brain changes and (vi) disruption of the brain default mode network. In a third part of this talk I discuss mechanisms of endogenous pain modulation.
Supported by the German Research Network "Neuropathic Pain Syndromes" (German Federal Ministry of Education and Research, BMBF).

## C4. Complex Regional Pain Syndrome: From Human Model to the Clinic

### 71
### WORKSHOP SUMMARY: COMPLEX REGIONAL PAIN SYNDROME: FROM HUMAN MODEL TO THE CLINIC

T.S. Staehelin Jensen[1], A.J. Terkelsen[2], A. Dickenson[3]. *[1]Danish Pain Research Center, Aarhus University Hospital, Aarhus, [2]Aarhus University Hospital Neurology & Danish Pain Research Center, Aarhus, Denmark; [3]University College London Department of Neuropharmacology, London, UK*

Complex Regional Pain Syndrome (CRPS) type I and II are as the name indicate complex conditions with unclear pathology and unsolved underlying mechanisms. The main clinical characteristics of CRPS are: spontaneous pain, hyperalgesia, movement disorders with bradykinesia, tremor and dystonia, edema, autonomic and trophic changes in skin and adjacent subcutaneous and muscle tissue. Symptoms and objective findings are localized distally in limbs but the distribution of symptoms and signs does not correspond to the innervation territory of any specific nerve. Troels S. Jensen will present the main clinical characteristics of CRPS and link them to findings with pure nerve injury and discuss similarities and differences between CRPS and neuropathic pain. The lack of human models for CRPS may be one of the reasons for our ignorance in understanding the pathohysiology of CRPS. Dr. Astrid Terkelsen will present a human forearm immobilization model mimicking some of the features seen in CRPS. This model induces signs and symptoms of CRPS with movement-induced pain, increased hair growth, cold and mechanical hyperalgesia and reduced capsaicin induced pain and flare. These symptoms are discussed in relation to central symptoms in CRPS. Over the last years interesting findings have emerged showing how tissue or nerve injury may induce spinal plasticity (central sensitization), which alters sensory transmission and sensorimotor processing in the spinal cord and is associated with disinhibition. Anthony Dickenson wil give an overview of the main elements of central sensitization including wind-up and long term potentiation and how these can be targeted pharmacologically. In a final debate the audience is invited to contribute to a pathophysiological discussion of the CRPS syndrome.

### 72
### THE CLINICAL CHARACTERISTICS OF COMPLEX REGIONAL PAIN SYNDROME

T.S. Staehelin Jensen. *Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark*

Complex Regional Pain Syndrome (CRPS) type I and II are conditions with unclear pathology and unsolved underlying mechanisms. The main characteristics of CRPS are: spontaneous pain and evoked pain with hyperalgesia, allodynia, movement disorders including bradykinesia, tremor and dystonia, edema, autonomic and trophic changes in skin and adjacent subcutaneous and muscle tissue. Symptoms and objective findings are localized distally in limbs but the distribution of symptoms and signs does not correspond to the innervation territory of any specific nerve or nerveroot. The CRPS condition has both peripheral and central changes. The peripheral changes are manifested in part by inflammatory reactions along vessels, by the presence of inflammatory cells in skin and subcutaneous tissue and by alterations in neuropeptides. The central changes is seen for example by changes in the processing of somatic stimuli and by the fact that the initial trauma is in deep somatic structures while the accomanying skin phenomena must be induced by central changes. As in several other chronic pain conditions there is an interaction between peripheral and central mechanisms in generating CRPS and one single pathophysiology is unlikely to exist. The similarities and differences between nerve injury pain and CRPS may perhaps provide important information about underlying mechanisms.

### 73
### CENTRAL SENSITIZATION

A. Dickenson. *Neuroscience, Physiology, Pharmacology, University College London, London, UK*

Within the spinal cord, a number of changes underlie central sensitization whereby the response to a given input is increased by central spinal mechanisms. One first stage in this process seems to involve calcium channels that are essential for transmitter release onto spinal neurones – gabapentin and pregabalin act on these changed channels. This increase in transmitter release leads to greater levels of activation of spinal receptors and increased neuronal excitability.
In the spinal cord, the release of peptides and glutamate causes activation of the N-methyl-D-aspartate (NMDA) receptor for glutamate in persistent pain states which, in concert with other spinal systems, generates spinal hypersensitivity.
Activation of the NMDA receptor underlies 2 key processes, wind-up and long term potentiation (LTP). The former is an increase in neuronal responses to a given constant stimulus – this is also known as temporal summation. If the input continues, the responses remain elevated. Wind-up is induced by C and A-delta fibre inputs but once produced, enhances all responses, including those to low threshold inputs. Once the peripheral input declines, there is a slow return in neuronal responses back to baseline. Here, blocking peripheral drives should attenuate central sensitization. LTP is a longer lasting version of wind-up where a high frequency C-fibre input now produces hours of excitability, an event that persists even though the input is terminated. Genes that are implicated in memory processes add to the neuronal changes and many intracellular processes are altered.
Spinal neurones that become hyperexcitable show reduced thresholds, increased receptive field sizes and ongoing stimulus independent activity as well as greater evoked responses. This activity is a likely basis for the allodynias, hyperalgesia and spontaneous pains seen in patients since many of these spinal neurones project to higher centres of the brain. Ketamine blocks the NMDA receptor complex and use of NMDA antagonists has been a useful tool for demonstration of NMDA receptor mediated hypersensitivity in patients with post-operative, tissue damage, neuropathic and recently, CRPS pains. Understanding downstream events beyond the surface receptor or designing drugs that act on sub-types of the NMDA receptor may improve the clinical acceptability of drugs that block this sensitization.

### 74
### A HUMAN EXPERIMENTAL IMMOBILIZATION MODEL AND COMPLEX REGIONAL PAIN SYNDROME

A.J. Terkelsen, T.S. Jensen. *Department of Neurology and Danish Pain Research Center, University Hospital of Aarhus, Aarhus, Denmark*

The mechanisms responsible for inducing and maintaining Complex Regional Pain Syndrome (CRPS) are still unclear, and the lack of human models for CRPS has been an obstacle in further studying the underlying mechanisms. Several observations suggest that limb immobilization could be one contributing factor, since the patients have often been immobilized prior to the development of CRPS and often do not use the affected extremity and maintain it in a

protective posture to avoid evoked pains. Moreover, preliminary findings in healthy subjects and experimental observations in animals suggest that immobilization may play a role in CRPS [1–3]. To further investigate the role of immobilization on regional sensory and autonomic functions in healthy subjects, a human forearm immobilization model was introduced [4,5]. Healthy volunteers were included and wore a circular scaphoid cast for four weeks. The immobilization model induced transient signs and symptoms of CRPS with movement-induced pain, increased skin temperature, hair growth, cold and mechanical hyperalgesia and reduced capsaicin-induced pain and flare. The immobilization did not affect the sympathetically mediated vascular tone or heat pain thresholds. The overlapping features between CRPS and immobilization-induced findings in normal volunteers raise the possibility that immobilization may play a role in at least elements of CRPS.

However, immobilization does not explain all symptoms in CRPS, which is also underlined by new results that point towards a global autonomic disturbance in CRPS (Terkelsen et al. submitted). To further understand the mechanisms inducing and maintaining CRPS, it is important to combine the results from both human and animal models of CRPS.

**Reference(s)**

[1] Butler S, Nyman M, Gordh T. Immobility in Volunteers Transiently Produces Signs and Symptoms of Complex Regional Pain Syndrome. In: Devor M, Rowbotham M, Wiesenfeld-Hallin Z, editors. Proceedings of the 9th World Congress on Pain, Progress in Pain Research and Management. Seattle: IASP Press; 2000. p. 657–60.

[2] Ushida T, Willis WD. Changes in dorsal horn neuronal responses in an experimental wrist contracture model. J Orthop Sci 2001; 6(1): 46–52.

[3] Guo TZ, Offley SC, Boyd EA, Jacobs CR, Kingery WS. Substance P signaling contributes to the vascular and nociceptive abnormalities observed in a tibial fracture rat model of complex regional pain syndrome type I. Pain 2004; 108(1–2): 95–107.

[4] Terkelsen AJ, Bach FW, Jensen TS. Experimental forearm immobilization in humans induces cold and mechanical hyperalgesia. Anesthesiology 2008; 109(2): 297–307.

.Terkelsen AJ, Bach FW, Jensen TS

[5] Experimental forearm immobilization in humans reduces capsaicin-induced pain and flare. Brain Res 2009; 1263: 43–9.

## M4. Sodium Channels in Inherited and Acquired Pain Disorders

### 75
### WORKSHOP SUMMARY: SODIUM CHANNELS IN INHERITED AND ACQUIRED PAIN DISORDERS

S. Dib-Hajj[1,2], G. Strichartz[3], M. Devor[4]. *[1]Neurology & Center for Neuroscience and Regeneration Research, Yale School of Medicine, [2]Rehabilitation Research Center, VA Connecticut Healthcare System, West Haven, CT, [3]Anaesthesia, Harvard Medical School Brigham and Women's Hospital, Boston, MA, USA; [4]Department of Cell & Developmental Biology, Institute of Life Sciences and Center for Research on Pain/The Hebrew University of Jerusalem, Jerusalem, Israel*

Human studies have revealed a critical role of voltage-gated sodium channels in pain states. We will present data from molecular, cellular and electrophysiological approaches highlighting the role of sodium channel $Na_v1.7$ in pathophysiological aspects of afferent hyperexcitability in inherited painful neuropathies. We will also discuss modeling and pharmacological studies in animals which provide testable hypotheses regarding: **1**) the contribution of specific channels, or components of sodium conductances, to neuronal excitability and **2**) responses of pain states to pharmacological treatments. This evidence validates voltage-gated sodium channels as promising targets for future therapeutic intervention. **S. Dib-Hajj** will discuss characterization of gain-of-function mutations of $Na_v1.7$ from patients with two hereditary pain syndromes: inherited erythromelalgia and paroxysmal extreme pain disorder. He will also discuss modulation of $Na_v1.7$ gating properties by ERK1/2 MAPK. Together with the dynamic regulation of this channel in diabetic and inflammatory pain models in rodents, and its accumulation within painful neuromas in humans, these data provide compelling evidence that $Na_v1.7$ acts as a threshold channel in DRG neurons and suggest that it may act as a rheostat that sets the gain on pain. **G. Strichartz** will discuss mechanistic aspects for selectively abolishing abnormal nerve impulses by a non-selective sodium channel blocker, lidocaine. Results from both experiments on isolated nerves, where a small fraction of fast-gating sodium channels is acutely converted to a slow-inactivation mode by pharmacological treatment, and from computer simulations, suggest an underlying mechanism for this clinical phenomenon. These findings should be useful for mechanistic understanding and for the directed development of drugs that target the electrophysiological "fingerprint" for abnormal pain rather than a particular type of ion channel. **M. Devor** will discuss the emergence of repetitive firing capability in injured afferents and numerical simulations which highlight an altered spectrum of sodium conductances as a potential inducer of membrane resonance, subthreshold oscillations and enhance repetitive firing. The data focus attention on a small delayed sodium current component which occurs at a latency of about 2–20 msec, which is distinct from "persistent" sodium currents, and which might be associated with a variety of different sodium channel isoforms. Selective suppression of this current component might normalize exaggerated repetitive firing in injured afferents and hence resolve neuropathic pain, without interfering with normal impulse propagation.

### 76
### $NA_V1.7$ IS A THRESHOLD CHANNEL FOR PAIN

S. Dib-Hajj[1,2], S. Waxman[1,2]. *[1]Neurology & Center for Neuroscience & Regeneration Research, Yale School of Medicine, [2]Rehabilitation Research Center, VA Connecticut Healthcare System, West Haven, CT, USA*

Neuropathic pain is associated with hyperexcitability of dorsal root ganglion (DRG) neurons, and is in many cases unresponsive, or only partially responsive, to pharmacotherapy. First-line drug treatments of neuropathic pain, including sodium channel blockers, often manifest serious side effects which limit clinical efficacy. Thus, there has been considerable interest in targeting pain-related molecules that are expressed within peripheral DRG neurons. Voltage-gated sodium channel $Na_v1.7$ is preferentially expressed within DRG and sympathetic ganglion neurons, and its gating properties permit amplification of small, slow depolarizations. $Na_v1.7$ has recently been shown to play a key role in acquired and inherited human pain syndromes, making this channel a desirable target for pain treatment.

$Na_v1.7$ was previously shown to be up-regulated in DRG neurons in animal models of diabetic neuropathy and inflammation, conditions that involve activation of mitogen-activated protein kinases, p38 and ERK1/2. Recently, we have shown that Nav1.7 co-accumulates with p38 and ERK1/2 at axon endings in painful human neuromas. We have now shown that activated ERK1/2 phosphorylates the channel and modulates its voltage-dependence of activation and inactivation, consistent with a contribution of this channel to injury-induced neuronal hyperexcitability.

Two sets of autosomal dominant $Na_v1.7$ gain-of-function mutations linked to distinct pain syndromes have recently been identified. $Na_v1.7$ mutations that hyperpolarize activation (thus making it easier to activate the channel), slow deactivation (keeping the channel open longer), and increase the ramp response to small depolarizations cause Inherited Erythromelalgia, a disorder characterized by searing, burning pain in distal extremities in response to mild warmth (entering a warm room, putting on