Title of the ISN Sponsored Symposium: Purines: Forgotten Mediators of CNS Injury
Main Meeting: National Neurotrauma Symposium
Locale: Santa Fe, New Mexico USA
Dates: June 28-July 1, 2015

The National Neurotrauma Symposium was one of our more successful meetings with
the number of attendees (627) and abstracts (340) submitted for presentation close to
the highest. The attendees were composed of 148 students/postdocs, 37 exhibitors
and 442 faculty/speakers. A breakdown by country participation is as follows: 22
Canada, 3 China, 8 Finland, 1 France, 3 Germany, 1 India, 1 Israel, 2 Italy, 3 Japan, 1
South Korea, 1 Malaysia, 1 Mexico, 1 South Africa, 2 Sweden, 1 Switzerland, 4 United
Kingdom, 565 USA.

Our ISN sponsored symposium was organized and chaired by Dr. Patrick Kochanek
from the University of Pittsburgh School of Medicine. Our outstanding group of
speakers presented novel and interesting data on purines from a variety of
perspectives. Edwin Jackson, PhD from the University of Pittsburgh gave a talk on
“Role of The 2’,3’-Camp-Adenosine Pathway In Traumatic Brain Injury”. Our second
speaker, Detlev Boison, PhD from the Robert Stone Dow Neurobiology Laboratories,
Legacy Research Institute presented a talk on the “Role of Adenosine in Posttraumatic
Seizures and Epilepsy: A Potential New Target”. Our final speaker for the session was
Michael Schwarzschild, MD, PhD from Harvard Medical School and MassGeneral
Institute for Neurodegenerative Disease presented on “Urate – A Novel Potential
Therapy in CNS Injury and Neurodegeneration”. All three speakers discussed purines
as an emerging area of research in CNS injury. This topic had not been previously
discussed in such detail at the National Neurotrauma Symposium. The session was
well attended, approximately 120 people, and a lively discussion followed each
presentation.

The ISN support of $4200 provided partial reimbursement for all three speakers. The
breakdown of costs were as follows: Domestic Speaker Transportation (flights) = $700 x
3 = $2100, Domestic Speaker Transportation (ground transport) = $100 x 3 = $300,
Speaker Hotel Accommodation (2 nights) = $500 x 3 = $1500, Registration for
conference = $575 x 3 = $1725, Total = $5625.

Abstracts for the session:

ROLE OF THE 2’,3’-CAMP-ADENOSINE PATHWAY IN TRAUMATIC BRAIN INJURY
Edwin Jackson1, Patrick Kochanek2; 1University of Pittsburgh, Pharmacology and Chemical
Biology, Pittsburgh, USA, 2 University of Pittsburgh, Critical Care Medicine, Pittsburgh, USA
Using mass spectrometry, we recently discovered that some tissues generate a positional isomer of 3',5'-cAMP, namely 2',3'-cAMP. Additionally, we established that: 1) the bio-synthesis of 2',3'-cAMP is stimulated by cellular injury; 2) 2',3'-cAMP derives from the breakdown of mRNA; 3) 2',3'-cAMP is exported to the extra-cellular com-partment; and 4) extra-cellular 2',3'-cAMP is metabolized to 2'-AMP and 3'-AMP, which are subsequently metabolized to extra-cellular ade-no-sine. We call this bio-chemical sequence (in-tra-cellular 2',3'-cAMP ⇒ extra-cellular 2',3'-cAMP ⇒ 2'-AMP/3'-AMP ⇒ ade-no-sine) the “2',3'-cAMP-ade-no-sine pathway.” Emerging evidence sug-gests that in-tra-cellular 2',3'-cAMP pro-motes opening of brain mito-chondrial perme-ability trans-ition pores and that extra-cellular ade-no-sine is a key neuro-pro-tective autacoid. Thus we hypo-thesize that the 2',3'-cAMP-ade-no-sine pathway may be an important mecha-nism for pro-lec-tion against neuro-trauma. In support of this concept, we find that neu-rons, oligo-dendro-cytes, astro-cytes, and micro-glia con-vert 2',3'-cAMP mostly to 2'-AMP (with oligo-dendro-cytes being most efficient) and 2'-AMP to ade-no-sine (with micro-glia being most efficient), and knock-out of 2',3'-cyclic nucleotide 3'-phos-phodiesterase (CNPase) attenuates the ability of oligo-dendro-cytes to metabolize 2',3'-cAMP to 2'-AMP. Micro-dialysis experiments in mice demon-strate that traumatic brain injury (TBI; controlled cortical impact) activates the brain 2',3'-cAMP-ade-no-sine pathway; similar experiments in CNPase knock-out mice sug-gest that CNPase is involved in the meta-bolism of endo-genous 2',3'-cAMP to 2'-AMP and to ade-no-sine and pro-vides neuro-pro-tection. In CSF from TBI patients, 2',3'-cAMP is in-creased in the initial 12 hours after injury and cor-re-lates with CSF levels of 2'-AMP and ade-no-sine. We conclude that the 2',3'-cAMP-ade-no-sine pathway exists in the brain and is likely neuro-pro-tective.

ROLE OF ADENOSINE IN POSTTRAUMATIC SEIZURES AND EPILEPSY: A POTENTIAL NEW TARGET

Detlev Boison; Legacy Research Institute, Robert Stone Dow Neurobiology Laboratories, Portland, USA

Brain trauma and related injuries trigger a sequela of events that cause glial activation. Astroglio-sis is a major consequence of traumatic brain injury and as-so-ci-ated with in-creased ex-pres-sion of the major ade-no-sine metabolizing enzyme ade-no-sine kinase (ADK); those changes result in ade-no-sine deficiency as char-acter-istic chronic re-sponse of affected brain areas to a prior injury. In rodent models of neu-ronal injury and epilepsy we have demon-strated that (i) overex-pression of ADK and resulting ade-no-sine deficiency can be a direct cause for epileptic seizures, and (ii) that ade-no-sine deficiency induces changes to the epigenome resulting in in-creased DNA methyl-ation status. Based on those mecha-nisms, ade-no-sine augmentation therapies hold pro-mise for the treat-ment, as well as pre-vention, of post-traumatic epilepsy. Data are pre-sented showing that therapies that recon-struct ade-no-sine homeo-stasis locally (e.g. by ade-no-sine releasing bio-engineered brain implants, or gene therapy) can effectively suppre-ss epileptic seizures in rodent models of epilepsy. Further-more, trans-lent thera-peutic ade-no-sine augmentation affects patho-genic changes of the epigenome (i.e. hyper-methyl-ation of DNA) long-term and thereby pre-vents the de-velop-ment and pro-gression of epilepsy.

URATE - A NOVEL POTENTIAL THERAPY IN CNS INJURY AND NEURODEGENERATION

Michael Schwarzschild; MGH, Neurology, Boston, USA

Urate elevation has recently emerged as a pro-mising and realistic neuro-pro-tective strategy for the treat-ment neuro-degenerative dis-eases and acute neu-ronal injury. Urate (a.k.a. uric acid) circulates at higher levels in humans and other hominoids due to mutations in the gene encoding the urate-catabolizing enzyme urate oxidase (UOX) during primate evolution. Although the in-creased levels now pre-dis-pose humans to urate crystal dis-orders like gout, they likely conferred an evolutionary advantage to our ancestors. The dis-covery that urate has po-tent anti-oxidant pro-perties equivalent to those of ascorbate and is the main source of anti-oxidant capacity in human plasma led to the theory that urate serves as an endo-genous pro-tec-tant against dis-eases char-acter-ized by oxi-dative damage, including Parkinson’s dis-ease (PD). Higher urate has been iden-tified as a robust inverse risk factor for PD and as a favorable pro-gnostic bio-marker among people already diagnosed with PD. Similarly, lower urate levels have been linked to the de-velop-ment or more rapid pro-gression of other neuro-degenerative dis-eases including ALS. Laboratory studies in cellular and animal models of PD have further sub-stanti-ated the
neuro-protective potential of urate, and interestingly have implicated an astrocyte-dependent mechanism through the Nrf2 antioxidant response pathway. Of note, the urate precursor inosine has been found to be improve recovery in animal models of spinal cord and traumatic brain injury (TBI), and both inosine and urate are markedly increased locally after TBI. Based on convergent lines of evidence suggesting that urate may be a mediator as well as a marker for slower disease progression, a randomized double-blind placebo-controlled phase 2 clinical trial of the inosine in early PD was conducted, finding that urate levels in blood and CSF could be effectively, safely and chronically elevated in this population. In parallel, urate itself has been shown to confer protection against acute cerebral ischemia in rodent models of stroke and led to a phase 2 randomized double-blind placebo-controlled phase 2 clinical trial of intravenous urate in the setting of an acute ischemic stroke, with encouraging safety and efficacy results.

**Symposium Chair and Speakers:**

Left to right: Edwin Jackson, PhD, Detlev Boison, PhD, Michael Schwarzschild, MD, PhD and Patrick Kochanek, MD

I would like to thank ISN for sponsoring this exciting session and your support and presence truly enhanced the meeting.

Best regards,

Helen M. Bramlett, PhD