46th Annual Meeting

Atlanta, Georgia – 2015

Tuesday, March 17, 2015

1:00 pm – 3:00 pm ASN Scientific Sessions

Regency V

Symposium S20

Neuron–Oligodendrocyte Interactions in Development and Disease

Chair: Vittorio Gallo

Co-Chair: David Pleasure

S20-01 Bruce Appel
ACTIVITY-BIASED SELECTION OF AXONS FOR MYELINATION IN VIVO

S20-02 Vittorio Gallo
NEONATAL BRAIN INJURY CAUSES ABNORMALITIES IN NEURON-NG2 CELL SYNAPTIC COMMUNICATION

S20-03 David Pleasure
IMMUNE-MEDIATED DEMYELINATION AND NEURONOPATHY IN AN AUTOIMMUNE MULTIPLE SCLEROSIS MODEL

S20-04 Jeff Rothstein
OLIGODENDROCYTE SUPPORT OF NEURONS AS A BASIS FOR NEURODEGENERATION INITIATION

Regency VI

Symposium S21

Glia Amino Acid Transporters in Health and Disease

Chair: Arturo Ortega

S21-01 Georgi Gegelashvili
FUNCTIONAL CROSS-TALK BETWEEN DIFFERENT SYSTEMS OF GLUTAMATE TRANSPORT AND METABOLISM IN THE SPINAL CORD

S21-02 Farrukh Chaudry
THE SLC38 FAMILY OF GLUTAMINE TRANSPORTERS AND THEIR CONTRIBUTION TO THE GLUTAMATE/GABA-GLUTAMINE CYCLE

S21-03 Arturo Ortega
GLAST-DEPENDENT CONTROL OF THE GLUTAMATE/GLUTAMINE SHUTTLE: MOLECULAR TARGETS OF POLLUTANTS

S21-04 Michael Aschner
GPR30 REGULATES GLUTAMATE TRANSPORTER GLT-1 EXPRESSION IN RAT PRIMARY ASTROCYTESITLE

Hanover C, D

Symposium S22

Calpain Inhibitors in Preclinical Models of Neurodegenertion and Neurotrauma

Chair: Naren Banik

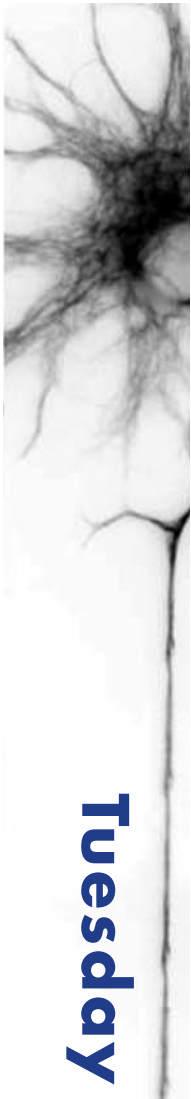
Co-Chair: Supriti Samantaray

S22-01 Kathryn Saatman
EFFECTS OF CALPAIN INHIBITION IN TRAUMATIC BRAIN INJURY AND AXONAL DEGENERATION

S22-02 Yoshiyuki Tamada
ISCHEMIA ACTIVATES CALPAINS IN EXPERIMENTAL RETINAL NEUROPATHIES

S22-03 Supriti Samantaray
CHRONIC INTERMITTENT ETHANOL-INDUCED AXON AND MYELIN DEGENERATION IS ATTENUATED BY CALPAIN INHIBITION

S22-04 Isaac Donkor
CALPAIN INHIBITORS: A SURVEY OF COMPOUNDS IN THE PATENT AND SCIENTIFIC LITERATURE



S21 Glia Amino Acid Transporters in Health and Disease

S21-01

FUNCTIONAL CROSS-TALK BETWEEN DIFFERENT SYSTEMS OF GLUTAMATE TRANSPORT AND METABOLISM IN THE SPINAL CORD

Georgi Gegelashvili [1, 2], Ole Jannik Bjerrum [2]

[1] *Ilia State University, Institute of Chemical Biology, Tbilisi, Georgia*

[2] *University of Copenhagen, Drug Design and Pharmacology, Copenhagen, Denmark*

Neurons sensing noxious stimuli and conducting pain signals from periphery to the spinal cord are predominantly glutamatergic. Members of the SLC1A family of high-affinity glutamate transporters, GluTs (GLAST/EAAT1, GLT1/EAAT2, EAAC1/EAAT3, and EAAT4) are differentially expressed in sensory neurons and surrounding glial cells. These plasma membrane proteins together with glutamate/cystine exchanger, xCT, are responsible for fine tuning of glutamate concentrations at glutamate receptors and, thus, modulation of excitatory signalling in the spinal cord. Several compounds, believed to affect high-affinity glutamate transport system, including therapeutically promising beta-lactams, have been examined in an *in vivo* model of neuropathic pain. Both pain behavior and glutamate transporter expression have been investigated in this model at various time-points. For the first time, changes in the expression of rare splice variants of glial glutamate transporter GLT1 have been demonstrated in rats with induced neuropathic pain. The dynamics of expression of high-affinity glutamate transporter subtypes and pattern of nociceptive pointed at complex relations between the functional state of glutamate transport system and the levels of analgesia provided by the tested compounds. The glutamate transport system has been also studied in co-cultures of dorsal root ganglion (DRG) neurons and spinal glial cells. In this *in vitro* model system, that partially recapitulates primary pain signaling path, both glial and neuronal glutamate carrier proteins undergo changes in expression, as well as post-translational modifications, including proteolytic truncation. Such regulated cleavage depends on phosphorylation state of intracellular domains of glutamate carrier proteins. These functional modifications alter cell surface targeting of glutamate transporters, as well as elicit downstream signaling. This also affects GluT interaction with other components of the glutamate sensing- and metabolizing machinery, including mechanisms of refilling and recycling of synaptic vesicles in DRG neurons and spinal glia. The elucidated regulatory pathways seem to provide fine tuning of excitatory signaling in the spinal cord and, can, thus, emerge as prospective drug targets for chronic pain treatment.

S21-02

THE SLC38 FAMILY OF GLUTAMINE TRANSPORTERS AND THEIR CONTRIBUTION TO THE GLUTAMATE/GABA-GLUTAMINE CYCLE

Farrukh Chaudhry

University of Oslo, Institute of Basic Medical Sciences, Oslo, Norway

Replenishment of the fast neurotransmitters glutamate and GABA in the central nervous system has been enigmatic. According to the glutamate/GABA-glutamine cycle (GGG cycle) hypothesis glutamate and GABA are released exocytotically and activate their specific receptors. Such neuronal signaling is terminated by transport of the neurotransmitters out of the synaptic cleft by specific plasma membrane transporters to a large extent into astroglial cells. Here they are converted to glutamine which is then shuttled back to the nerve terminals for resynthesis of these neurotransmitters. Although existence of such a cycle is widely accepted, the transport of glutamine across astroglial and neuronal membranes has eluded characterization and regulation of the GGG cycle remains unknown. We have provided compelling evidence that the system N transporters SN1 (Slc38a3) and SN2 (Slc38a5) mediate Na^+-dependent transport of glutamine which is coupled to counter-transport of H^+. This makes the transport electroneutral and allows these transporters to work in both directions. In particular, it allows SN1 and SN2 to release glutamine from astroglial cells. The homologoues system A transporters SAT1 (Slc38a1) and SAT2 (Slc38a2) are localized on the cell membranes of GABAergic and glutamatergic neurons, respectively, and mediate Na^+-dependent transport of glutamine. As this is not coupled to counter-transport of H^+ such electrogenic transport is unidirectional and allows for accumulation of glutamine in neurons for resynthesis of GABA and glutamate. We now show that the complementary expression of the system A and system N transporters is widespread and allows for intercellular and interorgan shuttling of glutamine to sustain glutamine metabolism involved in a variety of pathways. Furthermore, we show that the activity and membrane trafficking of the transporters of the Slc38 family are dynamically regulated by ions and intracellular phosphorylation events with potential impact on neurotransmitter synthesis and synaptic plasticity.

S21-03