ISN Symposium Report

20th International Neuroscience Winter Conference

Das Central, Sölden, Austria

11-15 April 2018

The ISN-sponsored symposium **"Molecular Mechanisms of Neuropathic Pain"** was selected as a **Special Interest Symposium** in the program of the **20th International Neuroscience Winter Conference**, which brought together more than 100 neuroscientists and included 50 oral presentations and 25 poster presentations.

Organising Committee

Tobias Bonhoeffer (Germany)

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ISN Symposium: Molecular Mechanisms of Neuropathic Pain

Chairs: Marc Landry, Jenny Gunnersen

Chronic pain arising from nervous system injury or disease, termed neuropathic pain, is debilitating for sufferers, difficult to treat and an enormous societal burden. Sensitization in neuropathic pain is a consequence of maladaptive changes at synapses between peripheral sensory afferent neurons and central dorsal horn spinal neurons after peripheral nerve damage or disease. As a multidimensional experience, pain is also processed and modulated in higher brain structures including cortical areas. These brain circuits underlie the affective component of pain, and patients often suffer from comorbid disorders such as depression. As pain transitions from acute to "chronic" and becomes pathological, maladaptive plasticity not only exacerbates sensory modalities, but also worsens the comorbidities. In this symposium, key aspects of molecular signalling mechanisms underlying pathological plasticity in pain circuits were presented along with progress towards developing more effective analgesics.

Symposium highlights

Michaela Kress (Medical University, Innsbruck, Austria) presented a comprehensive picture of Lipid storage disorders (LSD), inherited metabolic disorders in which harmful amounts of lipids accumulate in particular cells and tissues. Her work focuses on the genetic and associated metabolic causes of Fabry disease (FD), a rare life-limiting multi-organ LSD resulting from α-galactosidase A (α-Gal A, GLA) deficiency. Mutations in the encoding GLA gene lead to progressive lysosomal accumulation of globotriaosyl-ceramide-3 (Gb3) and related glycosphingolipids. Symptoms include severe episodes of pain starting in childhood, increasing autonomic as well as sensory impairment, which reflects damage to small fibers of the peripheral and autonomic nervous systems at older age, and cardiac, renal and gastrointestinal symptoms. The functional deficits in the nociceptive system in humans are largely reflected by corresponding gene expression changes and altered excitability of sensory neurons in dorsal root ganglia (DRG) and brain in a transgenic FD mouse model. Dr Kress's elegant work has implicated elevated serum levels of sphingolipids, particularly sphingosine 1-phosphate (S1P), in the severe pain phenotype of young FD patients through the activation of S1P3 receptors and excitatory chloride conductances in sensory neurons. With increasing age, FD patients develop hyposensitivity to pain stimuli, associated with a loss of small fiber innervation in peripheral target tissues. Murine sensory neurons respond to S1P with a rapid retraction of neurites and growth cone collapse which are associated with the activation of RhoA, ROCK and collapsin response-mediated protein-2 (CRMP2). S1P was also found to modulate synaptic transmission via S1P3. Thus, increased levels of S1P in the brain may contribute to FD- associated cognitive deficits and psychological disorders.

Marc Landry (Bordeaux University, France) reported on his exciting discovery that expression of LIM Kinase1 (LIMK1; a protein kinase responsible for actin polymerization) is controlled by a microRNA, miR-134, that represses LIMK1-mRNA translation. MiR-134 is a negative regulator of dendritic spine volume while LIMK1 has been reported to promote actin polymerization in dendrites. Moreover, LIMK1/cofilin regulates the insertion and trafficking of the AMPA excitatory glutamate receptors (AMPAR) at the synapse. In the spinal cord dorsal horn, miR-134 is preferentially localized in the postsynaptic compartments. qRT-PCR revealed that miR-134 expression is decreased in neuropathic animals (compared to shams), concomitant with an increase of LIMK1. Endogenous miR-134 down-regulation in excitatory post-synaptic compartment limits pain sensitization in neuropathic rats and knocking down miR-134, or overexpressing LIMK1, by intrathecal injection, significantly increases pain withdrawal threshold (decreases pain) in evoked (Von Frey) or spontaneous (dynamic weight bearing) pain behaviour tests. Mechanistically, knocking down miR-134 was shown to limit AMPAR insertion to the plasma membrane of the excitatory post-synaptic density, indicating that this could contribute to the antinociceptive effect of MiR-134 knockdown.

Nigel Bunnett (Columbia University, NY, USA) presented his fascinating work on the continued signalling of G-protein coupled receptors (GPCRs) from endosomes after receptor internalization. He has established, using FRET biosensors to assess signaling in subcellular compartments, that activated and endocytosed substance P (SP) neurokinin 1 receptor (NK1R), calcitonin gene-related peptide (CGRP) calcitonin receptor-like receptor (CLR), and protease-activated receptor-2 (PAR2) have major influences on pain transmission. Of great interest to the audience, Dr Bunnett has devised lipid-conjugated antagonists with the ability to selectively inhibit endosomal GPCR signalling and blunt nociception by preventing sustained excitation of

pain-transmitting neurons. Thus, endosomal GPCRs can generate compartmentalized signals that underlie complex pathophysiological events in vivo, and GPCRs in endosomes are a viable therapeutic target.

Ipek Yalcin (University of Strasbourg, France) described how chronic pain often leads to anxiety and depression. Among cortical areas, the anterior cingulate cortex (ACC, areas 24a and 24b) appears to be important for mood disorders, including for the anxiodepressive consequences of neuropathic pain. Dr. Yalcin has demonstrated that a lesion of the ACC prevents both chronic pain-induced anxiodepressive-like behaviours and the aversiveness of ongoing pain while optogenetic activation of pyramidal neurons within the ACC is sufficient to induce anxiodepressive-like behaviors in naive mice. Dr. Yalcin also presented details of molecular mechanisms contributing to the comorbidity of chronic pain and mood disorders.

Jenny Gunnersen (University of Melbourne, Australia) reported on recent findings that the neuronal surface protein Sez6 contributes to synaptic gain-of-function in spinal cord dorsal horn neurons in neuropathic pain. In Sez6 knockout mice, heat hyperalgesia developing after chronic constriction injury of the sciatic nerve was effectively abolished and mechanical allodynia was attenuated. TrpV1-dependent activity in spinal cord dorsal horn was reduced after CCI although this reduction was seen in both Sez6 KO and control mice. In the brain, the injury-induced increase in mature dendritic spines in the prefrontal cortex seen in controls was not observed in Sez6 KO mice. These results indicate that blocking Sez6 function after peripheral nerve injury could prevent the development of hyperalgesia and pathological plasticity in ascending pain pathways.

The symposium was well-attended, given that this Special Interest Symposium was scheduled in a less-than ideal time slot (in the middle of the main period of free time when most delegates were taking advantage of the perfect skiing conditions). We estimate that there were 20 people in the audience at the symposium and those that did attend were clearly interested and engaged, evidenced by their enthusiastic participation in question time.

Feedback from Symposium Attendees

Dr Kai Kummer, Division of Physiology, Medical University of Innsbruck

“I attended the ISN Symposium on “Molecular mechanisms of neuropathic pain” held at the International Neuroscience Winter Conference 2018 in Sölden, Austria. The speakers presented their most recent experimental results thereby providing insights in more or less all the different fields of pain research, spanning from endosome signaling and lipid storage disorders to microRNAs. Especially the talk from Prof. Ipek Yalcin on changes occurring in the brains of neuropathic pain mice showed from how many different angles the molecular mechanisms underlying pain can be approached. All in all an inspiring and very well organized symposium.”

Mr Miodrag Mitric, PhD Student, Neuroscience - Medizinische Universität Innsbruck

“The symposium "Molecular mechanisms of neuropathic pain”, organised as part of the WNC 2018 in Soelden, was a special interest session discussing molecular and functional consequences of pain

chronification. Employing animal models of neuropathic pain, M. Landry drew attention to the role of non-coding RNAs in pain processing while the Gunnersen Lab highlighted Sez6 family as synaptic amplifiers of neuropathic states. On a different note, M. Kress presented a link between pain and lipid storage disorders, while I. Yalcin discussed affective aspects of chronic pain. Particularly fascinating was the talk of N. Bennett, revealing endosomal GPCRs as regulators of pain transmission in the spinal cord, and identifying them as a new potential target for therapy. In summary, a disease oriented symposium accompanied by lively discussions and diverse scientific approaches."

Ms Floriane Louboutin, Research Ingénieur, Poncer/Renner Lab, Sorbonne Université, Paris, France

"A recent focus of my research is neuropathic pain and I was particularly interested to attend this ISN Symposium on this topic. I found the presentations and discussions with the speakers very stimulating and I was inspired to take my research in new directions."

Financial Report

We are extremely grateful to the ISN for partially supporting the travel and accommodation expenses of our speakers, enabling diverse representation from 4 countries in 3 continents. The total expenses to be reimbursed to speakers and funded by the ISN Symposia Award are shown below:

Michaela Kress	Transport	0 €
	Accommodation Das Central	
	200 €/night (4 nights)	800 €
Marc Landry	Transport	0 €
	Accommodation Das Central	
	215 €/night (5 nights)	1075 €
Nigel Bunnett	Transport - flight tickets and	
	shuttle transport	1150 €
	Accommodation Das Central	
	200 €/night (5 nights)	1000 €
Ipek Yalcin	Transport - flight tickets and	
	shuttle transport	220 €
	Accommodation Das Central	
	206.33 €night (3 nights)	619 €
Jenny Gunnersen	Transport - flight tickets, train	
	and shuttle transport	833 €
	Accommodation Das Central	
	200 €/night (4 nights)	800 €

Total expenses for ISN-Session speakers: 6500 € 8000 $