Conference

TRAUMATIC BRAIN INJURY AND NEUROLOGICAL DISEASES: FROM BENCH TO BEDSIDE

Faculty of Medicine, University of Rijeka, Rijeka, Croatia

March 1-2, 2012

FINAL PROGRAMME AND ABSTRACT BOOK

CONFERENCE

TRAUMATIC BRAIN INJURY AND NEUROLOGICAL DISEASES: FROM BENCH TO BEDSIDE

March 1-2, 2012

Faculty of Medicine, University of Rijeka
Braće Branchetta 20, Rijeka, Croatia

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Novel in vitro models to investigate the acute phase of spinal cord injury

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Moderator: Gordana Župan

II Abstracts

NOVEL IN VITRO MODELS TO INVESTIGATE THE ACUTE PHASE OF SPINAL CORD INJURY

Andrea Nistri

International School for Advanced Studies (SISSA), Trieste, Italy

An acute lesion to the spinal cord triggers complex mechanisms responsible for amplification of the initial damage and its chronicity. In vitro preparations of the rodent spinal cord retain the intrinsic ability to produce locomotor-like discharges from lumbar ventral roots and, thus, offer the opportunity to study the still unclear process of lesion progression in relation to cell number (and topography), and deficit of locomotor-like function. In our laboratory we have set up lesion models based on either excitotoxicity induced by the glutamate agonist kainate, or metabolic distress by applying conditions of oxygen/glucose deprivation. Excitotoxicity is associated with an irreversible loss of locomotor network activity in an all-or-none manner and a limited decrease in the number of spinal neurons, while glia is little affected. Conversely, hypoxic challenge to the spinal cord together with toxic radicals primarily damages white matter cells with deficit (without full suppression) of locomotor network function, while neurons are less vulnerable. These data suggest an early-onset, differential pathophysiology of spinal cord injury depending on the nature of the insult, and outline the need to address distinct metabolic targets to attempt early neuroprotection.

Abstract

MOLECULAR MECHANISMS OF CELL DEATH TRIGGERED BY SPINAL CORD INJURY

Miranda Mladinić Pejatović

International School for Advanced Studies (SISSA), Trieste, Italy

Understanding the pathophysiological changes triggered by an acute spinal cord injury (SCI) is a primary goal to prevent and treat chronic disability with a mechanism-based approach. After the primary phase of rapid cell death at the injury site, secondary damage occurs via autodestruction of unscathed tissue through complex cell death mechanisms that comprise caspase-dependent and caspase-independent pathways. To devise novel neuroprotective strategies to restore locomotion, it is, therefore, necessary to focus on the death mechanisms of neurons and glia within spinal locomotor networks. Using rat neonatal spinal cord as an in vitro SCI model, we have shown that neurons are more vulnerable to excitotoxicity and more resistant to metabolic perturbation, while the opposite holds true for glia. Neurons mainly die because of hyperactivation of poly(ADP-ribose) polymerase-1 (PARP-1) with subsequent DNA damage and mitochondrial energy collapse. Conversely, glial cells die predominantly by apoptosis. It is likely that early neuroprotection against acute spinal injury may require tailor-made drugs targeted to specific cell death processes of certain cell types within the locomotor circuitry

Abstract

TRAUMATIC BRAIN INJURY – TRANSLATIONAL STUDIES IN EXPERIMENTAL MODELS AND HUMAN PATIENTS

Lars Hillered

Division of Neurosurgery, Department of Neuroscience, Uppsala University,

Uppsala, Sweden

In the first part of my talk I will summarize many years of work in our animal models of TBI, and some recent cell culture work, with particular focus on energy metabolic perturbations, molecular injury mechanisms, including oxidative stress and inflammation, as well as neuroprotection and neurorepair.

In the second part I will describe efforts to translate these experimental findings into the neurointensive care setting, focusing on energy metabolic monitoring and biomarker studies in human TBI patients. Finally, a recent line of research aiming at developing robust microdialysis methodology for the study of the human proteome, protein biomarkers of TBI and early clinical drug development will be addressed.

Abstract

MRI MARKERS OF DAMAGE AND RECOVERY AFTER TRAUMATIC BRAIN INJURY IN RAT

Olli Gröhn

A.I.Virtanen Institute, University of Eastern Finland, Kuopio, Finland

Brain has remarkable ability to recover after brain insult. However, brain plasticity launched by TBI cannot be as tightly regulated as during development and may trigger epileptogenesis, which is traditionally defined as the development of epilepsy before occurrence of the spontaneous seizures. However, only relatively small percentage of patients for after traumatic brain injury (TBI) develops epilepsy and it can take 10 years or more until patients have spontaneous seizures. The consequence of this is that clinical trial for possible antiepileptic drug or recovery enhancing substances is practically impossible unless right subpopulation of the patients can be selected and progression of the disease and possible disease modification can be non-invasively monitored. The aim of our work has been to find MRI surrogate markers for different aspects of damage and recovery processes after traumatic brain injury. To achieve this we have used multimodal MRI approach including for example fMRI, diffusion tensor imaging, MEMRI and phase imaging and correlated results with behvioural testing and histology. Our results show that we can detect both structural and functional plasticity launched by initial damage using MRI and indicate that MRI may help in future to individualize treatment of head trauma patients.

Abstract

TRANSFORMING RESEARCH AND CLINICAL KNOWLEDGE IN TRAUMATIC BRAIN INJURY: LESSONS FROM THE NIH TBI COMMON DATA ELEMENTS PROJECT

David O. Okonkwo

Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, USA

Traumatic Brain Injury (TBI) remains one of the greatest unmet needs in medicine and public health. Advances in basic science research in the past 20 years have created new opportunities for targeted therapies for TBI. However, these advances have failed to translate into a successful clinical trial or a new treatment for TBI patients. The TRACK TBI study (Transforming Research and Clinical Knowledge in Traumatic Brain Injury) is a multicenter, prospective collaboration among four U.S. centers to develop test and refine standards in TBI research in four domains: 1. Demographics; 2. Neuroimaging; 3. Biomarkers; and 4. Outcome measures.

The TRACK TBI study represents one of the most extensive TBI efforts ever. The goal is to test and refine standards for data collection suitable for use across the broad spectrum of TBI, to explore novel approaches for TBI classification and outcome, and to engage emerging technology. A unique feature is that it spans the entire range of TBI from mild to severe, from early to late presentation and from infancy to the age of seniors. The lessons learned from the TRACK-TBI study inform future directions of basic science research, lay the foundation for more efficient translational, and establish a framework for successful clinical trials in traumatic brain injury

Abstract

EMPLOYING ALZHEIMER'S DISEASE ANIMAL MODELS FOR TRANSLATIONAL RESEARCH

Fiorella Casamenti

Department of Pharmacology, University of Florence, Florence, Italy

The translational research emphasizes the need for valid animal models of disease to produce new drugs, devices, and treatment options for patients. Spontaneous and experimentally induced animal models of Alzheimer's disease (AD) are mainly used. The best model is probably the aged monkey however, because of the time and cost involved in utilizing this model, most studies have been focused on rodents. AD-related memory deficits and neuropathological features can be partially reproduced by lesioning brain structures essential for learning and memory and by intracerebral injection/infusion of Aß peptides. The success of the developed transgenic mouse models of AD has been dramatic in terms of understanding mechanisms relating to Aβ production, deposition and clearance and in terms of engendering therapeutic strategies. Strategies for evaluating neuroprotection typically involve measurement of markers of disease progression, such as levels of Aβ, plaque and tangle formation in animal models that develop these features. In humans, greater adherence to the Mediterranean diet is associated with reduced risk for AD and polyphenols attenuate AD-like pathology and cognitive deterioration in the transgenic mice. Here, we report on oleuropein aglycon activation of autophagy and reduction of AD-like neuropathological aspects and behavioural deficits in a mouse model of Aß deposition.

MODEL SYSTEMS FOR BIOPHOTONIC IMAGING OF BRAIN REPONSES TO INJURY AND THERAPIES

Jasna Križ

Department of Psychiatry and Neurosciences, Faculty of Medicine, Laval University, Québec, Canada

Abstract

Recently, imaging strategies employing different reporter molecules have been developed to study biological processes as they occur in living animals or as they appear in real time in cell assays. These new technologies are based on sources of light emitted from fluorescent proteins such as GFP or luminescent enzymes (firefly luciferase - Fluc). Following the addition of appropriate substrate (luciferin), luciferase catalyses the cleavage of the substrate luciferin in presence of oxygen and ATP, resulting in the emission of light with broad spectral emission that peaks at 560 nm with substantial fraction of light above 600 nm making it suitable for in vivo imaging. The photons emitted by Fluc reporter activity pass the host tissue and are detectable at the surface with sensitive photo detectors based on a CCD camera. Using this approach in our laboratory we recently generated and validated several new transgenic mouse models of bioluminescence and fluorescence for live imaging of processes associated with CNS injury and repair including inflammation/innate immune response, neuronal stress damage/recovery and neurogenesis. These mice represent unique tools for understanding brain responses to acute and chronic injuries and disease pathology. Furthermore, our recent studies suggest that biophotonic/bioluminescence signals imaged from the live animals can be used as valid biomarkers to screen for novel biocompatible molecules and/or to visualize distinct pathological events and/or therapeutic efficacy.

Abstract

TDP-43 DRIVES NF-KB IN AMYOTROPHIC LATERAL SCLEROSIS

Jean-Pierre Julien

Department of Psychiatry and Neurosciences, Faculty of Medicine, Laval University, Québec, Canada

TDP-43 inclusions are a hallmark of amyotrophic lateral sclerosis (ALS) and dominant mutations in TARDBP, which codes for TDP-43, were reported by several groups as a primary cause of ALS. However, the physiological role of TDP-43 and the pathogenic pathways of TDP-43 abnormalities are not well understood. We have found that TDP-43 and NF-κB p65 mRNA and protein expression is higher in spinal cords if ALS patients than healthy individuals. TDP-43 interacts with and colocalizes with p65 in glial and neuronal cells from ALS patients and mice expressing wild-type and mutant TDP-43 transgenes, but not in cells from healthy individuals or nontransgenic mice. TDP-43 acted as a co-activator of p65, and glial cells expressing higher amounts of TDP-43 produced more proinflammatory cytokines and neurotoxic mediators after stimulation with lipopolysaccharide or reactive oxygen species. TDP-43 overexpression in neurons also increased their vulnerability to toxic mediators. Treatment of TDP-43 mice with withaferin A, an inhibitor of NF-κB activity, reduced denervation in the neuromuscular junction and ALS disease symptoms. We conclude that TDP-43 deregulation contributes to ALS pathogenesis in part by enhancing NF-κB activation, and that NF-κB may constitute a therapeutic target for the disease.

III Speaker info

Speaker info

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SCIENTIFIC INTERESTS

In vivo use of animal models for the discovery of innovative drug targets for the development of new therapeutic approaches in Alzheimer's disease and other neurodegenerative diseases.

Role and modulation of adult hippocampal neurogenesis in young and aged wild type and transgenic mice.

Contribution of autophagy to the maintenance of normal cellular homoeostasis, its changes in neurodegenerative disorders, and the role of aggravating factors such as oxidative stress and ageing on autophagic failure in these pathologies.

Evaluation of drug treatment on neuropathology, behaviour and morphology in animal models of neurodegenerative diseases.

SELECTED PUBLICATIONS

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2. Rosi MC, Luccarini I, Grossi C, Fiorentini A, Spillantini MG, Prisco A, Scali C, Gianfriddo M, Caricasole A, Terstappen GC, Casamenti F. Increased DKK-1 expression in transgenic mouse models of neurodegenerative disease. J Neurochem 2010; 112(6):1539-51.

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5. Luccarini I, Ballerini C, Biagioli T, Biamonte F, Bellucci A, Rosi MC, Grossi C, Fiorentini A, Massacesi L, Casamenti F. Combined treatment with atorvastatin and minocycline suppresses severity in experimental autoimmune encephalomyelitis. Exp Neurol 2008;211(1):214-26.

Professor Olli Gröhn, PhD

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SCIENTIFIC INTERESTS

Development of small animal MRI, especially to detect changes associated with secondary damage, recovery and epileptogenesis after traumatic brain injury.

SELECTED PUBLICATIONS

1. Sierra A, Laitinen T, Lehtimäki K, Rieppo L, Pitkänen A, Gröhn O. Diffusion tensor MRI with tract-based spatial statistics and histology reveals undiscovered lesioned areas in kainate model of epilepsy in rat. Brain Struct Funct 2011;216(2):123-35.

2. Hayward NM, Tuunanen PI, Immonen R, Ndode-Ekane XE, Pitkänen A, Gröhn O Magnetic resonance imaging of regional hemodynamic and cerebrovascular recovery after lateral fluid-percussion brain injury in rats. J Cereb Blood Flow Metab 2010; 31(4):1119-32.

3. Hayward NM, Immonen R, Tuunanen PI, Ndode-Ekane XE, Gröhn O, Pitkänen A. Association of chronic vascular changes with functional outcome after traumatic brain injury in rats. J Neurotrauma 2010;27(12):2203-19.

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5. Immonen R, Kharatishvili I, Gröhn H, Pitkänen A, Gröhn O. Quantitative MRI predicts long-term structural and functional outcome after experimental traumatic brain injury. Neuroimage 2009;45(1):1-9.

Speaker info

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SCIENTIFIC INTERESTS

My long term research interest is dedicated to the understanding of the pathobiology of acute brain injury with particular focus on neurochemical mechanisms and biomarkers of injury, neuroprotection and neurorepair. I did pioneering work introducing cerebral microdialysis as a neurochemical monitoring tool in neurointensive care. As the Director of Uppsala Brain Injury Center (UBIC; www.neuro.uu.se/ubic) and Co-director of the Centre of Excellence Neurotrauma (www.neurotrauma.se/eng) I am currently focusing on translational research to combat Traumatic Brain Injury (TBI), utilizing cell culture and animal models of TBI combined with clinical studies on human TBI patients in the neurointensive care setting.

SELECTED PUBLICATIONS

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2. Marklund N, Hillered L. Animal modeling of traumatic brain injury in pre-clinical drug development-Where do we go from here? Br J Pharmacol 2011;164(4):1207-29 (review).

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5. Hillered L, Vespa P, Hovda D. Translational neurochemical research in acute human brain injury: The current status and potential future for cerebral microdialysis. J Neurotrauma 2005;22:3-41 (review).

Professor Jean-Pierre Julien, PhD

Department of Psychiatry and Neurosciences, Faculty of Medicine, Laval University, Québec, Canada

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SCIENTIFIC INTERESTS

I am recognized mainly for my contributions in the field of neurofilament biology and the neurobiology of amyotrophic lateral sclerosis (ALS). We are currently working on development of immunotherapy for ALS, on elucidating the role of chromogranins in ALS pathogenesis, on development of immunotherapy for ALS, on the generation of new transgenic mouse models of TDP-43 proteinopathies and on the pathogenic pathways of TDP-43 abnormalities.

SELECTED PUBLICATIONS

1. Swarup V, Phaneuf D, Dupré N, Petri S, Strong M, Kriz J, Julien JP. Deregulation of TDP-43 in ALS triggers nuclear factor-κB-mediated pathogenic pathways. J Exp Med 2011;208(12):2429-47.

2. Swarup V, Phaneuf D, Bareil C, Robertson J, Kriz J, Julien JP. Pathological hallmarks of ALS/FTLD in transgenic mice produced with genomic fragments encoding wild-type or mutant forms of human TDP-43. Brain 2011;134:2610-26.

3. Gros-Louis F, Larivière R, Julien, JP. Intracerebroventricular infusion of monoclonal antibody or its derived Fab fragment against misfolded forms of SOD1 mutant delays mortality in a mouse model of ALS. J Neurochem 2010;113:1188-99.

4. Gowing G, Philips T, Audet JN, Robberecht W, Julien JP. Ablation of proliferating microglia does not affect motor neuron degeneration in ALS caused by SOD1 mutations. J Neurosci 2008;28:10234-44.

5. Urushitani M, Abou Ezzi S, Julien JP. Therapeutic effects of immunization with mutant superoxide dismutase in mice models of amyotrophic lateral sclerosis. Proc Natl Acad Sci 2007;104:2495-500.

Speaker info

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SCIENTIFIC INTERESTS

Dr. Križ scientific interest is to study the role of immune system and non-neuronal cells on brain response to acute injuries as well as in the models of chronic neurodegenerative disorders including ALS/frontotemporal dementia. To study these events from the brains of living animals she developed series of biophotonic transgenic models for in vivo analysis of microglial activation/innate immune response, astrogliosis, neuronal stress/. Recent studies from Dr. Kriz laboratory suggest that biophotonic/bioluminescence signals imaged from the brains of live animals can be used as valid biomarkers to screen for novel biocompatible molecules, to visualize distinct pathological events and/or therapeutic efficacy.

SELECTED PUBLICATIONS

1. Swarup V, Phaneuf D, Dupré N, Petri S, Strong M, Kriz J, Julien JP. Deregulation of TDP-43 in amyotrophic lateral sclerosis triggers nuclear factor-κB-mediated pathogenic pathways. J Exp Med 2011;208(12):2429-47.

2. Swarup V, Phaneuf D, Bareil C, Roberston J, Kriz J, Julien JP. Pathological hallmarks of ALS/FTLD in transgenic mice produced with genomic fragments encoding wild-type or mutant forms of human TDP-43. Brain 2011;42(10):2903-9.

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4. Lalancette–Hébert M, Julien C, Cordeau P, Bohacek I , Weng YC, Calon F, Kriz J. Accumulation of dietary DHA in the brain attenuates acute immune response and development of post-ischemic neuronal damage. Stroke 2011;42(10):2903-9.

5. Lalancette-Hébert M, Phaneuf D, Soucy G, Weng YC, Kriz J. Live imaging of Toll-like receptor 2 response in cerebral ischaemia reveals a role of olfactory bulb microglia as modulators of inflammation. Brain 2009;132:940-54.

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SCIENTIFIC INTERESTS

The adult mammalian central nervous system (CNS) has little or no capacity to regenerate: thus, brain or spinal cord injury (SCI) results in severe dysfunction and disability. Damage to the spinal cord, whether caused by injury or disease, cannot currently be repaired by any therapy. To develop therapies for the SCI, animal models are used to study and understand molecular and cellular mechanisms underlying the pathophysiology of SCI and regenerative capacities of mammalian CNS. Particularly, the mechanisms of neuronal cell death after SCI or molecular mechanisms underlying regeneration are studied using neonatal rat or opossum in vitro spinal cord.

SELECTED PUBLICATIONS

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2. Kuzhandaivel A, Margaryan G, Nistri A, Mladinic M. Extensive occurrence of glial apoptosis develops early after hypoxic-dysmetabolic insult to the neonatal rat spinal cord in vitro. Neuroscience 2010;169:325-38.

3. Kuzhandaivel A, Nistri A, Mladinic M. Kainate-mediated excitotoxicity induces neuronal death in the rat spinal cord in vitro via a PARP-1 dependent cell death pathway (parthanatos). Cell Mol Neurobiol 2010;30:1001–12.

4. Mladinic M, Lefevre C, Del Bel E, Digby M. Developmental changes of gene expression after spinal cord injury in neonatal opossums. Brain Res 2010;1363:20-39.

5. Mladinic M, Muller KJ, Nicholls JG. Central nervous system regeneration: from leech to opossum. J Physiol 2009;587(Pt 12):2775-82.

Speaker info

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SCIENTIFIC INTERESTS

Structural and functional changes in spinal networks after experimental lesion.

Electrophysiological and molecular mechanisms of locomotor program generation.

Molecular mechanisms of motoneuron disease.

SELECTED PUBLICATIONS

1. Nasrabady SE, Kuzhandaivel A, Nistri A. Studies of locomotor network neuroprotection by the selective PARP-1 inhibitor PJ-34 against excitotoxic injury to the rat spinal cord in vitro. Eur J Neurosci 2011;33:2216-27.

2. Mazzone G, Nistri A. Delayed neuroprotection by riluzole against excitotoxic damage evoked by kainate on rat organotypic spinal cord cultures. Neuroscience 2011;190:318-27.

3. Nistri A, Taccola G, Mladinic M, Margaryan G, Kuzhandaivel A. Deconstructing locomotor networks with experimental injury to define their membership. Ann NY Acad Sci 2010;1198:242-51.

4. Mazzone GL, Margaryan G, Kuzhandaivel A, Nasrabady SE, Mladinic M, Nistri A. Kainate-induced delayed onset of excitotoxicity with functional loss unrelated to the extent of neuronal damage in the in vitro spinal cord. Neuroscience 2010;168:451-462.

5. Taccola G, Mladinic M, Nistri A. Dynamics of early locomotor network dysfunction following a focal lesion in an in vitro model of spinal injury. Eur J Neurosci 2010;31:60-78.

Professor David O. Okonkwo, MD, PhD

Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, USA

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SCIENTIFIC INTERESTS

David O. Okonkwo, MD, PhD, is associate professor, and clinical director of the Brain Trauma Research Center of the University of Pittsburgh. Dr. Okonkwo's clinical interests are traumatic injuries to the brain and spine as well as scoliosis and spinal deformity. His research endeavors involve developing novel therapeutic interventions for brain and spinal cord injury. He is principal investigator of a nationally funded core center of excellence for traumatic brain injury. Dr. Okonkwo has published more than 60 papers in refereed journals, authored numerous book chapters, and garnered several awards for his scientific research.

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2. Clifton GL, Valadka A, Zygun D, Coffey CS, Drever P, Fourwinds S, Janis LS, Wilde E, Taylor P, Harshman K, Conley A, Puccio A, Levin HS, McCauley SR, Bucholz RD, Smith KR, Schmidt JH, Scott JN, Yonas H, Okonkwo DO. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. Lancet Neurol 2011;10(2):131-9.

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4. Hoh NZ, Wagner AK, Alexander SA, Clark R, Beers SR, Okonkwo DO, Ren D, Conley YP. BCL2 genotypes: functional and neurocognitive outcomes after severe traumatic brain injury. J Neurotrauma 2010;27(8):1413-27.

5. Clifton, GL, Drever P, Zygun D, Okonkwo DO. Multicenter trial of early hypothermia in severe brain injury. J Neurotrauma 2009;26(3):393-7.

Notes