The pathophysiology of pain

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Recent advances in elucidating the physiologic transmission of pain have lead to new targets for analgesic drug development. New agents are being studied in animal trials and familiar drugs are being investigated in novel ways. This paper was written to familiarize nurse anesthetists with one of the new targets, ionotropic glutamate receptors.

This article begins with a brief survey of several alternate theories of the origin of pain, then, in more detail, describes the anatomical and physiological basis of pain, focusing on the phenomenon of central sensitization and the role of ionotropic glutamate receptors. An exploration of several recent pharmacological studies targeting N-methyl-D-aspartate receptors concludes the review.

Key words: Acupuncture, glutamate receptors, pain.

Introduction

Pain is a complex physiologic and psychologic reaction to potential or real tissue damage or disease that has sociologic implications. Anyone who has personally experienced pain as a result of surgical intervention can well appreciate the physical and psychological aspects of pain and the impact that pain has on significant others. Pain has been defined by the International Association for the Study of Pain Subcommittee on Taxonomy as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” It is clear that pain is not simply a physiologic event, but an event modified by experience, culture, and emotions.

The ability to provide universally effective pain control still eludes healthcare practitioners. Many studies indicate that ineffective pain control often has little to do with available knowledge to treat pain but, rather, with readily using that knowledge. A study performed in 1972 found that pain was inadequately treated in hospitalized patients due to inadequate amounts of opioids prescribed. Recently it was reported that 9% of surgical patients had unbearable pain in the first 24 postoperative hours and 28% had severe pain; even 72 hours postoperatively, descriptions of pain relief were not much better with 5% still reporting unbearable pain and 21% still reporting severe pain. Efficacious pain treatment is complicated by the inappropriate reluctance of healthcare professionals to treat pain and by the elaborate physiologic transmission of pain that we are now just discerning.

Pain theories

- Western medicine. The immense interest in pain research, treatment, and therapy within the last few decades has been largely attributed to Melzak and Wall who proposed a theory of pain, the gate control theory, that accommodated some of the predominating theories of pain to that date. Their theory combined the tenets of the previous theories that had been experimentally supported. The evidence for physiologic specificity of the central nervous system, which was the basis of the specificity theory, and the evidence for central summation explained in the sensory interaction theory were incorporated into the gate
control theory. The original theory proposed that large inhibitory fibers and small diameter excitatory nerve fibers summate their activity in the dorsal horn (substantia gelatinosa) which is the “gate.” If small diameter fiber activity overwhelms large diameter fibers, the gate is opened. Central stimulation by ascending pathways in the dorsal column via large fibers can ultimately modulate the sensory input at the substantia gelatinosa by activating descending pathways, but if a critical level of excitatory input is reached, the action system is activated and pain is perceived.

Shortly after the publication of the gate control theory, it was expanded to include motivational-affective, sensory-discriminative, and cognitive-evaluative dimensions to pain. These aspects of the pain experience are governed by higher central nervous system processes, spinal cord systems, and the reticular and limbic structures, respectively. These 3 dimensions interact to provide information regarding the magnitude and location of the pain and information about the pain based on past experience. In other words, the addition of these components to the gate control theory provided a psychological/emotional domain to the theory.

The gate control theory has been updated based on experimental data and continues to be updated as new knowledge in the area of pain is uncovered. The basic underlying theory that pain is modulated remains, but our understanding of the way in which pain is transmitted and modulated has changed. In 1992, Katz and Melzak stated, “injury or disease produces neural signals that enter an active nervous system that (in the adult organism) is the substrate of past experience, culture, anxiety, and depression. Pain is not the end product of a linear sensory transmission system; rather, it is a dynamic process that involves continuous interactions among complex ascending and descending systems.”

Alternative pain theories

**Acupuncture.** Western medicine’s inability to effectively treat pain has led to an interest in alternative theories and treatments for pain and western style experimentation of those therapies. Traditional Chinese medicine views the body as having 3 vital substances: qi (or chi), blood, and body fluids. Qi is the life force or vital energy and is manifested in many forms. Qi is both inherited and acquired. Pathology is due to either an excess of internal stress or external stress, which causes a disturbance in 1 or more of the vital substances. Pathological conditions are categorized into 4 factors and 19 types. For example, fibromyalgia is classified as an exogenous factor and characterized as a damp disorder. Damp disorders are those that interfere with the normal circulation of qi and the body fluids. A stagnation of qi that leads to a blood stagnation causes the symptoms associated with fibromyalgia. When tendons are not irrigated properly and vitalized by blood, pain occurs.

Stress and anxiety can cause an obstruction of qi thereby preventing blood from nourishing the tendons. If qi is stagnated, blood cannot move. The main symptom of qi stagnation is pain. Pain, therefore, is a symptom of an imbalance in the vital forces. Treatment of qi stagnation involves acupuncture. In order to mobilize qi, basic acupuncture treatment points, as well as points unique for that individual, are selected for needling.

Western studies conducted to establish the efficacy of acupuncture have shown mixed results. One study reported that acupuncture was effective for a selected group of patients, but that there was no difference in pain relief between those patients whose acupuncture needles were placed in the traditional Chinese points compared to those who were needled in a tender area within the dermatomal distribution of the painful area. The study separated patients into 3 subsets by measuring pain relief to subarachnoid block prior to the acupuncture investigation. The first group of patients had pain relief with a subarachnoid injection of saline. Group 2 did not have pain relief with saline, but did report pain relief following a sensory block with lidocaine. The third group reported no pain relief even after a dense motor block with lidocaine. Patients in group 2, selected by differential subarachnoid block (those who had pain relief following a sympathetic/sensory blockade without motor block), reported favorable long-term pain relief to acupuncture. Groups 1 and 3 did not. The authors concluded that acupuncture, whether or not traditional Chinese points were used, was effective for long-term pain relief in this selected group. Other investigations have not been able to verify the efficacy of acupuncture. It is interesting to note that many of the Western experiments measuring the effectiveness of acupuncture postulate the mechanism of pain relief to be a release of endogenous opioids or modulation or inhibition of central input (gate control theory).

**Homeopathy.** Homeopathy is similar to traditional Chinese medicine. Those who practice
Homeopathic medicine believe that all symptoms are a reflection of an imbalance in the patient's inner force, called the vital force. As in traditional Chinese medicine, the vital force is hereditary. An imbalance in the vital force can be caused by exogenous or endogenous stressors. An imbalance in the vital force is exhibited by symptoms; pain for example. Homeopathic treatments involve the preparation of ultra-dilute substances that are said to gain strength at each successive dilution. Substances are selected that mimic the presenting symptom or symptoms. The actual process by which homeopathic substances bring about balance are not known; however, a molecular mechanism has been described. Homeopathic diluents may form clathrate-like crystals (homeopathic substances surrounded by a cage of water molecules) during repeated dilutions. The resultant crystals may react with cell-surface proteins. Interestingly, Linus Pauling postulated this same mechanism of action for anesthetic inhalation agents. The outcomes of various clinical trials involving homeopathic medicine have been mixed. In one double blind study consisting of postsurgical patients there was no difference between control (placebo) and experimental group. Homoeopathic medicine has not been as well researched through traditional scientific methods as has acupuncture.

Therapeutic touch. The pain relief technique known as therapeutic touch adopts both Eastern and Western philosophies as a guide to treatment. Therapeutic touch relies on the belief of a unitary life force that can be instrumental in assisting a patient to reduce stress. The reduced stress can decrease central nervous system responses that exacerbate pain. Most practitioners in the West believe that the effectiveness of these treatments is due to modulation of the painful input (i.e., the gate control theory). While many attribute the results (if any) to a placebo or psychologically mediated effect, this should not be discounted.

The anatomical basis of pain

Acute pain transmission begins with activation of pain receptors called nociceptors that detect tissue trauma. The majority of nociceptors are nonspecific, free nerve endings that respond primarily to chemical, mechanical, or thermal stimulation. Nociceptive receptors are present in skin, subcutaneous tissue, bone, joint, muscles, and viscera. Cutaneous mechanical nociceptors are stimulated by moderately intense mechanical stimulation, mechanothermal nociceptors respond to mechanical and thermal stimulation, and C-polymodal nociceptors respond to mechanical, thermal, and chemical stimuli. Cold nociceptors have been described that respond to intense cold and "silent" unmyelinated nociceptors that under normal conditions do not fire, but do so in the presence of inflammation, have been identified. The C-polymodal nociceptors are important in that they constitute 95% of the sensory C receptors in human skin. Deep somatic nociceptors are also of the free nerve ending type and respond to mechanical and chemical stimulation.

Once stimulated, nociceptive-free nerve endings transmit their signals to the spinal cord predominantly on 2 types of fibers, A delta (A\(\delta\)) and C-fibers. A\(\delta\)-fibers are small myelinated fibers that are specialized for transmitting impulses quickly. These fibers are associated with fast pain or first pain, which generally produces the sensation of pricking pain, sharp pain, and other sensations. The C-polymodals, in addition to responding to mechanical and thermal stimulation, respond to chemical stimulation including that produced by tissue trauma. These fibers transmit their impulses to the spinal cord on C-fibers, small unmyelinated fibers that are responsible for the establishment of slow pain or the second response. This pain is described as burning or throbbing.

The cell bodies of the A\(\delta\)-fibers and C-fibers are located in the dorsal root ganglion. Branches of the axons from these cell bodies ascend and descend for a few spinal segments in the tract of Lissauer. Ad nociceptive fibers terminate mostly in Rexed laminae I (some terminate in laminae II and V) while C-fibers terminate in Rexed laminae II (known as the substantia gelatinosa), laminae I, and less often in V.

The axons then synapse with second order pain fibers. Nociceptor afferents that terminate in laminae I generally synapse with nociceptive specific neurons, class I neurons, that respond only to thermal stimuli or they synapse with wide dynamic range neurons that respond to multiple stimulation. Many of these second order neurons are projection neurons that relay the information to higher brain centers such as the thalamus, brain stem, and cerebellum. Laminae II is abundant with small interneurons. Some of these interneurons are excitatory and relay input from the first order neurons to projecting neurons in laminae I and V. Others are inhibitory neurons. There is evidence that a small number of cells in laminae II have long axons that may project to the brain. It is in laminae V that the neurons of the major ascending tract, the spinthala-
Brain

Pain transmission from the periphery through the spinal cord to the brain

O = Second order neuron (possibly wide dynamic range)
● = Interneuron
★ = Second order neuron
— — = Peripheral nerves
— — = Interneuron connections
— — — = Projection to brain
— — — — = Diffuse connections throughout brain

Figure 1. Pain transmission from the periphery through the spinal cord to the brain

aminic, arise. Laminae V receives input from both Aδ-fibers and C-fibers. The axons of the spinothalamic tract generally terminate in the thalamus. Neurons in laminae I and V also project via the spinomesencephalic tract and terminate in the mesencephalic reticular formation, the periaqueductal grey region and other midbrain sites. Other tracts have also been described.

The final site of pain integration is the somatosensory cortex. Upon reaching the thalamus, pain impulses are distributed widely throughout the sensory cortex. These cortical areas are responsible for our individual responses to pain. It is here that the individual interprets the quality of the pain impulse (Figure 1).

The physiological basis of pain

- Peripheral sensitization. The means by which these neurons communicate their information is by chemical transmitters. Tissue trauma, such as that which occurs during surgery, is accompanied by the escape of potassium ions and the local release of a variety of chemical mediators. These mediators mostly arise from the damage done to cells in the immediate location of the injury. Bradykinin, one of the chemicals produced by proteolytic enzymes at the site of injury and released by cellular damage, is a powerful pain mediating peptide that directly excites Aδ and C-polymodal receptors. Bradykinin also induces increased capillary permeability with a resultant
plasma extravasation, and stimulates cytokine production indirectly activating the phospholipase A, cyclooxygenase cascade that results in the formation of prostaglandins.

The activation of phospholipase A, causes the release of arachidonic acid from cell membrane phospholipids. Arachidonic acid is rapidly metabolized by cyclooxygenase and lipoxygenase pathways. In inflammation, cytokines stimulate cyclooxygenase 2 (COX-2), an alternative cyclooxygenase pathway, that causes a large production of prostaglandins. Prostaglandin E, and prostaglandin I, are generated by this pathway and are the prostaglandins most associated with hyperalgesia. Prostaglandins do not directly stimulate nociceptors, instead they sensitize peripheral sensory neurons to other stimuli, possibly by enhancing Na+ and Ca2+ conductance. Lipoxygenase pathway produces leukotrienes that promote sensitization of local primary afferents as well.

As C-polymodal receptors are excited, they release substance P that causes a release of histamine from nearby mast cells furthering the activation of the free nerve endings. Other peptides have been found in C-polymodal nociceptors that probably contribute to increased inflammation. Prostaglandins, leukotrienes, and others of these substances potentiate the activation of polymodal nociceptors. These substances help to sensitize the primary afferent receptors causing any subsequent painful stimuli to be enhanced. The increase in sensitivity is exhibited by a lowering of the threshold for stimulation of nociceptors and activation of nociceptors that were previously not responsive to the stimuli. This sensitization and stimulation by tissue damage is known as peripheral sensitization. Peripheral sensitization may lead to increased transmission to the second order neurons.

**Central sensitization.** Primary afferents, at their synapse with second order neurons, release many substances including calcitonin gene-related peptide that enhances the release of glutamate from the dorsal horn, substance P, and the excitatory amino acids, glutamate and aspartate, that elicit both a fast and slow response to pain. Vesicular stores of these peptides are released upon activation, most notable of which are substance P and the excitatory amino acids. Substance P is released both peripherally, as previously described, and centrally. Under normal circumstances the release of glutamate from the primary afferent neuron activates glutamate receptors on second order neurons that have a high affinity for glutamate. These receptors, called non-N-methyl-D-aspartate (non-NMDA) glutamate receptors, propagate the pain impulse by mediating excitatory postsynaptic potentials (Figure 2).

Increased afferent traffic into the dorsal horn due to peripheral sensitization can cause subsequent changes in the dorsal horn neurons. Neuronal threshold for stimuli may decrease, the frequency of discharge may increase, and the neurons may recruit other neurons to become excited. In particular, wide dynamic range neurons progressively increase their response to repeated C-fiber stimulation. Many neurons within the dorsal horn have the ability to extend their receptive fields and can recruit these new areas when pain or stimulation persists. The release of neurotransmitters, including the excitatory amino acids, at the synapses of the Aδ-fibers in laminae I and C-fibers in laminae II are most likely the mediators of this phenomenon of increased discharge and expanded recruitment. The continued release of glutamate and activation of the non-NMDA glutamate receptors maximizes depolarization of the second order neuron.

With the bombardment of the neuron by excitatory amino acids, glutamate eventually stimulates N-methyl-D aspartate (NMDA) glutamate receptors that do not respond as readily to glut-
Figure 3. N-methyl-D-aspartate glutamate receptor

Glutamate \( \rightarrow \) Glycine \( \square \)

In the presence of glycine, glutamate binds to its binding site. With maximal depolarization, Mg\(^{+}+\) is released from the channel allowing free flow of Na\(^{+}\) and Ca\(^{++}\) intracellularly and K\(^{+}\) extracellularly.

Properties greatly increase the intensity and duration of the painful stimulus. Pain perception is enhanced. The increased response to pain is known as hyperalgesia. Once central sensitization, or hyperalgesia, is propagated, it is very difficult to stop (Figure 4).

Anesthetic considerations

Anesthesia practitioners find patients experiencing hyperalgesia in acute pain settings such as postoperative care units or in chronic pain settings. It is well known that once pain is entrenched, it is difficult to treat with opioids. There is, in fact, some evidence that proposes opioids themselves are contributory to the development of opioid intolerant hyperalgesia. Clearly other pharmacological agents in addition to the opioids are necessary to adequately treat patients experiencing hyperalgesic type pain. Characterizing the physiological mechanism of pain allows researchers to develop alternative drug therapies.

It is beyond the scope of this paper to describe all of the possible pharmacological interventions available that may, to some extent, inhibit hyperalgesia. None to date are effective in fully relieving it. Much of the newest research in the treatment of hyperalgesia consists of studies of the glutamate receptors because they appear to have a crucial role in the development of hyperalgesia. It is believed that drugs modulating these receptors may be more efficacious in relieving hyperalgesia.

Researchers are currently working on pharmacological agents that block NMDA receptors. Some old drugs are undergoing reexamination. Clinical trials evaluating the efficacy of ketamine, a noncompetitive NMDA antagonist, in the treatment of chronic pain and hyperalgesia have shown promise. In a randomized, double-blind, crossover study, researchers compared ketamine to alfentanil and placebo. They demonstrated the effectiveness of an intravenous ketamine bolus (60 \( \mu \)g/kg) followed by an infusion (6 \( \mu \)g/kg per minute for 20 minutes during which time pain measurements were performed) in treating continuous pain, alldynia (pain from a stimulus that does not normally cause pain such as a gentle touch), and wind-up pain (hyperalgesia) in patients with traumatic spinal cord injuries. Only 1 patient of the 9 in the ketamine group complained of bothersome side effects (dizziness), whereas 3 in the alfentanil group complained of nausea, fatigue, and dizziness. There was no significant difference between the effect of alfentanil and ketamine in relieving symptoms, but in this
case ketamine displayed less side effects."

A second experiment by different investigators compared the same 3 drugs in a double-blind crossover study in healthy patients using intradermal capsaicin (an irritant found in hot peppers) injection to simulate central sensitization. Ongoing pain, allodynia, and hyperalgesia were assessed up to 110 minutes after capsaicin injection. The results were similar, with alfentanil producing more side effects. The same researcher in an earlier study demonstrated intravenous ketamine (0.15 mg/kg) to be more effective than morphine (0.075 mg/kg) in decreasing the pain associated with postherpetic neuralgia. In this study, morphine aggravated hyperalgesia, but ketamine effectively inhibited it. Unfortunately, in this study, all 8 patients in the ketamine group suffered side effects more bothersome than those of the morphine group. The most bothersome side effects reported were itching and painful indurations at the site of injection. Nausea was also a common complaint. Interestingly, no patient complained of psychotomimetic side effects. The follow-up study using ketamine subcutaneously illustrated the effectiveness of ketamine, but again it was associated with unacceptable side effects. The results of a investigation by Sorensen et al revealed ketamine to be significantly more effective in reducing hyperalgesia associated with fibromyalgia than morphine. Again 10 of 11 patients in the ketamine group experienced side effects."
The current interest in acetaminophen as a preemptive analgesic has most likely come about by its recently elucidated mechanism of action as an indirect inhibitor of the NMDA receptor. The studies evaluating the effectiveness of acetaminophen as a preemptive analgesic are inconclusive. Dizocilpine (MK-801) and 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid are both NMDA antagonists that effectively inhibit wind-up and hyperalgesia. There is one report of the effectiveness of intrathecal 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid in a patient with severe neuropathic pain. Studies of both of these drugs so far have been limited to animals.

Human studies point out the limited usefulness of NMDA antagonists intravenously due to side effects. However, the effectiveness of NMDA antagonists administered intrathecally, thus avoiding side effects seen when administered intravenously, seems promising.

It is clear that the transmission of pain is an intricate and elaborate mechanism that has not been fully elucidated. The role of excitatory amino acids is only part of the story. Many other chemicals participate in the transmission of pain such as cytokines, nerve growth factor, neuropeptides, and purines. These too are pharmacologic targets for antinoceception. Development of future pain therapy is directed in these areas.

REFERENCES


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2. Greenberg RS, A randomized controlled trial comparing the cuffed oropharyngeal airway and the laryngeal mask airway in spontaneously breathing anesthetized adults, Anes 1998;88:970-7
3. Cros AM, Does COPA prevent agitation and respiratory incidents during recovery? Anes 1997;87 No 3A
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