Pain Physiology and Pharmacology: Clinical Relevance

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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) 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 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.

The internal environment is also extensively monitored by nerve fibers, although most of this information is relayed to subconscious centers in the spinal cord or brainstem and result in regulation of homeostasis – gut motility, cardiac output, vascular tone, etc. The anatomy of fibers innervating the internal organs is quite different from those which innervate somatic structures. Visceral fibers are relatively few in number, comprising only 5% of all afferent nerve fibers, are almost exclusively C fibers, and terminate in the spinal cord in a diffuse manner, with a single fiber forming synapses over several dermatomes, deep into the dorsal horn, and even to the contralateral dorsal horn. Pain from visceral organs is usually poorly localized and diffuse, reflecting in part the anatomy of central termination of visceral afferents in the spinal cord. Pain from internal organs is not produced by tissue injury or inflammation, as it is in somatic structures, but rather is produced by distension. Although less is known about the proteins on visceral nerve terminals which transduce the local environment to lead to the sensation of pain, ATP, acting on very specific proteins, is important in some visceral organs, especially the bladder (2).

Aristotle envisioned pain as originating from specific types of stimulation – heat, cold, toxins, crush – leading to activation of acute awareness for the need to escape and understanding, the latter occurring in the heart rather than the brain. Nearly two millennia later, Descartes replaced the heart with the brain, and suggested that pain traveled along specific, hardwired pathways from the periphery through the spinal cord and to the brain. Nearly two centuries later, Melzack and Wall (3) described the gate control theory of pain, which indicated that there were circuits within the spinal cord and elsewhere which could regulate whether a signal coming from the periphery elicited or did not elicit pain. This has spurred considerable research into endogenous circuits, neurotransmitters, and interactions which either facilitate or inhibit the perception of pain, among them the opioid and α2-adrenergic receptors which are commonly mimicked in clinical medicine to provide relief from acute pain.

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 (4). 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 (5). 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 (6).

Obstetric Pain

The first stage of labor results in moderate to severe pain, experienced as a diffuse area referred to the lower thoracic and upper lumbar dermatomes and due to distension of the lower uterine segment and the cervix. It is the most common type of visceral pain treated by anesthesiologists, yet relatively little is known regarding the excitatory or inhibitory proteins located on these afferent nerve endings in the periphery or spinal cord, or the circuits activated by these afferents. As noted above, visceral afferents terminate both superficially and deep in the spinal cord, whereas somatic afferents terminate superficially only. This difference in anatomy may underlie the clinical observation that intrathecal injection of the water soluble opioid, morphine, is effective in small doses (< 100 μg) for the treatment of primarily somatic pain after cesarean section, but is ineffective, even in large doses (> 2 mg) to treat the pain of the first stage of labor. The lipid soluble opioids, such as fentanyl, which perhaps penetrate the spinal cord more efficiently, are equally potent and effective in the two settings.

Most research into visceral pain has examined responses to colorectal distension in rats, a model developed by another anesthesiologist then at the University of Iowa, Tim Ness (7). Most interesting has been the observation that, in normal conditions, peripheral terminals of these visceral nerve fibers are not inhibited by μ-opioid receptor agonists such as morphine or fentanyl, but are sensitive to inhibition by experimental κ-opioid receptor agonists. We have subsequently observed that experimental κ-opioid receptor agonists inhibit the response to distension of the uterine cervix in rats (8)and also relieve chronic visceral pain (9).

Inflammation amplifies the perception of pain by altering protein function in nerve endings, and also by releasing substances, such as growth factors and cytokines, which can be transported to afferent cell bodies in the dorsal root ganglion and even to the spinal cord, causing changes in protein expression and function in these cells (10). These

changes may contribute importantly to clinical pain in the postoperative conditions and in patients with chronic pain from injury to peripheral nerves. However, they may also be relevant to the pain of the first stage of labor, since cervical ripening, a necessary precedent to labor, involves release of inflammatory mediators – cytokines, prostaglandins, growth factors – important in the dissolution of collagen. It is conceivable that this cervical ripening process sensitizes nerve endings in the uterine cervix and results in perceptions of pain from uterine contractions in early labor, but not from uterine contractions of similar strength before ripening (Braxton-Hicks contractions). The role of inflammatory mediators on uterine cervical afferent responses and the mechanisms by which they may be sensitized are actively being investigated currently in our laboratory.

Chronic Pain

A host of anatomic, genetic expression, and circuit changes occur in animal models of chronic pain, and some of these changes may be relevant to humans with chronic pain. For example, some types of chronic pain can be effectively treated by reducing sympathetic nervous system activity in the region of pain, either by systemic drugs or regional nerve blocks. In animal models of peripheral nerve injury associated pain, there is increased sensitivity of nerve endings in the affected area to noradrenergic agonists, and sprouting of sympathetic nerve fibers to surround afferent cell bodies in the dorsal root ganglion. The causes for these changes and how they might be interrupted or returned to normal are under intense investigation.

The pharmacology of analgesics is strikingly different in patients with chronic pain compared to acute pain. Although opioids are effective in each, there is some evidence that potency of opioids is reduced in patients with chronic neuropathic pain. Just the opposite occurs with epidural or intrathecal injection of the $\alpha 2$-adrenergic agonist, clonidine, which is more potent and effective in neuropathic pain than in acute pain (11). The reasons for these shifts in analgesic efficacy are only partially understood. In the example of clonidine, peripheral nerve injury appears to induce release of growth factors from injured afferents and their uninjured neighbors in the spinal cord, resulting in sprouting of descending noradrenergic nerve fibers and establishment of new synaptic contacts.

Chronic pain can also respond to treatments which are relatively ineffective in acute pain. Tricyclic antidepressants have little activity after surgery, yet produce significant analgesia in many patients with chronic pain at relatively low doses. Whether this reflects the plethora of action of these drugs, which inhibit monoamine reuptake, block NMDA receptors, and block sodium channels, or whether it is due to one of these actions or a heretofore unknown mechanism is unknown. Other, non-traditional analgesics, may be effective in both chronic pain and surgical settings. For example, gabapentin, originally demonstrated to relieve neuropathic pain in many patients, has recently been demonstrated to dramatically reduce pain and opioid consumption after surgery, leading some to speculate that there is a close spectrum of pharmacologic changes which occur in the transition from acute to chronic pain (12).

As noted above, the immune system interacts in a complex manner with the peripheral nervous system to alter, and, in many cases, amplify pain sensations, and there is intense interest in immune-neural interactions which may underlie chronic pain. For example, we recently observed that peripheral nerve block with clonidine alone produces very long lasting (weeks) analgesia in an animal model of peripheral nerve injury and chronic pain (13). Further study indicates that this effect is most likely on immune cells in the area of nerve injury, to alter the balance between pro- and anti-inflammatory signals released by immune cells and subsequently altering neural function.

Summary

There has been an explosion in our understanding of the molecular mechanisms by which environmental stimuli activate nerve endings to result in the perception of pain, especially for somatic sensations. The historical concept of pain as reflecting a hard-wired, fixed nervous system has been replaced by an understanding of the remarkably rapid and extensive plasticity which occurs with either acute or sustained noxious stimulation. This has been coupled with an understanding that the two systems with billions of cells which contain memory and

communication – the nervous system and the immune system – interact in multiple ways in the setting of pain. Anesthesiologists have been instrumental in driving our fundamental understanding, not only of chronic pain, but also of postoperative and visceral pain, and clear differences among these pain conditions are emerging. These differences not only underlie our traditionally different treatment of these pains, but also suggest that specific, novel treatment methods may soon emerge for each type of pain.

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