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Plenary Abstracts

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The efficacy of SCS as a treatment of chronic neuropathic pain has improved during more than 40 years of clinical use. SCS has the advantage of being minimally invasive and reversible. Also, an even-less invasive screening trial offers evidence of treatment outcome before implantation in individual patients. The best results occur when the right equipment is correctly implanted in appropriately selected patients by experienced clinicians. In neuropathic pain states, activation of peripheral nerve fibers increases the activity of wide dynamic range neurons in the superficial laminae of the corresponding dorsal horns, which, in turn, causes hyperalgesia and/or allodynia. SCS suppresses long-term potentiation of these wide dynamic range dorsal horn neurons by reducing the C-fiber response. SCS also changes the concentration of several neurotransmitters and their metabolites in cerebrospinal fluid. Among the common neuropathic pain indications for SCS are failed back surgery syndrome (FBSS), peripheral nerve injury (e.g., postherpetic neuralgia and CRPS), stump neuroma pain, phantom limb pain, and post-herpetic neuralgia. Patient-rated pain relief is the usual primary outcome criterion, with “success” commonly defined as a minimum 50% relief. In the first RCT of SCS versus reoperation in FBSS patients, 45 subjects (90%) were available for a mean follow-up of 3 years. SCS success was 9/19, whereas reoperation success was 3/26. Only 5/24 subjects randomized to SCS crossed to the opposite treatment versus 14/26 randomized to reoperation. In an international multi-center RCT (the PROCESS study), 100 subjects with FBSS were randomized to conventional medical management (CMM) or SCS plus CMM. By 6 months, the subjects randomized to SCS achieved significantly greater pain relief and improved functional capacity and health-related quality of life than did those randomized to CMM. The investigators followed the 42 subjects randomized to SCS who actually received SCS for 24 months and found significantly improved leg pain relief, functional capacity, and quality of life. In the RCT on the use of SCS plus physical therapy versus physical therapy alone to treat reflex sympathetic dystrophy (CRPS), only two-thirds of the subjects randomized to SCS received implants. Nevertheless the intent-to-treat analysis showed significant improvements in pain intensity and global perceived effect in the SCS group versus the physical therapy group. The initial cost of an SCS system notwithstanding, several cost-effectiveness analyses have demonstrated that the total cost of health care for patients with neuropathic pain is lower for SCS than for alternative treatments. In a cost study based on data from the first 40/42 (of 50) patients enrolled in the RCT of SCS versus reoperation every analysis (intention-to-treat, treated-as-intended with cross over counted as failure of randomized treatment, and final treatment) showed that SCS achieved economic dominance by being more effective and less expensive. An evaluation of the cost of SCS versus physical therapy, compared costs before and after treatment and projected costs to life expectancy. The initial year disadvantage for SCS was eliminated by analysis to expected time of death, which yielded a mean as-randomized cost per patient of 171,153 Euro in the SCS group versus 229,624 Euro in the physical therapy alone group. These investigators concluded that, in addition to being a more effective therapy for CRPS, SCS becomes cost effective after 3 years. In 2008, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom conducted a systematic review and technology assessment of the use of SCS that assumed a battery life of four years. In the case of SCS versus CMM and versus reoperation for FBSS and SCS versus CMM for CRPS, the model predicted that SCS would produce additional quality-adjusted life years at a cost the health service would be willing to pay. Despite their higher initial cost, the new long-life rechargeable systems should improve cost-effectiveness by reducing the cost and potential morbidity associated with battery replacements.
MOTOR CORTEX STIMULATION (MCS) FOR NEUROPATHIC PAIN: CAN WE PROCEED FROM PHENOMENOLOGY TO MECHANISMS?

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Motor cortex stimulation (MCS) is relatively recent neurosurgical technique for pain control, the use of which is growing steadily since its description in the last decade. While clinical series show that at least 50% of patients with chronic, pharmacoresistant neuropathic pain may benefit from this technique, the mechanisms of action of MCS remain elusive. In this talk we will synthesise a number of studies that, combining electrophysiology and functional imaging, have permitted to proceed from phenomenology to models that may account for part of such mechanisms. MCS appears to trigger rapid and phasic activation in the lateral thalamus, leading to a cascade of events of longer time-course in medial thalamus, anterior cingulate/orbitofrontal cortices and periaqueductal grey matter. Activity in these latter structures is delayed relative to actual cortical neurostimulation and becomes maximal during the hours that follow MCS arrest. Current hypotheses suggest that MCS may act through at least two mechanisms: activation of perigenual cingulate and orbitofrontal areas may modulate the emotional appraisal of pain, rather than its intensity, while top down activation of brainstem PAG may lead to descending inhibition toward the spinal cord. Recent evidence also points to a possible secretion of endogenous opioids triggered by chronic MCS. This, along with the delayed and long-lasting activation of several brain structures, is consistent with the clinical effects of MCS, which may also last for hours or days after MCS discontinuation.

Non-invasive magnetic stimulation of the motor cortex (rTMS) has also proved analgesic in placebo-controlled, double-blind studies. Although the magnitude of the analgesic effect has been so far insufficient to consider rTMS as a stand-alone therapy for neuropathic pain, a positive effect of high-frequency rTMS may predict a good effect of subsequently implanted MCS. It is unknown whether the mechanisms underlying analgesia by magnetic and electric motor cortex stimulation are comparable. Recent evidence suggests that both methods converge in activating structures related to high-order, motivational aspects of the pain experience, but other mechanisms including plastic changes in the cortical representation of the painful territories may also play a role.
PERIPHERAL SODIUM CHANNELS AS GATE-KEEPERS FOR PAIN

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Normal pain is essential for survival whereas pathological pain is maladaptive, often does not respond to pharmacotherapy. Hyperexcitability of peripheral nociceptors underlies the majority of inflammatory and neuropathic pain conditions. Even pain that originates centrally, for example spinal cord injury, may also have a peripheral component. Thus, therapeutic intervention at peripheral targets may ameliorate chronic pain.

Signal transduction along the pain-signaling axes is dependent upon voltage-gated sodium channels. Three of the nine sodium channels, Na\textsubscript{v}1.7, Na\textsubscript{v}1.8 and Na\textsubscript{v}1.9, are only expressed in peripheral neurons, with Na\textsubscript{v}1.8 and Na\textsubscript{v}1.9 restricted to sensory neurons. Several lines of evidence support the conclusion that these channels play a critical role in pain states. First, animal studies have causally linked altered expression and modulation of Na\textsubscript{v}1.7, Na\textsubscript{v}1.8 and Na\textsubscript{v}1.9, within sensory neurons, with development of pain. Second, these three channels regulate firing of action potential in DRG neurons with Na\textsubscript{v}1.7 and Na\textsubscript{v}1.9 acting as threshold channels, while Na\textsubscript{v}1.8 is critical for robust and high fidelity action potential generation and repetitive firing. Third, gain-of-function mutations of Na\textsubscript{v}1.7 underlie two distinct human pain disorders, while, loss-of-function mutations of Na\textsubscript{v}1.7 channels cause congenital insensitivity to pain but without cognitive, motor, cardiac or most other sensory modalities. Fourth, the co-expression of Na\textsubscript{v}1.7 and Na\textsubscript{v}1.8 appears to be necessary for manifestation of neuronal hyperexcitability induced by gain-of-function Na\textsubscript{v}1.7 mutations. Despite gaps in our understanding of the role of these channels, by virtue of their roles in regulating neuronal firing and their restricted expression within peripheral neurons, specific blockers of these three channels hold the promise of a potentially effective and safe therapy for human pain disorders.
NOVEL OPIOID ACTIONS IN THE SPINAL CORD

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µ-Opioid receptor (MOR) agonists represent the gold standard for the treatment of moderate to severe pain. Opioids are further used for pre-emptive analgesia but paradoxically, opioids may also lead to opioid-induced hyperalgesia (OIH). Recent studies now provide novel insights into the underlying mechanisms at the synaptic level and constitute a rational framework for the clinical use of opioids.

Opioid analgesia: To assess opioid actions on synaptic transmission in pain pathways we used a spinal cord slice preparation. Bath application of MORs (Remifentanil, Fentanyl or DAMGO) all blocked synaptic transmission in C-fibres, mainly by a presynaptic action. The inhibition involved blockage of presynaptic voltage-gated Ca$^{2+}$ channels but not K$^+$ channels and interference with the downstream neurotransmitter release machinery.

Pre-emptive analgesia: Synaptic strength at C-fibres can be potentiated (long-term potentiation, LTP) by peripheral inflammation, trauma or nerve injury, or by direct electrical stimulation of C-fibres$^{2,3}$. LTP at C-fibre synapses is a likely mechanism of some forms of mechanical and thermal hyperalgesia$^4$. Spinal, systemic or bath application of opioids fully prevented LTP-induction by the same conditioning stimuli.

Opioid-induced hyperalgesia: Abrupt withdrawal of MORs after an acute application in vitro and in vivo induced LTP at C-fibre synapses in superficial spinal dorsal horn$^1$. This opioid withdrawal LTP required postsynaptic G-protein coupling and involved rise in postsynaptic [Ca$^{2+}$] via activation of NMDA receptors and via Ca$^{2+}$ release from intracellular stores. Using Ca$^{2+}$ imaging techniques, we could demonstrate that in superficial dorsal horn neurons [Ca$^{2+}$], rises both, during opioid application and/or upon washout. The selective block of [Ca$^{2+}$] rise during opioid withdrawal was, however, sufficient to abolish the induction of withdrawal LTP. When withdrawal was tempered by slowly reducing the infusion rate, no withdrawal LTP was observed. Thus, abrupt, but not tempered withdrawal from opioids may induce LTP in pain pathways by a postsynaptic mechanism. Opioidergic LTP shares pharmacology and signal transduction pathways with OIH and with injury-induced hyperalgesia and provides a novel target to combat OIH without weakening opioid analgesia.

References:


Chronic pain following spinal cord injury is very common and affects approximately 70-80% of the patients. About 35-40% suffers from neuropathic pain. To distinguish neuropathic from nociceptive pain states, the IASP has introduced a mechanism-oriented classification of chronic pains in spinal cord injury (Siddall et al., 2002). Pain below the level of injury, so called below-level pain, is of central origin as a direct consequence of spinal cord damage. Pain at the level of injury, so-called at-level pain, may be a driven by damage of the spinal cord, of the nerve roots or by a combination of both. Central below-level pain seems to be the most serious types of pain and its treatment is often insufficient. Clinically, central pain typically develops with a delay after the initial trauma. The pain is typically localized in an area of abnormal sensitivity corresponding to the preceding central lesion. Being types of neuropathic pain, ongoing pain as well as evoked pains are frequently found in below-level pain as well as in at-level pain.

Pathophysiologically, recent studies indicate that factors which have been already suggested to be involved in peripheral neuropathic pain, such as alterations in expression of sodium channels and inflammatory processes, may play a key role in the development of neuropathic pain after spinal cord injury. It has been demonstrated that a combination of lesioned and residual spinothalamic pathways seems to predict development of central pain (Wasner et al., 2008). Anatomical changes within pain-related regions as well as within regions of the classic reward circuitry, have been identified by recent diffusion tensor imaging studies indicating additional pain-related structural changes at supraspinal level (Gustin et al., 2009).

Pharmacological treatment of neuropathic pain in spinal cord injury is still a great challenge, but evidence points efficacy of pregabalin (grade A), gabapentin, tricyclic antidepressants, lamotrigine and opioids (grade B). Whether interesting new treatment strategies involving imagination of movement have an analgesic effect needs to be evaluated (Moseley, 2007).


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Epidemiology is an important clinical tool in designing and evaluating management and prevention strategies, as well as in assessing and targeting resource requirements. Its aims - to identify incidence, prevalence, distribution and determinants - are particularly relevant to neuropathic pain. However, there is a relative lack of accurate information available. This is for several good reasons, including lack of a gold standard case definition, or means of applying any agreed definition in population-based research. In one sense, neuropathic pain describes a symptom or a mechanism, rather than a specific disease. On the other hand, there may be sufficient similarities in the risk factors, effects and response to treatment between different causes of neuropathic pain to make it worthwhile considering it as one or more distinct conditions. Estimates of overall prevalence that are based on specific causes of neuropathic pain tend to be lower (1% to 2%) than those that are based on reports of the classic symptoms (6% to 8%). While the former is probably an under-estimate, the latter may be an over-estimate, and further methodological research is still needed. Even condition-specific estimates (for example painful diabetic neuropathy, or postherpetic neuralgia) vary considerably between studies. Neuropathic pain of any cause is associated with poor general health, probably more so than non-neuropathic pain of equivalent severity, and is comparable to other severe chronic diseases in this regard. Psychosocial risk factors for neuropathic pain are similar to those for other chronic pain and can be addressed globally; there are, however, important mechanism-based risk factors that need to be considered, with a view to preventing specific causes of neuropathic pain, including painful diabetic neuropathy and postsurgical pain. The importance of newly proposed risk factors, including genetic factors, is still to be assessed at a population level.
PAIN GENES

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A bright blue sky looks about the same to all observers. But in response to noxious stimuli and injuries different people tend to report very different levels of pain. Variability in pain response has traditionally been attributed to psychosocial, cultural and other environmental factors, the main exception being when painful conditions “run in the family”, such as for specific types of migraine headache and certain peripheral neuropathies. New evidence, however, points to an important role for genetics across the spectrum of pain response. Genetic differences among people, both rare mutations and common polymorphisms, can affect the likelihood of acquiring a painful condition. Such differences reflect the action of “disease susceptibility genes”. Other genetic variants appear to influence the amount of pain experienced by different individuals in the presence of an identical injury or disease. Such variation reflects the action of “pain susceptibility genes”. In principle, both types of pain genes can be discovered by studying cohorts of people with contrasting pain response. Such work is challenging, however, given the difficulty of defining the relevant injury, the small effect sizes expected and costs. The discovery of pain susceptibility genes can be facilitated using animal models. The advantage of this approach is that identical injury or disease can be imposed on all subjects, and environmental variables can be controlled. The discovery of pain genes holds out promise both for advancing the understanding of pain mechanisms, and for developing better prognostic, diagnostic and treatment options. But even before this hope is realized, the simple knowledge that “the luck of the (genetic) draw” can affect how pain is experienced ought to reduce the degree to which individuals are stigmatized when they appear to be suffering excessively from a given painful condition.
THE THREAT OF CHRONIC PAIN

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Pain is a biologically relevant and vital signal of bodily threat, which urges the individual to protect him/herself (Eccleston and Crombez, 1999). Immediate protective responses to pain include increased arousal, attention to the sources of threat, and various safety-seeking behaviors including avoidance and escape. Despite this biologically hard-wired system, there are individual differences in how pain is interpreted as threat, and the expression of pain usually is dependent on social context variables and current goals (e.g. Vlaeyen et al., 2009). Also, learning takes place rapidly. In order to reduce the impact of pain, and to facilitate early and effective protection against bodily threat, previously neutral stimuli (interoceptive, proprioceptive or exteroceptive) that somehow are causally related to the threat of pain can receive the propensity to elicit similar defensive responses as well (De Peuter et al., 2009). For example, a previously benign movement that was followed by severe shooting pain will now be avoided (Leeuw et al., 2007; Vlaeyen and Linton, 2000).

Chronic disability may develop when the individual subsequently overgeneralizes the 'movement-threat' knowledge, and starts to avoid various movements and activities, despite medical reassurance about rather innocent causes and the transient character of the pain. Three pathways exist through which such 'threat knowledge' and associated protective responses can develop: observation, verbal instruction, and direct experience. Once acquired, this knowledge representations remain stored in memory, and the extinction of protective responses can only occur through inhibitory processes.

In this presentation, the underlying mechanisms of both the acquisition of pain-related fear responses, as well as the available cognitive-behavioral interventions to extinguish these fears will be reviewed. This will be done from an affective-motivational perspective.

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References:


In an increasing number recent randomized clinical trials of treatments for neuropathic pain, the medications being evaluated did not significantly differ from placebo in the primary efficacy analysis. Prior to these trials, there was considerable reason to believe that these antidepressant, antiepileptic, and other medications would demonstrate efficacy because of encouraging results from earlier preclinical and clinical studies. It is therefore difficult to determine whether these trials were unsuccessful because the medications truly lack efficacy in the conditions studied or whether other factors compromised the ability of these trials to demonstrate benefits of these medications. Understanding and attenuating any factors that adversely impact outcomes of neuropathic pain trials could reduce the risk of failure in demonstrating the benefits of truly efficacious treatments. This presentation will discuss a number of possible explanations for why many recent neuropathic pain trials have been negative. These include: (1) preclinical models and methods and early phase clinical trials are identifying drugs with no or limited efficacy; (2) the recent studies are really failed trials, not negative trials; (3) the wrong conditions were studied; and (4) the response in placebo groups was too great to allow efficacy to be demonstrated. The challenging implications of the results of these recent clinical trials for developing treatment recommendations for patients with neuropathic pain will also be briefly discussed.
Increasingly, for all painful conditions, attention is turning to what constitutes a clinically useful outcome - an outcome that is important, not just one that is measurable. OMERACT, OARSI, IMMPACT, and Cochrane groups are focusing in to this critical question.

Initial work indicates one important thing - that not every patient benefits from a particular treatment, and that in many painful conditions most do not benefit enough. However, we are beginning to see is that those patients whose pain is reduced significantly (leaving the little question of what significantly means for a moment) also benefit in a range of other ways - with improved sleep, being less depressed, and having improved quality of life. Good pain treatment is the key.

So what's a significant pain benefit? It depends - you can choose response (decrease from where you started) or state (where you end up). As long as the pain benefit is big enough, the results can be startling for individuals.

What we can also begin to do is to compare treatments - but the bottom line is that one treatment does not fit all, and that a range of options is needed to be able to get the best results, for the most patients, at the lowest cost, and in the shortest time.
Dr Peter Nathan (1914-2002) was a distinguished British neurologist, who devoted most of his career to clinical and research aspects of pain. An honorary consultant physician, he was appointed a member of the External Staff of the Medical Research Council at the National Hospital for Nervous Diseases (now the National Hospital for Neurology and Neurosurgery) at Queen Square in London, where he remained throughout most of his working life.

He wrote on a number of neurological topics, in particular the bladder and its control, and spasticity, and over the years contributed to various textbooks as well as writing his own account of the nervous system, now in its 4th edition. However, his most notable and pioneering achievements were in the field of pain. He developed probably the first pain clinic for patients with neurological disorders in the UK and introduced acupuncture into mainstream medical practice; with Pat Wall was one of the first to use TENS as a therapy; and was an early advocate of intrathecal phenol in selected patients. His shrewd observations on patients, and his highly original thinking, led to extraordinarily wide-ranging publications on subjects ranging from pain memories to absence of pain due to trance states, and from causalgia to the newly-described syndrome of 'painful legs and moving toes'. Major theoretical publications included a comprehensive and sceptical critique of Pat Wall's gate control theory, which was not entirely well received by Pat. However, Peter Nathan's most enduring contribution has been the clinico-pathological studies he undertook, together with the neuropathologist Dr Marian ('Mai') Smith, on patients undergoing open anterolateral cordotomy for relief of cancer pain. Peter's clinical evaluations before and after surgery were subsequently correlated with the post-mortem anatomical findings in the spinal cord, allowing many of the intrinsic pathways of the human spinal cord to be identified and mapped in a detail never achieved before or since. Amongst the many pathways clarified were those subserving pain, and publications spanning 50 years on these clinico-pathological correlations are considered definitive.

Peter, whose family founded the firm Glaxo which was to grow into today's GSK, was modest, erudite, cultured, and charming. He was a most caring and philanthropic physician who used his personal wealth for the benefit of science and the arts.
WS SUMMARY: INTRAVENOUS APPLICATION OF LOCAL ANESTHETICS FOR THE TREATMENT OF NEUROPATHIES

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Systemic administration of local anesthetics, in particular lidocaine, as analgesic therapy especially for neuropathic pain has a long tradition. In a first part of the workshop the poly-phasic actions of i.v. lidocaine on experimental neuropathic pain, indicating multiple mechanisms of action, will be presented by Gary Strichartz. Tactile allodynia that results from tight ligation of rat spinal nerves (SNL) has become a "classic" model for neuropathic pain. Allodynia can quantitated by measured changes in the paw withdrawal threshold force. Allodynia of the ipsilateral paw is almost fully achieved at 1-2 days after SNL. Intravenous infusion of lidocaine, at 2-3 days after SNL, reveals a 'threshold concentration' for alleviation of allodynia of ~1 ug/mL plasma, and a 'ceiling concentration'², that achieves maximum relief, of ~ 5 ug/mL. Despite the fact that lidocaine’s plasma half-life is 2-3h, allodynia is depressed for many days-weeks. The effects of i.v. lidocaine have been resolved into an acute, transient relief during the infusion followed by a persistent relief that slowly develops over 6-20h after the infusion ends. The acute phase is consistent with effects of lidocaine on abnormal impulses occurring in nerve injury models. The duration of the persistent phase is shorter when lidocaine is infused 7 d after SNL compared to 2 days. These and other observations suggest that an intermediate stage connects nerve injury to pain hypersensitivity, a stage that is selectively susceptible to i.v. lidocaine. We suggest that there is a series of processes that occur in the CNS after peripheral nerve injury that lead to prolonged allodynia and that i.v. lidocaine disrupts one or several of these processes.

The next presentation by Misha Backonja will provide illustrative cases and patients’ series. Individual cases will include illustrations where administration of IV lidocaine provided: a. an aid in narrowing down diagnostic decision making supporting proposed pain mechanisms (case: Gabe - spinal cord AVM); b. treatment option of acute severe neuropathic pain (case: Bryan - post-traumatic neuralgia); c. long term treatment of neuropathic pain with intermittent IV infusions (case: Lana - post-traumatic neuralgia); d. long term treatment of neuropathic pain with intermittent subcutaneous infusions (case: Dan - post-traumatic neuralgia). Patient series include groups of patients treated on trial basis with single infusion sessions either as IV slow push up to 5mg/kg or as single continuous infusions of up to 500 mg/hr.

Finally, an overview of the currently available literature will be presented (Guy Hans).
WS SUMMARY: RADICULAR PAIN. A NEW PERSPECTIVE

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Clinical observations on a group of patients complaining of radicular pain due to an acute herniated disc, both in the cervical or in the lumbar area have drawn the attention on the nature of the symptoms who mimics a Complex Regional Pain Syndrome. In fact these patients beside the traditional description of pain along the arm or the leg with paresthesias, loss of sensation and/or weakness present with allodynia, hyperalgesia, vasomotor changes, skin changes and local sweating. The interesting thing is that in the clinical setting this patients usually don’t respond very well to the traditional epidural or foraminal blocks as they do to sympathetic blocks as well as to a multimodal treatment including anticonvulsants, antidepressants, analgesics and opioids.

The workshop will present to the audience clinical examples and will discuss probable explanations for signs and symptoms as well as to the response to sympathetic block with the hypothesis that in these patients probably the radicular pain is an expression of a Complex Regional Pain Syndrome with the aim to recall the attention of the clinicians to a different protocol of treatment beyond the traditional blocks or pain medication.
WS SUMMARY: PRIMARY HEADACHE SYMPOSIUM

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This symposium is designed to introduce headache both through classification and epidemiology. It is understood that headache might not be the major workload for those interested in Neuropathic pain, however a knowledge of the subject could only be beneficial to the attendees. In migraine and especially Chronic Headache neuropathic symptoms are common and addressing them improves clinical outcomes.

An overview of the epidemiology of headaches and an understanding of what is seen in headache clinics will act as the basis for a review of Headache Theories

Migraine headache is believed to depend on pain signals arising in the meninges. In recent years, it has been discovered that the network of neurons that sense pain signals from the dura, changes rapidly during the course of a single migraine attack and that the treatment of an attack is a moving target. If the pain is not stopped within 10-20 minutes after it starts, the first set of neurons in the network, those located in the trigeminal ganglion, undergo molecular changes that make them hypersensitive to the changing pressure inside the head which explains why migraine headache throbs and is worsened by bending over and sneezing. If the pain is not stopped within 60-120 minutes, the second group of neurons in the network, those located in the spinal trigeminal nucleus, undergoes molecular changes that convert them from being dependent on sensory signals they receive from the dura by the first set of neurons, into an independent state in which they themselves become the pain generator of the headache. When this happen, patients notice that brushing their hair, taking a shower, touching their periorbital skin, shaving, wearing earrings, etc become painful, a condition called cutaneous allodynia. 120-240 min after onset of migraine, the third group of neurons in the thalamus become sensitized and process innocuous sensory signals from the skin all over the body as if they were noxious. When this happens, patients exhibit signs of whole-body allodynia and hyperalgesia. Based on this scenario, the success rate of rendering migraine patients pain-free increased dramatically if treatment is given before the establishment of cutaneous allodynia and central sensitization.

In addition to the prevailing view that migraine headache involves activation of intracranial pain fibers, a neural substrate for mechanisms that enable induction of migraine by stimulation of extracranial nociceptors that innervate head and neck muscles, the periosteum and scalp arteries will be explored.
Recent progress points to an important role of spinal glial cells in facilitating neuropathic pain states after nerve injury and spinal cord injury. Glial cells such as microglia and astrocytes in the spinal cord and brain enhance and prolong neuropathic pain via neural-glial interactions. Upon activation, glial cells produce multiple proinflammatory and pronociceptive mediators, such as cytokines (e.g., IL-1β, IL-18, TNF-α) and chemokines (e.g., MCP-1). These glial mediators can activate on their receptors expressed on nociceptive neurons and powerfully regulate excitatory and inhibitory synaptic transmission, leading to central sensitization. They can further activate other glial cells to produce additional pain mediators. Mounting evidence has shown a critical role of microglia activation for the development of neuropathic pain. However, much less is known about the role of astrocytes in neuropathic pain regulation. Notably, astrocytes make close contacts with synapses and exhibit very persistent changes after nerve and spinal cord injury. Thus, targeting astrocytes may provide new therapies for treating neuropathic pain. This workshop will focus on (1) how astrocyte activation contributes to the persistence of neuropathic pain and (2) how astrocyte-produced mediators regulate neuronal and synaptic plasticity in the pain circuit. Dr. Ji will discuss how astrocytes regulate neuropathic pain via the chemokine MCP-1. Dr. Noguchi will present his research on microglia-astrocyte interaction in neuropathic pain via IL-18. Finally, Dr. Ren will show how astrocytes produce IL-1β to enhance nociceptive neuron sensitivity and promote pain.
Central neuropathic pain remains a notoriously difficult condition to manage successfully. Until recently there has been a dearth of studies on the epidemiology, pathophysiology and therapy of central pain and this has reflected negatively on patient management. Physical disability commonly associated with lesions in the central nervous system has tended to guide the research on both the pathology and treatment. However, as understanding of the relationship between a lesion in the central nervous system and pain has become better recognised, and the high prevalence of the pain acknowledged, there has been a surge of research activity in this type of pain, resulting in some surprising and promising findings.

This workshop will focus on the three most common central neuropathic pain conditions: pain associated with multiple sclerosis, spinal cord injury and stroke. Turo Nurmikko will discuss the assessment and management of dysaesthetic pain and trigeminal neuralgia in MS. Nanna Brix Finnerup will present an overview of recent studies on pathophysiological mechanisms of spinal cord injury pain and discuss its pharmacotherapy on the basis of randomised controlled trials. Roland Peyron will discuss the neurosurgical management of central post stroke pain with an emphasis on the efficacy of motor cortex stimulation and how brain imaging studies performed in conjunction with this treatment have resulted in new insights into this condition.

The attendees will learn about prevailing concepts of pain generating mechanisms, trends in ongoing research and current treatment options for central neuropathic pain. The presentations will be followed by a general discussion led by questions from the floor which are expected to include pragmatic management issues.
This workshop will be chaired by Professor Tesfaye and will have 3 speakers covering recent advances in epidemilogy, pathogenesis and treatment of diabetic peripheral neuropathic pain (DPNP).

The prevalence of diabetes is increasing and this is having a major impact on the burden associated with diabetic complications including diabetic peripheral neuropathy (DPN). Although estimates of the prevalence of DPN vary substantially, depending on diagnostic criteria and the intensity of investigation, most studies suggest that about one-third of diabetic patients are affected. There is now little doubt that poor blood glucose control is an important risk factor for for DPN. Recently, traditional cardiovascular risk factors for macrovascular disease have also been associated with an increased risk of DPN. In contrast, data on the prevalence of DPNP is limited. The risk factors for DPNP are also not known although data from the EURODIAB cohort has suggested that female sex is an independent risk factor. There is relatively little epidemiological data on DPNP, with the prevalence ranging from 6-26%.

There is now strong evidence implicating nerve ischaemia as the cause of DPN. Studies in man and animal models have revealed reduced nerve perfusion and endoneurial hypoxia. Investigations on biopsy material from patients with mild to severe neuropathy show graded structural changes in nerve microvasculature. Arterio-venous shunting also contributes to reduced endoneurial perfusion. These vascular changes strongly correlate with clinical defects and nerve pathology. However, research has failed to identify a characteristic peripheral nerve histological abnormality in DPNP.

In addition the molecular processes leading to DPNP remain unknown. Hyperglycemia induced pathways result in nerve dysfunction and damage, which lead to hyperexcitable peripheral and central pathways of pain. A recent study in has shown that DPN was associated with increased biochemical markers of inflammation and endothelial dysfunction. Furthermore, DPNP was associated with further increase in inflammation and markers of endothelial dysfunction and preservation of the nerve axon reflex. Therefore, inflammation and endothelial dysfunction may be important contributors in the development of DPNP.

Finally, pharmacological treatment of DPNP includes Tricyclic compounds, SNRIs, SSRIs, anticonvulsants, opiates, membrane stabilisers, the antioxidant alpha lipoic acid etc. Over the past 6 years new agents with perhaps less side effect profiles have immerged. Management of the patient with DPNP must be tailored to individual requirements and will depend on the presence of other co morbidities. Combination treatment is the next step but there is limited literature in this regard.
WS SUMMARY: NEUROPATHIC PAIN MANAGEMENT: EFFICACY, SAFETY, COMPLICATIONS OF INTERVENTIONAL TECHNIQUES

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Treatment of chronic neuropathic pain syndromes continues to compose a big problem for patients and doctors. Significant scientific advances in pathophysiologic mechanisms have facilitated the development of targeted pharmacological and interventional treatments.

The treatment algorithm for interventional therapies for neuropathic pain should be; failure of refractory treatments and combination therapy.

Interventional Techniques or Therapies considered for neuropathic pain syndromes are: Neuroablative procedures, Nerve blocks, Percutaneous RF techniques or the new approach of Pulsed Radiofrequency, Neuromodulation Techniques which include Spinal infusion or Intrathecal Drug Delivery (IDD) and Stimulation of the Central Nervous System (CNS) or Peripheral Nervous System (PNS).

Local anaesthetic peripheral and sympathetic blocks provide useful diagnostic information but tend to afford only temporary therapeutic benefits in patients with peripheral neuropathy.

Percutaneous radiofrequency techniques are also used for the palliation of pain in several neuropathic pain syndromes. Recently a new mode of radiofrequency, pulsed radiofrequency (PRF) have been appearing in the literature. PRF was conceived as a novel, potentially safer mode of administration of RF energy. In order to further elucidate the mode of action of PRF and to define its true value in the management of chronic pain, more research on this promising technique is justified.

When these techniques do not sustain adequate pain relief, spinal cord stimulation (SCS) or intrathecal therapy represent reasonable options. The level of evidence supporting this modality remains moderate. Pooled results of a recent systematic review of the SCS literature (one RCT, one cohort, 72 case studies) suggest significant benefit, with 50% or greater improvement in pain relief, in roughly 62.5% of patients.

Long-term intrathecal analgesic therapy (LTIAT) has significantly progressed over the past 25 years. The evidence for implantable intrathecal infusion systems is strong for short-term improvement in pain of malignancy or neuropathic pain. The evidence is moderate for long term management of persistent pain. Future studies are needed to better define the role of LTIAT in persistent pain, especially with respect to which pain conditions or subpopulations of patients are most responsive and which agents or combination of agents are most appropriate. Novel combinations of intrathecal analgesics (e.g. ketamine and clonidine) may deserve future study.

Further clinical studies are needed to evaluate the efficacy and safety of new intrathecal drugs (e.g. ziconotide, gabapentin), the combination of intrathecal drugs, the potential complications of therapy or those related to these devices and the proper selection of patients to receive these treatments.
Neuropathic pain shares some important features with other pathophysiologicals. Obvious examples of shared mechanisms are indicated by shared treatments; antiepileptic agents for example suppress hyperexcitability in neuronal circuits and are therefore effective in the treatment of epilepsy and neuropathic pain. Likewise, antidepressant drugs are able to correct neuropathic pain and depression since both pathophysiology utilise similar neurochemical substrates, namely noradrenaline and 5HT (antidepressants confer analgesic efficacy in the absence of depressive symptoms, and vice versa, but since both pain and depression can be co-morbidly expressed and incite and influence the other, treating either pain or depression can have a positive impact on the other). Other mechanistic analogies are less apparent; cough for example originates in the afferent nervous system and detects and transduces signals by virtue of A- and C-fibres. In its transient form, cough, like pain, serves as a protective reflex that warns of impending or real threats to the organism, yet the system can become sensitised such that cough can be evoked by non-tussive stimuli (akin to allodynia) and thus outlast its biological usefulness to compromise quality of life. In both circumstances, the ‘sign’, be it cough or pain is given more prominence with respect to treatment than the underlying cause, and in their extreme form such signs can be treated with opioid agents such as morphine. Parallels can also be drawn between nausea and nociception since both are unpleasant sensations that subserve biological warning functions, are multifactorial in origin, can be triggered by excessive activation of chemoreceptors and mechanoreceptors and are amplified by anticipation. Shared mechanisms are once again indicated by the analgesic capacity of certain antiemetic agents such as ondansetron.

Similarities between pathophysiology may be instructive, and so in this workshop we aim to draw attention towards them. The speakers will give talks on shared mechanisms, pharmacotherapy and certain psychophysical aspects to show that some of the concepts, investigational methods and solutions which are applicable to one research field are relevant to another.
WS SUMMARY: HOW TO DIAGNOSE NEUROPATHIC PAIN

P. Hansson\textsuperscript{1,2}, M. Backonja\textsuperscript{3}, D. Bouhassira\textsuperscript{4}

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There is currently lack of widely accepted consensus by experts on how to diagnose neuropathic pain. Recently the IASP definition of neuropathic pain (Merskey & Bogduk, 1994) was challenged by a group of neuroscientists and clinicians who also put forth a diagnostic work-up algorithm (Treede et al. 2008). Dr Hansson will introduce important features of the output of this group.

Dr Backonja will then highlight the neurological decision making process, built on a strong and longstanding neurological tradition, starting with the interview to extract sensory symptoms relevant to neuropathic pain followed by the basic principles of conducting sensory examination with the goal of determining type and extent of sensory abnormalities. Symptoms are often distressing and confusing to patients who have great difficulties in understanding conflicting symptoms (“The skin is numb, I don’t feel it but it hurts”). Though important information is gained from sensory symptoms the critical step leading to confirmation of the diagnosis is somatosensory examination and such measures should be performed to allow detection of both positive and negative signs. The integration of all findings serves as a basis to deduce whether the diagnosis of neuropathic pain is justified. The final step to consider is the likelihood that each patient has more than one type of pain at any given time and that non-neuropathic types of pain also can manifest with sensory abnormalities, thus mimicking neuropathic pain.

Dr Bouhassira will discuss the usefulness and limitations of neuropathic pain questionnaires in light of the recently proposed new definition and graded diagnostic system of neuropathic pain (Treede et al. 2008). The suggested work-up of mainly relies on identification of a neurological lesion or disease and does not take into account the characteristics of pain. Over the last few years, a series of studies have demonstrated that some symptoms (i.e. pain descriptors) can discriminate between neuropathic and non neuropathic pain. This finding allowed the development and validation of a series of simple clinical tools, in the form of questionnaires. Although none of the single pain descriptors was specific, these studies showed consistently that the combination of a relatively small number of items was sufficient to discriminate pain due to a definite neurological lesion. The fact that these different questionnaires, developed independently and in parallel in different countries, share a large number of items strongly supports the validity of this approach.
WS SUMMARY: INTERACTION OF AUTONOMIC AND MICROVASCULAR DYSFUNCTION IN CRPS

G. Wasner¹, F.J.P.M. Huygen², T.J. Coderre³

¹Universitätsklinikum Kiel, Kiel, Germany, ²Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands, ³Anesthesia & Alan Edwards Centre for Research on Pain, McGill University, Montreal, QC, Canada

Growing evidence suggests that as well as autonomic abnormalities (leading to temperature and blood flow asymmetry), endothelial cell injury and microvascular dysfunction, may contribute to CRPS. Evidence indicates that the pain of CRPS is accompanied by arterial vasospasms, endothelial cell swelling, arterial-venous shunting, poor nutritive blood flow and ischemia in skin and deep tissue. Thus, sympathetic vascular hypersensitivity and microvascular dysfunction may maintain CRPS pain by promoting chronic tissue ischemia. Investigations of the interaction of autonomic and microvascular dysfunction should help to improve diagnostics, treatment and pathophysiological understanding of the disease.

Dr. Wasner will discuss new insights concerning dysfunction of the autonomic nervous system in CRPS, including long-term skin temperature measurements as a new diagnostic tool. He will discuss evidence that early vasodilation in CRPS might be related to a functional deficit of postganglionic sympathetic activity associated with autoantibodies binding to the surface of peripheral autonomic neurons. He will also discuss evidence that chronic vasoconstriction may occur because initial functional inhibition of vasoconstrictor activity in the acute stage leads to secondary vascular hyper-reactivity either by postjunctional changes or alterations in alpha-adrenoceptor sensitivity.

Dr. Huygen will discuss new insights concerning microvascular dysfunction and inflammation in CRPS, including studies indicating there are increases in pro-inflammatory cytokines (IL-6 and TNFα) and mast cell activity in CRPS limbs. He will also discuss evidence that endothelial cell dysfunction may lead to an imbalance between the vasodilating substance nitric oxide and the vasoconstrictive substance endothelin-1 in cold CRPS limbs. Finally, he will present results from studies examining the effects of anti-TNF antibodies, a nitric oxide donor (isosorbide dinitrate) and a phosphodiesterase inhibitor (tadalafil) on CRPS pain and limb temperature asymmetry.

Dr. Coderre will discuss new insights concerning sympathetic and microvascular dysfunction in an animal model of CRPS-I -- chronic post-ischemia pain (CPIP) induced following an ischemic-reperfusion injury. He will present data demonstrating that allodynia and/or norepinephrine-induced pain in CPIP animals depends on arterial vasospasms, capillary no-reflow, and the generation of oxygen free radicals, pro-inflammatory cytokines and lactic acid in the muscle of the affected limb. He will also present evidence that non-adrenergic vasoconstrictors, such as endothelin-1 and vasopressin, produce enhanced painful responses in CPIP mice or rats, as well as evidence that nitric oxide donors and phosphodiesterase inhibitors both relieve allodynia and increase hind limb blood flow in this animal model.
A number of pharmacological treatments are currently available for neuropathic pain (NP) including antiepileptics, antidepressants and opioids. However more than 50 % of the patients do not respond to these treatments .Therefore there is a need for new therapies with more predictable efficacy and improved tolerability. In recent years several compounds have been evaluated in clinical studies and may represent potentially attractive therapeutic options. This workshop will present the rationale behind a number of these therapeutic approaches and discuss specific challenges that they face. Nadine Attal (France) will present a panorama of existing and emerging therapies of NP and will outline recent therapeutic algorithms. Mark Ware (Canada) will present the results of recent clinical trials of cannabinoids in NP. Finally Ralf Baron (Germany) will develop the importance of defining responder profiles to current and emerging drug treatments in NP.
Herpes zoster and postherpetic neuralgia (PHN) are not only important in the context of neuropathic pain, but are also diseases that are predicted to expand in terms of global significance with the increased prevalence of herpes zoster as a result of an ageing developed world population, the world-wide pandemic of HIV disease and the increasing number of people receiving organ transplants. We are currently witnessing major and exciting developments, from several quarters, in our understanding of the mechanisms, prevention and treatment of herpes zoster and PHN. The workshop will focus on three of these:

Participants will learn about:

1. Recent developments in attempting to model aspects of zoster associated pain in experimental animals. The use of complex behavioral paradigms to measure comorbidities such as anxiety in these models. (Rice)

2. Approaches for the prevention of both herpes zoster and PHN and their potential impact on the prevalence of these conditions. (Dworkin)

3. Appropriate clinical management strategies for the treatment of PHN based upon a systematic review of the available evidence, with a particular focus on the problems of prescribing in elderly patients. (Haanpaa)

There will be 30 minutes for discussion
WS SUMMARY: WHICH PATIENTS MIGHT BENEFIT FROM SCS?

M. Bedder

Providence Regional Medical Center, Everett, WA, USA

This SCS symposium will examine patient selection, rechargeable technology and financial cost modeling for SCS treatments. Patient selection includes selecting the appropriate SCS technology for the treatment of a diverse group of patients. Discussions will separate the indications of SCS into two broad subsets:

1. Neuropathic/neurological indications, and

2. Vascular etiology indications.

There will also be a presentation on patient selection for rechargeable SCS technology, which now represents a growing portion of the implant market.

All presentations will utilize evidence based literature as well as the experiences in both North America and Europe markets. Patient outcomes and complications will be discussed as well as cost efficacy and financial modeling data. This symposium will be of interest not only to clinicians active in the broad field of Neuromodulation, but also to health care administrators and financial planners.
WS SUMMARY: WIDESPREAD NON DERMATOMAL SOMATOSENSORY DEFICITS: WHERE ARE THEY COMING FROM?

A. Mailis Gagnon¹, C. Geber², N. Egloff³

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This workshop aims to review the modern literature concerning Nondermatomal Somatosensory Deficits (NDSDs) not conforming to the distribution of peripheral nerves or dermatomes, and often following minor injury or no known injury, in regards to their prevalence, phenomenology and clinical presentation, clinical assessment, etiology and pathophysiology, relationship with Conversion Disorder and psychological factors, as well their treatment and prognosis.

Dr. C. Geber will discuss functional hypoesthesiae in different human pain models, such as intradermal capsaicin injection, electrical nociceptive stimulation or intramuscular hypertonic saline injection applied to healthy volunteers. In these experimental situations, functional hypoesthesia in the area surrounding the site of nociceptive stimulation could be induced and even modified. He will additionally describe psychophysical methods that allow quantification of these sensory deficits, characterization of their spatial distribution, time course of onset and their reversibility.

Dr. A. Mailis Gagnon will discuss the prevalence of NDSDs in samples of chronic pain populations and describe the temporal, spatial, qualitative, motor, sensory, and behavioural characteristics of NDSDs; their association with certain demographic variables and possibly psychological factors, and empirical evidence that indicates poor response to conventional treatments. She will present illustrative clinical case reports to show the remarkable NDSD phenomenology, variability, and reversibility. She will also present the first functional imaging study on patients with NDSDs that shows significant alterations in brain activation patterns.

Dr. N. Egloff will discuss his team's study of 60 consecutive chronic pain patients with pain worse in one side of the body (not explained by persistent peripheral tissue damage) and ipsilateral NDSD. Brain CT or MRI scans revealed no structural changes. In 11 patients FDG-PET (18-fluorodeoxyglucose positron emission tomography) showed significant hypometabolic pattern of changes in cortical and subcortical areas, mainly in the postcentral gyrus, posterior insula, putamen, and anterior cingulate cortex. Measures of pain severity and depression were used as covariates in the analysis of the findings, but certain hypometabolic regions were not correlated with pain and depression scores. The authors assumed that these hypometabolic areas are related to NDSDs themselves.

The presenters will collectively discuss possible peripheral as well CNS mechanisms that may account for NDSDs. NDSDs seem to be important and prevalent clinical phenomena associated with chronic pain, but their prevalence in the general population, primary care settings and non pain patients is unknown. Directions for future research will also be discussed.
The magnitude of placebo analgesic effects has been shown to be large and highly variable. One of the factors that influence their magnitude is the way in which the placebo effect is induced. Lene Vase will discuss some possible causes of this variability, with particular emphasis on learning. For example, placebo effects induced via associative learning and/or reinforcement of expectations generally seem to be larger than placebo effects induced via verbal suggestions alone. Also, placebo effects which are induced via long lasting pain stimuli (< 20 sec) and which reflect anti-hyperalgesic effects appears to be the largest. Most research on placebo analgesia has been conducted on experimental or acute pain but more recently placebo effects are being explored in hyperalgesic states and in neuropathic pain conditions. By taking the important role of learning into account, the neural mechanisms linking prior experience of effectiveness with the development of placebo analgesia have only recently been investigated in healthy volunteers, using functional magnetic resonance imaging (fMRI). Carlo Porro will describe recent studies with fMRI which have used a well-known conditioning paradigm, whereby the intensity of noxious stimuli is surreptitiously reduced in the training session, to reinforce volunteers’ beliefs about the effectiveness of the sham analgesic procedure. These studies show that, during the training session, a medial prefrontal and lateral prefrontal activation occurs, and that this activity increases over time in the training session, suggesting a learning-related process. In addition, these prefrontal activations partly overlap with regions showing placebo-related activity in the test session. Therefore, these findings point to the prefrontal cortex as a key structure in placebo conditioning, and further support the role of this region in placebo-induced modulation of the pain system. Finally, Fabrizio Benedetti will discuss the possible implications of learning both in clinical practice and in clinical trials. In fact, it is now possible to modulate the magnitude of the placebo effect in a number of ways. For example, it is possible to disrupt placebo analgesia by means of the pharmacological blockade of prefrontal opioidergic transmission as well as through the inactivation of the prefrontal cortex with transcranial magnetic stimulation. It is also possible to use conditioning procedures to create placebo responders and non-responders in the laboratory, thus raising important ethical and methodological questions, e.g. whether laboratory-created placebo non-responders can be used in clinical trials.
WS SUMMARY: MECHANISMS OF TRIGEMINAL NEURALGIA CHAIRMAN'S INTRODUCTION

J. Zakrzewska

*Facial Pain, University College London, London, UK*

This session will present work from two basic scientists. Dr Iwata will explore the role of astrogial activation in trigeminal nerve injuries showing that their activation results in sensitisation of a nociceptive response. Dr Ren will demonstrate that primary afferent inputs will not only activate astroglia but will also result in upregulation of IL-1beta, as well as neuronal NMDA receptor activation. Prof Zakrzewska will then discuss ways in which these complex scientific findings can be explained to patients during a consultation to improve their understanding of their pain and the reasons for why currently many cannot be cured.
Recent advances in the knowledge of genetic and epigenetic factors that underlie complex disorders or affect the response to drugs raise the prospect of personalized treatment for many diseases including chronic pain. However, only few gene variations associated with an increased risk to develop neuropathic pain have been identified. High costs dampen the expectations for a broad application of pharmacogenetic screens to optimize treatment strategies in individual patients. As a consequence, treatment algorithms for neuropathic pain continue to rely on etiological disease classifications. And therapeutic decisions are usually based on comorbidity and the potential side effects of analgesics, not the specific genetic makeup of patients. We review the challenges and opportunities of genotype-based neuropathic pain treatment. We present new strategies for classifying patients according to their clinical pain phenotype, which reflects the activity of distinct pathophysiological mechanisms independent of disease etiology. We discuss the potential for improving the characterization of a patient's pain phenotype through the imaging of pain-processing networks in the brain. A standardized classification of neuropathic pain phenotypes may support the development of strategies for targeted analgesic treatment when genetic determinants of pain or treatment response are elusive.
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 pathophysiology 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 will 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.
Neuropathic pain (NP) may be cancer related, namely, may result due to tumor invasion of nervous tissue, surgical nerve damage during tumor removal, radiation-induced nerve damage, chemotherapy-related neuropathy or may be of benign origin unrelated to cancer.

Cancer related NP derives from peripheral or central lesions of the nervous system and is often associated with the hallmark symptoms of allodynia and hyperalgesia. Pain is prevalent in patients with cancer and considerably degrades their quality of life thereby making the development of a comprehensive pain management approach essential.

The present Workshop targets to equip the participants with:

1. the knowledge of NCP prevalence and the recent relevant diagnostic tools
2. the perception of cancer related NP mechanisms and finally
3. the skills for evidence based pharmacological management and the new ways to treat intractable NCP.

Coanalgesics have been well integrated into cancer pain management strategies and are often used as first line options for the treatment of certain disease processes such as neuropathic pain. These drugs including antidepressant and anticonvulsant agents are recommended by evidence-based guidelines whereas others such as lidocaine patch 5% are supported by randomized controlled clinical data.

Cancer pain includes a 30% neuropathic component

NCP can be relieved by multimodal treatment according to WHO guidelines as the majority of cancer patients suffer multiple types of pain. Recent evidence-based reviews of RCT’s on NP were selected (6 reviews) and specific RCTs on NCP were also identified (2 trials). Study of the bibliography reveals that the management of NCP has changed dramatically in the last few years thanks to new approaches and novel drugs. The vast majority of these drugs have been proven to be useful in benign NP syndromes. The intrinsic difficulties in performing RCTs in cancer pain have traditionally justified the acceptance of drugs already known to be effective in benign NP despite the insufficient evidence in malignant NP. In the last three decades the introduction and development of totally implanted drug delivery systems has created new ways to treat intractable cancer NP. The brief review of pain medication delivery systems definitely shows that this method, despite the rare complication of mass formation of the catheter tip, is helpful in NCP treatment.

References:


*Vadalouca A etal.2006Therapeutic management of chronic Neuropathic pain Ann NY Acad.Sci.1088:164-186
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\textsubscript{v}1.7 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\textsubscript{v}1.7 from patients with two hereditary pain syndromes: inherited erythromelalgia and paroxysmal extreme pain disorder. He will also discuss modulation of Na\textsubscript{v}1.7 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\textsubscript{v}1.7 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.
The majority of the patients with neuropathic pain will receive most of their care by primary care doctors. Complexity of neuropathic pain poses challenge to pain specialists and disproportionately to primary care clinicians. Primary care doctors face incredible pressure to provide standard of care in a very fast paced practice, and patients with chronic pain disorders, especially in case of neuropathic pain, are usually treated in primary care with traditional analgesics, according to most of the survey, thought there is no evidence to support this and other similar treatment approaches. There are international efforts to assist primary care physicians in reaching more specific neuropathic pain diagnosis. There are relatively simple symptoms based tools which can aid in this process, and this presentation will discuss efforts to bring additional tools, such as quantitative sensory testing, to primary care. The first step in evaluation in determining the role of quantitative sensory testing to be undertaken is feasibility of such testing within the time constraints and cognitive demands in primary care practice setting. Consequently, procedure of the exam would be focused and limited not to more than a couple of minutes. Attention to the problem of neuropathic pain, its severity and location, would be aided by simple symptoms assessment tools such as ID Pain or Neuropathic Pain Questionnaire and pain diagram, which could be administered by the nursing staff. This workshop will discuss the need for standardizing and validating a bedside clinical examination. Complex and technologically-intensive quantitative sensory testing protocols have been developed and used for detailed phenotyping in research contexts. However, this sort of examination is not possible in primary care. We will explore methods to develop and teach primary care physicians how to do a rapid and effective bedside sensory examination.

In addition to Canadian and US experiences, we will discuss French experience, that although the diagnosis of neuropathic pain appears to be easier today by means of validated screening tools, the clinical examination of putative sensory abnormalities remains a problem for non neurologists in daily practice. We will present proposals for a guide pertaining with the objectives of demonstration of sensory abnormalities suitable for general practitioners (GPs) and specialists (SPs) that are not neurologists but have to face daily with patients presenting with neuropathic pain (orthopedic surgeons, rheumatologists). Use of the DN4 as a primary diagnostic tool will be proposed through an evaluation of its daily use by French GPs and SPs. An algorithm for the choice of a convenient multimodal treatment (pharmacological and non pharmacological) will summarize the basis regarding safety and evaluation. With the advent of new therapies for pharmacological treatment of neuropathic pain, it is increasingly important to teach primary care physicians how to diagnose and initiate treatment of neuropathic pain.
The spinothalamic tract (STT) represents a major ascending pathway conveying nociceptive information from the dorsal horn via the thalamus to brain regions involved in pain. This workshop will discuss the assessment of STT function and possible roles of STT dysfunction in hyperalgesia and neuropathic pain based on findings from basic science and clinical studies.

Jürgen Sandkühler will address synaptic plasticity in lamina I projection neurons and how long-term potentiation (LTP) in neurokinin 1 expressing neurons at the first synapse in the pain pathways may underlie some forms of hyperalgesia following nerve injury and inflammation. Jürgen Sandkühler will also present new observations showing that activity-dependent LTP and opioid-withdrawal LTP share induction protocols, pharmacology, and signal transduction pathways with afferent-induced forms of hyperalgesia and opioid-withdrawal hyperalgesia.

Luis Garcia-Larrea will address the use of laser-evoked potentials (LEPs) for the assessment of the STT in humans. The study of discrete STT lesions of similar sizes at different points of the STT (medulla, mesencephalon, thalamus) has shown that thalamic VPL lesions cause minimal distortion of LEPs suggesting that a sizeable part of the STT in humans goes to other non-VPL/VPI thalamic nuclei. Alteration of the STT is a common rule in central neuropathic pain patients, and subtle alterations in remnant STT transmission have been associated with a greater probability of provoked pain (alldynia, hyperalgesia). Nevertheless, even small lesions restricted to the VPL (and altering relatively little the LEPs) seem to be able to generate strong central pain, and data will be presented showing that neuropathic pain can exist in patients with large peripheral fiber or dorsal column lesions and normal STT conduction.

Nanna Finnerup will review the role of STT dysfunction for central pain. While lesions of the STT have been considered a prerequisite for central pain, such lesions have been found to be equally frequent in patients without central pain. Recent experimental and human studies suggest that dysfunction of residual STT neurons is important in patients with spinal cord injury pain. Studies will be presented suggesting that the STT may trigger neuronal hyperexcitability and central pain by spontaneous activity in residual neurons or by signaling remote neuroimmune activation.
Opioids are highly effective for managing acute and chronic pain. The development of opioid tolerance, physical dependence, and withdrawal phenomena limits their long-term efficacy. In animals, intermittent or continuous opioid administration produces rapid and essentially complete analgesic tolerance. Yet, in man the extent to which opioid analgesic tolerance and hyperalgesia develops during treatment of chronic pain has not been firmly established. Opioid analgesic tolerance and hyperalgesia will be discussed from both 3 perspectives: laboratory research, human experimental pain model studies, and clinical studies of longer-term opioid-therapy. Dr. Petersen will begin with a brief overview and then discuss how healthy volunteer human experimental pain models have been used to explore both tolerance and hyperalgesia. Dr. Clark will follow with a discussion of the laboratory research on this topic. While dozens of individual molecules seem to be involved, we might best conceptualize these adaptations as involving specific neuronal circuits, nuclei and cell types. Some of the most important participants include the rostral ventromedial medulla (RVM), the cells intrinsic to the dorsal horn of the spinal cord and both the central and peripheral terminals of primary sensory neurons. Special emphasis will be placed on recent reports demonstrating the genetic basis for tolerance and opioid hyperalgesia, the roles of glial cells and the unexpected plasticity of sensory neurons during chronic exposure to opioids. Dr. Rowbotham will discuss studies in pain patients, with special emphasis on the few prospective, controlled, studies that have specifically searched for both tolerance and hyperalgesia.
The trigeminal system mediates all the facial pains, whether neuropathic or nociceptive. Some conditions, such as classic trigeminal neuralgia are characterized by very clear clinical symptoms. Several other conditions, ranging from primary and secondary trigeminal neuropathy to atypical facial pain may pose difficult diagnostic problems. The physician should be able to differentiate at least three categories: major neurological disease, “idiopathic” conditions that require neurological treatment, and pain with a predominant psychogenic component. According to recent Euro-American guidelines, with the aid of some neurophysiological investigations it is often possible to reach a diagnosis and begin the adequate treatment earlier. In this workshop we will summarize the clinical aspects of the various trigeminal pains, then to describe the results of neurophysiological testing and indicate when this is useful, and finally give an update of the most recent treatment options.

Program: Overview of trigeminal pains (M Haanpaa). Neurophysiological testing (G Cruccu). Treatment options (J Zakrzewska).
WS SUMMARY: WHICH BLOCKS WORK FOR NEUROPATHIC PAIN?

S.N. Raja¹, J. Richardson², J.D. Loeser³

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The optimal management of neuropathic pain requires a multi-faceted approach. However, pain is inadequately controlled in some patients with non-interventional approaches. In these patients, nerve blocks are used as diagnostic, therapeutic, or prognostic tools. We will discuss the appropriate use of common somatic and sympathetic nerve blocks, provide an overview of the level of evidence for their beneficial effect, and the role nerve blocks should play in the overall management of patients with chronic neuropathic pain.

Nerve blocks for radicular pain: Srinivasa Raja

Chronic low back pain with radicular symptoms is the most common scenario where local anesthetic nerve blocks with or without steroids are used as diagnostic or therapeutic modalities. However, the role and effectiveness of these blocks are still debatable (Staal et al 2009). Critical reviews of the literature indicate that there is insufficient evidence that nerve blocks provide long term benefits for radicular pain, but it cannot be ruled out that specific subgroups of patients may respond to a specific type of injection therapy or radiofrequency (RF) lesioning.

Sympathetic nerve blocks for neuropathic pain: Jonathan Richardson

The sympathetic nervous system has been shown, through various pre-clinical and clinical studies, to be relevant to neuropathic pain (Taylor 2001). In neuropathic pains with this association significant benefits can be achieved through sympathetic blockade (Day 2008). The presentation will discuss the choice of where and how to block the sympathetic nerves for head, neck, trunk, pelvic and peripheral sites. The beneficial effects of local anaesthetic sympathetic block can be surprisingly long lived, but if necessary long term benefit through radiofrequency or chemical sympathectomy can often be provided.

Trigeminal Neuralgia: John D. Loeser

Nerve blocks of the gasserian ganglion have been used for the treatment of tic douloureux. Lesioning the Gasserian ganglion with heat, cold, or mechanical means has utility for the treatment of tic douloureux, but the role of blocks with local anesthetics for treatment prognostication or diagnosis has never been demonstrated with RCTs. Spinal injections as predictors of surgical outcomes lack appropriate studies (Cohen and Hurley 2007). Selective nerve root blocks with image guidance and low volume of injectate may be helpful in confirming the level of the pathology and directing surgical attention to the correct location (Sasso et al. 2005). By preventing operation at the wrong level, they do influence outcome.
WS SUMMARY: SURROGATE MODELS OF NEUROPATHIC HYPERALGESIA

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Experimental models of hyperalgesia in humans have been developed in recent years as tools for investigating the mechanisms of clinical hyperalgesia and for screening analgesics. The most widely used model is that induced by intradermal or cutaneous capsaicin administration. More recently other surrogate models have been proposed to mimic cold hyperalgesia; these include menthol applications (Wasner et al 2006; Hatem et al 2006) and a recently described thermal grill illusion of pain (Bouhassira et al 2007). The objectives of this workshop will be to discuss the relevance of these surrogate models to better understand some of the mechanisms of peripheral or central pain and their contribution to the study of antineuropathic drugs. RD Treede will present an overview of surrogate models, their advantages and limitations with particular emphasis on the capsaicin model. D Bouhassira will present recent data from a thermal grill illusion of pain. Finally G Wasner will present data recently obtained with the model of cold hyperalgesia induced by menthol.
WS SUMMARY: ATTENTION TO PAIN AND ITS DISABLING CONSEQUENCES

G. Crombez

Experimental Clinical and Health Psychology, Ghent University, Gent, Belgium

Many chronic pain patients experience persistent, distressing and overwhelming pain. They often complain of cognitive problems such as difficulties in concentrating and in focusing their attention. Research reveals that pain, as a biological hard-wired signal of bodily threat, demands attention and interferes with cognitive functioning. Although the capture of attention by pain is automatic, it may be controlled to some extent. Directing attention away has been shown to diminish the pain experience. In this workshop we address how and when attention is paid to pain in experimental and clinical situations, we address the cognitive, emotional and behavioural costs of attention to pain, and, finally, how psychological interventions may be used to diminish these costs.

Geert Crombez will review the extant literature on the effects of pain on attention and memory, and provide an integrative neurocognitive model of attention to pain (Legrain et al., 2009). Building upon this model, Christopher Eccleston will discuss how attempts to control the disabling nature of pain may in some situations prove futile and fuel the attentional, emotional and behavioural costs of chronic pain. More specifically, he will argue that a persistent search to solve the problem of chronic pain at the expense of other activities, may sometimes be better conceived of as misdirected problem solving (Eccleston et al., 2007). Finally, Johan Vlaeyen will discuss the value of psychological intervention to address this myriad of cognitive, emotional and behavioural consequences. He will argue that attentional distraction strategies may not be the treatment of first choice, and provide evidence showing that behavioural treatments, such as exposure to pain-eliciting stimuli, may lead to a redefinition of the problem (“my low back pain is not caused by serious injury”) and to a reduction of pain and attention to pain (e.g. Leeuw et al., 2007).

References:


WS SUMMARY: GENES INVOLVED IN PERIPHERAL NEUROPATHY AND ITS TREATMENT

P. Kamerman

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Changes in gene expression and gene polymorphisms contribute to the development of neuropathic pain. In this workshop the speakers will discuss: i) the use of gene expression profiling in animal and human models of persistent pain to identify genes whose altered expression following peripheral injury may be related to the development of hypernociception; ii) ethnic differences in genetic risk factors for developing peripheral neuropathy; and iii) the relationship between opioid use and immunogenetics in an attempt to link opioid phenotype with polymorphisms in immune-related genes.
The long-term use of opioids for the management of chronic neuropathic pain remains controversial. Care providers are challenged by the need to balance the legitimate and appropriate use of opioids with screening and monitoring of patients to minimize the societal concerns of increasing drug abuse and diversion. We will provide an overview of the evidence of the efficacy of opioids in the management of neuropathic pain, discuss ways to optimize the use of opioids for chronic non-cancer pain and discuss the adverse effects associated with opioid therapy, including abuse and addiction, and suggest tools to minimize these risks.

Opioids for the treatment of chronic neuropathic pain: The Evidence- Raja

Several randomized trials in the last decade have provided convincing evidence that at least in the short term period of weeks, opioid therapy leads to a reduction in pain intensity, and possible improvements in sleep and ability to function. The evidence does not support the notion that opioids are less effective in the management of neuropathic pain, when compared to nociceptive pain. More careful prospective studies on the long term effectiveness of opioids need to be conducted, but available cohort studies suggest that tolerance to opioids is not a major limiting factor in their use.

Optimizing management of chronic pain with opioids- Kontinen

Strategies for optimizing the management of chronic neuropathic pain with opioids should focus on patient selection-- the type of pain, patient characteristics, and discussion of known predictors of poor versus good outcome. The strategy should consider the choice of opioid based on preclinical and clinical evidence on the differences between different opioids. Opioids are not the first-line treatment for chronic neuropathic pain, and therefore rarely used alone in the treatment, but combined to other neuropathic pain drugs with different mechanisms of action. Additionally, new approaches to counteract the opioid-induced adverse effects, especially constipation, have become available.

Minimizing adverse effects associated with chronic opioid use- Gourlay

Opioid risk management is the strategy of minimizing harm associated with opioid therapy while maintaining appropriate access to therapy. This public health issue requires a coordinated and balanced effort among several stakeholders at the federal, state, industry, practitioner, and patient levels. The principles of pharmacovigilance and universal precautions: understanding the potential for opioid abuse in patients with chronic pain, the use of screening measures for high risk individuals and tools to monitor aberrant drug-related behaviors to minimize risks of abuse will be discussed.
Persistent postsurgical pain represent a major problem, where approximately 5-10% of patients undergoing surgery develop persistent pain problems. The mechanisms underlying these postsurgical pain has until recently been unclear. However, experimental and clinical studies have shown that a series of factors including intraoperative nerve injury are at play here. This workshop will mainly consider the potential role of nerve injury as a risk factor for persistent postsurgical pain. Other factors such as preoperative functional status, genetic, psycho-social and postoperative factors may also be involved in the development and maintenance of persistent pain. This workshop will take the participant from basic findings to clinical aspects of postsurgical pain. The content of the workshop will be as follows: Mike Salter will describe molecular mechanisms in the spinal cord involved in chronic inflammatory and neuropathic pain. He will stress the importance of pathological changes in signalling in neurons and in glial cells within the dorsal horn following traumatic surgical injury. Blair Smith will highlight the astonishing high prevalence of persistent pain following some operations and discuss the challenges in identifying risk factors for this multifactorial condition. Finally, Troels S. Jensen will present the clinical diagnostic dilemma in post-injury pain and emphasize the requirements for claiming a neuropathic pain mechanism.
WS SUMMARY: TREATMENT FOR TRIGEMINAL NEURALGIA, WHAT WORKS FOR WHO?

S. Erdine

*Department of Algology, Medical faculty of Isçtanbul, Istanbul, Turkey*

Chaired by Prof. Serdar Erdine,

Speakers will be Prof. Serdar Erdine giving a lecture on percutaneous interventions for the treatment of trigeminal neuralgia, Prof. John Loeser speaking on MVD for the treatment of trigeminal neuralgia, Prof. Robert M. Levy will give a lecture on Gamma Knife and algorithms to conclude.
WS SUMMARY: ABETA FIBRES IN PAROXYSMAL PAIN

A. Truini

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An established notion postulates that whereas neuropathic pain is provoked by nociceptive myelinated A-delta and unmyelinated C-fibre damage, non-nociceptive A-beta-fibre damage manifests only with non-painful sensory disturbances. Patients with neuropathic pain usually describe various types of pain, which include ongoing pain, paroxysmal pain, and provoked pains. Recent clinical-neurophysiological studies in patients with neuropathic pain secondary to peripheral and central nervous system disease (postherpetic neuralgia, carpal tunnel syndrome, and multiple sclerosis) suggest that paroxysmal pain may be related to focally demyelinated A-beta fibres. This workshop deals with the role of non-nociceptive A-beta fibres in neuropathic pain, reports the most recent data on A-beta-fibre function in patients with neuropathic pain and debates whether A-beta fibres can provoke pain per se or rather through central mechanisms.

Proposed Program:

Introduction: A historic question that defies an established notion: R. Baron

Evidence from neurophysiological testing: A. Truini

Peripheral or central mechanisms?: R. Baron
Clinical assessment of neuropathic pain (NP) is crucial for a better understanding of its mechanisms and for implementing appropriate treatment. Over the past years a number of questionnaires have been developed specifically for the assessment of NP or its impact on quality of life. Quantitative sensory testing is also increasingly used for clinical research and practice and normative data based on large population groups have appeared a few years ago. The objectives of this workshop will be to present evidence based recommendations from the NeuPsig on neuropathic pain assessment for both clinical practice and research. Nadine ATTAL (France) will present outcome measures used in NP trials with special emphasis on specific questionnaires and their relevance to assess efficacy of treatments. Turo Nurmikko (UK) will present quality of life instruments with focus on recently validated tools specifically for NP. Finally Rolf Detlef Treede (Germany) will present evidence based recommendations on quantitative sensory testing for assessing pain mechanisms and treatments effects.
Central neuropathic pain (CNP) which frequently develops as a direct consequence of a lesion or disease affecting the somatosensory system remains very poorly understood and is one of the most challenging pain problems to treat. The workshop will commence with a brief overview by Dr. Dostrovsky of some of the key clinical features of CNP and the main pathophysiological mechanisms that have been proposed. Dr. Henry will then describe recent findings from his animal studies in a rat model of central post-stroke pain (CPSP). In this model unilateral microinjection of collagenase within and around the thalamus is used to produce an haemorrhagic stroke and animals develop tactile and cold hypersensitivity. Dr. Bouhassira will conclude the workshop with a presentation on multimodal assessment of CNP and use his recent studies on patients with pain associated with syringomyelia as an example. He will show that the combination of psychophysical (QST), electrophysiological (laser and somatosensory evoked potentials) and neuroimaging (diffusion tensor imaging and fiber tracking) techniques allows one to identify different profiles of patients. Patients with spontaneous pain and evoked pains were found to differ from patients without pain or with solely spontaneous pain. These new important findings in animals and humans point the way for further research and should lead to improved understanding and treatment of CNP.
WS SUMMARY: COST EFFECTIVENESS OF DIFFERENT TREATMENT PATHWAYS FOR NEUROPATHIC PAIN

J. Fox-Rushby

Health Economics Research Group, Brunel University, Uxbridge, UK

his workshop will present the results of a recent systematic review (funded by the National Institute for Health Research - UK) exploring the efficacy and cost effectiveness of different treatment pathways for neuropathic pain. The workshop will consist of 3 sections: 1. Clinical pathways for cost effective prescribing - matching the efficacy literature with cost effectiveness analysis. 2. Health Economic methodology used in the assessment of treatments for neuropathic pain - including the latest techniques for analysis and comparative assessments 3. Statistical methodology used in systematic reviews of drug treatment for neuropathic pain.
Currently about 33 million people worldwide are living with HIV disease and an increasing percentage of those are gaining access to antiretroviral therapy (ART). As more people become infected and those infected live longer because of the benefits of ART, the burden of the complications of the disease and its therapy become ever more important. In about 40% of cases, distal sensory polyneuropathies complicate HIV infection and/or its treatment with ART. A significant proportion of patients with such neuropathies suffer from neuropathic pain. Our knowledge about these neuropathies has greatly increased over the last few years, from laboratory studies investigating mechanisms through epidemiological and mechanistic studies in patients through to large clinical trials of analgesic therapies.

Andrew Rice: will discuss data from animal models regarding mechanisms of neuropathic pain in HIV and ART associated neuropathies.

Catherine Cherry: will describe the epidemiology, clinical presentation and assessment of sensory polyneuropathies in HIV disease

David Simpson: will review the increasing evidence base emanating from large randomised controlled trials of analgesic therapies in HIV-associated sensory polyneuropathies.

There will be 30 minutes for discussion.
Radicular pain, is defined as pain arising in the back and radiating into the limbs, and is caused by nerve root irritation /inflammation, mainly due to leakage of nucleus pulposus material and/or compression. Besides the inflammatory reaction, changes in ion channel functioning may occur. These two processes result in a pattern of hyperexcitability and spontaneous activity in the Dorsal Root Ganglion (DRG) which is interpreted as pain. In addition discharges enter the spinal cord and induce central sensitization at the synapses located in the dorsal horn.

(Pulsed) radiofrequency treatment adjacent to the DRG has been used for the management of chronic cervical and lumbar radicular pain. The effect of conventional RF treatment at cervical level is supported by two RCT's that both show a pain reduction. Pulsed RF was assessed in an RCT indicating that this treatment results in pain relief and improved patient satisfaction. At lumbar level, treatment with conventional RF did not result in better outcome than sham intervention. All RCT's were rated high quality according to a review in Anesthesiology 2008 (Malik and Benzon). Retrospective and prospective analysis of the outcome of PRF treatment adjacent to the lumbar DRG illustrates pain reduction in patients suffering lumbar radicular pain.

Published information on 295 PRF procedures does not report side effects or complications.

PRF treatment is minimally neurodestructive. The mode of action of PRF treatment is not clarified. Laboratory reports focusing on the effects of PRF in non-neuropathic pain models show that PRF: (1) is less/minimal neurodestructive in comparison to conventional RF (2) is temperature independent and (3) is selective for the small and medium calibre DRG neurons. PRF treatment adjacent to the rat cervical DRG induces early and late cellular activity in the dorsal horn, an effect which does not seem to be mediated by heat.

The high output generates a strong electric field that is thought to modulate nerve structure. Using a rat adjuvant induced inflammatory pain model, it was demonstrated that PRF is involved in the enhancement of noradrenergic and serotonergic descending pain inhibitory pathways. (Cohen, Van Zundert: RAPM 2010)

The dorsal root ganglion plays an important role in radicular pain. Clinical efficacy of PRF treatment starts to accumulate. The exact mechanism still needs further clarification.

In this workshop we will cover, according to the principles of translational medicine, pathophysiology of radicular pain, basic research and clinical evidence.
Activity in the nociceptive system is modulated by descending inhibitory and facilitatory endogenous control from supraspinal areas. In the clinical arena, altered balance between inhibition and facilitation with a net loss of inhibition has been demonstrated in fibromyalgia, tension-type headache, migraine and temporomandibular disorders. The crucial question whether such imbalance causes pain or is the result of activity in the nociceptive system is perhaps the most pressing issue in this field of research. Dr Hansson will provide introductory remarks on this area of research with special reference to nomenclature, methodology and current understanding.

Dr David Yarnitzky will raise the point that the case of neuropathic pain is more complex from a conceptual standpoint than several previously studied conditions with unknown etiology. Theoretically, there are many possibilities. Lesions in the peripheral nervous system may induce positive signs that overcome inhibition, or negative signs with excessive inhibition. Lesions in the central nervous system may affect the inhibitory or the facilitatory systems, with opposing results. He will argue that studies are needed that cover a variety of neuropathic pain disorders before this understanding is obtained. He will report findings from current research on painful chemotherapy-induced neuropathy, showing a normal inhibitory conditioned pain modulation (CPM) effect in intact body parts, with an inverse correlation between CPM efficiency and clinical pain intensity. He will also describe CPM function in Parkinsonian patients, showing mostly intact inhibitory ability, and in neuropathic post operative pain.

Dr Ann-Sofie Leffler will discuss data from patients with peripheral or central neuropathic pain. CPM reduced spontaneous ongoing pain but not dynamic mechanical allodynia in peripheral neuropathic pain but did not affect either parameter in patients with central post stroke pain. In addition, CPM induced a decreased sensitivity to pressure pain in a remote pain free area in patients with peripheral neuropathy and healthy controls alike. However, the ongoing activity in the nociceptive system did not influence pain sensitivity in a remote area. In contrast, before CPM stroke patients reported increased pressure pain sensitivity in a non-painful area when compared with controls, indicating a condition-induced alteration of endogenous pain control. The latter may be due to stroke-induced damage of inhibitory activity or nociceptive activity induced facilitation. Further, CPM induced a decreased sensitivity to pressure pain in a remote non-painful area in patients and controls alike, indicating normal function of pain modulation when test stimuli are applied in body areas with spinal nociceptive input.
The main complaint of neuropathic pain patients is spontaneous pain. There is animal evidence of spontaneous impulse generation in diseased large myelinated afferents, and human recordings using microneurography have clearly shown ectopic nerve impulses generated in single myelinated sensory fibers as the mechanism of spontaneous paresthesias. However, the basis of the different spontaneous pains is still obscure, one of the main reasons being the fact that conventional electrophysiological methods are unable to record discharges in single sensory axons. Therefore, the study of positive sensory phenomena has largely relied on quantitative psychophysical tests.

There is a lack of preclinical surrogate models of spontaneous pain. Almost all preclinical models of neuropathic pain are behavioural models of evoked pain in which a lesion is induced in the peripheral nervous system, and several measures of mechanical and thermal hypersensitivity are obtained using calibrated filaments and thermal stimulators. Therefore, current preclinical models of neuropathic pain are actually models of hyperalgesia and allodynia, but not of spontaneous pains. In the clinical setting, it is spontaneous pains that really bother the patient. Not surprisingly, the primary outcome of proof-of-concept phase II and regulatory phase III clinical trials has always been reduction in spontaneous pain.

Microneurography can record individual action potentials from single sensory fibers. It is the only available technique to detect and quantify positive sensory phenomena of peripheral origin in humans as it can produce objective records of the abnormal nerve impulse activity responsible for paresthesias (myelinated fibers) and spontaneous pain (unmyelinated fibers). Recent microneurographic techniques permit recording from individual unmyelinated C fibers and allow their segregation into different functional classes having discrete electrophysiological properties of their membranes. Particularly important for the study of physiological and neuropathic pain is the recording from mechano-sensitive as well as mechano-insensitive, or silent, nociceptors. Using microneurography, it has become evident that ectopic discharges from C nociceptors is probably the basis of spontaneous burning pain in peripheral neuropathic pain conditions. Surprisingly, ectopia from identified C nociceptors has only been reported a few times from animals and even less frequently from humans (n=67 patients).

This workshop will present an update of the most recent microneurographic findings in animal and human neuropathic pain conditions and will discuss the crucial importance of understanding the mechanisms behind ectopic impulse generation in C-nociceptors as the most powerful method to design new neuropathic pain drugs.
WS SUMMARY: GENETICS OF NEUROPATHIC PAIN

Z. Seltzer\(^1\), M. Devor\(^2\), M.W. Salter\(^1\)

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Pain genetics carries hopes for a major impact on pain medicine, including the production of diagnostic and prognostic kits, preventive and palliative treatments, and personalized treatment. Following in the footsteps of the Genome Project, new pain genes are reported every year.

There are robust genotyping assays to identify candidate pain genes throughout the genome. However, there are no validated tools, or even suggested guidelines, for the phenotypes that should be collected for genetic association studies ("pain phenomics"). In this session Ze'ev Seltzer will propose a new core questionnaire useful for defining pain phenotypes in genetic association studies. This instrument includes clinically-relevant items and mechanism-based phenotypes, and forms a single, concise tool that includes the most important aspects of pain chronicity for which one would wish to see genes identified and clinical solutions developed. It is proposed as a basis for debate leading to consensus and future use in research. Such use will hopefully facilitate comparison of reported results across publications.

Marshall Devor will present a study aimed at identifying pain genes. Using the neuroma model of neuropathic pain in the mouse, a broad interval on chromosome 15 was identified that contains a pain gene. To identify the gene, the investigators applied two fine mapping strategies that refined the location to an interval of \(\sim 2.4\)Mb, harboring 78 genes. Then they carried out four analyses that together highlighted one of the 78 genes. Candidacy of this gene was supported using a knockout strain. Finally, they showed that SNPs in this gene significantly associate with neuropathic pain in women following breast surgery. This study illustrates the advantage of combining work in animal models and pain patients. The gene, which encodes a calcium channel subunit, is of considerable functional interest.

Mike Salter will introduce another approach, capable of identifying pain genes that uses 'reverse genetics', moving from molecules in neurons and glia back to candidate pain genes. The starting point was the discovery of a non-receptor tyrosine kinase Src that phosphorylates NMDA receptors in dorsal horn neurons, thereby maintaining neuropathic pain in an animal model. Src null mutant mice showed reduced pain hypersensitivity. Likewise, studies on spinal microglia implicated the purinoceptor P2X4 in a mouse model of neuropathic pain. P2X4 knockout mice do not develop these behaviors. Thus, one may predict that SNPs or copy-number variants in Src or P2X4 could contribute to the susceptibility for neuropathic pain in humans as well.