

Pain Pathways and Transmission

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Pain has been a major concern of humankind since the ancient times, and it remains one of the most important subjects of all health care professionals. Despite the obvious overwhelming clinical importance, the major advances in its diagnosis and therapy have been made only recently.

"How do the sensory apparatus of the body and system of signal transmission relate to pain of peripheral origin?" is the topic of discussion. To do this, it is important to understand what constitutes the total pain experience. It consists of: 1) signal transduction at the peripheral receptor site, 2) signal conduction along the peripheral nerve, 3) pain modulation at the level of the spinal cord, 4) pain perception at the supraspinal site, and 5) the associated sensations, emotional reactions, and affective state.

The signal transmission related to pain may be modified by various analgesic agents. Specific analgesic agent has a specific site of action which may be at peripheral receptors, at peripheral nerves, at the level of the spinal cord, at supraspinal levels by activating descending inhibitory systems, or at more cephalad levels by reducing the affective component of pain.

PAIN PATHWAYS

Pain transduction at the peripheral receptors

Peripheral receptors for pain are naked, free nerve endings that spread out among epidermal cells, and that for temperature are free nerve terminals, end-bulbs of Krause, and Ruffini's corpuscles. These structures are affected by aspirin, acetaminophen, and other nonsteroidal anti-inflammatory drugs used as analgesic agents. Although these compounds represent diverse chemical entities, their common mechanism of action is inhibition of prostaglandin-mediated amplification of chemical and mechanical irritants on sensory pathways. The majority of these agents modulate prostaglandin synthesis through inhibition of the action of the enzyme cyclo-oxygenase, which is one of the first steps in the conversion of arachidonic acid into prostaglandins. By reducing prostaglandin synthesis, cyclo-oxygenase inhibitors block the nociceptive response to endogenous mediators of inflammation, and the effect is greatest in tissues that have been subjected to trauma and inflammation. The actions of cyclo-oxygenase inhibition on platelet function and vascular responses to inflammation may be undesirable, and understanding of these factors is important for the selection of agent. Since all the compounds in this group do not block cyclo-oxygenase, the membrane stabilization theory has been postulated. Membrane stabilization could account for decreased prostaglandin release seen at concentrations that are lower than those needed for effective cyclo-oxygenase inhibition. Corticosteroids, tricyclic anti-depressants, and local anesthetics are also considered to possess membrane-stabilizing effects.

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^b Abbreviations used: WDR, wide dynamic range.

Signal conduction at the peripheral nerves

Nociceptive information is transmitted through the first-order neurons with small diameter nerve fibers. The distal part of the axon brings nociceptive information from the receptor toward the cell body, the ganglion cells of which are the cell bodies located in the dorsal root ganglia. The central branch of the axon extends to the spinal cord at the dorsal root entry zone. Pain and temperature are transmitted through A-delta fiber and C-fiber. This transmission of nociceptive impulses can be blocked completely by the use of local anesthetics [1, 2].

Modulation at the spinal cord level

The dorsal horn of the spinal cord is the first site of modulating nociceptive information arriving from periphery and reaching the central nervous system [3–5]. Melzack and Wall [6] proposed a so-called gate control theory of pain in 1965 which has had major historical significance but has been refuted in most, if not all, of its specific details. Wall has updated the gate control theory several times to make it consonant with advancing knowledge in the field. Unfortunately, he has continued to use the same name "gate control theory of pain," for his updated versions. Significant modulation of nociceptive input through the dorsal horn of the spinal cord may be exerted by the use of opioid analgesics [7–18] and general anesthetics [19–24]. The better terminology to describe the basic mechanism of this modulation could be "gain control" rather than "gate control" [25]. Another form of modulation is descending inhibition.

Descending inhibition

The concept of descending pain modulation was proposed during the early part of this century by Sherrington [26], who emphasized that the interaction between excitatory and inhibitory systems was crucial in the processing of sensory information from the body structures to the brain. Hagbarth and Kerr [27] were the first to provide evidence that corticospinal fibers influenced afferent transmission and the conduction at the spinal levels. Descending systems from the brainstem to the dorsal horn of the spinal cord have been implicated in the production of analgesia following electrostimulation of periaqueductal gray matter [28, 29] or microinjection of morphine into the brainstem nuclei [30–32]. In addition, serotonergic and adrenergic systems play an important role in exerting descending inhibition on the dorsal horn neurons, thereby producing analgesia [33–35].

Methodological assessment techniques have improved considerably during the past several years [36]. Utilizing the improved assessment techniques, many old concepts have been re-examined. For instance, the belief that barbiturates are hyperalgesic or antianalgesic has been held for the past three decades based on two clinical studies without the benefits of basic scientific studies. Recently, Collins et al. [37] examined the influence of pentobarbital on the descending inhibition utilizing a sophisticated neurophysiological technique. They have demonstrated reduction in tonic descending inhibition of spinal dorsal horn neurons by barbiturate, supporting the three decade old concept of barbiturate hyperalgesia.

Perception at the supra spinal sites

Axons of second-order neurons have nerve cell bodies in the dorsal horn of the spinal cord. The axons cross to the opposite side, and turn cranially to enter the lateral spinothalamic tract and reach the medulla. Some fibers send collateral to the brainstem reticular formation in the medulla and pons. In the mid-brain, this tract is located at the posterolateral aspect of the medial lemniscus. Before these second-order neurons end in

the specific thalamic nucleus, some fibers enter the reticular system. The nucleus reticularis gigantocellularis is one of those nuclei which receives terminal endings of the nociceptive second-order neurons. This group of specific nociceptive neurons are profoundly suppressed by general anesthetics and opioid analgesics [38–41].

TYPES OF PAIN

The experiences of pain may be classified into four distinctive types and phases: 1) processing of brief noxious information, 2) prolonged noxious stimulation secondary to peripheral tissue damage and inflammation, 3) neuropathic pain and 4) sympathetically maintained pain.

Brief noxious processing is a result of brief noxious mechanical, chemical and/or thermal stimulation of the peripheral receptors or peripheral nerves, more specifically A-delta fibers. In the spinal ascending system, "the lateral system", including the spinothalamic tract is concerned with processing of brief noxious information. Phasic and discriminative nociceptive information is transmitted rapidly through this system. Local anesthetics can completely block the processing of brief noxious information.

Prolonged noxious stimulation mainly through unmyelinated C fibers of the peripheral nerves is further transmitted in the spinal ascending system through "the medial system", which includes spinoreticular and spinomesencephalic tracts. Tonic and nondescriptive nociceptive information is transmitted slowly through this system. This type of pain can be blocked with the use of local anesthetics, opioid analgesics and/or various anti-inflammatory drugs.

Neuropathic pain occurs when persistent noxious C fiber barrage of peripheral nerves causes sensitization of central sensory neurons which results in "central hyperalgesia" [42]. Tricyclic antidepressant or anticonvulsant drugs have been shown to be effective in reducing this pain phenomenon. Prolonged state of central hyperalgesia will result in neuropathic pain which includes deafferentation pain [43]. Critical manifestations of deafferentation pain as a result of injury or surgical trauma are associated with the diverse lesions in the nervous system. The role of peripheral and central processes in deafferentation pain has been extensively studied in our laboratory [43]. The use of local anesthetics to block axon conduction of the first-order neurons, or the use of opiate analgesics in the spinal neural axis, have been shown to play an important role in the new concept of "pre-emptive analgesia" [44–46].

In addition to the somatic nervous system, the sympathetic nervous system plays an important role in producing so called sympathetically maintained pain. Following trauma, action potentials in nociceptive afferents propagate through the dorsal root ganglia to the spinal cord, where they activate WDR^b neurons whose axons are sent to higher centers. The available data suggest that persistent sensitization of WDR neurons in the dorsal horn of the spinal cord occurs as a result of the initial massive input from nociceptive afferents that occurs at the time of injury. In this situation, low-threshold mechanoreceptive afferents activated by light tactile stimulation can provoke increased excitation of the WDR neurons and thus produce allodynia. In turn, the low-threshold mechanoreceptor afferents can be activated by the sympathetic efferent activity and thus produce sympathetically maintained pain.

PAIN REACTION

Affective state and emotional reactions play a significant role in the perception of pain. It is important to recognize the motivational and cognitive contributions to pain. Psychologic approaches are known to produce some measure of pain relief.

FUTURE PROSPECTS

It should include valid clinical studies on the subject of preemptive analgesia. There has been considerable experimental evidence for the phenomenon of central hyperalgesia which could be prevented by blocking the peripheral nociceptive conduction with the use of local anesthetics [42]. Clinical evidence has been accumulating which suggests that certain analgesic techniques initiated prior to noxious surgical stimulation are capable of reducing postoperative pain levels [44–46]. However, as Kehlet and Dahl [47] have pointed out, good clinical studies to document the quantitative role of central neuroplasticity on the magnitude and duration of the pain states are needed.

Pain has been a major concern of humankind since our beginnings. It has been the object of ubiquitous efforts to understand and to control it. In the future, we must exert greater efforts and expend greater energy to solve the mystery of pain and to carry out more effective therapy. In order to achieve this goal, proper understanding of pain pathways and transmission is essential. This will require that basic scientists must join forces with clinical scientists and clinicians to further elucidate the intimate nature of this most vexing human problem.

SUMMARY

There is little question that pain is a sensation with special structural, functional, and perceptual properties. The total pain experience is the result of nociceptive signal transduction at the peripheral receptors, nociceptive signal conduction along the peripheral nerves, modulation at the spinal level, pain perception at the supraspinal sites, and emotional reactions and associated sensations. Each analgesic agent has its own sites and mechanisms of action. When one administers such drugs to provide pain relief, optimum analgesia may be obtained by understanding the specific sites and mechanisms of action of each drug.

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