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Mechanism of Pain

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Abstract

Word "pain" derives its origin from the Indo-European root aleg meaning to suffer. Word "pain" is later and comes from the Latin word "poena" meaning punishment. Since ancient times there has been disagreement regarding the perception of pain and its evaluation. Unlike sight, hearing and smell, pain does not seem to be a primary sensation, but rather an emotional experience. Most pain researchers view pain as a complex perception, induced by noxious stimuli. Although pain is the most frequent symptom in medicine and despite the enormous advances that have been made in the field of analgesia and anesthesia, the pathophysiological mechanisms involved in its generation and maintenance are not fully understood. Definition of pain was given in 1979 by the classification committee of the international association for the study of pain (IASP) "as an unpleasant aesthetic and emotional experience, associated with actual or potential tissue damage or described in terms of such damage". In other words, although physiology and anatomy determine a precise point of reference for the detection and transmission of messages interpreted as painful, what differentiates the experience of pain is the fact that there is always an emotional gradient to the experience of pain. The purpose of the review is to investigate the analgesic system. Pain signals can be blocked at their initial point of entry into the spinal cord. Analgesia system may also inhibit pain transmission elsewhere in the nociceptive pathway. Because most drugs that alter neuronal excitability act on synaptic receptors, it has been suggested that the "morphine receptors" of the analgesia system must actually be receptors for some morphine-like neurotransmitter that is secreted normally from the brain.

Keywords: Pain; Physiology; Enkephalins; Nociceptors; Nerves; Spinal

1. Introduction

Pain affects the person's daily life, the financial life and the relatives of the sufferer. In order to treat it as effectively as possible, it is necessary to have the perception of pain, as well as to be able to describe its characteristics (intensity, duration, etc.) by the patient himself. Various measurable biochemical changes are indicators of surgical stress and pain, which the anesthesiologist can take advantage of to observe in depth the effect of analgesia and its possible complications. Acupuncture is one of the methods of dealing with pain, it has been used for thousands of years in traditional medicine of Asian countries and in recent decades has joined the quiver of anesthesiologists of classical medicine. It is claimed that the application of acupuncture preoperatively and intraoperatively can reduce the need for co-administration of anesthetic substances, or even replace anesthesia. In such a case the improvement in pain management after surgery should be reflected both in the subjective testimonies of the patients and in the biochemical indicators. Pain acts as a protective mechanism of the body, as it forces the person to react in such a way as to move away from the painful stimulus. It is important not only for cases where there is marked tissue damage, but also for everyday simple activities. Thus, when a person sits on the hips for a long time, it is possible to cause tissue damage due to the inhibition of blood supply to the skin where the skin is compressed by the weight of the body. When the skin begins to hurt due to ischemia, the person completely unconsciously changes position. When the sensation of pain has

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been lost, as happens after damage to the spinal cord, the person cannot feel the pain and as a result does not change position. This condition very quickly leads to ulceration in the area where the pressure is applied (1).

2. Results

Feeling of pain is created by the stimulation of nerve receptors located in the skin and deep tissues. There are two different types of pain: fast pain and slow pain (fast and slow pain). Fast pain occurs within 0.1 second after the application of a painful stimulus, while slow pain begins to be felt after a second or more. Subsequently, its intensity increases slowly over several seconds, and in many cases even over several minutes. Fast pain is also described as sharp pain, dull pain, electric pain, etc. pain of this type is felt by inserting a needle into the skin, or by cutting the skin with a knife, as well as by the effect of electric discharge on the skin. Rapid pain is not felt by most deep tissues of the body. Slow pain is characterized as burning pain, deep pain, throbbing pain, chronic pain, etc. Pain of this type is usually associated with tissue destruction. It can become excruciating and can lead to long-term unbearable hopeless anguish. It can come from the skin as well as from any deep tissue or organ. Ways to treat these two types of pain are different. The centromere fibers that conduct fast pain are thin, myelinated type a-d, while the fibers for slow pain are type c and myelinated. Feeling of pain they transmit is characterized as "slow", prolonged, dull and diffuse pain. All nociceptors are free nerve endings. They abound in the superficial layers of the skin, as well as in some internal tissues, such as the periosteum, the walls of the arteries, the articular surfaces, as well as the sickle and tentacle of the skull. Most other deep tissues are not richly endowed with pain nerve endings. However, any extensive tissue damage can cause dull-type pain from these areas. Nociceptors are stimulated by mechanical, thermal and chemical stimuli. Although most pain nerve fibers are stimulated by multiple stimuli, some fibers are more responsive to excessive mechanical stretch, others to excessively high or low temperature, while others are more responsive to specific chemicals within the tissues. Nerve endings are respectively classified as mechanical, thermal and chemical nociceptors. Fast pain is triggered by mechanical and thermal receptors, while slow pain can be triggered by all three types of nociceptors. Some of the chemicals that stimulate nociceptors are bradykinin, serotonin, histamine, potassium ions, acids, acetylcholine, and proteolytic enzymes. In addition, prostaglandins enhance the sensitivity of pain nerve endings, without causing their direct stimulation. These chemicals are especially important in triggering the slow excruciating pain that occurs after tissue damage (2).

Although all pain nerve endings are free nerve endings, two separate nerve pathways are used to conduct these nerve impulses to the central nervous system. These two nerve pathways correspond to the two types of pain, i.e. one pathway for rapid, acute pain and another pathway for slow, chronic pain. Because of this dual nociceptive system, a sudden application of a painful stimulus produces a "double" pain sensation: a quick-sharp pain, followed after about a second by a slow, burning pain. Rapid pain informs the person about the effect of the harmful agent, therefore, pain of this type plays an important role for the immediate reaction of the person and his removal from the stimulus. Moreover, the slow burning sensation tends to become, over time, increasingly painful. Eventually, this feeling becomes unbearable constant pain (1, 2).

After entering the spinal cord with the posterior roots of the spinal nerves, the pain nerve fibers ascend or descend for one to three neurotomies in the tract of lissauer, which is located immediately behind the posterior horn of the spinal gray matter medulla, and then make synapses with neurons of the posterior horns. But also at this point there are two systems for processing the pain signals on their way to the brain. Skin nociceptors are called mechanoreceptors and are stimulated by the application of pressure, nudge or high temperature mechanoreceptors and α-δ fibers have a "threshold", while c fibers lack this because they carry a variety of stimuli. However, the pain tolerance in the CNS determines the requirements for analgesics and not the "threshold" of the peripheral nerves. A-d and c fibers enter the gray matter of the posterior horns of the spinal cord. Fibers a-d terminate in zone 1, while fibers c in zone 2 of the rexed (gelatinous substance). Then they synapse through the ascending aorta with the dorsothalamic tract. The first and basic processing of painful stimuli takes place in the spinal cord through or with the help of inhibitory neurons or suppressive neurons of the formation cation. This mechanism is part of the "pain gate" as proposed by Melzack and Wall. A small number of the fibers of the neospinothalamic tract terminate in the reticular regions of the brainstem, but most fibers reach the optic thalamus and terminate in the ventromedial complex, along with the posterior fasciculi-internal pons tract. Also, a small number of these fibers terminate in the posterior nuclei of the optic chamber. From these areas signals are transmitted to other areas at the base of the brain, as well as to the somatosensory region of the cerebral cortex (1, 3).

Acute pain is caused by a painful stimulus, such as by superficial or deeper injuries, by muscle spasm of striated or smooth muscle fibers, by some disease of the viscera, or by pathopsychological mechanisms that can cause muscle spasm of striated and smooth muscle fibers. Acute pain causes alesthesia, i.e. a nervous response to painful stimuli. Receptors that convert painful stimuli into perceived stimuli are called nociceptors. Nociceptors are free nerve endings

that can perceive chemical, thermal and mechanical damage. Under normal conditions thermal, mechanical and chemical stimuli activate high pathway nociceptors. Nociceptors in turn activate the first order neuron in the spinal cord. Noxious stimuli are accompanied by tissue damage, which causes inflammation and leads to further stimulation of nociceptors. Pain is divided into two categories: normal and pathophysiological. Normal pain is protective and warns of further damage, is temporary and localized. The pathophysiological is accompanied by inflammation, neuropathy, and results from central or peripheral sensitization and extends to healthy areas (4).

The surgical trauma creates a body response known as an inflammatory response. algesia in the inflammatory response is due to release of substance p, neurokinin α, and calcitonin-related peptide (cgrp) at nociceptor nerve endings. These peptides act on sympathetic nerve fibers and lead to vasodilation, extravasation of plasma proteins, and release of chemical messengers from inflammatory cells. Then follows a cascade of inflammatory substances such as serotonin, histamine, bradykinin, potassium, cytokines, substance p, and nitric oxide, products of cyclooxygenase and lipoxygenase, which sensitize high pathway nociceptors, resulting in peripheral sensitization, where low-intensity stimuli are perceived as painfully. An area of primary hyperalgesia is created around the trauma, i.e. an enhanced perception of pain to a stimulus which is normally painful. In the region of the posterior horns of the spinal cord, the first-order centromeres terminate, and more specifically in lobes i, ii and v. in the posterior horns of the spinal cord, first-order centromeres connect to many second-order neurons. Some fibers ascend or descend several myelotomy within the bundle of lissauer before reaching synapses with neurons of higher or lower levels. In the posterior horns of the spinal cord the amino acids glutamate and aspartate play a dominant role in the transmission of painful stimuli and act on nmda receptors, non-nmda receptors and glutamate receptors. Other peptides released by first-order centrioles are substance p, neurokinin α that act on neurokinin receptors, and cgrp (calcitonin-related peptide). Other receptors such as opioid, γ-aminobutyric acid (gaba), serotonin, α-adrenergic and adenosine receptors, participate in the transmission and modulation of painful stimuli in the posterior horns of the spinal cord. After the injury, allodynia occurs, that is, an increased response to mechanical painless stimuli in an area around the wound zone (area of secondary hyperalgesia). This phenomenon is called central sensitization, in the context of the "plasticity" of the CNS, resulting in the modification of pain. After the transmission of the stimuli in the posterior horn of the spinal cord, inhibitory mechanisms are released, through local inhibitory neurons and descending fibers from the brain. Acute pain originates in epidermal, deep somatic or visceral areas. Acute superficial pain is characterized as cutting, burning, stabbing, throbbing, exfoliating and localized. Deep body pain is dull, deep, and less well localized. The visceral pain is diffuse, vaguely located, dull, deep, and when the pain worsens, nausea, vomiting, sweat appear. Also accompanied by hyperactivity of the sympathetic system, hyperalgesia and reflex muscle spasm(1,2,4).

Acute pain is often associated with neurotomy and supra-neurotomy reflex responses, which help homeostasis of the body's organs. Local Spinal Neurotomy reflexes, such as during stimulation of pre-ganglionic sympathetic neurons in the anterolateral horn of the spinal cord cause tachycardia, hypertension, increase in pulse volume, increase in cardiac work, metabolism, myocardial oxygen consumption and can lead to even in ileus, urinary retention and arrhythmias on worsening pain. Increased musculoskeletal tone may occur upon stimulation of somatomotor cells resulting in muscle spasm in the trunk and decreased compliance of the chest wall, increased intra-abdominal pressure and possible hypoxemia. Supra-Neurotomy reflexes occur in the premechanic centers of respiration, circulation and hypothalamus. They can influence hypothalamic sympathetic tone by releasing catecholamines resulting in an increase in cardiac output, blood pressure, peripheral resistance, oxygen consumption and an increase in the production of endocrine substances such as cortisol, glucagon, adrenocorticotropic hormone (acth), growth hormone, of renin, angiotensin ii and aldosterone. After stress, the cascade of these endocrine substances leads to: hyperglycemia, glucose tolerance, insulin resistance, protein muscle catabolism, increased lipolysis and oxidation, water and sodium retention, as well as increased potassium excretion, due to increased aldosterone, cortisol and ADH. Through cortical stimulation, anxiety and fear increase the hypothalamic stress response. Cortisol and catecholamines released due to intense stress can affect the hypothalamus. Intense stress through the cortex can lead to increased blood viscosity, clotting time, fibrinolysis and platelet aggregation. Fear and anxiety are the main psychological concomitants of acute pain, resulting in a vicious circle, where pain and anxiety reinforce each other (5, 6).

Inhibition of the stress response, through analgesic treatment, can lead to an improvement in the outcome of surgical patients. Therapeutic goal is a VAS scale (visual analog scale) below 4, both at rest and during mobilization, stable hemodynamic status, satisfactory respiratory rate, absence of significant sedation, and control of adverse reactions such as nausea, vomiting, pruritus, urinary retention and bowel motility disorder. The pain gate theory was proposed in 1965 by Melzack and Wall in an attempt to explain the endogenous mechanisms of pain control. It has to do with how a stimulus can be differentiated at the level of the spinal cord. Melzack and wall hypothesized that the painful stimulus to reach the brain must pass through a "gate". The portal is located in the gel substance of the posterior horn of the spinal cord. In the posterior horns there are transmitting (efferent) neurons or "t" cells and inhibitory interneurons or "y" cells. Stimulation of t cells transmits pain to higher levels of the CNS. C cells when stimulated inhibit t cells. Ab fibers

stimulate c cells, while ad and c fibers inhibit them. A low-intensity stimulus excites the ab fibers and closes the gateway to the painful impulses carried by the ad and c fibers. If the stimulus continues, the ad and c fibers are activated, the portal of entry opens and the stimulus becomes painful. The portal is also controlled by impulses, which travel to the spinal cord from higher centers (stem). The existence of these mechanisms seems to explain how analgesia is achieved by acupuncture, transcutaneous electrical nerve stimulation, pressure and rubbing of the area. The goal is to activate the ab fibers and close the gate. The infiltration of the wound with local anesthetics aims to interrupt the activity of the ad and c fibers to give the avins the opportunity to close the gate (7).

Painful push releases excitatory neurotransmitters (substance p) from ad or c fibers and activates class b neurons, which then carry the information to higher centers. Interneurons of the substantia nigra can modulate neurotransmitter release by activating inhibitory presynaptic receptors. The inhibitory neurotransmitters are thought to be enkephalins. Endogenous opioids work in the same way. Serotonin and norepinephrine modulate the release of excitatory neurotransmitters in the substantia nigra following activation of descending inhibitory pathways. The activity of αb fibers also suppresses the response to painful stimulation by release of gaba. The posterior horns are thought to be the gateway for completing and modifying the treatment of painful stimuli. Thus the notion that the posterior horns are a gate which can be closed by the processes of conversion, transference and modification forms the postulate which forms the basis for the effective treatment of pain. The proposed pain gate mechanism is part of the endogenous analgesia system, which the nervous system possesses and which explains, among other things, the differences in the response to pain from person to person. Analgesia system consists of three main parts: Gray matter, located around the aqueduct of silvius in the midbrain and upper pons; neurons from this area send nerve impulses to the Large Nucleus of the suture, a thin nucleus located in the midline, at the level of the lower part of the pons and the upper part of the longus. From this point nerve impulses are transmitted down the lateral posterior bundles of the spinal cord to a Nociceptive Complex located in the posterior horns of the spinal cord. In this position, the analgesia system blocks pain before it is channeled to the brain. By electrical stimulation of the gray matter around the aqueduct or large nucleus of the suture, numerous but very strong pain signals, which enter the nervous system with the posterior roots of the spinal cord, can be almost completely suppressed. Also, by stimulating areas located at even higher levels of the brain, which in turn stimulate the gray matter around the aqueduct and especially the periventricular nuclei of the hypothalamus, located next to the third ventricle and to a lesser extent the medial precerebral fasciculus, also located in the hypothalamus may suppress pain, although possibly to a lesser extent (8).

Among the various neurotransmitters involved in this analgesia system, enkephalin and serotonin stand out. Many of the nerve fibers originating in both the periventricular nuclei and the gray matter around the aqueduct secrete enkephalin from their endings. Thus, the endings of many nerve fibers within the nucleus accumbens secrete enkephalin. The nerve fibers that start from this nucleus and end in the posterior horns of the gray matter of the spinal cord secrete serotonin at their endings. Serotonin in turn acts on another group of neurons in the spinal cord, which secrete enkephalin. Enkephalin causes presynaptic inhibition of both type c pain afferents and type ad fibers at their synapse points within the posterior horns. Possibly this is done by blocking calcium channels in the cell membrane of the nerve endings. Since calcium ions are what because neurotransmitter release at the synapse, blocking calcium channels obviously results in presynaptic inhibition. In addition, this blockade appears to be long-lasting, because after activation of the analgesia system, analgesia is usually maintained for several minutes, or even hours. Thus, with the analgesia system, pain signals can be blocked at their initial point of entry into the spinal cord. It is possible that this analgesia system may also inhibit pain transmission elsewhere in the nociceptive pathway, and particularly in the reticular nuclei of the brainstem and the optic interlobular nuclei. It has been found that the injection of extremely small amounts of morphine into the periventricular nucleus around the third ventricle in the diencephalon, or in the gray matter around the aqueduct in the brainstem produces an extraordinary degree of analgesia. Morphine has also been found to exert actions at many other sites of the analgesia system, including the dorsal horns of the spinal cord gray matter. Because most drugs that alter neuronal excitability act on synaptic receptors, it has been suggested that the "morphine receptors" of the analgesia system must actually be receptors for some morphine-like neurotransmitter that is secreted normally from the brain. About a dozen opioid substances have been found to date in various parts of the nervous system, all of which are breakdown products of three major protein molecules: proopiomelanocortin, pro-enkephalin, and prodynorphin. In addition, the presence of receptors for opioids was demonstrated in many parts of the brain, and especially in the areas included in the analgesia system. Among the most important of the opioid substances are beta-endorphin, metekephalin, leu-enkephalin (leucine-enkephalin), and dynorphin. The two enkephalins are found in the parts of the analgesia system described above, while β-endorphin is found in both the hypothalamus and pituitary gland. dynorphin, although found in only small amounts in nervous tissue, is an important substance because it is an extremely powerful opioid, with an analgesic effect 200 times stronger than that of morphine, when injected directly into the analgesia system (5,9,10).

3. Conclusion

Thus, although all the details of the brain's opioid system are not yet fully understood, nevertheless activation of the analgesia system, either by nerve impulses carried to the gray matter around the aqueduct, or by morphinoid drugs, can suppress many signals pain, which enter the central nervous system with the peripheral nerves.

Compliance with ethical standards

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