally, we present data regarding two independent pilot trials that used different selenium sources - Brazil nuts, a naturally high selenium food source, and sodium selenate - aiming to improve selenium status and cognition. Indeed, mild cognitively impaired elderly who received Brazil nuts for 6 months improved cognition performance measured by constructional praxis and verbal fluency tests. Moreover, Alzheimer's disease patients treated with sodium selenate for 24 weeks presented higher selenium concentration in CSF, which was associated with better performance on MMSE. Our data shows the relevance of selenium as strategy to slow the progression of cognitive decline and the onset of dementia.

Audience take away:

- I will report strategies that can be used to reduce the risk for Alzheimer's disease, which has increased prevalence worldwide
- The data I will present will foster future research on Alzheimer's disease diagnosis and treatment
- This work reinforces selenium as strategy to modulate ferroptosis, the newly discovered cell death pathway involved in neurodegeneration.

Biography

Dr Barbara Rita Cardoso received her BS as a nutritionist for the Federal University of Santa Catarina (Brazil). She has Master's degree in Human Applied Nutrition and finished her Ph.D in Food Science Program at the University of São Paulo (Brazil). Since 2007 she has been studying the association between selenium and Alzheimer's disease, and in 2014 obtained a fellowship to work at Florey Institute of Neuroscience (Melbourne – Australia) for further researching the association between selenium status and cognition in The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) study, which has the purpose to discover which biomarkers, cognitive characteristics, and health and lifestyle factors determine subsequent development of symptomatic AD. She is currently postdoctoral research scientist at the Nutrition-Minerals Lab at the Faculty of Pharmaceutical Science – University of Sao Paulo (Brazil) and seeks the effects of selenium status and intake on cognition.

Urgent carotid endarterectomy after acute stroke

Hassan Ravari
Mashhad university of medical sciences, Iran

Early intervention within 2 weeks of symptom onset has been advocated and become standard of care for most patients with transient ischemic attacks. The optimal timing of carotid endarterectomy after a recent ischemic stroke is a subject of controversy because of a presumed high risk for intracerebral bleedings. Accepted practice in many centers is to wait 4 to 6 weeks after the onset of the deficit before proceeding with carotid endarterectomy because of the fear that early revascularization will increase the size of the infarct.

New data suggest that carotid revascularization can be safely performed within the first week (0–7 days) from symptom onset to prevent the peak of early recurrence without intervention. Urgent carotid endarterectomy (<48 hours after symptoms) may be associated with increased periprocedural stroke risks, especially in high risk patients. However, there are insufficient data on the natural history and the clinical instability of this subgroup of patients to assess the benefits and risk exposure of delaying treatment. Some studies reports their 2-day risk of stroke may be as high as 5.2%, 14-day risk may be as high as 11%, and the 90-day risk of stroke ranges between 20% and 30%. Urgent carotid endarterectomy, within 48 hours from the index neurological event, has been promoted by some reports to prevent the peak of recurrences during this first hours.

Probably in the future, the effect of modern, more intensive medical therapy good intraoperative monitoring by transcranial electroencephalography, cerebral oximeter and transcranial color Doppler and aggressively control blood pressure in intensive care unit, Urgent carotid endarterectomy, more will be.

In our study urgent carotid endarterectomy is safe in selected patients. All patients underwent preoperative bilateral carotid artery duplex examination and were found to have stenosis 70% and more (NASCET criteria). Patients received either a CT or MRI of the neck and brain to assess the carotid and cerebral circulation and the presence, location, and size of any infarct. All patients in stable neurological condition with minor stroke were inclusion criteria.

Audience take away:

The optimal time of carotid endarterectomy after stroke. 2-Carotid endarterectomy with lowest complication.3- Perioperative care and monitoring for carotid endarterectomy.

Biography

I completed General Surgery from Shiraz University of Medical Sciences and Vascular Surgery from Tehran University of Medical Sciences. Director of Vascular and Endovascular Surgery Research Center. I published 36 papers in PubMed central till now.

magnus Group

Poster Presentation

International Conference on

Neurology and Brain Disorders

June 26-28, 2017 | Valencia, Spain

INBC 2017

Poster Presentations

P1 **Title: Draining the brain: Neuronal plasticity and hydration control**
Maria P. Mcgee, Wake Forest University Medical School, USA

P2 **Title: Chronic alcohol-mediated egress of a subunit of glucosidase ii out of the rough endoplasmic reticulum**
Antje Anji, Kansas State University, USA

P3 **Title: S1PR-1 as a new target for the treatment of tau-related pathologies?**
Guy Massicotte, University of Alberta, Canada

P4 **Title: Olfactory hallucination in a super smeller**
Weller Alexandra, Carribbean Medical University School of Medicine, Netherlands

P5 **Title: Synergistic interaction of TP-427 (a novel antiepileptic compound) with valproate in the mouse model of tonic-clonic seizures – an isobolographic transformation**
Maria Kondrat-Wrobel, Medical University of Lublin, Poland

P6 **Title: In vivo characterisation of microamperometric sensors in the brain extracellular fluid of immunocompromised mice**
Caroline Reid, Maynooth University, Ireland

P7 **Title: Improvement of the functional state of the brain in patients in disorders of consciousness as result of the treatment of generalized spasticity with incobotulinumtoxin A (Xeomin®)**
Korotkov Alexander, N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences, Russian Federation

P8 **Title: Change of functional state of the brain at the time of botulinum toxin therapy of generalized spasticity in patients with disorders of consciousness**
Vainshenker Yulia, N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences, Russian Federation

P9 **Title: Changes in expression of metalloproteinase 2 and 9 and their inhibitors in the neurotoxic effects of fluoride**
Agnieszka Lukomska, Pomeranian Medical University, Poland

P10 **Title: The influence of pre and neonatal exposure to sodium fluoride on cyclooxygenases activity in rats brain**
Karolina Dec, Pomeranian Medical University, Poland

P11 **Title: Dronedarone potentiates the anticonvulsant activity of lamotrigine in the model of tonic-clonic seizures in mice**
Katarzyna Zaluska, Medical University of ublin, Poland

P12 **Title: Quantitative analysis of 7.04T magnetic resonance images in the formation of white matter lesion in chronic hypertensive model rat**
Takashi Koizumi, Kyoto Prefectural University of Medicine, Japan

P13 **Title: miR-196a enhances neuronal morphology through suppressing RANBP10 to provide neuroprotection in huntington's disease**
Shang-Hsun Yang, National Cheng Kung University College of Medicine, Taiwan

P14 **Title: Psychiatric disorders caused by chronic pain and the underlying neural mechanisms**
Yuanyuan Wu, Zhejiang Chinese Medical University, China

P15 **Title: Behavioral and pharmacological characterization of thiosemicarbazide convulsions in the rat**
ANWAR SATEF, University of hassan 1 SETTAT, Morocco

P16 **Title: Arachidonyl-2'-chloroethylamide enhances the anticonvulsant potency of levetiracetam in psychomotor seizure test in mice**
Maria Kondrat-Wróbel, Medical University of Lublin, Poland

P17 **Title: The relationship between global acetylation histone H4 levels and spinal cord injury: an experimental study**
Viviane Rostirola Elsner, IPA Methodist University, Brazil

P18 **Title: Effectiveness and safety of intrathecal ziconotide: Interim analysis results from a single center of the patient registry of intrathecal ziconotide management**
Gladstone C McDowell, Integrated Pain Solutions, USA

P19 **Title: Impact of changes in intraoperative evoked potential monitoring on stroke rates in intracranial aneurysmal surgery**
Jihye Park, Seoul St.Mary Hospital, Korea

P20 **Title: Neuroinflammation, glial activation, oxidative stress and behavioral deficit in the hippocampus following short-term adrenalectomy**
Naserddine Hamadi, United Arab Emirates University, UAE

P21 **Title: Long-term effects of perinatal undernutrition in the brain and behavioral gustatory development of the rat**
MARIA DIANA LORENA RUBIO NAVARRO, Universidad Nacional Autonoma de Mexico, Mexico.

P22 **Title: Cardinal signs in parkinson's disease and agonists, antagonists, stabilisers**
KHIN MAUNG BO, Northern Lincolnshire and Goole NHS Foundation Trust, UK

Draining the brain: Neuronal plasticity and hydration control

Maria McGee* MD, Michael Morykwas PhD, Anirudh Vashisht PhD, Ashok Hegde1PhD and Louis Argenta MD.Departments of Plastic and Reconstructive Surgery of Wake Forest University Medical School and Biological and Environmental Sciences1 Georgia College and State University. USA
Wake Forest University Medical School, USA

Aging is associated with gradual and variable changes of some cognitive functions in humans and animals but the causes of these changes and their individual variability remain unclear. Similarly, hydration is variable among individuals and the proportion of brain weight relative to total body weight decreases with age but it is not known how much of the change is due to water loses. In this study we quantify age–dependent changes in brain hydration and manipulate interstitial water chemical potential μw in hippocampal slices to explore possible causal connections.

Hydration, basal synaptic transmission, and LTP (late-phase long term potentiation, a model of synaptic plasticity) were studied in the brains of aging inbred mice. The hydration potential was determined from fluid transfer kinetics across brain explants submerged in baths of cerebrospinal fluid solutions of known colloidosmotic pressure. This potential equals the bath pressure at which there is no fluid transfer; that is when the μw in explant and bath are the same.

The hydration potential of brain tissue is surprisingly large and increases with age from 75 mmHg at 6 weeks to 106 mmHg at 40 weeks. This progressive dehydration is rapid during 1.5 to 10 months of age but appears to level off afterwards reaching approximately 15% loss of brain water. These same levels of dehydration were also achieved in juvenile mice after 12 hours of water deprivation. When dehydration was reproduced ex-vivo within these ranges in hippocampal slices of young mice <2 months-old, the basal synaptic responses in C1 pyramidal cells increased. Further, while the threshold for phosphorylation of the cAMP response-binding protein (a key step in the induction of gene expression in L-LTP) was reduced, the induction of L-LTP in tetanization protocols was inhibited.

These results indicate that compared to juvenile mice the brain of middle and old age mice is dehydrated and that dehydration induces changes in neuronal excitability and deregulates synaptic plasticity of C1 pyramidal cells in the hippocampus. Because hydration level plateaus at middle age, we speculate that mild dehydration in the mature brain could reflect selective adaptive responses in C1 hippocampal neurons to other age-dependent changes. For example, lower water activity -and the consequent increase in the activity of all solutes- could compensate for slower receptor turnover rates at synapses. This is consistent with the idea that physiologically, global optimization of brain function over the animal lifespan may come at the expense of adaptive changes in the efficiency of some cognitive processes; first to learn and follow later to teach and lead.

Audience Take away:

- Changes in water activity modulate neuronal function
- Water activity in brain tissue decreases with age
- water activity in the brain interstitium is lower than in cerebrospinal fluid.

Biography

Maria P. McGee is Associate Professor in the Department of Plastic and Reconstructive Surgery of Wake Forest University School of Medicine. Her current research aims at understanding interstitial fluid-transfer and hydration under physiological and pathological conditions to improve treatments of injured tissues; additional research experiences and interests include Chronic Inflammation, Blood Coagulation Kinetics and the Mathematics of Biology. She is a member of the research group headed by Dr. Louis Argenta and directed by Dr. Michael Morykwas, inventors of a regulated pressure device that among other effects has been proven to modulate water potential.

Chronic alcohol-mediated egress of a subunit of glucosidase ii out of the rough endoplasmic reticulum

Antje Anji*, MD., Ph.D., and Meena Kumari, Ph.D., Kansas State University
Kansas State University, USA

The heterodimeric enzyme a-glucosidase II (GII), an important enzyme in chaperone-assisted folding of nascent glycoproteins in the rough endoplasmic reticulum (RER) is comprised of a beta subunit (GIIb) and the catalytic alpha subunit (GIIa). The soluble GIIa is retained in the RER through its interaction with RER membrane associated GIIb subunit. Recently our laboratory showed that GIIb is a novel RNA binding protein as it binds specifically to a cis-acting region in the 3-UTR of NMDAR1 receptor mRNA. Interaction between GIIb and NMDAR1 mRNA increases following chronic ethanol exposure of fetal cortical neurons and cerebral cortex of adult mouse. Levels of GIIb polypeptide increase significantly in chronic ethanol exposed fetal cortical neurons and cerebral cortex of adult mouse. We examined whether increased levels of GIIb protein in ethanol-exposed FCN are differentially distributed between different subcellular fractions. We show that the 80 kDa GIIb protein is present mainly in the membrane fraction (P100 fraction containing RER) of cultured neurons irrespective of the ethanol treatment. GIIb is absent from pure nuclei although it has a nuclear localization signal. The organelle free cytosol (S100) contains immunoreactive GIIb protein with a calculated molecular weight higher than 100 kDa. Serendipitously we found that chronic ethanol exposure results in redistribution of the GIIa subunit from RER lumen to the organelle free cytosol. The cytosolic GIIa subunit is enzymatically active. Reduction of GII activity in RER may result in inappropriate expression/secretion of neuronal proteins in chronic ethanol exposed neurons. We propose that active GIIa in cytosol may contribute to abnormal protein folding seen in certain neuronal pathologies.

Audience take away:

- Can use the information in teaching neuroscience and biochemistry of proteins
- Can associate the information with “unexplained” ER stress and/or retention of proteins in ER;
- can relate to abnormal protein folding in neurodegenerative diseases.

Biography:

Dr. Antje Anji is currently an Associate Professor in the Department of Anatomy and Physiology, Kansas State University. She received her M.D. degree from Bangalore University, India and a PhD. in Pharmacology from the University of Texas Health Science Center at San Antonio. The major focus of her research is on molecular mechanisms underlying alcohol addiction.

S1PR-1 as a new target for the treatment of Tau-related pathologies?

Guy Massicotte* (Ph.D.), Frederic St-Cyr Giguere (M.Sc.), Michel Cyr (Ph.D.)
Quebec University, Canada

Background: Tau proteins are known to help maintaining the structure of a neuron, including tiny tube-like structures called microtubules, which deliver nutrients throughout cells. However, when hyperphosphorylated, these proteins can become toxic for neurons by forming tangles in the hippocampus; one important region of the brain early affected by Alzheimer's disease. Researchers believe that therapies capable to limit Tau phosphorylation in the hippocampus may reduce tangle formation and ultimately intervene in the development of Alzheimer's disease and other Tau-related disorders. Global sphingosine-1-phosphate receptor (S1PR) agonists were recently found to exert neuroprotective effects in several model systems reproducing different brain disorders. Consequently, we assessed the influence of such compounds on Tau phosphorylation in the hippocampus.

Methods and Results: Transverse rat hippocampal slices were prepared with a McIlwain tissue chopper and placed on a nylon mesh in a liquid-gas interface chamber. They were treated for a period of 3 hours with S1PR-1 (SEW2871) and S1PR-3 (CYM5541) agonists. Tau phosphorylation was then estimated by Western blotting procedures.We noticed an important reduction in Tau-Ser262 phosphorylation after hippocampal slice treatments with the S1PR-1 agonist SEW2871. In terms of molecular mechanisms, SEW2871-induced Tau-Ser262 dephosphorylation seems to be dependent on AMPK (AMP-activated protein kinase) inactivation, a process involving the protein phosphatase PP2A. Comparable experiments indicate that neither Tau nor AMPK were influenced by the S1PR-3 agonist CYM5541 (data not shown). Our results suggest a new target for Tau dephosphorylation and provide an insight into the potential therapeutic effects of S1PR agonists in Alzheimer's disease and other Tau-related pathologies.

Acknowledgements: This work was supported by the Canadian Research Chair in Molecular Neuropharmacology (Michel Cyr) and by the National Sciences and Engineering Council of Canada (Guy Massicotte).

Highlights of this presentation: Tau-related pathologies are extremely common in the central nervous of patients suffering with Alzheimer's disease. For many scientists, avoiding brain cells from developing hyperphosphorylated Tau could eventually prevent Alzheimer's from robbing people of their minds. On that line, Guy Massicotte has identified a new compound that may be able to reduce Tau phosphorylation in the brain. The molecular target might be the receptor subtype 1 for the ceramide derivative sphingosine-1-phosphate (S1P). Guy Massicotte and his colleagues are currently testing with various drugs how this receptor complex might reduce inflammation and protect the brain from Tau-related insults.

Biography

Dr. Guy Massicotte earned an undergraduate diploma in medical biology from the University of Québec at Trois-Rivières, and went to earn his Ph.D. in Clinical Sciences form the University of Montréal, researching the mechanisms underlying blood pressure variations during pregnancy. He completed a post-doctoral training at UC Irvine in neurobiology under the supervision of professors Michel Baudry and Gary Lynch. His work was then focusing on the role phospholipase enzymes in glutamate receptor regulation during both normal and pathological synaptic plasticity. Now full professor in human physiology at the University of Québec, Dr. Massicotte is investigating the role of ceramide derivatives in premature ageing of the brain. He is the author of 80 publications, some being published in top-quality journals such as Nature, Proceedings of the National Academy of Sciences, FASEB Journal, Diabetes, Neuroscience and Biobehavioral Reviews.

Olfactory hallucination in a super smeller

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Introduction: True hyperosmia in a patient with phantosmia has not heretofore been described.

Case study: A 19-year-old right –handed female presented with a 4-month history of sudden onset of hallucinated smell and taste after swimming, when water infused her nostrils. The phantosmia was an unpleasant, fruity, rotten aroma which was always concurrent with the taste of rotten fruit. The phantom taste was 7/10 in intensity. The smell was always the same aroma but of variable intensity. It would occur every day up to three times a day, and usually 6-7/10 in intensity, and it would last from 1 hour to many hours. Since the onset of this, she found that some odorants when phantosmia is present have enhanced intensity, more than 150 % of normal, including kitchen aromas, bleach, and soap.

Results: Abnormalities in Chemosensory Testing: in the absence of phantosmia: Olfaction: Alcohol Sniff Test: 30 (normosmia). Suprathreshold Amyl Acetate Odor Intensity Testing: hyperosmia. Retronasal Olfactory Testing: Retronasal Smell Index: 3 (reduced). Gustatory Testing: Propylthiouracil Disc Taste Test: 8 (normogeusia). When phantosmia is present: Alcohol Sniff Test: 13 (hyposmia).

Discussion: Possibly the phantosmia changed her focus of attention to ambient aroma, enhancing her intensity perception and thus reducing her olfactory threshold; such attention reduced olfactory stimuli threshold has been seen in industrial workers exposed to solvents (Schwartz, 1989). Possibly the primary abnormality is hyperosmia: her olfactory sensitivity threshold may be so low that she detects odors in the environment that others don't, which are interpreted as phantosmia and phantogeusia (due to reverse retronasal olfaction). This case highlights the need to test those who complains of phantogeusia and phantosmia for olfactory sensitivity, it also suggests treatment approaches for resistant phantosmia and phantogeusia including physical or pharmacological measures to reduce the underlying olfactory ability. Further studies in this arena are warranted.

Biography

Alexandra Weller, 4th year Medical Student with extensive research in Neurology and Neurodegenerative Disorders. Associate Degree in Psychology, Bachelor Degree in Business, currently pursuing Masters in Public Health.

Interested in all type of Neurology Research as I consider it as an enormous and expanding field of medicine.

Synergistic interaction of TP-427 (a novel antiepileptic compound) with valproate in the mouse model of tonic-clonic seizures – an isobolographic transformation

Maria W. Kondrat-Wrobel*, Ph.D., Katarzyna Zaluska Ph.D., Magdalena Florek-Luszczki Ph. D., Professor Jarogniew J. Luszczki.
Medical University of Lublin, Poland

The aim of this study was to evaluate the influence of TP-427 (a novel antiepileptic compound) on the anticonvulsant potency of four classical antiepileptic drugs (carbamazepine, phenytoin, phenobarbital and valproate) in the mouse maximal electroshock-induced seizure model.

Tonic hindlimb extension (seizure activity) was evoked in adult male albino Swiss mice by a current (25mA, 500V, 50Hz, 0.2s stimulus duration) delivered via ear-clip electrodes.Potential concurrent side effects of interaction between TP-427 and four selected antiepileptic drugs were evaluated in the chimney test (motor performance), passive avoidance task (long-term memory) and grip-strength test (skeletal muscular strength) in mice. Total brain antiepileptic drug concentrations were measured with fluorescence polarization immunoassay technique to exclude any pharmacokinetic interaction between drugs.

Results indicate that TP-427 significantly potentiated the anticonvulsant potency of valproate in the mouse maximal electroshock-induced seizure model and after isobolographic transformation of data, the observed interaction was synergistic in nature. In contrast, TP-427 in combination with carbamazepine, phenytoin and phenobarbital did not considerably affect the anticonvulsant effects of the latter drugs. The isobolographic transformation revealed that the reported interactions between TP-427 and carbamazepine, phenytoin or phenobarbital were additive in the mouse maximal electroshock-induced seizure test. No side effects associated with the combined treatment of TP-427 and classical antiepileptic drugs were observed in 3 behavioral tests in mice. No pharmacokinetic changes in total brain concentrations of valproate were documented in mice additionally receiving TP-427 and thus, the observed interaction was pharmacodynamic in nature.

In conclusions, significant potentiation of the anticonvulsant effects of valproate by TP-427 in the mouse maximal electroshock-induced seizure model might be translated to clinical conditions as a new treatment option for patients inadequately medicated with classical antiepileptic drugs.

Audience take away:

- This study shows TP-427 as a substance that can support treatment in patients that receive carbamazepine, phenytoin or phenobarbital. It can allow to give lower doses of antiepileptic drugs.
- TP-427 is another substance that can be treated in the future, as a substance that protects agains sizures.
- The study can be used as an exaple to teach about novel substance in medicine that protects again seizures.
- TP-427 translated to clinical studies can be a solution for patients who suffer because of side effects of carbamazepine, phenytoin or phenobarbital.

Biography

My name is Maria Kondrat-Wrobel, I was born in 1988 in Lublin, a town on the east part of Poland. In 2007, I finished high school and in 2013 I graduated from Medical University in Lublin. Since my graduation I have been practicing internal medicine on a Cardiology Unit in a Specialist Hospital in Lublin. Currently, I am pursuing a doctoral degree in the Department of Pathophysiology, mentoring students on the subjects relating to pathophysiology and working on research to discover new substances which could help potentiate the anticonvulsant effects of antiepileptic medications.

In vivo characterisation of microamperometric sensors in the brain extracellular fluid of immunocompromised mice

Caroline Reid, Niall Finnerty
Maynooth University, Ireland

This presentation details the in vivo characterisation of microamperometric sensors for the real-time monitoring of nitric oxide (NO), oxygen (O2) and hydrogen peroxide (H2O2) in the brain extracellular fluid of immunocompromised NOD SCID mice. Highly selective and sensitive NO, O2 and H2O2 sensors were implanted into NOD SCID mice having been previously characterised in vitro and in freely moving rats. The performance of the sensors was confirmed by systemic administration of characterisation compounds to the animal which lead to perturbation of the respective amperometric currents. In summary, control saline administrations caused transient changes in amperometric current for all sensors that were not significantly different than baseline levels. Systemic administration of the nitric oxide synthase inhibitor, L-NAME, and the pre-cursor for NO synthesis, L-arginine, caused a significant decrease and increase respectively, in NO current. Similarly, administration of L-NAME, the carbonic anhydrase inhibitor, Diamox, and the non-volatile anaesthetic, chloral hydrate, resulted in a significant decrease and increase respectively in O2 current. Furthermore, the H2O2 biosensor responded to increasing concentrations in vivo following local administrations of exogenous H2O2 and anti-oxidant inhibitors. In vivo interference investigations, performed using systemic administrations of sodium ascorbate indicated only slight deviations in H2O2 current over a two-hour period. The latter indicates the ability of the H2O2 sensor to retain its selectivity once implanted. In addition, 24-hour recordings were investigated for all sensors to identify any diurnal variations in the recorded current. It was concluded that diurnal variations were present in the recorded signal of all three sensor types. Moreover, the stability of the sensors was examined to allow for long term recordings. The stability of the current recorded of each of the sensors was observed to remain stable for a period of at least 5 days. These findings corroborate the reliability of the amperometric sensors to perform continuous, long-term recordings in NOD SCID mice.

Audience take away:

- How to characterise a microamperometric sensor in the in vivo environment.
- How to measure neurochemical events in real-time by perturbation of the brain microenvironment
- The use of amperometry for its application in the study of brain disorders.
- The identification of diurnal and nocturnal variations in the rodent brain.
- The ability to record neurochemical events over a number of days due to the stability of the amperometric sensors.

Awareness of work being undertaken by the SysMedPD Consortium into developing a neuroprotective compound in the treatment of PD.

Biography

Caroline Reid, BSc, is a postgraduate researcher currently under the supervision of Dr. Niall Finnerty in the Department of Chemistry at Maynooth University, Ireland. She specialises in the manufacture of NO, O2 and H2O2 microelectrochemical sensors for the real-time monitoring of neurochemical events associated with Parkinson's Disease. Currently, Caroline works as part of the SysMedPD project. Her work will contribute to the long term amperometric and microdialysis recordings in the striatum of humanised mouse models throughout the project.

Improvement of the functional state of the brain in patients in disorders of consciousness as result of the treatment of generalized spasticity withincobotulinumtoxin A (Xeomin®)

Korotkov Alexander*, MD, PhD. Neuroimaging Laboratory, N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences
Vainshenker Yulia, MD, PhD. Intensive Care Department, N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences
Medvedev Svyatoslav, Prof., Dr.Sci. N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences)
N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences, Russia

Monitoring of patients with disorders of consciousness after coma with 18F FDG positron emission tomography (18F-FDG PET) revealed an improvement of consciousness and behavioral signs of awareness, as well as increases of regional metabolic activity after correction of generalized spasticity. These increases were detected in numerous yet different brain areas of different patients.

The aim of the current study was to identify changes of metabolic activity that are common for the entire group of patients and to estimate their relation to the improvement of consciousness, including higher brain functions.

We analyzed clinical data (muscle tone by modified Ashworth scale (MAS) and level of consciousness (Coma Recovery Scale–Revised, Loewenstein Communication Scale)) and 18F-FDG PET data of 25 patients with disorders of consciousness after coma (including permanent vegetative state) and generalized spasticity, who received "multipattern" botulinum toxin therapy with Xeomin (the total dose up to 1400 u). Clinical neurological assessment and 18F-FDG PET studies were conducted before the therapy and 3 weeks after that.

We found that clinical effects of botulinum toxin (reduction of muscle tone ≥1 MAS scores and improvement of consciousness, including higher brain functions) are associated with improvement of metabolic activity in brain areas maintaining movement as well as visual, auditory, and higher mental functions.

Taking into account the functional variability of neurons (S. Medvedev), blocking neuromuscular transmission in all spastic muscles with botulinum toxin therapy with Xeomin leads to a reduction of abnormal afferent and efferent hyperactivity of neuronal circuits, which releases the brain for other activities.

Audience take away:

The data we presented in this poster are valuable for a better understanding of the central effect of botulinum toxin therapy. These data may be useful for designing of future research and for teaching.

Biography

Dr. Korotkov finished graduation and received his MD in 1988. After5 years of having worked as a clinical neurologist, he started working as a research fellow and neuroradioilogist at the Neuroimaging Laboratory, N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences. He received his PhD degree in 2005. Research interests of Dr Korotkov include investigating the pathogenesis of neurological and mental disorders by using methods of functional neurovisualisation (PET, fMRI).

Change of functional state of the brain at the time of botulinum toxin therapy of generalized spasticity in patients with disorders of consciousness

Vainshenker Yulia*, MD, PhD. Intensive Care Department, N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences
Korotkov Alexander, MD, PhD. Neuroimaging Laboratory, N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences
Medvedev Svyatoslav, Prof., Dr.Sci. N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences
N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences, Russia

Introduction and Objectives: Previously we found that botulinum toxin therapy of generalized spasticity in patients with disorders of consciousness after coma improves the functional state of the brain and consciousness. However, when do these central changes start and how they develop remains unclear. The aim of the current study was to analyze the changes of bioelectric activity of the brain (BEA) during botulinum toxin therapy of generalized spasticity.

Methods: Botulinum toxin therapy of generalized spasticity was performed under electroencephalography and clinical monitoring in 17 patients with disorders of consciousness after coma (including permanent vegetative state). IncobotulinumtoxinA (Xeomin) was successively injected in all hypertonic muscles. The dose into each muscle did not exceed the mean-recommended (the total dose up to 1400 u). Additionally, a test with injection of saline was done in 2 patients.

Results: Changes of BEA that are associated with Xeomin were detected within 1 to 2 minutes after the first injection of Xeomin in all patients and have initially caught the motor cortex in 16 patients. The more muscles were injected, the more widespread changes of BEA were registered with an appearance of beta and other rhythms ($P<0.05$). Fewer oscillations of rhythms and a tendency to return to the initial background of BEA were observed. Both an initial transient decrease of muscle tone (in all patients) and an improvement of consciousness (in 10 patients) appeared immediately after injections into all muscles; the changes of BEA covered all parts of the brain and remained present for 30-60 minutes.

Conclusions: The central effect of botulinum toxin therapy of generalized spasticity starts immediately with the beginning of the reduction of afferentation from the muscles. We believe that the early transient clinical effect reflects the appearance of the process of liberation of neurons formaintaining other functions, including consciousness.

Audience take away: New data, shown in this poster presentation, are helpful for a better understanding of the central effect of botulinum toxin therapy. They could be used in the designing of future research and in teaching.

Biography

Dr. Vainshenker completed graduation in 1994, and started to work as neurosurgeon after receiving MD and, since 2001, as a neurologist. She received her PhD degree in neurology in the A.L. Polenov Russian Neurosurgical Institute (St. Petersburg, Russia). Since 2005, Dr. Vainshenker works at the N.P.Bechtereva Institute of the Human Brain of the Russian Academy of Sciences. Her research interests include disorders of consciousness, effects of botulinum toxin therapy on central nervous system, and immunologic and chronic infectious diseases of the CNS.

Changes in expression of metalloproteinase 2 and 9 and their inhibitors in the neurotoxic effects of fluoride

AgnieszkaLukomska*, Karolina Dec, Anna Pilutin, Maciej Tarnowski, Irena Baranowska-Bosiacka, Dariusz Chlubek, Izabela Gutowska
Pomeranian Medical University, Poland

Fluorine is a strong neurotoxin which can decrease the intelligence quotient and cause problems with learning and concentration. The Extracellular Matrix (ECM) of the central nervous system serves as the environment for neurons and glial cells, and at the same time, it plays the role of a modifier of these cells. Changes in the structure and the functioning of synapses are caused by ECM enzymes. These enzymes, especially matrix metalloproteinases (MMPs), accompany both physiological processes, such as learning or memorizing, and pathological processes. Metalloproteinases 9 and 2 (MMP-9 and MMP-2) and the inhibitors of metalloproteinases-3 and -2 (TIMP-3 and TIMP-2) seem to be particularly interesting. There is no data regarding the influence of fluorine on the expression of these enzymes and their inhibitors in the brain.

In the research, the rats were exposed to sodium fluoride (50 mg/L) already in the prenatal period until they reached the age of three months. After this time, the hippocampus, prefrontal cortex, cerebellum, and striatum were collected. In all of the aforementioned structures, the expression of proteins MMP-9, MMP-2, TIMP-3 and TIMP-2 was carried out by means of ELISA, gene expression by qRT PCR and immunolocalization by immunohistochemistry and microscopic visualization.

On the basis of the results, it can be concluded that fluorine influences the expression of MMP-9, MMP-2, TIMP-3 and TIMP-2. In the study group, a statistically significant expression of MMP-2 was observed in the prefrontal cortex, striatum, and cerebellum, and a decrease in the expression of MMP-9 was noted in the prefrontal cortex and cerebellum in relation to the control group. We also saw the difference between TIMP-3 and TIMP-2 levels in the study group compared to control.

Our research suggests that changes in the expression of metalloproteinases and their inhibitors in the brain, caused by fluorine, could be an important factor of neurotoxicity of fluorine. The disorders of neuroplasticity processes can be considered as a biochemical basis for the decrease in the intelligence quotient caused by fluorine.

The influence of pre and neonatal exposure to sodium fluoride on cyclooxygenases activity in rats brain

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Long term exposure to fluorine in pre and neonatal period is dangerous because this element is able to penetrate through the placenta and to cross the blood-brain barrier. Young individuals are less resistant to the toxic influence of fluorine due to the fact that their defensive mechanisms are not fully developed and the permeability of the blood-brain barrier is higher than among adults. Prolonged exposure to fluorine during the development affects metabolism and physiology of neurons and glia which results in the impairment of cognitive functions. Epidemiological studies have shown that children who live in geographical regions in which drinking water is contaminated with fluoride, have a statistically significant decreased level of intelligence in comparison to children from regions not contaminated with this element. The exact mechanisms by which fluorine influence cognitive functions and decreases learning abilities are not clearly defined. Changes in central nervous system functioning after fluorine exposure have been studied in terms of its influence on the synthesis of neurotransmitters and proinflammatory factors, initiation of oxidative stress and the apoptosis of cells.The aim of this study was to determine whether exposure to fluorine during the development affects cyclooxygenases activity and the synthesis of prostanoids.

Toxicity model in vivo in male and female Wistar rats was used. Pregnant experimental females received 50 mg/L of sodium fluoride (NaF) in drinking water ad libitum since the first day of pregnancy till the labour and during breast-feeding. Offsprings were being fed by their mothers till 4th week (21st day of their life). After that they have been weaned and they received drinking water with sodium fluoride until the end of 3rd month. Control animals received tap water. Animals were killed and organs were removed including brain. In different brain structures (cerebral cortex, hippocampus, cerebellum and striatum) were measured fluoride concentration, cyclooxyganse-1 (COX-1) and cyclooxygenase-2 (COX-2) genes expression, immunolocalization of the enzymatic proteins and concentration of PGE2 and TXB2. Potentiometry, RT-PCR, immunohistochemistry and immunoenzimatic methods were used to receive the results.

Results of this study showed statistically significant changes in the concentration of fluorine in different brain structures between experimental group and control animals. Moreover.significant changes in the expression level of COX-1 and COX-2, and in the concentration of PGE2 and TXB2 were obsered after pre and neonatal exposure to sodium fluoride.

Fluorine is able to cross blood-brain barrier and accumulate in central nervous system (CNS). Pre- and neonatal exposure to this element affects COX-genes expression. Prostanoids such as PGE2 and TXB2 - products of COX activity, under normal conditions control some brain functions but changes in their concentrations can initiate inflammation and disturb homeostasis of CNS. Exposure to fluorine during the development affects neurons metabolism by changes in prostanoids synthesis.

Dronedarone potentiates the anticonvulsant activity of lamotrigine in the model of tonic-clonic seizures in mice

Katarzyna Zaluska*, Maria W. Kondrat-Wrobel, Katarzyna M. Sawicka, Agnieszka Wawryniuk, Magdalena Florek-Luszczki, Jadwiga Daniluk, Jarogniew J. Luszczki.
Medical University of ublin, Poland

The purpose of this study was to evaluate the effect of dronedarone (a multi-channel blocker inhibiting outward potassium currents, inward rapid sodium current and L-type calcium channels) on the anticonvulsant properties of some selected antiepileptic drugs (i.e., carbamazepine, lacosamide, lamotrigine and phenytoin) in the mouse maximal electroshock-induced seizure model.

Tonic hindlimb extension (seizure activity) was evoked in adult male albino Swiss mice by a current (25mA, 500V, 50Hz, 0.2s stimulus duration) delivered via ear-clip electrodes.Potential concurrent side effects of interaction between dronedarone and four selected antiepileptic drugs were evaluated in the chimney test (motor performance), passive avoidance task (long-term memory) and grip-strength test (skeletal muscular strength) in mice. Total brain antiepileptic drug concentrations were measured with HPLC to exclude any pharmacokinetic interaction between drugs.

Results provide evidence that dronedarone significantly potentiated the anticonvulsant effects of lamotrigine, but not those of carbamazepine, lacosamide or phenytoin in the maximal electroshock-induced seizure model in mice. No acute adverse effects were associated with the combined treatment of dronedarone with the antiepileptic drugs in the chimney, passive avoidance and grip-strength tests in mice. Pharmacokinetic study revealed that dronedarone did not alter total brain concentrations of lamotrigine in mice, suggesting pharmacodynamic nature of the observed interaction.

In conclusions, significant potentiation of the anticonvulsant effects of lamotrigine by the multi-channel blocker dronedarone in the mouse model of tonic-clonic seizures might suggest that the favorable interaction between drugs could be expected also in humans.

Quantitative analysis of 7.04T magnetic resonance images in the formation of white matter lesion in chronic hypertensive model rat

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The preclinical diagnosis of hypertensive cerebral vascular dementia (CVD) is important in an aging society. Cerebral white matter lesions (CWMLs) accompanied by hypertension are often visualized by magnetic resonance imaging (MRI) in the early stage, but after the onset of cognitive dysfunction. For an earlier diagnosis and the prevention of CVD, we aimed to detect white matter changes earlier than those conventional identified by MRI. To address this issue, we quantitatively analyzed MR images using Deoxycorticosterone acetate (DOCA)-salt-treated male rats. One week after hemi-nephrectomy, the rats were randomly divided into two groups: DOCA-salt-treated rats received a weekly subcutaneous injection of DOCA (40 mg/kg) and 1% NaCl in drinking water; Control rats received a weekly subcutaneous injection of vehicle and tap water (n=3 in each). Systolic blood pressure (sBP) was measured in a conscious rat by the tail-cuff method. After 0, 2, 3, or 4 weeks (n=3 for each group) of DOCA-salt treatment and control, all rats were subjected to 7.04T MRI under anesthesia. T2-weighted images (T2WI) were acquired using the following parameters: fast spin echo sequence, echo time = 50 ms, repetition time = 2000 ms, field of view = 2.5×2.5 cm2, matrix = 512×512 with zero-filling, and slice thickness 1 mm. MR images were quantified based on their signal to noise ratio (SNR) using aerial-noise method. After MRI, brain tissue was subjected to histochemical study. Our results indicated that sBP was gradually increased after DOCA treatment and the mean value of the SNR of DOCA-salt-treated rats also increased over time. It is of note that a significant increase of SNR was observed in the DOCA-salt-treated rats at 2 weeks (DOCA-2W), when CWMLs and état criblé had yet to be observed. Histochemical changes including CWMLs, hemorrhage, and vascular impairment were clearly observed in DOCA-3W and -4W. Taken together, these results suggest that quantitative analysis of T2WI can detect preclinical vascular changes. Now, we perform cell biological study to understand the mechanisms for CWML formation.

Audience take away:

- Deoxycorticosterone acetate (DOCA)-salt-treated rats were used to detect early hypertensive white matter changes.
- Quantification of T2WI on 7.04T MRI by aerial-noise method could detect signal elevation prior to white matter hyperintensity or état criblé.
- Applying our finding to clinical use may improve preclinical diagnosis of hypertensive vascular dementia.

Biography

Takashi Koizumi is a graduate student at Kyoto Prefectural University of Medicine in Kyoto, Japan. He graduated from Kyoto Prefectural University of Medicine in 2007, and has been a board-certified specialist in clinical neurology. His research aims to uncover pathophysiological process and mechanism of cerebral small vessel diseases.

MiR-196a enhances neuronal morphology through suppressing RANBP10 to provide neuroprotection in Huntington's disease

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National Cheng Kung University Medical College, Taiwan

MicroRNAs (miRNAs) play important roles in several neurobiological processes, including the development and progression of diseases. Previously, we identified that one specific miRNA, miR-196a, provides neuroprotective effects on Huntington's disease (HD), although the detailed mechanism is still unclear. Based on our bioinformatic analyses, we hypothesize miR-196a might offer neuroprotective functions through improving cytoskeletons of brain cells. Here, we show that miR-196a could enhance neuronal morphology, further ameliorating intracellular transport, synaptic plasticity, neuronal activity, and learning and memory abilities. Additionally, we found that miR-196a could suppress the expression of RAN binding protein 10 (RANBP10) through binding to its 3' untranslatedregion, and higher expression of RANBP10 exacerbates neuronal morphology and intracellular transport. Furthermore, miR-196a enhances neuronal morphology through suppressing RANBP10 and increasing the ability of β-tubulin polymerization. Most importantly, we observed higher expression of RANBP10 in the brains of HD transgenic mice, and higher expression of RANBP10 might exacerbate the pathological aggregates in HD. Taken together, we provide evidence that enhancement of neuronal morphology through RANBP10 is one of the neuroprotective mechanisms for miR-196a. Since miR-196a has also been reported in other neuronal diseases, this study might offer insights with regard to the therapeutic use of miR-196a in other neuronal diseases.

Audience take away:

- The neuroprotective effects of miR-196a on Huntington's disease
- The potential working mechanism of miR-196a
- Application of miRNA for the therapy of neuronal diseases

Biography

Dr. Shang-Hsun Yang is the Associate Professor in Department of Physiology at NCKU, Taiwan. He received his B.Sc. degree at National Chung Hsing University in 1998, M.Sc. degree at National Taiwan University in 2000 and Ph.D. degree at Emory University, USA, in 2008. He has developed his own research career at NCKU since 2009. His research interests focus on the regulation of microRNAs on HD, and tries to understand the regulatory mechanisms and potentially therapeutic directions for this neurodegenerative disease. Additionally, he also attempts to expand his research fields to other neurodegenerative diseases, and wishs to demonstrate the relationship between specific microRNAs and neurodegenerative diseases.

Psychiatric disorders caused by chronic pain and the underlying neural mechanisms

Yuanyuan Wu
Zhejiang Chinese Medical University, China

Part 1: Electro-acupincture influence inflammation induced pain memory via cAMP/PKA/CREB pathway in the Anterior Cingulate Cortex.

Our precious studies demonstrate that inflammation indused pai memory can be indeed caused by reapeated injections in rats. EA stimulation could influence pain memory by delaying the awaken time of pain memory and reduceing the intensity of pain. The pain memory and its retrival are related to the increase of p-CREB and co-location of p-CREB with GFAP, OX-42-, or neuN-positive cells in ACC. The proper mechanism of EA on pain Memory is that EA could inhibit the cAMP/PKA/CREb signalling pathway partiality. Therefore, EA may be a pivotal therapy on chronic pain induced by pain.

Part 2: Strong Manual Acupuncture simulation of (Huantiao) Reduces Pain Induced Anxiety and p-ERK in the ACC

sMA Stimulation may relieve both mechanical hyperalgesia and pain-induced anxiety in a rat model of neuropathic pain, While moderate MA only reduces anxiety and EA only alleviates mechanical hypersensitivity. We propose that sMA could be a two dimension of pain. The Different acupuncture stimulation of pain. The Effect of Defferent acupuncture stimulation on anxiety like behaviour may arise from the regulation of p-ERK in ACC neurons.

Biography

Yuanyuan wu, MD, PhD, postdocter in Zhejiang Chinese Medical University, mainly worked in neuropsychological research of pain.

Behavioral and pharmacological characterization of thiosemicarbazide convulsions in the rat

Anwar SATEF*, student on PhD, laboratory of neurosciences and biochemistry.BAGRI Abdallah, Pr, laboratory of neurosciences and biochemistry.
University of hassan 1 SETTAT, Morocco

Alteration of GABAergique neurotransmission in the central nervous systeme is involved in the generation of neuronal hyperexitability and seizures. GABAergique transmission blocked by GABA antagonists injected i.p. intracerebrally induce seizures. In the present study, we characterize the effect of an inhibitory of glutamate decarbocylase, the enzyme responsible of the synthesis of GABA by injection of differentes doses of Thiosemicarbazide (TSC). Eight groups of six wistar rats were selected for behavioral assessement, seizure scoring, reactivity to sound and antiepileptic substances efficiency.

The dose of 2,5mg/kg did not induce noticeable behavioral reaction whereas 5mg/kg induce a significant reduction in rearing and groominge. However, this reduction was reversed at the dose of 7,5mg/kg and 10mg/kg. tonico-clonic seizure induction appeared at the dose of 7,5mg/kg with an incidence of 7,69% and a latency of 75 min. the incidence and the severity of seizures increased with the doses 10mg/kg and 20mg/kg wheras the latencies decreased. At 20mg/kg, status epilepticus and death were observed. Interestingly, audiogenic seizur (AG) susceptibility was elicited with the dose of 7,5mg/kg. AG included wild running fits followed by tonic seizure.

Phenobarbital (PB) (30mg/kg), Phenetoin (PH) (30mg/kg) and valproic acid (VA) (200mg/kg) inhibited tonico-clonic seizures elicited by 10mg/kg of TSC. PB resulted in 100% inhibition in minimal and maximal seizures. PH an VA reduced maximal seizures by 65,73% and 80,25% respectively. for minimal siezures, PH and VA induced similar reduction (46,16% and 44,42%)($p<0.05$). Gradual inhibition of GABAergique neurotransmission resulted in appearance of behavioral changes indicating anxiogenic effect then minimal tonico-clonic seizures followed by maximal tonico-clonic seizures and at the gigh inhibition status epilepticus and death. First generation of antiepileptic substances were effecient to reduce both minimal and maximal seizures.

This study will accomplish with a genetic effect when a i.p injection of TSC on female rat and we will get results on the next generation if a spontaneous convulsions have place even without i.p injection of TSC.

Audience take away:

- The audience will take away from my presentation the mechanism of action of some antiepileptic drugs
- Also a new model of epilepsy in rat
- They can teach in different university this model and try to confirm it in their universities

Biography

currently a PhD student in laboratory of neurosciences and biochemistry, I studied all my university curriculum in the faculty of sciences and techniques and I started in the field of neuroscience with mr bagri who is my professor enrolling in PhD from my first project of end of study as degree bachelor (3 years at university) so it was For four years when i started in this amazing field.

Arachidonyl-2'-chloroethylamide enhances the anticonvulsant potency of levetiracetam in psychomotor seizure test in mice

Maria W. Kondrat-Wrobel*, Ph.D., Katarzyna Zaluska, Ph.D., Pawel Patrzylas, Miroslaw Zagaja, Ph. D., Marta Andres-Mach, Ph. D., Magdalena Florek-Luszczki, Ph. D., Professor Jarogniew J. Luszczki.
Medical University of Lublin, Poland

The aim of this study was to evaluate the influence of arachidonyl-2'-chloroethylamide (ACEA – a potent and selective cannabinoid CB1 receptor agonist) on the anticonvulsant properties of six selected antiepileptic drugs (i.e., clobazam, lacosamide, levetiracetam, phenobarbital, tiagabine and valproate) in the mouse psychomotor (limbic) seizure model.

Psychomotor (limbic) seizures were evoked in adult male albino Swiss mice by a current (6 Hz, 0.2 ms rectangular pulse width, 32 mA, 3 s duration) delivered via ocular electrodes.Potential concurrent adverse-effect profiles of interaction between ACEA and six selected antiepileptic drugs were evaluated in the chimney test (motor performance), passive avoidance task (long-term memory) and grip-strength test (skeletal muscular strength) in mice. Total brain antiepileptic drug concentrations were measured with HPLC to exclude any pharmacokinetic interaction between drugs.

Results indicate that the selective cannabinoid CB1 receptor agonist ACEA significantly potentiated the anticonvulsant effects of levetiracetam against psychomotor (limbic) seizures in mice. In contrast, ACEA had no significant impact on the anticonvulsant effects of clobazam, lacosamide, phenobarbital, tiagabine and valproate in this seizure model. No potential adverse effects associated with the combined treatment of ACEA with six antiepileptic drugs were observed in these behavioral tests in mice. Pharmacokinetic experiments revealed that ACEA did not significantly affect total brain concentrations of levetiracetam in mice and thus, the observed interaction was pharmacodynamic in nature.

In conclusions, significant potentiation of the anticonvulsant effects of levetiracetam by the selective cannabinoid CB1 receptor agonist ACEA in the mouse psychomotor seizure model might be translated to clinical conditions. It seems that activation of cannabinoid system in the brain results in suppression of psychomotor seizures, however, this fact needs confirmation in further clinical studies.

Audience take away:

- This study is another example that cannabinoids with some drugs can protect agains sizures. Interaction between levetriacetam and ACEA can be translated to clinical conditions in the future.
- ACEA is another substance that can be treated in the future, as a substance that protects agains sizures.
- The study can be used as an exaple to teach about effects of cannabinoid receptors.
- ACEA can be a solution for patients treated by levetriacetam, as a substance that increase antiepileptic effect.

Biography

My name is Maria Kondrat-Wrobel, I was born in 1988 in Lublin, a town on the east part of Poland. In 2007, I finished high school and in 2013 I graduated from Medical University in Lublin. Since my graduation I have been practicing internal medicine on a Cardiology Unit in a Specialist Hospital in Lublin. Currently, I am pursuing a doctoral degree in the Department of Pathophysiology, mentoring students on the subjects relating to pathophysiology and working on research to discover new substances which could help potentiate the anticonvulsant effects of antiepileptic medications.

The relationship between global acetylation histone H4 levels and spinal cord injury: An experimental study

Viviane Rostirola Elsner*; Mayara Ferraz de Menezes; Fabrício Nicola; Ivy Reichert Vital da Silva; Leder Leal Xavier; Adriana Vizuete; Carlos Alberto Goncalves; Carlos Alexandre Netto; Regis Gemerasca Mestriner.
IPA Methodist University, Brazil

Emerging evidences have been pointed out that the imbalance on epigenetic machinery exert a pivotal role in the physiopathology of several neurological, neurodegenerative and neuropsychiatric conditions. However, this relationship in spinal cord injury (SCI) have been poorly investigated. Therefore, this study aimed to evaluate the modulation of global histone H4 acetylation levels, an important epigenetic mark, after a thoracic SCI model in rats. Male Wistar rats aged 3 months were submitted to a thoracic SCI model and global histone H4 acetylation levels were measured at different time-points: 6h, 24h, 48h, 72h and 7days after. The global histone H4 acetylation levels were determined using the Global Histone H4 Acetylation Assay Kit (Colorimetric Detection, EpiQuik USA) according to the manufacturer's instructions. The Animal Bioethics Committee of both Federal University of Rio Grande do Sul (number 26116) and Pontifical Catholic University of Rio Grande do Sul (number 15/00492) approved the study protocol. It was observed that global histone H4 acetylation levels changed at the evaluated time-groups (P=0.0001). Post hoc tests showed the 72h post-SCI group was significantly increased from all the other groups (P≤0.03). Moreover, there was an additional difference between the 24h and 7 day post-SCI groups (P=0.01). Taken together, our findings suggest histone H4 acetylation levels as novel possible biomarker in SCI. We also showed that this modulation in the perilesional tissue are time-dependent after SCI.

Biography

Dr. Viviane Elsner has completed her PhD at the age of 28 years from Universidade Federal do Rio Grande do Sul, Brazil. Currently she has 31 years old and is professor/research in a Post Graduate Program and guides 8 master students. She coordinates the "Interdisciplinary Group of Study on Epigenetics Applied to Health and Disease" and their academic production primarily involves the line of research related to the effects of physical exercise on the modulation of epigenetic mechanisms in healthy subjects or patients with chronic diseases". She has published 14 papers in reputed journals in the last years.

Effectiveness and safety of intrathecal ziconotide: Interim analysis results from a single center of the patient registry of intrathecal ziconotide management

Gladstone McDowell*, MD; Michael F. Saulino, MD, PhD; Richard L. Rauck, MD; Philip Kim, MD; Mark Wallace, MD; I-Zu Huang, MD; Fannie Mori, MS; Geertrui F. Vanhove, MD, PhD; Timothy Deer, MD
Integrated Pain Solutions, USA

Introduction: The Patient Registry of Intrathecal Ziconotide Management (PRIZM) evaluates effectiveness and safety of intrathecal (IT) ziconotide.

Methods: PRIZM is an open-label, long-term, multicenter (23 sites), observational study of adult patients with severe chronic pain who meet ziconotide prescribing information criteria. Study assessments are scheduled at baseline, weeks 1, 2, 3, 4, 8, and 12, and every 3 months thereafter through month 18. This interim analysis (data as of July 10, 2015) reports change from baseline to month 12 in "average pain for the past 24 hours" on the 11-point Numeric Pain Rating Scale (NPRS; primary efficacy measure) from the PRIZM site with the highest enrollment (site 9; n=13).

Results: Enrollment closed at 93 patients; data collection has completed. Site 9 enrolled 13 patients, 12 of whom received ziconotide as the first agent in pump (FIP+) and 1 as the second-or-later intrathecal agent in pump (FIP-). Mean (SD) baseline NPRS score was 7.8 (1.5) in FIP+ patients; baseline NPRS score was 4.0 for the FIP- patient. At the time of this analysis, 10/12 FIP+ patients (83.3%) were enrolled ≥12 months prior; 80.0% (8/10) of patients were still active in the study at month 12, of whom 37.5% (3/8) remained on ziconotide monotherapy. The FIP- patient was not enrolled in the study at month 12. The number of patient visits corresponded with the study schedule through week 8, after which patients were seen approximately 2 to 5 times more frequently than with per-protocol visits. In addition to continuous infusion dosing, all patients except for 1 in the FIP+ group had patient-administered bolus dosing enabled (via the Medtronic® Personal Therapy Manager). The onset and duration of patient-administered dosing varied. Mean (SD) ziconotide dose in FIP+ patients was 1.03 (0.08) mcg/d at baseline, 4.46 (5.76) mcg/d at week 12, 3.44 (2.92) mcg/d at month 6, and 1.52 (1.08) mcg/d at month 12. Dosing for FIP- patient was 1.20 mcg/d at baseline, 2.50 mcg/d at week 12 and 1.00 mcg/d at month 6. Mean (SEM) percentage change in NPRS score in FIP+ patients was -34.6% (9.0%) at week 12, -37.3% (9.3%) at month 6, and -46.1% (12.6%) at month 12. In the FIP- patient, percentage change in NPRS score was 100.0% at week 12 and month 6. In FIP+ patients, treatment response rates were 50.0% at week 12, 55.6% at month 6, and 50.0% at month 12 for response defined as ≥30% decrease in NPRS score. The FIP- patient did not respond to treatment. The most common adverse events (≥3 patients overall) were amnesia (38.5%), peripheral edema (30.8%), memory impairment (23.1%), nausea (23.1%), and vertigo (23.1%).

Conclusion: Pain reduction through month 12 was observed at the highest-enrolling PRIZM site and may be related to ziconotide use as the first IT agent in pump and/or investigator-specific practices (high frequency of patient contact, opportunity for dose adjustment, high use of patient-administered IT bolus dosing). The analysis was limited by the small patient population. The adverse events reported are consistent with ziconotide prescribing information.

Biography

Gladstone C McDowell II, MD, is the Founder and Medical Director of Integrated Pain Solutions, a multimodal private practice in Columbus, Ohio. Dr McDowell is a founding member and on the board of the Cancer Pain Research Consortium. He has held faculty appointments at US Patient Safety Congress meetings, National Press Club Safety Congress, The National Institute on Health Care Fraud, Cancer Pain Conference, Targeted Drug Delivery Conference, International Association for Study of Pain, and numerous US and European pain meetings. Dr McDowell was on the Polyanalgesic Consensus Conference (PACC) panels of 2007, 2012, and 2017 and the Neuromodulation Appropriateness Consensus Committee (NACC) panels of 2013 and 2016. Dr McDowell is the Chairman of the Steering Committee for the US PRIZM intrathecal registry.

Impact of changes in intraoperative evoked potential monitoring on stroke rates in intracranial aneurysmal surgery

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Seoul St.Mary Hospital, Korea

Objectives: To present the outcomes of 191 cases treated surgically for intracranial aneurysmal who underwent intraoperative SSEP and MEP monitoring and to analyze the sensitivity, specificity and predictive value of changes in predicting postoperative stroke. for intracranial aneurysmal who underwent intraoperative SSEP and MEP monitoring and to analyze the sensitivity, specificity and predictive value of changes in predicting postoperative stroke.

Methods: We retrospectively reviewed of data of 191 patients who underwent intracranial aneurysmal neck clipping and intraoperative MEP and SEP monitoring were carried out in all cases. Postoperatively, all patients underwent computed tomography(CT) or magnetic resonance imaging(MRI) within 72 hours. Sensitivity, specificity, positive predictive value(PPV), negative predictive value(NPV) of SSEP and MEP were calculated with a Fisher exact test.

Results: The patient population of 191 had a mean age of 58.6 years and consisted of 125 women (65.4%). The 22 (all anterior circulation) were ruptured aneurysm, and 169 (167 anterior, 2 posterior) were unruptured. Changes of SSEP occurred in 4 of 191 cases (20.9%): 2 of 4 (50%) were reversible. Changes of MEP occurred in 4 of 191 cases (20.9%): 1 of 4 (25%) were reversible. Postoperative CT or MRI findings were recorded as stroke in 5 patients. The sensitivity, specificity, PPV, NPV were 42.9%, 99.4%, 75%, 97.9% in only SEP change, 28.6%, 98.9%, 50%, 97.3% in only MEP change, 71.4%, 98.3%, 62.5%, 98.4% in SEP or MEP changes, respectively.

Conclusion: Detection of either MEP or SEP changes can provide higher sensitivity than single SEP, MEP monitoring for predicting postoperative stroke. Although specificity and NPV were very high because of large number of cases without SSEP changes and no postoperative stroke, this information is helpful during the intraoperative assessment of intracranial aneurysm.

Biography

I graduated from Catholic University Medical College and trained Catholic University rehabilitation department residency course. Currently, I am a clinical instructor of the Rehabilitation Department of Seoul St. Mary's Hospital. My major fields are neurorehabilitation in stroke or traumatic brain injury patients, and intraoperative monitoring in neurosurgery.

Neuroinflammation, glial activation, oxidative stress and behavioral deficit in the hippocampus following short-term adrenalectomy

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United Arab Emirates university, UAE

Bilateral adrenalectomy (ADX) has been shown to damage the hippocampal neurons. However, the effects of short-term ADX is not studied. Therefore, we aimed to investigate the effects of short-term ADX on the levels of pro-inflammatory cytokines, response of microglia, astrocytes, neuronal cell death and oxidative stress markers over the course of time (4 h, 24 h, 3 days, 1 week and 2 weeks) in the hippocampus.

Our results showed a transient significant elevation of pro-inflammatory cytokines IL-1β and IL-6 from 4 h to 3 days in the ADX compared to sham. TNF-α levels were significantly elevated at 4 h only in ADX compared to sham. Time dependent increase in degenerated neurons in the dorsal blade of the dentate gyrus from 3 days to 2 weeks after ADX. Quantitative analysis showed significant increase in the number of microglia (3, 7 and 14 days) and astrocytes (7 and 14 days) of ADX compared to sham. A progression of microglia and astroglia activation all over the dentate gyrus and their appearance for the first time in CA3 of adrenalectomized rats hippocampi compared to sham was seen after 2 weeks. A significant decrease of GSH levels and SOD activity and increase in MDA levels were found after 2 weeks of ADX compared to sham. In order to investigate the effect of adrenalectomy on the behavior of the animals we used a passive avoidance test at 3, 7 and 14 days after adrenalectomy. Our results showed a significant reduction in the latency time in the adrenalectomized rats compared to the sham operated rats 3, 7 and 14days after adrenalectomy.

Our study showed an early increase in the pro-inflammatory cytokines followed by neurodegeneration and activation of glial cells as well as oxidative stress. Hence, early inflammatory components might contribute to the initiation of the biological cascade responsible for subsequent neuronal death. These findings suggest that inflammatory mechanisms precede neurodegeneration and glial activation. In addition, the neural death was accompanied by a behavioral deficit in the ADX animals.

Long-term effects of perinatal undernutrition in the brain and behavioral gustatory development of the rat

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Universidad NacionalAutonoma de Mexico, Mexico

Gestational and lactating period is a time of rapid development for the mammals. The effects of restriction of nutrients in these periods produce alterations in fetal neurogenesis, morphogenesis, synaptogenesis; and during the lactating period interferes migration, synaptogenesis, networks and behavior of the progeny. These effects can be permanent at long-term in the acquisition of cognitive development that includes alterations in attention, learning, memory and inhibition control. In the other hand, these periods are essential for normal development including food behavior, because is concurrent in a period of transition between maternal milk to solid food in which different mechanisms are conjugated to obtain self-selection and self-gratification diet. In this study we evaluate the long-term impact of the undernutrition on some gustatory structures including, tongue, papillae, taste buds, morphological and neuronal activation in the nucleus of the solitary tract in the brain of developing rats. Pregnant dams were undernourished by giving 50% of a balanced diet from G6 to G12, 60% from G13-G18, and 100% from G19-G21. On postpartum day 1, prenatally underfed (UG) pups continued the undernourishment by remaining 12h with a foster dam and 12h with a nipple-ligatted mother. The results show consistent effects associated with age and diet; undernutrition in early life leads to irreversible damage, including body and brain weight and decreased offspring birth weight. In the rat model the undernutrition in gestation and lactation period affect the development in circumvallate papillae, affecting the size and morphology, the number of taste buds and the number of apoptotic cells. Undernutrition alters the pattern of neuronal induction by sweet and sour stimuli at the second postnatal week in the nucleus of the solitary tract, particularly in the caudal and medial areas that are involved in the gustatory reflex. The early restriction in nutriments alters the social transmission in food preference showing decreased social interaction and alterations in food recognition and preferences. These data suggest that perinatal undernutrition affects the basic component of the gustatory system necessary to produce the early responses, and possibly interfering with the integration of taste input to produce the food intake interfering with food learning and the hedonic aspects of the gustatory stimuli's.

This information is useful to know the damage suffered in early life that leads to permanent impairment in the gustatory system affecting future generations. This information would be helpful to asses in health and educational programs. In the other hand, undernutrition is responsible for the highest mortality rate in children and has long-lasting effects including, insulin resistance in adulthood, hypertension, dyslipidemia and reduce de capacity for cognitive work and possibly to understand transgenerational effects.

Biography

Area: Neurobiology of development and neurophysiology. We are particularly interested in gustatory system and aspects of social behavior. We are investigating the neurobiological alteration of perinatal undernutrition of social learning whereby an individual acquires information from other individual, adjustments of the taste structures of the tongue produces by early nutrients restriction. We are also investigating c-Fos based activity maps generated by stimulation with sour and sweet in early development in the nucleus of the solitary tract. Our research involves rats and integration of various aspects of neuroscience from, histological, morphological, immunohistochemistry and ethological.

Cardinal signs in parkinson's disease and agonists, antagonists, stabilisers

KHIN MAUNG BO
Northern Lincolnshire & Goole NHS Foundation Trust, UK

Background: Basal Ganglion Neuronal Network (BGNN) dysfunction in Parkinson's disease (PD)is a complex one to explain Cardinal Signs (CS) satisfactorily. CS of PD are:

- Tremor,
- Rigidity,
- Bradykinesia and
- Postural Instability (PI).

Objective:

To propose adjunct explanation in PD in terms of Agonists, Antagonists and Stabilisers during movements.

Adjunct explanation proposal:

1.Rigidity: Co-contraction of Agonists and Antagonists.

2.Tremors: Alternate Agonists and Antagonists contractions

3. PI: Impaired involvement of Stabilisers

4. Bradykinesia: Reduction in numbers of Agonists and Antagonists taking part in motor programs.

In addition:

5.Dystonia: Unopposed strong Agonists

6.Freezing: Momentary jam of motor programs of all muscles involved (e.g. Freezing od Gait)

7.Dyskinesia: Automatic execution of sequential motor programs involving multiple agonists and antagonists in more than one part of a limb or more than one limb.

8. Apraxia: Total loss of normal sequence of motor programs

Conclusion: It is much easier to understand CS of PD using above explanation as an adjunct to dysfunction of BGNN.

Audience Takeaway:

- Above model of explanation can be used in adjunct to dysfunction of BGNN in teaching, patient education and understanding postural instability in PD.
- Therapist involve in PD management needs to engage all muscle groups (agonists, antagonists and stabilisers), Research using EMG of above muscles will shed more light on disturbance of synchrony among these muscle groups, Research on DBS affecting synchrony of above muscle groups

Biography

Dr Khin Bo is involved in NeuroRehabilitation over 20 years. He is also a Lecturer (Hon) in Hull and York Medical School teaching 4th Year Medical Students in CNS and Musculoskeletal Blocks. He is doing Botulinum Toxin injection in Spasticity, Dystonia and Involuntary Movement disorders over 15 years and done Poster presentations in International NeuroRehabilitation Conferences. He is also involved in using Functional Electrical Stimulation (FES) over 10 years and presented regularly in International FES Conferences. He is working on developing Hypertonic Hand Monitoring Scale.

magnus Group

DAY 3

Keynote Forum

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Stroke in very old patinets

Mira Rakacolli

University Hospital Center" Mother Theresa" Tirana, Albania

Introduction: Presently, there is limited information on stroke care in the very old (80 years and older).

Aim: To evaluate vascular risk factors, stroke subtypes and clinical outcomes in very old patients admitted at our hospital with acute stroke.

Methods: We included in this study 504 stroke patients admitted to the Neurovascular Service at the University Hospital Center "Mother Teresa", Tirana, Albania from February 2011 to December 2014.We assess if there were any significant differences between patients under 80 years old compared with older patients (80 years or older), with regard to vascular risk factors, stroke type and clinical outcome.

Results: Of 504patients, 378patients were less than 80 years, 126 were 80 years old and older. Younger patients were more likely to have diabetes (30, 6% versus 16, 2%, p<0,001). Older patients were more likely to have ischemic heart disease (38% versus 30, 1% p=0, 02), or atrial fibrillation (34, 5% versus 15, 2%, p<0,001).

Older patients were more likely to have Total Anterior Circulation Infarcts (TACI) strokes (17, 6% versus 11, 1%, p<0,009) or Partial Anterior Circulation Infarct strokes (PACI) (30, 1% versus 23, 5%, p=0, 04) Outcome data, which was available for 91% patients, showed that older patients stayed longer in hospital (median length of stay 23 days versus 18 days, (p=0,008) and had a higher inpatient mortality 14% versus 3, 7%, (p<0,001).

Conclusion: Very elderly patients have a different risk factor profile, have more anterior circulation infarcts and have a worse prognosis-with increased mortality and increased length of stay in hospital. Aging of poulation is a reality in the majority of countries all over the world. In our study patients with stroke over 80 had higher fatality and needed longer stay in the hospitals or in the neurocritical care. On the other hand the majority of them needed assistance after diacharge from the hospital, and were not able to live indipendently in their own homes. So, there is an increasing demand on healthcare system, Strategies need to be implemented to face the problem.

Biography

Prof. Mira Rakacolli-Kapisyzi, Chief of Neurovascular Service, University Hospital "Mother Theresa" Tirana, Albania. Graduated from the Faculty of Medicine, University of Tirana, Albania, in 1983, received her certification in Neurology in 1987. From 1993 to 1995 different training courses focused in epidemiology, movement disorders and headache in Italy and France. In 2001 visiting Professor in Columbia University, USA, Movement Disorders Unit. Since 1997 Neurologist at the University Hospital "Mother Theresa" Tirana, Albania. Lecturer of Neurology, Faculty of Medicine, University of Medicine, since 1991. Dean of the Faculty of Medicine University of Medicine, Tirana, 2014-2016. President of Albanian Society of Neurology since 2008. Member of European Academy of Neurology, American Academy of Neurology, International Movement Disorder Society. From 2005-2009 ex officio member of European Committee Movement Disorder Society. Member of Pain Panel, Neuroepidemiology Panel, Movement Disorders Panel, European Academy of Neurology. Her publication are mainly focused on epidemiology of neurological disorders in Albania, especially neurodegenerative disorders and headache.

Detoxication therapy in stroke

Henry Bakunts

International Medical Centre "STROKE", Armania

At present, due to introduction of highly informative instrumental methods of assessment of cerebral blood flow state, microcirculation system and brain tissue metabolism diagnosis or vascular diseases of the brain is significantly improved. This brought to reassessment of existent conventional methods of pharmacological treatment of cerebrovascular disorders. Therefore, currently methods and tools that could positively influence different stages of disturbed homeostasis during cerebral blood flow disturbance, and primarily its immunoreactivity are searched. Application of efferent medicine methods is considered promising. This is based on removal of xenobiotics or endogenous toxic compounds exerting harmful influence on function and structure of different organs and systems and determining features of pathological process during different diseases. Detoxication methods are not widely applied in clinical neurology, although there is some experience in patients with multiple sclerosis, myasthenia gravis, toxic radiculoneuropathy and chronic atherosclerotic encephalopathy. Cellular and molecular mechanisms of cerebrovascular disease have been studied, establishing that products of catabolite disintegration of cellular receptors (R-proteins) are the markers of development of pathological process in cerebrovascular diseases. While accumulating in pathological locus, R-proteins enter bloodstream and reach other organs and tissues. Competing with cellular receptors for hormones, the other mediators of cellular metabolism, they, through intercepting ligands, are able to disrupt homeostasis either on the level of a single cell and in the whole organism. According to current concept, disturbance of cellular reception or its inversion are the mechanisms responsible for complicated interconnected and interdependent processes that bring to shift of homeostasis on different levels and eventually to development of cerebral discirculatory lesions. Therefore, application of modern detoxication agents for elimination of homeostatic and metabolic disturbances developed on the different levels of stroke evolution is becoming justified. We widely use colloid plasma-substituting solutions, particularly OslaDex with mean molecular weight of 200.000 daltons. There are different points of view regarding use of therapeutic hemodilution (TH) in acute ischemic stroke. Guided by packed cell volume and blood viscosity, clinicians often underestimate importance of hemorheology indices, plasma viscosity and erythrocyte aggregation. Therefore, improvement of collateral blood supply in the brain areas adjoining to the lesion is an important component of therapeutic measures in the treatment of acute ischemic stroke. TH should provide sufficient decrease in viscosity of the whole blood and plasma. Hematocrite indices are in direct proportion to indices of the whole blood viscosity. Having correctly calculated packed cell volume blood circulation will improve and delivery of oxygen to brain tissues will increase. Hemodilution is indicated in ischemic stroke, because of dehydratation and hypovolemia symptoms revealed in these patients, therefore even simple use of substitution therapy promotes improvement of cerebral circulation and optimal results are enabled by hypervolemic TH. At the same time possible hypovolemia should be avoided. Hypervolemic TH reliably and quickly increases cardiac output, while incorrect application of isovolemic TH could induce negative hemodynamic effects. Further treatment is based on individual bases and includes hypervolemia TH, local and general use of fibrinolytics, heparinisation, injection of vasoactive medications and plasmapheresis.

Biography

Neurologist, MD, Professor Henry Bakunts is the Head of the Department of Angioneurology and Lifelong Learning in Yerevan State Medical University after M.Heratsi, the Head of the Clinic of Angioneurology in the Medical Centre "Nairi". He is a member of the World Federation of Neurologists (WFN), the World Stroke Organization (WSO) and the European Federation of Neurological Studies (EFNS). He is an academic of the Academy of Medical Science of RA. Professor Bakunts is the head of the Armenian Angioneurological Services from 1977. Under his leadership was organized the first Clinic of Angioneurology in Armenia with Neuroresuscitational Services, the Department of Neurodetoxication and the Chair of Angioneurology.

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DAY 3

Speakers

International Conference on

Neurology and Brain Disorders

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Session on: Neuroimmunology & Neurological Infections; Neuromuscular Disorders

Session Chair
Michael Ugrumov
Institute of Developmental Biology RAS, Russian Federation

Session Co-Chair
Meena Kumari
Kansas State University, USA

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Joanna Czarzasta, University of Warmia and Mazury, Poland

Theory of vulnerability to suicide through hippocampal indifference in depression

Lars Hankan Thorell
Linkoping University, Sweden

The very strong relationship between electrodermal hyporeactivity and suicide and other suicidal behaviors in depressed patients (Edman et al., 1986; Thorell, 1987, 2009; Eriksson et al., 2008; Thorell et al., 2013, 2014; Sarchiapone et al., 2017, 2017 (not published yet); Sarchiapone, 2017 (oral)) indicate a common explanatory factor.

Electrodermal hyporeactivity is the loss of specific orienting responses to insignificant tone stimuli in an electrodermal habituation test that may lead to a failure in creating detailed memory models of neutral stimuli and a loss of normal emotional reactions to it, i.e. a failure in the essential ability of "learning the usual". The neurons evoking the orienting reactions have been found in rabbit to be located in the CA1 and CA3 neurons of hippocampus (Sokolov et al. 2002).

Also, the depressive suicide are two objectively observable behaviors that may be linked to hippocampal dysfunction. It is known that suicide is related to deviances in hippocampal anatomy and function which in turn have several causes. One important cause seems to be long lasting high steroid levels that affect hippocampus in various ways (see for example review by Dwivedi 2012).

Electrodermal hyporeactivity and the depressive suicide are two objectively observable behaviors. The repeated unanimously findings of the valid and powerful results are much dependent on the objective nature and robustness of these two variables.

Many observations that have been made regarding behavioral and biological concomitants in relation to suicidal behavior, such as biological conditions, cognitive dysfunctions, and potential treatment measures can be theoretically related to orienting hyporeactivity in hippocampus.

Why we need more than technical and procedural competencies in themedical industry to improve the team and patient safety

Martin Egerth and Münzberg Mathias
Lufthansa Aviation Training GmbH, Germany, BG Klinik Ludwigshafen, Germany

Between 300 and 500 people die every year in plane crashes worldwide. Despite this seemingly high number, the number of preventable deaths annually as a result of medical errors is far greater. Patients die daily due to human errors committed by doctors, nurses and hospital staff. Why then is there such a great emphasis on rules, regulations and standardised simulations and trainings in the aviation industry, but not in the medical sector? How do we define safety and how can we continuously improve this notion? What similarities and differences exist between the aviation and medical industries and what can medical professionals learn from the established human factors and safety trainings already in place for pilots, flights attendants and non-flying staff. And what can aviation learn from medicine? A clear distinction is that trainings in aviation industry focus not only on technical and procedural competencies, but also interpersonal and personal skills. Interpersonal and personal skills must be strengthened for those working with or on patients and a safetyculture needs to be introduced. This will result in proper error management, a positive working environment and ultimately less patients dying due to staff fatigue, a lack of assertiveness and hierarchy. Lufthansa Aviation Training and the German Society of Orthopedic and Trauma Surgery (DGOU) have implemented a new trainings philosophy to strengthen interpersonal and personal competencies. From basic trainings to leadership trainings to assessments in the surgery room, this philosophy encompasses a broad implementation of human factors. The overarching goal is to make hospitals safer and toimprove overall patient safety. During these training, strategies to combat complacency and fatigue are introduced, incidents are openly discussed and risk assessment is fine-tuned. Additionally, the trainings focus on improving communication within the team, providing decision making tools and making individuals aware of their own strength and weaknesses.

Audience Take away:

This speech will emphasise the importance of safety, human factors, team work, decision making and error management for the medical sector. It will stress that human factors trainings must not only continue to develop in terms of subject matter and training methods, but continue to be an integral part of a hospital's strategy regardless of how safe current operations are. It will critically examine the current methods used in human factors trainings to see what needs to be done preemptively to adapt to the requirements of future generations of trainees and of the medical industry in general. It will highlight the importance of thinking creatively and "outside of the box" to push human factors trainings of the future and patient safety standards. New research results of these trainings and the effects will be presented.

Biography

Martin Egerth is a Product Manager Human Factors Training at Lufthansa Aviation Training. As apsychologist and human factors expert, he manages Lufthansa's entire portfolio of human factors andsecurity trainings for the aviation industry and also for external industries.During his ten years at Lufthansa, Martin has developed, overseen and conducted trainings that havedeveloped the skill sets of pilots, flights attendants and non-flying staff. From basic trainings, to recurrenttrainings to management trainings for Lufthansa and external airlines, he has trained over 8,000 flyingstaff.Martin has also founded a human factors working group comprised of 26 European and internationalairlines that meets annually to exchange CRM best practices, discuss how to avoid incidents andaccidents, identify the influence that culture and safety culture has on CRM and develop CRM for thefuture.

Mr. Egerth holds a Master's Degree in Psychology from the University of Innsbruck and is currentlypursuing his doctorate.Dr Matthias Muenzberg is a senior consultant in trauma surgery at one Germany's largest traumacentres. As an emergency physician, he is also the head of medicine for the air rescue centre. He is anassistant professor of trauma surgery at the Univerity of Heidelberg. He teaches about managingseverely injured patients pre-hospital and at the clinic, trauma education from personal experience andhuman factors.As an executive committee member of the German Society of Orthopedic and Trauma Surgery (DGOU),Matthias was part of the task force to implement a "safety culture in medicine" and was responsible withdeveloping the new course concept of IC (Interpersonel Competence).Dr. Muenzberg is the national director of the Pre-hospital Trauma Life Support (PHTLS) programme aswell as the director of several other international trauma programmes. Matthias has authored a numberof highly regarded publications about the standardisation in trauma and burn care. Additionally, he is afrequent speaker at international conferences in the field of trauma, education and emergency medicine.

Dystrophin Dp71 isoforms are differentially expressed in the mouse retina and brain structures

Cecilia Montanez*, Ph. D., Mayram Gonzalez-Reyes, M. Sc., Jorge Aragon, Ph. D., Jose Romo-Yanez, Ph. D., Alvaro Rendon, Ph. D. and Cyrille Vaillend, Ph. D.
Centro de Investigacion y de EstudiosAvanzados del IPN, Mexico

Cognitive impairment and retinal abnormalities have been reported in the X-linked Duchenne muscular dystrophy. The intellectual disabilities are associated with mutations in the shortest dystrophins Dp71 and Dp40. Molecular, cellular, physiological and behavioral alterations are related with the loss of Dp71 in the brain and retina, supporting a major role for this protein in Central Nervous System (CNS). Dp71 is expressed from a promoter located in intron 62 of the DMD gene, being the most abundant product of this gene in the CNS. The Dp71 mRNA undergoes alternative splicing events in the exons 71, 71-74, 78 and intron 77, generating several isoforms of this protein that are expressed in different tissues including the brain. Three main groups of Dp71 proteins are defined based on their C-terminal specificities: Dp71d, Dp71f, and Dp71e; however, their function is unknown.The aim of this work is to identify the dystrophin Dp71 isoforms expressed in the retina and in specific brain structures and steps during brain postnatal development. For this, total RNA was isolated from adult mice C57BL/6 brain, cortex and cerebellum of mice 1, 7, 14 and 21 days old and retina. RT-PCR assays were carried out and the PCR products were cloned. These products were analyzed by multiplex PCR assay to determine the presence or absence of the exons 71, 71-74 and 78. The Dp71 isoform cDNAs were sequenced and their expression frequency was determined. Up to now, the results show that brain and retina express Dp71d, Dp71dΔ71, Dp71dΔ71-74, Dp71f, Dp71fΔ71, Dp71fΔ71-74 and Dp40, at different frequencies. Additionally, new alternative splicing for Dp71 mRNA products were found: Dp71dΔ74, Dp71dΔ71,74, Dp71dΔ71,73-74 and Dp71fΔ74 [1]. Further, a differential expression of Dp71d and Dp71f isoform groups, at protein level, was also observed in the brain and retina. The analysis of Dp71 isoforms in the brain structures demonstrated that the Dp71d, Dp71dΔ71, Dp71dΔ71-74, Dp71f, Dp71fΔ71 and Dp71fΔ71-74 isoforms are expressed at different frequencies in the cortex and cerebellum at postnatal and adult stages. The Dp71dΔ74 and Dp71fΔ74 were observed at late postnatal and adult stages in the cortex, while Dp71dΔ74 mRNA was found in the cerebellum since early postnatal stages. In conclusion, we demonstrated the expression of Dp71d, Dp71dΔ71, Dp71dΔ74, Dp71dΔ71,74, Dp71dΔ71,73-74, Dp71dΔ71-74, Dp71f, Dp71fΔ71, Dp71fΔ74 and Dp71fΔ71-74 transcriptsin the mouse brain and retina. The Dp71d group of isoforms is highly expressed in adult whole brain and in the cortex and cerebellum during the brain postnatal development, while the Dp71f group predominates in the retina.

Biography

Cecilia Montanez Ph.D. Born in México (1955). B. Sc. in Bacteriology, Escuela Nacional de Ciencias Biologicas (ENCB IPN), México (1997), Ph.D. in Microbiology; ENCB IPN, México (1982). Postdoctoral fellow; MRC, Cambridge, U.K. (1982). Full professor at the Department of Genetics and Molecular Biology (DGMB), Cinvestav IPN, Mexico (1982-to date). Head of the DGMB (1989-1993 and 2005-2009). Author of 55 publications in peer-reviewed journals. Director of 29 Ph.D. thesis and 43 M. Sc. thesis. Fellow (Level III), National System of Researchers, Mexico (2005-present), member since 1984. Research topics: Expression and function of short dystrophins in cellular models, neural stem cells and CNS.

Efficacy of biofeedback training on bladder and erectile dysfunction in paraplegic patients

Moataz M. El Semary*, Nawal A. Abou Shady, Wael S. Shendy, Mohamed S. Abdel-Azim
Cairo University, Egypt

To evaluate efficacy of biofeedback training on treatment of bladder and erectile dysfunction in paraplegic patients. Methods: Thirty male paraplegic patients within 6 to 18 months after injury, ages ranged from 20 to 35 years, participated in this study for a treatment period of six weeks; they were divided into two equal groups. Patients in group I were treated with pelvic floor exercises two times weekly, while patients in group II were treated with biofeedback training plus pelvic floor exercises two times weekly. All subjects were assessed for; 1) voiding cystometry, 2) EMG of pelvic-floor muscles, 3) International Index of Erectile Function (IIEF-5) Questionnaire. Results showed highly significant improvement in both groups in IIEF-5. There was significant improvement in group II and non-significant improvement in group I in values of an EMG biofeedback assessment of pelvic-floor muscles. There was highly significant improvement in group II in the bladder volume at the first desire to void and at maximum cystometric capacity, the detrusor pressure at maximum flow rate, the maximum flow rate, detrusor stability and significant improvement in bladder compliance while there was no significant difference in group I in the bladder volume at the first desire to void and at maximum cystometric capacity, the bladder compliance and detrusor stability & significant improvement the detrusor pressure at maximum flow rate & highly significant improvement in the the maximum flow rate.

Conclusion: Biofeedback training should be considered as valuable adjacent to conventional treatment in the control of bladder & erectile dysfunction in paraplegic patients.

The defining cerebral vascular pathology of the new clinical histopathologic entity ACTA2-related cerebrovascular disease (ARCD)

Maria-Magdalena Georgescu
Louisiana State University, USA

Smooth muscle cell (SMC) contractility is essential for the function of vessels and viscera and relies on the integrity of the actin-myosin apparatus. Two tissue-specific actin isoforms, α2-smooth muscle actin (SMA), encoded by the ACTA2 gene, and α-SMA are predominantly expressed in vascular and visceral SM, respectively. ACTA2 mutations induce vascular abnormalities that lead, among other manifestations, to aortic aneurysms, coronary artery and cerebrovascular disease. A distinct variant of cerebrovascular disease has been proposed for patients with the α2-SMA R179H mutation. We present here an integrated analysis of a severely compromised adult patient succumbing from massive stroke and carrying the R179H mutation that defines the new entity of ACTA2-related cerebrovascular disease (ARCD). A second infant patient carrying this disease succumbed of pulmonary hypertension. The presence of aortic aneurysms, persistence of patent ductus arteriosus, congenital absence of iris and characteristic radiologic appearance of the internal carotid artery and its major branches are confirmed as defining clinical features. The striking underlying histologic abnormalities in both patients involved arteries of all sizes and included massive intimal SMC proliferation, elastic lamina dissection/fragmentation, disorganized media and prominent increase in vessel wall extracellular matrix, suggesting impaired function of arterial SMCs. Actin three-dimensional molecular modeling revealed critical positioning of R179 at the interface between the two strands of filamentous (F)-actin and destabilization of interstrand bundling by the R179H mutation, thus explaining the severe associated phenotype. In conclusion, these characteristic clinical and pathologic findings establish ARCD as a new syndrome for which therapeutic implications are discussed.

A novel method to deliver therapeutic and diagnostic molecules to the brain

Teruna J. Siahaan
The University of Kansas, USA

One of the major challenges in studying brain function and diseaseslies in the difficulty in deliveringmoleculesto the brain due to the presence of the blood-brain barrier (BBB). This project is aimed at developing a novel and effective method to deliver molecules to the brain for analyzing the molecular and cellular levels of brain functions in normal and brain-diseased animals (Alzheimer's, multiple sclerosis, and brain tumors animal models). The central hypothesis is thatcadherin peptides(HAV and ADT) modulate cell-cell adhesion in the intercellular junctions of the BBB to enhance paracellular permeation of small-to-large molecules through the BBB. The results showed that cadherin peptidesincrease the in vivo brain delivery of drugs (camptothecin), paracellular marker molecules (C-mannitol, gadopentetic acid), H-PEG, and 25 kDa IRdye800cw-PEG), efflux pump substrates (rhodamine 800 (R800), H-daunomycin), 8–12 amino acid peptides (i.e., cIBR7 and cLABL), and proteins (i.e., 65 kDa galbumin) in mice and rats. These results strongly support the possibility of using cadherin peptides for non-invasive delivery of various molecules for diagnostic or therapeutic purposes to the brains of brain diseased animal models.The HAV and ADT peptides are non-toxic, and they can safely modulate the BBB for a short period to allow BBB penetration of large proteins. We also found that ADT and HAV peptides bind to the EC1 domain of E-cadherin at different binding sites.In summary,our work is the first to show that modulating cell-cell adhesion can safely increase the delivery of molecules to the brain in living mice and rats. The concept of modulating cell-cell adhesion of the BBB to improve delivery of molecules to the brain is novel and would have a broad impact on the diagnosis and treatment of brain diseases.

Lesson from the Hereditary cerebral small vessel disease

Toshiki Mizuno
Kyoto Prefectural University of Medicine, Japan

Hereditary Cerebral Small Vessel Disease (CSVD) can be divided into three types. autosomal dominant, autosomal recessive and X-linked. While CADASIL is most common in autosomal dominant type, CARASIL is the only one recessive type. CADASIL and CARASIL have a couple of similar characters, such as juvenile onset stroke, repeated subcoritcal infarcts and cerebral white matter lesion and vascular dementia. Otherwise, there are different characters, such as frequent consanguineous marriage, alopecia, and spondylosis in CARASIL. In addition, while CADASIL exists in all over the world, CARASIL is reported from only Japan and Korea.

HTRA1, regulating TGF-beta1 signaling, is detected as a causative gene of CARASIL. We found a mild CARASIL phenotype caused by the heterozygous mutation of HTRA1. These cases suggested that the increase of TGF-beta1 signaling by the mutation of HTRA1 can induce the accumulation of extracellular matrix including fibronectin and versican.

The aggregation of the extracellular domain of NOTCH3 (N3ECD) is observed by immunostaining or electron microscopy in CADASIL. The complex of N3ECD and TIMP3 can induce the accumulation of extracellular matrix. Both diseases suggested that accumulation of extracellular matrix may be important for developing CSVD.

Audience take away:

We can learn the pathomechanism of cerebral small vessel disease from hereditary disease. The audience can get a hint of new approach for treating sporadic cerebral small vessel disease.

Biography

Toshiki Mizuno, MD, PhD is a professor in Department of Neurology, KyotoPrefectural University of Medicine (Kyoto, Japan). I work for theInternalmedicine as an assistant editor. My major interests are hereditary cerebral small vessel disease, including CADASIL and CARASIL, andvascular dementia. I reported several interesting articles about clinical and genetic study of CADASIL and CARASIL. I'm also interested in the pathomechanism of neurodegenerative disease and to develop a new therapy for neurodegenerative disease using by cellular model and drosophila model.

Optimizing medication management for mothers with depression

Katherine L. Wisner
Northwestern University Feinberg School of Medicine, USA

During pregnancy, the activities of Cytochrome (CYP) P450 enzymes are altered. However, minimal information is available to inform dosing guidelines. My team has published data demonstrating that the plasma concentrations of sertraline, fluoxetine, citalopram and escitalopram decline across pregnancy.Sertraline is produced as the S-isomeric compound and is extensively metabolized by the following CYP450 enzymes: major pathway, 2B6; minor pathways, 2C9, 2C19, 2D6, 3A4/5. We examined dose requirements and plasma concentration-to-dose (C/D) ratios in six women at 20, 30, 36 weeks, delivery, and 2, 4-6 weeks and 3 months after birth. The mean C/D ratios for sertraline decreased by an average of 60% between 20 weeks and delivery, which reflects elevated drug metabolism. By 4-6 weeks postpartum, C/D ratios of sertraline were similar to those in early pregnancy. Although CYP2D6 is the primary enzyme that metabolizes fluoxetine (FLX) to N-desmethylfluoxetine, 3A4 and 2C9 play a moderate role and 1A2, 2B6, 2C8 and 2C19 also contribute. In 17 pregnant women treated with FLX, we observed that the C/D ratios declined in the third trimester, and a significant negative relationship between depression scores and FLX was observed. Citalopram (CIT) is a racemic mixture of S- and R-CIT, with only the S-enantiomer having biological activity. Two compounds are marketed as antidepressants (CIT =Celexa, and esCIT=Lexapro). Both enantiomers of CIT are initially metabolized by CYP2C19 and CYP3A4 and further metabolized by CYP2D6. We studied 3 pregnant women treated with CIT and 2 treated with esCIT. In 4 of 5 subjects, the C/D ratios for the stereoisomers of the parent compound and primary metabolite decreased between 20 weeks gestation and delivery. By 12 weeks postpartum the C/D ratios were similar to those at 20 weeks gestation. These limited studies illustrate that the mean C/D ratios for sertraline, FLX, and CIT/esCIT decrease in the second half and specifically in the third trimester, presumably due to increased hepatic metabolism. However, the impact of these changes on depressive symptom relapse, and, in response, dose escalation has not been elucidated. My team was awarded funding from the National Institute of Child Health and Human Development to study the disposition of these drugs in 200 women. Due to the long half-lives of the SSRIs, it was impractical to conduct formal pharmacokinetic studies because doses would need to be withheld for several days, which risks increased depressive and discontinuation symptoms.

We will measure serial trough plasma concentrations, with women acting as their own controls across pregnancy. Plasma SSRI parent drug and metabolite concentrations will be measured as well as plasma concentration to dose (C/D) ratios of the parent drug and metabolite-to-parent drug concentration ratios. The effect of changing maternal SSRI concentrations on disease expression will be determined by assessing depressive symptoms and side effects monthly and before dose changes. We will repeat these assessments twice postpartum as non-pregnant physiology is re-established. Probe studies will be conducted in the third trimester and after birth to assess the relative contributions of CYP 450 enzymes as they act in concert to metabolize these drugs. The probe medications and their metabolic pathways are: dextromethorphan, O-demethylation by CYP2D6; omeprazole, 5-hydroxylation by CYP2C19; midazolam, 1'-hydroxylation by CYP3A4; and tolbutamide 4-hydroxylation by CYP2C9. We also will investigate the effect of genomic variability on inter-individual differences in SSRI plasma concentrations. At study entry, subjects will be categorized as ultrarapid, extensive, intermediate, or poor metabolizers. Those taking fluoxetine will be classified based on CYP2D6 genotypes, citalopram and escitalopram on CYP2C19, and sertraline on CYP2C19. Primary outcomes of interest include: C/D ratios for each drug; and depression and side effects scores. These data will inform guidelines for optimal dosing of these SSRIs.

Biography

Katherine L. Wisner M.D., M.S., is the Norman and Helen Asher Professor of Psychiatry and Obstetrics and Gynecology and Director, Asher Center for the Study and Treatment of Depressive Disorders, Northwestern University in Chicago, Illinois. She is internationally recognized as an expert in the treatment of mood disorders during pregnancy and the postpartum period. She is a fellow in the American College of Neuropsychopharmacology and has authored 210 peer-reviewed articles and 18 book chapters. She received the Woman in Science Award from the American Medical Women's Association, the Alexandra Symonds Award from the American Psychiatric Association and the Marce International Society for Perinatal Mental Health's Medal for lifetime contributions.

RNA-binding protein caught moonlighting

Meena Kumari*, Philip R. Hardwidge, and Antje Anji.
Kansas State University, USA

The N-methyl-D-aspartate (NMDA) receptors are important in neuronal development, synaptic plasticity, long-term potentiation, and neuronal cell death. NMDA receptors consisting of NR1 and NR2B subunits are a target of alcohol and are believed to play a role in the development, at least in part, of alcohol dependence and withdrawal syndrome. The NR1 subunit is the functional subunit, as NMDA receptors do not form without it. Chronic alcohol exposure increases NR1 polypeptide levels in cortical neurons through post-transcriptional mechanisms. A closer scrutiny of alcohol-mediated alterations of cellular processes revealed a switch in the expression of NR1 splice variants at the mRNA and protein levels; as well as; an increased half-life of NR1 variant mRNA. Neurons begin to show significantly increased expression of the NR1-4a variant – a variant that has maximum cell surface expression and thus makes neurons more vulnerable to excitotoxicity. Inhibition of new protein synthesis in the presence of alcohol reversed changes in NR1 mRNA half-life suggesting a changing protein landscape within neurons following chronic exposure to alcohol. Scanning of deletion mutants spanning the NR1-4 mRNA 3'-untranslated region identified a small region of 50 nucleotides that interacts with three RNA binding proteins (RBPs) in vivo and in vitro. One RBP is an alcohol-sensitive protein and its protein levels as well as binding to RNA were significantly increased in chronic alcohol-exposed cortical neurons. This protein was purified and identified by mass spectrometry as beta subunit of alpha glucosidase II (GII□) – a protein normally associated with the ER membrane. GII□ binds to the GII□ subunit to constitute heteromeric alpha glucosidase II (GII), which participates in the folding of nascent proteins in the ER. Data will be presented with regard to how changing the inner landscape of neurons following exposure to chronic alcohol is self-destructive or self-repairing.

Audience take away:

Explain how the audience will be able to use what they learn?

1) Can use the information in teaching neuroscience and biochemistry of proteins; 2) Can associate the information with "unexplained" ER stress and/or retention of proteins in ER; 3) can think of RNA-protein interactions as "hot spots" for novel therapeutic interventions in alcohol addiction

How will this help the audience in their job? Is this research that other faculty could use to expand their research or teaching? Does this provide a practical solution to a problem that could simplify or make a designer's job more efficient? Will it improve the accuracy of a design, or provide new information to assist in a design problem? List all other benefits.

1) Yes, other faculty can use this research (such as neurodegenerative diseases, neuropathy) to expand their research, 2) We are currently testing in vivo how RNA-protein interaction inhibition affects alcohol consumption. So yes, if we have success in these experiments then certainly RNA-protein interaction sites can become target of novel sites for developing targeted medicine.

Biography

Dr. Meena Kumari is currently an Associate Professor in the Department of Anatomy and Physiology, Kansas State University. She is the coordinator of the Physiology II course and teaches reproductive physiology to first year veterinary medicine students. Dr. Kumari was the recipient of a prestigious Alexander-von-Humboldt fellowship and spent two years at Phillips University, Marburg, Germany. The major thrusts of her research are focused on the molecular mechanism controlling NR1 subunit expression in cerebral cortex and the modulation of these processes by chronic alcohol. More recently, she developed an interest in exosomes. Her interest centers around examining exosome release in response to drug addiction.

Brain damage and neurological impairment in newborns

Magnus Gram*, Olga Romantsik, SuviVallius, Alex Agyemang, MatteoBruschettini, AsaJungner, KristbjorgSveinsdottir, SnjolaugSveinsdottir, David Ley
Lund University, Sweden

Rapid development in neonatal and cardiac surgery care in newborns has enabled survival of an increasing number of infants following preterm birth and of infants with congenital heart defects. Unfortunately this is accompanied by a significant prevalence of neurological and cognitive impairment detectable during childhood. This presentation will discuss pathophysiological mechanisms and targets that can be addressed therapeutically in order to prevent development of brain damage and subsequent neurological impairment. Intravascular and extravascular hemolysis of blood and the subsequent release of extracellular hemoglobin will be suggested as central disease generating events that causes irreversible disruption of the white- and grey matter, blood-brain-barrier disruption and deadly brain edema leading to massive brain cell death. From a clinical perspective, the research targets two groups of infants; 1) preterm birth infants who develop cerebral intraventricular hemorrhage and 2) newborns with congenital heart defects requiring cardiopulmonary bypass. The presentation focuses on development and implementation of novel neuroprotective strategies with the aim of promoting brain development in newborns with high risk for neurodevelopmental impairment.

Biography

The majority of the presenting authors work is focused on a) hemoglobin pathophysiology, with special emphasis on characterizing the role of extracellular hemoglobin and its scavenger system in human diseases; and b) free radical research, emphasizing the importance of redox biology c) A1M, a human endogenous heme and radical scavenger involved in endogenous protection and d) brain damage following preterm intraventricular hemorrhage (IVH). These subject matters are all part of this presentation. Along with the presenting author's academic research career, he is a senior scientist in the pharmaceutical company A1M Pharma.

The presenting authors work in the field has been recognized in several contexts; including a 3 year position for the research program "Brain damage and neurological impairment in newborns molecular mechanisms, clinical significance and novel therapeutic Interventions"; a 2 year support for the research program "Cell-free hemoglobin, hyperoxia and brain development in newborn infants with congenital heart defect requiring surgery with cardiopulmonary bypass"; the Young Investigator Exchange Program Award, "In recognition of research achievements in pediatrics" by the Society for Pediatric Research in 2014.I have authored and co-authored 39 publications. Furthermore, I serve as regular editor and reviewer in several international scientific journals in the current research field.

Identification of cytokines/chemokines in the blood serum and cerebrospinal fluids after transplantation of bone marrow MSCs to ALS patients.

Czarzasta J, Ph.D*, Juranek J, DVM, Ph.D., Siwek T, MD, Ph.D., Barczewska M, MD, Ph.D., Maksymowicz W MD, Ph.D., Prof, & Wojtkiewicz J, DVM, Ph.D.
University of Warmia and Mazury, Poland

Neuroinflammation is a major player in the course of amyotrophic lateral sclerosis (ALS), and is characterized by astrocyte and microglial activation, T cell infiltration and the overproduction of proinflammatory factors. Among many components/molecules engaged in the inflammatory response, cytokines/chemokines are involved in pathogenesis of ALS. Therefore, the goal of the study was to ivestigate proteome profile of cytokines/chemokines in blood serum, cerebrospinal fluid (CSF) after/before transplantation of bone marrow-derived mesenchymal stem cells (BM-MSCs) to ALS patients, and find out potential biomarkers associated with the course of the disease.

Blood and CSF samples were drawn from 10 ALS patients before BM-MSCs transplantation and after (performed in 2-months intervals) and 10 patients with other non-inflammatory neurological disorders (NND) served as a control group. The experiment has been approved by the Ethic Committee of University of Warmia and Mazury (UWM) in Olsztyn, and trial has been registered under NCT02881489. Identification of cytokines and chemokines has been checked in blood serum and CSF using Huamn XL Cytokine Array Kit (R&D Systems, Minneapolis, MN). Chemiluminescence was detected by ChemDoc MP imaging system, and mean pixel density was analyzed by the Image Lab software (4.1. Bio-Rad Laboratories). Subsequently, the concentration of interleukin/IL/-17 and 18 and chemokin CCL2 and CXCL12 has been checked in the blood serum and CSF using Quantikine ELISA Kit (R&D Systems, MN, USA, # D1700, 7620, DSA00 and DCP00, respectively). Data were statistically analyzed using one-way analysis of variance (ANOVA) followed by the Bonferroni test and statistical significance was defined as a p-values below 0.05.

Cytokines (IL-1α and β, IL-2, 4, 5, 6, 8, 10, 11, 12, 13, 15, 16, 17, 18, 19, 22, 23, 24, 27, 31, 32, 33, 34, INFγ, TGF-α, and TNF-α) and chemokines (CXCL1, 4, 5, 9, 10, 11, 12 as well as CCL2. 3. 4, 5, 7, 17, 19 and 20) were detectable in blood serum and CSF of NND group, ALS patients after and before BM-MSCs transplantation of ALS patients. In all human physiological fluids, most of identified factors were present on the lower level, only concentrations of IL-17 and 18 as well as CXCL12 and CCL2 were increased. This up-regulation has been confirmed by ELISA method, but not in the case of IL-17. Both, Proteome Profiler and ELISA analysis indicate that IL-18, CXCL12 and CCL2 levels were the greatest ($P<0.05$) in the blood serum and CSF of ALS patients, than in the fluids of NND group and ALS patients after BM-MSCs transplantation.

Obtained data suggest that the most increase in the levels of IL-18, CXCL12 and CCL2 in blood serum and CSF of ALS patients, may serve be a prognostic biomarkers during the course of the disease. What is more, lower levels of these three factors in the studied fluids of ALS patients after BM-MSCs transplantation may indicate the therapeutic action of these cells.

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Specific Items:

1.Neuroinflammation is a major player in the course of amyotrophic lateral sclerosis.

2.Upregulation of IL-18, CXCL12 and CCL2 in the blood serum and CSF of ALS patients may serve as a prognostic tool during the course of the disease.

3.Autological transplantation of bone marrow derived mesenchymal stem cells to ALS patients may offer regeneration effect in the ALS therapy.

Biography

Joanna Czarzasta graduated PhD degree in 2014 from the Institute of Animal Reproduction and Food Research of the Polish Academy of Sciences in Olsztyn. Her interest in PhD studies was focused mainly on immuno-neuro-endocrine patho-mechanisms of disturbances of the reproductive organs in females. At the moment, She is working as a Research Assistant at the Department of Pathophysiology, Faculty of Medical Sciences, University of Warmia and Mazury. Joanna's main interest are neurodegenerative disorders and looking for a therapeutic tools, which would help to slow down the course of the disease.

Session on: Epilepsy & Seizure Disorders and Neuroimaging & Brain engineering

Session Chair
Dennis J. Dlugos
University of Pennsylvania School of Medicine, USA

Session Co-Chair
Lynda El-Hassar
Yale School of Medicine, USA

Session Introduction

Title: KCNT1 epileptic encephalopathy – phenotype, genotype, precision therapy
Dennis J. Dlugos, University of Pennsylvania School of Medicine, USA

Title: Modulators of Kv3 channels regulate firing rate and temporal accuracy of auditory brainstem neurons in a mouse model of Fragile X syndrome
Lynda El-Hassar, Yale School of Medicine, USA

Title: De novo status epilepticus is associated with adverse outcome: An 11-year retrospective study in Hong Kong
Hoi Ki Kate Lui, Tseung Kwan O Hospital, Hong Kong

Title: Association of cognitive and motor functions with brain network in elderly
Shuhei Yamaguchi, Shimane University, Japan

Title: Local alpha block as a new tool in neuromagnetic studies
Victor Vvedensky, Kurchatov Inststute, Russian Federation

Title: Importance of medical device usability studies and image analysis measurement techniques
Michael Luedtke, Johnson & Johnson, USA

Title: Diagnosis and treatment of late-onset pompe disease in the middle east and north africa region
Fatimah Alqarni, King Abdullah bin Abdulaziz University hospital, Saudi Arabia

Title: Prevalence of orthostatic hypotension in patients with Restless legs syndrome
Bilgehan Atilgan ACAR, Sakarya University Faculty of Medicine, Turkey

Title: The field of emergence as a model for determining potentiality of linguistic fuzzy sets
Albekov Nurvadi, Chechen State University, Russia

Title: Cellular models of Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) reveal mitochondrial dysfunction and cytoskeletal reorganisation
Paul Chapple, Queen Mary University of London, UK

Title: Medication-overuse headache in elderly
Turkan ACAR, Sakarya University Faculty of Medicine, Turkey

KCNT1 Epileptic encephalopathy– Phenotype, Genotype, Precision therapy

Dennis Dlugos MD*, Mark Fitzgerald MD/PhD, Margaret O'Brien BS, Ingo HelbigMD, David Bearden MD
University of Pennsylvania School of Medicine, USA

Epilepsy of infancy with migrating focal seizures (EIMFS) is a severe infant-onset epileptic encephalopathy, often caused by mutations in the KCNT1 gene, and standard treatments are ineffective.The cardiac anti-arrhythmic drug quinidine is a partial antagonist of KCNT1, making it a candidate drug for treatment of EIMFS. An existing in-vitro model has documented gain-of-function and quinidine responsiveness in recurring human KCNT1 mutations(Milligan C et al. Ann Neurol 2014). Since 2014, case reports of patients with EIMFS indicate asometimes dramatic, but not universal, reduction in seizures and developmental improvement following treatment with quinidine (Bearden D et al. Ann Neurol 2014; Mikati et al. Ann Neurol, 2015). An international KCNT1 registry is in place to gather structured data on EIMFS phenotypes, genotypes and treatment response.

During the presentation:

- The phenotypic and genotypic spectrum of EIMFS and KCNT1 will be reviewed, including strategies for and importance of early diagnosis.
- The pros and cons of quinidine use in EIMFS will be discussed, as well as steps for further study of the safety and efficacy of quinidine in EIMFSas a prototype of precision medicine in epilepsy.
- Both unique and generalizable clinical, genetic and study design features of EIMFS-KCNT1 and other epileptic encephalopathies will be highlighted.

Audience take away:

- The program will help clinicians more efficiently and confidently approach the diagnosis and treatment of epileptic encephalopathies in general, using EIMFS-KCNT1 as an example.
- The program will help researchers, including drug designers, see the opportunities and challenges in the study of epileptic encephalopathies and precision medicine, using EIMFS-KCNT1 as an example.
- The program will provide an example of the opportunities and challenges with re-purposing existing drugs for treatment of rare disorders.
- The program will facilitate discussion of how precision medicine clinical trials in epilepsy can be designed.
- The program will facilitate discussion of managing patient and caregiver expectations in the era of potential, but unproven, precision therapy for epilepsy.

Biography

Dennis J. Dlugos, MD, is Professor of Neurology and Pediatrics in the Perelman School of Medicine at the University of Pennsylvania; and Director, Pediatric Regional Epilepsy Program at The Children's Hospital of Philadelphia (CHOP). He received his MD from Columbia University College of Physicians and Surgeons, New York. He went on to complete his internship in Pediatrics at the National Naval Medical Center, Bethesda, Maryland; a residency in Pediatrics at Thomas Jefferson University, Philadelphia, Pennsylvania, and Alfred I. duPont Institute, Wilmington, Delaware; a residency in Neurology / Child Neurology at the University of Pennsylvania Medical Center and CHOP; and his fellowship in Epilepsy and Clinical Neurophysiology, CHOP. He is a member of the American Epilepsy Society, and serves as Chair of the Education and Professional Development Committee. Dr. Dlugos serves as Vice-President of the Epilepsy Study Consortium, which is dedicated to improving the quality of epilepsy clinical trials. His clinical and research interests include epilepsy genetics and pharmacogenetics, clinical trials, epilepsy surgery, and intensive-care EEG monitoring. Articles authored or co-authored by Dr. Dlugos have been published in Neurology, Annals of Neurology, Lancet Neurology, Epilepsia, Nature, the New England Journal of Medicine, and other journals. Dr. Dlugos has been NIH-funded since 2001, and has mentored 25 pediatric epilepsy fellows. He has lectured extensively throughout the US, in Europe and Asia.

Modulators of Kv3 channels regulate firing rate and temporal accuracy of auditory brainstem neurons in a mouse model of Fragile X syndrome

L. El-HassarPhD*, L. Song Phd, G. Alvaro PhD, C. H. Large PhD, L. K. KaczmarekPhD.
Yale School of Medicine, USA

Fragile X syndrome (FXS) is the most common form of inherited intellectual disability. In common with autism, FXS is characterized by hypersensitivity to many types of sensory stimuli, including environmental sounds. Our previous work has shown that mice lacking the gene for FMRP (Fmr1-/y or Fragile X mice) have abnormally elevated levels of Kv3.1 potassium currents ("high threshold" K+ currents) and significantly decreased levels of Na+-activated K+ currents in auditory brainstem neurons in the medial nucleus of the trapezoid body (MNTB). Both of these changes in K+ currents are predicted to increase the firing rate of the postsynaptic neurons and to substantially degrade the accuracy of timing of action potentials. Consistent with this, we have found that the firing pattern of MNTB neurons in response to stimulation is severely abnormal in Fragile X mice. The threshold for action potential generation is significantly reduced in Fragile X mice over that in wild type mice. Moreover, in contrast to MNTB neurons from wild type animals, sustained depolarization triggers repetitive firing rather a single action potential at the onset of a stimulus pulse. We have also found that wave IV of the Auditory Brainstem Response (ABR) recorded in vivo is significantly enhanced in Fragile X mice, suggesting that loss of FMRP alters central processing of auditory signals. Based on these results we are now testing, in Fragile X mice, the physiological effects of potential therapeutic compound, AUT2, which modulate the activity of Kv3 family channels in cell lines. We found that, in Fragile X mice, AUT2 improved the accuracy of timing of action potentials in response to repetitive stimulation, presumably by shifting the activation curve of high threshold potassium currents to hyperpolarizing potentials, thereby increasing the low threshold potassium currents and restoring the accuracy and the timing of action potentials.

Audience take away:

- This work will help provide alternative strategies to cure symptoms of fragile syndrome.
- The results presented here will help the audience to think about alternative mechanisms to rescue deficits observed in brain disorders.
- This is typically the type of research that could be useful for teaching as it illustrates how deficit in a single protein can alter neuronal function through different pathways and mechanisms.
- This work can create collaborations with pharmaceutical companies in order to develop clinical trials.

Ultimately, this finding suggests that pharmaceutical modulation of Kv3.1 currents represents a novel avenue for manipulation of neuronal excitability, and has the potential for therapeutic benefit in the treatment of hearing disorders.

Biography

Lynda El-Hassar is a research scientist working currently at Yale School of Medicine in the Neurobiology and Pharmacology departments. As electrophysiologist in brain slices of rodents, she focuses her research on the functional reorganization of voltage-gated potassium channels, ionotropic and metabotropic glutamatergic receptors involved in neurological disorders such as Epilepsy, Schizophrenia abd Fragile X syndrome.

De novo status epilepticus is associated with adverse outcome: An 11-year retrospective study in Hong Kong.

Hoi Ki Kate Lui* , Kwok Fai Hui, Wing Chi Fong, Chun Tak Ip Hiu, Tung Colin Lui.
Tseung Kwan O Hospital, Hong Kong

Theclinical characteristics of Chinese adults patients presenting with status epilepticus to intensive care units were be discussed. A retrospective review was performed on patients admitting to the intensive care units with status epilepticus (SE) over a 11-year period from 2003 to 2013 in Hong Kong. A total of 87 SE cases were analyzed. The mean age of patients was 49.3 (SD 14.9).Twenty four subjects (21 %) hadbreakthrough seizure, which was the commonest etiology for status epilepticus. Seventy eight subjects (90 %) had convulsive status epilepticus (21 %) and 9 subjects (10%) had non-convulsive status epilepticus (NCSE) on presentation. The 30 day mortality rate of all subjects was 18.4 %. Older age was an independent predictor associated with poor outcome (odds ratio 1.08, 95 % confidence interval, CI 1.03 to 1.13). There were significantly more patients without history of epilepsy developing non-convulsive status epilepticus (15.5 % Vs. 0 %, p=0.03). Besides, those without history of epilepsy were more likely to have poor outcome upon discharge (56.9% Vs. 24.1 %, p=0.004).

Conclusions: For patients admitting to intensive care units presenting with status epilepticus, there were significantly more patients without history of epilepsy developing non-convulsive status epilepticus, and those without history of epilepsy were more likely to have poor outcome upon discharge. Older age was an independent predictor associated with poor outcome. Continuous EEG monitoring would help identifying NCSE and potentially help improving clinical outcomes.

Audience take away:

The key findings of this retrospective review will be stressed

- De novo status epilepticus is associated with higher risk of developing non-convulsive status epilepticus.
- De novo status epilepticus is associated with poorer outcome.

Biography

Dr. Lui is a neurologist currently working in Tseung Kwan O Hospital in Hong Kong. She graduated from the Chinese University of Hong Kong and received neurology training in Hong Kong at Queen Elizabeth Hospital and Tseung Kwan O Hospital. She was awarded the Hospital Authority Corporate Scholarship for her post-fellowship overseas training in epilepsy in Massachusetts General Hospital, Boston, USA. She completed certification in Neurosonology (Carotid Doppler) from the American Society of Neuroimaging. In addition to being a council member of the Hong Kong Epilepsy Society, she is also a member of the editorial board of Neurological Disorder and Epilepsy Journal.

Association of cognitive and motor functions with brain network in elderly

Shuhei Yamaguchi
Shimane University, Japan

Aging is associated with deterioration in a number of cognitive functions. Many studies have demonstrated the beneficial effect of physical fitness on cognitive function, especially executive function. The graph theoretical approach models the brain as a complex network represented graphically as nodes and edges. In this study, we analyzed several measures of executive function, an index of physical fitness, and resting-state functional magnetic resonance imaging data from healthy elderly volunteers to examine the associations among executive function, cardiorespiratory fitness, and brain network properties. The topological neural properties were related to the level of executive function and/or physical fitness. Global efficiency, which represents how well the whole brain is integrated, was positively related, whereas local efficiency, which represents how well the brain is functionally segregated, was negatively related, to the level of executive function and fitness. The associations among executive function, physical fitness and topological resting state functional network property appear related to compensation and dedifferentiation in older age. A mediation analysis showed that high-fit older adults gain higher global efficiency of the brain at the expense of lower local efficiency. Our data suggest that physical fitness may be beneficial in maintaining executive function in healthy aging by enhancing the efficiency of the global brain network.

Audience take away:

- The audience would understand the beneficial effects of physical exercise on executive functions in elderly.
- I will also illustrate how this beneficial effect emerges through enhanced efficiency of functional connectivity of the brain.

This presentation will give the utility of graph theory for analyzing the complex brain network obtained from resting state BOLD signals using MRI.

Biography

Shuhei Yamaguchi, MD. PhD. is a Chairman and Professor of the department of Neurology and a Dean of Faculty of Medicine, Shimane University. He also has an appointment of the Director of Shimane Dementia Center.

Dr. Yamaguchi's research interest focuses on understanding brain functional changes associated with aging and dementia processes, and developing novel approach of functional brain imaging on behavioral and emotional alterations after brain damage by degenerative or vascular insults. He is also engaged in a cohort research regarding lifestyle and risk factors for stroke and dementia by means of a brain check-up system.

Local alpha block as a new tool in neuromagnetic studies

Victor Vvedensky
Kurchatov Institute, Russia

High spatial selectivity of multichannel SQUID-magnetometers (MEG) provides opportunity to distinguish contributions of different cortical electric sources into magnetic signals measured around the head. One can extract activity of a single source with specific behavior, when many other cortical areas are busy with their own tasks. MEG detects cortical sources much better than the scalp EEG. Standard procedure requires many repetitions of stimulus to average out spontaneous oscillations and to select the event related signal, which is usually small in comparison with the running brain activity. However, spontaneous activity, where alpha (10Hz) oscillations play the dominant role, is not irrelevant to the task performed by the subject under study. We see many magnetic signals of highest possible amplitude, which are clearly related to the task. Most obvious is the blocking of alpha oscillations for short periods of time during each cycle of repetitive self-paced finger movements. It was seen only in few sensors out of 306 surrounding the head. We observed similar alpha block using visual stimulation with short trains of light flashes imitating alpha spindles. This local suppression of high amplitude alpha oscillations was robust during tens of seconds, though it became invisible during comparable time spans when alpha oscillations in the monitored area virtually disappeared. This pattern of permanent waxing and waning of spontaneous activity was common for all our subjects (about 20). We see that magnetic sensors can monitor task related activity of a certain neural population in a real time, detecting highly reproducible signals during considerable time span. The monitored population is not a single one related to the task, there are others, sometimes invisible for our sensors. We often see trains of waves in the alpha and beta ranges sharply (with millisecond precision) synchronized in several cortical sites. They switch on and off simultaneously, highly resembling alpha block. We believe that the phenomena we observe are manifestations of cortical computations supporting mental activity. MEG is a good tool to study in fine detail these cortical processes.

Audience take away:

- We want to make clear that the comfortable device (MEG) can accurately monitor on line changes in the internal state of the human brain during mental tasks.
- Data, recorded in long experimental sessions, should be processed separately for the periods of time, when brain signals manifest clearly different patterns of spontaneous cortical activity.
- A certain characteristic event in the brain can be most pronounced for some subjects and virtually absent for others. This can be used for the selection of subgroups in the group under study.
- We believe that the measurement techniques have come to the point when the study of statistical properties of the brain signals should be supplemented with the study of dynamic interactions between cortical areas during particular mental tasks on a single-trial basis.

Biography

Born January 28, 1948. 1971 - Graduate of Moscow Institue of Physics and Technology. 1977 - Ph.D. in physics, Kapitza Institute of Physical Problems. From 1980 – senior researcher in the field of magnetic encephalography, Kurchatov Institute, Moscow. Design and construction of SQUID-magnetometers, neuromagnetic measurements, data processing.

Importance of medical device usability studies and image analysis measurement techniques

Michael A Luedtke*, Alan J Dextradeur, Allison H Bedwinek, Joseph A Mowry, Jr., Thomas B Boden Jr., Alexander Arazawa,Patricia D'Aoust, Jogi V Pattisapu and Benjamin Douglass Hoehn.
Johnson & Johnson Company, USA

International medical device development and proper design control methods require formative and summative validation studies. In the past, some company usability studies were conducted with employees and submitted for Regulatory clearance for Medical Devices. Recently, FDA has released guidance documents that clarify such studies are no longer accepted. This is also apparent in similar international regulations and stresses the importance of these validation / usability studies.These studies when coupled with image analysis techniques these qualitative provide measurable quantitative data that can be used to improve medical devices with neurologist, neurosurgeon and health care professional input. Close collaboration with industry, clinicians and researchers is very important to evaluate devices for such use errors prior to launch to avoid product improvement via device recalls.

Audience take away:

The neurologists, surgeons and neuro health care professionals in the audience may not often get a view as to how industry validates their medical devices. They may not also be aware of the new International Regulatory requirementsand the methods usedby Industry. The audience will have a quick review of the regulatory requirements as well as see very tangible examples(use errors observed using medical devices as well as image analysis techniques). This will be a great tour into howneurosurgeons could partner with industry and how we needthis information to develop and improve medical devices prior to launch. As employees may no longer be used as representative populations (as clarified in latest FDA guidance document), this partnership is very critical.

By demonstrating how surgeons could better partner with industry, they can better understand how to help and ensure their feedback is captured in such medical device design studies (in early voice of customer phases) or by helping with summative usability studies (last step before launch) that will ultimately drive better or improve medical device design.

In summary, this talk would highlight the most important International Regulatory Impact to usability studies in device development, image analysis technique examples in combination with surgeon / health care professional usability study outcomes that helpedquantify use errors and help medical device designers to design such use errors away prior to launch.

Biography

Michael Luedtke started his Johnson & Johnson career within J&J Consumer and Personal Products Worldwide (Skillman, NJ) as an intern in 1998. In 2001 he served as a Senior Scientist where he developed and used innovative methodologies to conduct clinical trials that substantiated consumer product safety and effectiveness for the New Technology, Models and Methods and Scientific Affairs departments. He then transitioned into a program manager role managing cross enterprise research teams for Ethicon-Endo Surgery, Ortho Dermatologics and OraPharma and led medical device, imaging and pharmaceutical research projects. In 2010, Michael transitioned to Codman Neuro where he served in various Clinical Research roles of increasing responsibility working on peripheral nerve stimulation (neuromodulation). He then transitioned to serving on product lifecycle and new product development project teams within the Codman Neuro neurosurgical and neurovascular divisions. In November of 2012, he transitioned to Medical Affairs where he served in increasing roles of responsibility and currently serves in the Medical Affairs Medical Operations Life Cycle Management (LCM) as Manager LCM. Michael achieved an MS in Biomedical Engineering (Materials – Tissue Optics) from Drexel University and a BS in Bioengineering (Instrumentation) from Syracuse University. His research and efforts have led to various poster and podium presentations at international meetings, peer reviewed journal publications and a book chapter.

Diagnosis and treatment of late-onset Pompe disease in the Middle East and North Africa region

Fatimah Alqarni
King Abdullah bin Abdulaziz University hospital, Saudi Arabia

Pompe disease is a rare autosomal recessive disorder caused by a deficiency of the lysosomal enzyme alpha-glucosidase. Late-onset Pompe disease has a complex multisystem phenotype characterized by arange of symptoms which has led to underestimate the disease among adult population. Consensus-based guidelines for the diagnosis and treatment of late-onset Pompe disease was created by an expert panel from the Middle East and North Africa (MENA) region, where the relative prevalence of Pompe disease is thought to be high but there is a lack of awareness and diagnostic facilities.These guidelines set out practical recommendations and include algorithms for the diagnosis and treatment of late-onset Pompe disease. In addition, we recently diagnosed the first two patients with Late-onset Pompe disease in the middle east.

Audience take away:

- These consensus recommendations from an expert group set out practical guidelines including algorithms for the diagnosis and treatment of late-onset Pompe disease.
- They detail the ideal diagnostic workup, indicate the patients in whom enzyme replacement therapy should be initiated, and provide guidance on appropriate patient monitoring.

These guidelines will serve to increase awareness of the condition, optimize patient diagnosis and treatment, reduce disease burden, and improve patient outcomes

Biography

- April 10th 2015, Joined King Abdullah bin Abdulaziz University Hospital in Riyadh, Saudi Arabia as neurology Consultant and medical operation director.
- worked as Neurology Subspecialty Consultant, Neuromuscular Disorders and Electrodiagnostic Medicine Consultant , Mitochondrial Medicine consultant, at King Fahad Medical City (KFMC) in Riyadh, Saudi Arabia from August 2011-January 2015.
- Program director of Comprehensive Neuromuscular disorders program at national neuroscience institute in KFMC August 2011-January 2015.
- 2008-2010 completed clinical fellowship in neuromuscular disorders and electro diagnostic medicine from McMaster University, Canada.
- 2010–2011 completed Mitochondrial Diseases clinical fellowship at McMaster University, Canada.
- April 30th 2011 passed American Board of Electrodiagnostic Medicine (ABEM).
- Holding medical education research certificate (MERC).
- Holding master of clinical epidemiology from University of Newcastle, Australia, graduated 2015.
- Project leader of rare disease diagnostic awareness project

Prevalence of orthostatic hypotension in patients with restless legs syndrome

BilgehanAtılganAcar*, MD, Assistant Professor, Department of Neurology, Sakarya University Faculty of Medicine, Sakarya, Turkey.
Turkan Acar, MD, Assistant Professor, Department of Neurology, Sakarya University Faculty of Medicine, Sakarya, Turkey.
Sakarya University Faculty of Medicine, Sakarya, Turkey

Objectives: Patients with primary restless legs syndrome (pRLS) often have signs or symptoms of autonomic failure, including cardiovascular system. Gastrointestinal, sudomotor, thermoregulation, and bladder abnormalities are often reported in Restless Legs Syndrome but there is limited data concerning orthostatic hypotension (OH) in patients with pRLS. The aim of this study was to investigate the prevalence of OH in pRLS patients relative to controls.

Methods: Consecutive adult drug-naive pRLS patients and age- and sex-matched healthy controls were enrolled in the study. Blood pressure was measured first in a supine position and after rests of 3 minutes it was re-measured in seating and standing positions early in the morning. Orthostatic hypotension was considered as a sustained reduction of systolic blood pressure (SBP) of at least 20 mm Hg or diastolic blood pressure (DBP) of 10 mm Hg within these measurements. Diagnosis of pRLS was based on International Restless Legs Syndrome Study Group (IRLSSG) 2012 revised diagnostic criteria for RLS. To rule out secondary causes of RLS blood tests including full blood count, thyroid function tests, serum iron, ferritin, vitamin B12, folic acid, urea, creatinine, electrolytes, glucose and HbA1C levels were performed. Presence of anxiety (by Beck Anxiety Inventory), depression (by Beck Depression Inventory), severity of sleep disturbances (by Pittsburgh Sleep Quality Index) were determined by validated self-reported questionnaires.

Results: The mean age of 88 pRLS (70 women) and 110 control subjects (63 women) patients participated in the study was 50.3±9.3 and 50.1±9.2 respectively. Statistically, there was a significant difference between two groups for the presence of orthostatic hypotension ($p<0.001$), and also PSQI, Beck-A, Beck-D scores were higher in pRLS patients than the control group ($p<0.001$). Orthostatic hypotension, anxiety, depression and also sleep disturbance are significantly frequent in pRLS patients.

Conclusion: In recent studies orthostatic hypotension was found to be associated with increased risk of all causes of death including coronary heart disease, heart failure and stroke. Orthostatic hypotension is a serious finding accompanying to pRLS, needed attention.

Audience take away:

- These findings are remarkable for management of primary restless legs syndrome

Biography

He was born in Erzurum in 1979. He graduated from Medical School of Ankara University in 2004. He completed neurology residency at Ministry of Health, Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey between 2004 and 2009. After his clinical services as a specialist at Karabük State Hospital he worked as a neurologist and instructor at Sakarya University, Medical Faculty, Education and Research Hospital, Sakarya, Turkey and he became an assistant professor (2013) at the same institution. He studied in Neuro-intensive Care Unit at Hacettepe University at 2014. Is a member of World Stroke Organization, Turkish Neurological Society and Turkish Society of Cerebrovascular Diseases.

The field of emergence as a model for determining potentiality of linguistic fuzzy sets

Nurvadi Albekov*, PhD, ZaurKindarov, Doctor of medicine.
Chechen State University, Russia

The article discusses the hypothesis of possibility of determining the fuzzy linguistic sets of communicative situation based on field of emergence. It is assumed that on the base of a communicative situation there caused a field of emergence, which denotes the boundary of structural and semantic model, that prognosticates a verbal form of the communicative situation. The conception "the field emergence" is understood as a unit of a language system, having polidirected universal structure, implying the existence of the core, the center and the periphery. The field of emergence is a semantic reality that emerges as a result of communicative situation on the base of which a certain verbal variants of the communicative situation can be prognosticated.

The cause of the field of emergence is observed in the analysis of different translations of the same text, for any text can be assumed as a model of the communicative situation for the next interpretation. The main task, which is placed in the article is an attempt to determine a fuzzy model, which is capable in maximal degree of probability to calculate the volume of linguistic fuzzy sets at the lexical level, that potentially useful as language material for a modeling a text on the base of the field of emergence.

Based on the fact that the variability of verbal form of communicative situation is strictly individual, the question arises whether it is possible to predict the verbal model of the communicative situation, regardless of the individual, i.e. person. Is it possible to design a fuzzy model of verbal forms of communicative situation in the framework of the field of emergence?

In seeking an answer to the question above indicated, the work was conducted to identify the linguistic potential (in the aspect of the use of lexical units) of the field of emergence, caused on the basis of a particular communicative situation. As a material for our analysis of more than 1,600 various texts were studied on the theme of: love, friendship, work, leisure, school, family etc. In the course of our research, we used the methods of a) statistical calculations, i.e., frequency of use of certain lexical units, the presence in the text of lexical items that are not directly relevant to the topic, the types of syntactic constructions, case method, to determine the extra-linguistic factors, and others.

Audience take away:

The benefit of using the model of field of emergence is that it helps to analyze a communicative situation and with the help of the model of field of emergence it is possible to determine the most effective variant of text to verbalize the communicative situation.

Biography

1988-1993 - Department of Romano-Germanic Philology of the Chechen-Ingush State University, specializing in Teaching English and French. Qualification by diploma is "Philologist, Teacher of English and French". 2009 - defense of the thesis for the degree of Candidate of Philology on the topic: "Emergence as a component of invariantly-variable structures of translated texts" (10.02.19). Work experience: 1993-2003. - Worked in different organizations. 2003-2006 - Assistant Professor of General Linguistics chair philology department of Chechen State University. 2006-2009 - Senior Lecturer of General Linguistics chair, 2009-2015. - Associate Professor of the of General Linguistics chair. From 2015 to present day - Dean of the Foreign Languages department of Chechen State University.

Cellular models of Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) reveal mitochondrial dysfunction and cytoskeletal reorganisation

Teisha Y. Bradshaw, Emma J. Duncan, Lisa E.L. Romano and J. Paul Chapple*
Queen Mary University of London, UK

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is a childhood-onset neurological disease, with pyramidal spasticity and cerebellar ataxia. ARSACS results from mutations in the SACS gene that encodes sacsin, a modular protein with conserved domains that indicate a molecular chaperone linked function.

We have used sacsin knockdown SH-SY5Y cells and ARSACS patient human dermal fibroblasts to investigate the cellular consequences of loss of sacsin function. These analyses initially identified mitochondrial dysfunction as a feature of sacsin null cells. Specifically, we have shown that loss of sacsin impairsoxidative phosphorylation and leads to increased levels of oxidative stress. In elucidating mechanism, we found that mitochondrial recruitment of the fission factor dynamin-related protein 1 (Drp1) is decreased in sacsin null cells. This suggests that impaired Drp1-mediated fission contributes to reduced mitochondrial health in cellular models of ARSACS.

Further investigation of our cellular models identified that loss of sacsin also leads to altered organisation and dynamics of the vimentin intermediate filament (IF) cytoskeleton. This is consistent with the observation that neurons from the sacsin knockout mouse have neurofilament abnormalities (Larivière et al. 2015; Hum Mol Genet. 24:727-39). The vimentin IF is important for maintenance of cellular architecture, and we observed altered organelle distribution in cells without functional sacsin. This included repositioning of lysosomes to a perinuclear localisation, where we also observed accumulation of components of protein quality control systems.

We will discuss how these phenotypes of ARSACS cellular models may be integrated and their relevance to the molecular pathogenesis of this neurodegenerative disease.

Audience take away:

- This talk will raise awareness of the recessive ataxia ARSACS. This disease was initially described in a Canadian population, but patients have now been identified worldwide.
- Knowledge of the ARSACS cellular phenotype will be useful for diagnosing patients with this ataxia. For example, if sequencing of the SACS gene identifies a variant that may or may not be pathogenic, it would be possible to screen patient fibroblasts for the phenotype we describe.

This talk will highlight similarities between molecular pathogenic mechanisms of ARSACS and other neurodegenerative conditions. Being able to cluster neuronal disorders based on common cellular mechanisms is likely to be relevant to the identification of potential strategies for pharmacological intervention. This is particularly relevant for rare conditions like ARSACS.

Biography

Paul Chapple was awarded a PhD by University College London (UCL) in 1997, this investigated the Hsp70 molecular chaperone system in a marine organism. He then worked in the laboratory of Professor Michael Cheetham at the UCL Institute of Ophthalmology, where he researched the cell biology of chaperone proteins involved in neurodegeneration and blindness. In 2004 he moved to the Institute of Psychiatry to work with Dr Jean-Marc Gallo on the Alzheimer's protein Tau. He started his own research group at Barts and The London School of Medicine in 2006 and was made Professor in 2014. His research investigates how chaperone systems are specialised in different cell types and organelles, with a focus on human disease.

Medication-overuse headache in elderly

Turkan ACAR
SakaryaUniversitesi, Turkey

Objectives: Medication overuse headache (MOH) is a type of chronic headache disorder caused by excessive use of acute medications and a public health problem with a worldwide prevalence of 1–2%. Each medication class has a specific threshold. In this study we wanted to demonstrate clinical features of MOH in the elderly patients.

Methods: Data of all patients referred to our outpatient clinic at the University Hospital of Sakarya between January 2016 and January 2017 were retrospectively analyzed. Patients aged 65 years and over with a diagnosis of MOH were enrolled into the study. Demographic data as well as data about use of medication, history of primary headache, have been collected. For the classification of headache types the International Classification of Headache Disorders 3rd edition (Beta version) [ICHD-3 (beta)] were used.

Results: A total of 80 patients (16 male, 20%) were included in the study. Ages were between 65-79 (mean age 68,5). Migraine was the frequent primary headache among the elderly female MOH patients with the ratio of 55 %. Use of combination analgesic was more prevalent (%50) in all patients.

Conclusion: Medication should always be used with care in elderly patients and it should be confirmed that the patients are aware of the treatment. More research on medication use in relation to age is required.

Audience take away:

These findings are remarkable for management of medication overuse headache

Biography

She was born in Kayseri in 1981. She graduated from Medical School of Cumhuriyet University in 2004. She completed neurology residency at Ministry of Health, Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey between 2006 and 2010. After her clinical services as a specialist at Sakarya Yenikent State Hospital she worked as a neurologist and instructor at Sakarya University, Medical Faculty, Education and Research Hospital, Sakarya, Turkey and she became an assistant professor (2017) at the same institution. Is a member of World Stroke Organization, Turkish Neurological Society and Turkish Society of Cerebrovascular Diseases.

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