The treatment of pain: remaining challenges and future opportunities

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There clearly has been an explosion of knowledge at the preclinical level of the transmission of pain, the plasticity of sensory systems following inflammation and injury, and the unique pharmacologies which apply to analgesia to unique settings of pain. Similarly, our understanding of the organization of pain related information in the cortex and subcortical structures and its plasticity is rapidly evolving through noninvasive imaging methods. There remain, however, significant obstacles to application of new and old knowledge regarding the neurobiology and pharmacology of pain, both within academic institutions, extramural funding agencies, and pharmaceutical industry. My purpose is to summarize some of these obstacles and suggest approaches which could be implemented to move us forward.

The unmet clinical need

The concept of the unmet clinical need most clearly applies to 'orphan' diseases which occur in a small number of patients and for which market forces discourage drug development. One could describe certain pain populations in these terms, and at least one drug (epidural clonidine) was developed under protection of the Orphan Products Act of the Food and Drug Administration for the treatment of an orphan disease (intractable cancer pain despite side effect limiting therapy with spinal morphine). Definition of such an unmet clinical need requires clear description of unique populations with specific pain etiologies or responses (or lack thereof) to traditional analgesics.

A related, but alternate concept of the unmet clinical need is a disease for which there is no effective therapy. Since neuropathic pain is poorly treated by traditional analgesics, at least in doses which fail to induce side effects, this syndrome is often described as an unmet clinical need. Since the number of patients with at least a component of neuropathic pain (many patients with low back pain, for example), is considerable, and since the disease is chronic requiring long-term therapy, there is considerable industry interest in

developing drugs for this indication. Since these patients suffer from pain for long periods of time, clinical relevance of the study of nerve injury-associated pain is high and obvious to extramural funding agencies, and academic pain research and the pain literature are dominated by study of the neurologic plasticity and pharmacology which underlie this type of pain.

A less obvious example of an unmet clinical need is a common, mild to moderate pain syndrome which is usually treated with simple methods and few side effects. Daily aches and pains, occasional mild headaches, and musculoskeletal sprains responsive to NSAIDS exemplify this type of population. The tremendous success of the COX-2 selective inhibitors, although partially reflecting successful marketing and irrational choices by prescribers and consumers, probably also indicates that there is an unmet clinical need in this group. By reducing the incidence of common, bothersome, but not dangerous side effects and by reducing the incidence of rare, but life-threatening side effects, these agents enlarged a drug market by a considerable amount. Their success has led to a large effort by the pharmaceutical industry to develop other selective agents of this type and by academia to investigate the mechanisms by which COX is activated or its expression enhanced at different sites in the periphery or the central nervous system in different types of acute or chronic pain.

This last concept of the unmet clinical need applies similarly to common pain syndromes treated by anesthesiologists, especially pain after surgery and labour pain. It is often argued that postoperative pain is brief, is easily treated with current drugs, does not result in significant long term morbidity, and that barriers to effective treatment lie in education, not understanding of mechanisms or the need for other drugs. If this were the case, one might expect some improvement in postoperative pain control with time, education, and recognition of the simple methods and drugs for its treatment. Yet hospital surveys demonstrate a high incidence of severe pain after surgery, short- and long-

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term morbidity tied to inadequate pain treatment, and little change over the last three decades. A common barrier to effective treatment of postoperative pain in the past reflected organizational and conceptual difficulties – over concern by physicians, nurses, and patients of the risk of addiction from the temporary use of opioids, prescription of opioid doses which were too low, too infrequent, and given at the discretion of the nurse, and lengthy delays from the time of patient request to receipt of analgesic treatment. These have since been removed by common application of patient controlled analgesia (PCA), yet studies continue to show poor pain treatment with PCA, associated with a high incidence of myocardial ischemia in high-risk patients. Patients restrict their use of PCA opioids primarily due to side effects from these drugs. Clearly, there is a need for better drugs to treat postoperative pain.

Similar arguments have been made regarding labour pain. Historically, women were not allowed pain relief during labour for religious reasoning ('in pain shall you give birth'). Delivery can be hastened by severe pain in some patients, as they may push more vigorously because of the severe pain. It is perhaps for this reason that many obstetricians and labour nurses prefer that their patients not receive pain relief during labour. Systemic opioids, in small doses which do not affect the fetal heart rate pattern, provide little or no analgesia during labour. Pain relief can be rapidly achieved by intrathecal or epidural injection of local anesthetics with or without opioids. Although this therapy is effective, it is invasive, costly, associated with both short- and long-term morbidity and mortality, not universally available, and not desired by most women. Medico-legal concerns inhibit drug development by industry in this area, which remains, in this author's opinion, an unmet clinical need.

Because of the perceptions described above and the focus on nerve injury associated plasticity and pain, little is known regarding the neurophysiology or pharmacology of either postoperative or labour pain. Dr. Brennan, an anesthesiologist at the University of Iowa, has pioneered the study of postoperative pain, using a simple paw incision model in the rat. His initial studies indicate a large discrepancy between the pharmacology of inhibition of postoperative pain (sensitivity to spinal AMPA/kainite antagonists and to opioids) and that of nerve injury associated pain (sensitivity to spinal NMDA antagonists and α_2 -adren-ergic agonists). There is no preclinical model of labour pain. In our initial studies with a novel model of uterine cervical distension nociception, we have observed similar responses to those in other viscera – hemody-

namic and abdominal muscular contraction reflexes which respond in a stimulus dependent manner to distension at similar distension intensities as those needed to induce afferent activity, and inhibition of responses by peripheral kappa, but not mu-opioid receptor agonists.

Challenges to improved pain therapy

There are two fundamental obstacles in the progress of preclinical understanding to improved treatment of pain. First is the near complete uncertainty of the predictive value of preclinical models for human treatment. This reflects several factors. Preclinical models typically rely on threshold events – latency to withdrawal of an appendage from a noxious thermal stimulus, or pressure or force of touch which results in limb withdrawal. The meaning of such threshold events to clinical pain is far from certain. For example, we have observed with at least two classes of analgesics in humans that these agents have only modest effects on pain threshold detection, but yield much larger reductions in perceived pain to supra-threshold events. The concept of hypersensitivity as a mechanism of pain is now well entrenched, yet, at least in the acute postoperative condition, some clinical trials demonstrate that agents which abolish hypersensitivity phenomena (mechanical allodynia) have minimal or no effect on perceived pain and the need for opioid analgesics.

Others have stated that threshold testing, such as with the tail flick, has been extremely predictive of clinical efficacy of analgesics, and that one can calculate very precisely a new drug's potency in man based on its relative potency in such assays. The only basis for this statement is the comparison of drugs within a single class, which is that of the opioids. In other words, the clinical potency of a new opioid can be predicted reasonably well from its potency in these preclinical models. Predictive value for drug potency across classes is virtually unknown, and the small number of potent non-opioid analgesics which have come to the human do not support the contention that comparison of non-opioid drug potency in the preclinical model to a standard opioid helps in predicting clinical potency.

A major challenge to pain research lies in development of more appropriate behavioural models, just as much as in the sophistication of genetic or focal neurochemical manipulations. For example, cyclooxygenase inhibitors are known to produce analgesia in humans to nearly all types of acute and chronic pain, although with varying efficacy across pain types. Yet aspirin is clearly effective in a rodent model of escape avoidance following acute peripheral inflammation at doses much lower

than those necessary to affect withdrawal to exogenous mechanical stimulation. Clearly, more complex models than withdrawal threshold are needed.

There is little interest by either the pharmaceutical industry or the large extramural funding agencies to build a matrix of animal testing results to human clinical pain conditions. Such a matrix across drug classes would be extremely costly, as it would require adequate preclinical toxicity testing to bring multiple drug classes into man for testing, and many might fail. However, without just such a matrix, there is a chronic uncertainty as to the reliability and predictive value of animal models. The uncertainty is even greater considering the more complex chronic inflammation, nerve injury, or metabolic neuropathy models recently developed.

Another barrier to translational application of preclinical research is the uncertainty of experimental human pain to clinical situations. Given the difficulties in diagnosis of etiology or classification of chronic pain (see below), there is considerable variability in drug response in clinical trials, and effective drugs for certain types of chronic pain could be missed by dilution in a larger, mixed population of a variety of subsets. Several acute human models of nociception have been described, using mechanical, electrical, or thermal stimulation. Acute inflammation or hypersensitivity-inducing manipulations (ultraviolet or thermal burn, formalin injection, capsaicin injection, continuous electrical or thermal stimulation) have been examined in humans and their mechanisms probed in animals. These have the advantages of being highly uniform and stable over reasonable periods of time for drug screening. However, as in the case of the preclinical models, there has been practically no effort to generate a matrix to determine the predictive value of these models to clinical pain states.

A third major barrier to improved pain treatment is the imprecise diagnosis of pain etiology or mechanism, especially prominent in patients with chronic pain. For example, postherpetic neuropathy is associated with hypersensitivity and chronic pain, but careful psychophysical testing suggests that at least two subgroups of patients with this condition exist – those with a peripheral nociceptor hyperexcitability, and those with central sensitization. These subgroups respond very differently to adjunctive pain medications, such as antidepressants or anti-epileptic agents. Similarly, patients with ‘sympathetically maintained pain’ may be divided according to pharmacologic testing into those with response to acute adrenoceptor antagonism and those without. The pain community is just now beginning to examine and disseminate

large population descriptions of psychophysical abnormalities in patients with various chronic pain diagnoses. More precise description of sensory abnormalities associated with pain may allow more precise definition of appropriate animal models, and allow for more appropriate clinical examination, often with smaller group size.

The role of basic and clinical research

Important findings of the last two decades of pain research – descending inhibitory and facilitatory modulation of sensory transmission, central and peripheral sensitization, and potent neural-immune interactions, may have important implications for improved pain therapy. Much of preclinical neurophysiologic studies focus on understanding the mechanisms for these plastic events and possible common pathways which could be manipulated. Although inhibition of facilitation could be effective, the multiple and redundant excitatory mechanisms involved in complex pain phenomena make this approach unlikely to succeed. For that reason, we and others have focused on common inhibitory mechanisms, many of which may also be plastic. For example, α_2 -adrenergic agonists are capable of producing analgesia to acute nociceptive events, such as surgery, but become more potent in patients with neuropathic pain. Our recent studies in animals with peripheral nerve injury suggest that this increased potency of α_2 -adrenergic agonists reflects plasticity of descending noradrenergic innervation in the spinal cord, generation of new α_2 -adrenoceptors in the spinal cord, and new circuits activated by these agents. As noted above, there is a heavy emphasis on neurophysiologic understanding of plasticity associated with chronic inflammation and nerve injury, yet common, acute and severe pain syndromes for which treatment is inadequate (labour, postoperative pain), are largely ignored.

Recent clinical research has provided potentially important new models of acute nociception and hypersensitivity, and the pharmacology of inhibition of pain in these models is just now being systematically examined. More sophisticated and widespread psychophysical testing in normals and those with clinical diagnoses of chronic pain will likely yield important new approaches to both preclinical model development and rationale for testing new drugs.