

Expanding Our Understanding of Central Sensitization

Jeffrey A. Gudin, MD

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INTRODUCTION

Why does local injury resulting from trauma lead to chronic, intractable pain in some patients? What is responsible for the translation of local injury with acute pain into a chronic pain state? Why does some pain respond to anti-inflammatory drugs, whereas other types require opiates?

Pain is a complex process involving both the peripheral nervous system (PNS) and the central nervous system (CNS). Tissue injury activates the PNS, which sends signals through the spinal cord to the brain, where pain perception occurs. But what causes the acute experience of pain to become an unremitting phenomenon? Can anything be done to prevent it? Evidence suggests that chronic pain results from a combination of mechanisms, including neural "memories" of previous pain.

Nociception: The Simplest Path

Acute or nociceptive pain is the everyday experience of discomfort that occurs in response to a simple insult or injury. It is protective, warning us to move away from the cause of the injury and take care of the trauma. The mechanisms that generate nociceptive pain include transduction, which converts the external traumatic stimulus into electrical activity in specialized nociceptive primary afferent nerves. The afferent nerves then conduct the sensory information from the PNS to the CNS. In the CNS, the pain information is transmitted from the primary sensory neurons to central projection neurons. When the information is transferred to those parts of the brain that are responsible for our perception, the actual sensory experience occurs. Nociceptive pain is a relatively simple response to a relatively simple, acute stimulus. But the mechanisms responsible for nociceptive pain cannot explain phenomena, such as pain that persists despite removal or healing of the stimulus, such as in phantom limb pain.

Pain and the Inflammatory Response

In cases of more severe trauma (including surgical wounds), tissue damage stimulates an inflammatory response. But other conditions, notably arthritis, are also characterized by ongoing inflammation associated with severe pain. The mechanisms for this sort of pain related to tissue damage and inflammation are distinct from early-warning nociceptive pain. Following the incision or other trauma, a cascade of hyperexcitable events occurs in the nervous system. This physiologic "wind-up" phenomenon starts at the skin, is potentiated along the peripheral nerves, and culminates in a hypersensitivity response from the spinal cord (dorsal horn) and brain.

Inflammatory cells surround the areas of tissue damage and produce cytokines and chemokines, substances that are meant to mediate the process of healing and tissue regeneration. However, these agents are also irritants and change the properties of the primary sensory neurons surrounding the area of trauma.

Thus, the major features triggering inflammatory pain include damage to the high-threshold nociceptors (peripheral sensitization), modifications and modulation of the neurons in the nervous system, and amplification of the excitability of neurons within the CNS. This represents central sensitization and is responsible for hypersensitivity, in which areas adjacent to those of the actual injury hurt as if injured. These tissues also can respond to stimuli that ordinarily do not produce pain, such as a touch, clothing, light pressure, or a hairbrush, as if they are painful (allodynia).

Other Mechanisms in the Pain Mix

Neuropathic pain results from an insult to the nervous system, such as carpal tunnel syndrome, postherpetic neuralgia, diabetic neuropathy, etc. Although some of the mechanisms that seem to cause neuropathic pain overlap with those responsible for inflammatory pain, many of them are distinct, and thus will require a different approach to management.

The process of peripheral and central sensitization is maintained, at least theoretically and experimentally, through the excitatory neurotransmitter, glutamate, which is believed to be released when the *N*-methyl-D-aspartate (NMDA) receptor is activated.

Our nervous system includes either inhibitory or excitatory neurotransmitters. Most of what allows our nervous system to react appropriately is the fine-tuning or inhibition of many processes. The overexcitation of the nervous system is seen to be a problem in a number of different disorders. For example, overactivation of an NMDA receptor is also associated with affective disorders, sympathetic abnormalities, and even opiate tolerance.

Even normal nociceptive pain, in part, activates the NMDA receptor and may result in glutamate release. However, in neuropathic pain oversensitivity to the NMDA receptor is key.

With other types of chronic pain, such as fibromyalgia and tension-type headache, some of the mechanisms active in inflammatory and neuropathic pain may also produce similar changes in the pain system, including central sensitization, greater excitability of the somatosensory pathways, and reductions in CNS inhibitory mechanisms.

Peripheral Sensitization

Cyclo-oxygenase (COX) also plays an important role in both peripheral and central sensitizations. COX-2 is among the enzymes that are induced during the inflammatory process; COX-2 converts arachidonic acid to prostaglandins, which increase the sensitivity of peripheral nociceptor terminals. Of interest, peripheral inflammation also causes COX-2 to be released in the CNS. Signals from peripheral nociceptors are partially responsible for this upregulation, but there also appears to be a humoral component to the transduction of the pain signal across the blood-brain barrier. For example, in experimental models, COX-2 is produced in the CNS even when animals receive a sensory nerve block *before* peripheral inflammatory stimulation. The COX-2 that is expressed within the dorsal horn neurons of the spinal cord produces prostaglandins, which act on the central terminals -- the presynaptic terminals of nociceptive sensory fibers -- to increase transmitter release. In addition, they act postsynaptically on the dorsal horn neurons to produce direct depolarization. And finally, they inhibit the action of glycine receptor, which is an inhibitory transmitter. Thus, the prostaglandins produce an increase in excitability of neurons centrally.

Brain Plasticity and Central Sensitization

Central sensitization describes changes that occur in the brain in response to repeated nerve stimulation. Following repeated stimulation, levels of neurotransmitters and brain electrical signals change as neurons develop a "memory" for responding to those signals. Frequent stimulation results in a stronger brain memory, so that the brain will respond more rapidly and effectively when experiencing the same stimulation in the future. The resulting changes in brain wiring and response are referred to as *nerve plasticity* (describing the ability of the brain to change easily) or central sensitization. Thus, the brain is activated or sensitized by previous or repeated stimuli to become more excitable.

The changes of central sensitization occur after repeated experiences with pain. Research in animals shows that repeated exposure to a painful stimulus will change the animal's pain threshold and result in a stronger pain response. Researchers believe that these changes may explain the persistent pain that can occur even after successful back surgery. Although a herniated disc may be removed from a pinched nerve, pain may continue as a memory of the nerve compression. Newborns undergoing circumcision without anesthesia will respond more profoundly to future painful stimuli, such as routine injections, vaccinations, and other painful

procedures. These children have not only a greater hemodynamic response (tachycardia and tachypnea), but increased crying as well.

This neural memory of pain has been studied extensively. In a review of his earlier studies, Woolf^[1] noted that the enhanced reflex excitability after peripheral tissue damage does not depend on continuing peripheral input; rather, hours after a peripheral injury, spinal dorsal horn neuron receptive fields continued to expand. Investigators have also documented the importance of the spinal NMDA receptor to the induction and maintenance of central sensitization.^[2]

Implications for Pain Management

Once central sensitization is established, larger doses of analgesics are required to suppress it. Preemptive analgesia, or treatment before pain progresses, may reduce the impact of all these stimuli on the CNS. Woolf^[3] demonstrated that the morphine dose needed to prevent central hyperexcitability, given before brief noxious electrical stimulation in rats, was one tenth the dose required to abolish activity after it had developed. This translates to clinical practice. In a clinical trial of 60 patients undergoing abdominal hysterectomy,^[4] those who received 10 mg of morphine intravenously at the time of induction of anesthesia required significantly less morphine for postoperative pain control. Furthermore, pain sensitivity around the wound (secondary hyperalgesia) was also reduced in the morphine pretreated group.

Preemptive analgesia has been used with similar success in a variety of surgical settings, including prespinal surgery^[5] and postorthopaedic surgery.^[6]

A single dose of 40 or 60 mg/kg of rectal acetaminophen has a clear morphine-sparing effect in day-case surgery in children, if administered at the induction of anesthesia. Moreover, children with adequate analgesia with acetaminophen have less postoperative nausea and vomiting.^[7]

NMDA receptor antagonists have imparted postoperative analgesia when administered preoperatively. Various reports exist in the literature supporting the use of ketamine and dextromethorphan in the perioperative period. In patients undergoing anterior cruciate ligament reconstruction, 24-hour patient-controlled analgesia opioid consumption was significantly less in the preoperative dextromethorphan group vs the placebo group.^[8]

In double-blind, placebo-controlled studies, gabapentin has been suggested as a premedicant analgesic for patients undergoing mastectomy and hysterectomy. Preoperative oral gabapentin reduced pain scores and postoperative analgesic consumption without difference in side effects as compared with placebo.^[9,10]

Preoperative administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has shown a significant reduction in opioid use postoperatively. COX-2s are preferable because of their relative lack of platelet effects and significant gastrointestinal safety profile as compared with traditional NSAIDs. Celecoxib, rofecoxib, valdecoxib, and parecoxib (outside the United States) administered preoperatively reduce postoperative narcotic use by more than 40%, with many patients using less than half of the opioids as compared with placebo.^[11,12]

Blocking nerve conduction in the perioperative period appears to prevent the development of central sensitization. Phantom limb syndrome (PLS) has been attributed to a spinal wind-up phenomenon. For patients undergoing lower-extremity amputation under epidural anesthesia, none of the 11 patients who received lumbar epidural blockade with bupivacaine and morphine for 72 hours before surgery developed PLS. For those who underwent general anesthesia without prior lumbar epidural blockade, 5 of 14 patients had PLS at 6 months and 3 continued to experience PLS at 1 year.^[13]

Woolf and Chong^[14] have noted that ideal preoperative, intraoperative, and postoperative treatment includes "NSAIDs to reduce the activation/centralization of nociceptors, local anesthetics to block sensory inflow, and centrally acting drugs such as opiates." Decreasing perioperative pain with preemptive techniques improves satisfaction, hastens discharge, spares opioid use (decreased constipation, sedation, nausea, and urinary retention), and may even

prevent the development of chronic pain. Anesthesiologists and surgeons should consider incorporating these techniques into their everyday practices.

When pain occurs as a consequence of injury or surgery, the spinal cord can reach a hyperexcitable state wherein excessive pain responses occur that may persist for days or weeks (or even years).

Conclusion

Why does local injury resulting from trauma lead to chronic, intractable pain in some patients? Tissue injury leads to a constellation of changes in spinal excitability, which includes elevated spontaneous firing, increased response amplitude and duration, decreased threshold, enhanced discharge to repeated stimuli, and expanded receptive fields.^[3] The persistence of these changes, which are collectively termed central sensitization, appears to be fundamental to the prolonged enhancement of pain sensitivity that defines chronic pain. Various medications and local anesthetic neural blockade may limit the magnitude of this CNS windup, as evidenced by diminished pain and reduced opioid consumption in the preemptive analgesic models.

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