Abstract Book

3RD DANISH PAIN RESEARCH SEMINAR

PERSISTENT POSTSURGICAL PAIN: MECHANISMS AND PREVENTION

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PERSISTENT POSTSURGICAL PAIN: MECHANISMS AND PREVENTION

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will be open during all breaks.

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Abstracts

Epidemiology of Persistent Post-surgical pain - Identifying the Path to Prevention

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In the U.S.A, it is estimated that about 45 million surgical procedures are performed every year. Studies that have examined the incidence of chronic pain after various surgeries indicate that 10-50% of patients may experience chronic postoperative pain that may be associated with significant disability and interference with quality of life.[1] About 20% of patients attending a pain clinic in Northern Britain had chronic pain following surgery. If these figures are extrapolated more globally, the health care utilization and economic implications of persistent pain after surgery are staggering. Hence, the urgent need for a concerted effort to formulate preventive measures to minimize persistent postsurgical pain.

The fundamental concepts of preventive medicine include: identifying a clinical problem, defining the magnitude of the problem, examining factors (e.g., predictors and pathophysiological mechanisms) that may contribute to the problem, application of scientific knowledge to develop strategies to prevent the clinical condition, and finally providing evidence for the effectiveness of the preventive strategy. Utilizing the concepts of translational research to develop protective strategies will require the formulation of preventive measures based on basic research and testing their effectiveness in appropriate clinical populations. Pain researchers and clinicians should learn from the experiences of pioneers in infectious disease prevention. The development of vaccines for poliomyelitis and the eradication of smallpox are excellent examples of successful strategies that have led to major advances in health care.

Recent reports have reviewed the epidemiology of chronic post-surgical pain.[1,2] Certain risk factors have been clearly identified. For example, surgeries with a higher likelihood of nerve injury such as amputation, thoracotomy, and breast surgery may have a higher incidence of persistent pain after surgery. Several other potential risk factors have also been described, including moderate to severe pre- and post- operative pain and type of anesthetic. Yet, there are unexplained differences in incidence of persistent pain after surgeries at similar sites. A recent epidemiological survey determined the incidence and predictive factors of persistent pain after hysterectomy. Pain was reported by about 32% of subjects surveyed one year after hysterectomy, and 13.7% had pain more than 2 days a week.[3] The risk of chronic pain was similar after vaginal *versus* total abdominal hysterectomy. In contrast, an earlier similar study in patients undergoing caesarean sections found that about 12% of patients reported pain and a smaller fraction (5.9%) reported daily or almost daily pain.[4] Examining the factors that may explain these variabilities across surgeries may provide valuable insights on the mechanisms of persistent post-surgical pain. In both studies anesthetic management was a predictive risk factor. Spinal anesthesia was associated with less chronic pain compared to general anesthesia (OR, 0.42)[3] in both studies.

Several investigators have examined other risk factors that may explain inter-individual variability in pain and its persistence. Psychosocial factors such as fear, anxiety, depression and catastrophizing may play a significant role. Age and sex have been observed to predictive factors for chronic pain after certain surgeries. More recently, it has been suggested that genetic factors are likely to be involved.[5] Thus, similar to other public health fields, researchers in various disciplines related to pain- epidemiology, neuroscience, genetics, psychology, and clinical trials, need to pool their efforts to contribute to the better understanding of gene-environment interactions and develop rational risk reduction strategies for the surgical population.

The goal of this symposium of developing strategic plans for future directions to alleviate persistent pain after surgery is a worthy cause. Developing preventive healthcare strategies to avoid/reduce chronic postsurgical pain is likely to present several challenges, but directions from this meeting of the leaders in the field is likely to provide reasonable starting points for future research endeavors.

References

1. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: Risk factors and prevention. Lancet 2006; 367: 1618–25
2. Visser EJ. Chronic post-surgical pain: Epidemiology and clinical implications for acute pain management. Acute Pain 2006; 8: 73-81
3. Risk factors for chronic pain after hysterectomy: a nationwide questionnaire and database study. Anesthesiology 2007; 106: 1003-12.
4. Nikolajsen L, Sorensen HC, Jensen TS, Kehlet H: Chronic pain following caesarean section. Acta Anaesthesiol Scand 2004; 48: 111–6
5. Tegeder I et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 2006; 12: 1269-77.

Pathophysiology of acute (incisional) pain

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Postoperative pain has a unique clinical profile compared to inflammatory and neuropathic conditions. This indicates that the etiology of pain behaviors produced by incisions must be unique compared to antigen injection and nerve injury in animal models. We have examined putative pain mediators, nociceptor sensitization and coincident pain-related behaviors produced by incision in attempt to understand the mechanisms of postoperative pain.

Several characteristics of incisional pain point to unique properties compared to inflammatory and neuropathic models. First pH is decreased in incisions, however, this is not necessarily the case for inflammation.[1,2] In fact, lactic acidosis is present in incisions.[3] Second the time course of NGF production and release is different in incision compared to nerve injury.[4] Finally, the time course of pain related behaviors caused by incision is different than that of inflammation and nerve injury with incisional pain being short-lived. Incisional models do not result in persistent pain in most cases.

The importance of experimental models in postoperative pain research is to more rigorously examine etiology so that new treatment strategies can be developed. A limitation with experimental models is to identify precise correlates to human postoperative pain to better advance therapies.[5] The relationship of theses pain-related behaviors to pain at rest and pain with activities after surgery is not clear (see table below).

A challenge for research in postoperative pain mechanisms and for pain research in general is to quantify exaggerated nociceptive responses in both patients and nonhuman models even though the clinical state, the experimental model and the tests may not be precisely the same among species. From the preclinical models, mechanisms will be understood and from the patients, clinical relevance of these tests and treatments that affect the exaggerated processing will be determined. The factors influencing variable time courses and chronicity will be an even greater challenge.

Table 1. Postoperative Pain Measurements – Clinical and Experimental

Postoperative Pain Models	**Clinical Postoperative Pain**
Heat withdrawal latency	Pain at rest
Primary mechanical withdrawal threshold	Pain during activities (i.e., ambulation, coughing, flexion/extension of an extremity
Secondary mechanical withdrawal threshold	Pressure pain threshold
Guarding	Area of mechanical hyperalgesia
Weight bearing	
General activity	
Conditioned responses	
Primary mechanical Allodynia	
Secondar mechanical Allodynia	
Graded hyperalgesia	
Graded allodynia	

References

1. Woo YC, Park SS, Subieta AR, Brennan TJ. Changes in tissue pH and temperature after incision indicate acidosis may contribute to postoperative pain. Anesthesiology 2004; 101: 468-475.
2. Radhakrishnan R, Sluka KA. Acetazolamide, a carbonic anhydrase inhibitor, reverses inflammation induced thermal hyperalgesia in rats. J Pharmacol Exp Ther 200; 313: 921-7.
3. Kim TJ, Freml L, Park SS, Brennan TJ. Lactate concentrations in incisions indicate ischemic-like conditions may contribute to postoperative pain. J Pain 2007; 8: 59-66.
4. Banik RK, Subieta AR, Wu C, Brennan TJ. Increased nerve growth factor after rat plantar incision contributes to guarding behavior and heat hyperalgesia. Pain 2005; 117: 68-76.
5. Brennan TJ. Incisional sensitivity and pain measurements – Dissecting mechanisms for post-operative pain. Anesthesiology 2005; 03: 3-4.

Pathophysiology of Neuropathic Pain: Peripheral Mechanisms

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Cutting a telephone line makes the line go dead. Likewise, cutting or otherwise damaging a peripheral nerve ought to reduce or eliminate sensation, including pain. Why, then, does neuropathy often induce pain? Answering this question requires identifying the sources of abnormal impulse discharge that are interpreted by a conscious brain as pain, and uncovering the neurobiological processes responsible for the discharge. Except for central pain, these sources and processes almost certainly reside in the peripheral nervous system (PNS), even in the case of very prolonged pain. The idea that that sources of persistent pain originate in the periphery but, if unrelieved, migrate into the brain has little foundation. For example, consider the rapid pain relief obtained by passage of a kidney stone, by replacement of an osteoarthritic hip, and by diagnostic plexus or spinal block in chronic neuropathy. If the pain signal originated centrally, these peripheral events should not provide relief.

But this does not mean that the CNS plays no role. Peripheral sources of abnormal discharge, and other injury-induced signals, can set the CNS into a sensitized state such that: 1) pain signals originating peripherally are amplified, and 2) impulses carried in low threshold touch afferents are felt as painful. This so-called "central sensitization" state is dynamic. Although it may persist for long periods of time when maintained by peripheral input, it decays rapidly when the peripheral signal that sustains it is eliminated (Gracely et al., 1992). Understanding PNS pathophysiology is therefore important for two reasons: 1) Suppressing abnormal discharge originating in the periphery is expected to eliminate the primary neuropathic pain signal. 2) At the same time it is expected to eliminate a major factor, perhaps THE major factor, that maintains CNS amplification processes.

Healthy PNS neurons are for the most part incapable of generating impulse discharge upon natural stimulation except at the peripheral sensory ending. Pressing on your median nerve does not normally induce impulses. If it did, you would feel a sensation in the hand. The same pressure at a site of median nerve entrapment however, or on a median nerve neuroma, does evoke pain in the hand (the Tinel sign). Neuropathy renders afferent neurons hyperexcitable by changing their basic electrogenic (impulse generating) properties.This change occurs both at mid-nerve sites of axonal injury, and in the afferent soma in the dorsal root ganglion (DRG).

The primary cause of hyperexcitability in injured afferents appears to be the emergence of high-frequency subthreshold oscillatory potentials and the enhancement of post-spike depolarizing afterpotentials (DAPs, Amir et al., 2002). These newly emergent resonances enhance the neuron's repetitive firing capability and promote ectopic discharge. Numerical simulations show that oscillations enhance electrogenesis more by overcoming membrane accommodation than by adding an increment to membrane depolarization. Enhanced electrogenesis is thought to result from a change in the disposition of ion channels in the cell membrane, and perhaps also from altered gene expression in the cell soma. Analysis of nerve injury-induced changes in gene expression has been facilitated by the use of genetic linkage analysis, and gene expression arrays ("gene chips"). These tools have been used to compare rodents with and without nerve injury, and rodent strains with a high *versus* a low congenital predisposition to various neuropathic pain phenotypes.

At the time of pain onset in neuropathy models the bulk of the ectopia is carried centrally in A-beta touch afferents. The resulting pain may be due to upregulation in these neurons of peptides (e.g. substance P) that are normally associated with C-nociceptors. This is one of the outcomes of axotomy-induced reorganization of gene expression. Another possibility is the induction of central sensitization. The central sensitization, in turn, may be a consequence of ectopic activity in injured and/or uninjured C-fiber afferents, or in altered A-beta touch afferents.

Unlike telephone lines, nerves are composed of axonal extensions of live neurons. Injury or disease affecting these neurons can lead directly to changes in their electrogenic and signaling properties, changes that can result in chronic neuropathic pain.

References

1. Amir, R., Michaelis, M. and Devor, M., Burst discharge in primary sensory neurons: triggered by subthreshold oscillations, maintained by depolarizing afterpotentials. J. Neurosci. 22 (2002) 1187-1198.

2. Devor, M. Response of nerves to injury in relation to neuropathic pain. Chapter 58 in McMahon SL and Koltzenburg, M. eds. Wall and Melzack's Textbook of Pain, 5th edition, Churchill Livingstone, London, 2006; 905-927.

3. Gracely, R., Lynch, S. and Bennett, G., Painful neuropathy: altered central processing, maintained dynamically by peripheral input. Pain, 51 (1992) 175-194.

Central Mechanisms

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In addition to the obvious central contribution to the central neuropathic pain that may result from surgical procedures to the spinal cord and brain, peripheral surgical procedures can produce changes in the CNS that alter sensory processing and thereby produce pain and heightened pain sensitivity. These changes may be transient, long lasting but reversible, and irreversible and all can contribute to persistent pain.

It is convenient mechanistically to differentiate surgery that produces: 1. Tissue damage that heals. 2. Localized changes that continue to activate nociceptors. 3. Persistent inflammation, and 4. Damage to peripheral nerves.

Generally, once damaged tissue has fully healed and inflammation has resolved pain and pain hypersensitivity subside.

Persistent activation of nociceptors by intense local mechanical or chemical stimuli, however, can produce pain for as long as the stimuli are present and, depending on the degree of input, also activity-dependent changes in the CNS that lead to allodynia and secondary hyperalgesia.

Persistent inflammation, by virtue of post-translational and transcriptional changes both in primary sensory neurons and neurons in the CNS, can produce longer lasting and more widespread alterations in neural function that require though, ongoing peripheral pathology for its maintenance.

Damage to peripheral nerves in susceptible individuals can produce permanent changes in the CNS including a loss of neurons (neurodegeneration), disrupted synaptic transmission and altered synaptic organization, changes in facilitatory and inhibitory pathways. These changes may become fully autonomous.

The challenges we face are identifying what mechanism(s) contribute to a patient's persistent pain, and developing treatment strategies targeted at those mechanisms. Ideally we need to be able to identify those individuals at risk and institute strategies to prevent the establishment of permanent central alterations.

Neuropathic vs. inflammatory persistent postsurgical pain

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Neuropathic pain has been known for centuries and mostly been appreciated in the setting of nerve diseases such as neuropathies or postherpetic neuralgia, but neuropathic pain may also be a manifestation of postsurgical pain where smaller or larger nerves have been lesioned intentionally or unintentionally. Whenever the afferent somatosensory is disturbed, neuroplastic changes occur which may involve reorganization processes in the spinal cord and even in the brain.

It is now clear that long-lasting noxious stimulation as seen in inflammation or damage to the nervous system may give rise to a neuronal hyperexcitability and that this sensitization of the nervous system plays an important role for the development and maintenance of chronic pain. The manifestations of such hyperexcitability are multiple and include among others: increased neuronal response to a suprathreshold stimulus, lowering of threshold for cell activation, expansion of peripheral areas from where a central neuron can be activated and the recruitment of previous non-responding nociceptive neurons. The clinical manifestations of inflammatory pain are pain, swelling, and hypersensitivity in the area of tissue damage and this hypersensitivity may also extend outside the painful area. The changes are reversible and usually disappear as the inflammation subsides. The signs of neuropathic pain include in addition to the same positive signs seen in inflammatory pain also negative sensory signs with sensory loss in those areas that have lost their normal sensory innervation due to the nerve damage.

The nervous system changes after noxious stimulation or tissue injury and this change in responsiveness appear to be partly time and intensity dependent and partly dependent on cause of injury. Short-lasting and moderate noxious input leads to reversible plastic changes, while more intense and long-lasting noxious stimulation implies a risk for persistent and more profound changes in transmitters, receptors, ion channels and in neuronal connectivity. The changes following nerve damage are probably longer lasting than those after inflammation and the risk for chronic pain may therefore be higher after nerve injury than after inflammation

References

1. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. Lancet 2006; 367: 1618-1625.
2. Flor H, Nikolajsen L, Jensen TS. Phantom limb pain – a case of maladaptive central nervous system plasticity. Nature Rev Neurosci 2006; 7: 873-881.
3. Finnerup NB, Jensen TS. Mechanisms of neuropathic pain. Advances in Pain Management 2007; 1: 12-18.
4. Witting N, Kupers RC, Svensson P, Jensen TS. A PET activation study of brush-evoked allodynia in patients with nerve injury pain. Pain 2006; 120: 145-154.

Persistent postsurgical pain – the role of acute pain?

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It is well established that the intensity of preoperative as well as the intensity of postoperative pain relates to the risk of developing a persistent postsurgical state in a variety of procedures (amputation, mastectomy, thoracotomy, herniotomy, etc.). This relationship raises several important questions: are the functional characteristics of the nociceptive system in the uninjured preoperative state related to the risk of developing high-intensity acute and persistent postoperative pain?; is a preoperative activation of the nociceptive system leading to pain and central sensitisation responsible for the high-intensity acute – and persistent pain?; is there in addition to the acute inflammatory pain in some patients an acute neuropathic pain which subsequently is responsible for persistent pain?; and finally can improved acute pain treatment decrease the risk of persistent postsurgical pain? The relative role of these factors will be discussed and it is concluded that the main pathogenic mechanisms may include preoperative (genetic?) patient characteristics together with acute neuropathic postoperative pain due to intraoperative nerve injury. So far, the data are disappointing on the effect of effective acute pain relief to reduce persistent postsurgical pain.

References

1. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367: 1618-1625.
2. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000; 93: 1123-1133.
3. Werner MU, Duun P, Kehlet H. Prediction of postoperative pain by preoperative nociceptive responses to heat stimulation. Anesthesiology 2004; 100: 115-119.
4. Pan PH, Coghill R, Houle TT, Seid MH, Lindel M, Parker RL, Washburn SA, Harris L, Eisenach JC. Multifactorial preoperative predictors for postcesarean section pain and analgesic requirement. Anesthesiology 2006; 104: 417-425
5. Nielsen PR, Norgaard L, Rasmussen LS, Kehlet H. Prediction of post-operative pain by an electrical pain stimulus. Acta Anaesthesiol Scand 2007;51: 582-586.

Genetic mechanisms of persistent pain

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Based on the Mogil group's findings that 22 pain phenotypes, including postoperative pain, have heritabilities of 40-60% in rodents, we initiated human genetic association studies of pain phenotypes as complex genetic traits. Two major strategies using candidate gene approach have been chosen: genotyping of genetic markers in prioritized genes that encode known molecules involved in human pain processing; and genotyping of genetic markers in genes selected by our basic science collaborators based on their up & down regulation in animal pain models. These studies were carried out on multiple cohorts including clinical neuropathic pain and experimental pain populations.

Our strongest findings emerged from collaboration with the Woolf laboratory at Harvard. They selected 4 high-priority molecular candidates from dorsal root ganglion mRNA expression microarray studies of in 3 rat models of neuropathic pain and followup pain behavior studies. We found that one of their high priority genes, GTP cyclohydrolase I (*GCH1*), had a common haplotype that appeared to protect our patients with lumbar nerve root compression from chronic pain after discectomy in 168 patients ($p = .009$). We then replicated the protective effect of this haplotype in 547 normal subjects phenotyped for experimental pressure pain at the University of North Carolina and University of Florida ($p < .01$). We are studying the effects of this *GCH1* haplotype on molecular expression in our spine patients' lymphocyte cell lines.

One of the Woolf lab medium priority genes, a potassium channel-related gene had a common non-synonymous SNP; the allele corresponding to amino acid isoleucine was protective against persistent postoperative spinal root pain ($p = .003$) in our 168 patients. We have replicated this result in 205 Israeli amputees; this SNP was associated with the magnitude of chronic phantom limb pain ($p = .002$) and stump pain ($p = .03$).

We conclude that combined physiological and clinical genetic approaches in animals and humans can identify genes that contribute to the variability in human pain. We propose to extend this approach by carrying out whole genome association studies in larger cohorts of patients with relatively homogeneous clinical pain phenotypes.

References

1. Mogil JS, Wilson SG, Bon K, Lee SE, Chung K, Raber P, Pieper JO, Hain HS, Belknap JK, Hubert L, Elmer GI, Chung JM, Devor M. Heritability of nociception I: responses of 11 inbred mouse strains on 12 measures of nociception. Pain 1999; 80: 67-82.
2. Belfer I, Wu T, Kingman A, Krishnaraju RK, Goldman D, Max MB. Sindrup SH, Jensen TS. Candidate gene studies of human pain mechanisms: methods for optimizing choice of polymorphisms and sample size. Anesthesiology 2004; 100: 1562-72.
3. Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejim J, Marian C, Scholz J, Wu T, Allchorne A, Diatchenko L, Binshtok AM, Goldman D, Adolph J, Sama S, Atlas SJ, Carlezon WA, Parsegian A, Lotsch J, Fillingim RB, Maixner W, Geisslinger G, Max MB, Woolf CJ. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 2006; 12: 1269-77.

Chronic postherniotomy pain

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Groin hernia repair is one of the most frequent operations with an annual rate of 2800 per million population in Europe and the USA, resulting in chronic pain in about 10% of patients, whereof approx. 5% experiences moderate to severe pain affecting everyday activities (Aasvang and Kehlet 2005). This surgical model may be ideal for a detailed analysis of the pathogenic mechanisms involved in development of a chronic postoperative/neuropathic pain state, as these patients do not have a number of other risk factors for chronic pain such as cancer, chemotherapy or radiation therapy, or predominant psychosocial characteristics,.

Groin hernia repair poses the risk of intraoperative nerve injury as the operative field is being traversed by three major sensory nerves (nn. ilioingunialis, iliohypogastricus, and genitofemoralis), but the inflammation caused by the inserted mesh may also contribute to a chronic pain state. The possibility of an underlying intraoperative nerve injury, is supported by the finding of sensory disturbances, and the use of sensory pain descriptors by chronic pain patients, and the finding that postoperative complications predicts long-term pain (Franneby et al. 2006). However, sensory disturbances are also found in pain free patients after groin hernia repair, indicating that a nerve lesion is a prerequisite but not sufficient to result in chronic postherniotomy pain (Aasvang et al. 2007). Quantitative sensory testing (QST) shows that cutaneous hypoalgesia, rather than hyperalgesia dominates the clinical picture, However, hyperalgesia to direct pressure is significantly increased in chronic pain patients vs pain free patients after groin hernia repair, suggesting that the localization of pain is situated in deeper layers rather than arising from cutaneous structures (Aasvang et al. 2007). Sensory mapping has shown a homogeneous localization of maximum pain with a varying distribution of sensory disturbances (fig. 1) Repetitative pinprick stimulation causes increased pain in pain patients but not in pain free patients, suggesting that central sensitization is a part of this chronic pain syndrome.

A specific complaint is pain related sexual dysfunction and dysejaculation (pain during ejaculation) in about 3% of patients and anatomically specifically located to the spermatic cord (Aasvang et al. 2006)

Ongoing prospective studies investigate the role of preoperative pain, response to standardized pain stimulation, psychosocial factors, genetics, the role of intraoperative nerve handling/injury, operative technique (open vs. laparoscopic repair), acute postoperative pain, management complications and the development of sensory disturbances (QST), and the indication for reoperation (neurectomy, mesh removal) and/or pharmacotherapy.

References:

1. Aasvang E, Kehlet H. Chronic postoperative pain-the case of inguinal herniorrhaphy. Br J Anaesth 2005; 95: 69-76.
2. Aasvang EK, Mohl B, Bay-Nielsen M, Kehlet H. Pain related sexual dysfunction after inguinal herniorrhaphy. Pain 2006; 122: 258-263.
3. Aasvang EK, Mohl B, Kehlet H. Ejaculatory pain – a specific postherniotomy pain syndrome? Anesthesiology 2007. In press.
4. Aasvang EK, Brandsborg B, Christensen B, Jensen TS, Kehlet H. Neurophysiological characterization of postherniotomy pain. Pain 2007. Submitted.
5. Franneby U, Sandblom G, Nordin P, Nyren O, Gunnarsson U. Risk factors for long-term pain after hernia surgery. Ann Surg 2006; 244: 212-219.

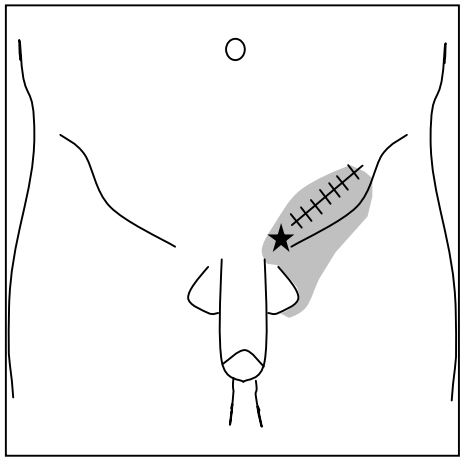

Figure. Localization of pain and sensory disturbances found in patients with chronic postherniotomy pain. The star indicates the typical location of maximum pain, and the shaded area shows the typical area with sensory disturbances/pain

Mechanisms and Prevention of Persistent Post-Thoracotomy Pain

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Prevention and treatment of the pain that accompanies thoracic surgery remains a challenge. Acutely, the pain is severe, and the requirements of respiratory effort and pulmonary toilet make it unrelenting. More chronically, pain can persist, and postthoracotomy pain syndrome develops at a rate second only to extremity amputation. A large number of surgical and analgesic interventions have been proposed for the prevention and treatment of the acute and chronic manifestations of the pain associated with thoracic surgery.

Even in individuals who do not experience long-term pain following major thoracic surgery, the acute phase of perioperative pain is prolonged, and often associated with decreases in outcomes such as physical activity and pulmonary function. Even in this early phase, individuals whose pain is more likely to persist can be identified. Although post-thoracotomy pain syndrome has been defined by the IASP as "pain that recurs or persists along a thoracotomy scar at least two months following the surgical procedure," the benchmark used by many authors is pain that persists for at least one year following surgery. The prevalence of pain one year after thoracotomy appears to be about 50%, without the anticipated reduction that was expected to accompany minimally invasive thoracocopic procedures. However, not all studies observe long-term pain to be as prevalent, suggesting that there may be modifiable factors that could reduce the likelihood of persistent pain following thoracotomy.

Thoracotomy and the pain which accompanies it manifest several features that appear to be common to the development of persistent postoperative pain. The first is nerve damage. Intercostal nerve injury is frequent following thoracotomy. However, the extent of injury does not appear to be associated with the development of chronic pain. The second is the intensity and persistence of pain during the acute phase, which reaches a level not seen in many other procedures and may potentiate the development of longer-term pain. Consequently, strategies for preventing persistent pain following thoracotomy are built around preserving intercostal nerve function and aggressive perioperative pain control.

Some modifications of surgical technique have been proposed to prevent intercostal nerve damage. Although they are associated with other benefits, muscle sparing incisions appear to offer no advantage when only pain is taken into consideration. Despite the minimally invasive nature of thoracoscopic procedures, the opportunity to damage intercostal nerves is still present and may be the basis for the significant amount of long-term pain following these minimally invasive procedures.

Analgesic strategies are built around a preemptive multimodal approach, with the optimal approach yet to be defined. It now seems clear that efforts, however intense, made for only a portion of the perioperative period have little impact on long-term outcomes. Although thoracic epidural analgesia remains the mainstay of analgesic therapy, many adjuncts have been identified that could augment therapy, particularly in vulnerable individuals already experiencing chronic painful conditions.

Persistent pain may develop regardless of preventive efforts. Current treatment strategies are built from more general approaches to chronic painful conditions, as relatively few studies specific to persistent thoracotomy pain have been performed. However, issues related to disease progression and mechanical complications from the prior surgery also guide analgesic therapy.

Overall, there appears to be no magic bullet to prevent persistent pain following major thoracic surgery. Moreover, due to the paucity of relevant studies, treatment of this problem once it develops remains more art than science. Aggressive individualized therapy and early identification and treatment of patients experiencing pain that is greater than expected may, one day, limit the personal, economic and social burdens of this painful condition.

References

1. Gottschalk A, Cohen SP, Yang S, Ochroch EA: Preventing and treating pain after thoracic surgery. Anesthesiology 2006; 104: 594-600.
2. Ochroch EA, Gottschalk A, Augostides J, Carson KA, Kent L, Malayaman N, Kaiser LR, Aukburg SJ: Long-term pain and activity during recovery from major thoracotomy using thoracic epidural analgesia. Anesthesiology 2002; 97: 1234-44.
3. Bong CL, Samuel M, Ng JM, Ip-Yam C: Effects of preemptive epidural analgesia on post-thoracotomy pain. J Cardiothorac Vasc.Anesth 2005; 19: 786-93.
4. Landreneau RJ, Mack MJ, Hazelrigg SR, Naunheim K, Dowling RD, Ritter P, Magee MJ, Nunchuck S, Keenan RJ, Ferson PF: Prevalence of chronic pain after pulmonary resection by thoracotomy or video-assisted thoracic surgery. J Thorac.Cardiovasc.Surg 1994; 107: 1079-85.

Mandibular surgery

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Bilateral sagittal split osteotomy (BSSO) of mandible is the most common orthognathic surgical procedure for the treatment of dentofacial deformities. The inferior alveolar nerve (IAN), located within the mandibular canal, is often injured during the osteotomy. This injury is the most common complication of BSSO, with an incidence around 70-90 %. Persistent sensory disturbances are present at 2 years in 35-40 % of the patients. The type and degree of nerve injury vary from segmental demyelination to partial axonal damage due to stretching, ischemia, or laceration; also mixed injuries after high energy crush, or total sectioning of the nerve may occur. BSSO thus offers a human model for various types of peripheral nerve injury, enabling the study of sensory nerve regeneration, diagnostics of sensory neuropathy, and post surgical neuropathic pain. However, macroscopic events and inspection during BSSO do not suffice for reliable detection and classification of intraoperative IAN injury; even visibly intact nerves may have suffered axonal injury.[1,2]

Intraoperative neurophysiologic monitoring (IOM) is the gold standard for detection of threatening nerve injury and prevention of persistent postoperative neurological morbidity. IOM also allows direct classification and grading of iatrogenic nerve injury. We have developed a method, based on sensory nerve conduction study (NCS), for continuous monitoring of the function of the IAN during BSSO[3]. We utilized this technique in a prospective one-year follow-up study on 20 patients undergoing BSSO. The surgical risk factors of nerve injury, postoperative sensory disturbances, value of clinical, quantitative sensory (QST) and neurophysiologic tests in the diagnosis of IAN neuropathy, as well as sensory recovery and incidence of neuropathic pain in relation to the type and degree of nerve injury were evaluated[2,4,5].

IAN injury occurred in 38 out of 40 nerves at risk (58% primarily demyelinating and 42% partial axonal lesions). Clinical sensory examination was insensitive in the diagnosis of postoperative neuropathy, especially at late follow-up times, and it did not correlate with the IOM findings. QST of the innocuous thermal modalities increased the diagnostic yield, while the sensory NCS showed the best diagnostic accuracy both at the early and late control times (Table). 73% of the axonal lesions showed incomplete recovery at 1 yr, whereas most of the demyelinating injuries were back to normal by 3 months. Neuropathic pain occurred only after axonal injury (2 nerves); in both subjects, the clinical sensory examination and heat pain detection thresholds were normal, while other thermal QST and neurophysiologic tests showed Aβ-, Aδ- and C-fibre damage at 1 year.

While IOM provides the best method for detection of surgical nerve injury, thermal QST and neurophysiologic recordings are needed for reliable postoperative diagnosis and study of neuropathic pain.

Table. Clinical, quantitative sensory and neurophysiologic tests in the diagnosis of IAN neuropathy. *Gold standard: IOM results (2 weeks); in combination with subjective sensory disturbance (1 year).*

Test	% sensitivity at 2 weeks / 1 yr	% specificity at 2 weeks / 1 yr
BSD	40 / 0	89 / 100
S/B	40 / 0	89 / 100
W/C	44 / 7	100 / 100
GO	59 / 27	73 / 88
TDT	58 / 33	56 / 88
CDT	64 / 40	100 / 88
WDT	50 / 47	100 / 92
HPT	43 / 13	100 / 96
BR	59 / 27	60 / 100
NCS	88 / 82	55 / 100

BSD= brush stroke direction, S/B=sharp blunt discrimination, W/C=warm cold discrimination, GO=grating orientation discrimination, TDT=tactile detection threshold (monofilaments), CDT=cold detection threshold, WDT=warm detection threshold, HPT=heat pain detection threshold, BR= blink reflex of the mental nerve distribution, NCS= nerve conduction study of the IAN

References

1. Jääskeläinen SK, Peltola JK, Forssell K, Vähätalo K. Evaluating the function of the inferior alveolar nerve during mandibular sagittal split osteotomy with repeated nerve conduction tests. J Oral Maxillofac Surg 1995; 53: 269-279.
2. Teerijoki-Oksa T, Jääskeläinen SK, Forssell K, Forssell H, Vähätalo K, Tammisalo T, Virtanen A. Risk factors of nerve injury during mandibular sagittal split osteotomy. Int J Oral Maxillofac Surg 2002; 31: 33-39.
3. Jääskeläinen SK, Teerijoki-Oksa T, Forssell K, Vähätalo K, Peltola J, Forssell H. Intraoperative monitoring of the inferior alveolar nerve during mandibular sagittal split osteotomy. Muscle Nerve 2000; 23: 368-375.
4. Teerijoki-Oksa T, Jääskeläinen SK, Forssell K, Virtanen A, Forssell H. Recovery of nerve injury after mandibular sagittal split osteotomy. Diagnostic value of clinical and electrophysiologic tests in the follow-up. Int J Oral Maxillofac Surg 2004; 33: 134-140.
5. Jääskeläinen SK, Teerijoki-Oksa T, Forssell K, Virtanen A, Forssell H. Sensory regeneration following intraoperatively verified trigeminal nerve injury. Neurology 2004; 62: 1951-1957.

Postamputation pain

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Virtually all amputees experience phantom phenomena following limb amputation. Non-painful phantom sensations rarely pose any clinical problem, but 60-80% of all amputees also have painful sensations located to the missing limb. Some patients develop chronic pain located to the stump.

The mechanisms underlying chronic postamputation pain have not been completely clarified, but both peripheral and central mechanisms are likely to play a role.

Preamputation pain is know to be a risk factor but it is probably not possible to prevent phantom pain by a preoperative epidural blockade.

Treatment of chronic postamputation pain represents a major challenge to the clinician; in particular the treatment of phantom pain. Unfortunately, most studies dealing with phantom pain suffer from major methodological errors. Guidelines in analogy with treatment regimens used for other neuropathic pain conditions are probably the best approximation

Figure 1 Both peripheral and central mechanic.sms are involved in the generation of phantom limb pain.

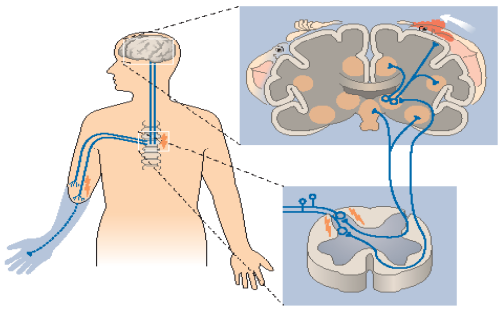

Table 1: Interventions supported by evidence
Gabapentin
Tricyclic antidepressants
Opioids (morphine, tramadol)
Ketamine (i.v.)
Calcitonin (i.v)
Use of a Farabloc (a metal treaded sock)
Sensory discrimination training

Table 2: Commonly used interventions currently unproven
Pregabalin
Various anticonvulsants (except gabapentin)
Antidepressants (except tricyclic antidepressants)
Opioids (methadone, oxycodone)
Physical therapy
Acupuncture
Hypnosis
Mirror treatment
Spinal cord stimulation

Table 3: Interventions refuted by evidence
Memantine (20-30 mg/day)
Epidural treatment (started 18 hrs before amputation)
Perineural blocks (started postoperatively)

References

1. Flor H, Nikolajsen L, Jensen TS. Phantom limb pain: a case of maladaptive CNS plasticity? Nature Review Neuroscience 2006; 7: 873-81.
2. Nikolajsen L, Ilkjær S, Krøner K *et al.* Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. Lancet. 1997; 350: 1353–1357.
3. N.B. Finnerup, M. Otto, H.J McQuay, T.S. Jensen, S.H. Sindrup. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118: 289-305.

Complex Regional Pain Syndrome

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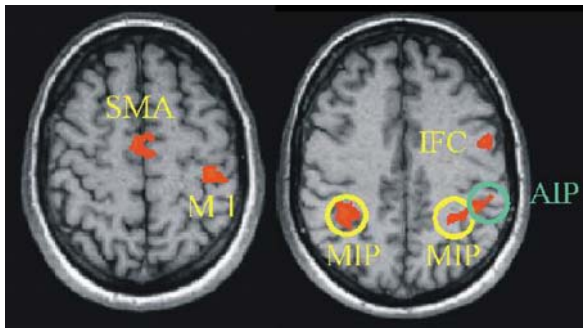
Complex regional pain syndromes (CRPS, reflex sympathetic dystrophy, causalgia) are painful disorders that develop after trauma affecting a limb with (type I) or without (type II) nerve injury. Clinical features are pain (spontaneous, hyperalgesia), impairment of motor function, swelling and autonomic abnormalities (changes in sweating and blood flow).

Pain. Spontaneous pain and various forms of hyperalgesia at the distal extremity are generated by processes of peripheral and central sensitization and changes in the central representation in the thalamus and cortex. FMRI studies demonstrated a shortened distance between little finger and thumb representations in the SI cortex on the painful side which resolved after successful therapy.

Autonomic abnormalities. 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 and an endothelial damage 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 to distinguish CRPS from other extremity pain syndromes.

Pathophysiology of SMP. Cutaneous sympathetic out-flow to the painful extremity was experimentally activated to the highest possible physiological degree. The intensity and area of spontaneous pain and mechanical hyperalgesia increased considerably in patients with SMP but not in SIP patients. A pathological interaction between sympathetic vasoconstrictor and afferent neurons within the affected skin is the likely explanation.

Motor abnormalities. Kinematic analysis of target reaching as well as grip force analysis and functional imaging investigations on the cerebral representation of finger movements were used to quantitatively assess motor deficits. Compared to controls, CRPS patients particularly showed a significant prolongation of the target phase. The pattern of motor impairment was consistent with a disturbed integration of visual and proprioceptive inputs in the posterior parietal cortex. During finger tapping of the affected extremity, CRPS patients showed a significant reorganization of central motor circuits, with an increased activation of primary motor and supplementary motor cortices (SMA). Furthermore, the ipsilateral motor cortex showed a markedly increased activation. When the individual amount of motor impairment was introduced as regressor in the fMRI analysis, we were able to demonstrate that activations of the posterior parietal cortices (i.e. areas within the intraparietal sulcus), SMA and primary motor cortex were correlated with the extent of motor dysfunction (Fig.). Substantial adaptive changes within the central nervous system may contribute to motor symptoms in CRPS.



Inflammation. 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.

Do the genes predispose for CRPS? Gene technology has been used to characterise the genetic pattern of patients at risk to develop CRPS. The frequency of HLA-DQ1 was increased compared with control frequencies. Furthermore, a locus centromeric in HLA-class I, was associated with spontaneous development of CRPS, suggesting an interaction between trauma severity and genetic factors in CRPS susceptibility.

References

1. Maihöfner C, Baron R et al. The motor cortex shows adaptive changes in complex regional pain syndrome. Brain 2007. In press.
2. Schattschneider J et al. Endothelial dysfunction in cold type complex regional pain syndrome. Neurology 2006; 67: 673-5.

Temporomandibular Joint Disorders - Contribution of Biopsychosocial and Genetic Factors

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Temporomandibular disorders (TMJD) are a heterogeneous family of musculoskeletal disorders that represent the most common orofacial pain conditions[1,2]. Although there are several forms of TMJD, the most common and debilitating forms are associated with persistent pain in the region of the temporomandibular joint, the periauricular region, and muscles of the head and neck[1,2]. Worldwide epidemiological studies report the prevalence of TMD to range from 5 to 50% with most studies reporting a prevalence rate of approximately 10%[2]. The annual cost to society is also considerable, since it has been estimated that TMD result in 17,800,000 lost work days per year for every 100,000,000 working adults in the United States[3]. TMD is associated with several co-morbid signs and symptoms - including, but not limited to, fatigue, sleep abnormalities, anxiety and irritable bowel syndrome.

At present, we have a relatively poor understanding of the pathophysiological mechanisms that mediate TMJD and related conditions[4]. However, several studies have provided outcomes that demonstrate that both TMJD is associated with a state of pain amplification and psychological distress[5-7]. In an attempt to further our understanding of the etiological factors that mediate the development of TMJD, we conducted a prospective study that was designed to identify biopsychosocial and genetic determinants that contribute to TMD onset[8]. Two hundred and forty four female volunteers aged 18-34 who were diagnosed free of TMD and other persistent pain conditions were recruited. At baseline, they completed psychological questionnaires and experimental sensory tests that evaluated responsiveness to noxious mechanical, thermal, and ischemic stimuli. Peripheral blood samples were obtained and candidate gene association studies were conducted that examined the association of genetic polymorphisms on the core endophenotypes associated with TMJD[8-10]. Findings that support view that genetic and environmental factors, which influence pain sensitivity and psychological function, contribute to the risk of TMD onset will be presented. (Supported by DE07509; AR/AI-44564; AR-30701;AR/AI-44030; NS45685).

References

1. Dworkin SF et al. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. Journal of Craniomandibular Disorders Facial Pain and Oral Pain 6, 302-355 (1992).
2. Okeson JP et al. Orofacial Pain. Okeson,J.P. (ed.), pp. 113-184 (Quintessence, Chicago,1996).
3. Dworkin SF & LeResche L. Temporomandibular disorder pain: Epidemiologic data. APS Bulletin April/May, 12 (1993).
4. Diatchenko L, Nackley AG, Slade GD, Fillingim RB & Maixner W. Idiopathic pain disorders--pathways of vulnerability. Pain 2006. Aug. 226-230 (123).
5. Maixner W, Fillingim R, Sigurdsson A, Kincaid S & Silva S. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: evidence for altered temporal summation of pain. Pain 76, 71-81 (1998).
6. Maixner W, Fillingim R, Booker D & Sigurdsson A. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. Pain 63, 341-351 (1995).
7. Maixner W, Sigurdsson A, Fillingim R, Lundeen T & Booker D. Orofacial Pain and Temporo-mandibular Disorders. Fricton,J.R. & Dubner,R.B. (eds.), pp. 85-102 (Raven Press, Ltd., New York, 1995).
8. Diatchenko L et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mo. Genet 14, 135-143 (2005).
9. Diatchenko L et al. Three major haplotypes of the beta2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. Am J Med Genet. B Neuropsychiatr. Genet. 2006. Jul. 5 449-462 (141).
10. Nackley AG et al. Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. Science 2006. Dec. 22. 1930-1933 (314).

Rethinking the Relationship of Herpes Zoster to Post-herpetic Neuralgia

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Postherpetic neuralgia (PHN) has been thought of as a uniform disorder caused by deafferentation during herpes zoster (HZ). PHN is characterized by chronic deep, burning pain and allodynia. Noordenbos (1959) suggested a relationship between pain, sensory function and pathology. Rowbotham et al. (1998) suggested that neural dysfunction spans a spectrum from a preserved, but possibly sensitized, primary afferent nociceptor system to severe deafferentation. Age is a predictor of PHN. Antivirals and vaccination reduce the incidence of PHN.

Using selective nociceptor stimulation by capsaicin, we have shown that allodynia in some PHN patients resembles secondary hyperalgesia maintained by peripheral input to a sensitized CNS (Petersen et al. 2000). Skin excision in one patient with chronic PHN relieved pain initially, but pain eventually returned to presurgical levels (Petersen et al. 2002). Multiple biopsies across the excised skin suggested that PHN skin can be a mosaic of reduced and preserved innervation, suggesting that testing a single site may be insufficient. To further characterize the relationship between HZ and PHN, we followed 94 subjects for 6-months after HZ-onset on measures of pain, psychosocial profile, sensory function, and response to capsaicin. While lingering pain was common, severe pain was rare (1%). High initial pain predicted PHN, psychological factors, loss of sensory function, or cutaneous innervation did not. Recovery of sensory function and cutaneous innervation was limited during the 6 months, but the enhanced response to capsaicin application recovered along with most symptoms.

Patients who met criteria for 'any pain' at 6-months were different from the patient population enrolled in clinical/mechanistic trials. Clarifying the definition with the addition of 'clinically meaningful' PHN (≥30/100) is a precondition for mechanism-oriented research on how severe chronic PHN evolves (Thyregod et al. 2007). Comparing 'cases' with chronic severe PHN to 'controls' who recovered without pain after HZ, we demonstrated that patients with chronic severe PHN were deafferented when examined with QST and skin biopsies, but retained enhanced response to capsaicin. The pattern of cutaneous deafferentation suggests selectivity among the neuronal populations, which could more narrowly focus the studies of neuroprotection and therapeutic targets. It remains to be determined who should get protective therapies beyond antiviral and vaccine, since so few develop chronic severe PHN.

References:

1. Noordenbos, W. Pain. Elsevier, Amsterdam, 1959, pp.68-80.
2. Rowbotham MC, Petersen KL, Fields HF. Is post-herpetic neuralgia more than one disorder? Pain Forum 1998; 7: 231-237.
3. Petersen KL, Fields HL, Brennum J, Sandroni P, Rowbotham MC. Capsaicin evoked pain and allodynia in post-herpetic neuralgia. Pain 2000; 88: 125-133.
4. Petersen KL, Rice F, Suess F, Berro M, Rowbotham MC. Relief of post-herpetic neuralgia by surgical removal of painful skin. Pain 2002; 98: 119-126.
5. Thyregod HG, Rowbotham MC, Peters M, Possehn J, Berro M, Petersen KL. Natural history of pain following herpes zoster. Pain; 2007; 128 (1-2): 148-156.

FMRI as a Biomarker for Pain and its Underlying Mechanisms

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Until recently it has been difficult to obtain reliable objective information from normal subjects and patients regarding their subjective pain experience. Relating specific neurophysiologic markers to perceptual changes induced by sensitisation, behavioural or pharmacological mechanisms and identifying their site of action within the CNS has been a major goal for scientists, clinicians and the pharmaceutical industry. This information provides a powerful means of understanding not only the central mechanisms contributing to the chronicity of pain states but also potential diagnostic information (1). Identifying non-invasively where plasticity, sensitisation and other amplification processes might occur along the pain neuraxis for an *individual* and relating this to their specific pain experience or measure of pain relief has considerable value. With the advent of functional neuroimaging methods, such as functional magnetic resonance imaging (FMRI), positron emission tomography (PET) and electroencephalography (EEG) this has been made feasible. Robust and reproducible activation in response to nociceptive stimulation within the human brain and spinal cord has been shown (Figure 1). This activation can be related to what the subject describes and issues such as how anxiety, depression, attention, distraction and anticipation alter pain perception can be better understood at a neuroanatomical level. This provides not only potential diagnostic information but also targets for intervention. We have performed several experiments that have specifically isolated areas of cortex and brainstem that are central to the processes of expecting pain, being anxious about pain and altering your attention to pain (2). Furthermore, the central relevance of descending brainstem modulatory pathways in the generation and maintenance of chronic pain states in clinical conditions is becoming increasingly accepted. Advances in our ability to image this challenging area are occurring (3) and many examples of dysfunction in this system found across various chronic pain conditions (4). More recently, pharmacological functional magnetic resonance imaging (phMRI) has been developed and applied to the field of pain research. Again, many advances have been made that illustrate the neural correlates of analgesia in the human brain (5). Recent advances in our ability to image functional activation in the human spinal cord show considerable promise and provide a novel and exciting area of further investigation. In summary, functional imaging methods provide a powerful means to directly examine pain mechanisms in human subjects and patients at a systems level, providing potential diagnostic information as well as identifying targets for therapeutic intervention.

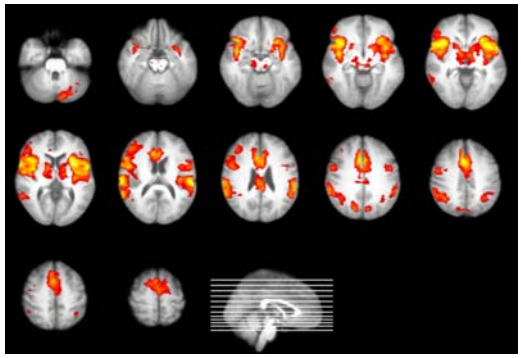

Figure 1. Representation of Pain in the Human Brain in response to a Thermal Nociceptive Stimulus. Axial slices showing activity within: insular, anterior cingulate, somatosensory and frontal cortices, as well as thalamus, basal ganglia and brainstem.

References

1. Schweinhardt P, Lee M, Tracey I.Imaging pain in patients: is it meaningful? Curr Opin Neurol 2006; 19: 392-400. Review.
2. Ploghaus A et al. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci 2001; 21: 9896-903.
3. Dunckley P, Wise RG, Fairhurst M, Hobden P, Aziz Q, Chang L, Tracey I. A comparison of visceral and somatic pain processing in the human brainstem using FMRI. Journal of Neuroscience 2005; 25: 7333-41.
4. Mayer EA, Berman S, Suyenobu B, Labus J, Mandelkern MA, Naliboff BD, Chang L. Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis. Pain 2005; 115: 398-409.
5. Iannetti GD, Zambreanu L, Wise RG, Buchanan TJ, Huggins JP, Smart TS, Vennart W, Tracey I. Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans. Proc Natl Acad Sci U S A 2005; 102: 18195-200.

Brain imaging in acute and chronic pain states
Receptor studies

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During the last decades, functional imaging studies have fostered our knowledge about cerebral pain processing in humans. Among these imaging methods, PET not only allows *in vivo* measurements of brain metabolism (FDG-PET) and blood flow changes ($H_2{}^{15}O$-PET), but also the 3D determination of receptor distributions in fully conscious humans. Nearly every neurotransmitter system and neurochemical pathway can thereby be studied. With ligand-PET, it is not only possible to display neuroanatomical receptor distributions, but also to evidence changes in receptor occupancy due to pharmacological/cognitive or other challenges and to investigate pathological states such as chronic pain. Lively interest has been focussing on possible opioidergic mechanism of pain transmission and modulation. Today, reliable knowledge about in-vivo distribution of opioid receptors in healthy human subjects is available from PET studies of opioidergic neurotransmission (figure 1). Gender dependent differences in receptor distribution and ligand metabolism have been evidenced (1). Moreover, an increasing number of studies are reporting alterations of receptor distribution patterns in painful disease states such as rheumatoid arthritis, trigeminal neuralgia, central post stroke pain and cluster headache (2). Ongoing opioid use in drug abusers also leads to alterations of the cerebral opioid receptor distribution and various acute painful challenges (e.g. heat pain, topical capsaicin) have been shown to induce measurable changes in receptor availability in multiple brain areas, e.g. thalamus, insula, amygdala, prefrontal and perigenual anterior cingulate cortex (ACC) (3). The ACC has been identified as one brain region of major impact in opioidergic pain modulation. Thereby, the ACC apparently executes cortical top-down control on brainstem structures in (exogenous) pharmacological opioid analgesia. In addition, accumulating evidence suggests that also non-pharmacological treatment approaches utilize similar endogenous opioid dependent pathways to exert pain modulation. Moreover, it was recently shown that opioids modulate neurotransmission in the nigrostriatal dopaminergic pathway as pharmacologically relevant doses of the mu-agonist Alfentanil increased the binding potential of the dopamine D2 radioligands in striatal and extrastriatal cortical brain areas (4). In turn, dopaminergic changes such as increases or decreases in COMT enzyme activity affect opioidergic neurotransmission (5).

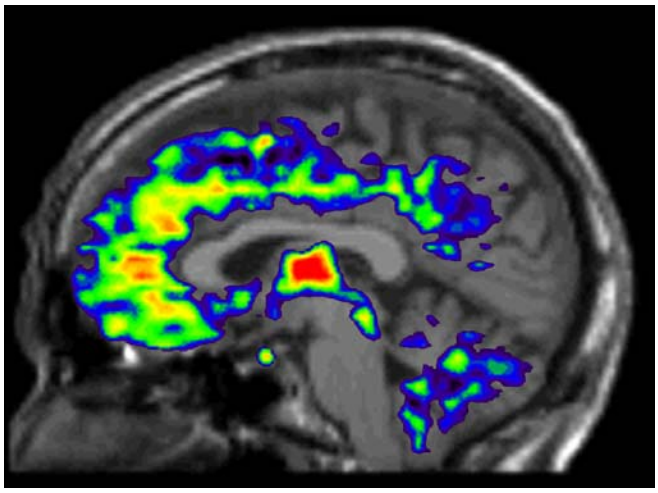

Figure 1. The figure illustrates the binding pattern of the unselective opioidergic antagonist [11C]diprenorphine in the human brain

References

1. Henriksen G, Spilker ME, Sprenger T, Hauser A, Platzer S, Boecker H, Toelle TR, Schwaiger M, Wester HJ. Gender dependent rate of metabolism of the opioid receptor–PET ligand [18F] fluoroethyl-diprenorphine. Nuklear-medizin 2006; 45: 197-200.
2. Willoch F, Schindler F, Wester HJ, Empl M, Straube A, Schwaiger M, Conrad B, Tolle TR. Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: a [11C]diprenorphine PET study. Pain 2004; 108: 213-20.
3. Sprenger T, Valet M, Boecker H, Henriksen G, Spilker ME, Willoch F, Wagner K, Wester HJ, Tölle TR. Opioidergic activation in the medial pain system after heat pain. Pain 2006; 122: 63-67.
4. Hagelberg N, Jaaskelainen SK, Martikainen IK, Mansikka H, Forssell H, Scheinin H, Hietala J, Pertovaara A. Striatal dopamine D2 receptors in modulation of pain in humans: a review. Eur J Pharmacol. 2004; 500: 187-92.
5. Zubieta JK, Heitzeg MM, Smith YR et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 2003; 299: 1240-3.

Persistent postsurgical pain – the role of preventive analgesia, intraoperative nerve handling and neurectomy

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Post-injury neuroplastic changes leading to both peripheral and central sensitisation is well established from experimental and clinical studies. Consequently, it has been hypothesized that reduction of these changes by pre-injury analgesia may reduce the intensity and duration of acute pain and thereby the development of persistent pain. Unfortunately, the vast literature from randomised trials is negative or with major design problems to document that timing of analgesia is important to modify post-injury pain. However, the hypothesis may still be valid based upon the experimental data and future clinical studies should include a combination of different analgesic approaches (afferent blockade / peripherally and centrally acting drugs) as well as to have a sufficient duration until the peripheral stimulus has been reduced to a certain minimal intensity.

More importantly, intraoperative nerve-sparing techniques (minimal invasive surgery/ detailed nerve dissection) may be important and require further analyses. Prophylactic nerve transection has not been proven effective (or detrimental) in randomised studies by cutting one of the three nerves in inguinal herniorrhaphy. Well-designed intraoperative prophylactic nerve transection studies are required in high-risk patients for developing persistent pain (thoracotomy, etc.). Also, the role of intraoperative handling of nerves (cutting vs. ligation) has been neglected and requires evaluation. The data on neurectomy after development of a persistent postsurgical pain state have been reported to be positive, but due to major design problems in these trials no conclusions can be made.

In summary, a surgical focus on intraoperative nerve handling may be the most effective method to reduce a persistent pain state.

References

1. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology 2002; 96: 725-741.
2. Aasvang E, Kehlet H. Surgical management of chronic pain after inguinal hernia repair. Br J Surg 2005; 92: 795-801.
3. Rasmussen S, Kehlet H. Nerve handling during amputation - a nationwide questionnaire study. Acta Anaesthesiol Scand 2007; (in press).
4. Wijsmuller AR, van Veen RN, Bosch JL, Lange JF, Kleinrensink GJ, Jeekel J, Lange JF. Nerve management during open hernia repair. Br J Surg 2007; 94: 17-22.

Currently available drugs

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A number of drugs have been tested in chronic peripheral neuropathic pain (1). The trials have mainly been performed in painful diabetic neuropathy and postherpetic neuralgia, but it is anticipated that drugs found to work in these conditions will also relieve pain in other peripheral neuropathic pain conditions, e.g. post-surgical neuropathic pain (2). Based on the current evidence, a treatment algorithm as shown in Figure 1 can be suggested.

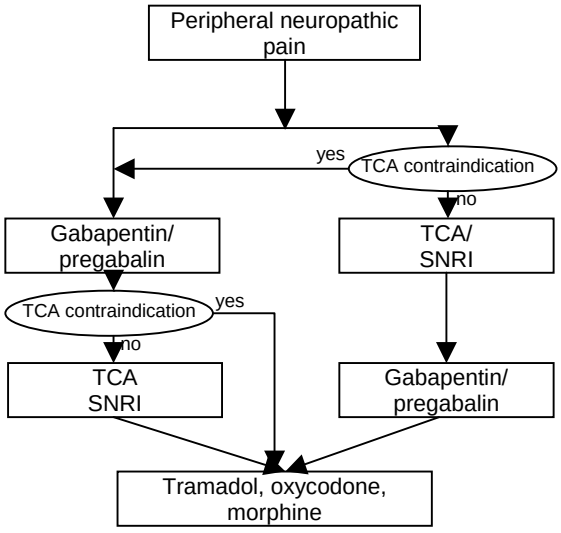

Figure 1. Treatment algorithm for peripheral neuropathic pain (modified from Finnerup et al. 2005).

It may be interesting to take a closer look at some of the drugs which have been tested but did not find the way to the treatment algorithm. Drugs such as oxcarbazepine, lamotrigine, topiramate, valprate and memantine were studied since their pharmacological action fitted with the mechanisms of neuropathic pain. Trials on these drugs have shown no effect at all, low efficacy or conflicting results. In a league table (Table 1) based on NNT for more than 50% pain relief, they are ranked markedly lower than TCA and somewhat lower than pregabalin and SNRI. The difference in efficacy as measured by NNT between TCA and the other compounds may in part be explained by different trial methodology of the studies on which the NNT calculations were based. Another explanation for the apparent lower efficacy could be that the specific pain mechanism which each drug targets may only be present in a small proportion of the patients in the trials. This would tend to dilute the efficacy, and thereby a high efficacy in a specific subgroup can be overlooked. Some of the drugs with high NNT should probably not be completely discharged (3).

Table 1. League table in painful polyneuropathy

Drug	NNT ≥50% (95% CI)	n
TCA	2.1 (1.9-2.6)	249
Oxycodone	2.6 (1.9-4.1)	36
Tramadol	3.5 (2.4-6.4)	161
Pregabalin	4.7 (3.8-6.3)	1160
SNRI	5.1 (3.9-7.5)	911
Oxcarbazepine	6.0 (3.3-41)	146
Memantine	6.6 (3.6-36.7)	242
SSRI	6.8 (3.4-441)	81
Topiramate	7.4 (4.3-28.5)	323

Drugs specifically tested in post-surgical neuropathic pain are sparse. In post-mastectomy pain syndrome, TCA showed some effect whereas SNRI had no effect. Trials showed that mexiletine had a marked effect and capsaicin some effect in pain after peripheral nerve injury which is in contrast to data from some other peripheral neuropathic pain conditions. The current first line treatments for peripheral neuropathic pain deserve to be systematically tested in post-surgical neuropathic pain. Furthermore, some of the drugs with low efficacy in postherpetic neuralgia and/or painful diabetic polyneuropathy should also be considered in trials of post-surgical neuropathic pain, since this may be a case for the more selectively acting drugs.

Drug treatment of peripheral neuropathic pain in general will probably not be improved by introduction of a single new compound with a selective pharmacological action. It is more likely that use of clever drug combinations and targeted drug treatment will benefit the patients.

References

1. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH.Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118: 289-305.
2. Hansson PT, Dickenson AH. Pharmacological treatment of peripheral neuropathic pain conditions based on shared commonalities despite multiple etiologies. Pain 2005; 113: 251-254 .
3. Sindrup SH, Jensen TS. Are sodium channel blockers useless in peripheral neuropathic pain? Pain 2007; 128: 6-7.

Future Candidates

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Symptom control or disease modification that is the question?

The success in dissecting out the mechanisms that contribute to the establishment and maintenance of chronic neuropathic pain has led to the identification of multiple potential targets for novel analgesics and disease-modifying strategies. These include ion channels, G-protein coupled receptors, membrane tyrosine kinase receptors, and enzymes localized in primary sensory neurons, central neurons and glia. The real problem now is an embarrassment of potential riches, so many targets, how to prioritize?

We also need to recognize that preclinical models are not surrogates of neuropathic pain in patients and that validation studies in rodents do not guarantee success in the clinic.

We must therefore, find new ways of choosing, validating and testing new putative analgesics.

Psychological interventions for postoperative and neuropathic pain

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Psychological interventions can be implemented in three phases: (a) to prevent postoperative pain and later neuropathic pain in the preoperative phase; (b) to ameliorate postoperative pain and thus prevent chronicity; (c) to treat chronic neuropathic pain.

1. Prevention of pain in the preoperative phase

A number of psychological variables such as depression, anxiety, catastrophizing, enhanced pain memories, and a lack of coping skills have been identified as important predictors of neuropathic pain, for example, after the amputation of a limb. Thus, cognitive-behavioral interventions that enhance predictability and controllability of pain are important and have been shown to be effective whereas more passive interventions such as relaxation are not.

2. Treatment of postoperative pain and prevention of chronicity

In the postoperative phase the focus should be on the reduction of pain and pain-related distress, which is best achieved by a cognitive-behavioral approach. Interventions designed to prevent maladaptive brain changes related to nerve injury should also be considered but must be viewed as experimental. These include, for example, imagery, mirror treatment and stimulation training.

3. Treatment of chronic neuropathic pain

Once pain has become chronic psychological treatments should focus on the extinction of pain behaviors and pain-related memory traces as well as maladaptive brain changes. Behavioral extinction training seems to be more effective than cognitive-behavioral treatment in this phase, but sensory discrimination training and mirror training or imagery-based methods may also be effective. The combination of pharmacological enhancers of extinction such as d-cycloserine, cannbinoids, or pregabalin with behavioral extinction training may be especially effective.

An active approach to treatment with a focus on establishing pain-incompatible behaviors and inputs to the brain is warranted.

References

1. Flor, H., & Diers, M. (2007). Limitations of pharmacotherapy. In C. Stein (Ed.), Handbook of experimental pharmacology, Vol. 177: Analgesia (pp. 415-427). Berlin: Springer.
2. Flor, H., Nikolajsen, L., & Jensen, T. S. (2006). Phantom limb pain - a case of maladaptive central nervous system plasticity? Nature Reviews Neuroscience, 7, 873-881.
3. Flor, H., & Turk, D. C. (2006). Cognitive and learning aspects. In S. McMahon, & M. Koltzenburg, (Eds.), Wall & Melzack's textbook of *pain* (5th edition, pp. 241-258). London: Elsevier.
4. Flor, H., Denke, C., Schäfer M., & Grüsser, S. (2001). Effects of sensory discrimination training on cortical reorganization and phantom limb pain. Lancet, 357, 1763-1764.
5. Flor, H. (2002). Phantom limb pain: characteristics, causes and treatment. Lancet Neurology, 3,182-189.
6. Flor, H., & Turk, D. C. (in press). A biobehavioral perspective of chronic pain and its management. Washington, DC: APA Press.

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