Pain: A View From the Spinal Cord

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Normal Pain Transduction

Pain is a sensori-emotional experience which results from stimulation of nerve fibers which report from structures interacting with our external environment or which report from internal, visceral structures. In the former case, our mind localizes the source of the pain very precisely and conscious and subconscious systems cause us to examine the painful area of the body, protect it, and stop the painful stimulus. As wonderfully reviewed by Julius and Basbaum (1), scientists have identified the proteins embedded in nerve endings which monitor the local environment and cause nerves to fire in a manner which is perceived as painful. Thus, there are a series of related proteins which respond to temperature, some in the noxious cold range, some at body temperature, and some in the noxious heat range, by opening a channel, allowing cations, especially Calcium, to enter, and depolarizing the nerve terminal, leading to generation of an action potential. Some of these same proteins also respond to chemicals which are perceived by the mind as hot (capsaicin, wasabe) or cold (menthol), and it was actually from this property of binding specifically to these chemicals that originally allowed these proteins to be recognized and identified by scientists. In addition to these temperature- and chemical-sensitive proteins, other proteins open their cation channel when exposed to hydrogen ions, are termed Acid Sensing Ion Channels (ASICs), and transduce the pain related to local falls in pH, such as would occur during ischemia of skeletal or myocardial muscle, during inflammation of tissue, or during exposure to environmental acids. Finally, there are a series of proteins, including some ASICs, which open their cation channel when the membrane of the nerve terminal is deformed by pressure. Some are exquisitely sensitive to small deformations of the membrane, and transduce the sensation of light touch, whereas others only respond to more marked deformations of the membrane, and transduce the sensation of noxious pressure or pinch. In addition to these specialized proteins, pain is also selectively elicited in the normal condition by activation of certain types of nerve fibers – the unmyelinated, small diameter C fibers and the sparsely myelinated, small diameter Aδ fibers. Stimulation of large myelinated fibers, the Aβ fibers, normally is not perceived as painful.

Postoperative Pain

Pain related to tissue inflammation has been extensively studied in animals and humans for several decades, and, until recently, it was tacitly assumed that postoperative pain was essentially the pain of inflammation plus, perhaps, some direct pain from cutting nerves. About 10 years ago, Tim Brennan, an anesthesiologist at the University of Iowa, described a simple model of surgery, incision of the rat paw, in order to test whether this was true (2). He subsequently has demonstrated important differences between pain after surgery and that from inflammation. For example, there is sensitization of nerve endings, leading to spontaneous firing of nerve fibers, which constantly drives a pain system in the spinal cord after surgery, whereas this is not the case with simple inflammation. More important from a clinical perspective, some drugs are effective to treat either surgery or inflammation, such as the opioids, whereas others are unique to the setting. At the spinal cord, for example, glutamate receptors of the n-methyl-d-aspartate (NMDA) subtype are essential to driving pain after inflammation, but are not involved in pain after surgery. Other drugs may be active in both settings, but for different reasons. For example, cyclo-oxygenase (COX) inhibitors are effective analgesics in both inflammatory and surgical conditions. Whereas some of this analgesia occurs by actions in the periphery in areas of inflammation and immune response, there is also a central site of action for COX inhibitors (3). Recent work by our laboratory suggests that, at the spinal cord level, the isoenzyme of COX activated by inflammation (COX-2) is different from that activated by surgery (COX-1). Although we currently do not target the spinal cord for COX inhibition, initial clinical trials with the COX-1 preferring inhibitor, ketorolac, for intrathecal injection, suggest that we may be able to test the relevance of these observations in animals to humans after surgery.

Opioids are commonly administered to treat surgical pain, and some have suggested that pre-emptive administration of large doses of opioids during surgery may prevent some of the amplification or sensitization of pain processing which contributes to postoperative pain. Certainly, opioids should be administered for the treatment of moderate to severe postoperative pain. However, whether large doses of opioids help or hurt the situation is less clear, since opioids themselves stimulate a sensitizing system and can result in prolonged increases rather than decreases in pain (4).

Transition of acute to chronic pain: Can chronic pain be prevented?

Chronic pain often begins as acute pain, and as much as 1/3 of the population seen in chronic pain clinics date the onset of their pain to the trauma and acute pain of surgery (5). Risk factors for chronic pain following surgery include the type of surgery itself (e.g., major limb amputation resulting in a greater risk than abdominal hysterectomy), anxiety state, degree of somatization, and response to experimental pain (6). Additionally, severe postoperative pain carries an increased risk of chronic pain after surgery, and its is tempting to speculate that better

treatment of pain in these individuals would not only benefit them in the peri-operative period, but also for many months or years to come.

There is some experimental evidence to suggest that the spinal cord plays a key role in the transition of acute to chronic pain. For example, surgery in rats results in activation of spinal microglia and stimulation of cyclooxygenase (COX) enzymes and release of prostaglandins (7). Inhibition of this process by spinally administered COX inhibitor, especially COX-1 inhibitors, at the time of surgery in animals reduces acute hypersensitivity and, more importantly, prevents permanently the development of chronic hypersensitivity (8). We recently introduce intrathecal ketorolac, a COX-1 preferring inhibitor, into clinical trials. Initial results suggest that intrathecal ketorolac produces postoperative analgesia in patients, and we are currently testing whether it also reduces acute hypersensitivity in the perioperative period and reduces the incidence of persistent pain after surgery.

Other studies suggest a relationship between hypersensitivity to mechanical stimuli surrounding the wound after surgery and the risk of chronic pain after surgery. De Kock and colleagues have led this field of investigation, asking whether systemic administration of the NMDA receptor antagonist ketamine (9), or epidural or spinal administration of opioids, local anesthetics, or clonidine (10,11) alters acute perioperative hypersensitivity and chronic pain in patients undergoing colectomy. These studies have resulted in two major conclusions. First, there is a highly significant correlation between the ability of these therapies to reduce hypersensitivity surrounding the wound 48 hr after surgery and their ability to reduce pain 1 year after surgery. Some of these therapies, like low dose ketamine infusion, have minimal impact on acute perioperative pain and morphine use, yet have a large effect on acute hypersensitivity surrounding the wound and on the incidence of chronic pain. This suggests that we should pay attention to hypersensitivity phenomena in addition to pain in the acute perioperative period in studies to prevent chronic pain after surgery. Second, several manipulations to reduce spinal cord activation, including intraoperative neuraxial opioids, clonidine, and local anesthetics dramatically reduce the incidence of chronic pain after surgery. Should these results be further replicated, they would provide a strong rationale for more widespread use of regional anesthesia, at least epidural or spinal anesthesia and analgesia, for surgery.

Changes in the nervous system associated with chronic pain

Alterations in sensory neurotransmission are observed in 4 general sites after peripheral nerve injury, and are these alterations are argued to underlie chronic neuropathic pain. Some investigators believe that nerve injury, whether from physical trauma, invasion of local or metastatic cancer, viral infection, diabetes, or chemotherapy results in fundamental changes that drive changes elsewhere in the central nervous system in states of chronic pain (12). According to this argument, blocking abnormal activity of injured peripheral nerves makes pain and hypersensitivity disappear, and the key to novel and effective analgesia for chronic pain should target these peripheral sites.

Two fundamental changes occur in the periphery after injury. First, there is an increase in excitation state of peripheral nerves. This reflects increased expression and activity of excitatory ion channels and receptors along the nerve and at nerve endings, such as the transient receptor potential ion channel, TRPV-1, which responds to capsaicin, heat, and low pH. The result is depolarization of the resting membrane potential, bringing it closer to the threshold for action potential firing. This in turn could lead to spontaneous firing of single pulses or short bursts, and increased sensitivity to normal stimuli, resulting in allodynia and hyperalgesia. It's important to recognize, however, that these changes will never result in abnormal, repetitive firing, such as occurs in humans at the site of neuroma formation and is thought to underlie spontaneous, ongoing pain. A second process, increased excitability, is thought to underlie this ability to spontaneously fire. This change reflects altered or increased expression of voltage gated ion channels, leading to abnormal pacemaker activity, or oscillations of resting membrane potential causing spontaneous and repetitive firing. Both of these phenomena may be driven, not just from the injury itself, but by the immune response at the site of injury and Wallerian degeneration. As such, recruited immune cells release growth factors, cytokines, and prostaglandins, some of which are taken up by nerves and result in change in their expression of ion channels and receptors and the sensitization processes described above (13).

A second site of neuroplasticity thought to result in chronic pain is the spinal cord. Following chronic inflammation or nerve injury in the periphery, several aspects of the spinal cord view of afferent input change (14). Changes occur both in neurons as well as in glia, in general increasing excitatory mechanisms and decreasing inhibitory mechanisms. Aβ fibers may change anatomic location in the cord, and upregulate synthesis of excitatory neurotransmitters such as CGRP, which normally is only present in nociceptors. Abnormal small and perhaps large diameter fiber input not only leads to spontaneous pain by the normal transmission system, but stimulates a series of changes in the spinal cord which are associated with central sensitization. These processes classically involve NK1 and NMDA receptor activation by ongoing release of substance P and glutamate, respectively. These result in abnormal expression of activated transcription factors in spinal neurons, including CREB and cFos, altering ion channel and receptor expression. There may additionally be a loss of inhibitory tone in the cord, either through a

permanent loss of GABA containing neurons and opioid receptors or a reduction in their activation. Neurotrophins, especially BDNF, are transported from the periphery and released by afferents into the spinal cord, further enhancing excitation. Interestingly, recent data from our laboratory suggests that BDNF also stimulates sprouting of inhibitory noradrenergic fibers in the spinal cord. Finally, resident immune / support cells, first microglia and later astrocytes, become activated, resulting in further release of BDNF, cytokines, and neurotransmitters which maintain the sensitized state.

The spinal cord receives descending inhibitory and excitatory influences from higher centers, and these modulate the pain gate in the cord, according to the gate control theory of pain (15). Peripheral nerve injury also alters descending influences to the spinal cord which can lead to central sensitization. Medullary centers project to the cord, releasing both inhibitory (norepinephrine) and excitatory (serotonin) catecholamines and other neurotransmitters. The relative role of descending inhibition and facilitation after inflammation or nerve injury is complex, depending on time after initiation of the injury and phenomenon of pain studied. In general with long standing nerve injury there is little change in descending inhibition with a large increase in descending facilitation (16). As such, hypersensitivity behaviors in animals after peripheral nerve injury are abolished by destruction of facilitatory centers in the brainstem. Thus, the essentials of chronic pain transmission include abnormal small and large diameter afferent input, altered gene transcription in spinal cord neurons, loss of inhibitory tone, activation of microglia and astrocytes, and increased descending facilitation.

Finally, cortical neuroplasticity occurs in chronic pain states. Although much less is known regarding changes in the brain then in the spinal cord or periphery, two general phenomena have been described. The first relates to cortical plasticity in the representation of body parts associated with pain. In an elegant series of studies in non human primates (17), repetitive motion injury of the hand results in hypersensitivity to light touch and inability to use the fingers for fine motions. Receptive fields of cortical neurons which respond to stimuli in the hand become enlarged, disorganized, and overlapping. Physical therapy by training the monkey to discern small differences in strength or location of tactile stimuli to the hand result not only in return to the ability to use the hand for fine motions and alleviation of hypersensitivity, but also in a remarkable return of receptive fields of cortical neurons to the normal state. These findings underscore the ability of the adult brain to undergo remarkable plasticity, and may represent the basis for improvement in function and pain by physical therapy.

Targeting the spinal cord for treatment of chronic pain

Regardless of the sites of plasticity responsible for ongoing pain and hypersensitivity, the spinal cord plays a key role to gate sensory processing, and we as anesthesiologists and pain physicians manipulate this site directly by intrathecal administration of drugs. A recent consensus conference (18) described currently used drugs for chronic spinal infusion in the treatment of chronic pain, including an algorithm for stepped treatment and considerations regarding safe use of this technology and pharmacology.

Opioids represent the first step in this approach, and morphine has been approved by the Food and Drug Administration for epidural and spinal administration the treatment of acute and chronic pain for over 20 years. Opioid receptors are densely expressed in the superficial regions of the spinal cord dorsal horn and their activation reduces release of excitatory neurotransmitters as well as inhibits response of dorsal horn neurons which project to higher centers. Although some studies in animals show a reduction in spinal opioid receptor expression after nerve injury and failure of intrathecal morphine to treat hypersensitivity after such injury, more recent studies using blinded conditions, demonstrate potent and effective anti-allodynia from intrathecal morphine in these models of neuropathic pain. Many clinicians use spinal morphine or hydromorphone as their first choice in the treatment of chronic pain, including those with neuropathic pain.

Although spinal morphine can produce delayed respiratory depression, especially in opioid naive postoperative patients, it has been remarkably safe in the treatment of chronic pain. Dose escalation occurs commonly with chronic therapy, probably reflecting disease progression in some patients and tolerance in others, and effective therapy may be limited by central and peripheral side effects from large doses. There are many parallels in animals in changes in the spinal cord between peripheral injury leading to hypersensitivity and during opioid tolerance, including n-methyl-d-aspartate (NMDA) receptor activation and enhanced release of excitatory neurotransmitters and modulators, including glutamate, NO, and prostaglandins. Blockade of these phenomena prevent and treat opioid tolerance in animals, but their clinical utility is unknown. Dose escalation also poses a risk for granuloma formation which occurs in the spinal meninges in response to high local concentrations of opioids and may result in neural deficits and require surgical decompression (19). For this reason, concentrations and daily dose of morphine should not exceed 30 mg/ml and 15 mg/day, respectively (18).

Bupivacaine and clonidine are commonly added to spinal opioids as adjuncts for chronic therapy, especially in patients with neuropathic pain. Clonidine inhibits pain and hypersensitivity by mimicking the actions of norepinephrine released from bulbo-spinal pathways in the dorsal horn. Interestingly, the potency and efficacy of

clonidine to relieve pain increases in hypersensitivity states such as the nerve injury model of neuropathic pain. We have spent considerable effort trying to understand the causes of this change in potency and efficacy, and this has resulted in several insights into plasticity which influences neuropathic pain. As noted above, peripheral nerve injury results in release of the growth factor, BDNF, which is thought to induce sensitization. A byproduct of this, however, is action of BDNF on terminals of descending noradrenergic fibers, causing them to sprout. As a result, the density of noradrenergic fibers and norepinephrine content in the dorsal horn of the spinal cord increase. Thus, the capacity for obtaining analgesia from release of norepinephrine increases, and this may represent part of the explanation for analgesia in chronic pain from agents which activate descending inhibitory pathways, such as gabapentin, or prevent the reuptake of norepinephrine, such as antidepressants.

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