Az SZTE Kutatóegyetemi Kiválósági Központ tudásbázisának
kiszélesítése és hosszú távú szakmai fenntarthatóságának megalapozása
a kiváló tudományos utánpótlás biztosításával”

Elméleti Orvostudományok Doktori Iskola

IBRO International Workshop

January 20, 2012

Pain mechanisms: hot topics

Professor Gábor Jancsó

TÁMOP-4.2.2/B-10/1-2010-0012 projekt

A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

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ÚJ SZÉCHENYI TERV

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Amazing TRP cation channels: sensors, pain and malady

Professor Bernd Nilius

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MAGYARORSZÁG MEGÚJUL

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The cortical representation of pain

Professor Rolf-Detlef Treede

TÁMOP-4.2.2/B-10/1-2010-0012 projekt

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Anandamide of primary sensory neuron origin

Professor István Nagy

TÁMOP-4.2.2/B-10/1-2010-0012 projekt

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Activation of meningeal TRPV1-expressing chemosensitive afferents - a mechanism contributing to the pathophysiology of headaches

Dr. Mária Dux

MAGYARORSZÁG MEGÚJUL

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Predominant expression of insulin receptors in visceral primary afferent neurons and their co-localization with the capsaicin receptor

Dr. Péter Sántha

TÁMOP-4.2.2/B-10/1-2010-0012 projekt

MAGYARORSZÁG MEGÚJUL

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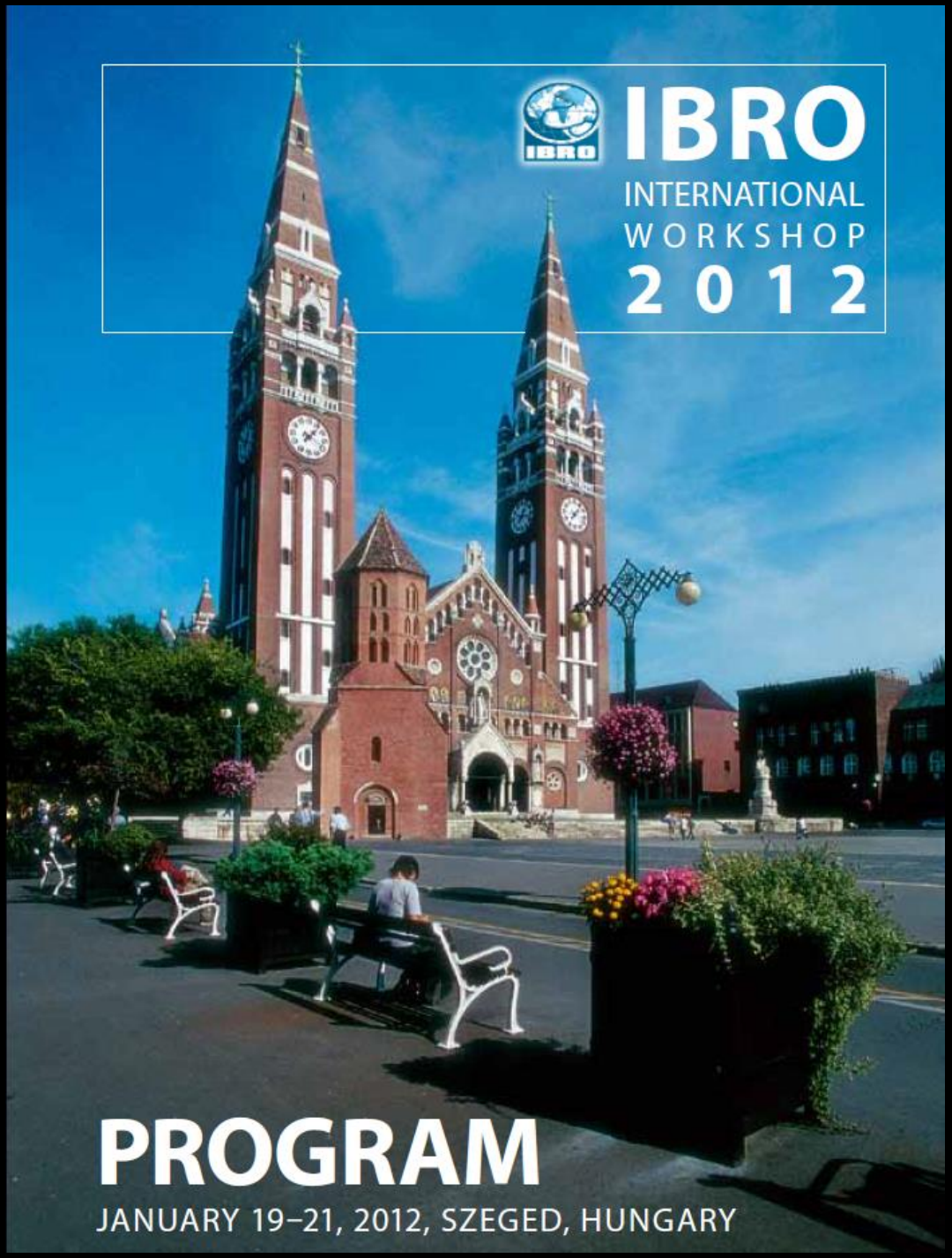
IBRO
INTERNATIONAL
WORKSHOP
2012
PROGRAM
JANUARY 19–21, 2012, SZEGED, HUNGARY


January 19, Thursday
January 20, Friday
January 21, Saturday
mounting posters
opening 9:30 – 10:00
symposium #1: 'Cortical Circuits in the Service of Time' organized by: Péter Somogyi 10:00 – 13:05
János Szentágothai Memorial Lecture: Wolf Singer
cofee break 10:05 – 11:05
symposium speakers: Sonja Hofer Rafael Yuste Carl Petersen Thomas Klausberger
sandwich lunch and poster session #1 13:05 – 14:30
plenary lecture 14:30 – 15:15 Peter Jonas
symposium#2 'The Impact of Next Generation Neurobiologist' organized by: Gábor Tamás László Siklós 15:15 – 17:35
symposium speakers: Judit Makara Csaba Fekete Andrea Lőrincz János Szabadics Tibor Hajszán Árpád Dobolyi Viktor Szegedi
cofee break 17:35 – 17:55
plenary lecture 17:55 – 18:40 László Zaborszky
MITT assembly
removing posters
free program 20:00 –
mounting posters
symposium #3: 'Pain Mechanism: Hot Topics' organized by: Gábor Jancsó 9:00 – 12:15
sandwich lunch and poster session #2 12:15 – 14:15
symposium #4: 'Retinal Degeneration and Rescue' organized by: Róbert Gábriel 14:15 – 18:00
MITT assembly 18:00 – 18:45
removing posters
banquet reception 20:00 – 23:00
plenary lecture 9:00 – 9:45 Bernd Nilius
cofee break 9:45 – 10:15
symposium speakers: Sally N. Lawson Rolf-Detlef Treede István Nagy Mária Dux Péter Sántha
plenary lecture 14:15 – 15:00 Ernst Bamberg
cofee break 15:00 – 15:30
symposium speakers: Róbert Gábriel Enrica Strettoi Jens Dübel Krisztina Szabadfi Viktória Dénes Tibor Ertl
symposium #5: 'Yin-yang Properties of the Stress Regulation' organized by: Dóra Zelena 9:00 – 12:15
closing remarks 12:15 – 12:30
sandwich lunch and free program 12:30 –
plenary lecture 9:00 – 9:45 Daniela Ježová
cofee break 9:45 – 10:15
symposium speakers: Tamás Kozicz Dóra Zelena Ludmila Filaretova Nela Pivac

January 20, 2012 (Friday)

ÚJ SZÉCHENYI TERV

09:00 – 12:15 **SYMPOSIUM #3:** PAIN MECHANISMS: HOT TOPICS

Organized and chaired by **Gábor Jancsó** (Department of Physiology, Faculty of Medicine, University of Szeged, Szeged, Hungary) (Sponsored by the TÁMOP Program)

MAGYARORSZÁG MEGÚJUL

A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

SYMPOSIUM #3

PAIN MECHANISMS: HOT TOPICS

Synopsis by GÁBOR JANCSÓ

There are only few areas of neuroscience research to the development of which the contribution of Hungarian neuroscientists, initiated by the work of Nicolas (Miklós) Jancsó on the unique pharmacological actions of capsaicin, has made such a decisive impact than the field of pain research. Investigations into the molecular mechanisms of the actions of capsaicin have led to the discovery of its receptor, the transient receptor potential vanilloid type 1 (TRPV1) receptor. This observation has opened up the way to the identification of a number of related ion channels which play pivotal roles not only in the mechanisms of pain sensation but also in diverse biological phenomena in health and disease. The speakers of this symposium will cover some of the intriguing aspects of the functions of nociceptive primary afferent neurons, the nociceptive and non-nociceptive functions of ion channels of the TRP superfamily and the cortical representation of pain.

Keynote Speaker: Nilius, Bernd
Laboratory of Ion Channel Research, Department of Molecular Cell Biology, Katholieke Universiteit Leuven, Leuven, Belgium

Amazing TRP cation channels: sensors, pain and malady

Transient Receptor Potential (TRP) cation channels are unique cell sensors responding to a plethora of gating stimuli. The TRP superfamily comprises in human 27 channels subdivided into six subfamilies: TRPC, TRPV, TRPM, TRPP, TRPML, and TRPA. The role of TRP channels in the development of pain and inflammation will be shortly described. In more detail, the molecular biology, regulation and the functional impact of TRPA1, a nociceptive and irritant channel, will be discussed. As a novel player in pain and pain management, the "steroid" activated melastatin TRPM3 channel will be introduced. Finally, the role of TRP channels in causing channelopathies will be critically evaluated. It will be demonstrated how TRPV4 plays a surprising role in synaptic plasticity, in pain development but also in some acquired diseases such as painful overactive bladder syndrome, which develops during cystitis and can be successfully treated with selective inhibitors of TRPV4. Surprisingly, many mutations in TRPV4 have been discovered which lead mostly to gain-of-function phenotypes and leading to several human diseases, such as bone diseases (brachyolmia, spondylometaphyseal dysplasia, metatropic dysplasia, …) but also the scapuloperoneal spinal muscle atrophy and Charcot-Marie-Tooth disease 2C, genetically heterogeneous inherited disorders caused by degeneration of peripheral nerves. Finally, the role of TRPA1 channel in a pain syndrome will be evaluated and some unexpected roles of this channel in causing headache will be shown, as well as the dramatic involvement of TRPA1 in the development of neuropathic pain during tumor chemotherapy.

Treede, Rolf-Detlef
Chair of Neurophysiology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

The cortical representation of pain

Pain had long been considered the only sensory modality that would not require cortical activation to be consciously perceived. This concept goes back to an influential paper by Sir Henry Head who published a small case series of cortical and subcortical lesions, of which the subcortical ones had a much larger effect on pain perception than the cortical ones. Whereas this observation is still consistent with current evidence, the conclusion is not. Single neurons that encode noxious stimuli have been recorded in the somatosensory cortex of rats and monkeys, and there is good anatomical evidence for spino-thalamo-cortical projections to the primary and secondary somatosensory cortices in monkey. In humans, evoked potentials in response to nociceptive stimuli have been recorded from S1, S2, insula and the mid and anterior cingulate cortex. Moreover, electrical stimulation in parts of the insula can elicit a very unpleasant pain, and lesions in this region can impair pain sensitivity. Thus, there is plenty of evidence for nociceptive signal processing in the brain of humans and other species. Instead of one unique "pain center", current concepts consider a wide nociceptive network in the brain. Precisely how distributed activity in this network can lead to the conscious perception of a painful experience is not yet understood.

Nagy, István
Department of Anesthetics, Pain Medicine and Intensive Care, Faculty of Medicine, Imperial College London, London, UK

Anandamide of primary sensory neuron origin

The endogenous agent N-arachidonoylethanolamine (anandamide), through acting on two main target molecules, the excitatory transient receptor potential vanilloid type 1 ion channel (TRPV1) and the inhibitory cannabinoid 1 (CB1) receptor, is involved in a series of physiological and pathological events including nociceptive processing in primary sensory neurons which is critical in the development and maintenance of pain of various peripheral origins. Previous findings suggest that the anandamide-evoked activation of TRPV1 and the CB1 receptor may occur predominantly through autocrine signalling in primary sensory neurons. This presentation will first describe, in cultured primary sensory neurons, the expression pattern, and activity, of the enzymes, which have been implicated in anandamide synthesis. Next, data on the effect of exogenous anandamide, and anandamide of primary sensory neuron origin, on TRPV1- and CB1 receptor activity in cultured primary sensory neurons will be presented. Finally, possible approaches to reduce the nociceptive input into the spinal dorsal horn through controlling signalling by anandamide of primary sensory neuron origin will be discussed.

Dux, Mária
Department of Physiology, University of Szeged, Szeged, Hungary

Activation of meningeal TRPV1-expressing chemosensitive afferents – a mechanism contributing to the pathophysiology of headaches

Meningeal nociceptors play a pivotal role in the development, maintenance and mediation of headaches. The aim of our studies was to morphologically identify and functionally characterize the meningeal trigeminovascular nociceptive nerves which express the capsaicin/TRPV1 receptor. Morphological studies using electron microscopy and immunohistochemistry disclosed the existence and tissue distribution of $TRPV1^+$ sensory nerves in the rat dura mater. TRPV1 receptor activation-induced peptide release and subsequent sensory effector/local regulatory responses are fundamental functional traits of chemosensitive nociceptive neurons. Therefore, meningeal vascular reactions were studied to functionally characterize these nociceptive afferent nerves. Measurement of meningeal blood flow with laser Doppler flowmetry in an open cranial window preparation, an accepted modell of experimentally induced headache, has shown that chemical stimulation of meningeal nociceptive fibres by capsaicin at low concentrations elicits a significant vasodilatory response. This response is mediated through a TRPV1 receptor activation-induced release of CGRP from chemosensitive afferent nerves. Higher concentrations of capsaicin (≥ 1 µM) induced dose-dependent constrictions of meningeal blood vessels. The capsaicin-induced vasodilatation was abolished, whereas the vasoconstriction was augmented by prior systemic capsaicin desensitization. The activation of protease-activated receptor 2 significantly enhanced the capsaicin-induced vasodilatation indicating the sensitization of the TRPV1 receptor. Finally, our studies on rats with experimentally induced metabolic and neuropathic disturbances showed marked impairments of meningeal nociceptor functions. In conclusion, our findings provided experimental evidence for the complex vasoregulatory function of trigeminal TRPV1-expressing nociceptive afferents, which may bear implications for the pathophysiology of headaches.

Sántha, Péter
Department of Physiology, University of Szeged, Szeged, Hungary

Predominant expression of insulin receptors in visceral primary afferent neurons and their co-localization with the capsaicin receptor

The neurotrophic effects of insulin and related growth factors are well documented in the central nervous system. Recent findings indicated functional interaction between the insulin receptor (InsR) and the transient receptor potential vanilloid type 1 receptor (TRPV1) co-expressed in a subset of nociceptive primary sensory neurons. To disclose the target specificity of InsR+ capsaicin-sensitive afferents, retrograde labeling of dorsal root ganglion (DRG) neurons and immunohistochemistry were employed. Retrograde labeling, using diamidino yellow, demonstrated that 47±6%, 16±4% and 19±3% of DRG neurons innervating the urinary bladder, skin and muscle, respectively, express the InsR. To demonstrate the co-localization of the InsR with TRPV1 in visceral sensory neurons serving the urinary bladder and the pancreas, biotinylated wheat germ agglutinin (bWGA) or FITC-labeled choleratoxin B subunit (CTB-FITC) was injected into these organs. Retrograde tracing with bWGA, as compared with CTB-FITC, identified significantly higher proportions of TRPV1+ DRG neurons. Co-localizations of TRPV1 with the InsR were observed in 27±5% and 15±3% of neurons labeled retrogradely from the urinary bladder with bWGA and CTB-FITC, respectively. Of bWGA-labeled pancreatic DRG neurons, the proportion of TRPV1/InsR double labeled neurons amounted to 25±4% and 34±5% in the Th9-L1 DRGs and the nodose ganglia, respectively. The proportions of DRG neurons of urinary bladder and pancreatic origin showing co-localization of the InsR with calcitonin gene-related peptide amounted to 23% and 16%, respectively. The present study disclosed a more abundant co-expression of the InsRs with the TRPV1 receptor in visceral primary sensory neurons as compared to somatic ones and suggests that InsR-mediated potentiation of the TRPV1 activation, as observed *in vitro*, may play a distinct role in visceral nociceptive and inflammatory mechanisms.