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Primary and Secondary Hyperalgesia

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ABSTRACT

According to the definition of the International Association for the Study of Pain, hyperalgesia means "an excessive reaction to moderate nociceptive stimulation". Primary hyperalgesia or peripheral sensitization is a reflection of activation and sensitization of nociceptive A-delta fibers and terminal windows of polymodal C-fibers in injured tissues. The basis of secondary hyperalgesia or central sensitization is spinal neuroplasticity and facilitating the transfer of nociceptive information to supraspinal structures.

Primary hyperalgesia .Primary hyperalgesia develops following the primary activation of nociceptors (transduction) in response to mechanical, thermal or chemical stimulation. Peripheral mediators of mechanical and thermal damage include K+ and H+ ions , prostaglandins (PGE2), cytokines (IL-6, IL-10, TNFa) and so -called autokoids (substance P, angiotensin II, bradykinin, histamine, serotonin). Under the influence of pain and inflammation mediators , nociceptors become sensitized, they depolarize spontaneously or under the influence of low-threshold stimulation. Nociceptor terminals contain a number of membrane receptors and ion channels, including vaniloid (TPRV-1) receptors, purinergic receptors. TPRV-1 receptors initiate the formation of potentials in peripheral terminals, they are also responsible for the transformation of nociceptive stimuli into a stream of action potentials. An increase in the activity of COX-2 promotes the conversion of arachidonic acid released from the membranes of damaged cells into PGE2, primary mediator of nociception and initiator of transduction. Bradykinin and callidin bind to constitutional G-protein receptors (called B2 receptors), which, in turn, activate phospholipases A and C, as well as protein kinase C. Bradykinin also activates potential-dependent ion channels, changing the ion fluxes of K+ and Na+, which leads to an increase in the sensitivity of thermomechanical C-nociceptors.

The interaction of bradykinin with TPRV-1 receptors plays a significant role in the mechanisms of bradykinin-induced hyperalgesia. Bradykinin-sensitized TPRV-1 receptors acquire the ability to activate at a lower temperature. In the mechanisms of the early phases of primary hyperalgesia, inflammatory mediators are of primary importance , at later stages

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pathophysiological changes play a role, including damage to neurons, the effects of effective sympathetic potentiation, the influence of neutrophil and lymphocytic infiltration. The late phase is associated with the appearance of ectopic discharges and other manifestations of neural activity independent of external stimulation.

Secondary hyperalgesia. Secondary hyperalgesia is a form of central sensitization resulting from tissue damage and tissue inflammation. Its clinical manifestations are a significant increase in responses to nociceptive and non-nociceptive stimulation of intact tissue around the injury zone. Secondary hyperalgesia plays an important role in increasing the intensity of pain caused by physical exertion and limiting the mobility of patients. Besides, it serves as the basis for the transformation of acute pain into chronic pain.

Secondary hyperalgesia is a reflection of activation and progressive sensitization of nociceptive specific neurons of the second order, as well as neurons of the SDD of the posterior horns of the spinal cord. In addition, activation of neurons of the brainstem and thalamus plays a role in its formation . These cells are activated by streams of nociceptive afferent stimuli from damaged tissues.

Two forms of secondary hyperalgesia are described:

a) hyperalgesia for mild nociceptive stimulation (with a puncture needle);

b) hyperalgesia for mild non-nociceptive stimulation (allodynia).

The mechanisms that are the basis of the sensitization of the neurons of the SPSM include enhanced affective stimulation, the phenomenon of "inflating" and long-term potentiation. The combined effect of HAC and neurokinin (NC) on facilitating nociceptive pathways is the pharmacological cornerstone of the phenomenon of secondary hyperalgesia . Glutamate and aspartate are responsible for rapid synaptic transmission and rapid depolarization of neurons. Glutamate is released by all primary afferents, while as a substance, P is found only in nociceptors . HAC activates AMPA receptors, which regulate the entry of K+ and Na+ ions into the cell, as well as the intraneuronal potential. The enhanced entry of Na+ into the cell facilitates the "launch" and activation of NMDA receptors. Spinal and supraspinal NMDA receptors increase the entry of Ca2+ ions into neurons, which is the basis for long-term potentiation. The sensitization of CNS neurons is the basis for the transformation of acute pain into chronic pain. Clinical significance of primary and secondary hyperalgesia The control of nociceptor transduction and the formation of primary hyperalgesia is the key to reducing the intensity and duration of acute pain. The sensitization of nociceptors leads to a decrease in pain thresholds, an increase in the intensity of pain sensations and an extension of the rehabilitation period. The physiological response to transduction (initiation of nociception) may be limited by the perioperative administration of non-opioid analgesics (primarily NSAIDs). Opioid analgesics can, to a certain extent, prevent the release of substance P from the terminals of primary afferents. However, their analgesic effect will be limited in the conditions of sensitization of nociceptors by prosta- glandins, bradykinin and other inflammatory mediators. Central sensitization plays a crucial role in the mechanisms of pain chronization. The formation of chronic pain syndrome implies the development of plastic changes in the structures of the central nervous system, the rate of which increases under the condition of inadequate pharmacotherapy in the early postoperative period. Prolonged "bombardment" of the neurons of the posterior horns of the spinal cord by nociceptive stimuli from damaged tissues leads to a progressive increase in the number of their connections with SDD neurons, as well as an increase in the number of NMDA receptors on postsynaptic membranes. The axons of SDD neurons penetrate into the

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zones where the cell bodies of nociceptive neurons are located. Thus, receptive fields expand, which acquire the ability to perceive non- receptive stimuli.As a result of all these changes , non-nociceptive afferent stimulation (mechanical and proprioceptive) is perceived as nociceptive, which creates conditions for maintaining sensitization even after the healing of primary tissue damage. Knowledge of the basics of the pathophysiology of acute pain is the key to the success of complex treatment and prevention of acute postoperative pain syndrome.

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