Neuropathic Pain. Changing Paradigms in Diagnosis and Treatment. An International Congress of NeuPSIG

Madrid, Spain

May 13 - 16, 2004

PROGRAM AND ABSTRACTS
Thursday, May 13, 2004

14:00 - 14:45 HALLA
Opening Ceremony
Chairperson: P. Bejarano, SPAIN

14:00 CHAIRMAN, IASP SPECIAL INTEREST GROUP ON NEUROPATHIC PAIN
T. Nurmikko
United Kingdom;

14:05 PRESIDENT-ELECT, IASP
T.J. Jensen
Denmark;

14:10 TREASURER, EUROPEAN FEDERATION OF IASP CHAPTERS
C.D. Wells
United Kingdom;

14:20 CHAIR, SCIENTIFIC PROGRAMME COMMITTEE
R-D. Treede
Germany;

14:30 - 14:45 HALLA
Introductory Note
Chairperson: P. Bejarano, SPAIN

14:30 FROM CAJAL TO CONTEMPORARY PAIN AND NEUROSCIENCES RESEARCH IN SPAIN
C. Belmonte
Institue De Neurociencias, University Miguel Hernandez, San Juan De Alicante, Spain;

14:45 - 15:30 HALLA
Keynote Address
Chairperson: P. Hansson, SWEDEN

14:45 MECHANISM-BASED DIAGNOSIS AND TREATMENT OF NEUROPATHIC PAIN
C.J. Woolf 1
Neural Plasticity Research Group, Department Of Anesthesia, Massachusetts General Hospital, Harvard Medical School, Boston, USA;

15:30 COFFEE BREAK Sponsored by Pfizer Inc

16:00 - 17:30 HALLA
Pregabalin: From Molecule To Medicine - Pfizer Industry Sponsored Symposium
Chairperson: P. Hansson, SWEDEN
PREGABALIN - FROM MOLECULE TO MEDICINE
P.H. Hansson 1, D.J. Rowbotham 2, A.H. Dickenson 3, R.H. Dworkin 4
1 Neurogenic Pain Unit Multidisciplinary Pain Center And Department Of Rehabilitation Medicine, Karolinska Hospital/Institute, Stockholm, Sweden;
2 Anaesthesia And Pain Management - University Of Leicester, Pain Management Service - University Hospital Of Leicester, Leicester, United Kingdom;
3 Department Of Pharmacology, University College London, London, United Kingdom;
4 Departments Of Anesthesiology And Neurology, University Of Rochester School Of Medicine And Dentistry, Rochester, NY, USA;

16:00  INTRODUCTION
P. Hansson
Neurogenic Pain Unit, Multidisciplinary Pain Center & Department Of Rehabilitation Medicine, Karolinska Hospital/Institute, Stockholm, Sweden;

16:05  NEUROPATHIC PAIN - OBSTACLES TO PROGRESS
D. Rowbotham
Anaesthesia & Pain Management, Division Of Anaesthesia, University Of Leicester, Leicester, United Kingdom;

16:30  PREGABALIN PHARMACOLOGY AND ITS RELEVANCE TO CLINICAL PRACTICE
A.H. Dickenson
Department Of Pharmacology, University College London, London, United Kingdom;

16:50  CLINICAL TRIALS OF PREGABALIN IN PATIENTS WITH NEUROPATHIC PAIN
R.H. Dworkin
Departments Of Anesthesiology & Neurology, University Of Rochester School Of Medicine & Dentistry, Rochester, NY, USA;

17:15  DISCUSSION

17:30  COFFEE BREAK

18:00 - 19:30  HALLB
Advances In Spinal Cord Injury Pain Research And Management
Chairperson: P. Siddall, AUSTRALIA
ADVANCES IN SPINAL CORD INJURY PAIN RESEARCH AND MANAGEMENT
P.J. Siddall 1, R.P. Yezierski 2, N.B. Finnerup 3
1 Pain Management Research Institute, University Of Sydney, Royal North Shore Hospital, Sydney, Australia;
2 Comprehensive Center For Pain Research, University Of Florida, Gainesville FL, USA;
3 Danish Pain Research Center / Department Of Neurology, Aarhus University Hospital, Aarhus C, Denmark;

18:00  PREVALENCE, FEATURES AND CLASSIFICATION OF PAIN FOLLOWING SPINAL CORD INJURY
P. Siddall
Pain Management Research Institute, University Of Sydney, Royal North Shore Hospital, Sydney, Australia;

18:20  MODELS AND MECHANISMS OF SPINAL CORD INJURY PAIN
R. Yezierski
Comprehensive Center For Pain Research, University Of Florida, Gainesville, USA;

18:40  PHARMACOLOGICAL TREATMENT OF SPINAL CORD INJURY PAIN
N. Finnerup
Danish Pain Research Center / Department Of Neurology, Aarhus University Hospital, Aarhus, Denmark;

19:00  DISCUSSION

18:00 - 19:30  HALLC
Practical Issues in the Use of Opioids for Neuropathic Pain
Chairperson: C. Wells, UK

18:00  THE HISTORY OF OPIUM
C.D. Wells
Liverpool, United Kingdom;

18:20 USING OPIOIDS FOR PATIENTS WITH NEUROPATHIC PAIN
M.C. Rowbotham
Pain Clinical Research Center, University Of California, San Francisco, USA;

18:40 USING OPIOIDS FOR MALIGNANT NEUROPATHIC
U.E. Kongsgaard
Department Of Anaesthesia, The Norwegian Radium Hospital, Oslo, Norway;

18:00 - 19:30 HALLD
Similarities And Dissimilarities Between Neuropathic Pain And Other Pain Conditions
Chairperson: N. Attal, FRANCE
SIMILARITIES AND DISSIMILARITIES BETWEEN NEUROPATHIC PAIN AND OTHER PAIN CONDITIONS
N. Attal 1, P. Hansson 2, J. Haythornthwaite 3
1 INSERM E-332 And Centre D Evaluation Et De Traitement De La Douleur, Hopital Ambroise Pare, Boulogne-Billancourt, France;
2 Department Of Surgical Sciences, Section Of Clinical Pain Research And Neurogenic Pain Unit, Multidisciplinary Pain Center And Department Of Rehabilitation Medicine, Karolinska Institute/Hospital, Stockholm, Sweden;
3 Department Of Psychiatry And Behavioural Sciences, John Hopkins Medical Institutions, Baltimore, USA;

18:00 DIFFERENTIATING NEUROPATHIC FROM NON-NEUROPATHIC PAINS
N. Attal
INSERM E-332 And Centre D Evaluation Et De Traitement De La Douleur, Hopital Ambroise Pare, Boulogne, France;

18:20 CLINICAL OVERLAP BETWEEN NEUROPATHIC AND NON-NEUROPATHIC PAINS
P. Hansson
Section Of Clinical Pain Research, Dept. Of Surgical Science, Karolinska Institute/hospital, Stockholm, Sweden;

18:40 ROLE OF PSYCHOLOGICAL FACTORS IN NEUROPATHIC AND NON-NEUROPATHIC PAINS
J.A. Haythornthwaite
Johns Hopkins Medical Institutions, Baltimore, USA;

19:00 DISCUSSION

18:00 - 19:30 HALLE
Trigeminal Brainstem And Thalamic Sensitisation: Neural Substrates And Clinical Implications
Chairperson: B. Sessle, CANADA
TRIGEMINAL BRAINSTEM AND THALAMIC SENSITISATION: NEURAL SUBSTRATES AND CLINICAL IMPLICATIONS
B.J. Sessle 1, J.O. Dostrovsky 2, T.S. Jensen 3
1 Faculty Of Dentistry, University Of Toronto, Toronto, Canada;
2 Department Of Physiology, Faculty Of Medicine, University Of Toronto,Canada;
3 Department Of Neurology And Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark;

18:00 ROLE OF SUBNUCLEUS CAUDALIS AND NMDA AND PURINERGIC RECEPTOR MECHANISMS
B. Sessle
Faculty Of Dentistry, University Of Toronto,Canada;
18:20 NEURONAL PROPERTIES AND CENTRAL SENSITISATION IN V BRAINSTEM AND THALAMUS
J. Dostrovsky
Department Of Physiology, Faculty Of Medicine, University Of Toronto, Canada;

18:40 CLINICAL ASPECTS OF CENTRAL SENSITIZATION IN THE OROFACIAL REGION
T.S. Jensen
Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark;

19:00 DISCUSSION

18:00 - 19:30 HALLF
Dynamic Mechanical Allodynia In Patients With Peripheral Neuropathic Pain: An In-Depth Discussion
DYNAMIC MECHANICAL ALLODYnia IN PATIENTS WITH PERIPHERAL NEUROPATHIC PAIN: AN IN-DEPTH DISCUSSION
J. Serra 1, R-D. Treede 2, W. Janig 3
1 Neuropathic Pain Unit, Hospital General De Catalunya, Spain;
2 Institut Fur Physiologie Und Pathophysiologie, Johannes Gutenberg-Universitat, Germany;
3 Physiologisches Institut, Christian-Albrechts-Universitat, Germany;

18:00 WHAT CAN ANIMAL MODELS TELL US ABOUT DYNAMIC MECHANICAL ALLODYnia?
W. Janig
Physiologisches Institut, Christian-Albrechts-Universitat, Kiel, Germany;

18:20 DYNAMIC MECHANICAL ALLODYnia IN PATIENTS WITH PERIPHERAL NEUROPATHIC PAIN: EVIDENCE FOR A PERIPHERAL MECHANISM
J. Serra
Neuropathic Pain Unit, Hospital General De Catalunya, Barcelona, Spain;

18:40 DYNAMIC MECHANICAL ALLODYnia IN PATIENTS WITH PERIPHERAL NEUROPATHIC PAIN: EVIDENCE FOR A CENTRAL MECHANISM
R-D. Treede
Institute Of Physiology And Pathophysiology, Johannes Gutenberg-University, Mainz, Germany;

19:00 DISCUSSION
MECHANISM-BASED DIAGNOSIS AND TREATMENT OF NEUROPATHIC PAIN

C.J. Woolf

Neural Plasticity Research Group, Department of Anesthesia, Massachusetts General Hospital, Harvard Medical School, Boston, USA

What is responsible for the pain that occurs after damage to or dysfunction of the nervous system and how can we treat it most effectively? We are beginning to be able to dissect out the alterations at the genetic, molecular, cellular and system levels that generate spontaneous or stimulus-evoked pain. This will enable us to move from a clinical classification of neuropathic pain based solely on either the etiology of the disease or the symptoms experienced, to one that identifies the neurobiological mechanisms responsible. The goal is to move from an empirical to a rational based approach to the management of neuropathic pain. The challenges we face to achieve this are to understand these mechanisms, develop tools to identify their presence in particular patients and develop treatment strategies targeted specifically at the mechanisms. Unraveling the mechanisms of pain should help identify molecular targets suitable for the development of novel analgesics. High density oligonucleotide microarrays are a powerful tool that will help identify novel molecular targets and diagnostic tools for neuropathic pain.
Neuropathic pain remains one of the most significant challenges facing clinicians today. Studies have illustrated the magnitude of the individual, social and economic burden of chronic pain, and a major effort is currently underway to identify and remove obstacles to therapeutic progress. Such obstacles include lack of awareness and knowledge about neuropathic pain among general physicians, problems with definition and diagnosis, and ultimately difficulties with management. Despite advances in basic science, translating the findings of animal models into clinical practice has remained challenging. This symposium will address these challenges before reviewing the data for pregabalin, a new treatment for neuropathic pain, partial epilepsy and anxiety. The mechanism of action of pregabalin has recently been elucidated. Potent binding to the α2-δ auxiliary protein of voltage-gated calcium channels reduces depolarization-induced calcium influx with a consequential reduction in the release of several neurotransmitters, including glutamate, noradrenaline and substance P. Pregabalin is structurally, but not functionally, related to GABA and thus is not active at GABA_A or GABA_B receptors, and does not alter GABA uptake or degradation. Pregabalin demonstrates highly predictable and linear pharmacokinetics. Absorption is extensive, rapid and proportional to dose. Time to maximal plasma concentration (T_max) is approximately 1 hour and steady state is achieved within 24-48 hours. The bioavailability of ≥90% is independent of dose as is the elimination half life (t_1/2) of approximately 6 hours. Pregabalin does not bind to plasma proteins, is excreted virtually unchanged (c. 2% metabolism) by the kidneys and has therefore minimal drug interaction potential. However, dose adjustment may be necessary in patients with renal insufficiency. An extensive clinical trials programme involving more than 2750 patients has demonstrated the efficacy of pregabalin in the treatment of neuropathic pain. Ten pivotal double-blind, placebo-controlled studies will be presented. These involved 5 – 13 weeks’ treatment of patients ≥18 years of age with DPN and PHN receiving pregabalin doses up to 600mg/day. Efficacy, based on the endpoint mean pain score derived from a daily pain diary, was evident early in treatment with a significant separation from placebo generally within the first week. Significant differences in favour of pregabalin were seen for daily sleep interference scores, Patient and Clinician Global Impression of Change, and quality of life and mood assessment measures. Pregabalin was generally well tolerated. The most common treatment-related adverse events in the clinical trials program were dizziness, somnolence and peripheral oedema, occurring in 21.2%, 13.5% and 7.4% of pregabalin patients compared with 6.2%, 3.6% and 2.1% of placebo recipients, respectively; however, these led to discontinuation rates of only 3.5%, 2.6% and 0.9% of the pregabalin patients.
Pain is a major problem for many people who experience a spinal cord injury (SCI). There are now a number of studies demonstrating both the high prevalence of SCI pain and the major impact it can have on function and quality of life. Several distinctive types of pain have been described following SCI. Each of these types of pain has different features in regards to location, descriptors and possible underlying pathology and mechanisms. of the different types of SCI pain, neuropathic pain is often the most difficult to treat and the most poorly understood. Neuropathic SCI pain is not a single entity and has a least two major subtypes that have different patterns of presentation, onset times, mechanisms and response to treatment. Dr Philip Siddall and his colleagues have conducted several studies examining the prevalence and features of different types of pain following SCI. These studies demonstrate the distinctive characteristics of different types of pain that suggest differences in underlying mechanisms and possible response to treatment. In addition to discussing these topics, he will also discuss how these different types of pain may be classified using a recently proposed taxonomy developed by the IASP Task force on Spinal Cord Injury Pain. There are a number of animal models that have been used to study the problem of neuropathic SCI pain. Professor Robert Yezierski and his colleagues have employed an excitotoxic model of neuropathic at- and below-level pain that results in selective damage to the spinal grey matter and a pattern of behaviors that appear to parallel the clinical features of neuropathic pain. Studies using this model have identified a number of physiological, anatomical, inflammatory and neurochemical changes that may underlie neuropathic pain and may present targets for therapeutic intervention. A population of spinal neurons believed to represent a substrate responsible for the condition of injury induced at-level pain is one such target along with different intracellular signalling cascades. Dr Nanna Finnerup and her colleagues have performed a number of studies investigating the efficacy of treatments in neuropathic SCI pain and have recently reviewed the literature of drugs used for this type of pain. Randomised controlled trials support the use of tricyclic antidepressants and antiepileptic drugs in neuropathic pain. However, few studies exist in SCI pain and despite the promising mechanisms of action of many analgesics, no oral treatment has so far proven to be effective. Recently, a mechanism-based approach has been emphasized to facilitate more rational treatment strategies of individual patients. It is assumed that studying the effect of drugs on specific pain phenomena such as spontaneous and evoked pain may help elucidate single pain generating mechanisms and their treatment. The sodium channel blocker lidocaine is effective in relieving spontaneous pain and brush-evoked dysesthesia in spinal cord injured patients with and without evoked pains. Hence, the efficacy of the systemic use of sodium channel blockers and N-methyl-D-aspartate antagonists on SCI pain provides some insight into the pathophysiological mechanisms and supports the role of neuronal hyperexcitability in SCI pain.
OPIOIDS IN NEUROPATHIC PAIN: WHERE DO WE STAND?

C.D. Wells, M.C. Rowbotham, M. H. Hanna

Abstract not available
SIMILARITIES AND DISSIMILARITIES BETWEEN NEUROPATHIC PAIN AND OTHER PAIN CONDITIONS

N. Attal\textsuperscript{1}, P.T. Hansson\textsuperscript{2}, J. Haythornthwaite\textsuperscript{3}

\textsuperscript{1}INSERM E-332 and Centre D' Evaluation Et De Traitement De La Douleur, Hopital Ambroise Pare, Boulogne-Billancourt, France, \textsuperscript{2}Department of Surgical Sciences, Section of Clinical Pain Research and Neurogenic Pain Unit, Multidisciplinary Pain Center and Department of Rehabilitation Medicine, Karolinska Institute/Hospital, Stockholm, Sweden, \textsuperscript{3}Department of Psychiatry and Behavioural Sciences, John Hopkins Medical Institutions, Baltimore, USA

Neuropathic pains are characterized by the combination of unspecified positive and negative symptoms, but there are still no validated diagnostic criteria for such pains. It is therefore necessary to address whether simple clinical criteria may differentiate pains associated with a definite injury to the nervous system from non-neuropathic pains and which are their main common clinical characteristics. This workshop will present updated clinical data pointing to the similarities and dissimilarities between neuropathic pains and other pain conditions, in terms of symptoms, signs and psychological factors. Nadine Attal (France) will present the results of recent clinical studies showing that some clinical descriptors may discriminate between pains associated with an injury to the nervous system from those related to other somatic lesions. Per Hansson (Sweden) will discuss differential diagnostic issues based on the literature, and recent clinical studies showing some overlap between different pain conditions, particularly with regards to sensory deficits. Finally Jennifer Haythornthwaite (USA) will emphasize the role of psychological factors, such as pain coping strategies, in neuropathic and non neuropathic pain conditions.
TRIGEMINAL BRAINSTEM AND THALAMIC SENSITISATION: NEURAL SUBSTRATES AND CLINICAL IMPLICATIONS

B.J. Sessle¹, J.O. Dostrovsky², T.S. Jensen³

¹Faculty of Dentistry, University of Toronto, Toronto, Canada, ²Department of Physiology, Faculty of Medicine, University of Toronto, Canada, ³Department of Neurology and Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark

Background and Aims: Nerve injury or other tissue damage or inflammation in the orofacial region can induce pain and other sensory changes in the damaged region. These changes can be acute or chronic and involve superficial as well as deep structures. This workshop focusses on recent findings in animal models of orofacial neuropathic and inflammatory-related pain conditions and their clinical correlates that suggest that trigeminal (V) brainstem and thalamic central sensitisation may contribute to these conditions. Clinical Aspects of Central Sensitisation in the Orofacial Region: Dr Jensen will outline data indicating that the pain and other sensory changes that may occur after peripheral injury or inflammation include hypersensitivity to mechanical, electrical and thermal stimuli. This hypersensitivity is not linked to a particular aetiological condition but may be seen after inflammatory conditions, neuropathic disorders and migraine, for example, neuropathic conditions such as trigeminal neuralgia may be associated with signs of mechanical or cold allodynia, and even after central lesions such as lateral medullary infarctions or multiple sclerosis, sensitisation phenomena can be demonstrated in the orofacial region. and in patients with musculoskeletal pain involving the head region (e.g. headache and whiplash injury), hypersensitivity can be seen as a manifestation of referral. Finally, sensory hypersensitivity can occur after deafferentation of body parts within or adjacent to the orofacial region. Neuronal Properties and Central Sensitisation in V Brainstem and Thalamus: Dr Dostrovsky will review evidence that V subnucleus caudalis is the integral orofacial nociceptive relay in the brainstem, and that it shares several functional and morphological features with the spinal dorsal horn. Recent evidence also shows that orofacial nerve injury or inflammatory irritants induce a prolonged increase in excitability of caudalis nociceptive neurones that is reflected in enhancement of mechanoreceptive field and response properties, and that may be accompanied by pain behaviour including reflexly induced jaw muscle activity. These changes indicative of central sensitisation can be induced in regions to which caudalis projects (e.g. subnucleus oralis and VPM thalamus) as well as in caudalis itself. Role of Subnucleus Caudalis and NMDA and Purinergic Receptor Mechanisms: Dr. Sessle will show that caudalis is crucial in the development of oralis and VPM thalamus sensitisation by documenting that caudalis synaptic blockade disrupts central sensitisation induced in oralis and VPM nociceptive neurones. Glutamate released within caudalis from orofacial primary afferents and acting through NMDA receptor processes has been shown to be critical in the development of caudalis central sensitisation. Nonetheless, recent in vitro as well as in vivo studies reveal that purinergic receptor mechanisms may also be involved in the initiation of central sensitisation in caudalis, and that oralis central sensitisation is dependent on the influence of purinergic receptor mechanisms within caudalis. Conclusions: These findings point to the crucial role of subnucleus caudalis in orofacial nociceptive transmission and central sensitisation and to the involvement of purinergic as well as NMDA receptor mechanisms, and their likely involvement in acute and chronic orofacial pain induced by peripheral injury or inflammation.
Some neuropathic pain patients have tactile allodynia – that is, very gentle touch stimuli are able to evoke what they describe as pain. In these cases, the sensory experience of pain appears to be mediated by activity in large myelinated fibers. This poses an important question regarding somatosensory physiology because there appears to be a change in the quality percept from that of touch to that of pain. Current hypothesis favor a central mechanism mediating this phenomenon. Actually, selective nerve block studies in patients and in human surrogate models have shown that activation of A-beta fiber tactile afferents (possibly of the rapidly-adapting RA type) is sufficient to elicit the percept of allodynia. It is proposed that to elicit pain, those afferents have to gain access to the nociceptive system in the CNS. At least two mechanisms (central sensitization and sprouting) have been demonstrated experimentally and may account for the touch-evoked pain of allodynia. However, alternative explanations involving a peripheral mechanism cannot be discarded. Psychophysical experiments relating type of peripheral fiber excited to quality of perception evoked, and several microneurographic findings in patients suffering from neuropathic pain conditions, suggest that at least in some cases, mechanisms operating at a peripheral level may be the cause of mechanical allodynia. These experiments suggest that increased axonal membrane hyperexcitability results in chaotic spontaneous discharges and afterdischarges evoked by the passage of impulses through hyperexcitable segments of damaged axons, resulting in the perception of an unpleasant sensation due to the severe distortion of the natural spatio-temporal sequence of impulses reaching consciousness. During this workshop available animal evidence explaining this phenomenon will be presented. Also, possible, and sometimes conflicting, proposed mechanisms for dynamic mechanical allodynia will be discussed.
At present there are no established research criteria for classifying neuropathic pain. Neuropathic pain have been classified in various ways clinically and experimentally, but a pathophysiological useful classification distinguishes between: stimulus dependent and stimulus independent types of neuropathic pain. The stimulus dependent types of pains includes mechanical and thermal evoked pains, while the stimulus independent types are characterised by spontaneous, ongoing types of pain. In the individual patient the various types of pain may coexist in different combinations and contribute to the heterogeneity of the clinical picture. Neuropathic types of pain has irrespective of underlying pathology certain essential characteristics: sensory deficit in the painful area, alldynia or hyperalgesia in the painful area, 3) afternature, 4) gradual increase of pain following repetitive stimulation, and 5) paroxysms of pain. In particular the two paradoxical clinical features: loss of sensation and increased sensation are met by most neuropathic pain conditions and reflect the deafferentation and neuronal hyperexcitability. Sensory examination permit an analysis of sensory modalities and mechanisms involved (e.g. peripheral vs. central). Simple bedside testing will in large scale studies be sufficient to demonstrate hyperalgesia, alldynia or hypoesthesia to different sensory modalities and may also provide important information about pain. for example, in stroke patients with somatosensory deficits the occurrence of central pain can be predicted from the presence of hyperalgesia or alldynia to touch, pinprick or temperature as assessed by simple testing. Quantitative measures using stimulus-dependent or response-dependent measures allow determination of thresholds to increasing stimuli and generation of stimulus-response functions. It is possible that such detailed analysis of sensory function can be used in a subclassification of different types of neuropathic pain. However, at present it is unknown if quantitative measures add to our understanding of neuropathic pain. Pharmacological modulation of different receptor systems acting either peripherally or centrally may add another dimension and assist in clarifying whether etiological or topographical different neuropathic pain conditions can be separated on basis of their pharmacological response profile. Further studies are needed to determine the possible value of quantitative and other sophisticated measures in clarifying mechanisms, in treating neuropathic pain patients and in predicting outcome.
Relieving chronic pain associated with injury or disease affecting the peripheral or central nervous system remains a difficult treatment challenge. Pharmacologic management is not a cure and should be considered an integral component of a more comprehensive approach to treatment. Fortunately, well-designed and appropriately controlled clinical trials expand the list of proven treatments with every passing year. Four medication categories form the majority of treatment options for chronic neuropathic pain: antidepressants, anticonvulsants, opioids and topical agents. As none provide ‘moderate’ or better relief in more than about 60% of treated patients, new treatments with better efficacy and fewer side effects continue to be urgently needed. Animal models of acute pain and chronic neuropathic pain, extremely useful for elucidating pain mechanisms and developing new treatment targets, are now widely used for pre-clinical testing of analgesic drug candidates. However, many clinical syndromes encountered by the neurologist have no analogous animal pain model, and likewise, many clinical syndromes have never been the subject of a controlled treatment trial. We are slowly gathering an evidence base on which to make informed treatment decisions from both an efficacy and cost perspective, but too few trials have directly compared drugs with different mechanisms of action.
Surgical approaches to neuropathic pain fall into three categories: restorative, ablative, and augmentative. Decompression of an entrapped nerve is an example of a restorative procedure. Radiofrequency rhizotomy is an example of an ablative procedure for trigeminal neuralgia. Dorsal column stimulation for treatment of radicular pain is an example of an augmentative procedure. Knowing the variety of surgical therapies and their indications is the cornerstone of good pain-practice. This lecture will concentrate on procedures, use of which may be overlooked by many pain-practitioners. Easily treated occult nerve entrapments may be mistaken for complex regional pain syndrome, for example. Emphasis will be placed also on newer modalities such as motor cortex stimulation for pain from stroke, and midline myelotomy for pelvic pain.
NEW PARTNERSHIPS IN MANAGING NEUROPATHIC PAIN

T.S. Jensen¹, U.E. Kongsgaard², M. Hanna³

¹Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark, ²Department of Anaesthesia, The Norwegian Radium Hospital, Oslo, Norway, ³Pain Relief Research Unit, Academic Department of Anaesthetics, King’s College Hospital, London, United Kingdom

Treatment of neuropathic pain conditions is still unsatisfactory and fewer than a third of patients with neuropathic pain conditions get moderate or better pain relief with current existing treatments. Professor Troels Jensen, Department of Neurology and Danish Pain Research Center, Aarhus, Denmark raises the question whether the currently used diagnosis and classification is the best way to find the optimal treatment for the pain. Mechanism-based classification of pain may be a rational approach to classify patients, but we only have a vague idea about how neuropathic symptoms translate into mechanisms and vice versa. There may be several symptoms present, each caused by separate mechanisms. Moreover, one mechanism can cause different symptoms. A straightforward approach is to categorise only those conditions as neuropathic, where a clear injury of the peripheral or central nervous system can be documented. However, hyperexcitability, a classic feature in neuropathic pain, is also seen in non-neuropathic conditions such as musculoskeletal pain. The dynamic nature of the nociceptive system will result in plastic changes, which may also cause a temporal shift in the pain complaint. The drift from a disease and aetiology-based classification to a more mechanism-based classification of chronic pain emphasises the need to solve issues related to diagnosis, classification and treatment. In line with this there is a need to review the agents available for the treatment of neuropathic pain. The traditional view with respect to opioids is that neuropathic pain is opioid resistant. However, according to Professor Ulf E. Kongsgaard, Dept of Anaesthesia, Intensive Care and Pain Management, The Norwegian Radium Hospital, Oslo, Norway, this view is being challenged by an expanding body of clinical experience and data that supports a continuum of opioid responsiveness in neuropathic pain syndromes. Many factors will influence opioid responsiveness; type of pain, temporal pattern of pain, nature of disease, drug specificity and so on. Additionally, there are some unanswered questions: Which patients will benefit from opioid therapy? Which opioids are the most appropriate to use? Will tolerance develop? What about long-term opioid use? However, several double-blind randomised trials of opioid analgesics have been published in recent years. Considered together, the results of these studies provide a reliable base of evidence for considering opioids as a component for treating neuropathic pain. One further question might be what are the benefits of combining opioids such as oxycodone with the standard of therapy, α2 δ compounds such as gabapentin? According to Dr Magdi Hanna, Pain Research Unit, King’s College Hospital, London, United Kingdom, evidence is growing that supports the use of opioid / α2 δ combination. Given limited treatment options we must look at combining existing therapies to induce analgesia through separate or overlapping mechanisms, preferably with separate adverse events profiles, aimed at amplifying the desired effect (analgesia or increase in responder rate) while reducing, or at least not increasing, side effects. α2 δ compounds bind to the α2−δ protein, associated with voltage-gated calcium channels. However, in clinical trials, pain scores are significantly reduced against placebo and the overall responder rate is still under 50% of patients, even amongst responders significant numbers still have residual pain. Meanwhile, full agonist opioids act through the opioid receptor system modulating nociceptive transmission. They remain the most efficacious drugs for controlling moderate to severe pain but their use in neuropathic pain has produced mixed results. However, the combination of α2−δ compounds and opioids has now been tested in pre-clinical models for neuropathic pain, surrogate pain models in volunteers and in acute postoperative pain. These studies so far have revealed encouraging results, which if translated in chronic neuropathic pain, could improve outcome for those patients.
Trigeminal neuralgia is unique among neuropathic pain conditions in that there are several effective treatments available. There are, however, no set guidelines and very few comparative studies published. Treatment choice therefore in the newly diagnosed cases remains a matter of clinical judgement, local resources and personal preferences. For the not so uncommon cases of recurrence of pain after many years, there are no agreed guidelines for the choice of treatment. There are also conflicting reports on treatment efficacy in patients with atypical trigeminal neuralgia and those with concomitant MS. This workshop is aimed at addressing these issues. It will discuss how to reach a precision diagnosis of trigeminal nerve pain by employing novel radiological and neurophysiological methods, go over the existing evidence for the efficacy of various treatments, and offer a treatment paradigm for the particular subtype of trigeminal nerve pain the patient has. There will be three lectures, each 20 minutes followed by a general discussion for 30 minutes. (1) PATHOLOGY AND PATHOPHYSIOLOGY OF TRIGEMINAL NEURALGIA by Prof Nurmikko who will present an overview of hypotheses regarding the origin and generation of trigeminal neuralgia, with particular attention to different types of neuralgia. He will further introduce the concept of precision diagnosis in these patients with emphasis on how it relates to the choice of treatment. (2) NEUROABLATIVE PROCEDURES by Dr van Zundert who will discuss the indications for and efficacy of main ganglion and root level procedures, highlight the advantages and disadvantages of these methods, and address some of the new developments in the field. (3) MICROVASCULAR DECOMPRESSION by Prof. Shulev who will focus on the preoperative clinical, neurophysiological and radiological evaluation of the patient and the operative technique used. He will also present data on long-term success rates and discuss the suitability of this method for different types of trigeminal neuralgia. The general discussion is expected to centre around the issue of choosing the right treatment modality for the patient. The focus is on problems that arise when usually effective pharmacotherapy fails. In particular these questions will be discussed: (1) at what stage of the disease should interventionist treatment be considered, (2) are there particular qualities of trigeminal neuralgia pain that either favour or rule out certain treatments, (3) how to deal with recurrence of pain following a procedure, and (4) how a patient with pain due to MS is best treated. Following the discussion, the chairman will draft a set of recommendations that will cover many of these issues.
NON-OPIOID DRUGS IN THE TREATMENT OF NEUROPATHIC PAIN

F.W. Bach¹, A.H. Dickenson², S.H. Sindrup³

¹Danish Pain Research Center, Aarhus, Denmark, ²Department of Pharmacology, University College, London, United Kingdom, ³Department of Neurology, Odense University Hospital, Odense, Denmark

Currently, antidepressants and anticonvulsants are the most widely used drugs in neuropathic pain, but other non-opioid drug classes begin to play a role. Basic and clinical research provides the rationale for using the different types of drugs and gives us an impression of their potential efficacy. Basic science has gone some way to explaining some of the mechanisms of non-opioid drugs in neuropathic pain. In addition, a number of new targets have been revealed. Thus, although lidocaine and carbamazepine are likely to act through sodium channel blockade, new data reveal that there are novel variants of these channels in peripheral nerves. Potassium channel openers also show some promise. Calcium channels are keys to transmitter release and also neuronal activity. New data not only indicate how gabapentin and pregabalin act but reveal interesting regulatory controls on these channels. The present issues of side-effects of NMDA antagonists such as ketamine may be circumvented by drugs acting on subtypes of this receptor. Finally, although antidepressants are old drugs there has been much new data on monoamine controls. Better understanding of mechanisms should aid the treatment of neuropathic pain with non-opioid drugs. Carbamazepine treatment of trigeminal neuralgia probably represents the first evidenced treatment of a neurogenic pain with anticonvulsants. Carbamazepine also reduces pain in diabetic neuropathy, and lamotrigine, another anticonvulsants with sodium channel blocking effects, has been shown to relieve a variety of neuropathic pain conditions. However, at the present time, gabapentin is the most widely used anticonvulsant in neuropathic pain and its efficacy is evidenced in several large trials. The clinical usefulness of anticonvulsants such as valproic acid, oxcarbazepine, topiramate and levetiracetam still remains to be settled. The evidence for using tricyclic antidepressants with presynaptic inhibition of monoamine reuptake and possibly additional pharmacological actions is overwhelming and indicates an acceptable efficacy of this drug class. The new and more selectively acting antidepressants have also been tried. Selective serotonin reuptake inhibitors appear to be much less effective than the tricyclics, whereas recent data on a serotonin noradrenaline reuptake inhibitor indicate that this type of antidepressants may have an efficacy in the same range as the tricyclics. Selective noradrenaline reuptake inhibitors may deserve attention in future drug trials. Basic science has pointed at the NMDA-receptors as a potential target for drugs in neuropathic pain, but so far, no NMDA-receptor antagonist drugs have been used in clinical neuropathic pain. Intravenously infused ketamine can relieve neuropathic pain, but this route of administration is inconvenient in chronic pain conditions and psychomimetic side effects are also a clear-cut limitation for the use of ketamine. Dextromethorphan, riluzole and memantine are NMDA-receptor antagonists for oral use. The clinical data on these drugs are limited and give equivocal results. There is a need for both focused and large scale trials with NMDA-receptor antagonists in neuropathic pain. A novel treatment approach in neuropathic pain is cannabinoids, which in two recent randomised, controlled trials have shown some efficacy in pain in multiple sclerosis.
CLINICAL NEUROPHYSIOLOGICAL TOOLS FOR THE ASSESSMENT OF NEUROPATHIC PAIN

U. Baumgaertner¹, L. Garcia-Larrea², G. Cruccu³

¹Johannes Gutenberg University, Institute of Physiology and Pathophysiology, Mainz, Germany, ²Human Neuro. Laboratory at CERMEP, Hopital Neurologique, Lyon, France, ³University 'La Sapienza', Department of Neurological Sciences, Rome, Italy

In this workshop, three neurophysiological tools for diagnosis and/or documentation of lesions of the nociceptive system are presented: Quantitative Sensory Testing (QST), Laser evoked potentials (LEP) and nociceptive reflexes. Is it possible to draw conclusions upon the underlying pain mechanism in the individual patient based on the results obtained by application of these methods? QST is a psychophysical method to assess threshold changes of different sensory modalities such as touch, vibration, or mechanical and heat pain. Other than simply testing whether a stimulus is perceived or not, QST can detect subtle changes of sensory function yielding degree and direction of change (loss or gain) within the same subject or between groups of subjects. Other than QST which is based on ratings given by the patient, LEPs are an objective electrophysiological measure. Laser heat pulses, which selectively excite the free nerve endings (A-delta and C) in superficial skin layers evoke typical cortical responses in EEG recordings. They proved reliable in assessing damage to the peripheral and central nociceptive pathway in various types of lesions and diseases. The techniques of QST and LEP are presented in the first presentation (Ulf Baumgaertner), as well as comparison of the results obtained in pain patients (emphasis on QST). The second talk (Luis Garcia-Larrea) will focus on LEPs in patients with neuropathic pain of central origin. The finding of LEP attenuation / suppression to stimulation of a painful territory substantiates the diagnosis of neuropathic pain. Such LEP attenuation is observed even in case of hyperalgesia or allodynia; in these latter cases, ultra-late components (800-900 ms) may appear concomitantly with the attenuation or disappearance of late (200-400 ms) responses. Conversely, in fibromyalgia and myofascial syndromes, chronic fatigue syndrome, chronic inflammatory pains, and psychogenic pain, LEPs have been found normal or even facilitated. In selected patients, normal or enhanced LEPs to stimulation of a painful territory may reflect enhanced attention toward the laser stimulus, and increase the diagnostic probability of psychogenic pain. Main topic of the third presentation (Giorgio Cruccu) is the application of laser stimulation in the trigeminal system. Because of a high receptor density in the facial skin and the very short conduction distance, LEP recordings after trigeminal stimulation are easier and quicker than those after stimulation of the limb extremities. Therefore, stimulus intensities close to perception threshold and fewer trials are sufficient to yield well-defined late and also ultralate LEPs. Trigeminal LEPs have been found absent or delayed in patients with trigeminal neuralgia, trigeminal neuropathies, tumours, brainstem infarctions, or demyelinating plaques. High-intensity pulses directed to any trigeminal division also elicit reflex responses: a blink-like reflex in the orbicularis oculi and a single silent period in the contracting masseter muscle. The availability of a neurophysiological method of assessing function of the trigeminal nociceptive pathways reaching both the cerebral cortex and the brainstem reflex circuits, has provided new opportunities for investigating the pathophysiology of orofacial pain syndromes.
THE ROLE OF ECTOPIC IMPULSE ACTIVITY IN THE GENESIS OF NEUROPATHIC PAIN

M. Devor\textsuperscript{1}, J. Wood\textsuperscript{2}, G.R. Strichartz\textsuperscript{3}

\textsuperscript{1}Institute of Life Sciences, Hebrew University of Jerusalem, Israel, \textsuperscript{2}University College London , United Kingdom, \textsuperscript{3}Harvard Medical School, Boston, USA

Overall goal: The object of this workshop is to present the most modern evidence for the importance of ectopic impulse firing in the peripheral nervous system in the genesis or maintenance of neuropathic pain. Doctor Devor will summarize the data from experimental animal studies that demonstrate the nature and locations in peripheral nerve where ectopic activity occurs, will discuss the importance of sub-threshold oscillations in membrane potential as an essential substrate for ectopic firing and will suggest which types of ion channels in nerve support such activities. Doctor Wood will present data from experiments in which specific ion channels have been deleted ('knocked out') from the genome. What changes in physiology and neuropathic pain behavior do these deletions produce? Doctor Strichartz will present data showing how acute pharmacological modifications with specific neurotoxins can induce spontaneous ectopic firing and how kinetically 'tailored' channel blockers can suppress such firing in vitro and reverse neuropathic pain in vivo. This is a topic that will be interesting to both researchers and clinicians who seek a deeper understanding of the conditions that they treat. Ample time will be reserved for questions from the audience.
INTERACTION BETWEEN BASIC AND CLINICAL RESEARCH ON NEUROPATHIC PAIN

A Pertovaara¹, C.J. Woolf², P.T. Hansson³

¹Department of Physiology, Institute of Biomedicine, University of Turku, Finland, ²Neural Plasticity Research Group, Department of Anesthesia and Critical Care, Harvard Medical School, Charlestown, USA, ³Section of Clinical Pain Research, Department of Surgical Science, Karolinska Institute/Hospital, Stockholm, Sweden

The field of neuropathic pain is particularly suitable for interaction between clinical pain researchers and pre-clinical scientists working with animal models to join forces in our efforts to reduce the relentless suffering of patients. The main objectives of the workshop are to define areas where close interaction is warranted to facilitate progress. Dr Hansson will point out the variety of symptoms and signs in clinical neuropathic pain conditions, emphasizing that conditions with similar etiology may have a heterogeneous clinical phenomenology. This is in contrast with reports from animal models of neuropathic pain where behavioral abnormalities are reported to be present on a group level. Possible reasons for this mismatch will be debated in the context of animal models and behavioral testing techniques currently in use to try to reflect clinical conditions. Dr Pertovaara will focus on behavioral findings in animal models of neuropathic pain and raise questions about their validity. He will discuss, e.g., if the von Frey hair-induced withdrawal is a sign of allodynia or tickle; what the relevance is of heat hypersensitivity; if animal models tell us anything about spontaneous pain; if an experimental model producing identical symptoms/signs in close to 100% of animals resembles human conditions with highly variable symptoms and signs. Dr Woolf will discuss the difficulties of relating pain mechanisms, defined as identifiable neurobiological states driven by particular molecular/cellular and system processes, and the symptoms that patients experience. These include identifying putative pain mechanisms in animals with manipulations of their nervous systems and identifying pain mechanisms in patients. One of many problems is that animals may exhibit pain-like behavior in defined models but the models may neither model human disease nor even the mechanisms responsible for human pain. Animal models provide important clues as to the pathophysiological situation in patients but they are not surrogates. We need to model mechanisms in animals and use these to evaluate new analgesics and develop diagnostic tools to identify mechanisms in patients.
Neurostimulation is a proven therapeutic option for patients with Failed Back Surgery Syndrome (FBSS) and Complex Regional Pain Syndrome (CRPS), for whom conservative therapies lack effectiveness and oral analgesics cause intolerable side-effects. Studies have demonstrated that neurostimulation, with a device such as the Synergy system, provides long-term improvement in pain relief and health-related quality of life in patients with FBSS and CRPS. This symposium presents an overview on the role of neurostimulation for the management of these two chronic neuropathic pain conditions.

**Mechanism of action:** The mechanism of action of SCS in neuropathic pain will be discussed. Traditionally, the mechanism of action of SCS was based on the ‘gate control’ theory of Melzack and Wall. This theory is no longer considered to be entirely accurate and, recently, four hypotheses have been put forward to explain the mechanism of action of SCS: blockage of the spinal-thalamic tract, antidromic activation of large afferent fibres, activation of supraspinal loops and direct activation of descending inhibitory systems of the spinal cord. Activation of supraspinal loops and antidromic activation of large afferent fibres are perceived to be the more accurate of these theories.

**Health Technology Assessment (HTA):** Results from a recent HTA, which was carried out to evaluate the clinical effectiveness and cost-effectiveness of SCS for the treatment of FBSS and CRPS will be outlined. In CRPS, data from the HTA has shown that SCS is a clinically effective and cost-effective treatment for patients with type I CRPS. In FBSS/chronic back and leg pain, data from one randomised controlled trial, one cohort study and 72 cases series has consistently demonstrated that SCS reduces pain, improves health-related quality of life and increases the proportion of patients able to return to work.

**Complex Regional Pain Syndrome (CRPS):** The use of spinal cord stimulation (SCS) for the treatment of CRPS will be examined. The majority of studies have shown SCS to have substantial beneficial effects in the management of CRPS, providing long-term reduction in pain intensity and an improvement in health-related quality of life. Consequently, according to a recent consensus, it is now recommended that CRPS patients who do not respond to an acceptable level of conventional treatment within 12−16 weeks should be given a trial of more interventional therapies such as SCS.

**FBSS/chronic back and leg pain:** Finally, the use of SCS for chronic neuropathic pain in FBSS will be discussed. Studies have demonstrated that approximately 60% of FBSS patients treated with SCS experience 50% or more pain relief. In particular, early treatment with SCS has been shown to yield the best results. A recent study has demonstrated that in patients who had undergone previous surgical procedures, the shorter the duration of time to implantation of a SCS system, the greater the rate of success. Importantly, dual-lead, dual channel systems increase the chance of successfully treating more patients with FBSS because of the inherent flexibility of the system.
PAIN IN DIABETIC AND OTHER SMALL-FIBER NEUROPATHIES

J.W. Griffin

Abstract not available
Cytokines are a heterogeneous group of polypeptides that were originally found to mediate activation of the immune system and inflammatory responses. They are extracellular signaling proteins, part of a bi-directional circuit between the immune system and the nervous system, acting at hormonal concentrations through high-affinity receptors. Interest in the modulation of pain by cytokines arose through observations on the ‘illness response’, the response of the organism to infection, associated with fever, fatigue, loss of appetite, and hyperalgesia. In recent years, a number of animal studies have shown direct actions of cytokines on nociceptive fibers and a role of cytokines in the initiation and maintenance of pain. In particular, inhibition of pro-inflammatory cytokines is able to reduce hyperalgesia, and exogenous cytokines applied to nerves or to their receptive fields induce pain associated symptoms and directly elicit neuronal activity. In clinical medicine, prototypic examples of diseases in which high cytokine levels correlate with pain, are rheumatoid arthritis or the neuropathy in erythema nodosum leprosum. In other peripheral neuropathies, there is a less stringent correlation between painfulness and the expression of proinflammatory cytokines. Recently, pain from spinal root lesions has been associated with the release of tumor-necrosis-factor-alpha (TNF), and case reports show promising results of TNF inhibition. The use of cytokine modulating drugs in refractory neuropathic pain syndromes will have to be studied in controlled trials.
Some of the important questions regarding pain in multiple sclerosis (MS) are: How common is pain in MS? What kind of pain do MS patients have? How much of this pain is directly caused by the lesions in the CNS, i.e. central pain? Which are the characteristic features of central pain in MS? How much is secondary to other MS dysfunctions like spasticity, paresis, etc? Do MS patients have any particular nociceptive pains? Which pain treatments can be recommended? In the lecture, these matters will be discussed and the current knowledge will be reviewed with an emphasis on central pain. Neurology textbooks inform that patients with MS might suffer from trigeminal neuralgia, painful tonic seizures or pain caused by spasticity. They give the impression that pain is rather uncommon in MS, but it is now well known from research that in fact pain affects a considerable fraction of MS patients. Studies from the last 20 years indicate that 30-70% of MS patients have longstanding pain, not including headache. In assessing pain in MS one difficulty is the differentiation of central pain from peripheral neuropathic, nociceptive and primary psychogenic pain. For instance, how can it be decided if back pain is neuropathic or not. In our studies based on 364 MS patients, it was found that 58% had longstanding pain and that 27.5% had central pain, including 4.9% with trigeminal neuralgia (caused by demyelinating lesions in the brain stem). Among those with non-trigeminal central pain, the pain dominated in the lower extremities (87%) over that in the upper extremities (31%). Among the pain qualities the most common were burning (40%), aching (40%) and pricking (24%). Only a few patients had non-trigeminal paroxysmal pain. In 23% of the patients with central pain, the pain started at the onset of the disease or within one year of the onset. A large majority had constant pain at the time of the examination. In a few patients the pain was present mainly during relapses. Many experienced increased pain after physical activities. All patients except two were found to have somatosensory abnormalities as shown with clinical and quantitative sensory testing. In the majority the abnormalities affected almost all modalities, but they were most pronounced for innocuous and noxious temperatures. Some of the patients had spasticity, but based on a thorough clinical analyses it was concluded that only a few of them had pain that was caused by the spastic contractions, i.e. nociceptive muscle contraction pain. Like in other diseases the treatment of the pain in patients with MS has to be tailored individually. Trigeminal neuralgia and other paroxysmal pains are treated like in non-MS patients. for the non-trigeminal pain tricyclic antidepressants and antiepileptic drugs are preferably used, but side effects are often a problem and no controlled trials have been published showing the effects in MS-patients. Some patients may benefit from analgesics.
CENTRAL POST-STROKE PAIN: NEW DEVELOPEMENTS

J. Boivie¹, W. Magerl², T.S. Jensen³

¹Department of Neurology, Linköping University Hospital, Linköping, Sweden, ²Institute of Physiology and Pathophysiology, Johannes-Gutenberg University, Mainz, Germany, ³Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark

Central post stroke pain (CPSP) is a well-known and rather common complication following a stroke. CPSP is not only limited to lesions involving the thalamus but can be seen following any vascular lesion, which involves the spinothalamic tract or other central nociceptive pathways. Several aspects of CPSP are still unknown and unclarified. CPSP is probably only identified in a minority of patients. Several factors may contribute to the difficulties in diagnosing CPSP. Among these can be mentioned variation in how CPSP starts, variation in quality of pain, and in the contribution of pain to other neurological symptoms and signs in CPSP patients. The problems with correct diagnosis in defining criteria for CPSP will be discussed by dr. Jörgen Boivie in the workshop. He will also discuss whether the increased ability to localize stroke lesions by newer imaging techniques has improved our ability to identify CPSP. Lateral brainstem infarction (Wallenberg’s syndrome) is a classical condition giving rise to CPSP. Dr. Walter Magerl will review a study using MRI-based identification of brain stem areas involved in conjunction with clinical testing, recording of evoked potentials, blink reflexes and a detailed quantitative sensory testing (QST). The majority of patients developed chronic pain of the ipsilateral face and/or contralateral trunk and limbs after a delay of several weeks to months. Lesions of the central pathways (spinothalamic tract / trigeminothalamic tract) were not strictly related to development of chronic pain. However, analysis of chronic facial pain revealed that in all patients examined the development of facial pain was related to lesions of the lower trigeminal tract (i.e. the axons of the nociceptive primary afferents). Based on these data it is suggested that chronic facial pain after lateral brainstem infarction is due to deafferentation of the central nociceptive pathways. CPSP is characterised by somatosensory disturbances, which almost always involves thermal functions. Previous studies show consistent increased thermal detection threshold and a reduced thermal sensibility index. Sometimes these changes are associated with a hyperalgesia to thermal stimuli and a paradox response to different temperature stimuli. The mechanisms responsible for the ongoing and abnormal evoked pain in post-stroke pain are not clear. One hypothesis proposes that central pain is related to loss of temperature sensation and the result of a lost normal cold inhibition of third order neurons. The unmasking of these previously inhibited neurons is then assumed to result in pain. Dr. Troels S.Jensen will present results from a QST study in which cold detection thresholds and cold pain thresholds are related to ongoing and evoked pain pain in CPSP patients. Findings indicate that there is no direct relationship between ongoing pain and the perception of cold or cold pain.
Neuropathic pain is a field that is currently at an important crossroads. Treatment can be addressed from a traditional diagnosis-oriented approach or from a mechanism-based approach. Medications with higher efficacy and fewer side effects have recently been introduced to the market. Most major pharmaceutical companies have active R&D programs to develop new drugs that attack the targets identified in basic research on neuropathic pain. Regulatory agencies (FDA, EMEA) have started to set guidelines for the approval of drugs for the treatment of neuropathic pain. This workshop aims to outline the pro’s and con’s of narrow versus wide licencing strategies, indications being based on diseases or mechanisms, and the problem of orphan drugs.

Dr. Sampaio will speak about requirements for the clinical development of a new neuropathic pain treatment in the CPMP perspective. Dr. Dworkin will speak about requirements for the clinical development of a new neuropathic pain treatment in the FDA perspective. Dr. Cruccu will speak on the EFNS guidelines for the treatment of neuropathic pain. These three presentations will provide, although indirectly, an overview of how drugs were developed so far.

Participants will learn about the scientific and legal aspects of the process that makes new treatments available for patients in pain. Participants will also be able to add their views to this ongoing debate.
ROLE OF THE CEREBRAL CORTEX IN PATHOLOGICAL PAIN STATES

M.C. Bushnell¹, J. Lorenz³, C. Maihöfner²

¹Department of Anesthesia, McGill University, Montreal, Canada, ²Departments of Neurology and Physiology, University of Erlangen-Nuremberg, Erlangen, Germany, ³Institute of Physiology, University Hospital Eppendorf, Hamburg, Germany

There is accumulating evidence that there are multiple mechanisms underlying neuropathic and other pathological pain states, including changes in pain transmission and modulation at various levels of the nervous system. This workshop will address ways in which the cerebral cortex participates in the creation and maintenance of pathological pain. Dr. Juergen Lorenz will discuss “Functional imaging of allodynic pain states in the human brain.” He will present evidence from functional brain imaging studies that characteristic signs of pathological pain states, such as exaggerated sensitivity to painful stimuli (hyperalgesia) or pain following tactile or warm stimuli (allodynia) are not simply the result of a leftward-shifted intensity dependence of the normal pain network. Rather, they indicate unique features of the underlying pain type. His data challenge a rigid dichotomy of sensory-discriminative versus affective-motivational pain dimensions determining different pain states, but instead suggest a more complex integration of nociceptive and non-nociceptive input from the injured body part and its intact neighborhood. Dr. Christian Maihöfner will discuss “Cortical mechanisms of pain and hyperalgesia in complex-regional pain syndromes.” Pain and mechanical hyperalgesia are hallmarks of Complex Regional Pain Syndromes (CRPS). Magnetoencephalography was used to explore changes in the cortical representation of digits (D) 1 and 5 in relation to the lower lip on the unaffected and affected CRPS side and found a significant shrinkage of the extension of the cortical hand representation for the CRPS affected side. The cortical reorganization correlated with the amount of CRPS pain and the extent of mechanical hyperalgesia. In a second study fMRI was used to delineate the neuronal matrix of mechanical hyperalgesia in CRPS. His results suggest the recruitment of a complex brain network underlying mechanical hyperalgesia in CRPS pain. The most important cortical areas identified within this network were S2, the insula, prefrontal cortices, parietal cortices and the cingulate cortex. These studies provide further evidence for an involvement of the CNS in the pathophysiology of CRPS. Dr. Catherine Bushnell will discuss “Attentional and emotional influences on cortical pain processing.” She will show evidence that attentional and emotional states alter cortical processing of normal and neuropathic pain. She will describe the case of a neuropathic pain patient, for which unpleasant odors cause a rapid increase in the ongoing pain. Functional MRI studies revealed that the pain-related forebrain regions, including insular cortex and thalamus, were activated when the patient experienced the odor-evoked pain. These data suggest that stimuli that alter emotional state can have a profound effect on pain processing.
NEUROGENIC INFLAMMATION IN NEUROPATHIC PAIN

S.D. Brain\textsuperscript{2}, W.S. Kingery\textsuperscript{3}, F. Birklein\textsuperscript{1}

\textsuperscript{1}University of Mainz, Neurology, Mainz, Germany, \textsuperscript{2}King’s College, Guy’s Campus, Centre for Cardiovascular Biology & Medicine, London, United Kingdom, \textsuperscript{3}Veterans Affairs Palo Alto Health Care System, Physical Medicine and Rehabilitation Service, Palo Alto, USA

The scope of our workshop is to present data that neurogenic inflammation is very important to understand symptoms of posttraumatic neuropathic pains, in particular Complex Regional Pain Syndromes. In the first presentation, Susan Brain from London will introduce into “The neurogenic inflammatory component”. She will explain symptoms and nature of neurogenic inflammation employing data from animal studies including knock-outs. For example, acute neurogenic inflammation is observed after application of the TrpV1 agonist capsaicin to skin. Inflammatory oedema is not detectable in the substance P NK1 receptor knockout mouse, indicating the importance of this receptor and class of neuropeptides in mediating neurogenic oedema formation. Furthermore, neurogenic vasodilatation remains, not only in the NK1 receptor knockout mouse, but also in the CGRP knockout mouse after sensory nerve stimulation. It is abolished when both the CGRP and substance P dilator pathways are blocked. This has led to the suggestion that there is a facilitatory interaction between endogenously-released CGRP and substance P in the periphery, such that when both are present there is redundancy in terms of dilator mechanisms. The second presentation from Wade Kingery, Stanford, focuses on substance P effects after limb trauma. He will report about how “Substance P signaling contributes to the vascular and nociceptive abnormalities observed in rat models for complex regional pain syndrome types I and II”. His group has recently observed that a distal tibial fracture in rats can generate chronic hindlimb warmth, edema, spontaneous protein extravasation, allodynia, and periarticular osteoporosis, changes resembling those observed in complex regional pain syndrome (CRPS I). Symptoms are similar after sciatic nerve section (CRPS II). Postulating that substance P may contribute to the vascular and nociceptive abnormalities observed in these CRPS models he attempted to reverse these changes with the long acting substance P receptor (NK1) antagonist LY303870. Systemic administration of LY303870 reversed hindpaw edema and cutaneous warmth. Intrathecal administration had an antinociceptive effect. In the final presentation Frank Birklein, Mainz, reports evidence of “Neurogenic inflammation in CRPS”. There was increased CGRP in CRPS serum samples, in particular if there was evidence for trauma related nerve lesion. Furthermore, stimulation of C-fibers resulted in an intensified flare in both affected and unaffected body regions and significant protein extravasation (PPE) on the affected CRPS side, in contrast to healthy subjects. These results offer two possibilities leading to facilitated neurogenic inflammation – either increased release or hampered inactivation of neuropeptides, or both. Therefore we applied exogenous SP and found it significantly more effective to induce PPE in CRPS patients than in controls. In summary, the results indicate trauma-related upregulation of neuropeptide release from primary afferent locally on the affected side. In addition, there must be trauma-independent impaired neuropeptide inactivation, which predisposes to CRPS. This workshop was supported by Pfizer, Germany.
Specific cutaneous cold receptors have been defined as slowly conducting units that exhibit a steady-state discharge at constant skin temperature, a dynamic response to temperature changes and insensitivity to mechanical stimuli (Hensel et al. 1960; Hensel, 1973). Recently cold-specific receptors can be readily distinguished from nociceptors that respond to noxious low temperatures (< 20 °C) with microneurography in humans (Campero et al. 2001). One possible transduction mechanism for cold pain was lately described by an ion channel in sensory neurones which was activated by cooling (Reid et al. 2001). This current is not only activated by cooling but by menthol which shifts the temperature threshold towards warmer temperatures. The current showed adaptation, which depended on extracellular Ca2+ and consisted of a shift in the temperature sensitivity of the channel. Thus this current is likely to account for the known transduction properties of intact cold receptors. The underlying current is now identified as CMR1 (which is very likely to be TRPM 8 in humans). However, very recent findings suggest that other TRP channels are activated at varying cold temperatures thus accounting for different cold sensations. The second presentation will describe cold allodynia in humans which revealed thresholds of 20 – 30 °C for cold pain in contrast to usual 10 – 15 °C. In most clinical cases, the finding of cold allodynia coincides with subjective sensations of cold-hypersensitivity. In addition cold allodynia is a frequent finding in neuropathic pain. In a study of cold allodynia in patients with post-traumatic neuralgia, the opioid alfentanil significantly reduced the cold pain detection threshold, while the NMDA-receptor antagonist ketamine slightly attenuated the threshold. Typically the patients suffered from severe pain at threshold level, and the VAS-score was significantly reduced by both alfentanil and the NMDA-receptor antagonist. Central mechanisms are supposed to be responsible for cold allodynia in neuropathic pain. Interestingly in a 4 year-fellow-up study the peripheral neuropathy have normalised in most cases, but cold allodynia may persist. The differences in the clinical presentation from cold allodynia vs hyperalgesia is likely to indicate differences in underlying mechanisms. The third presentation will describe the contribution of the various cellular mechanisms to cold transduction in peripheral terminals and injured peripheral nerves. These data describe differences observed in temperature activation threshold between mammalian cell lines overexpressing recombinant TRPM8 and cultured trigeminal ganglion neurons activated by cooling and menthol. Therefore the role of TRPM8 channels and the contribution of K+ channels to cold-evoked responses in axotomized fibers from mice neuromas of the sapheneous nerve were investigated. In this model responded about 20% of fibers to cold stimuli (threshold >15 °C). In 70% of cold-sensitive fibers, threshold was shifted to warmer temperatures by menthol, suggesting the participation of TRPM8 channels. Intriguingly the application of submillimolar doses of 4-AP to the neuroma induced de novo cold responsiveness in many units. The discharge pattern of this newly recruited units was also different from menthol- and cold-sensitive neurons suggesting that other ionic conductances are underlying.
DIAGNOSTIC CRITERIA AND MANAGEMENT OF CRPS: A REAPPRAISAL

M. Stanton-Hicks¹, P. Wilson², R.N. Harden³

¹Pain Management, Cleveland Clinic Foundation, Cleveland, USA, ²Department of Anesthesia, Mayo Clinic, USA, ³Pain Management, Rehabilitation Institute of Chicago, USA

Introduction-Overview: This workshop on Complex Regional Pain Syndrome will address the new IASP definition of CRPS as it has affected medical practice, clinical and basic research, and management of the group of painful medical conditions formerly known as reflex sympathetic dystrophy and causalgia. Changes of diagnostic criteria necessarily alter not only the specificity but also the sensitivity of testing for the condition being studied. The mechanisms and pathophysiology of CRPS remain elusive, but significant progress has been made. It is probable that CRPS has primary neuropathic components, but secondary changes are also prominent. Sympathetically maintained pain (SMP) is no longer necessary for the diagnosis of CRPS, so response to sympathetic blockade is not an essential criterion. SMP can occur with or without sympathetically independent pain. Diagnostic criteria: The pathophysiology of Complex Regional Pain Syndrome remains obscure, but unfortunately, there is still no single test or combination of tests that have acceptable specificity and sensitivity. This Gold Standard remains elusive and the condition remains a Syndrome in the sense that the diagnosis must still be made on clinical grounds. The previous diagnostic criteria developed were very useful, but flawed in several areas. Although the sensitivity is very high, the specificity is low. Internal validation has revealed that motor abnormalities are very common, and must be included in any comprehensive diagnostic criteria. Several studies have now indicated that diagnostic criteria fall into four groups: sensory, motor, vasomotor and sudomotor. Each group contains both symptoms and signs. Pain (spontaneous and/or evoked) is the sine qua non of the condition. Current evidence suggests that fewer criteria may be justified for the clinical diagnosis than for the research diagnosis. Treatment algorithm: The lack of widely used diagnostic criteria for CRPS and the lack of generally acceptable outcome criteria for chronic pain states have made it difficult to evaluate treatments of CRPS. However, there have been more good clinical studies in the years since the publication of the IASP diagnostic criteria and SIG treatment algorithm. These studies demonstrate that outcome measures must have greater functional emphasis. Evidence-based recommendations support the existing treatment algorithm. Current treatment options fall under the following general headings: comprehensive rehabilitation, physical restoration, pharmacologic management, autonomic manipulations, interventional techniques, and investigational techniques. The improved diagnostic criteria give important new directions for revision of this treatment algorithm. In particular, it has become easier to address the individual pathologic processes on a rational basis, and determine treatment options and outcome measures with greater reliability. Interventions are used to reverse the primary (neuropathology), secondary (physical) and tertiary (psychosocial) impairments. The evidence indicates that an interdisciplinary approach for CRPS management is optimal, especially for those cases that fail to respond quickly to simple symptomatic measures.
NEUROSTIMULATION AS A CLINICAL TOOL FOR THE MANAGEMENT OF NEUROPATHIC PAIN

J-P. Van Buyten, Y. Keravel, P. Marchettini

Abstract not available
The validation of appropriate methods for assessment of neuropathic pains represent a crucial step in the development of new therapeutical strategies. Such methods should notably allow identification and, as far as possible, quantification of all the components (i.e. spontaneous and evoked pains) of these complex painful syndromes. In this topical workshop we will first present new questionnaires which have been specifically developed recently for the assessment of neuropathic pains. These new tools should be helpful notably to identify and characterize subgroups of neuropathic pain patients that may respond differentially to various pharmacological agents. Then, we will deal with assessment based on Quantitative Sensory Testing (QST). These methods, derived from psychophysics, include the measurement of detection and pain thresholds in response to various thermal (heat or cold) and mechanical stimuli. They are particularly adapted for quantification of evoked pains (ie allodynia and hyperalgesia), analysis of the function of the different types of afferent fibers and investigation of the relationship between symptoms and the pathophysiological mechanisms. Specific applications of these methods in the clinical setting will be illustrated by the presentation of a new standardized protocol developed by the German Research Network on Neuropathic Pain. Finally, we will address the role of QST in the differential diagnosis of neuropathic pains. Indeed, alterations of sensory testing have also been described in the context of muculoskeletal pains suggesting that they might share some pathophysiological mechanisms with neuropathic pains.
THE ROLE OF CHOLECYSTOKININ AND ITS ANTAGONISTS IN NEUROPATHIC PAIN MANAGEMENT

G.J. McCleane\textsuperscript{1}, A. Rothaul\textsuperscript{2}, J. Bannister\textsuperscript{3}

\textsuperscript{1}Rampark Pain Centre, Lurgan, United Kingdom, \textsuperscript{2}Arakis, Little Chesterford, United Kingdom, \textsuperscript{3}Ninewells Hospital and Medical School, Dundee, Scotland

While increasing evidence confirms an analgesic effect of opioids in neuropathic pain, the issue of the extent of analgesic response and the occurrence of analgesic tolerance still complicates their use. Any strategy that could augment the analgesic effect of an opioid when used in a patient with neuropathic pain or reduce the dose required to achieve analgesia merits consideration. Cholecystokinin antagonists may represent such an option. The peptide cholecystokinin (CCK), originally attributed with a gastrointestinal function is now known to be co-localised in the gastrointestinal tract and central nervous system. Immunochemical studies confirm that levels of CCK mRNA and CCK are increased after neural injury (and chronic opioid administration). Administration of CCK to an animal on which an injury is inflicted reduces the antinociceptive effect of any subsequently applied opioid while administration of a CCK antagonist enhances the antinociceptive effect of the opioid. Furthermore, a significant body of animal evidence suggests that administration of a CCK antagonist can reduce the magnitude of, and even reverse established antinociceptive tolerance to opioids. CCK exists in two forms: CCK 1 (previously A) and CCK 2 (previously B). In the animal models CCK 2 antagonists appear to have greater potential for enhancing opioid derived antinociception and preventing antinociceptive tolerance. As well as specific CCK 1 and 2 antagonists, mixed antagonists such as proglumide are also available. In terms of side effects, animal studies fail to show any increase in opioid related side effects when a CCK antagonist is administered along with an opioid. In particular, co-administration of a CCK antagonist with an opioid does not have any greater effect on respiratory rate when compared to use of a similar dose of opioid alone. A number of human studies have now been performed and again confirm that opioid related side effects are not increased when a CCK antagonist is given along with an opioid. A number of human studies suggest an increased quality of pain relief when the mixed CCK 1 & 2 antagonist proglumide is given along with dihydrocodeine and morphine in subjects with pain of mixed aetiology, including that of neuropathic origin. Indeed case report evidence suggests that proglumide given alone without an opioid can also produce analgesia. A human study with the CCK 2 antagonist L365,260 in subjects with neuropathic pain failed to show any improved analgesia when given along with sustained release morphine, in contrast to the animal studies. No human studies have yet investigated the effect of CCK antagonists on analgesic tolerance to opioids. During this workshop an outline will be given of the pharmacology of CCK antagonists along with an insight into the animal and human studies that have investigated their effect on opioid derived analgesia. It is hoped that this will stimulate interest in this method of enhancing opioid derived analgesia when these opioids are used to treat.
HUMAN SURROGATE MODELS OF NEUROPATHIC PAIN

W. Magerl¹, J. Serra², G.L. Wasner³

¹Institute of Physiology and Pathophysiology, Johannes Gutenberg University, Mainz, Germany, ²Neuropathic Pain Unit, Hospital General De Catalunya, Barcelona, Spain, ³Klinik Für Neurology, Universitätsklinikum Schleswig-Holstein, Kiel, Germany

Along the concept of mechanism-based classification of pain the mechanisms of neuropathic pain and related potential treatment options can be explored at a preclinical level by the use of human experimental models of neuropathic pain. These surrogate models aim primarily at understanding the plasticity of the nociceptive system. This workshop focuses on human surrogate models, which mimic major neuropathic symptoms, namely tactile dysesthesia, cold hyperalgesia, and mechanical hyperalgesia and allodynia. Some neuropathic pain patients exhibit tactile allodynia, when even gentle touch stimuli are able to elicit pain apparently mediated by activity in large myelinated fibers. Importantly, this represents a change in the quality percept from touch to pain. Current hypothesis to explain dynamic mechanical allodynia maintain that large myelinated afferents may excite the nociceptive system via central sensitisation and/or sprouting at the dorsal horn level. However, alternative explanations involving a peripheral mechanism cannot be discarded. Dr. Jordi Serra will present evidence that increased axonal membrane hyperexcitability, resulting in chaotic spontaneous discharges and afterdischarges, may be the underlying cause of dynamic mechanical allodynia in some neuropathic pain patients. Dr. Gunnar Wasner will present a human model of cold hyperalgesia, which is a frequent but poorly understood symptom in neuropathic pain in particular after major nerve lesion. A-fiber conduction block is a suitable model to induce cold hyperalgesia suggesting that cold-specific A-delta fibers normally suppress the sensation of pain originating from C-nociceptors and blockade of A-fibers will unmask cold-induced pain. It has been proposed that cold hyperalgesia is due to a change in the central coding of afferent input due to lack of inhibition normally exerted by concomitant activation of myelinated fibers. Alternatively, sensitized C-nociceptors may have a role in cold pain. Topical cutaneous application of menthol in human induced significant pain and cold sensations, punctate and cold hyperalgesia (Wasner et al., Brain 2004). It is suggested that menthol acts to sensitize cold sensitive peripheral C-nociceptors and activates cold-specific A-delta fibers via a recently identified cold and menthol sensitive receptor (TRPM8). Punctate hyperalgesia is due to central sensitization based on the ongoing activity in the sensitized cold-sensitive peripheral C nociceptors. The most widely studied human model of neuropathic pain is secondary hyperalgesia to mechanical stimuli induced by short lasting intensely painful conditioning chemical and/or heat stimuli. Dr. Walter Magerl will present human data showing that two independent nociceptive subsystems synergize in eliciting the state of secondary hyperalgesia, which mimic the symptoms of neuropathic pain: it is induced by activation of capsaicin-sensitive (TRPV1-positive) nociceptors, which then amplify the synaptic transmission of input from capsaicin-insensitive (TRPV1-negative) nociceptors (Magerl et al., Brain 2001). Further, it will be shown that secondary hyperalgesia is a variety of heterosynaptic spinal long-term potentiation (LTP; Klein et al., J. Neurosci. 2004) linking this area of pain research to a most extensively studied field of neurobiology. Finally, it will be focused on the distinction of homosynaptic and heterosynaptic forms of nociceptive human LTP, on the conditions of its induction, its prevention and its reversion (metaplasticity).
NEUROIMAGING OF NEUROPATHIC PAIN

M. Miederer, T. Sprenger, M. Valet, T.R. Toelle

Neurologische Klinik Der TU-Muenchen, Klinikum Rechts Der Isar, Munich, Germany

Modern imaging technologies have evolved to powerful tools in assessing functional aspects of neuropathic pain. Functional Magnetic Resonance Imaging (fMRI) and H215O-Positron Emission Tomography (PET) enable high-resolution measurement of brain activation and ligand PET becomes increasingly available for different cerebral receptor systems. However, investigation of clinical neuropathic pain with functional imaging encounters still major obstacles. Clinical pain rarely presents in the two different states of pain and no pain within the short period of functional imaging, which is mandatory for data interpretation. Thus, assessment and interpretation of functional CNS changes are challenging. Allostetha is one of the clinical manifestations of neuropathic pain where the binary situation pain and no-pain can be reasonably studied. Especially experimental induction of allostetha in healthy volunteers has yielded substantial insight into anatomical sites activated by neuropathic pain versus sites activated by other acute painful stimuli. Currently, the most widely used model is transient induction of allostetha in healthy subjects by application of Capsaicin (either by intradermal or topical application). Many studies utilizing this model have confirmed a relatively specific activation of pathways including thalamus and prefrontal cortex. However, the exact role of brain regions, such as the prefrontal and the cingulate cortex, that are also involved in many other higher cognitive tasks remains poorly understood. To date, results of functional imaging studies in clinical neuropathic pain are still inconsistent. Striking differences between results in artificially modeled allostetha and clinical allostetha after Wallenbergs infarct occurred for example in the anterior cingulate cortex (ACC). The experimental study showed activation of this region during allosthetic pain stimulation as opposed to the clinical study demonstrating decrease of rCBF in the rostral ACC. We showed in patients with trigeminal allostetha that electrostimulation of the trigeminal ganglion induced multiple activations and de-activations. A significant inverse relationship of pain and rCBF in the ipsilateral rostral ACC and a parallel rCBF decrease at alleviated pain in the caudal part of the contra-lateral ACC was observed. In ligand PET studies of clinical pain conditions (trigeminal neuralgia, central post stroke pain), changes in the endogenous opioid system have been shown in a variety of brain structures. Thereby, studies during the pain state were either compared with sequential scans in the same individuals out of pain or with a group of healthy volunteers. With relative consistency, decreases in ligand binding in association with present pain were reported in (pre-) frontal, insular, cingular and, parietal cortices and thalamus. Although regions, for example in the prefrontal cortices, displaying significant impact on neuropathic pain have been found, most evidence points to neuropathic pain as a result of a pathologically functioning network with neuroplasticity playing a key role. Further understanding of the functional interaction between the involved regions will foster advances in development of specific diagnosis and treatment of neuropathic pain.
COMPLEX REGIONAL PAIN SYNDROME

R. Baron

Neurological Clinic, University Kiel, Germany

Complex regional pain syndromes are painful disorders that develop after trauma affecting a limb with (type I) or without (type II) nerve injury. Clinical features are pain (spontaneous, hyperalgesia), impairment of motor function, swelling and autonomic abnormalities (changes in sweating and blood flow). All symptoms show a distal generalized distribution not confined to a territory of a peripheral nerve or root. In a subgroup of patients the symptoms can be relieved by sympathetic blockade (sympathetically maintained pain, SMP). Autonomic abnormalities and SMP: Controlled thermoregulatory reflexes (whole-body warming, cooling) were used to experimentally alter cutaneous sympathetic vasoconstrictor activity to the extremities. Three distinct vascular regulation patterns were identified related to the duration of the disorder: In the warm regulation type (acute stage) the affected limb was warmer and skin perfusion values were higher than contralaterally during the entire spectrum of sympathetic activity. Even massive body cooling failed to activate sympathetic vasoconstrictor neurons. In the intermediate type temperature and perfusion were either warmer or colder depending on the degree of sympathetic activity. In the cold type (chronic stage) temperature and perfusion were lower on the affected side during the entire thermoregulatory cycle. In conclusion, a central unilateral inhibition of cutaneous sympathetic vasoconstrictor neurons leads to a warmer affected limb in the acute stage. Secondary changes in the neurovascular transmission induce vasoconstriction and cold skin in chronic CRPS. The maximal skin temperature difference between the affected and unaffected extremity that occurs during the thermoregulatory cycle can be used as a diagnostic tool. Cutaneous sympathetic outflow to the painful extremity was experimentally activated to the highest possible physiological degree. The intensity as well as area of spontaneous pain and mechanical hyperalgesia (dynamic and punctate) increased considerably in patients that had been classified as having SMP by positive sympathetic blocks but not in SIP patients. Motor abnormalities: Kinematic analysis of target reaching as well as grip force analysis were used to quantitatively assess motor deficits. A pathological sensorimotor integration located in the parietal cortex may induce an abnormal central programming and processing of motor tasks. Furthermore, MEG studies demonstrated a continuous inhibition of the primary motor cortex. Neurogenic Inflammation: Some features of acute CRPS (vasodilatation, swelling, pain) could be explained by a localized inflammatory process. Consistently, scintigraphic investigations with radiolabelled immunoglobulins show extensive plasma extravasation in patients with acute CRPS. Furthermore, transcutaneous electrical stimulation of nociceptive C-fibers provoked protein extravasation into the interstitial fluid (measured by microdialysis) only in CRPS patients and not in controls. Treatment: No evidence-based treatment regimens for CRPS are available so far. Treatment of the individual patient is empiric using mechanism-based techniques that have been proven to be effective in other neuropathic conditions. In acute CRPS, many patients report a positive effect of sympathetic blockade, but fewer patients with chronic CRPS experience relief. Treatment should be immediate and most importantly directed toward restoration of full function of the extremity. This objective is best attained in a comprehensive interdisciplinary setting with particular emphasis on pain management and functional restoration.
TOWARD A CLINICAL NEUROBIOLOGY OF NEUROPATHIC PAIN,
THE KEY TO IMPROVED TREATMENT

H.L. Fields

Department of Neurology, UCSF, San Francisco, USA

Neuropathic pain is a major challenge. Although many patients currently receive effective treatment, most have significant residual pain and many, especially those with central nervous system lesions, obtain little or no relief with any known medication. We have no idea why this is and we have made little progress in addressing this problem. Since the implicit goal of all pain research is to overcome the intractability of pain to treatment, it is essential to examine why progress in understanding mechanisms and in treatment development for neuropathic pain has been so slow. The one area where we have made progress is in understanding how damaged or dysfunctional primary afferent nociceptors (PANs) become hyper-excitable. Progress in this area is due to the fact that PANs can be studied directly, and because they are similar in humans and other animals. To the extent that peripheral changes contribute to the clinical problem of neuropathic pain, effective treatments are available and we are on track to discover more drug targets. This is a major triumph of high quality, hypothesis driven animal research, and it represents a model for applying neurobiological approaches to a clinical problem. Unfortunately, for many patients with neuropathic pain, hyper-excitable PANs seem unlikely to entirely explain their pain, either because the PANs are gone, or because the lesion is in the central nervous system. For these patients, particularly those with pain that is tonic, the near term outlook is uncertain at best. There are a variety of reasons for our lack of clues. First, there are currently no validated animal models of tonic pain. Second, there are no treatments proven effective specifically for tonic neuropathic pain. Third, while there is some evidence for specific CNS changes in such patients, there is no way to know if these changes relate to the cause of the patient's pain.

The time has come to elucidate the central nervous system mechanisms of neuropathic pain through the study of patients in a clinical laboratory setting. Until we do such studies, we cannot know the significance of animal experiments. In this lecture, I will discuss several potential pain mechanisms and, in particular, how they might be studied in patients. The tools available include functional imaging, brain stimulation and recording, genetic studies, cytochemistry and controlled pharmacological interventions. In short, to study the disease we must investigate neurobiology in humans. This work will be difficult and slow, so it is essential to initiate the research immediately and to develop collaborative multicenter teams.
NEW DEVELOPMENTS IN POSTHERPETIC NEURALGIA

C. Sommer¹, R. Baron², M. Haanpaa³

¹Department of Neurology, University of Wuerzburg, Germany, ²Neurological Clinic, CAU-Kiel, Germany, ³Pain Clinic, Helsinki University Hospital, Helsinki, Finland

There is increasing evidence from animal work and research in patients that several mechanisms operate in postherpetic neuralgia. Recently, a novel animal model for PHN (virus injection into the skin of mice) was introduced. The link between human and animal research will be described in these models. Pain researchers as well as clinicians will learn about pain mechanisms and the translation of this knowledge into clinical practice. The workshop will cover the mechanism-based classification of postherpetic neuralgia. Recent advances in neurobiology will be addressed. The novel animal model and behavioral testing in infected animals will be demonstrated. Thorough assessment of symptoms in order to identify underlying mechanisms using various techniques will be discussed. Available treatment options and novel therapy strategies will be communicated.
THERAPEUTIC IMPLICATIONS OF NEUROPLASTIC PHENOMENA IN NEUROPATHIC PAIN

C. Maier, P.W. Halligan, C. Köeppe, A. Schwarz, S. Gustin

1Department of Pain Management, Ruhr University, Bochum, Germany, 2School of Psychology, Cardiff University, Cardiff, United Kingdom, 3Department of Neuropsychology, University of Heidelberg, Germany, 4Institute of Medical Psychology and Behavioural Neurobiology, University of Tuebingen, Germany

CRPS AND NEUROPLASTIC CHANGES The representations of the index fingers within SI and SII in patients with CRPS-I were assessed using electrical stimulation and fMRI. BOLD-contrast was significantly reduced within the hemisphere contralateral to the CRPS affected side. Patients showed impaired discrimination-thresholds on the CRPS-side, which was linearly related to side-corrected deficits in BOLD-contrast of contralateral SI/SII. Low persistent pain levels were associated with small side-to-side-differences, patients with a distinctive hemispherical and discriminative asymmetry reported the highest pain levels. In the following weeks, pain treatment was extended to desensitization to reinforce peripheral sensory input. Pain-relief was paralleled by perceptual improvement and increased BOLD-contrast in contralateral SI/SII. Altered SI/SII activity is linked to pain perception and altered tactile performance in CRPS-I.

RESOLUTION AND SIMULATION OF PAIN BY MIRROR VISUAL FEEDBACK A conflict between motor/sensory processing has been suggested as one cause of pain conditions with unknown aetiology. To investigate this, a novel treatment utilising mirror visual feedback was employed. Additionally it was investigated whether the same sensory symptomology could be produced experimentally in healthy volunteers. Three patients with acute, three with chronic CRPS were treated. The painful limb was obscured and substituted with a mirror image of the normal limb to which the patient attended while actively moving their normal limb. Infra-red thermal imaging was utilised to quantify the associated vasomotor disturbances, pre and post treatment. Forty-one healthy volunteers performed bilateral upper and lower limb movements whilst viewing a mirror/whiteboard which created varied degrees of sensory/motor conflict during congruent/incongruent limb movements. Changes in sensory experience were recorded. Only in patients with acute CRPS an almost immediate analgesic effect was observed, rapidly reverting when treatment was stopped. Continued treatment led to a complete reversal of pain and normalisation of thermal differences. Twenty-seven of the healthy subjects reported sensory changes, mostly within the condition of maximum sensory/motor conflict. Once normal visual input was restored, the anomalous sensations rapidly resolved. When conflict arises within the motor control system, (acute/chronic) pain can arise and result in CRPS.

TREATMENT OF PHANTOM-LIMP PAIN AND CRPS AND CORTICAL REORGANIZATION Based on findings on reorganization in SI and data showing that behaviorally relevant training alters the cortical map, a sensory discrimination training for phantom pain patients was developed. Compared with a control group of medically treated patients, the training group had significant reductions in phantom pain and cortical reorganization. Another approach aimed at the up-regulation of CNS-activity that is mediated by N-methyl-D-aspartate-(NMDA)-receptors and might lead to plastic changes in SI. Eleven chronic phantom pain patients were treated with the NMDA-antagonist memantine in a double-blind placebo-controlled paradigm in two four-week-blocks. In seven patients cortical reorganization was determined by neuroelectric source imaging before and after each block. Pain intensity was recorded continuously. There is a clear drop of both pain intensity and cortical reorganization in the group mean after memantine compared to placebo. In a pilot study (double-blind placebo-controlled) the effect of memantine combined with morphine on pain relief, increase of movements and cerebral reorganization (MEG/fMRI) was investigated in CRPS-I.
QUALITY OF LIFE IN NEUROPATHIC PAIN

H.M. Poole\textsuperscript{1,2}, J. Haythornthwaite\textsuperscript{3}, C. Daniel\textsuperscript{4}

\textsuperscript{1}Pain Research Institute, Liverpool, United Kingdom, \textsuperscript{2}School of Psychology, Liverpool John Moores University, Liverpool, United Kingdom, \textsuperscript{3}Department of Psychiatry and Behavioural Sciences, Johns Hopkins Hospital, Baltimore, USA, \textsuperscript{4}Department of Anaesthetics and Intensive Care, Imperial College London, United Kingdom

Background: Non-pain outcomes, such as health related quality of life are increasingly used to supplement more traditional measures of safety and efficacy when evaluating treatments in both clinical and research settings. Combined with this is a growing awareness of the need to evaluate treatment outcome from the perspective of the patient. Obtaining such information requires valid and reliable means of assessment. Workshop aims: Examine evidence for the impact neuropathic pain can have on quality of life Explore non-pain outcomes that are important to patients, practitioners and providers Evaluate measures used in quality of life assessment for patients with neuropathic pain Consider recent advances in the development of quality of life measures for this patient population Jennifer A Haythornthwaite PhD; Psychosocial factors and neuropathic pain; The potential impact chronic pain can have on an individuals psychological, social and physical function and thus quality of life is well documented. Such data in the neuropathic pain literature is less well developed. Dr Haythornthwaite will review evidence for the effect neuropathic pain can have psychosocial functioning. The importance of assessing psychosocial factors when determining treatment and evaluating outcome will be addressed. In addition, potential methods of assessment will be described. Dr Clare Daniel; Evaluation of measures used to assess non-pain outcomes in neuropathic pain; A variety measures are available to aid assessment of non-pain outcomes that contribute to quality of life. However, the use of generic tools has been criticised due to their lack of disease or pain specificity. Dr Daniel will consider the suitability of available measures for the assessment of the multidimensional experience of neuropathic pain. Currently available tools will be reviewed and critical appraisal of their utility for evaluating treatment and outcome will be presented. Helen Poole PhD; Development of a tool to assess quality of life in neuropathic pain; Assessment of the impact neuropathic pain has on quality of life presents a challenge, since existing tools predominantly focus on pain or function, to the exclusion of other aspects. It is argued that the experience of neuropathic pain is qualitatively different to that of other pains and thus a condition specific tool is required. Dr Poole will report on the development of a new measure of quality of life for neuropathic pain. The use of patient centred methods for initial item generation and reduction will be described and the results of the first field test outlined. Preliminary analysis of the psychometric properties of the instrument will be presented.
Endothelin (ET) is a peptide hormone with potent vasoconstrictor properties that is synthesized and secreted primarily by vascular endothelial cells. Two receptors have been identified - ETA and ETB. ET is usually induced during periods of hypoxia to stimulate glycolysis as an adaptation against impaired energy metabolism. In cancer cells ET-1 stimulates secretion of vascular endothelial growth factor (VEGF) resulting in angiogenesis.

**Endothelin causes pain**

Delivery of ET-1 directly on to the sciatic nerve or by injection into the plantar footpad of rats produces an acute pain-like behavioral response (hind paw flinching) at about 10 minutes. This hind paw flinching is greater in frequency and shorter in latency for appearance at higher doses of ET-1, and is abolished by an antagonist of the ETA receptor, whereas it is enlarged and accelerated by an antagonist of the ETB receptor.

Recordings of impulse activity in small fascicles of the teased sciatic nerve show that the same doses of ET-1 result in the induction of activity in otherwise unstimulated sensory fibers. Such activation is also ETA receptor dependent and occurs exclusively in mechano- and thermal nociceptors (of both C- and A delta- fiber conduction velocity), and never in low threshold mechanoreceptors (A beta-) fibers.

Endothelin-1, at 10-50 nanomolar, rapidly potentiates the voltage-dependent activation of the tetrodotoxin-resistant (TTX-R) form of Na+ current, without effecting the tetrodotoxin-sensitive type, in about half of the cells that express TTX-R. This effect was also mediated by ETA receptors, and persisted for the duration of the recording, at least 10-15 minutes after ET-1 was removed. The TTX-R current was activated at more negative voltages, closer to the threshold potential for impulse firing which may induce spontaneous and repetitive firing.

**Hyperalgesia and allodynia**

Twenty-four rats that developed hyperalgesia/allodynia after CCI were injected with atrasentan 10 mg/kg IP or an equal volume of saline on POD #5. Paw withdrawal latency to a heat stimulus and paw withdrawal response to tactile stimulus (von Frey monofilaments) were recorded before and 30 minutes after injection. There was a robust reversal of mechanical allodynia and a modest reversal of thermal hyperalgesia. There was highly significant reversal of the perfusion deficit, as measured by laser Doppler, following atrasentan administration.

**Pleotropic roles of endothelin in neuropathic pain**

Local upregulation of mRNA for ET and both its receptors occurs at the site of injury, following CCI. This suggests that local (rather than hormonal) ET responses may contribute to neuropathic pain after nerve injury. Using TUNEL assays, we observed large amounts of apoptosis in the perineurium at the site of injury. Very little apoptosis was detected around the site of sham surgery. A potential beneficial effect of ET upregulation at the site of CCI is the upregulation of heat shock proteins (HSP). Cultured PC 12 cells express both ET A and B receptors. Differentiation of these cells leads to significantly increased Hsp27 expression, paralleling increased expression of the ET-B receptor. PC12 cells may be a useful model for examining ET-mediated signaling effects relevant to neuropathic pain.
With life expectancy and carcinogenic environmental factors increasing, the incidence and prevalence of cancer is steadily rising worldwide\(^1\). The development of new antineoplastic therapies is progressively turning an otherwise short life-expectancy disease into a chronic survivor state with slowly progressive disease. As a consequence, painful manifestations of neoplastic body structures destruction and associated organ system dysfunction (nervous system included) is derived from a constantly changing and mixing source of virtually all types of pain that makes cancer pain a unique challenge for specific mechanism-based diagnosis and treatment. Studies show around 30\% of ambulatory cancer patients suffering moderate to severe pain.\(^{ii}\) With progressive disease the incidence is far higher, and the adding mixture of continuous, incidental and breakthrough pain\(^{iii}\) from nociceptive origin is complicated by increased excitability from structural and/or functional neural damage producing a unique type of pain on which the neuropathic components may become the dominant aggravating factor that severely impairs pain control in a variety of syndromes\(^{iv}\). Ethiological pain-mechanisms evaluation and treatment\(^v\) open the opportunity for more effective invasive antituumoral and loco-regional analgesic or opioid-sparing interventions. Early diagnosis of neuropathic pain in cancer requires a detailed clinical examination in order to appropriately prevent further damage. Though major plexopathies maybe easily diagnosed, the late recognition of such syndromes as well as other toxic and paraneoplastic neuropathies are a common source of unrecognized and refractory pain states whose treatment is frequently neglected. A practical approach to these diagnosis and selective evidence-based pharmacological or invasive interventions will be presented, as well as the rationale for a changing approach from standard analgesic management to a continuous structured and detailed clinical evaluation follow-up of both cancer mechanisms and symptoms. Basic science cancer pain mechanisms research has recently revealed previously unrecognized molecular and neuroplastic changes in the nervous system shifting the traditional cancer pain mechanisms understanding, and developing a new trend of pain therapy based on the clinical search for specific diagnosis on selective pain mechanisms leading to more focused pain therapies and selective local antitumour therapies\(^vi\) that may prevent further pain complexity by early intervention.

\(^1\) Clohisy DR, Mantyh PW. Bone cancer pain. Cancer 2003;97:866-73S.
Background and aims. Activation of adenosine A1 receptors in the spinal cord produces antinociception. The present study assessed the physiological role of adenosine A1 receptors using mice lacking the A1 receptor (A1R-/-). Methods. Sensitivity to mechanical, cold and heat stimulation was examined in A1R-/- mice in comparison to wild-type mice (A1R+/-) under normal conditions and after pharmacologically-induced partial sciatic nerve injury. Results. Under normal conditions the A1R-/- mice exhibited moderate heat hyperalgesia in comparison to the wild-type mice, but mechanical and cold sensitivity were unchanged. The hyperalgesic response of the A1R-/- mice was normalized by the non-competitive NMDA receptor/channel blocker dextromethorphan. The antinociceptive effect to intrathecal (i.t.), but not systemic, morphine was reduced in A1R-/- mice. In mice with photochemically-induced partial sciatic nerve injury, the neuropathic pain-like behaviors to heat or cold stimulation were significantly increased in the A1R-/-mice. Conclusions. These data suggest that the adenosine A1 receptor plays a physiological role in inhibiting nociceptive input at the spinal level. This physiological inhibition is mainly active on C-fiber input mediating noxious heat stimulation, maintained after nerve injury and may involve the inhibition of NMDA receptor function. A1 receptors also contribute to the antinociceptive effect of spinal morphine. Specific A1 receptor agonists may be useful as analgesics, particularly for conditions of neuropathic pain.

IX-2100-1: A SELECTIVE CAV 2.2 BLOCKER WITH POTENT ANTI- HYPERALGESIC ACTIVITY IN MODELS OF NEUROPATHIC AND INFLAMMATORY PAIN.

N. Lad, P. Birch, R. Burley, A. Fiumana, C. Hobbi, I.F. James, A. Kesingland, L. Knutsen, P. Lavan, F. Radford, D. Thomas, S. Ward

Ionix Pharmaceuticals Ltd, Cambridge, United Kingdom

Opiates and non-steroidal anti-inflammatory agents have limited efficacy in the treatment of neuropathic and chronic inflammatory pain. Studies with Ziconotide (omega-conopeptide-MVIIA) administered by the intrathecal route suggest that selective blockade of N-type (Cav2.2) calcium channels is effective in reducing pain associated with nerve injury and inflammation. Clinical use of Ziconotide is severely restricted by the need for intrathecal delivery and by its adverse cardiovascular and CNS side effect profile. IX-2100-1 is a selective small molecule blocker of Cav 2.2 in human neuroblastoma cell lines and in rat dorsal root ganglion neurons. The main objective of this study was to profile IX-2100-1 in models of neuropathic and inflammatory pain. Intravenous (i.v.) administration of IX-2100-1 to rats that had undergone partial left sciatic nerve ligation (Seltzer model) caused a dose and time dependent reversal of tactile allodynia on the left paw (DSO ~ 1mg/kg) as assessed by Von Frey hairs. In the same experiment, the compound had no effect on the paw withdrawal threshold on the contralateral paw. In the rat Freund’s complete adjuvant (FCA)-induced mechanical hyperalgesia model, IX-2100-1 reversed mechanical hyperalgesia on the ipsilateral paw (DSO ~ 0.6 mg/kg) as assessed by paw withdrawal thresholds (Randal-Sellito technique). At doses up to 30 times analgesic doses, IX-2100-1 had no significant effect on mean arterial blood pressure, heart rate or motor activity in conscious rats. These data show that IX-2100-1 has potential for the treatment of neuropathic and chronic inflammatory pain with a very good therapeutic index against cardiovascular and motor side effects.

NOVEL BLOCKERS OF CAV2.2: BRAIN PENETRATION AND EFFICACY IN RAT MODELS OF PAIN INCLUDING NEUROPATHIC PAIN.

C. Bowen', G. Bridson', A. Heiser', V. Gulullo', R. Winqvist', R. Zelle'

1Pharmacology, Scion Pharmaceuticals, Medford, USA, 2Chemistry, Scion Pharmaceuticals, Medford, USA

Both preclinical and clinical evidence have established that voltage-gated Cav2.2 channels are important for mediating nociception. The central localization of Cav2.2 (dorsal horn) portrays it as an attractive, downstream target for inhibiting neuropathic pain responses, mediated by various receptors, with therapeutics that access these central sites. We have identified novel and selective blockers of Cav2.2 that display potent, use-dependent inhibition of Cav2.2 in electrophysiology (EP) studies in Xenopus oocytes and HEK cells. We were interested in evaluating these compounds for their ability to penetrate the blood-brain barrier (BBB) and efficacy in animal models of pain (including neuropathic) in rats. Penetration of the BBB was assessed by measuring the cerebrovascular permeability coefficient (P cm/sec) as described previously (Ohno et al., 1978). Efficacy was evaluated in both the formalin and chronic constriction injury (CCI) rat models. The composite of cellular potency, in vivo pharmacokinetics and P was a better predictor of compound efficacy in the rat formalin model as compared to cLogP. Two compound series represented by S-2683A & S-2686C showed use-dependent block of Cav2.2 (EP IC50 in HEK of 1.1 & 7.9 M, respectively) and activity in formalin pain test (p<0.01). S-2683A, which has a high P (2x10-6 cm/sec), similar to glycerol, elicited a profound and sustained inhibition of mechanical allodynia (p=0.03 at 24 hrs) in the CCI; while S-26868, with a low P (5x10-8 cm/sec), similar to sucrose, was inactive in the CCI model. These results emphasize the utility, and importance, of P for helping to predict efficacy of Cav2.2 blockers in animal models of neuropathic pain. In addition, the S-2683A series are introduced as novel and selective Cav2.2 blockers which show promise for clinical syndromes associated with neuropathic pain.

Background: Gabapentin is widely used as an analgesic in neuropathic pain, although its efficacy is often limited. We examined the interaction between gabapentin and the NMDA receptor antagonists dextromethorphan and MK-801 in alleviating neuropathic pain-like behaviors in rats. Methods. Rats with photochemically-induced spinal cord or sciatic nerve injury were used. They exhibited allodynia-like response to mechanical and cold stimulation. Drugs were administered i.p. Results. In spinally injured rats the dose required to produce significant effect on mechanical and cold allodynia was 100 mg/kg gabapentin and 40 mg/kg dextromethorphan. At these doses, gabapentin and dextromethorphan produced numerous side effects, including sedation, motor impairment and/or hyperactivity. When combined, allodynia was reduced by 5 mg/kg dextromethorphan + 7.5 mg/kg gabapentin and totally reversed by 10 mg/kg dextromethorphan + 15 mg/kg gabapentin. The effect of gabapentin was also potentiated by very low dose of MK-801 in spinally injured rats. In rats with partial sciatic nerve injury, gabapentin and dextromethorphan were not effective at doses up to 100 mg/kg or 40 mg/kg respectively whereas combination of gabapentin at 30 mg/kg and dextromethorphan at 20 mg/kg produced significant alleviation of mechanical hypersensitivity. Conclusion. Significant synergistic interaction was present between gabapentin and NMDA receptor antagonists in the absence of increased side effects. This may provide a method to improve pharmacological management of neuropathic pain.
Background and aims: SPM 927 is a novel anticonvulsant under development for epilepsy and neuropathic pain. The aim of the study was to examine the effect of systemic administration of SPM 927 on neuropathic pain-like behaviors in rats after spinal cord injury or injury to the infraorbital nerve. Methods: Spinal cord and infraorbital nerve injury was produced using a photochemical method. The development of allodynia-like responses and the effect of acute and chronic SPM 927 treatment was assessed. Results: In spinal cord injured rats, acute SPM 927 at 10-20 mg/kg dose-dependently alleviated mechanical and cold allodynia-like behaviors without causing motor impairments or strong sedation. Chronic twice daily administration of SPM 927 at 20 mg/kg produced a total reversal of the allodynia-like state with no signs of tolerance. In rats with infraorbital nerve injury, SPM 927 at 30 mg/kg reduced facial mechanical hypersensitivity. SPM 927 also produced hypothermia in rats which is distinguishable from its antiallodynic effect. Conclusion: SPM 927 may be strongly active in patients with central neuropathic pain.

**THE ANALGESIC EFFECTS AND TOLERABILITY OF THE LOW AFFINITY N-METHYL-D- ASPARTATE RECEPTOR CHANNEL BLOCKER VER-2482**

J.W. Brooks¹, M.F. Snape², A.J. Nelson³, K.S. Ahmad¹, M.L. Dopsø¹, S.M. Weiss¹, R. Upton¹, E. Whawell³, R. Gillespie¹, C.T. Dourish², A.S. Rice¹

¹Pain Research Group, Department of Anaesthetics, Imperial College, London, United Kingdom, ²Vernalis Plc, Oakdene Court, Wokingham, Berkshire, United Kingdom

A substantial body of electrophysiological, in vivo and clinical data support the use of NMDA antagonists in the treatment of neuropathic pain. These experiments investigate the ability of the low affinity NMDA receptor antagonist VER-2482 (2-phenyl-2-adamantaneethanamine hydrochloride) to produce analgesia without producing the psychotomimetic side effects that limit the utility of NMDA receptor antagonists. VER-2482 has been compared to ketamine, an NMDA antagonist for which analgesic efficacy has been demonstrated clinically. Tolerability was investigated by means of assessing overt behaviour - the phencyclidine syndrome, and pre-pulse inhibition. The pre-pulse inhibition technique can be used to model the disruption of sensori-motor gating caused by psychotomimetic NMDA receptor antagonists. The analgesic properties of the VER-2482 and ketamine were investigated in a model of neuropathic pain. In male Wistar rats, bilateral hind limb withdrawal thresholds to cold, mechanical and noxious thermal stimuli were measured. Following this, 1/3 to 1/2 of the left sciatic nerve was ligated. Seven days later, sensory thresholds were reassessed and the development of allodynia to cold and mechanical stimuli and hyperalgesia to a noxious thermal stimulus confirmed. The effect of VER-2482 and ketamine on the signs of neuropathy was then determined. Ketamine (5, 10 and 20 mg/kg i.p.) induced the phencyclidine syndrome and deficits in pre-pulse inhibition, whereas VER-2482 (10, 20 and 40 mg/kg i.p.) had no effect in either tests. VER-2482 (5-40 mg/kg i.p.) and ketamine (1mg/kg i.p.) significantly attenuated all three signs of painful neuropathy. At lower doses 1 and 3 mg/kg i.p. VER-2482 reversed mechanical hyperalgesia. VER-2482, a low affinity non-competitive NMDA receptor channel antagonist has analgesic efficacy but appears to be devoid of psychotomimetic side effects.

**FURTHER PHARMACOLOGICAL EVALUATION OF THE SPARED NERVE INJURY MODEL, PHARMACODYNAMIC CONCLUSIONS ON THE EFFECTS OF MORPHINE, GABAPENTIN, MUSCIMOL AND GABOXADOL.**

R. Medina-Santillan¹, G. Reyes-García¹, N.L. Caram-Salas², J. Espinoza-Rayá³, G. Morales-Franco¹, V. Granados-Soto²

¹Sec. De Est. Posgrado E Investigacion, ESM-IPN, Mexico, ²Dep. De Farmacobiologia, CINVESTAV-IPN, Mexico, ³Clinica De Diabetes, Hospital General-SSA, Durango, Mexico

The purpose of this study was to assess the synergistic interaction between gabapentin and B-vitamins in neuropathic pain in rats and humans. In rats, neuropathic pain was induced by ligation of the left L5 and L6 spinal nerves of Wistar rats. Tactile allodynia was determined by measuring paw withdrawal in response to calibrated von Frey filaments. Oral gabapentin (30-360 mg/kg), B-vitamins (75-600 mg/kg) or the gabapentin-B-vitamins combination induced a dose-dependent antiallodynic effect. The theoretical ED50 value for the combination estimated from the isobologram was 273.5±48.6 mg/kg. This value was significantly higher than the experimental ED50 value (18.7±1.7 mg/kg). Results indicate that oral gabapentin and B vitamins synergistically reduced neuropathic pain in the rat. In order to evaluate the efficacy of this combination in humans with neuropathy, we carried out a comparative trial. The study included 12 patients assigned to two groups. Group 1 (n=6) received gabapentin and group 2 (n=6) received gabapentin (900-3600 mg/day) plus B vitamins (B1: 100 mg, B12: 0.2 mg). In both groups the dose was increased at weekly intervals, and characteristics of pain and parameters of quality of life were assessed. Both treatments significantly reduced pain and improved quality of life in patients. Both groups induced dizziness. Both preclinical and clinical studies suggest that the gabapentin-B vitamins combination could be an effective option to relieve neuropathic pain in humans.
SPM 927 DISPLAYS POTENT ANTINOCEPTIVE EFFECTS IN ANIMAL MODELS FOR NEUROPATHIC AND INFLAMMATORY PAIN

T. Störh, B. Beyreuther, E. Krause, N. Selve

1Pharmacology/Toxicology, Schwarz BioScience, Monheim, Germany; 2Institute for Pharmaceutical Biology and Pharmacology, Martin-Luther University, Halle, Germany

SPM 927 (R-2-acetamido-N-benzyl-3-methoxypropionamide) also formerly called Harkoside is a novel anticonvulsant drug. It belongs to a series of functionalized amino acids which have been synthesized as a new class of anticonvulsant agents. SPM 927 has shown activity in a wide variety of animal models for epilepsy and is currently evaluated in phase II clinical development for the treatment of epilepsy. Since it is well accepted that antiepileptic drugs have an analgesic effect in neuropathic pain it was of interest to profile SPM 927 in animal models for inflammatory and neuropathic pain. SPM 927 dose-dependently inhibited late-phase nociception in the formalin test as well as thermal and mechanical allodynia in two models of neuropathic pain (Bennett & Chung model). In addition, SPM 927 exhibited antinoceptive properties against thermal and mechanical hyperalgesia due to acute inflammation ( carrageenan model). Finally, mechanical hyperalgesia was attenuated in a rat model for chronic inflammation (Freund’s complete adjuvants). These results suggest SPM 927 to be active against various forms of chronic inflammatory and neuropathic pain in humans. This is currently under investigation in phase II clinical trials.

CHRONIC PAIN SYNDROM IN PATIENTS WITH END-STAGE RENAL DISEASE UNDER CHRONIC HEMODYALYSIS WITH THE VIEW OF PAIN TERM CLASSIFICATION

N.P. Vanchakova, N.N. Shestakova, K.V. Rybakova

1State Pavlov Medical University, St. Petersburg, Russia; 2Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, St. Petersburg, Russia

Aim of Investigation: Methodology of chronic pain treatment is associated with diagnostics and correct classification of a disorder but there is no chronic pain classification in patients with end-stage renal disease under chronic hemodialysis. The aim of investigation is to classify such disorders according to the basic criteria of “Classification of Chronic pain, IASP Press” (2002). Methods: Clinic studies of 100 patients with end-stage renal disease under chronic hemodialysis and chronic pain using multi-axes diagnostic method have shown that chronic uraemic intoxication, dystrophic etiological factors form clinical picture containing criteria of neuropathic and musculoskeletal pains. Using the III and the V axes of “Classification of Chronic pain” was difficult because of the necessity to apply more than one concurrent code once at a time. For example, such pain syndrome of a patient could be classified as 982.62, or 902.66, or 932.35 etc. up to nine combinations. Conclusion: Taking into account that the patients with end-stage renal disease under chronic hemodialysis and chronic pain do not make the unique group of patients with artificial form of life creating such a difficult pathogenesis of chronic pain some additional method for such state classification should be worked out.

THALAMIC VENTRAL POSTERIOR INFARCT WITH CENTRAL PAIN. CHANGES IN SPINOTHALAMIC AND LEMNISCAL-RELATED RESPONSES, AND THE ROLE OF VP AND VMPO IN THALAMIC PAIN

L. Garcia-Larrea, C. Montes, J. Maarrawi, M. Froit, P. Convers, F. Maignan

1INSERM EMI 342 (Central Integration of Pain), Hopital Neurologique, Lyon, France; 2Dept Fisiologia, University of Malaga, Spain; 3Functional Neurosurgery, Hopital Neurologique, Lyon, France; 4Neurology, Hopital Bellevue, Lyon, France

The respective role of the ventro posterior thalamic nuclei (VPL/VPM) and the recently described VMpO nucleus as specific relays for pain and temperature pathways, as well as their possible implication in the development of central pain, is currently the subject of considerable controversy. We present clinical, neuratomatrical and neurophysiologic data from one patient who presented sudden right-sided hypesthesia for membrical and spinothalamic modalities, as well as a discrete right hand tremor, and subsequently developed right-sided central pain, both spontaneous and provoked (brush and cold allodynia). 3D-MRI with projection onto the human thalamic atlas of Morel et al (1997) demonstrated a lesion within the left ventral posterior (VP) thalamus, including the anterior and posterior parts of the VPL (VPLa and VPLp) and to a lesser extent the ventro posteromedial (VPM) and ventral lateral (VLP) nuclei. Conversely, the lesion did not include the most posterior and medial part of VP, and respected the putative location of the specific spinothalamic nucleus VMpO. Neurophysiological studies showed very significant reduction (~65%) of cortical responses depending on dorsal column / lemniscal transmission, while spinothalamic-dependent cortical responses (laser EPs) were only moderately attenuated (~30%), and showed mostly a latency delay. Our results show that the VPL/VPM nuclei are definitely relevant for pain and temperature transmission in man, and that a discrete lesion within them can produce typical thalamic pain. On the other hand, the results also suggest that much of the spino-thalamo-cortical volley excited by painful heat does not transit through the VPL/VPM nuclei, lending therefore substance to the idea of a non-VPL, non-VPM focus in the human thalamus that should be important for thermo-algesic transduction - putatively the VMpO which was unaffected in this case.

CHRONIC PAIN AFTER SPINAL CORD INJURY: CLINICAL ASPECTS AND RESULTS OF CLINICAL, AND SURGICAL TREATMENTS

L. Rogano, L. Yeng, M.J. Teixeira

Pain Clinic of University of Sao Paulo, Brazil

Eighty one patients presenting with chronic pain due to myelopathies were treated. Fifty-seven (70.4%) patients were male with a mean age of 46.4 years. Myelopathy was caused by gunshot wounds in 43.2% of the cases, and close traumatisms in 32.1%. Complete section of the spinal cord was diagnosed in 35.8%, segmental pain in 30.9 and distal pain in 69.1%. The mean VAS score initially was 9.4. All patients underwent psychiatric treatment and received antidepressants, neuroleptics, and or anticonvulsivants. In 50 (61.7%) patients, neurological procedures were necessary to control pain (DREZ, spinal stimulation or morphine pump for intrathecal infusion). The mean follow-up period lasted 19.1 months. The original pain at the end of the follow-up period was reduced from 9.4 to 3.4 (p<0.001).
CORTICAL REPRESENTATION OF MECHANICAL ALLODYnia. An Exploratory FMRI Study of 27 Patients

R. Peyron1, F. Schneider1, I. Faillenot2, L. Garcia-Larrea3, P. Converti1, F-G. Barral1, B. Laurent1,2

1Department of Neurology, CHU Saint-Etienne, France, 2Pain Center, CHU Saint-Etienne, France, 3Department of Neuroradiology, CHU Saint-Etienne, France, 4INSERM UMI 0342, UCB Lyon1 & UJM-St-Etienne, France

Background: In this exploratory FMRI study, we investigated the cerebral activity associated to allodynia in 27 patients with neuropathic pain after peripheral (5), spinal (3), brainstem (4), thalamic (5), lenticular (5) and cortical (5) lesions. Methods: Innocuous mechanical stimuli were addressed to either the allosyndric territory or the homologous contralateral region. Results: When applied to the normal side, stimuli did not evoke pain and activated a somatosensory (øcontrolo) network including contralateral SI, SII and insular regions. The same stimuli became severely painful when applied to the allosyndric side, and activated regions in the contralateral hemisphere that mirrored the controlo network, with however lesser activation of the SI and insular cortices. Increased activation volumes were found in contralateral SI and MI. While ipsilateral responses appeared very small and restricted after control stimuli, they represented the most salient effect of allosyndia, and were observed mainly in the ipsilateral parietal operculum (SII), SI, and insula. Allosyndic stimuli also recruited additional responses in motor/pre-motor areas (MI, SMA), in regions involved in spatial attention (posterior parietal cortices) and in regions linking attention and motor control (mid-ACC). Conclusions: On a background of deafferentation in the hemisphere contralateral to stimuli, enhanced and/or additional responses to innocuous stimuli in the ipsilateral hemisphere may contribute to the shift of perception from innocuous towards painful and ill-defined sensations. These results emphasize the role of plastic reorganizations after a neural lesion, mainly in the hemisphere ipsilateral to allosyndia, in brain regions critical for pain processing.

MECHANICAL AND HEAT PAIN IN LATERAL AND MEDIAL THALAMIC LESIONS

D. Bowsher

Pain Research Institute, University Hospital Aintree, Liverpool, United Kingdom

Background, Methods, and Aims. Patients with central post-stroke pain (CPSp) were subjected to magnetic resonance imaging (MRI) and quantitative sensory testing (QST) in which perception thresholds in the most painful area and the contralateral unaffected mirror-image area were quantified and compared, with a view to establishing a correlation between sensory deficit and location of impact. Results. Twenty-four tested patients had lesions in the lateral thalamus (VPL) and three in the medial/intralaminar thalamus. Patients with VPL lesions had significant deficits for touch (von Frey filaments; mean affected-unaffected difference=1.2±1.2), sharpness (2.3±1.8g), warmth (6.0±4.8°C), cold (9.3±7.9°C) and heat pain (2.5±3.1°C); but no deficit for mechanical (skinfold pinch) pain (0.0±0.7°C), and a small difference for cold threshold (1.4°C), but a larger difference for sharpness (average 3.6g) than in VPL, and a very large difference for skinfold pinch pain (2.47kg). Conclusion: Impulses generated by two types of noxious stimulation - heat and skinfold (average 3.0g) than in VPL, and a very large difference for skinfold pinch pain (2.47kg). There is a high incidence of reflex sympathetic dystrophy (RSD) of the upper limbs in patients with hemiplegia and its painful and functional consequences present a problem to specialists in physical medicine and rehabilitation. This study was designed to assess the role of several factors in the occurrence of RSD in patients with hemiplegia. Ninety-five consecutive stroke patients (63 male and 32 female, mean age: 59 ±12 years) admitted to our hospital were evaluated. Of the study group 29 patients (30.5%) were found to develop RSD. There were no significant differences between the hemiplegic patient groups with or without RSD regarding age, gender, etiology, side of involvement, and the presence of comorbidities. The recovery stages of hemiplegia as shown by Brunstrom functional classification was significantly different between the two groups; patients in lower recovery stages tended to develop RSD more frequently (p<0.01). Additionally, the presence of flaccidity was also a significant factor in the development of RSD. Glenohumeral subluxation was present in 37 patients (39%) in our study group and the presence of this complication was related with the occurrence of RSD. The presence of glenohumeral subluxation was significantly higher in patients with RSD (21/29, 72.4%) when compared to the patients without RSD (16/66, 24.2%) (p<0.001). Also, hemiplegic patients with more severe shoulder subluxation were significantly more likely to develop RSD. These results suggest that lower recovery stages, reduced tone and glenohumeral subluxation significantly contribute to the occurrence of RSD in the hemiplegic patient. We believe that preventive and treatment measures should consider these factors as they seem to have in common a higher risk of traumatizing the paralyzed upper limb and cause RSD.

EVALUATION OF THE HEAT SHOCK PROTEIN 70 GENE POLYMORPHISM (HSPA1B) AND THE RISK OF CENTRAL POST STROKE PAIN


Research Group of Pain and Neuroscie In Vision 2006 Project, East-West Medical Research Institute, Kyung Hee University, Seoul, South Korea

Background and aims: Central post stroke pain (CPSp) can occur as a result of a lesion or dysfunction of the brain following a stroke. It has also been recognized as one of the more difficult types of pain to assess. Genetic polymorphisms of heat shock protein gene family have recently been hypothesized to be risk factors for neuropathic pain. However, a few report on this gene family was found. The present investigation was conducted to examine the possible associations between the HSPA70 genetic polymorphisms and the CPSp. Methods: 100 stroke patients with CPSp (cases) and 50 age- and sex-matched patients without CPSp (control) were evaluated. The genotype of the polymorphisms HSPA1B (HSPA1B) G1538A was determined by polymerase chain reaction and restriction cleavage with Psp I. Results: The allele and genotype distribution of the polymorphisms tested differed from that in cases and controls (heterozygote (AG)=20% and homozygote (GG)=80% for cases and heterozygote (AG)=30% and homozygote (GG)=70% for controls). The risk for CPSp in cases of GG genotype compared with those of AG genotype was 1.713 (95% CI: 0.694-4.229), but significant difference was not observed after adjustment for age, sex, smoking (adjusted odds ratio 1.830, 95% CI: 0.373-8.989). Conclusions: In this study, genetic polymorphisms in the HSPA70 genes were not associated with risk of CPSp. Screening for this polymorphism is unlikely to be a useful tool for risk assessment.
Background and aims: Central poststroke pain (CPSP) can occur as a result of lesion or dysfunction of the brain from stroke and may cause many difficulties in social activities and daily life, especially in the rehabilitation program. In this study, we evaluated the clinical effectiveness of pain management for CPSP patients during their rehabilitation.

Methods: Seventy patients diagnosed by their pain characteristics of central pain from stroke were enrolled. Modalities of pain treatment were sympathetic nerve block, gabapentin, amitriptyline with or without electric acupuncture for four weeks. Pain intensity through the visual analogue scale (VAS), and improvements of mobility and rehabilitation through the modified Barthel index (MBI) and Rankin scale (RS), respectively, before and after pain treatment were assessed. Results: VAS pain scores were significantly improved before and after pain treatment (p<0.05). In accordance with improvement of pain scores, RS and MBI scores were significantly improved before and after treatment (p<0.05). Conclusions: The rehabilitation scores, MBI and RS, were improved significantly in conjunction with an improvement of VAS pain score. Furthermore, we thought active management of CPSP patients could facilitate their rehabilitation from stroke.

CORTICAL ACTIVATION BY PHASIC COLD STIMULI IN PATIENTS WITH CENTRAL POST STROKE PAIN - A MAGNETOENCEPHALOGRAPHIC STUDY

E. Lang, C. Maihöfner, M. Kaltenhäuser, B. Neundörfer

Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany

Background: Central post stroke pain (CPSP) is hypothesized to result from disinhibition of pain by cold (Craig et al., Pain forum, 1998). In a previous study in healthy subjects, we demonstrated by magnetoencephalography that innocuous cold stimulation of one hand activates exclusively the contra- and ipsilateral insular cortex whereas noxious cold activates additionally the contra- and ipsilateral SII cortex and variably the cingulate cortex (Maihöfner et al., Pain, 2002). Aims: To test if in patients with CPSP due to thalamic stroke the insular cortex on the lesion side is deafferentated from innocuous cold input and if there are abnormal activation patterns. Methods: We examined 4 patients with CPSP following stroke in the posterothalamic thalamus (contralateral hemisymptomatic with pain and allodynia to cold). 100 innocuous cold stimuli (5 °C; 2 °C in 50 ms) were applied separately to each hand. Cortical responses were recorded with a dual 37-channel neuromagnetometer. Equivalent current dipoles were calculated from averaged signals and corresponding head coordinates were superimposed on magnetic resonance images of the brains. Results: Cold sensation on the symptomatic hand was markedly reduced. On the side of thalamic infarction, magnetic source localisation did not reveal activation of the insular cortex following cold stimulation at any of both hands. Instead, the SII cortex of this side was activated. On the side contralateral to thalamic stroke, posterior insular cortex was normally activated by cold stimulation of both hands. Conclusions: On the side of thalamic stroke in patients with CPSP, the insular cortex is deafferentated from cold afferents and the SII cortex abnormally activated. Absence of cold allodynia to short cold stimuli indicates that cold allodynia in CPSP needs longer temporal summation of cold.

ON THE RELATION BETWEEN THALAMIC ACTIVITY, PAIN AND DEAFFERENTATION IN WALLenberg’S SYNDROME. PET-SCAN SEQUENTIAL STUDIES AND MOTOR CORTEX STIMULATION

L. Garcia-Larrea1, J. Maarrawi2, N. Costes1, R. Peyron3, P. Mertens1, P. Convers1, M. Magnin1, B. Laurent1

1INSERM EMI 342 (Central Integration of Pain), Lyon, France, 2Functional Neurosurgery, Hôpital Neurologique, Lyon, France, 3Neurology Dept, Hôpital Bellevue, Lyon, France, 4CERMEP (Pet-Scan Center), Lyon, France

Decrease of thalamic blood flow contralateral to neuropathic pain has been described by several groups, but its relation with sensory deafferentation is unclear. Here we report one instance where the thalamic effects of sensory deafferentation were dissociated from those of neuropathic pain. A 50 year-old patient suffered left Wallenberg’s syndrome entailing right-sided spinothalamic hypeaesthesia up to the third trigeminal division (interruption of the spinothalamic tract), as well as crossed thermal hypeaesthesia in the left face (V2) (damage to the left Vth-nerve descending nucleus). During the following months thermal hypeaesthesia in the right hemibody and left face persisted, and the patient developed neuropathic pain strictly limited to the left side of the face. PET-scan demonstrated significant reduction of blood flow in the right thalamus (contralateral to the painful facial side) relative to its homologous region. Thus, although the deafferented territory was much wider in the right (non painful) than in the left side of the body, thalamic hypoactivity was deeper contralateral to the left painful area. After 3 months of precentral cortex stimulation the patient reported 60% relief of his left facial pain, and a new PET-scan showed correction of the thalamic asymmetry. These results show that (a) thalamic hypoactivity was maximal in the thalamus contralateral to pain, despite a lesser degree of deafferentation, and (b) such decrease was reverted in parallel with pain relief by cortical neurostimulation. Thus, thalamic hypoactivity contralateral to neuropathic pain does not merely reflect deafferentation, but appears related to the pathophysiology of the pain. Restoration of thalamic activity may represent one necessary condition to obtain successful relief of neuropathic pain by analgesic procedures, including cortical neurostimulation.
BEDSIDE SENSORY EXAMINATION OF NEUROPATHIC PAIN AFTER SPINAL CORD INJURY

S. Huelbes Alonso\textsuperscript{1}, J.R. Cabrera Feria\textsuperscript{2}, F. Calderón Muñoz\textsuperscript{3}, C. Fernández-Shaw Toda\textsuperscript{4}, D. García Marco\textsuperscript{5}, M. Nieto-Sampedro\textsuperscript{6}, J.S. Taylor\textsuperscript{7}

\textsuperscript{1}Unidad De Neurología Experimental, \textsuperscript{2}Unidad De Dolor Y Espasticidad and \textsuperscript{3}Servicio De Farmacia, Hospital Nacional De Parapléjicos, Toledo, Spain

Although the clinical history of neuropathic pain after spinal cord injury has been well documented (Siddall et al. Pain (2003) 103(3):249-57, Finnerup et al. Brain (2003) 126:67-70, the further characterization and documentation of symptoms and signs during the acute phase may lead to improved prognosis and treatment. Here we present preliminary data obtained using routine bedside sensory testing from a group of patients with a VAS of greater than 3 for ongoing pain (dysesthesia) below the level of lesion (above T10), with or without pharmacological treatment. Subsequent analysis revealed that the majority of patients reported an ongoing pain below the lesion level with a mean VAS of 5. Bedside sensory examination revealed greater prevalence of brush-evoked allodynia, sensitivity to pin-prick, cold and repetitive pin-prick, with half of the patient population responding at level rather than below the level of injury. The mean VAS score for each test was less than 3, probably reflecting modified pain responses in treated patients. In conclusion, initial results indicate that the utility of bedside sensory examination for the identification of common symptoms and signs of neuropathic pain is limited to the level of injury, and that the characterisation of ongoing pain below the injury level is more important, in regards to both prevalence and pain intensity during acute spinal cord injury. Work sponsored by the Consejería de Salud (Exp-GC02029) and SESCAM.

MANUAL THERAPY TREATMENT IN TRIGEMINAL NEURALGIA

C. Fernandez, C. Alonso, J.C. Miangolarra

Physical Medicine and Rehabilitation, Rey Juan Carlos University, Alcorcon, Spain

BACKGROUND AND AIMS. Trigeminal neuralgia (TN) is a common neuropathic disorder that affects the craniofacial region. V2 and V3 territories are the most common affected. Pharmacological treatment are commonly used in these patients, however some patients do not obtain satisfactory results. The aim of this paper is to expose the results of the manual therapy treatment in 5 patients suffering from TN. METHODS. 5 patients suffering from TN since 3 years were treated with the following protocol based on craniofacial manual therapy: equilibration of sphenobasilar junction, temporal and zygomatic bones mobilization, neurodramic mobilization of V2 and V3 nerves, temporomandibular joint mobilization, and myofascial release of atlanto-axial junction. Patients received twice sessions per week during one month. The outcome measures were the visual analogue scale (VAS) and the presence of autonomic phenomena (disethesias) in the craniofacial region. There were analyzed pre and post treatment, 1 month and 3 months after the treatment. RESULTS. At the beginning of the treatment the VAS value was 7.8 (1.2), whereas 100% of patients reported autonomic phenomena. After the treatment VAS value was 1.2 (0.3), and all patients reported no autonomic phenomena. One month after, VAS was 2.0 (0.6), however 1 patient reported a little autonomic phenomena than at the beginning. After 3 months, patients maintained the improvement in VAS, and 80% subjects maintained the improvement respect to the autonomic phenomena. Further researches are required to investigate the real effectiveness of manual therapy treatment in these patients.

SUCCESSFUL USE OF METHADONE IN THE TREATMENT OF CHRONIC NEUROPATHIC PAIN OF COMPLEX REGIONAL PAIN SYNDROME TYPE 2: A CASE STUDY

S. Rafaq\textsuperscript{1}, I. Jafri\textsuperscript{2}, T.E. Strax\textsuperscript{3}

\textsuperscript{1}Seton Hall University, New Jersey, \textsuperscript{2}New Jersey Neuroscience Institute at JFK Hospital, Edison, USA, \textsuperscript{3}University of Medical and Dentistry of New Jersey, JFK-Johnson Rehab Institute, JFK Hospital, Edison, USA

Setting: Outpatient pain management program. Case description: A 36-year-old white male developed pain, numbness and hypersensitivity of right anterolateral thigh on post-operative day 1 after inguinal hernia repair in 1993. The pain was constant and burning, scaled 9/10, relieved by heating pad, reclining, lying down and aggravated by standing, sexual activity, cold weather and stress. It interfered with activities of daily living. Physical examination revealed edema, trophic changes, and allodynia in anterolateral aspect of thigh with limited mobility. EMG/ NCS was inconclusive. He was diagnosed with Complex Regional Pain Syndrome (CRPS) Type 2. He had tried physical therapy, nerve blocks, trigger point injections, neurtontin, NSAIDs, tyleanol # 3, vicodin, without any relief. He was on oxycocntin, and Oxy IR, with some relief. He was admitted in a multi-disciplinary pain program from 09/1999 to 11/2002 (4 years), was on amitriptylin, gabapentine, ketamine gel, catapress TTS patch, lidoderm patch, exercise program, weight reduction, aqua therapy, trigger point injections and nerve block, with variable effect. The pain scaled down to 6/10, without functional improvement. On 12/02 patient was started on methadone 10mg bid, titrated to 20mg bid, after tapering oxycocntin. He improved significantly and pain scaled down to 3/10. He resumed his job after functioning status improved markedly. Discussion: Methadone is used increasingly in the management of cancer pain refractory to conventional opioids. Recent case studies suggest that its use as an analgesic could be extended to non-cancer neuropathic pain. The present case study reports, for the first time, the efficacy of methadone in CRPS Type 2 patient. Conclusion: Methadone offers a new treatment option in patients with neuropathic pain. It is less expensive and more effective than other opioids.

MANUAL THERAPY TREATMENT IN TRIGEMINAL NEURALGIA

C. Fernandez, C. Alonso, J.C. Miangolarra

Physical Medicine and Rehabilitation, Rey Juan Carlos University, Alcorcon, Spain

BACKGROUND AND AIMS. Trigeminal neuralgia (TN) is a common neuropathic disorder that affects the craniofacial region. V2 and V3 territories are the most common affected. Pharmacological treatment are commonly used in these patients, however some patients do not obtain satisfactory results. The aim of this paper is to expose the results of the manual therapy treatment in 5 patients suffering from TN. METHODS. 5 patients suffering from TN since 3 years were treated with the following protocol based on craniofacIAL manual therapy: equilibration of sphenobasilar junction, temporal and zygomatic bones mobilization, neurodramic mobilization of V2 and V3 nerves, temporomandibular joint mobilization, and myofascial release of atlanto-axial junction. Patients received twice sessions per week during one month. The outcome measures were the visual analogue scale (VAS) and the presence of autonomic phenomena (disethesias) in the craniofacial region. There were analyzed pre and post treatment, 1 month and 3 months after the treatment. RESULTS. At the beginning of the treatment the VAS value was 7.8 (1.2), whereas 100% of patients reported autonomic phenomena. After the treatment VAS value was 1.2 (0.3), and all patients reported no autonomic phenomena. One month after, VAS was 2.0 (0.6), however 1 patient reported a little autonomic phenomena. Three months after VAS was 2.1 (0.6) and the same patients referred the same autonomic phenomena than at the beginning. CONCLUSIONS. Manual therapy treatment in patients suffering from TN was effective reducing the VAS and autonomic phenomena own of these patients. After 3 months, patients maintained the improvement in VAS, and 80% subjects maintained the improvement respect to the autonomic phenomena. Further researches are required to investigate the real effectiveness of manual therapy treatment in these patients.

SPINAL CORD STIMULATION IN THE MANAGEMENT OF CHRONIC TESTICULAR PAIN

A.P. Gutve\textsuperscript{1}, S. Eldabe\textsuperscript{2}, R. Strachan\textsuperscript{3}

\textsuperscript{1}Pain Management Unit, The James Cook University Hospital, Middlesbrough, United Kingdom, \textsuperscript{2}Department of Neurosurgery, The James Cook University Hospital, Middlesbrough, United Kingdom

Introduction Phantom pain after orchidectomy is a disabling condition. Successful management of this pain is intricate challenge. Chronic testicular pain after vasectomy has incidence of 5-50%. A short discussion of two cases and details of neurostimulation will be presented. Case Reports A 45-year-old man presented to pain clinic 2 years after work related accident leading to crushed scrotum requiring left orchidectomy. 4 months after surgery he had shooting, piercing pain in the right side of scrotum and radiating to right groin. Pain was made worse by sexual intercourse. Treatment with antidepressants, anticonvulsants, TENS and opioids resulted in partial benefit. Lumbar sympathectomy and lumbar epidural failed to produce long term pain relief. Spinal Cord Stimulation (SCS) resulted in 90-100% reduction in pain scores. At 4 years follow up he is getting excellent pain relief from the device. A 35-year-old man presented to our pain clinic one year after left orchidectomy for seminoma. Eight months after the surgery he developed persistent pain of varying intensity on left side of the scrotum, radiating to left groin and thigh. It had a burning, aching, tingling, numb nature. He also described allodynia, hyperalgesia and painful phantom sensation. Pain was made worse by exercise, micturation and sexual intercourse. Antidepressants and Anticonvulsants produced partial pain relief. Illo-inguinal nerve block did not result in any pain relief. Lumbar sympathectomy resulted in 3 weeks of 50% analgesia but the pain returned to same intensity. Trial of nabilone resulted in significant side effects without any analgesic effects. SCS resulted in 50% reduction in pain scores and no phantom sensation. Conclusion SCS resulted in significant improvement in pain control and improved quality of life in patients with chronic post-surgical testicular pain.
CASE REPORT: TWO SIBLINGS WITH CONGENITAL INSENSITIVITY TO PAIN AND AVERSION TO COLD

M.J. Teixeira¹, M. Okada¹, D.C. Andrade¹, A. Camargo², A.M.M. Limo²

¹Department of Neurology, Hospital Das Clinicas of the Faculty of Medicine of The University of Sao Paulo, Sao Paulo, Brazil, ²Orthopedics Institute, Faculty of Medicine of The University of Sao Paulo, Sao Paulo, Brazil.

We report the case of R.P.A.M. (22ys.) and M.H.M. (16ys.) who report not to perceive painful stimuli since their birth. The patients have multiple scars and healed fractures throughout their bodies related to accidents that occurred because of their incapacity to perceive nociceptive stimuli. It's noteworthy that these patients report a strong feeling of discomfort when they come in contact with cold objects. They don't describe it as painful, but as an unpleasant sensation that forces them to move away from the cold material. This feature is unusual and has not been previously reported in patients with insensitivity to pain. They have been evaluated by general lab exams, magnetic resonance with spectroscopy, SPECT and nerve conduction studies, all compatible to Hereditary Sensory and Autonomic Neuropathy (HSAN) Type V, or Congenital Insensitivity to Pain.

EXTRACORPOREAL IMMUNOADSORPTION (ECI): POTENTIAL TREATMENT FOR MULTIFOCAL MOTOR NEUROPATHY (MMN). A CASE REPORT

C.F. Khamis

Department of Neurology, CHU Hotel Dieu De France, Beirut, Lebanon

Case presentation: A 48 years old female presented with 9 years history of progressive asymmetrical weakness of the arms predominant on the left side distally with muscular atrophy and no sensory signs. She had electrophysiological evidence of multifocal motor conduction blocks. MRI of both brachial plexuses showed abnormalities more evident on the left side; this was diffusely swollen with increased signal intensities mainly of the lower brachial plexus on the T2-weighted images. As the patient was diagnosed of having MMN, she received intravenous immunoglobulin (IVIG) maintenance therapy 1g/kg/day for 2 days every 6 weeks which resulted in a nearly complete recovery of muscular strength. However, a year later, she developed tolerance requiring more frequent administration of IVIG with only partial relief of her symptoms. A decision was made to treat the patient with ECI. This was conducted as follows: three weekly treatments for two weeks, then two weekly treatments for two weeks and then one weekly treatment for two weeks. One month after the beginning of the immunoadsorption therapy the patient showed remarkable improvement in her symptoms with near complete recovery of muscular strength. Six months after ECI the patient was still in clinical remission. ECI appeared to be an effective treatment for MMN, this for a very long time. This treatment needs be further investigated in larger studies in order to estimate objectively its efficacy.

COMPARATIVE EFFECT OF INTRATHECAL CALCITONIN AND BUPIVACAINE ON RELIEF OF NEUROPATHIC PAIN IN CANCER PATIENTS WITH REFERENCE TO THE CSF LEVELS OF NEUROKININS

M.O. Tawfik, M.A El-Hag, A.A Ghoneim

Anaesthesia and Pain Relief Department, National Cancer Institute, Cairo University, Cairo, Egypt.

BACKGROUND AND AIM Spinal opiates are relatively ineffective in treating neuropathic pain syndromes necessitating potentiation with local anesthetics and/or clonidine. Intrathecal administration of calcitonin has been proved promising for clinical alternative use in certain situations particularly with opioid intolerability. The mechanism of action and its clinical profile is in need of extensive clinical research in an attempt to develop a safe effective clinical application for calcitonin particularly in persistent neuropathic pain syndromes. PATIENTS AND METHODS forty patients having neuropathic pain related to lower thoracic dermatomes, downwards and caused by a malignant disease were randomly allocated into two groups by a double blind study, to receive either calcitonin 100 IU or bupivacaine 0.2 % 2 ml. CSF samples were analyzed for substance P and calcitonin gene related peptide by radioimmunoassay. Sequential vital signs were obtained. Pain score and time until analgesia was requested were assessed RESULTS Adequate analgesia was achieved and was longer in duration and more potent in calcitonin group than bupivacaine. Nausea and vomiting were the most notable side effects associated with the intrathecal calcitonin. CONCLUSION Salmon calcitonin administered intrathecally was an effective in chronic opioid resistant neuropathic pain. In using this hormone as an analgesic in therapy, we believe that the subarachnoid route of administration may, under the right conditions, be a practical solution provided that the dosages are markedly lower than those used in normal parental route. The dosage of 300 i.u. of salmon calcitonin into the cerebrospinal fluid, as suggested by Fraioli does not seem to be advisable because, at such doses, the drug cannot be prevented from passing into the peripheral circulation, and above all because comparable amounts have produced respiratory distress in animals.

EFFICIENCY OF GABAPENTINE IN VARIOUS CASES OF CHRONIC NEUROPATHIC PAIN (CNP)

K. Brzezinski

Pain Clinic, Institute of Agricultural Medicine, Lublin, Poland

Neuropathic pain is related to structural and/or functional changes of peripheral or central nervous system. The aim of the study was to investigate the efficiency of Gabapentin in various kinds of neuropathic pain. Material and methods: to the study 53 patients were included. The diagnosis were: postherpetic neuralgia (PHN), central pain (CP), trigeminal neuralgia (TN), diabetic polyneuropathy (DP), post-traumatic neuralgia (PTN) and oncological neuralgia (ON). The pain intensity was measured by Visual Analogue Scale (VAS) at the start and after 6 weeks. The initial dose of Gabapentin was 300 mg/day and increased up to the effective dose by 100 mg/day. Efficacy of therapy was determined at the end of the study as the diminution of the VAS score. Results: VAS lower than 5 was noted in 28 patients (52.83%). In the other cases we haven not observed pain relief. Effective dose of Gabapentin in the good response group (GRG) was 900 - 2400 mg/day (average 1617.86 mg/day, SD 359.07). Pain intensity was in average 7.49 (SD 0.68) and 3.58 VAS-score (SD 0.64) at the start and at the end of study, respectively. Relief of the pain intensity in this group was various and depended on diagnosis; the highest was in TN û 59.15% (SD 11.92), and the lowest in PTN-group û 43.07% (SD 1.04). The average value was (51.84 % SD 9.42). Conclusion: The use of Gabapentin gave good results in the treatment of various cases of chronic neuropathic pain. The effective dose of Gabapentin depended on the diagnosis.
Background and Aims: New immediate-release (IR) and extended-release (ER) formulations of the opioid oxymorphone are efficacious in treating acute and chronic, moderate to severe, nociceptive pain. Although neither formulation of oxymorphone has been specifically assessed in neuropathic pain, other opioids have been reported to be effective in treating neuropathic pain. In assessing whether oxymorphone should be considered for the treatment of neuropathic pain, we performed a review of the drug's safety during treatment of moderate to severe pain of predominantly nociceptive origin. Methods: Reported adverse events (AEs) were reviewed from 9 phase II/III oxymorphone clinical trials conducted through November 2001. Results: A total of 1064 patients were exposed to oxymorphone ER and/or IR during the phase II/III studies. The median exposure was 15 days (range, 1-691 days); 189 patients received oxymorphone ER for at least 6 months, and 85 received oxymorphone ER for at least 1 year. There were 205 patient-years of exposure to oxymorphone ER in phase II/III clinical studies. The most frequently reported AEs generally occurred at 2 to 3 times the rate reported in placebo-treated patients, and included nausea, constipation, dizziness, pruritus, vomiting, and somnolence. These characteristic opioid-related AEs occurred with similar frequency in oxymorphone-, oxycodone-, and morphine-treated groups. No deaths were attributable to study medication. Conclusions: Clinical experience in more than 1000 patients indicates that oxymorphone is safe, with an AE profile comparable to other opioids. Because other opioids have been used to successfully treat neuropathic pain, oxymorphone may provide a new option for clinicians managing neuropathic pain.

KETOROLAC AND NIMESIL IN BACK PAIN TREATMENT

Y.N. Bykov
Department of Neurology, State Medical University, Irkutsk, Russia

The aim of this study was to investigate effectiveness of combined therapy in patients with acute back pain. There were 40 patients with syndromes of lumbargia and lumboischialgia. KETOROLAC (ADD GENERIC NAME) was prescribed in a dose of 30 mg twice per day for 5 days in injections, NIMESIL (ADD GENERIC NAME) was prescribed in the following period in a dose of 100 mg twice per day for 10 days per os[DEFINE]. Effectiveness of treatment was estimated by clinical neurological investigation, and the Visual Analogue Scale (VAS) before and after the treatment period. Anxiety and depression levels were also determined. Statistical analysis indicated significant (p<0.077) decreases in the VAS, anxiety and depression indices. Results obtained in this trial reveal high clinical efficacy of combined therapy of KETOROLAC and NIMESIL.

PHARMACOEPIDEMIOLOGIC AND MULTIDISCIPLINARY STUDY OF GABAPENTIN IN NEUROPATHIC PAIN

R Galvez, Spanish Team for Study of Neuropathic Pain
Department of Anesthesiology, Pain Clinic, Hospital Virgen De Las Nieves, Granada, Spain

Background and Aims: A major pharmacoepidemiologic and multidisciplinary study of gabapentin was carried out to assess its efficacy and the variation in symptoms linked to comorbidities of neuropathic pain. Methods: An open, prospective and observational study was conducted in 2025 patients with neuropathic pain of varied aetiology, of whom 1837 were selected for intention to treat with gabapentin from an initial dosage of 300 mg/day up to 2400 mg/day, divided between three doses. Variations in the pain intensity, quality of life and other comorbid symptoms associated with neuropathic pain (anxiety, depression, sleep or mental state) were assessed, as was the tolerability after the use of gabapentin during the study period. Results: The study group comprised 1837 patients, with a mean age of 56.1 yrs; 60% were female. After the use of gabapentin, the McGill showed a change in VAS from 71.2 at baseline to 29.9 at 3 months. Sleep disturbance affected 53.6% at baseline and 26.3% at 3 months. The Raskin scale (for depression) reduced from 6.4 a 4.6 and the Covi scale (for anxiety) from 5.5 to 4.2. The Sheehan disability scale score improved from 17 points to 9.4. However, the Minimential State Test showed no important changes during the study period after using gabapentin. Conclusions: The main effects were somnolence, dizziness and cephalgia. Conclusions: 1. This is one of the largest studies of gabapentin in neuropathic pain. 2. The study confirms the efficacy of gabapentin and the improvement that its use produces in the comorbidities and disability associated with neuropathic pain. 3. Gabapentin presents a good safety profile.

STRUCTURAL FEATURES OF SOME ANTIDEPRESSANTS ACTING ON PATIENTS WITH END-STAGE RENAL DISEASE UNDER CHRONIC HEMODIALYSIS AND CHRONIC PAIN

N.N. Shestakova1, N.P. Vanchakova1, K.V. Rybakova1

1Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, St. Petersburg, Russia; 2State Pavlov Medical University, St. Petersburg, Russia

Aim of Investigation: To discover the differentiations in molecular structure of mianserin, tianeptin and citalopram, which determine their influence on pain syndrome in patients with end-stage renal disease under chronic hemodialysis. Methods: Chronic pain syndrome in patients with end-stage renal disease under chronic hemodialysis can be classified as neuropathic pain according “Classification of Chronic pain”. Studies of 100 such patients displayed that some antidepressants (mianserin, tianeptin and citalopram) influenced the intensity and the appreciation of pain. Mianserin and tianeptin decreased the intensity and appreciation of pain but citalopram was affective only in the appreciation of pain. Using theoretical conformational-functional analysis methods all equilibrium conformers of 3 antidepressants have been calculated by the molecular mechanics. The comparative analysis of their spatial structure sets has been carried out. Specific structure systems have been ranged. Various characteristics such as polarity, distribution of atomic charges, and chemical affinity of molecules are taken into account. Results: It is discovered that mianserin and tianeptin have the systems of two centralized aromatic rings that are directed to each other at obtuse angles. On the contrary, citalopram has although the system of two aromatic rings but with the other orientation. Conclusions: Interacting mechanisms between drug special aromatic systems and pain receptor molecules presumably determine the ability of antidepressant to suppress the intensity of chronic pain syndrome in patients with end-stage renal disease under chronic hemodialysis.
TREATMENT PATTERNS WITHIN A POST HERPETIC NEURALGIA (PHN) PATIENT POPULATION
M. Cummington1, D. Webb1, M. Calloway2
1Worldwide Epidemiology, GlaxoSmithKline, Harlow, United Kingdom, 2Global Health Outcomes, GlaxoSmithKline, Research Triangle Park, Triangle Park, USA

BACKGROUND AND AIMS: Post herpetic neuralgia (PHN) is a chronic, painful complication of herpes zoster (HZ). Approximately 25% of individuals in industrialised countries suffer HZ within their lifetime and 15-40% of patients then develop PHN. Only two medications (gabapentin and topical lidocaine) are currently licensed for PHN in the United States, though others are widely used (e.g. tricyclic anti-depressants (TCAs)). Treatment patterns were reviewed and unmet medical need estimated through additional narcotic analgesic use as a proxy for continued pain. METHODS: PHN cases were identified within the Integrated HealthCare Information Solutions (IHClS) database between 1997 and 2003 by the ICD-9 code 531.3. Cases without full medical and pharmacy coverage were excluded due to incomplete treatment history. Inclusion required at least 3 months pre- and post-diagnosis coverage to ensure capture of relevant medical information. Patient demographics and treatment patterns are described.

RESULTS: The median age of the 3,881 identified PHN cases was 56 years. 59.7% were female. The under-representation of the elderly within the IHClS (Medicare claims are not captured) may have lowered the median patient age. 1108 (28.5%) of PHN patients filled at least one prescription for gabapentin or topical lidocaine (alone or co-prescribed). Other common prescriptions included anti-convulsants, excluding gabapentin (10.1% of patients), and TCAs (12.8% of patients). Narcotic analgesic use ( singly or in an analgesic combination) was very common: 20.5% (797/3881) of PHN cases used a narcotic analgesic alone as did 54.0% (450/833) of gabapentin users and 60.4% (166/275) of combination therapies. CONCLUSIONS: A minority of patients received either of the medications. The common supplementary use of narcotic analgesics indicated a need for additional pain relief and that current therapeutics may not provide adequate pain management.

POSSIBILITIES OF OXCARBAZEPINE AS ANTI-CO-NVULSANT IN THE MANAGEMENT OF NEUROPATHIC PAIN
R. Galvez1, J. Caballero2, J. Romero1, S. Ruiz Ortiz1, M.J. Vilchez3, J. Reina1
1Pain Clinic, Department of Anesthesia, HU. Virgen De Las Nieves, Granada, Spain, 2Pain Clinic, Department of Anesthesia, HU. San Cecilio, Granada, Spain

Background and Aims: Oxcarbazepine is a novel antiepileptic drug related to carbamazepine. The present study describes the results of its application in patients with neuropathic pain and assesses its effectiveness and safety. Material and methods: Open, non-comparative prospective study conducted in 37 patients with chronic pain of neuropathic origin who were treated with oxcarbazepine for 180 days. The pain intensity, hyperalgesia and allodynia were assessed. Results: Thirty-seven patients were studied, mean age > 60 yrs, with neuropathic pain of varied aetiology, treated with oxcarbazepine at a daily dose of 600-900 mg (maximum 1200 mg). The intensity of crises was reduced, from VAT of 8.07 at baseline to 2.76. The hyperalgesia decreased from 6 at baseline to 2.11 and the allodynia from 4.07 to 1.7. At the beginning of the study, treatment was withdrawn from 7 patients due to adverse effects, and the remainder presented with vertigo (29%) and somnolence (25%). Conclusions: Oxcarbazepine shows adequate effectiveness to become a valid treatment option for spontaneous and evoked symptoms of neuropathic pain. Initial dose adjustment is essential to avoid major adverse effects. Controlled studies are required to confirm the effectiveness of oxcarbazepine in neuropathic pain.

THE APPROPRIATE INDICATIONS OF GABAPENTIN AND OTHER COMMONLY USED ANTI-NEUROPATHIC MEDICATIONS; RESULTS OF A SYSTEMATIC ANALYSIS OF EXPERT OPINION
B. Morlion, G. Hans1, H. Adriaensen, C. Boisante, F. Cann, J. Devulder, A. Joffroy, D. Lossignol, M. Rucquoi, M. Ventura, M. Zeicher, L. Plaghki

On Behalf of The Belgium-Luxembourg Expert Panel on the Appropriate Indications of Antineuropathic Medication, Leuven, Belgium

Background and aim - Currently, many different drugs are used for the treatment of neuropathic pain. Due to limited evidence from randomised controlled trials, clear indications for their appropriate use in different clinical situations are lacking. In this study, a systematic analysis of expert opinion (RAND Appropriateness Methodology) explored the appropriate indications of gabapentin in comparison to several other mono- and combination therapies. Method - A panel of 12 local pain experts assessed the appropriateness of (combinations of) three commonly used types of antineuropathic drugs (tricyclic antidepressants; TCA, first generation anticonvulsants; ACV, and gabapentin) for many well-defined patient profiles. These profiles were combinations of 8 clinical variables, considered relevant to treatment choice. Individual ratings (9-point scale) were aggregated to panel statements (appropriate, uncertain, inappropriate) on the basis of the median score and extent of agreement. Results - Strong disagreement existed for 21% of the indications. For the majority of cases, strong associations were found between the clinical characteristics and panel recommendations. For patients without previous treatment, monotherapy was considered appropriate in 74% of profiles. Gabapentin was preferred over ACV and TCA in 97% and 64% respectively, while TCA was favoured in 25% (versus ACV) and 8% (versus gabapentin). Logistic regression analysis revealed that type and severity of pain, and sedative effect of the drugs are the dominant factors in treatment choice. Conclusions - The RAND method proved to be a valuable tool in refining the indications of antineuropathic drugs in everyday practice. However, further research is needed to confirm their validity and applicability in daily practice. This study was supported by an unconditional educational grant from Pfizer Belgium. 1 BROOK RH et al. Int J Technol Assess Health Care 1986;2:53-63.

A SINGLE ONE-HOUR APPLICATION OF HIGH-CONCENTRATION TRANS-CAPSICAIN PATCHES LEADS TO AT LEAST TWELVE WEEKS OF PAIN RELIEF IN POSTHERPETIC NEURALGIA (PHN) PATIENTS
M. Backonja1, T.P. Malani2, M. Tuchman3, M. Pollen4, S. Brady5, E. Michna6, S. Ramanathan1, P. Thomas1, T. von Stein1
1Neurology Department, University of Wisconsin Hospital, Madison, USA, 2University of Arizona, Tucson, USA, 3Palm Beach Neurological Center, Palm Beach Gardens, USA, 4Arizona Research Center, Phoenix, USA, 5Anchor Research Center, Naples, USA, 6Brigham and Women's Hospital, Boston, USA

Capsaicin activates TRPV1 receptors in cutaneous nociceptors and thereby causes acute burning pain sensations followed by prolonged nociceptor inactivation. Low-concentration capsaicin creams have been used in painful neuropathies, but pain and inconvenience of multiple daily applications limit their use. We conducted a double-blind randomized controlled study of high-concentration (8%) trans-capsicain patches administered once for one hour, with a one-year open-label extension. Forty-four patients with PHN were treated once and then initially followed for four weeks. The treatment procedure consisted of the application of a topical anesthetic, followed by a one-hour trans-capsicain application to the affected area. The primary efficacy endpoint was the average change from baseline in pain intensity as recorded in patient diaries. Twenty-four patients enrolled into the one-year extension and were eligible for up to three more treatment cycles, at the earliest 12 weeks after initial treatment. In the active group, a mean pain decrease of 33% was observed, compared to 4% in the control group (p=0.004). Among the patients in the extension study, the mean pain decrease was 33% in the entire first treatment cycle (duration varied from 12 to 48 weeks), compared to 1% in the control group (p=0.01). Pain decreases were noted on the first day and remained stable throughout the entire observation period. Similar results were achieved with repeat treatment. Despite expected capsicain pungency, overall tolerability was good, and no safety concerns were identified. Plasma sample analyses established the lack of systemic absorption. This clinical trial, for the first time, demonstrates the pain reduction of high-concentration trans-capsicain for at least twelve weeks after a single one-hour application. As a topical therapy, high-concentration trans-capsicain could be a very safe and effective treatment for PHN.
Background and aims: To evaluate the long-term maintenance of pregabalin efficacy in relieving neuropathic pain (NP) associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN). Methods: Pregabalin was studied in patients with NP and PHN in several randomized, double-blind, placebo-controlled, fixed-dose, parallel-group trials (RCTs) ranging from 5 to 12 weeks in duration and, subsequently, in follow-on, open-label studies. To study the long-term maintenance of pregabalin’s efficacy, an ad hoc analysis was conducted in a cohort of 217 patients who had at least 1-year exposure to pregabalin and who had VAS pain scores during open-label phases. The year of open-label exposure was divided into 4 quarters; patients’ last available VAS scores in each quarter were summarized. The weighted mean dose over time for all patients who participated in open-label NP studies for at least 420 days (N=656) was calculated for 4 quarters, allowing for a 60-day dose optimization interval and a 360-day follow-up. Results: Analysis of the VAS pain scores in these patients during open-label extensions demonstrated that the scores were consistent from quarter to quarter, indicating that pain scores were stable over time. In a larger cohort of NP patients receiving pregabalin, allowing for dose flexibility from 75 to 600 mg/day, under open label, there did not appear to be any clinically meaningful differences in selected dose over time. Conclusions: Pregabalin has been shown to provide statistically significant pain relief in NP associated with DPN and PHN in RCTs up to 12 weeks long. The analyses here reported suggest pregabalin’s treatment effects extend well beyond this duration without requiring clinically meaningful dose increases over time. Supported by Pfizer.

**GABAPENTIN FOR IDIOPATHIC TRIGEMINAL NEURALGIA**

A.B. Danilov, A.B. Danilov

Moscow Medical Academy, Department of Neurology, Moscow, Russia

The preferred treatment for trigeminal neuralgia consists of antiepileptic drugs. Phenytoin and carbamazepine have been used for the treatment of trigeminal neuralgia for a number of years. However, they are not always effective and can sometimes cause central nervous system effects such as drowsiness, ataxia, somnolence, and diplopia. Recently gabapentin has shown promise in relieving some forms of neuropathic pain. We have studied 6 patients with trigeminal neuralgia, in whom paroxysmal facial pain was resistant to previous treatment with multiple medications, including carbamazepine and phenytoin. The age of patients varied from 58 to 69 years old. Pain scores on a visual analogue scale (0-10) and responses defined as excellent, good, poor or none, were monitored at baseline and at monthly intervals during treatment. Gabapentin was administered at a dose of 300 mg/day, titrated upwards until a therapeutic response was achieved. Five of the six patients obtained significant pain relief with gabapentin. In one patient the effect was moderate. Onset of pain relief occurred generally within 1 to 3 weeks, depending on the rate and end point of dose titration. The minimum effective dose was 900 mg/day, and the maximum was 2400mg/day. Gabapentin was well-tolerated and no any serious side effects were observed. The present study suggests that gabapentin can be effective treatment of trigeminal neuralgia, even in cases resistant to traditional treatment modalities. The fact that gabapentin was well-tolerated is an important advantage when prescribing for elderly patients.

**PREGABALIN SIGNIFICANTLY REDUCES NEUROPATHIC PAIN ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY AND POSTHERPETIC NEURALGIA BY DAY 3 OF TREATMENT**

M. Rowbotham1, J.P. Young Jr.1, U. Sharma2

1Pain Clinical Research Center, University of California, San Francisco, USA,
2Pfizer Global Research & Development, Ann Arbor, USA

Background and aims: Pregabalin has demonstrated efficacy in reducing neuropathic pain (NP) associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN). The analyses presented examine time to reduction of daily pain scores during the first 2 weeks of pregabalin treatment for NP with or without PHN. Methods: Results are presented for 6 major placebo-controlled studies, consisting of 8 pregabalin treatment groups. Patients kept diaries in which they circled the number which best corresponded with their pain over the preceding 24 hours (0=No Pain to 10=worst possible Pain). Daily pain scores were analyzed using ANCOVA. The first 2 weeks of treatment were analyzed for all patients in the intent-to-treat populations (1429 patients: 923 pregabalin and 506 placebo). Initial reduction in pain was defined as the first day for which pain scores from that day and the following day were shown to be significantly lower than placebo. Results: A significant reduction of pain was observed within the first day of treatment (0.75, 0.45, and 0.14) for patients receiving 300mg/day starting on Day 1, as well as in one additional treatment group. In the remaining treatment groups, in which initial doses ranged from 75 to 150 mg/day, reduction of pain was generally seen within the first 3 days; this ranged from 3 groups with a significant reduction by the second day of treatment (0.70, 0.55, 0.66) to 1 group which differed from placebo on day 4 (0.88) and 1 which differed from placebo on day 7 (0.78). Conclusions: Evidence suggests that reduction of pain associated with DPN and PHN occurs within 3 days of initiating pregabalin treatment. Study funded by Pfizer, Inc.
PREGABALIN/ES ANALGESIC ACTIONS ARE MEDIATED BY ITS BINDING TO THE TYPE 1 SUBUNIT OF VOLTAGE-GATED CALCIUM CHANNELS

M.J. Field,1 S. Bramwell,1 P.J. Cox,1 H. Melrose,1 J. offord,2 E. Richardson,2 T.Z. Su,1 D. Williams3

1Department of Pain Therapeutics, Pfizer Global Research and Development, Sandwich United Kingdom, 2Department of CNS Molecular Science, Pfizer Global Research and Development, Ann Arbor, USA

Background and aims: Pregabalin has proven clinical efficacy for the treatment of NeP associated with diabetic peripheral neuropathy and postherpetic neuralgia. This compound is unlike traditional analgesics. Despite extensive preclinical research, including the isolation and sequencing of the binding protein and its identification as the α2-δ-2 subunit of voltage-gated calcium channels, proof of the importance of this auxiliary protein in the mechanism of action of pregabalin had remained elusive. The findings here reported show that pregabalin has reduced binding affinity and no analgesic action in mice expressing a mutated gene encoding a specific auxiliary subunit protein (α2-δ type 1) of voltage-dependent calcium channels. Methods: The R217A mutant mouse has a single amino acid substitution at position 217 in the α2 protein. This mutation prevents pregabalin binding to the protein. The mutant demonstrates normal pain phenotypes which are indistinguishable from wild-type controls derived from the same breeding cohort. Results: In the mutant mice, pregabalin (30 to 100 mg/kg, s.c.) failed to block late-phase response in the formalin test as well as the static allodynia induced by the Chronic Constriction Injury (CCI) model, but in wild-type mice, pregabalin was fully active. Both mutant and wild-type mice showed typical responses to morphine (3 mg/kg, s.c.) in the formalin test and to amitriptyline (2 to 8 mg/kg, p.o.) in the CCI model. Conclusions: These data demonstrate that pregabalin′s analgesic action is mediated through its binding to the α2-δ type 1 subunit of voltage-gated calcium channels. Study funded by Pfizer Inc.

IMPROVEMENT OF HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH POSTHERPETIC NEURALGIA TREATED WITH PREGABALIN: RESULTS FROM THREE RANDOMIZED CLINICAL TRIALS

R. Dworkin1, B. Stacey1, S. Martin1, L. LaMoreaux2, U. Sharma2

1Department of Anesthesiology, University of Rochester Medical Center, Rochester, USA, 2Anesthesiology, Oregon Health and Science University, Portland, USA, 3Pfizer Global Research & Development, Ann Arbor, USA

Background and aims: Postherpetic neuralgia (PHN) affects millions of patients, is intensely painful, interferes with sleep, and impairs physical and psychosocial functioning. This analysis evaluates the effect of pregabalin (PGB) on health-related quality of life (HRQoL) in patients with PHN. Methods: Pregabalin was studied in three, randomized, double-blind, placebo-controlled, fixed-dose, parallel-group trials: 1008-030 (75 and 150 mg/day for 1 week; 600 mg/day thereafter) and flexible-dose pregabalin (IBD, 150-600 mg/day, with weekly adjustments based on response and tolerability) versus placebo. Methods: 65 (19.2%), 141 (41.7%), and 132 (39%) patients were randomized to placebo, pregabalin flexible-dose, and pregabalin fixed-dose groups, respectively. Patients completed pain and sleep diaries every morning on awakening. Primary efficacy parameter was mean pain score (from all 7 diary entries) at endpoint. Response to treatment (≥50% reduction in pain score) weekly mean pain score, and sleep interference were also evaluated. Results: Flexible- and fixed-dose pregabalin significantly reduced mean pain score at endpoint versus placebo (P=0.002 and P=0.001, respectively). Response to treatment was noted for 48% and 52% of patients in the pregabalin fixed- and flexible-dose groups, respectively, versus 24% for placebo (P=0.001 in each case). Both pregabalin groups were significantly superior to placebo in improving sleep interference (P<0.001). The most common adverse events (AEs) for pregabalin-treated patients were dizziness, peripheral edema (nonCV/renal origin), weight gain (not affecting diabetes control), and somnolence. 50 patients discontinued due to treatment-related AEs (5 [8%] placebo, 17 [12%] flexible-dose pregabalin, and 28 [21%] fixed-dose pregabalin). Conclusions: These results affirm those from previous studies demonstrating pregabalin′s efficacy, tolerability, and safety for treatment of chronic NeP due to DPN or PHN. Pregabalin dosing aimed at optimal balance of efficacy and tolerability provides significant pain relief and may reduce the risk for AEs and therapy discontinuation. Study funded by Pfizer.

EVALUATION OF FLEXIBLE AND FIXED DOSING OF THE NOVEL LIGAND, PREGABALIN, IN THE MANAGEMENT OF CHRONIC NEUROPATHIC PAIN SYNDROMES

R. Freynhagen1, K. Strojek2, T. Flinter1, W. Matters3, M. Balkenohl3, F. Xie3, T. Grising3

1Department of Anaesthesiology, University Clinic Dusseldorf, Germany, 2Internal Disease, Diabetology, Neph, Silesian Medical University, Zakrzew, Poland, 3Schrömerzentrum Frankfurt, Frankfurt, Germany, 4Schrömerzentrums, Bochum, Germany, 5Inernational Medical Research, Pfizer Global Pharmaceuticals, Freiburg, Germany, 6Pfizer Global Pharmaceuticals, New York, USA

Background and aims: This 12-week, randomized, double-blind, placebo-controlled study in 338 patients with chronic neuropathic pain (NeP) due to diabetic peripheral neuropathy (DPN, N=249) or postherpetic neuralgia (PHN, N=89) evaluated fixed-dose pregabalin (IBD, 300 mg/day for 1 week; 600 mg/day thereafter) and flexible-dose pregabalin (IBD, 150-600 mg/day, with weekly adjustments based on response and tolerability) versus placebo. Methods: 65 (19.2%), 141 (41.7%), and 132 (39%) patients were randomized to placebo, pregabalin flexible-dose, and pregabalin fixed-dose groups, respectively. Patients completed pain and sleep diaries every morning on awakening. Primary efficacy parameter was mean pain score (from all 7 diary entries) at endpoint. Response to treatment (≥50% reduction in pain score) weekly mean pain score, and sleep interference were also evaluated. Results: Flexible- and fixed-dose pregabalin significantly reduced mean pain score at endpoint versus placebo (P=0.002 and P=0.001, respectively). Response to treatment was noted for 48% and 52% of patients in the pregabalin flexible- and fixed-dose groups, respectively, versus 24% for placebo (P=0.001 in each case). Both pregabalin groups were significantly superior to placebo in improving sleep interference (P<0.001). The most common adverse events (AEs) for pregabalin-treated patients were dizziness, peripheral edema (nonCV/renal origin), weight gain (not affecting diabetes control), and somnolence. 50 patients discontinued due to treatment-related AEs (5 [8%] placebo, 17 [12%] flexible-dose pregabalin, and 28 [21%] fixed-dose pregabalin). Conclusions: These results affirm those from previous studies demonstrating pregabalin′s efficacy, tolerability, and safety for treatment of chronic NeP due to DPN or PHN. Pregabalin dosing aimed at optimal balance of efficacy and tolerability provides significant pain relief and may reduce the risk for AEs and therapy discontinuation. Study funded by Pfizer.

TWICE-DAILY PREGABALIN SAFELY AND EFFICACIOUSLY TREATS NEUROPATHIC PAIN AND SLEEP INTERFERENCE ASSOCIATED WITH POSTHERPETIC NEURALGIA

R. van Severen1, H. Feister1, J.P. Young Jr2, M. Versavel1

1Department of Anaesthesiology, Ambipa Ziekenhuis, Breda, The Netherlands, 2Pfizer Global Research and Development, Ann Arbor, USA, 3Pfizer Global Research and Development, Groton, USA

Background and aims: Postherpetic neuralgia (PHN) is a painful, often chronic, condition that significantly interferes with sleep and physical and psychosocial functioning. This study evaluated the efficacy of pregabalin, a novel alpha2-delta ligand, for relief of neuropathic pain (NeP) and sleep interference associated with PHN. Methods: Patients with PHN of ≥3 months;E duration were randomized into a 13-week, multicenter, double-blind, placebo-controlled study. Patients were assigned to 1 of 3 pregabalin BID groups: 300/600 mg/day (depending on creatinine clearance [n=90]); 300 mg/day (n=98), 150 mg/day (n=87); or placebo (n=93). Endpoint mean pain score from daily pain diaries was the primary efficacy parameter. Weekly mean pain scores, endpoint and weekly mean sleep interference scores, and adverse events (AEs) were also evaluated. Results: In all 3 groups, pregabalin was significantly better than placebo at endpoint for relief of pain (P<0.001) and sleep interference (P<0.001). Weekly mean pain and sleep interference scores also significantly improved as early as Week 1 in each group, and improvements were maintained through Week 13. Most AEs were mild or moderate, and the most commonly reported AEs were dizziness, somnolence, and peripheral edema for the pregabalin groups and peripheral edema and dizziness for the placebo group. 41 pregabalin patients withdrew due to AEs considered treatment related, including dizziness (n=16), somnolence (n=8), and ataxia (n=7). Conclusions: Pregabalin 150, 300, and 600 mg/day, administered BID, is efficacious and well tolerated in patients with NeP associated with PHN, and all three treatment regimens reduced pain-related sleep interference. Pregabalin′s effects on pain and sleep interference begin as early as Week 1 of treatment and are maintained for at least 13 weeks. Study funded by Pfizer.
Background: Clinical experience shows that neuropathic pain is one of the major problems of cancer pain treatment (1, 2). The aim of this study was to investigate the incidence of neuropathic pain component in a prevalence study of cancer pain in hospitalised patients.

Methods: A one-day prevalence study of clinically relevant pain in hospitalised cancer patients in the Southern Health Region of Norway was carried out. Registration of symptoms was done using the Brief Pain Inventory (BPI) questionnaire. In addition, to identify possible neuropathic pain components, one specific question was asked: "Do you have altered skin sensation in the area of pain?" This question was later correlated to the pain descriptors in the BPI. The use of analgesics (including co-analgesics) was also registered. Results: 309 patients from 14 different hospitals were included. 157 patients had pain. 104 of 290 patients (36%) answered yes to the question of altered skin sensation. This response correlated significantly to the pain descriptors typical of neuropathic pain (burning, stinging, shooting, pinching, warm/cold). Only 13 of these patients used anticonvulsants or tricyclic antidepressants. Conclusion: Using a questionnaire and not quantitative sensory tests when investigating neuropathic pain, carry a disappointingly low incidence of neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusions: Neuropathic pain is present in 36% of non-neuropathic pain patients and non-neuropathic pain patients, 23.6% mixed nociceptive and neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusion: Neuropathic pain is present in 36% of non-neuropathic pain patients.

Methods: A one-day prevalence study of clinically relevant pain in hospitalised cancer patients in the Southern Health Region of Norway was carried out. Registration of symptoms was done using the Brief Pain Inventory (BPI) questionnaire. In addition, to identify possible neuropathic pain components, one specific question was asked: "Do you have altered skin sensation in the area of pain?" This question was later correlated to the pain descriptors in the BPI. The use of analgesics (including co-analgesics) was also registered. Results: 309 patients from 14 different hospitals were included. 157 patients had pain. 104 of 290 patients (36%) answered yes to the question of altered skin sensation. This response correlated significantly to the pain descriptors typical of neuropathic pain (burning, stinging, shooting, pinching, warm/cold). Only 13 of these patients used anticonvulsants or tricyclic antidepressants. Conclusion: Using a questionnaire and not quantitative sensory tests when investigating neuropathic pain, carry a disappointingly low incidence of neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusions: Neuropathic pain is present in 36% of non-neuropathic pain patients and non-neuropathic pain patients, 23.6% mixed nociceptive and neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusion: Neuropathic pain is present in 36% of non-neuropathic pain patients.

Methods: A one-day prevalence study of clinically relevant pain in hospitalised cancer patients in the Southern Health Region of Norway was carried out. Registration of symptoms was done using the Brief Pain Inventory (BPI) questionnaire. In addition, to identify possible neuropathic pain components, one specific question was asked: "Do you have altered skin sensation in the area of pain?" This question was later correlated to the pain descriptors in the BPI. The use of analgesics (including co-analgesics) was also registered. Results: 309 patients from 14 different hospitals were included. 157 patients had pain. 104 of 290 patients (36%) answered yes to the question of altered skin sensation. This response correlated significantly to the pain descriptors typical of neuropathic pain (burning, stinging, shooting, pinching, warm/cold). Only 13 of these patients used anticonvulsants or tricyclic antidepressants. Conclusion: Using a questionnaire and not quantitative sensory tests when investigating neuropathic pain, carry a disappointingly low incidence of neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusions: Neuropathic pain is present in 36% of non-neuropathic pain patients and non-neuropathic pain patients, 23.6% mixed nociceptive and neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusion: Neuropathic pain is present in 36% of non-neuropathic pain patients.

Methods: A one-day prevalence study of clinically relevant pain in hospitalised cancer patients in the Southern Health Region of Norway was carried out. Registration of symptoms was done using the Brief Pain Inventory (BPI) questionnaire. In addition, to identify possible neuropathic pain components, one specific question was asked: "Do you have altered skin sensation in the area of pain?" This question was later correlated to the pain descriptors in the BPI. The use of analgesics (including co-analgesics) was also registered. Results: 309 patients from 14 different hospitals were included. 157 patients had pain. 104 of 290 patients (36%) answered yes to the question of altered skin sensation. This response correlated significantly to the pain descriptors typical of neuropathic pain (burning, stinging, shooting, pinching, warm/cold). Only 13 of these patients used anticonvulsants or tricyclic antidepressants. Conclusion: Using a questionnaire and not quantitative sensory tests when investigating neuropathic pain, carry a disappointingly low incidence of neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusions: Neuropathic pain is present in 36% of non-neuropathic pain patients and non-neuropathic pain patients, 23.6% mixed nociceptive and neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusion: Neuropathic pain is present in 36% of non-neuropathic pain patients.

Methods: A one-day prevalence study of clinically relevant pain in hospitalised cancer patients in the Southern Health Region of Norway was carried out. Registration of symptoms was done using the Brief Pain Inventory (BPI) questionnaire. In addition, to identify possible neuropathic pain components, one specific question was asked: "Do you have altered skin sensation in the area of pain?" This question was later correlated to the pain descriptors in the BPI. The use of analgesics (including co-analgesics) was also registered. Results: 309 patients from 14 different hospitals were included. 157 patients had pain. 104 of 290 patients (36%) answered yes to the question of altered skin sensation. This response correlated significantly to the pain descriptors typical of neuropathic pain (burning, stinging, shooting, pinching, warm/cold). Only 13 of these patients used anticonvulsants or tricyclic antidepressants. Conclusion: Using a questionnaire and not quantitative sensory tests when investigating neuropathic pain, carry a disappointingly low incidence of neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusions: Neuropathic pain is present in 36% of non-neuropathic pain patients and non-neuropathic pain patients, 23.6% mixed nociceptive and neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusion: Neuropathic pain is present in 36% of non-neuropathic pain patients.

Methods: A one-day prevalence study of clinically relevant pain in hospitalised cancer patients in the Southern Health Region of Norway was carried out. Registration of symptoms was done using the Brief Pain Inventory (BPI) questionnaire. In addition, to identify possible neuropathic pain components, one specific question was asked: "Do you have altered skin sensation in the area of pain?" This question was later correlated to the pain descriptors in the BPI. The use of analgesics (including co-analgesics) was also registered. Results: 309 patients from 14 different hospitals were included. 157 patients had pain. 104 of 290 patients (36%) answered yes to the question of altered skin sensation. This response correlated significantly to the pain descriptors typical of neuropathic pain (burning, stinging, shooting, pinching, warm/cold). Only 13 of these patients used anticonvulsants or tricyclic antidepressants. Conclusion: Using a questionnaire and not quantitative sensory tests when investigating neuropathic pain, carry a disappointingly low incidence of neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusions: Neuropathic pain is present in 36% of non-neuropathic pain patients and non-neuropathic pain patients, 23.6% mixed nociceptive and neuropathic pain. Tricyclic antidepressants (almost exclusively amitriptyline) were the most commonly used treatment. Conclusion: Neuropathic pain is present in 36% of non-neuropathic pain patients.
ALTERATION OF THE CEREBRAL REPRESENTATION OF MECHANICAL ALLODYNIA IN NEUROPATHIC PAIN PATIENTS DURING DIFFERENT LEVELS OF BACKGROUND PAIN

P. Schweinhardt1,2, J. Brooks1,2, H. McQuay1, C. Glynn1, T. Jack1, C. Bountra1, J. Tracey1,2

1Oxford University, Department of Human Anatomy and Genetics, Oxford, United Kingdom, 2FMRI Centre, John Radcliffe Hospital, Oxford, United Kingdom, 3Pain Relief Unit, Churchill Hospital, Oxford, United Kingdom, 4CEDD, Glaxo Smith Kline, Harlow, United Kingdom

Background: Investigation of ongoing pain causes substantial problems as subjective rating scales (e.g. VAS, numerical rating scale) do not provide a reliable measure of the experience of pain, especially when ongoing pain is studied over long time periods. Aims: FMRI (functional magnetic resonance imaging) should be able to provide a more objective read-out of ongoing pain than conventional rating scales. Methods: Neuropathic pain patients with mechanical allodynia and ongoing background pain were recruited. Patients were thoroughly characterised using Quantitative Sensory Testing. Subjects underwent a first imaging session in which their allodynic pain was provoked using a soft brush or von Frey filaments. Pain ratings were obtained for the ongoing background pain before and after each functional scan and for the provoked pain after each scan. Patients were imaged a second time using the same experimental protocol after having altered their pain medication being either carbamazepine, diclofenac or lidocaine patches. FMRI Imaging was carried out at 1.5 Tesla using a standard gradient echo EPI sequence. Image analysis was done using FEAT (FMRI Expert Analysis Tool). Results: Alteration of the analgesic medication led to a perceived change in pain intensity of the ongoing background pain whereas the allodynic pain remained unchanged in the majority of the cases. Preliminary data analysis shows that the fMRI signal during allodynic pain seems to be attenuated when a high level of background pain is present and seems to return partially when the background pain is reduced despite the behavioural report of the allodynic pain not changing. Conclusions: It seems to be feasible to image intensity alterations of ongoing background pain. We are currently investigating alternative fMRI methods for the study of ongoing pain.

BRAIN ACTIVATION PATTERNS FOLLOWING STIMULATION OF THE HEALTHY SKIN WITH TWO DIFFERENT VON FREY MONOFILAMENTS. INITIAL RESULTS FROM AN FMRI STUDY

D. Keizer1,2, J.M. Hoogdijin2, M. Van Wijhe2, J.H. Van der Hoeven1, J.M.K.H. Wierda1

1Anesthesiology, University Hospital Groningen, Groningen, The Netherlands, 2School of Behavioral and Cognitive Neurosciences, Neuroimaging Center, Groningen, The Netherlands, 3Neurology, University Hospital Groningen, Groningen, The Netherlands

Introduction: Von Frey Monofilaments (VFM) can be used to administer standardised painful stimuli in patients with allodynia. In healthy subjects, the application of VFMs evokes a light pricking sensation, but no pain. We plan to study brain responses to VFM stimuli in both patients and healthy subjects. In this preliminary study, we report the brain activation patterns following the application of VFM stimuli in a healthy subject using fMRI. Methods: Two nylons VFMs were used to administer cutaneous stimuli of relatively high (60 grams) and low (8 grams) intensity to a male volunteer (30 yr). In an event-related design, the stimuli were randomly applied onto the dorsum of the left hand for 6 seconds. Following each stimulus, the subject pushed a button when the pricking sensation had disappeared. The study was done on a 3 Tesla Philips Intera MR-scanner using single shot EPI. SPM99 was used for data analysis; the statistical threshold for activation was set at P < 0.05 (corrected for multiple comparisons). Results: When comparing the sensory VFM stimuli with the motor responses, activation was seen bilaterally in the dorsal part of the Anterior Cingulate Cortex (ACC), in the contralateral anterior insular cortex and the retro-insular/secondary somatosensory cortex (SII). Only the signal in the latter two cortices was modulated by the intensity of the VFM stimuli. Discussion: Interestingly, although application of the VFMs was not considered painful, the results are in agreement with reported brain activation patterns when painful stimuli are used.
FMRI EVIDENCE FOR MIDBRAIN RETICULAR FORMATION INVOLVEMENT IN A HUMAN MODEL OF NEUROPATHIC PAIN

L. Zambrano1,2, R.G. Wise1,3, J.C.W. Brooks1,2, G.D. Iannetti1,2

1Department of Human Anatomy and Genetics, Oxford University, Oxford, United Kingdom
2FMRIB Centre, John Radcliffe Hospital, Oxford University Department of Clinical Neurology, Headington, United Kingdom

Abstract: Hyperalgesia is the clinical manifestation of plastic changes in pain processing. It can be evident at the injury site - primary hyperalgesia or outside secondary hyperalgesia. Our aim was to investigate the neural correlates of pain-related mechanical secondary hyperalgesia. We used the heat/capsaicin sensitization model (45°C heat followed by topical 0.075% capsaicin) to induce secondary hyperalgesia on the lower legs in 12 healthy volunteers. We used whole-brain functional magnetic resonance imaging (fMRI) to look at brain activation elicited by mechanical stimulation with a 26 gram von Frey filament (254.8 mN; length 64 mm, width 10 mm) in the area of hyperalgesia and compared it with the response of normal, untreated skin, in the same subjects. Following heat/capsaicin, all subjects developed a secondary hyperalgesia area. The paired test between the brain activation maps to punctate stimulation of the secondary hyperalgesia area and the respective maps to control stimulation showed activation in the cerebellum, midbrain periaqueductal gray (PAG), nucleus cuneiformis (NCF), bilateral thalamus, left posterior somatosensory cortex (SI) and left primary somatosensory cortex (SII), anterior and posterior cingulate cortices, right middle frontal gyrus, right inferior parietal and right precuneus. Animal studies established role for the rostral ventromedial medulla (RVM) in the development and maintenance of central sensitization and secondary hyperalgesia. The RVM and the NCF are the major source of input to the RVM and therefore in a position to modulate its output. We believe this is the first evidence in humans for a role of the NCF and PAG in secondary hyperalgesia.

CEREBRAL ACTIVATION PATTERNS OF TACTILE, PHASIC AND TONIC PAINFUL STIMULATION IN HUMANS

U. Baumgaertner1, P. Stoeter2, T. Bauermann3, M. Oezcan1, R.-D. Treede1

1Johannes Gutenberg University, Institute of Physiology and Pathophysiology, Mainz, Germany, 2Johannes Gutenberg University, Institute of Neuroanatomy, Mainz, Germany

Abstract: Non-painful and painful stimuli are known to activate neighboring regions or even the same areas like the somatosensory cortices. Other activation areas seem to be predominantly, or exclusively, active when a stimulus is painful. In this fMRI study we compared different cerebral activation patterns evoked by three types of stimulation. 12 healthy subjects underwent a balanced series of (1) non painful tactile stimulation with a 128 mN von Frey hair, (2) phasic painful stimulation with a 128 mN pin prick stimulator, and (3) tonic painful stimulation using a mechanical force of 1.93 ± 0.54 s) post-injection of NGF 30 ng (n=12, p< 0.05). NGF did not evoke mechanical hyperalgesia, but significantly increased the mechanical heat threshold response to mechanical stimulation in all subjects included in the analysis. The pattern of activity during non painful cold stimulation in healthy subjects included controlateral activity in the anterior cingulate cortex. Similar pattern of activation was found in patients with allodynia to cold. Conclusions: These data suggest that the central processing of cold alldynia and physiological cold pain shares a common network.

FMRI STUDY OF COLD ALLODYNYA IN PATIENTS WITH SYRINGOMYELIA

N. Attal1, D. Ducros2, F. Parker3, D. Bouhassira1

1INSERM E-332, Centre D’Evaluation Et De Traitement De La Douleur, Hopital Ambroise ParT, Boulogne, France, 2Neuroradiology Department, Hopital Kremlin-Bic.Otre, Le Kremlin-Bic.Otre, France, 3Neurosurgical Department, Hopital Kremlin-Bic.Otre, Le Kremlin-Bic.Otre, France

Abstract: Aim of investigation : The objective of this study was to investigate the central processing of cold alldynia in patients with syringomyelia. Methods : Six patients with cervical syringomyelia and cold allodynia of the hand (ie, abnormal pain to innocuous cold stimulation) were included. The cerebral activation pattern during cold alldynia was imaged using fMRI and compared to those obtained during stimulation of the hand in 6 healthy paired volunteers using (i) a non painful cold stimulation (20°C) identical to that applied in patients and (ii) a normally noxious cold stimulation. Results : The pattern of activity during non painful cold stimulation in healthy subjects included controlateral activity in the primary and secondary sensory cortex/insula area. During normally cold painful stimuli in the same subjects, significantly higher activation was found in the anterior cingulate cortex. Similar pattern of activation was found in patients with alldynia to cold. Conclusions: These data suggest that the central processing of cold alldynia and physiological cold pain shares a common network.
Cold allodynia is frequently observed in patients with peripheral neuropathies. Several studies have demonstrated the presence of “cold” units in experimental neuromas, however the molecular mechanisms underlying this temperature sensitivity remain unknown. Here we have investigated the role of the recently cloned TRPM8 channel and the possible contribution of K⁺ channels to cold-evoked responses in axotomized fibres from mice neuromas. We used experimental neuromas maintained in vitro, formed at the saphenous nerves in mice 1-3 weeks beforehand. Spontaneous activity and cold sensitivity were recorded from identified single units innervating the neuroma. The total number of fibres were electrically identified and classified as Ad or C. The neuroma was stimulated by cooling the superfusion fluid from a baseline temperature of 35°C to 15°C with a Peltier device. Thereafter, the neuromas were superfused with either 100 microM Menthol or 50 microM 4-aminoypyridine and the cold stimulus was repeated. Cold responses were induced in 50/268 fibres and only 3 of those units exhibited spontaneous ectopic discharges. In general, the main response occurred during the cooling phase, becoming less active during re-warming. In the presence of menthol the temperature threshold for the response increased in 7/14 units, without affecting mean discharge rate, and 3 additional units became responsive to cold. In a separate series of experiments 50 mM 4-AP was applied to 7 fibres and induced de novo cold responsiveness, in at least one fibre, of all the filaments tested. In this case, responses were similar during cooling and re-warming. These results suggest that more than one molecular mechanisms appears to be involved in the cold responsiveness of axotomized fibers from peripheral neuromas. Supported by MICYT (SAF2001-1641).
ANALGESIC THERAPY IN POSTHERPETIC NEURALGIA: A QUANTITATIVE SYSTEMATIC REVIEW


1Department of Anaesthetics, Royal Hampshire County Hospital, Winchester, United Kingdom, 2Pain Research Institute, University of Liverpool, Liverpool, United Kingdom, 3Zoster Unit, Pain Management Clinic, Bristol Royal Infirmary, Bristol, United Kingdom, 4Department of Computing and Information, Royal Marsden Hospitals, London, United Kingdom, 5Pain Research Unit, Department of Anaesthetics, Faculty of Medicine, Imperial College, London, United Kingdom

Background: Despite advances in antiviral therapy and vaccination against varicella zoster, postherpetic neuralgia (PHN) continues to be a significant clinical problem. PHN is being increasingly recognised as a clinical trial model for neuropathic pain. Since the publication of previous systematic reviews on PHN treatment, the evidence base has fundamentally altered with the publication of several major clinical trials. We have therefore performed a quantitative systematic review of randomised controlled trials (RCTs) of analgesic therapy in PHN. Methods: Data bases (Medline, EMBASE, CINAHL, Cochrane) were searched for RCTs that examined PHN lasting for greater than 3 months, that were blinded, randomised and had at least one clinically relevant measure of pain outcome. Retrieved trials were quality scored by each author, using the Jadad 5 point scoring system, and a consensus score reached. Studies were excluded if they achieved a score of less than 3. Where possible dichotomous data were extracted and numbers needed to treat and numbers needed to harm calculated. Results: Fifty-six RCT were included in the review, covering a wide range of treatments. There is evidence for the analgesic efficacy in established PHN for the following oral therapies: tricyclic antidepressants, gabapentin, opioids and tramadol. Efficacy of the topical therapies capsaicin, lidocaine patches, aspirin/diethyl ether and indomethacin/diethyl ether are also supported by an evidence base. Intrathecal administration of lidocaine with methylprednisolone was also supported by an evidence base. Pain outcome. Retained trials were quality scored by each author, using the Jadad 5 point scoring system, and a consensus score reached. Studies were included if they achieved a score of less than 3. Where possible dichotomous data were extracted and numbers needed to treat and numbers needed to harm calculated. Results: Fifty-six RCT were included in the review, covering a wide range of treatments. There is evidence for the analgesic efficacy in established PHN for the following oral therapies: tricyclic antidepressants, gabapentin, opioids and tramadol. Efficacy of the topical therapies capsaicin, lidocaine patches, aspirin/diethyl ether and indomethacin/diethyl ether are also supported by an evidence base. Intrathecal administration of lidocaine with methylprednisolone was also supported by an evidence base. The following therapies were not associated with efficacy in PHN: oral NMDA receptor antagonists, codeine, ibuprofen, lorazepam, 5HT receptor agonists, acyclovir, acupuncture, vincristine, iontophoresis and topical diclofenac/diethyl ether.

THE ROLE OF THE CARNITINE METABOLISM IN THE PATHOPHYSIOLOGY IN CRPS-TYPE I PATIENTS WITH ALLODYNIA AND HYPERPATHIA

A. Moesker

Department of Anaesthesia and Pain treatment, Refugia Hospital, Stadskanaal, The Netherlands

There are several ways by which carmin can act in alleviating the disturbance which can cause the neuronal dysfunction leading to allodynia and hyperpathia. _stimulation of the mitochondrial fatty acid oxidation _stimulation of the pyruvate oxidation which decreases the production of lactic acid _stimulation of the oxidation of 2-ketogulurate and branched-chain amino acids conversion of excessive long-chain acyl-CoA into acylcarnitines, removing metabolic inhibition and preventing production of free radicals improvement of the microcirculation in ischemia by repletion of interstitial carmin which exchanges with LCAC (long chain acyl carmin) from cells membrane repair by reacylation of peroxidised fatty acid groups in phospholipids_ We discovered that the levels of plasma free and total carmin increased with age. Intravenous ketanserin in a younger group (19-42 years) caused an increase in these carmin levels. This effect decreased with age, and disappeared in the older group (44-70 years). We also showed that the plasma levels of free-carmin, acetylcarnitine and propionylcarmin in female CRPS patients are higher than the levels found in age matched controls, and become similar at old age. An other discovery was that in female CRPS patients, after intravenous administered ketanserin, the change in plethysmographic amplitude of the affected extremity is related to the change in the plasma free carmin level. In a pilot study of 12 patients, already treated with ketanserin, 5 remained severe alldony/hyperpathia. Adding carmin to their treatment, resolved in all 6 cases the symptom of allodynia/hyperpathia.

PILOT STUDY ON SAFETY AND EFFICACY OF SPM 927 IN POSTHERPETIC NEURALGIA

C. Maier1, R. Baroni2, T.S. Jensen3, B. Koch4, C. Rauschkolb5

1Ruhr University, Bochum, Germany, 2Kiel University, Kiel, Germany, 3Aarhus University, Aarhus, Denmark, 4Schwarz BioSciences, Monheim, Germany

Background and aims: This pilot trial was conducted to investigate the tolerability and analgesic effect of the novel anticonvulsant SPM 927 in patients with postherpetic neuralgia (PHN). Methods: This was a double-blind, placebo-controlled phase 2 trial. 44 patients were randomized to either placebo (PLC) or to SPM 927 in one of two dosing regimens (300 mg/d or 600 mg/d). After 6 weeks of titration, patients entered a 4 weeks maintenance phase, completed by a taper phase and safety follow-up. The primary variable was the change in average daily pain score using a 0-10 Likert scale. Secondary variables included assessment of sleep, general activity, and quality of life. All adverse events were recorded. Results: 32 of 44 patients completed the trial. Efficacy results did not demonstrate clinically relevant differences among SPM 927 treatment groups and PLC. Some improvement over PLC was seen during titration for the high dose regimen and for the low dose regimen during maintenance, but the effects were low. Analysis of safety data showed no serious safety issues, in particular no effect of SPM 927 on QTc was observed. Expected CNS-related side effects occurred mainly on the highest dose level. Conclusions: In this pilot trial including a fairly refractory population SPM 927 showed no statistically significant effect at reducing pain due to PHN. No serious safety issues were observed, indicating good tolerability of SPM 927 in PHN patients.

SPINAL CORD STIMULATION - AN OPTION IN SEVERE CASES OF CRPS-I IN GIRLS

G.L. Olsson1, B. Linderoth2, B. Meyerson2

1Pain Treatment Unit, Karolinska Institute, Astrid Lindgren Childrens Hospital, Stockholm, Sweden, 2Department of Neurosurgery, Karolinska Hospital, Stockholm, Sweden

Background and aim: CRPS-I in children is usually successfully treated with physiotherapy, sympathetic blocks, and cognitive behaviour therapy. In some severely handicapped patients none of these treatment modalities is effective. Spinal cord stimulation may be a therapeutic option. Method: In therapy-resistant cases of severe CRPS-I in children admitted to the Pain Treatment Unit at Astrid Lindgren Childrens Hospital, Stockholm, spinal cord stimulation was tried. Results: Seven girls, aged 11-19 years were included. Localisation of pain was a foot in 4 cases, hand (1), one knee (1) and both knees (1). In 4 cases the CRPS-I was initiated by a minor trauma, in four cases there was no history of preceding trauma. There was motor involvement in 6/7 cases. Duration of pain before SCS was 12 month û 6 years. The electrode was inserted awake in six cases and under general anaesthesia in on 11 year old girl. Five of the girls enjoyed complete pain relief and two had partial relief. There were no adverse effects. However in one case (performed in general anaesthesia) three procedures including change to a plate electrode was necessary to obtain good paraesthesiae and effect. In one girl with partial effect there were during the years, technical problems to get good effect. Conclusion: SCS is an invasive and relatively expensive method that in adults has proven to be very effective for certain forms of neuropathic pain. To the best of our knowledge SCS has hitherto not been tried in children but in our experience it can be a useful treatment also for severely incapacitated paediatric cases of otherwise therapy resistant CRPS-I conditions.
POSSIBLE ROLE OF AUTONOMIC NERVOUS SYSTEM IN HERPES ZOSTER AND POST HERPETIC NEURALGIA

N. Bhattacharya1, S.N. Bhattacharya2, AK. Saxena3, A. Bhattacharya3, O.P. Tandon1, N. Verma1

1Physiology, UCMS-GTB Hospital, Delhi, India, 2Dermatology, UCMS-GTB Hospital, Delhi, India, 3Anaesthesiology, UCMS-GTB Hospital, Delhi, India, 4Anaesthesiology, Sir Ganga Ram Hospital, Delhi, India

Relief of pain in some patients of Herpes Zoster (HZ) and Post Herpetic Neuralgia (PHN) with sympathetic blockade has been reported as well as refuted. Present study was undertaken to systematically evaluate the role of autonomic nervous system in HZ and PHN. The study was conducted on 30 normal subjects, 20 patients of HZ and 12 patients of PHN. A battery of six standard autonomic function tests (AFT), namely Heart Rate Variability (HRV), Blood pressure responses to postural change and hand grip, Respiratory to Inspiratory RR interval ratio (Ei), Valsalva Ratio (VR) and Heart Rate change on standing from supine posture (30:15) were recorded. An intra and inter group comparison was made by applying Tukey and ANOVA. The results showed an individual variability in the absolute value of every parameter within each group. Despite this variability, inter group comparisons revealed a significant decrease in parasympathetic and increase in sympathetic activity in HZ and PHN groups as compared to the normal controls. The significance of this association of increased sympathetic and decreased parasympathetic tone with PHN is not clear. However, not all patients demonstrate this alteration in autonomic status and this may explain failure to achieve pain relief with sympathetic blockade and merit of evaluation of autonomic status prior to adopting any therapeutic modality.

cAMP MEDIATES MECHANICAL SENSITISATION IN NERVE ENDINGS OF THE RAT SAPHENOUS NERVE NEUROMA. EIN VITRO.E

L. Rivera1, J. Gallar2, M.A. Pozo3, C. Belmonte2

1Departamento De Fisiologia, Facultad De Farmacia, Universidad Complutense, Madrid, Spain, 2Instituto De Neurociencias, Universidad Miguel Hernandez-CSIC, Alicante, Spain

In a previous study we demonstrated that nerve endings in the rat saphenous nerve neuroma in vitro exhibit properties of polymodal afferents, including their sensitisation by a mixture of algesic chemicals (inflammatory soup, IS) (Rivera et al., J. Physiol. 527: 305-313, 2000). Furthermore, since some of the chemicals of the IS exert their action through the increment in the cAMP levels, the aim of the present study was to investigate the role of the cAMP pathway on the mechanical sensitisation observed in these endings. Neuromas of the rat saphenous nerve were developed in in 5 mm silicone tubes. 1-17 weeks old neuromas were obtained, placed in a perfusion chamber with oxygenated physiological salt solution at 35°C (pH 7.4). The proximal stump of the nerve was located in a separated compartment filled with mineral oil. Monopolar recording of electrical activity was performed from thin nerve strands. Five units were studied and the mechanical threshold was measured by probing the neuroma surface with calibrated von Frey hairs. Then, the units were exposed to a mixture of algesic chemicals (IS). After that, 10mM of the cAMP analogue 8-Br-cAMP was applied and 5-10 min later the mechanical threshold was again measured. Five polymodal units were studied, two of them developed spontaneous activity. Mechanical threshold varied from 18 to 30 mN (n=5). A significant reduction of mechanical threshold was observed in these units following their exposure of the neuroma to 10 mM 8-Br-cAMP from 28.16±1.22 to 9.38±0.61 mN (n=5, p<0.01, 1 student test). These results suggest that neuroma nerve endings became mechanically sensitised by inflammatory mediators through the increment of cAMP levels, that could explain the generation of pain sensations by innocuous mechanical stimulation of neuromas.

CELECOXIB PREVENTS DEVELOPMENT OF DARK NEURONS INDUCED BY INFLAMMATORY PAIN IN SPINAL CORD DORSAL HORN

P. Hassanzadeh, A. Ahmadiani

Department of Pharmacology, Shahid Beheshti University of Medical Science, Tehran, Iran

Neuronal plastic changes within the spinal cord play a critical role in hyperalgesia associated with nerve injury and inflammation. Morphological changes as development of dark neurons, perhaps by way of programmed cell death, is of particular interest in this regard. In this study, the effects of acute and chronic administration of formalin, as model of peripheral inflammation, on development of dark neurons and effect of celecoxib as anti-inflammatory and proapoptotic drug, on this process, have been assessed in biochemical and morphological aspects. Acute and chronic intraplantar injections of formalin 1%, 2.5% and 5%, resulted to an increase of serum nitrite, metabolite of NO. Celecoxib at doses of 20 and 40 mg/kg, i.p., did not change the level of serum nitrite, but at dose of 100 mg, caused an increase in serum nitrite. Pretreatment with celecoxib, 100mg/kg/i.p., significantly reduced levels of nitrite induced by formalin. Microscopic observation of superficial lamina of lumbar spinal cord dorsal horn, showed that only after repeated administration of formalin 5%, dark neurons had developed. Celecoxib, a fast-acting drug in induction of apoptosis, resulted in morphological changes in spinal neurons at dose of 100mg/kg, 4h after injection, and as pretreatment, significantly reduced the numbers of dark neurons induced by chronic formalin treatment. Results indicate that celecoxib has suppressed function of formalin and despite essential role of NO in development of dark neurons, the role of other factors should also be considered.

SPINAL PATHWAYS INVOLVED IN ROSTRAL CONDUCTION OF NEUROPATHIC MANIFESTATIONS IN RATS

B. Safieh-Garabedian1, S. AbdelBaki1, S.F. Arweh1, S.J. Jabbar2, N.E. Saade1

1Department of Biology, American University of Beirut, Faculty of Arts and Sciences, Beirut, Lebanon

Background and aims: The dorsal column (DC) system has been postulated as the ascending tract carrying allodynia to supraspinal centers in neuropathic rats. However, previous work from our laboratory showed that DC lesions produced only transient decrease of all neuropathic manifestations in two rat models for mononeuropathy (Neuroscience, 2002, 115:403-). Our aim was to investigate the role of the spinal pathways in rostral transmission of the neuropathic manifestations. Methods: Several groups of rats (n=6 each) were subjected to selective lesion of the white columns of the spinal cord at cervical level, two weeks after the induction of mononeuropathy by ligation and cutting the perineal and tibial nerves of the left leg. The allodynia was assessed by Von Frey filaments (tactile) or by acetone drops test (cold). Thermal hyperalgesia was assessed by the paw withdrawal duration test. Results: The effects of bilateral lesions of either the DC or the dorsolateral funiculi (DLF) and of the contralateral anterolateral column or hemisection, were tested over a period of 4-8 weeks. All spinal tract lesions produced transient, but significant, decrease of allodynia and hyperalgesia over 2-3 weeks. The most pronounced effects were observed with DC lesions and to lesser extent by DLF lesions. Conclusions: 1) All spinal tracts can be involved in rostral transmission of the various aspects of neuropathic manifestations; 2) the recovery of symptoms following lesions provides illustration on the plasticity of the neural network involved in the processing of neuropathic syndromes. (Supported by grants from the LNCISR and USB).
The effects of a synthetic nonpeptide analogue to thymulin PAT was tested on nociceptive behavior in a rat model for mononeuropathy, using the spared nerve injury method. PAT was administered at different doses (0.1, 1 and 5 mg in 2 ml) into the lateral cerebral ventricles (ICV) and neuropathic manifestations were assessed during 3-5 h. Following the injection, ICV injection of PAT produced significant attenuation tactile and cold allodynia and heat hyperalgesia. The potency of the effects was as follows in decreasing order: heat hyperalgesia, tactile allodynia, cold allodynia. These effects were comparable to those observed followed ICV injection of equal or higher doses of morphine. The reported results suggest that PAT constitutes a potential candidate for the treatment of neuropathic pain.

One week after transplantation, animals received different doses of HN (0.5, 1, 3 ug/ml) or saline intrathecally. Behavioral tests were performed before induction of CCI, then one day following the CCI surgery, rats were again anesthetized with ketamine/xylazine and an i.t. cannula inserted. On day 11 following CCI-surgery, rats were received a bolus i.t. injection of Xen2174 (0.2-30 nmol), morphine (3.5-50 nmol) or saline (control rats) and tactile allodynia, the distinguishing feature of neuropathic pain, was quantified using calibrated von Frey filaments (2-20 g). Results: The i.t. administration of bolus doses of Xen2174 produced dose-dependent relief of tactile allodynia with a peak anti-allodynic effect observed at ~1 h post-dosing and a duration of action of up to ~48 h at higher doses. However, in contrast to the maximal responses evoked by the higher doses of i.t. Xen2174 (ED50 = 15.1 nmol), i.t. morphine (ED50 = 8.9 nmol) produced only a sub-maximal response in CCI-rats, indicating a pronounced ceiling effect. Conclusions: Xen2174 administered i.t. is efficacious for the relief of tactile allodynia in a rat model of neuropathic pain. This results highlights the important role in pain control played by noradrenaline released from descending inhibitory pathways. Xen2174 is being developed for i.t. administration to patients with intractable neuropathic pain.

Intrathecal transplantation of adrenal chromaffin cells have been shown to reduce allodynia and hyperalgesia through intervening in the NMDA cascade. Recent experiments have shown that Histogranin(HN) which has NMDA receptor antagonist activity can reduce chronic pain in animals. The aim of this study is to examine the cumulative effect of adrenal transplantation and intrathecal injection of HN on pain behavior in neuropathic rats. To examine this, one-week after unilateral sciatic nerve ligation using a chronic constriction injury (CCI) model, animals received either adrenal medulla or control striated muscle tissue transplant to the lumbar subarachnoid space. One week after transplantation, animals received different doses of HN (0.5, 1, 3 ug/ml) or saline inerathecally. Behavioral tests were performed before induction of CCI, then one day following the CCI-surgery, rats were again anesthetized with ketamine/xylazine and an i.t. cannula inserted. On day 11 following CCI-surgery, rats were received a bolus i.t. injection of Xen2174 (0.2-30 nmol), morphine (3.5-50 nmol) or saline (control rats) and tactile allodynia, the distinguishing feature of neuropathic pain, was quantified using calibrated von Frey filaments (2-20 g). Results: The i.t. administration of bolus doses of Xen2174 produced dose-dependent relief of tactile allodynia with a peak anti-allodynic effect observed at ~1 h post-dosing and a duration of action of up to ~48 h at higher doses. However, in contrast to the maximal responses evoked by the higher doses of i.t. Xen2174 (ED50 = 15.1 nmol), i.t. morphine (ED50 = 8.9 nmol) produced only a sub-maximal response in CCI-rats, indicating a pronounced ceiling effect. Conclusions: Xen2174 administered i.t. is efficacious for the relief of tactile allodynia in a rat model of neuropathic pain. This results highlights the important role in pain control played by noradrenaline released from descending inhibitory pathways. Xen2174 is being developed for i.t. administration to patients with intractable neuropathic pain.

Intrathecal transplantation of adrenal chromaffin cells have been shown to reduce allodynia and hyperalgesia through intervening in the NMDA cascade. Recent experiments have shown that Histogranin(HN) which has NMDA receptor antagonist activity can reduce chronic pain in animals. The aim of this study is to examine the cumulative effect of adrenal transplantation and intrathecal injection of HN on pain behavior in neuropathic rats. To examine this, one-week after unilateral sciatic nerve ligation using a chronic constriction injury (CCI) model, animals received either adrenal medulla or control striated muscle tissue transplant to the lumbar subarachnoid space. One week after transplantation, animals received different doses of HN (0.5, 1, 3 ug/ml) or saline inerathecally. Behavioral tests were performed before induction of CCI, then one day following the CCI-surgery, rats were again anesthetized with ketamine/xylazine and an i.t. cannula inserted. On day 11 following CCI-surgery, rats were received a bolus i.t. injection of Xen2174 (0.2-30 nmol), morphine (3.5-50 nmol) or saline (control rats) and tactile allodynia, the distinguishing feature of neuropathic pain, was quantified using calibrated von Frey filaments (2-20 g). Results: The i.t. administration of bolus doses of Xen2174 produced dose-dependent relief of tactile allodynia with a peak anti-allodynic effect observed at ~1 h post-dosing and a duration of action of up to ~48 h at higher doses. However, in contrast to the maximal responses evoked by the higher doses of i.t. Xen2174 (ED50 = 15.1 nmol), i.t. morphine (ED50 = 8.9 nmol) produced only a sub-maximal response in CCI-rats, indicating a pronounced ceiling effect. Conclusions: Xen2174 administered i.t. is efficacious for the relief of tactile allodynia in a rat model of neuropathic pain. This results highlights the important role in pain control played by noradrenaline released from descending inhibitory pathways. Xen2174 is being developed for i.t. administration to patients with intractable neuropathic pain.

Cannabinoids modulate nociceptive processing in models of acute, inflammatory and neuropathic pain. Cannabinoid receptors (CB1) are expressed in key areas involved in nociception (Tsou et al., 1998). The aim of this work is to study if peripheral mechanisms are involved in the antinociceptive cannabinoid activity. In the present study, we have examined the effects of cannabinoid agonist WIN 55,212-2, intraplantarly (i.pl.) administered, on heat-hyperalgesia and mecano-allodynia in a model of peripheral neuropathy induced by paclitaxel in rats (Polomano et al., 2001). Paclitaxel is one of the most effective and commonly used antineoplastic drugs for the treatment of solid tumours. It has serious side effects like peripheral neurotoxicity. Paclitaxel (1mg/kg) was administered intraperitoneally (i.p.) on four alternated days (days 1, 3, 5 and 7). The plantar surface of the hind paw (sciatic nerve territory) was tested for heat-hyperalgesia and mecano-allodynia. Heat-hyperalgesia was tested using method described by Bennett and Hargreaves, (1990) and mecano-allodynia was assessed with the von Frey filaments (Tal and Bennett, 1994). Paclitaxel produced a statistically-significant thermal hyperalgesia (29% vs control) and mechanical allodynia (78% vs control) in both hind paws. There no consistent left-right differences. In this model, WIN 55,212-2 (250ug, 100ug and 50ug i.pl.) was administered at day 29. The cannabinoid agonist at higher doses (250ug and 100ug) dose dependently returned the thermal hyperalgesia and mecano-allodynia to control values. This antinociceptive effect was induced in both ipsi and contralateral paws. Nevertheless, at the dose of 50ug i.pl., the cannabinoid had no ipsi and contralateral effect. Although more work is required, these data can suggest that WIN 55,212-2 has anti-hyperalgesic and anti-allodynic effect in this model of neuropathic pain and that this effect appears to be systemic.
SEGMENTAL REFLEX CORRELATES OF ALTERED NOCICEPTIVE PROCESSING BELOW THE LEVEL OF SPINAL CORD INJURY IN THE RAT

E. Gonzalez-Valdizan, S. Vazquez-Pérez, M. Nieto-Sampedro, J.S. Taylor

1Unidad De Neurologia Experimental, Hospital Nacional De Parapléjicos, Toledo, Spain

The development of central neuropathic pain below the level of spinal cord injury (SCI) is associated with clinical signs and symptoms of dysesthesia, and occasionally evoked pain. The majority of experimental studies of pain below SCI have involved the study of segmental nociceptive processing in animal models where learned nocifensive responses have not been defined. Here we document changes in segmental nociception in a standardized SCI pain model, where the operant responses to noxious stimuli are known to be enhanced, by recording electrophysiological and behavioral reflex responses below and ipsilateral to an under-hemisection (UH) combined with an hemotoxic injury at the T12 level in male Wistar rats. Stimulus-response analysis of the tibialis anterior EMG response to noxious electrical stimulation of the toes ipsilateral to the SCI revealed an enhanced reflex gain in the combined UH/hemotoxic lesion group when compared to UH injury alone, and that this cutaneous hyperreflexia was inhibited at lower intrathecal doses of MK801. In contrast this SCI pain model did not produce behavioral evidence of enhanced reflex responses to either thermal or mechanical stimulation of the ipsilateral plantar pad. We are currently identifying other reflex correlates of altered nociception below the SCI, including enhanced responses at threshold stimulation. Financial support to St. Gonzalez-Valdizán made possible from the Consejería de Salud de Castilla La Mancha, No: IE02005, No: 03019-00 and the SESCAM.

WIND-UP LIKE RESPONSES IN THE MOUSE NEUROMA - NERVE IN VITRO PREPARATION

I. Rivera-Arcosenda, C. Rozaa, J.A. Lopez-Garciaa

1Fisiología, Universidad De Alcalá, Madrid, Spain, 2Instituto Neurociencias, Universidad Miguel Hernandez, Alicante, Spain

Background and aims: Wind-up is commonly observed in spinal neurones but not in normal peripheral afferent fibres. Here we have studied the responses of neuramatosous nerve fibres to repetitive stimulation of the neurona. Methods: Loose ligatures or transection experimental neuromas were performed in saphenous nerves of male mice under halothane anesthesia. After 1-30 days of development, neuromas with a length of nerve (11-15 mm) were extracted under urethane anesthesia, placed in a perfusion chamber and maintained with a constant stream of oxygenated synthetic interstitial fluid (SIF) at room temperature. Neuromas were electrically stimulated and the whole nerve activity monitored by means of suction electrodes. Results: Repetitive electrical stimulation of neuromas produced a progressive increase in the firing of action potentials at unidentified afferent fibres in 10 out of 21 preparations. These wind-up like responses where optimally induced with stimulus intensities outside 12 times threshold for C-fibre activation at frequencies between 0.5 to 2 Hz. Maximum discharge frequencies were obtained after 5-15 stimuli. Prolonged after-discharges (up to 70 s) were commonly recorded on termination of stimulation. Stimulating sites outside the neuramatosous area never produced wind-up. Wind-up like responses were observed in neuromas of 1 to 3 days post-surgery but not in older neuromas. Similar success rates were obtained in both types of neuromas. Conclusions: Wind-up like responses generated by neuromas might depend on the expression of particular ion conductances and can be used to test their excitability. Acknowledgements: Supported by the Spanish Ministry of Science and Technology (BF02003-04045), the Madrid Regional Government (Contrato Programa) and the 'Instituto UPSA del Dolor'.
ATYPICAL FACIAL PAIN AND SYMPTOMATIC FACIAL PAIN: DIFFERENTIAL CHARACTERIZATION AS FOR THE CLINICAL PRESENTATION

J.C.M. Nobrega1, M.J. Teixeira1, J.T.T. Siqueira2
1Functional Neurosurgery, Sao Paulo University, Clinical Hospital, Sao Paulo, Brazil, 2Odontolgy Orofacial Pain, Sao Paulo University, Clinical Hospital, Sao Paulo, Brazil

Objectives: The purpose of the present study is to characterize a group of patients with atypical facial pain in comparison to patients with symptomatic facial pain and to determine the evolution of the occurrence of psychological abnormalities in these patients. Methods: Determination of the evolution of some aspects of pain, clinical examinations and laboratory and radiological exams of 41 patients with complaints suggestive of AFP. Results: In 21 (51.2%) patients, the final diagnosis was Atypical Facial Pain (AFP) and in 20 (48.0%), Symptomatic facial pain (SFP). 80.0% of the SFP patients (SFPSS) and 57.1% of the AFP (AFPPS) were women. Temporomandibular dysfunction (TMD)-toothless was diagnosed in 25.0% of the cases of SFP, intraparenchymal tumor in 20.0%, TMD-systemic disease in 15.0%, other TMDs in 15.0% and Wallenbreg syndrome in 10.0%, tongue carcinoma, intracranial tumor or burning mouth were diagnosed, in one patient, respectively (5%). AFP was more prevalent (28.6%) in 41 to 50 and 61 to 70 years old patients and SFP (30.0%) in 41 to 50 years old patients. In 40.0% SFPSS there was hyperalgesia, in 45.0%, hyperesthesia, in 20.0%, hypoesthesia, in 5.0% analgesia, in 5.0% deficit of masticatory function, in 5.0% amiotrophy and, in 5.0%, peripheral facial paresis. The emotions were the reasons for aggravation of the pain in 90.5% of AFPPs and 5.0% deficit of masticatory function, in 5.0% amiotrophy and, in 5.0%, peripheral facial paresis. Conclusions: Squeezing pain, pain in the territory of the second branch of the trigeminal nerve, induction of pain by emotions and absence of neurological abnormalities are more characteristic of AFP. Pain in the territory of the third branch of the trigeminal nerve, occurrence of neurological abnormalities and no induction of the symptomatology by emotions are more characteristic of SFP.

PAINFUL POLYNEUROPATHY IN CANCER PATIENTS AFTER CHEMOTHERAPY WITH ORAL DOXYFLURIDINE

Department of Neurology, Hallym University College of Medicine, Seoul, South Korea

Polyneuropathy is an important complication of antineoplastic agents, but the treatment for the complication is not well known. We present two cases developed disabling polyneuropathy after postoperative adjuvant chemotherapy with doxifluridine (converted into 5-Flourouracil by pyrimidine phosphorylase in tumor cell) for advanced gastric cancer. Case 1: A 57- year patient, who treated with oral doxifluridine after short-term intravenous 5-flourouracil (5-FU), was consulted due to paresthesia with pain of lower extremities and progressive weakness for 1 month. Nerve conduction studies (NCS) and electromyography were compatible with sensorimotor polyneuropathy. Vitamin replacement or discontinuation of doxifluridine for 2 weeks did not reverse his symptom. Methadone was 750.8 ± 464 mg. Methadone was administered 3 times a day. RESULTS: The only one with significant difference in algiometry in the last evaluation (p=0.091). Postoperatory evaluation, normalizing through time (p=0.013); 3 û Mandibular branch was lost in blink reflex. Conclusions: 1 û Ophthalmologic branch did not altered through time; 2-3: 3; V1: 2; V1-2: 2. Duration of pain ranged from 1 to 30 (median: 4 years). A û Before surgery: diminished sensitivity at the side affected in cold (4 û 13.3%), heat (7 û 23.3%); mechanical perception (3 û 10%). B û 7days after surgery: loss in thermal (9 û 28.1%) and mechanical sensitivity (11 û 34.8%). C û 30 days after surgery: loss in cold (4 û 13.3%), heat (5 û 15.6%) and mechanical sensitivity (7 û 23.3%). D û 120 days after surgery: loss in cold (6 û 18.8%), heat (7 û 23.3%) and mechanical sensitivity (10 û 31.3%). Recidive: 7 patients (23.3%), controlled with low doses of carbamazepine. None had loss in blink reflex. Conclusions: 1 û Ophthalmologic branch did not altered through time; 2 û There is statistically significant loss in the maxillary branch in the immediate postoperative evaluation, normalizing through time (p=0.013); 3 û Mandibular branch was the only one with significant difference in algiometry in the last evaluation (p=0.091).

THE ROLE OF METHADONE IN OPIOID ROTATION IN CANCER PATIENTS WITH NEUROPATHIC PAIN

W. Leppert, A. Kotlinska - Lemieszek, J. Luczak
1Karol Marcinkowski Medical University, Chair and Department of Palliative Medicine, Poznan, Poland

BACKGROUND: Methadone is often used in opioid rotation to improve analgesia and/or diminish side effects of morphine or other strong opioids. AIMS OF THE STUDY: To assess analgesia and side effects of methadone and calculation of equiparalgesic doses of oral morphine and methadone in an open clinical study. PATIENTS AND METHODS: Methadone was administered in 11 opioid tolerant patients (mean age 49.4 ± 14.9) orally (10 patients) and rectally (1 patient) with neuropathic cancer pain because of inadequate analgesia (VAS > 5) during treatment with morphine (4 patients), transdermal fentanyl (3), morphine with ketamine and transdermal fentanyl (1), morphine with ketamine and severe dryness (2), morphine and severe nausea (1). The dose ratio of morphine to methadone was 4 : 1 (up to 100 mg of daily morphine), 6 : 1 (100 û 300 mg) and 12 : 1 (over 300 mg). The mean equivalent daily dose of oral morphine before switching to methadone was 750.8 ± 464 mg. Methadone was administered 3 times a day. RESULTS: Time of the treatment was 32.2 ± 22 (range 7 û 82) days, mean daily doses 50.4 ± 18 mg at the beginning, maximal 142.5 ± 101.4 mg and 125.3 ± 98 mg at completing treatment. Good analgesia (VAS < 3) was observed in 5 patients, partial (VAS 3 û 5) in 5 patients, unsatisfactory in 1 patient (VAS > 5) who ceased methadone after 7 days. The most frequent side effects were drowsiness (5 patients), constipation (4 patients), nausea and vomiting (2 patients). CONCLUSIONS: The study confirmed analgesic efficacy, good adverse event profile of methadone, effectiveness and safety of the applied method of doses calculation.
THE EFFECT OF AMITRIPTYLINE ON THE DOSAGE OF CARBAMAZEPINE IN TRIGEMINAL NEURALGIA: A PROSPECTIVE OPEN LABEL TRIAL

C.K.S. Ong1, S.B. Keng2

1Department of Oral & Maxillofacial Surgery and 2Department of Restorative Dentistry, National University Hospital, Singapore

Aims: To test the hypothesis that amitriptyline as an add-on therapy could reduce the dosage of carbamazepine required to control the paroxysmal pain of trigeminal neuralgia (TN). Methodology: A 10-patients base with primary TN controlled with carbamazepine monotherapy, was used to evaluate the effect of amitriptyline 50mg as an add-on therapy for 1-month, in a prospective open label trial. After 7 days of amitriptyline therapy, the patients were instructed to reduce their daily dosage of carbamazepine by 100mg every 3 days until the paroxysmal pain or side-effects was intolerable. A baseline observation period of 1-month was used to evaluate the pain experience before start of the study. Patients were required to record in a pain diary 2 primary parameters before going to bed each evening 1-month before and during the trial: severity of pain on a 100-mm VAS scale and incidence of paroxysmal pain. Patient’s medication was assessed using the Hospital Anxiety and Depression Scale (HADS) during both periods. Results: A significant reduction of approximately 200 mg or 30% (range, 100 mg to 400 mg) of carbamazepine was achieved at the end of treatment (p<0.03), without any significant increase in the mean VAS scores (p=0.37) and incidence of paroxysmal pain (p=0.52). No difference was found for HADS scores between both periods. Conclusion: The results suggest that amitriptyline could reduce the dosage of carbamazepine required to control the paroxysmal pain of TN. Further evaluation of the effect of amitriptyline for TN in randomized control trial is warranted.
DEVELOPMENT OF A MEASURE TO ASSESS THE IMPACT OF NEUROPATHIC PAIN ON QUALITY OF LIFE

H.M. Poole1,2, T.J. Nurmikko1,3,4, P. Murphy3,4

1Faculty of Health and Applied Social Sciences, Liverpool John Moores University, Liverpool, United Kingdom, 2The Pain Research Institute, Liverpool, United Kingdom, 3The Walton Centre for Neurology and Neurosurgery, Liverpool, United Kingdom, 4Department of Neurological Sciences, The University of Liverpool, Liverpool, United Kingdom

Background: Patient based measures, such as health related quality of life (QoL), are commonly used to evaluate outcome in both clinical and research settings. One of the most frequently used is the SF36. The psychometric properties of the SF36 in British samples has been subject to criticism. As a generic measure the SF36 lacks disease or pain specificity. Supplementing the SF36 with a condition specific instrument will address this. Such an instrument is lacking within the neuropathic pain (NP) literature. This study represents the preliminary phases of a project designed to develop and validate a QoL measure for NP. Method 1: Three focus groups were conducted. N= 26 patients, 65% female with a mean age of 57.35 (SD) years participated. Results 1: Focus group data was used to identify potential questionnaire items. Initially 480 items were generated and examined by the authors. Items deemed ambiguous, too colloquial or repetitive were deleted and this reduced the number of draft questionnaire items to 152. Method 2: Length, face validity, content validity and response format of the questionnaire was tested in the context of a cognitive interview with 12 patients using a think aloud/E technique. Results 2: Analysis of interviews demonstrated the questionnaire has good content and face validity. A number of issues relating to length, item wording and response format were identified. These were addressed and further testing of the revised questionnaire is ongoing. Discussion: Initial testing of the draft questionnaire is encouraging and confirms the need for a disease specific measure. Following assessment of the changes, preliminary analysis of the psychometric properties will be presented and discussed.

TREATMENT OF NON-COMPRESSIVE RADICULAR PAIN: A COMPARISON OF INTERVENTIONAL VS. CONSERVATIVE MANAGEMENT

S. Kamran, A.I. Hamad

Department of Neurology, Hamad General Hospital, Doha, Qatar

Background: The treatment of non-compressive radicular pain is generally conservative. However it carries variable success and at times use of narcotic analogues. Design/Methods: Patients referred to pain clinic with radicular pain were included. Patients under went MRI to rule out root compression and were divided in to single nerve root injection (SNR) (group A) and conservative management (group B). Pain intensity was evaluated using VAS 1 to 10 scores, emergency room visits, at 3 and 6 months. Repeat SNR in group A were performed on monthly visits if necessary. One neurologist did all single nerve root injections and evaluations were done by blinded reviewer. Results: Total patients n=28 Group A (Acute radicular pain n=5, chronic radicular pain n=5, post-operative fibrosis n=4) patients underwent SNR with marcaine 0.5%/40mg prednisolone. All SNR were fluoro guided and roots outlined by contrast. Repeat SNR n=7 patients at 6-8 weeks and third SNR n=3, at 12 weeks. N=3 patients 3 SNR, n=6 had 2 SNR and n=5 only 1. Pre-treatment VAS 7 (range 5 to 9), VAS 3 months 3 (range 2-7), 6 months 2 (0-5).Total ER visits n=2, narcotic /tramadol n=1, Group B. (Acute disc n=4, chronic pain disc n=6, post-operative fibrosis n=4) n=7 patients took tramadol 200-400 mg/dl, n=6 neurontin, n=3 lamictal, n=8 tricyclic, n=4 hydrocodone VAS 3 months 6 (3-8), 6 months 5 (3-9), ER visits n=12. There were no procedure related complications. Pain was better controlled in group A, p<0.05.Conclusions: Pain intervention using SNR blocks are more effective than conservative management for sustained pain relief and avoiding ER visits. Most patients will need more than one SNR.

INTRATHecal MORPHINE AS A TREATMENT OPTION IN CHRONIC NEUROPATHIC PAIN

N.A. Lara Jr., M.J. Texeira, L.T. Yeng

University of Sao Paulo, Department of Neurology, Hospital Das Clinicas, Sao Paulo, Brazil

Background: Implantable pumps for the delivery of intrathecal morphine have become a common option for administering opiate medication for the management of chronic pain. Using opiate medication for neuropathic pain is more controversial, with some unsatisfactory results and higher doses of opiates. This study describes responses to intrathecal morphine for managing chronic neuropathic pain. Methods: 34 patients between ages 26 and 80, 16 with melenophactic (spinal cord origin) pain six with peripheral neuropathy, six with reflex sympathetic dystrophy, four with postherpetic neuralgia, one phantom limb pain and one with aracnoids were chosen from our multidisciplinary pain clinic. Patients were admitted to the hospital for therapeutics trials and were assessed for the appropriateness of their analgesic response and for adverse response to the medication. Morphine pump was implanted in 20 females and 14 males who were followed for up to 18 months. Results: A good to excellent analgesic response was seen in 24 patients (70%), a regular response was seen in four (12%), and a poor response in six (14%). One patient had device infection and the pump was changed. Other adverse effects of pump placement and morphine administration were rare and transient. Conclusion: The morphine pump was found to be a viable alternative in the management of neuropathic pain. Its use in long-term therapy, however, is not without limitations and should be a last choice option.

EFFECTS OF HIGH FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OF THE SENSORIMOTOR CORTEX ON THERMAL PERCEPTION

A. Oliviero, M. Rubio Esteban, L. Fernandez Cabredo, J.A. Godino Duran, F. Sebastian de la Cruz

Unidad De Neurologia Funcional, Hospital Nacional De Paraplejicos - SESCAM, Toledo, Spain

Repetitive transcranial magnetic stimulation (rTMS) has become a useful tool for investigating and even modulating human brain function. RTMS of the human motor cortex can produce changes in excitability that outlast the period of stimulation. We evaluated the persistent effect of high-frequency rTMS of sensorimotor cortex (SM1) on somatosensory function and specifically on the detection of thermal variation (cold and warm sensation) in fourteen normal subjects. Cold threshold was increased immediately after the rTMS of the left SM1 and no effects at all were noticed after occipital cortex (OC) stimulation. There was a slight, not significant, increase of warm threshold immediately after the rTMS of the left SM1 and no effects at all were noticed after OC stimulation. These effects of rTMS upon thermal threshold seems important because behaviour changes need to be demonstrated and quantified before thinking rTMS as useful therapeutic opportunity.
Background and Aims: The effect of the infra-red laser on the pain intensity in patients having trigeminal neuralgia was investigated. Method: 68 patients aged from 25 to 65 (42 females and 26 males) having trigeminal neuralgia of different etiology were studied. Patient examination: neurological status, magnetic resonance imaging, consultation with an otolaryngologist, a neuro-ophthalmologist and a dentist. The pain was examined and measured according to the visual analogue scale. The patients were divided into two groups. The first group (40 patients) received in addition their basic medication and physiotherapy, infra-red laser treatment on the trigeminal painful sites. The laser exposure was from 30 sec to 5 min to each site, and not more than 15 min in total in one day. The complete course was 10 - 12 procedures. The second group, the control one (28 patients), received only the basic medication and physiotherapy. Result: The pain intensity of the patients in the first group was reduced after 8 - 9 day of treatment (in 85% patients) compared to the control group, pain reduction occurred after 14 - 15 day of treatment (in 64,5% patients). We performed statistical analysis of the difference in pain reduction between the groups of treatment, thus this difference was statistically significant (p<0,01) . Conclusion: The addition of the laser therapy to the complex treatment of trigeminal neuralgia results in earlier remission.

Background and Aims: CRPS-1, not uncommon in girls aged 11-15 years, usually does not respond well to analgesics. Weather opioids are useful in this age group is not documented. Thus the effect of a potent short-acting opioid was tested in 12 girls with CRPS-1 compared to a group of children with postoperative pain. Method: Patients with CRPS-1 (Stanton-Hicks et al 1995) were consecutively included. Postoperative patients served as a control group. Seven microgram x kg BW-1 of alfentanil was equally divided in three syringes. Two syringes contained saline. The syringes were double-blinded randomly injected intravenously exactly every four minutes. VAS (0-100 mm) was measured before and 2 minutes after every injection. Side effects were asked for. At the end naloxone was given intravenously 4 microgram x kg BW-1. In the control group naloxone was not given. Results: In the CRPS-1 group (females = 11:1, age 11-17 y) starting VAS was 62 mm. The three alfentanil injections resulted in total in a mean decrease of VAS of 2.2 mm. The two saline injections gave a mean VAS decrease of 3.4 mm. Naloxone had no effect. Mean VAS at the end was 56 mm. In the postoperative group (females = 5:1, age 12-14 y) starting VAS was 49 mm. Alfentanil resulted in a mean VAS decrease of 26 mm. Saline gave a mean VAS decrease of 19mm. Mean VAS at the end was 4 mm. Side effects: Slight sedation and dizziness were common. Conclusion: Children with CRPS-1 do not get pain relief by alfentanil. This is opposite to the effects on postoperative nociceptive pain. These findings could have both diagnostic and therapeutic implication in clinical care of pain in children and adolescents.

Background and aims: Chronic neuropathic pain after inguinal surgery is a significant problem with a reported incidence of 10-15% post herniotomy (1). In these patients, nerve blocks are frequently performed and subsequent pulsed radiofrequency of the ilioinguinal nerve has recently been suggested an effective non-neurodestructive option to prolong analgesia (2). Although ultrasound-guidance has been shown to increase success and to decrease complication rates in other nerve blocks (3), it has not yet been described for the ilioinguinal nerve. Thus, we herein present the first case of a new methodological approach. Case: A 43-year old man, suffering from spontaneous chronic left-sided neuropathic groin pain (VAS 8) associated with cold hypoaesthesia (QST) after repeated laparoscopic varicocelectomy, underwent a series of 7 ilioinguinal nerve blocks. Because of inconsistent results of the first 4 blocks (blind conventional technique, bupivacaine 0.5%, 10 ml), the last 3 blocks were performed ultrasonography-guided (10 MHz, Toshiba). Ultrasound enabled easy identification of the ilioinguinal nerve at a depth of 1,5 cm, real-time guidance of the needle and reduction of local anaesthetic (5ml) due to observation of perineural spread. Subsequently, pulsed radiofrequency (22-gauge SMK-5cm cannula, Neurotherm) was performed for 120 sec. under direct sonographic vision of the nerve and the cannula. All 3 blocks were followed by a temporary-, pulsed radiofrequency by a permanent decrease in pain of 50% (VAS 4, follow up: 1 month). There were no complications. Conclusions: Although anecdotal, our case shows that ultrasound is a valuable guidance-tool with the potential for quality-improvement in invasive therapy of ilioinguinal neuropathy. References: 1. Kehlet H. Hernia 2002, 6: 178-81; 2. Cohen S.P. Urology 2003; 61: 645; 3. Greher M. Anesthesiology 2003; 99: 250-1

Aim of investigation: To establish the value of rehabilitation and physical therapy in the treatment of sympathetic dystrophy of the hand and wrist after the forearm inferior 1/3 fracture. Methods: We observed 3 groups of patients, consisting of 33 people each group - 23 women and 10 men per group, between the ages of 45 û 70, all patients suffering from sympathetic dystrophy of the hand and wrist, being after 4 weeks after a forearm inferior 1/3 fracture. The first group was treated with corticosteroids, NSAIDs, analgesics and decontracturants, the second with physical therapy and kinetotherapy (not medication due to their severe digestive associated diseases) and the third with corticotherapy, NSAIDs, analgesics, decontracturants + physical therapy and kinetotherapy. Each therapy was applied for 3 weeks. The patientsÆ pain, inflammation, range of motion (ROM), muscular force and ability of the hand and wrist were evaluated at the beginning of the treatment and after 3 weeks of treatment. Results: After 3 weeks of treatment all patients reported significant pain relief, some without inflammation, improved ROM, muscular force and ability of the hand and wrist. The group treated with both medication and physical therapy and kinetotherapy had much better results than those treated only with physical therapy and kinetotherapy and than those treated only with medication. Conclusions: The digestive disorders limit the recovery in case of sympathetic dystrophy of the hand and wrist. The less digestive disorders the patients had, the better their results due to the steroid and non-steroid antiinflammatory drugs that could be used apart from the physical therapy and kinetotherapy to reduce pain and inflammation mainly. Keywords: sympathetic dystrophy of the hand and wrist, corticotherapy, NSAIDs, analgesics, decontracturants, physical therapy, kinetotherapy.
GABAPENTIN AS AN ADJUVANT TO TRICYCLIC ANTIDEPRESSANTS FOR DIABETIC PERIPHERAL NEUROPATHY

M.S. Kokolaki1, A.C. Bairaktari1, P.A. Kamperi2, B.G. Raitsios2, S.K. Nikas3, M.G. Vafiadou1

1Pain Department and 2ICU Department, Sismanoglio General Hospital, Athens, Greece

Aim. The aim of this study was to determine if the addition of gabapentin had an effect on pain intensity at patients with diabetic peripheral neuropathy (DPN). Method. 18 patients, aged 55-74 yrs with diabetes mellitus type II, receiving insulin for 10 years at least, suffering from DPN for 1-5 year, and with daily pain score (VAS) above 6 were included in the study. All patients were being on amitriptyline 75 mg/day for 8 weeks at least. Patients were randomly allocated into two groups. Patients in group A (N=9) received placebo three times daily in addition to amitriptyline. Patients in group B (N=9) received in addition to amitriptyline, gabapentin three times daily in doses ranging from 900 mg/day to 2.400 mg/day for 8 weeks. Doses were titrated to the maximum tolerated for pain control without provoking intolerable side effects. The primary measure of efficacy was daily pain scores with visual analogue scale (VAS) Results : one patient in group B withdrew from the study. All patients in group B experienced dizziness and somnolence that were reduced during the treatment. Conclusion: The addition of gabapentin to a regimen of tricyclic antidepressants for diabetic peripheral neuropathy improves analgesia and appears safe. Backosha M. et al.


Diabetic peripheral neuropathy improves analgesia and appears safe. Bac konja M. et al.

Conclusion: The addition of gabapentin to a regimen of tricyclic antidepressants for diabetic peripheral neuropathy improves analgesia and appears safe. Backosha M. et al.

GABAPENTIN AS AN ADJUVANT TO TRICYCLIC ANTIDEPRESSANTS FOR DIABETIC PERIPHERAL NEUROPATHY

Case reports: Oxymorphone ER for Neuropathic Pain

G.W. Grass

Department of Anesthesiology, Mount Sinai Medical Center, New York, USA

Recent reports of a novel form of peripheral nerve stimulation known as Percutaneous Neurumodulation Therapy (PNT) have shown it to be an effective form of treatment in a growing number of disorders including neuropathic pain, low back pain and sciatica, neck pain, headaches, bone pain secondary to metastatic cancer, and painful diabetic neuropathy Although the exact mechanism of action of PNT remains unknown, the improvement brought about by this form of neuronal stimulation may be due to a re-organization of several or one of several of the parallel neuronal feedback systems involved in the regulation and maintenance of pain. Recent neurophysiological evidence suggests that patterned electrical stimulation of peripheral nerves may modulate sodium channel expression in sensory neurons and dorsal root ganglia thereby affecting neuronal discharge contributing to ongoing pain. In addition, electrical stimulation of peripheral nerves may also spread in an antidromic fashion to modify local reflex arcs regulating pain. This report describes the historical evolution and conceptual basis of this new technique, current clinical applications, details of its implementation and proposed mechanisms of action. It is hoped that this information will encourage other clinicians and researchers to utilize this procedure and report their findings to help determine the overall applicability of this treatment modality in other acute and chronic pain syndromes.

Percutaneous Neurumodulation Therapy: A Minimally Invasive Technique for the Treatment of Neuropathic Pain

G.W. Grass

Department of Anesthesiology, Mount Sinai Medical Center, New York, USA

Introduction. The clinical aspects and the results of ultrasonic block of the stellate ganglion in the treatment of the neuropathic pain of the upper limb are presented. Material and method. Twenty one patients (52.4% women) with neuropathic pain, aged 20 to 70 y.o. 76.3% presented Complex Regional Pain Syndrome (CRPS), 23.7% were ischemic neuropathic pain. The pain was moderate to severe, and referred as burning, tingling, Humor, sleep, daily activities and working capacities were frequently disturbed. All patients presented some improvement with local anesthetic blocks of stellate ganglion, then submitted to continuous ultrasonic blockage in the same point, using 2w/cm2 for 7 minutes, three times/week. The numbers of the blocks varies from 5 to 27. All were also submitted to physical therapy. Results. In 80.9% of the cases, there were transient satisfactory improvement of pain, facilitating the rehabilitation procedures, in 4.9%, the pain was worse, and in 14.2% of the patients, the pain was unchanged. The best results were observed in patients with ischemic pain. Conclusion. The preliminary result of the study, using ultrasonic block of stellate ganglion for neuropathic pain of the upper limb, are promising, and seemed to optimizing rehabilitation programs, and further studies are needed.

Ultrasound Block of the Stellate Ganglion in the Treatment of Neuropathic Pain of the Upper Limb

P.L. Gal, M.J. Texeira, Y. Lin

Pain Clinic and Department of Neurology, Hospital DusClinicas, University of Sao Paulo, School of Medicine, Sao Paulo, Brazil

Background and aims: Increasing evidence from randomized, controlled trials indicates that opioids are effective in treating neuropathic pain. The efficacy of a new opioid formulation, oxymorphone extended release (ER), has not been tested in a neuropathic pain trial. Therefore, we retrospectively analyzed data from a series of patients with moderate to severe neuropathic pain enrolled in a clinical trial of oxymorphone ER for cancer-associated pain. Methods: Data from a previous randomized, active-controlled, crossover trial were examined to identify all cancer cases with a neuropathic pain diagnosis; mixed pain diagnoses were excluded. Worst, least, and average pain scores (100-mm Visual Analog Scales) at screening, baseline, following 7 days of treatment with controlled-release (CR) morphine or oxycodone, and following treatment with oxymorphone ER for 7 days were assessed. Results: Eleven patients with neuropathic pain were enrolled, 9 completed the first treatment, and 8 completed treatment with oxymorphone ER (4 each received morphine or oxycodone in the first sequence). Patients were receiving opioid treatment at screening, with mean average daily pain intensity of approximately 35 mm, and most patients reporting worst pain >70 mm. Mean average daily pain intensity was similar during treatment with morphine or oxycodone (29 mm) compared with oxymorphone ER (24 mm), with most patients (5/8) reporting daily average pain <30 mm while receiving oxymorphone ER. A single patient withdrawal during treatment with oxymorphone ER was attributed to numerous adverse events (somnolence and pain). Conclusions: Oxymorphone ER appeared to provide similar analgesic efficacy compared with oxycodone or morphine in a set of cancer patients with neuropathic pain. This retrospective analysis suggests that oxymorphone ER should be tested prospectively in clinical trials of moderate to severe neuropathic pain.

Case Studies of Cancer Patients with Neuropathic Pain Treated with Oxymorphone

N. Slatkin1, H. Abdieh1

1City of Hope National Medical Center, Duarte, USA, 2Endo Pharmaceuticals, Inc., Chaddsford, USA

Background and aims: Increasing evidence from randomized, controlled trials indicates that opioids are effective in treating neuropathic pain. The efficacy of a new opioid formulation, oxymorphone extended release (ER), has not been tested in a neuropathic pain trial. Therefore, we retrospectively analyzed data from a series of patients with moderate to severe neuropathic pain enrolled in a clinical trial of oxymorphone ER for cancer-associated pain. Methods: Data from a previous randomized, active-controlled, crossover trial were examined to identify all cancer cases with a neuropathic pain diagnosis; mixed pain diagnoses were excluded. Worst, least, and average pain scores (100-mm Visual Analog Scales) at screening, baseline, following 7 days of treatment with controlled-release (CR) morphine or oxycodone, and following treatment with oxymorphone ER for 7 days were assessed. Results: Eleven patients with neuropathic pain were enrolled, 9 completed the first treatment, and 8 completed treatment with oxymorphone ER (4 each received morphine or oxycodone in the first sequence). Patients were receiving opioid treatment at screening, with mean average daily pain intensity of approximately 35 mm, and most patients reporting worst pain >70 mm. Mean average daily pain intensity was similar during treatment with morphine or oxycodone (29 mm) compared with oxymorphone ER (24 mm), with most patients (5/8) reporting daily average pain <30 mm while receiving oxymorphone ER. A single patient withdrawal during treatment with oxymorphone ER was attributed to numerous adverse events (somnolence and pain). Conclusions: Oxymorphone ER appeared to provide similar analgesic efficacy compared with oxycodone or morphine in a set of cancer patients with neuropathic pain. This retrospective analysis suggests that oxymorphone ER should be tested prospectively in clinical trials of moderate to severe neuropathic pain.
LONG TERM OUTCOME OF CERVICAL SCS FOR CHRONIC PAIN

H. Cameron1, 2, D.G. Quigley3, J. Arnold4, P.R. Eldridge5, K. McIver6, T.R.K. Varma7

1Pain Research Institute, University of Liverpool, United Kingdom. 2The Walton Centre for Neurology and Neurosurgery, Liverpool, United Kingdom

Background Spinal cord stimulation (SCS) has become an increasingly accepted and efficacious treatment modality for chronic pain. The literature however predominantly reports on thoracic placement of electrodes; only one specifically addresses cervical SCS. A retrospective study was therefore undertaken to review long-term outcomes and incidence of revisions in patients undergoing cervical SCS. Methods A postal survey of 42 patients who received a cervical implant between 1994 and 2001 (mean follow up 44 months, range 13 - 88). Data addressing pain relief and patient satisfaction was gathered. Clinicians impression of pain relief and complication / revision data was obtained by retrospective review of medical records. Results Main indications were CRPS (38%) and Brachial Plexus injury (23%). Response rate was 71% (30/42). Patient reported pain relief was > 50 % in 21/30(70%) Clinician reported relief was > 50 % in 23/30 (76 %)of those responding to the questionnaire. In non-responders this was 8/12(66%). A total of 23 revisions were carried out in 14 patients. Conclusion The majority of patients in this series undergoing cervical SCS derive significant pain relief. Outcomes are comparable to the case. 1. Van Butyen JP, Van Zundert J, Veughs P, Vanduffel L. (2001) Efficacy of spinal cord stimulation: 10 years of experience in a pain centre in Belgium. E J of pain. 5(3): 299-307. 2. Simpson BA, Bassett G, Davies K, Herbert C, Pierri. (2003) Cervical Spinal Cord Stimulation for Pain: A report on 41 patients. Neuromodulation 6 (1); 20-26

PAIN RELATED TO PARKINSON’S DISEASE

S.Y. Kirtaev, I.V. Litvinenko, M.M. Odinak

Medical Military Academy, Department of Neurology, Saint-Petersburg, Russia

OBJECT: The aim of this study was to determine the structure of painful sensations related to PD and the possibility to reduce mistakes in diagnosis and treatment of it. METHODS: 65 patients with PD were asked retrospectively about signs in the period before bradykinesia and other parkinsonian signs were found. RESULTS: Some patients have spontaneous pain and paresthesia like sensations before manifestation of motor signs. At the later period of PD this pain is related to severe muscular rigidity, akinesia, dystonia and dyskinesia. Often spontaneous pain and paresthesia may be the first symptom of PD marked by patients and treated by orthopedist with local blockade of a humeroscapular joint and by non-steroid anti-inflammatory drugs. But the significant results can’t be achieved due to this treatment until other symptoms of PD will not be found and adequate dopaminergic therapy will not begin. In our study 5 patients had spontaneous pain as a first symptom, 11 - had paresthesias and pains together with bradykinesia and rigidity which was revealed by us later, 5 patients has diffuse character of pain. CONCLUSION: Pain or/and paresthesia may be the first symptom in approximately 20% cases of PD. Most common localization of this pain is a neck and upper limbs. In case of such pain localization you must be sure there are no other symptoms of PD. The treatment of this pain in case of PD with ordinary non-steroid anti-inflammatory therapy is not effective. After start of PD treatment with dopaminergic drugs this pain is regressed.

NOICCEPTIVE AND/OR NEUROPATHIC RADICULAR SYMPTOMS ASSOCIATED WITH SPONDYLOLISTHESIS: OSTEOPATHIC CONSIDERATIONS

R.J.A Zegarra-Parodi

Ceeso Osteopathic College, Research Department, Saint-Denis, France

It has long been thought that joint complex dysfunctions (JCD) such as these treated by osteopaths only had detrimental effects on local joints and surrounding soft tissues due to the focus on the kinesiopathological component of JCD. More recent theories emphasize on the neurophysiological component, involving afferent inputs to the spinal cord. By reviewing recent papers, it has been shown that joint hypomobility is associated with altered reflex responses involving mechanoreceptive and nociceptive pathways. A clinical application of this model could be applied as possible explanations for radicular symptoms associated with spondylolisthesis. Radicular pain generator mechanisms involving physico-chemical alterations of the spinal nerve are not well understood. Some structures have been proposed as pain-generators, we will discuss mainly nervi nervorum (surrounding spinal nerve) irritation and vascular compression of the transforaminal ligament. Neurological examination could predict the treatment outcome as main radicular symptoms are nociceptive in nature and may respond favourably to appropriated manual procedures, which is not the case for neuropathic symptoms. While improving mobility to restricted joints, osteopathic treatment could have a favourable influence on several neurological reflex responses: by reducing abnormal inputs to the spinal cord, it could improve the body to recover an optimal function and modify the perception of radicular symptoms associated with spondylolisthesis which are not mainly neuropathic in nature.

SHORT LATENCY TRIGEMINO-Sternocleidomastoid Responses in Idiopathic Trigeminal Neuralgia

R. Nardone, E.C. Buffone, I. Florio, M. Matullo, F. Tezzon

"F. Tappeiner" Hospital, Merano, Italy

Objective: To investigate the central trigeminal system in idiopathic trigeminal neuralgia. (TN). Materials and methods: Short latency responses can be recorded in sternocleidomastoid (SCM) muscles after stimulation of the trigeminal nerve (the trigemino-cervical reflex). This brainstem reflex was investigated in 40 healthy subjects and in 17 patients suffering from idiopathic TN before and after a therapy for 2 months with carbamazepin. Results: Before therapy 6 patients presented abnormalities of SCM responses on the painful side, 6 patients bilateral abnormalities and 5 patients normal responses. A significant variation in the responses after therapy was found only in the patients with unilateral abnormalities; these patients and the patients with normal reflexes before therapy had also a good response to the therapy with significant pain relief. Conclusions: The bilateral location of the abnormalities in some patients seems to point to a centrally located dysfunction; therefore this study supports the idea that mechanisms in the central nervous system may play an important role in the pathophysiology of trigeminal neuralgic pain. The evaluation of the trigemino-cervical reflexes would allow the early identification of patients with idiopathic TN refractory to treatment with conventional medical therapy. In conclusion, our findings indicate that the trigemino-cervical reflex may be a useful tool in neurophysiological exploration of the trigeminal nerve; additionally, these procedures produce reliable evoked potential measures of trigeminal nerve function noninvasively which can provide an objective index of treatment efficacy.
Background and Goal of Study: Thermal quantitative sensory testing (QST) is an important method in human pain research. Measurements underlie a certain degree of variability and are therefore repetitively assessed and averaged. Repetition of thermal pain stimuli, however may induce sensitization and influence data. It was the aim to study changes during a series of repeated heat pain perception thresholds (HPPT) and to compare the measurements in hyperalgesic and in control skin. Materials and Methods: After approval by the ethics committee, 16 healthy volunteers (8 males, 8 females) were enrolled in this prospective study and blinded to the aim of the study. Before the study session they were trained during two different days to assess HPPT by means of a thermal sensory analyser (TS 2001, Medoc, Israel). A circular skin area (r = 2.5 cm) on the upper leg was irradiated with UVB-light to induce sunburn hyperalgesia [1]. 20 hours later HPPTs were measured in the erythema and on the contralateral leg three times at intervals of 15 seconds. This was repeated two hours later. Differences between 1st and 3rd and between the two time points were analysed by repeated measures ANOVA.

Results: Data at 2 hours did not differ from baseline. The mean of all HPPTs at 1st, 2nd and 3rd measurement were 38.91°C, 39.50°C, 39.54°C* in the sunburn and 43.40°C, 44.65°C and 45.32°C* in control. Differences between 1st and 3rd measurement were significant (*p<0.005, **p<0.001). Discussion and Conclusion: Repetition of HPPTs leads to a significant increase in both hyperalgesic and normal skin and does not induce sensitization. This may be explained by fatigue of nociceptive afferents. Reference: [1] Gustorff B et al, Anesth Analg 2004; 98:173-7.
LOW-GRADE STRESS INDUCED PAIN WITH CHARACTERISTICS OF CENTRAL SENSITIZATION IN PATIENTS WITH FIBROMYALGIA AND CHRONIC SHOULDER/NECK PAIN

K.B. Nissen1, T. Sand1, R.H. Westgaard1, L.J. Stuvner2, R.B. Leistad2, L. White1, G. Helde1, M. Ra1

1Department of Neuroscience, NTNU, Trondheim, Norway, 2Department of Industrial Economics and Technology Management, NTNU, Trondheim, Norway

Objective: Psychosocial stress is a risk factor for musculoskeletal pain, but the mechanisms involved are poorly understood. We examined the temporal characteristics of pain induced by low-grade stress in patients with fibromyalgia and in patients with chronic shoulder/neck pain (SNP), and we compared the pain reports with electromyographic activity. Methods: With a blinded study design we investigated 35 women with fibromyalgia, 29 women with chronic SNP, and 35 healthy women who performed a stressful task lasting 60 minutes. Pain was reported every 10th minute on a VAS scale from shoulder, neck, temples and forehead, and we recorded surface electromyographic activity at corresponding locations continuously before (10 minutes), during (60 minutes) and after (30 minutes) the stressful task. Results: Pain increased more in both FMS and SNP patients compared to healthy controls (p < 0.05). Fewer FMS (14%) and SNP (31%) patients had pain recovery during the rest period compared to healthy controls (51%, p < 0.05). Significant differences between FMS and SNP groups were not observed neither for muscular or subjective responses. For SNP patients and controls, pain responses were more marked in the trapezius and neck region than in the forehead and temples, whereas FMS patients had a more generalized pain response. Pain development responses were more marked in the trapezius and neck regions than in the forehead and temples, whereas FMS patients had a more generalized pain response. Pain development was not related to electromyographic activity for any group. Conclusion: The increased pain response to low grade stress may be explained by increased temporal summation. Reduced pain recovery may be regarded as (long-lasting) muscular pain afferentisations. Central sensitisation may accordingly be important in both FMS and SNP. Muscle activity was seemingly not related to pain neither in FMS or in SNP patients.

THE PROFILE OF SUPRASEGMENTAL STRUCTURES IN PATIENTS WITH MYOFASCIAL PAIN SYNDROME

A.R. Gaimutdinov, A.M. Nassyrova

Department of Neurology, Kazan State Medical Academy, Kazan, Russia

Objective. The aim of the present study is to investigate the brainstem activity and EEG-profile in patients with chronic myofascial pain syndrome (MPS) of the thoracic girdle and the upper limbs. Materials and methods. Reflex activity of the brainstem was studied by means of the blink-reflex (BR). Stimulation parameters were: impulse duration 0.1 to 0.5 msec, current intensity 5 to 15 mA, frequency 0.1 to 0.5 Hz. Recording and processing of bioelectrical brain activity was performed electromyographically. EEG parameters: a 10-15 min recording of the background EEG (patients being absolutely quiet, no mental activity), monopolar recording, time constant equal to 0.3, electrodes being placed according to the international system “10-20”. The following frequency ranges were established: delta- 0.5-4 Hz, beta- 4-7 Hz, alpha- 8-12 Hz, beta- 13-40 Hz. Results. Marked R2 disinhibition was revealed in the MPS-patients against the background of the R1 amplitude decrease (195±12 mV). Also the latency of R2 increased. Analysis of EEG profile in patients with hyper-reactive type of the BR revealed the decrease of alpha-rhythm intensity averagely to 54 % in cases of right-sided process and to 46 % in cases of the left-sided process. At this background the amplitude-increase of beta-rhythm was revealed. The current clinical-functional study allows to suggest that patients with chronic MPS show increased excitation of propriobulbar neurons responsible for realization of brainstem reflex activity. Possibly, EEG-desynchronizaton is the consequence of surplus afferentation of brainstem reticular systems. So, the results of this study allow to suggest the break of functional activity of higher (suprasegmental) levels of nervous system in patients with MPS.

HEAT PAIN HYPERALGESIA IN PATIENTS WITH FACIAL PALSY

C. Schallber1, R. Rolke1,2, P.P. Urban2, W. Magier1, M. Dietrich1, R.D. Treede1

1Institute of Physiology and Pathophysiology and 2Department of Neurology, University of Mainz, Germany

Aim of the study: Patients with facial palsy often report sensory symptoms over the parietal part of the face. To test for the presence of sensory disturbances we applied a battery of sensory tests according to the Quantitative Sensory Testing (QST) protocol of the German Research Network on Neuropathic Pain (GNPP) over ipsi and contralateral parts of the face. Methods: Sixteen patients with idiopathic facial palsy and 32 controls were studied. All patients were investigated within 3 days after onset of symptoms. Seven tests were performed determining 13 variables over ipsi and contralateral cheek and forehead including thermal (cold and warm perception threshold, thermal sensory limen, paradoxical heat sensations, cold pain and heat pain thresholds) and mechanical stimuli (von Frey-filaments, pinprick stimuli, vibration threshold using a tuning fork, and pressure pain thresholds using a handheld algometer). Results: Heat pain threshold was lowered by 1.3°C over ipsilateral face (p=0.036; ANOVA; LSD post hoc-test) without a significant cheek-face threshold difference. All other pain thresholds were not reduced (p=0.16). Additionally thermal and mechanical perception thresholds tended to be increased over the affected side of the face. However, this effect was only significant for cold perception threshold (p=0.02; ANOVA; LSD post hoc-test), again with no cheek-face difference. These findings were not related to the presence of dysesthesia (6 out of 16 patients). Conclusion: Our finding of heat pain hyperalgesia in patients with facial palsy is consistent with peripheral rather than central sensitization of nociceptive neurons, probably due to a trigeminal afferent. This result also contributes to the old concept of polymodal nociceptors cranialis rather than mononeurous facialis in patients with idiopathic facial palsy (Adour et al., Arch Otolarngol 1976;102:262-264). Supported by GNPP (BMBF grant 01EM0107).

METAPLASTICITY OF LTP-LIKE CHANGES IN A HUMAN SURROGATE MODEL OF NEUROPATHIC PAIN

N. Hansen, W. Magier, T. Klein, R.D. Treede

Institute of Physiology and Pathophysiology, Johannes Gutenberg University Mainz, Germany

We have recently established a model of nociceptive human long-term potentiation (LTP; Klein et al., J. Neurosci. 2004), which is commonly attributed as one of the underlying mechanisms of neuropathic pain. We now tested the modification of input-specific nociceptive LTP by preconditioning and deconditioning stimulus protocols. Twelve subjects were tested for the effect of three stimulus protocols on single electrical test pulses at 10 x detection threshold (T): (1) Control protocol: High-frequency stimulation at 1.5 mA (HFS: 5 x 1s trains of 100 Hz at 10 s intervals) was applied 1 hour after baseline testing with 60 single pulses at 10 x T. (2) Preconditioning protocol: Like (1), but additional conditioning stimulus (120 single stimuli at 2.5 x 40 x T) distributed over the baseline period preceded HFS. (3) Deconditioning protocol: Like (1), but 120 single conditioning stimuli at 2.5 x 40 x T were added at 60 ÷ 120 min after HFS. HFS induced a robust and long lasting increase of pain to 10 x T test stimuli in experiment 1 (LTP: +57 %, p < 0.002). Single pulse preconditioning prior to HFS completely prevented the induction of LTP in experiment 2. Likewise, single pulse conditioning at 60 ÷ 120 min after HFS completely reversed a previously established LTP in experiment 3. In conclusion, the capability to induce LTP-like changes of human pain perception is altered by preconditioning (metaplasticity). The same protocols that prevent LTP are also able to reverse an already established LTP (deconditioning). These insights into mechanisms of nociceptive LTP in humans may finally contribute to the development of mechanism-based treatment strategies of some forms of neuropathic pain. Supported by DFG grant (Tr 236/16-1)
The beneficial role of opioids in neuropathic pain is still controversial, and changes of endogenous opioids in human neuropathic pain have received little attention so far. We report data on in vivo density and distribution of opioid receptors in 10 patients suffering from chronic, unilateral, refractory neuropathic pain. Opioid receptors were assessed with Positron Emission Tomography (PET), using [11C]diprenorphine, a non-selective opiate antagonist. Each patient underwent two PET studies at two weeks interval, under the same conditions. Three of these patients were also studied following successful treatment with Pre-Central (Motor) Cortical Stimulation (PCCS). In the 10 subjects studied preoperatively, opioid receptors distribution remained stable in the two consecutive PET-scans. A decrease of the Binding Potential (BP) of [11C]diprenorphine contralateral to the pain side was observed in anterior cingulate, thalamus, striatum and insula, with different degrees of significance. In the 3 patients also studied postoperatively, BP of diprenorphine increased in the same structures as well as in orbito-frontal cortex and Periaqueductal Gray matter but with different patterns across subjects. This is the first report showing changes in opioid receptors in a group of patients with neuropathic pain. Changes in BP of diprenorphine are interpreted as reflecting corresponding changes in local receptor availability. These preliminary results suggest a decrease of such availability in the hemisphere contralateral to pain, and a possible reversibility of such changes by successful PCCS. Whether the preoperative distribution of opioid receptors is a possible predictor of PCCS efficacy remains to be demonstrated.

Background: Positron emission tomographic and fMRI studies demonstrate a substantial overlap in activity evoked by noxious and innocuous stimuli particularly within SII. Concordant results have been obtained recently with intra-cerebral recordings in humans. However, intracranial studies usually compared two different stimulations (non-noxious electrical vs noxious heat), and did not assess specifically whether the operculo-insular cortex was able to encode stimulation intensity within the thermo-algesic modality. Methods: In this study, we analysed the modifications induced by progressively increased stimulus intensities on the laser-evoked potentials (LEP) recorded in SII (12 patients) and insular (7 patients) cortex with intra-cerebral electrodes during stereotactic EEG assessment of patients with drug-resistant epilepsy. Results: There was a significant positive correlation between the LEP amplitude and the intensity of the thermal stimulus both in SII and insula. This amplitude increase was gradual then reached a plateau for intensities equal or superior to the subjective pain threshold +20%. There was no response in SII and insula when the stimulus intensity was under perception threshold. Conclusions: Our results suggest that at least some neurons of SII-insula are able to encode gradually the intensity of thermal stimulation, from sensation to pain thresholds. This is consistent with the existence of wide-dynamic-range and convergent neurons in monkey's SII and insular areas. According to these data, the amplitude of operculo-insular intra-cerebral LEPs (corresponding to the early lateralised response recorded on the scalp), could reflect the encoding of stimulus intensity. These results obtained in healthy subjects could be used to evaluate the function of nociceptive pathways and improve our understanding of neuropathic pain in patients.

Cold hyperalgesia in neuropathic pain is poorly understood. We investigated the mechanisms of cold pain by studying the effect of menthol on pain, temperature perception, touch sensation and skin perfusion. In 10 subjects L-menthol and ethanol (control) were topically applied to the forearm in a double-blinded two-way cross over study. Menthol induced significant pain and cold sensations, punctate and cold hyperalgesia and an increase in cutaneous perfusion. Other mechano-sensory and thermal tests were unchanged (touch, cold and warm detection thresholds, heat pain threshold; no dynamic and static hyperalgesia, no wind-up). To investigate the underlying mechanisms the effects of menthol versus ethanol on the dorsal of the hand were tested during A fibre conduction blockade of the superficial radial nerve in 10 subjects. The block itself led to hypothesia for mechanical stimuli and anesthesia for cold perception, but induced an increase in cold-mediated pain. This was due to lack of inhibition of C nociceptors normally exerted by concomitant activation of A fibres. Under these conditions menthol-induced cold sensation and punctate hyperalgesia were abolished. However, menthol induced spontaneous pain with a trend to higher values than without block. Furthermore, the hyperalgesia to cold stimuli, that was already present during A fibre block, further increased significantly by menthol. We suggested that menthol acts to sensitise cold sensitive peripheral vasoactive C nociceptors and activates cold specific A delta fibres. In conclusion, topical menthol is a human model for cold pain by exposing for the first time the mechanism of sensitised peripheral cold C nociceptors that may also be involved in neuropathic pain. Supported by the Deutsche Forschungsgemeinschaft (DFG Ba 1921/1-2) and the German Research Network on Neuropathic Pain (BMBF, 01EM01/04).

A POSITRON EMISSION TOMOGRAPHY STUDY OF CEREBRAL OPPI RRECEPTORS IN NEUROPATHIC PAIN

J.M. Maarravi1,2, R. Peyron1,2, P. Merten1,2, N. Costes2, M. Magnin1,3, M. Sindou2, B. Laurent1,3, L. Garcia-Larrea3

1INSERM EM 342 (Central Integration of Pain), Lyon, France; 2Functional Neurosurgery Department, Hospital Neurologique, Lyon, France; 3Neurology Department, Hospital Bellevue, Lyon, France; 4CERMEP (PET-Scan Centre), Lyon, France

A KINEMATIC ANALYSIS OF REACHING AND GRASPING MOVEMENTS OF THE UPPER EXTREMITY DURING EXPERIMENTAL TONIC CUTANEOUS PAIN

A. Binder, J. Schattschneider, R. Wenzelburger, G. Wasner, G. Deuschl, R. Baron

Klinik für Neurologie, Universitätshôpital Schleswig-Holstein, Campus Kiel, Kiel, Germany

A. Binder, J. Schattschneider, R. Wenzelburger, G. Wasner, G. Deuschl, R. Baron Klinik für Neurologie des Universitätsklinikums Schleswig-Holstein, Campus Kiel Aims: To evaluate the effect of tonic painful cutaneous stimulation by capsaicin on the motor performance of the upper extremity. Methods: Kinematic analysis data were obtained from 10 healthy right-handed volunteers. Standardised reaching and grasping movements of the right and left upper extremity without and with painful stimulation were performed (10 trials each). Kinematic data were recorded by using an optoelectronic motion analysis system. Tonic painful stimulation was achieved by topical application of capsaicin on the ulnar lower right arm with an attended level of NAS 4. Using this setup pain increase by the motor performance was excluded. Results: Statistical analysis revealed no significant differences if comparing the left and right extremity in both conditions: reaction time (p=0.13), maximum velocity (p=0.11), duration of reaching phase (p=0.3) and duration of ballistic period (p=0.5). Minimum pain intensity in all volunteers reached 4 on 11-point VAS. Conclusions: Experimental tonic painful stimulation of the skin does not lead to alterations of the motor performance that could be detected in the kinematic analysis. In contrast to these results patients with CRPS of the upper extremity show e.g. a prolongation of the reaching phase that might be due to a dysfunction of integrating visual and sensory afferent information within the parietal cortex (Schattschneider et al. 2001, IASP press). It could be assumed that chronic pain syndromes lead to specific changes within the central motor system in the course of the disease and acute experimental pain is not capable of resembling such detectable motor deficits. Acknowledgements: The study was supported by the German Ministry of Research and Education (01EM0104).

KINEMATIC ANALYSIS OF REACHING AND GRASPING MOVEMENTS OF THE UPPER EXTREMITY DURING EXPERIMENTAL TONIC CUTANEOUS PAIN

A. Binder, J. Schattschneider, R. Wenzelburger, G. Wasner, G. Deuschl, R. Baron Klinik für Neurologie des Universitätsklinikums Schleswig-Holstein, Campus Kiel Aims: To evaluate the effect of tonic painful cutaneous stimulation by capsaicin on the motor performance of the upper extremity. Methods: Kinematic analysis data were obtained from 10 healthy right-handed volunteers. Standardised reaching and grasping movements of the right and left upper extremity without and with painful stimulation were performed (10 trials each). Kinematic data were recorded by using an optoelectronic motion analysis system. Tonic painful stimulation was achieved by topical application of capsaicin on the ulnar lower right arm with an attended level of NAS 4. Using this setup pain increase by the motor performance was excluded. Results: Statistical analysis revealed no significant differences if comparing the left and right extremity in both conditions: reaction time (p=0.13), maximum velocity (p=0.11), duration of reaching phase (p=0.3) and duration of ballistic period (p=0.5). Minimum pain intensity in all volunteers reached 4 on 11-point VAS. Conclusions: Experimental tonic painful stimulation of the skin does not lead to alterations of the motor performance that could be detected in the kinematic analysis. In contrast to these results patients with CRPS of the upper extremity show e.g. a prolongation of the reaching phase that might be due to a dysfunction of integrating visual and sensory afferent information within the parietal cortex (Schattschneider et al. 2001, IASP press). It could be assumed that chronic pain syndromes lead to specific changes within the central motor system in the course of the disease and acute experimental pain is not capable of resembling such detectable motor deficits. Acknowledgements: The study was supported by the German Ministry of Research and Education (01EM0104).

PAIN INTENSITY CODING IN THE HUMAN SUPRA-SylvIAN OPERCULAR AND INSULAR CORTICES

M. Frut1, M. Magnin1, M. Guénot2, F. Mauguière2, L. Garcia-Larrea1

1EMI 0342, 2Functional Neurology Department and Neurosurgery Department, Neurological Hospital, Bron, France

COLD PAIN DUE TO SENSITISATION OF PERIPHERAL C NOCICEPTORS BY TOPICAL MENTHOL

G.L. Wasner, A. Binder, J. Schattschneider, R. Baron

Department of Neurology/Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany

Cold hyperalgesia in neuropathic pain is poorly understood. We investigated the mechanisms of cold pain by studying the effect of menthol on pain, temperature perception, touch sensation and skin perfusion. In 10 subjects L-menthol and ethanol (control) were topically applied to the forearm in a double-blinded two-way cross over study. Menthol induced significant pain and cold sensations, punctate and cold hyperalgesia and an increase in cutaneous perfusion. Other mechano-sensory and thermal tests were unchanged (touch, cold and warm detection thresholds, heat pain threshold; no dynamic and static hyperalgesia, no wind-up). To investigate the underlying mechanisms the effects of menthol versus ethanol on the dorsal of the hand were tested during A fibre conduction blockade of the superficial radial nerve in 10 subjects. The block itself led to hypothesia for mechanical stimuli and anesthesia for cold perception, but induced an increase in cold-mediated pain. This was due to lack of inhibition of C nociceptors normally exerted by concomitant activation of A fibres. Under these conditions menthol-induced cold sensation and punctate hyperalgesia were abolished. However, menthol induced spontaneous pain with a trend to higher values than without block. Furthermore, the hyperalgesia to cold stimuli, that was already present during A fibre block, further increased significantly by menthol. We suggested that menthol acts to sensitise cold sensitive peripheral vasoactive C nociceptors and activates cold specific A delta fibres. In conclusion, topical menthol is a human model for cold pain by exposing for the first time the mechanism of sensitised peripheral cold C nociceptors that may also be involved in neuropathic pain. Supported by the Deutsche Forschungsgemeinschaft (DFG Ba 1921/1-2) and the German Research Network on Neuropathic Pain (BMBF, 01EM01/04).
CAN PERCEPTION THRESHOLDS DISTINGUISH PHANTOM TOOTH PAIN BY OTHER FACIAL PAIN?

A. Ciaramella, A. Cardini, L. Lonia, P. Poli

Pain Therapy Unit, Santa Chiara Hospital, Azienda Ospedaliera Pisana, Pisa, Italy

Introduction: According to Marbach criteria (1978), Phantom Tooth Pain (PTP) is a persistent pain in endodontically treated teeth or edentate areas for which there is no explanation to be found by physical and radiographic examination. It is still unclear why some subjects complain the presence of pain after tooth injury. Several studies connect phantom pain with pre-amputated pain (Nikolauses et al 1997a). Other authors suggest that sensitization of nerve ending (Wall and Gutnick, 1994) or Spinal (Woolf and Mannion 1999) following the nerve transection are mechanisms able to evoke phantom pain. Aim: to evaluate psychophysiological differences between several kinds of facial pain and a pain-free sample with a history of teeth extractions. Patients and Methods: A Bilateral trago Current Perception Threshold (CPT) was administered to 76 subjects. CPT is an electrodiagnostic method which investigates perceptive and pain thresholds using 3 frequencies of electrical stimuli administered transcutaneously: 2000 Hz (A fibers), 250 Hz (Ad fibers) and 5 Hz (C fibers). Results: Statistical differences between groups were found for all thresholds (ANOVA). PTP group shows lower thresholds compared to all groups which are statistically significant for the Ad and C fibers when compared with Pain-free subjects (t-test analysis). Right trago: 250 Hz (F= 4.04, p= 0.054), 5 Hz (F= 7.35 p= 0.011). Conclusions: Only PTP group seems to have low pain thresholds, therefore it is right to suppose that low pain thresholds can predispose to onset of Phantom Tooth Pain.

PSYCHOPHYSICAL STUDY OF THE EFFECTS OF TOPICAL APPLICATIONS OF MENTHOL IN HEALTHY VOLUNTEERS

S. Hatem, N. Attal, J.C. Miller, D. Bouhassira

1INSERM E-332, APHP, Hopital Ambroise Paré, Boulogne and Université Versailles-Saint-Quentin, Boulogne-Billancourt, France, 1Hopital Pitié-Salpêtrière, Paris, France

Background and aims: A specific cold and menthol receptor has been identified recently in fine afferent fibers in mammals. However, the psychophysical effects of menthol have not been investigated thoroughly. In the present study we analysed the effects of topical applications of various concentrations of menthol on thermal, mechanical and vibratory detection and pain thresholds in healthy volunteers. Methods: Solutions of menthol (5, 10, or 30%) or vehicle (tween and alcohol) were applied on the volar surface of the forearm in a double-blind fashion according to a randomized cross-over design at one week interval. Measurements of detection and pain thresholds evoked by thermal (heat and cold) and mechanical (pressure) stimuli and vibration threshold were performed before and after application of menthol or placebo. Supraliminary stimulations were used for assessing pain intensity evoked by thermal and mechanical stimuli. Results: A significant reduction of cold pain threshold was observed after menthol 10% and 30% but not 5%. In addition, menthol 30% induced a significant enhancement of pain evoked by suprathreshold mechanical stimuli. In contrast, heat detection and pain thresholds and vibration threshold were not altered after menthol. Conclusion: These results suggest that topical applications of menthol induce a selective and dose-dependent hyperexcitability (sensitization) of fine afferent fibers involved in cold/mechanical pain.

ALGESIC AND ANTIHYPERALGESIC PROPERTIES OF THE NMDA RECEPTOR ANTAGONIST NERAMEXANE IN A HUMAN SURROGATE MODEL OF NEUROPATHIC PAIN (INTRADERMAL CAPSAICIN INJECTION)

W. Mage1, T. Klein1, A. Möllemann2, M. Althaus2, R.D. Treede3

1Institute of Physiology and Pathophysiology, Johannes Gutenberg University, Mainz, Germany, 2Merz Pharmaceuticals GmbH, Eckenheimer Landstr, Frankfurt, Germany

Secondary hyperalgesia adjacent to an intradermal capsaicin injection is a well characterized human surrogate model of neuropathic pain (HaugStern et al Pain 2002). Using this model, we have tested the efficacy of neramexane, a moderate affinity, uncompetitive NMDA receptor antagonist in a placebo controlled, double blind crossover study. Pain and hyperalgesia after intradermal capsaicin injection into the ventral forearm (40 g) were assessed adjacent to the injection and in a remote control area after a single oral dose of neramexane hydrochloride (40 mg) or placebo (p=18). Capsaicin-induced burning pain was significantly reduced by neramexane compared to placebo during the first minute after injection (21%, p=0.01) and remained lowered (33% at 2nd-5th min; n.s. due to increasing variability). The size of the capsaicin-induced axon reflex erythema remained unaltered. Neramexane reduced the pain to pin pricks in both the control and test areas prior to capsaicin injection by 27-31% compared to placebo (p=0.001; analgesia). Pain reduction in the test area was even more pronounced after capsaicin injection (39% compared to placebo, p=0.001; combined analgesia and antihyperalgesia). Antihyperalgesia alone as calculated from the ratio of test and control area (9%) was not significant. Neramexane reduced the pain to light touch stimuli, which occurred after capsaicin injection ("allodynia") by 22% across all test times (p > 0.87), and by 25% during the first 30 min (p=0.05). Summation of pain (wind-up) as tested by trains of 10 pin prick stimuli at 1 Hz was neither changed by neramexane nor by placebo. The combined effect of a strong analgesic along with a mild antihyperalgesic action suggests that the NMDA receptor antagonist neramexane may be a valuable drug for the treatment of neuropathic pain.

INVESTIGATION OF THE PARADOXICAL PAINFUL SENSATION ('ILLUSION OF PAIN') PRODUCED BY A THERMAL GRILL

D. Bouhassira, D Kern, E. Pellé-Lancien, J. Rouaud, F. Morain

1INSERM E-332, APHP, Hopital Ambroise Paré, Boulogne and Université Versailles-Saint-Quentin, Boulogne-Billancourt, France

Background and Aims: The simultaneous application of innocuous warm and cool stimuli to the skin can induce a paradoxical painful sensation of burning. This phenomenon, also referred to as ½ the thermal grill illusion of pain+, has been described at the end of the XIXth century but has not been characterized thoroughly. In the present study we analysed the conditions of production of such a paradoxical painful sensation in healthy volunteers. Particularly, we sought to determine the frequency and stability of the phenomenon, the temperatures of the thermal stimuli that produce such a paradoxical painful sensation in healthy volunteers. Methods: The experiments, approved by the Local Ethical Committee, were performed in 52 healthy volunteers. The stimuli were produced by a thermode composed of six bars whose temperature was controlled by Pelletier elements. The temperature of alternate (even and odd numbered) bars could be controlled independently to produce various patterns of the ½ thermal grill+. After measuring the cold and heat pain thresholds, a systematic series of combinations of warm and cool stimuli (ie below the pain threshold) were applied on the palmar surface of the right hand. Each stimulus was applied during 30 seconds with an interval of 3 minutes between two stimuli. After each stimulus the subjects had to rate their sensations on a visual analog scale for cold, heat and pain sensations. Results and conclusions: Paradoxical pain, mostly described as burning, was observed reliably in approximately 2 thirds of the subjects. The occurrence of such paradoxical sensations was directly related to the magnitude of the differential of the temperature between the warm and cool bars of the grill.
DISCOVERY OF NOVEL, ORALLY BIOAVAILABLE, N-TYPE CALCIUM CHANNEL BLOCKERS FOR TREATMENT OF NEUROPATHIC PAIN
R. Franco1, L. Dong2, V. Galullo2, A. Horsten1, J.Q. Pan1, J. Sui1, G. White1, R. Wincquart2, R. Zelle2
1Department of Biology, 2Department of Chemistry and 3Department of Pharmacology, Scion Pharmaceuticals, Medford, USA

The voltage-gated N-type calcium (Ca) channel (CaV2.2) plays an important role in the release of neurotransmitters associated with pain responses. Its predominant expression in the dorsal horn of the spinal cord suggests that blocking CaV2.2 channels could be broadly efficacious in treating pain, being in the common pathway downstream from a variety of receptors that mediate pain responses. This tenet is supported by the preclinical and clinical efficacy of intrathecal administration of ziconotide, a selective CaV2.2 conopeptide antagonist, in a neuropathic pain (chronic constriction injury) model (rats) and opioid-refractory malignant and non-malignant pain patients. The objective of this research is to develop selectively bioavailable, CaV2.2 blockers to treat severe, chronic and/or neuropathic pain states. Novel compounds from multiple, distinct, chemical series were discovered using Scion’s proprietary high throughput electrophysiology (iHTEPtM) platform. These leads were further optimized by electrophysiological (EP) assessment in Xenopus oocytes and/or mammalian (HEK293) cells for their potency against CaV2.2 and selectivity against the L-type (CaV1.2) and/or the P/Q-type CaV2.1 channels. The S-02686D lead series exhibited the greatest potency against CaV2.2 with IC50 in oocytes & HEK cells of 1.0 & 0.4 microM; followed by the S-02683A (13.9 and 1.1 microM) and S-02684D lead series. The S-02683A series was moderately selective against CaV2.1 (4X) and CaV1.2 (2X) in both oocytes and mammalian cells. The S-02686C series was non-selective in either system. The kinetics and pharmacological profiles of these series are being further evaluated in mammalian cells and/or in animal models.

EXAMINATION OF ANTIALLODYNIC AND SIDE EFFECTS OF COMPOUNDS WITH PROVEN EFFICACY IN A NEW MOUSE MODEL OF NEUROPATHIC PAIN
L. Felmerai, K. Saghy, A. Kis-Varga, C. Horvath
Gedeon Richter Ltd., Pharmacological and Drug Safety Research, Budapest, Hungary

We tested for the first time in a new mouse NP model (Malmberg et al., 1998) the effects of compounds with proven clinical efficacy for treating neuropathic pain (NP). Some NMDA antagonists having positive results in NP models in rats were also tested. Antiallodynic effects were analysed in comparison with results from tests for side effects. Methods: Allodynia was tested by von Frey hairs in this partial nerve ligation model. The following side effect tests were used: rotated (RR), locomotor activity (LA), and weight lifting (WL) (ability of mice weighing 22-24 g to bear a dumbbell of 44 g for 3 sec.) Results: Pregabalin produced 89 % reversal of allodynia at 100 mg/kg p.o. Its ID50 values were 161 and 498 mg/kg, in WL and RR tests. Fluoxetine and amitriptyline produced only about 50 % reversal of allodynia with maximum effect at 8 mg/kg p.o. and 4 mg/kg p.o., respectively. Increase in LA was observed with fluoxetine and decrease with amitriptyline at these doses. The non-selective NMDA antagonist MK-801 had no effect on allodynia at the highest dose without serious side effects (i.e. 0.3 mg/kg p.o., approximate ID50 in RR and LA tests). Ro 25-6981 and CI-1041, two NR2B selective antagonists, produced partial (~50 %) reversal of allodynia with maximal effect at 16 mg/kg p.o. and 8 mg/kg i.p., respectively. While Ro 25-6981 was without effect on LA up to 50 mg/kg i.p., CI-1041 caused an increase in the analgesic dose range (at 10 mg/kg and above). The results prove the usefulness of this mouse model in assessing efficacy of drugs on NP and support the possible utility of NR2B selective NMDA antagonists in the treatment of NP.

HIGH-AFFINITY BINDING AT ALPHA2-Delta (α2-δ) PROTEIN OF VOLTAGE-GATED CALCIUM CHANNELS AND THE ANALGESIC AND ANXIOLYTIC ACTION OF PREGABALIN IN ANIMAL MODELS
C.P. Taylor, S. Donevan, J. Offord, S. Baron
Pfizer Global Research and Development, Ann Arbor, USA

Background and aims: Pregabalin is a potent ligand for the α2-δ protein, a subunit of voltage-gated calcium channels. These experiments test whether high-affinity binding of pregabalin to α2-δ protein is required for its analgesic and anxiolytic-like effects. Methods: An amino acid mutation was incorporated into α2-δ type 1 protein to convert arginine at position 217 to alanine. Two stable fibroblast cell lines expressing recombinant wildtype and mutant R217A proteins were produced. Fresh frozen brain sections were obtained from wildtype and R217A mutant mice for [3H]pregabalin autoradiography. In vitro neurotransmitter release experiments using [3H]noradrenaline with neocortex slices were conducted with pregabalin, comparing tissues from wildtype and R217A mutant mice. Activity of pregabalin in a dorsal root ligation model of neuropathic pain and in the rat Vogel conflict test was compared in wildtype and R217A mice. Results: Autoradiography confirmed that mutant mice had greatly reduced binding of radioligand in forebrain structures but only modest decreases in cerebellum. Noradrenaline-release studies of wildtype and R217A cortex show reduced effect of pregabalin in mutant tissues. Results with mutant mice in the dorsal root ligation model and in the Vogel conflict test indicate that high-affinity binding of pregabalin to α2-δ type 1 protein contributes to its pharmacologic actions. Conclusions: These results suggest pregabalin has high-affinity binding to the α2-δ protein, and they define a novel class of CNS-active drugs with efficacy in animal models of pain and anxiety. Study supported by Pfizer Inc.

CYSTEINE PROTEASES CATHEPSIN S AND X: NOVEL TARGETS IN NEUROPATHIC PAIN
B. Schmitz1, M. Foguet-Luebbert1, B. Welters1, R. Hiltunsky1, U. Ebel1, F. Paris1, K. Kuehn1, S.B. McMahon1, S. Donevan, J. Offord, S. Baron1
1Biofrontera Pharmaceuticals GmbH, Leverkusen, Germany, 2Centre for Neuroscience Research, King's College, London, United Kingdom, 3Department of Animal Physiology, Ruhr-University Bochum, Germany

It is estimated that about three million people are diagnosed each year with neuropathic pain. However, treatment possibilities for this distress are limited due to the complexity of the symptoms and the fragmentary knowledge of the underlying pathomechanisms. Therefore, the comprehensive analysis of the transcriptome of tissues relevant for pain may provide important insight into the mechanisms involved in the establishment and maintenance of neuropathic pain. We performed such an analysis on tissues derived from 3 rat neuropathic pain models (Bennett, Seltzer, Chung) and 1 inflammatory pain model (CFA). Expression analyses of rat dorsal horn (DH) were performed by Digital Expression Pattern Display (DEPD), a highly sensitive, PCR-based method for transcriptome analysis, 4 time points (1d, 7d, 14d, 26d after surgery) were studied. DEPD data were validated by quantitative RT-PCR, in situ hybridisation (ISH), and enzyme activity assays. DEPD analysis revealed multiple genes that were significantly up-regulated at the 2 latest time points in the neuropathic models, but unchanged in the corresponding time points in the CFA model. From this group of genes, cathepsin S and the recently described cathepsin Y were selected and their differential expression confirmed by qRT-PCR for both proteases, and by ISH for cathepsin S. Measurement of cathepsin Y protein activity revealed enhanced activity in a neuropathic and only minor activity in CFA-treated rats. The comparative analysis of several animal models in parallel is an appropriate approach for limiting the number of genes relevant in the pathophysiology of the disease to manageable numbers.
OUR EXPERIENCE WITH GABAPENTIN IN THE TREATMENT OF NEUROPATHIC PAIN IN CHILDREN WITH CANCER OR HEMATOLOGICAL MALIGNANCY

P. Vondracek1, I. Pernikova1, K. Paderova1, J. Sterba1, M. Chanova1, R. Slapal1, H. Ostolekova1

1Department of Pediatric Neurology, Masaryk University Hospital, Brno, Czech Republic, 2Department of Pediatric Oncology, Masaryk University Hospital, Brno, Czech Republic, 3Department of Pediatric Oncology, Charles University and Motol Hospital, Prague, Czech Republic

Objective: To evaluate the efficacy and safety of gabapentin monotherapy in reducing neuropathic pain caused by a malignancy or an applied oncological treatment in pediatric patients. Design and methods: In open-label trial, children with neuropathic pain following oncological therapy according to standardized protocols, were treated with gabapentin. Daily doses varied from 200 to 1800 mg according to the age and weight of a treated child. With respect to the age of the children, the Visual Faces Scale (VFS) was used to assess the effect of medication. Assessments were performed at baseline and within 1 week thereafter in eight week follow-up. Results: Fifty-two patients (28 males, 24 females, aged 3–18, median 1.9) were enrolled and fifty (96%) completed the study. The mean dose of gabapentin was 600 mg/day (200-900 mg) in children aged 3–9 and 900 mg/day (600-1800 mg) in children aged 10–18. Mean VFS at baseline was 3.54 (range 2–5), at the final visit 1.34 (range 0–2) with a significant decrease versus baseline (p<0.01). A total of 42 (84%) children obtained a long lasting pain relief. The beneficial effect of medication was usually observed after 2–3 weeks of gabapentin administration. Only mild adverse effects (nausea, dizziness, diplopia) were noted in 4 patients (8%). Conclusions: Gabapentin is a safe and efficacious drug, which can provide a significant pain relief in children with neuropathic pain due to an underlying malignancy or oncological therapy. Gabapentin administration should therefore become a part of the algorithm of conservative treatment of neuropathic pain in both adult and pediatric oncological patients.

PAIN IN AVULSION OF LUMBOSSACRAL PLEXUS

M.J. Teixeira, Y. Lin, L.J. Nilton

Department of Neurology, University of Sao Paulo Medical School, Sao Paulo, Brazil

Introduction. Few cases were presented in the literature about patients presenting pain due to avulsion of lumbosacral plexus. The authors present the clinical findings and results of treatment of 3 patients with pain due to avulsion of lumbosacral roots. Patients and methods. 3 patients (2 male, 28–45 y) had traumatic amputation of the left lower limb distal to the coxofemoral joint (1 case), distal to thigh (1 case) and the right lower limb (1 case), 48 to 132 months before the first consultation. All presented severe pain in the lower limb, described as constant severe throbbing, burning and shocking sensations. In all, pain interfered with the sleep, appetite, humor and daily life activities. All presented moderate amyotrophy of the muscles in the ipsilateral gluteal region and hypoesthesia in the hemiplexicum. No trigger was identified. The electromyography showed severe paravertebral denervation. All were treated with tricyclic antidepressants, neuroleptics, anticonvulsants, tramadol and opii/ides, without improvement. Epidural morphine infusion and epidural spinal cord stimulation also weren’t satisfactory. The radiofrequency lesions of the dorsal root entry zone region from L1 to S1 in 1 case and from L3 to S2 in 2, resulted in complete alleviation of pain, but the phantom sensation didn’t disappeare in all patients. No complications has been occurred. The inspection revealed no roots in the dorsal root entry zone. Conclusion. Dorsal root entry zone lesions are safe and efficient in treatment of pain resulting from avulsion of lumbosacral plexus.

PROSTANOID RECEPTOR EP1 AND COX-2 IN INJURED HUMAN NERVES AND DORSAL ROOT GANGLIA

P.F. Durrenberger1, M.A. Cauna1, P. Facer1, I.P. Chessell1, R. Birch1, P. Anand1

1Peripheral Neurology Unit, Imperial College, Hammersmith Hospital, London, United Kingdom, 2Neurology CEDD, GlaxoSmithKline, Harlow, United Kingdom, 3Peripheral Nerve Injury Unit, Royal National Orthopaedic Hospital, Stanmore, United Kingdom

Recent studies show that inflammatory processes may contribute to neuropathic pain. Cyclooxygenase-2 (Cox-2) is an inducible enzyme responsible for production of prostanoids, which may sensitize sensory neurons via the receptor EP1. We have previously reported that while macrophages infiltrate injured nerves within days of injury, they express increased Cox-2-immunoreactivity from 2 to 3 weeks after injury, with a peak around 40 days, and a subsequent decline to values below control nerves. We have now investigated EP1 in injured human nerves and dorsal root ganglia (DRG). Tissue sections were immunostained with specific antibodies to EP1, neurofilaments and Cox-2. Immunohistochemistry of sections was performed to quantify EP1 in injured nerves. Cox-2 expression was observed in injured DRG (acute: n = 5; 4 to < 21 days post-injury and chronic: n = 6 from 21 days to 196 days), unjured nerves (n = 10), unjured dorsal root ganglia (DRG) (n = 7), and avulsion injured DRG (acute: n = 6, chronic: n = 6). EP1-immunoreactivity (EP1-IR, in % area) was significantly increased (p < 0.04) in injured acute proximal (4.62 ± 1.96) and distal (2.81 ± 0.81) and in chronic proximal (2.85 ± 0.84) and distal (2.01 ± 0.53) nerves, compared to uninjured nerves (0.6 ± 0.09). Further, the EP1-IR/NI-IR ratio was also significantly increased (p < 0.03) compared to controls in all injured groups, and paralleled Cox-2 increases from 3 weeks after injury. Sensory neurones in injured DRG showed a significant increase of EP1-IR intensity in the acute group (p < 0.02). EP1 receptor level increases in injured human sensory neurones are rapid and precede the Cox-2-expression by macrophages. EP1 antagonists are thus more likely to show therapeutic effects in chronic than acute neuropathic pain, in addition to inflammatory pain.

DYNAMIC MECHANICAL ALLODYNNIA (DMA) IN PERIPHERAL NEUROPATHIC PAIN: PSYCHOPHYSICAL OBSERVATIONS

M.I. Samuelsson, A-S. Leffler, P.T. Hansson

1Department of Surgical Science, Section of Clinical Pain Research, Karolinska University Hospital/Institutet, Stockholm, Sweden, 2Neuropathic Pain Unit, Department of Rehabilitation Medicine, Karolinska University Hospital / Institutet, Stockholm, Sweden

Background and aim: The study examined the relationship between temporo-spatial stimulus parameters and evoked pain intensity as well as pain duration in dma. In addition, choice of sensory-discriminative and affective pain descriptors was studied. Methods: Eleven female and seven male patients participated. With a modified von Frey equipment (SOMEDIC Sales AB, Sweden) brush-evoked pain was induced in the area of neuropathic pain by lightly stroking (2 or 4 times) different distances (20, 40, 60 mm) of the skin with brushes of different widths (4, 8, 16 mm) fitted to a pressure sensor. Using a computerized visual analogue scale (VAS) the subjects rated pain intensity and duration of the evoked pain. The total pain intensity was recorded as the area under the VAS curve. After each stimulus, sensory-discriminative and affective pain descriptors were selected from the Pain-O-Meter (Gaston-Johansson, 1996). Results: Significantly increased total pain intensity (p<0.001) was demonstrated with increased brushing length and number of strokes but not while altering brush width. Although activating mechanoreceptors of a similar area, brushing the skin with a thin brush over a longer distance had a greater impact on total pain intensity than a thick brush over a shorter distance. Brushing length, number of strokes and size of the brush had no influence on the duration of after-sensation.

The most commonly used sensory descriptors were shooting, burning and aching. Annoying and troublesome were the most common affective descriptors. Conclusions: These findings indicate a significant relationship between total pain intensity and temporo-spatial stimulus parameters such as brushing length and number of strokes, but not brush width. Possible pathophysiological mechanisms underlying these findings will be discussed.
Background and Aims: Diabetic peripheral neuropathy (DPN) is often associated with pain and its complications. The aim of this survey—in patients with painful DPN—was to assess the interrelationships between pain severity and interference with function, symptom levels of anxiety and depression, sleep problems, and functional status. Methods: Participants in a US burden of illness survey (N=255) completed the modified Brief Pain Inventory-DPN (m-BPI-DPN), the Hospital Anxiety and Depression Scale (HADS), the MOS Sleep Scale (MOS-S) and the Short Form-12v2 (SF-12). Results: Patients were 61±12.8 years old, 51% were female, and they had diabetes for 12±10.3 years and painful DPN for 6.4±4.6 years. Average and Worst Pain scores (m-BPI-DPN, 0–10 scale) were 5.6±2.5 and 5.6±2.8. Pain substantially interfered (≥5 on 0–10 scale) with walking ability, normal work, sleep, and enjoyment of life. Moderate to severe levels of anxiety and depression (HADS-A and HADS-D scores ≥11 on 0–21 scale) occurred in 35% and 28% of patients, respectively. Participants reported greater sleep problems compared with the general US population. Normalized physical (PCS) and mental health (MCS) component summary scores (SF-12) indicated significant impairment levels of anxiety and depression, more sleep problems, and decrements in physical and mental functioning. Conclusions: Painful DPN is associated with decrements in many aspects of patients’ lives: physical and emotional functioning, affective symptoms, and sleep problems. The negative impact increases with pain severity. Study funded by Pfizer, Inc.

Background and aims: The purpose of this study was to investigate whether neuropathic pain severity is related to an incremental fashion to symptom levels of anxiety and depression and to sleep problems in persons with spinal cord injury (SCI). Methods: SCI patients with continuous pain at or below their level of injury (N=113) completed pain ratings, the Hospital Anxiety and Depression Scale (HADS), and the MOS Sleep Scale. Weekly pain average was used to create pain groups of None/Mild (0-3 pain rating, n=48), Moderate (4-6, n=31), and Severe (7-10, n=34). Participants were predominantly male (69.9%), 63.7% had sustained paraplegic injuries, 92.9% were ASIA A (7.1% ASIA B), and 69.9% had sustained paraplegic injuries. Activity was assessed by daily diary entries using an 11-point Likert scale. Secondary endpoints included mood, quality of life, and adverse events. Results: Using hierarchical regression, age, gender, and race were entered in step one; ASIA impairment level, level of lesion, and years post injury in step two; and pain group in step three. Pain group was a significant independent predictor of sleep problems (R2 change=0.048, p=0.018). In addition to race and gender, pain group was a significant independent predictor of anxiety (R2 change=0.068, p=0.003). For depression, in addition to race, pain group significantly predicted depression (R2 change=0.035, p=0.041). Post-hoc forward regression analyses revealed pain group to be the single best predictor of anxiety and sleep problems. Conclusions: Severity of neuropathic pain is related to symptoms of anxiety, depression, and sleep disturbance among persons with spinal cord injury. Clinicians should be alert to these comorbid conditions in persons with SCI and high levels of pain, so appropriate management can be implemented. Unrestricted medical grant funded by Pfizer, Inc.
Background and aim: Myelinated peripheral fibres have been claimed to mediate dynamic mechanical allodynia (DMA) in neuropathic pain. Dynamic mechanical dysesthesia (DMD) may coexist with DMA or be present solely. The aim was to study if DMA is the hyperbole of DMD, both mediated by myelinated fibres in the periphery. Methods: 7 patients with DMA and peripheral neuropathic pain in a limb were included. Perception thresholds to warmth (WT) and cold (CT) and sensation magnitude to a painter's brush were assessed in an unaffected area neighbouring the area of DMA. A nerve block was obtained by a proximally placed opharyngomanometer cuff inflated to about 100 mm Hg above systolic blood pressure. During cuffing, somatosensory functions were repeatedly tested in the control area every 1-3 minutes as was the perception of brush-induced DMA/DMD. Altered sensation to touch indicated block of myelinated A-fibres and increased CT and WT block of A-fibres and C-fibres, respectively. Results: 6 patients experienced a transition of DMA to DMD before complete loss of touch sensation in the neuropathic area and 1 patient lost DMA without transition. All patients lost DMA/DMD before or at the same time as loss of touch sensation in the control area. 2 patients reported unaffected CT before DMA/DMD was lost while three patients demonstrated elevated CT. All patients lost DMA but not DMD before CT increased. All 7 patients with transition of DMA to DMD demonstrated no evident WT alteration when DMD was lost. The patient with no transition demonstrated a marked elevation of WT before loss of DMA. Conclusions: In 6/7 patients A-fibres seem to be the peripheral correlate to DMA/DMD. C-fibres may contribute to DMA in individual patients.

DURING NERVE COMPRESSION/ISCHEMIA THE TRANSITION OF ALLODYNA TO DYSESTHESIA WHILE BRUSHING THE SKIN IS PARALLELED BY A CONTINUOUS IMPAIRMENT OF A-FIBRE FUNCTION: A PRELIMINARY REPORT FROM EXPERIMENTS IN PERIPHERAL NEUROPATHIC PAIN PATIENTS

A.H. Landerholm, P.T. Hansson

Section of Clinical Pain Research, Department of Surgical Science, Karolinska Institute/Hospital, Stockholm, Sweden

ALTERNED EXPRESSION OF DORSAL HORN GABA-TRANSPORTER (GAT1) AND GLUTAMATE-TRANSPORTER (EAAT3) AFTER CHRONIC CONSTRUCTION OF THE SCIATIC NERVE IN TE RAT

M. Daemen, G. Houglund, T. De Nijs, G.H. Spincemaille

Department of Neurosurgery, University Hospital Maastricht, The Netherlands

Quoted from: Roth T. 1 Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, USA. 2 Pfizer Global Pharmaceuticals, New York, USA. 3 Pfizer Global Research and Development, Ann Arbor, USA.

Background and aims: The relationship between chronic pain and sleep disturbance is widely accepted. However, polysomnographic (PSG) studies in patients with chronic pain due to rheumatologic conditions have reported less severe sleep disturbance than is typically self-reported by patients. This study attempted to determine the degree to which self-reported sleep disturbance in neuropathic pain (NeP) patients predicts PSG documented insomnia. Methods: Patients with NeP due to postherpetic neuralgia (PHN) or diabetic peripheral neuropathy (DPN) reported disturbed sleep and neuropathic pain for ≥3 months prior to assessment. Clinical PSG studies were conducted for 2 consecutive nights following patients: (1) discontinuation from all hypnotics, antidepressants, benzodiazepines, AEDs, and opioids for 7 days. Results: Objective PSG criteria for insomnia (ie, sleep latency or wakefulness after sleep onset of greater than 20 minutes and at least 1 hour of wakefulness during an 8-hour recording) were met in 34 of the 35 patients. Ten of the subjects had sleep apnea with an Apnea-Hypopnea Index >10. The PSG of the remaining subjects revealed marked elevation of wakefulness, transient arousals, and sleep architecture disturbance. Conclusions: In this population, self-reported sleep disturbance was generally corroborated by PSG evidence. Patients with moderate to severe NeP and self-reported sleep disturbance demonstrated PSG evidence of disturbed sleep, meeting objective criteria for insomnia. Disturbed sleep, sleep loss, and insomnia have been shown to be associated with decreased pain tolerance, increased risk of depression, and decreased quality of life. These data thus emphasize the importance of addressing self-reported sleep disturbance in NeP patients. Study funded by Pfizer Inc.