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Clinical Pathophysiology and Anatomy of Acute Pain

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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.

Definition of acute pain.

According to the definition of the International Association for the Study of Pain (IASP), pain is an unpleasant sensation and emotional experience associated with existing or probable tissue damage, or described by the patient in terms of such an injury. This definition implies verbal contact with the patient, at the same time , the absence of such contact (patients without knowledge or with severe intellectual disabilities) does not mean that the patient does not experience pain and does not need anesthesia. Acute pain is usually defined as pain that has recently begun and (most likely) limited in duration, time of occurrence and localization of pain sensations associated with a disease or injury. Chronic pain persists even after the wound has healed or the disease has ended for a long time (sometimes throughout the patient's life), and in some cases it is impossible to determine the cause of its occurrence. Intense acute pain can become chronic over time. Understanding the pathophysiological mechanisms of acute pain contributes to improving the quality of its treatment and preventing transformation into a chronic form.

Nociception. Nociception is a complex neurophysiological process of generating the activity of peripheral afferent fibers induced by various stimuli of damaging intensity, followed by the transfer of nociceptive information to spinal structures and the cerebral cortex. There are four main stages in it:

• Transduction – activation of specialized nerve endings (nociceptors), formation of an

action potential.

• Transmission – carrying out the flow of nociceptive stimuli from peripheral tissues to the structures of the spinal cord and further to the supra- spinal centers and the cerebral cortex.

• Modulation – suppression by interneurons II plates of the posterior horns of the spinal cord release of neurotransmitters from nociceptive neurons, i.e. an obstacle to the activation of neurons of the 2nd order. • Perception is the culmination of the above processes, localization and conscious perception of pain by the cerebral cortex, the formation of an emotional–affective component.

Transduction.

Peripheral nociceptors The perception of nociceptive stimuli begins with the activation of peripheral sensory images (nociceptors), which transforms into an action potential (transduction) for subsequent transmission to spinal and supraspinal structures. Nociceptors are free (non-encapsulated) peripheral endings of afferent fibers. Cell bodies of nociceptive afferent fibers, innervated- the trunk, limbs and internal organs are located in the ganglia of the posterior roots, while how the bodies of afferent fibers innervating the head, mouth and neck lie in the trigeminal ganglia and are projected into the trigeminal the nucleus of the brainstem. The largest number of nociceptors is found in the skin, muscles, vascular walls, joints, membranes of internal organs, dura mater. The most common subclass of nociceptors is represented by the peripheral endings of thin myelin-free C-fibers. They are non- specialized (polymodal) nociceptors that can be activated by mechanical, chemical or thermal damaging stimuli. Normally, nociceptive afferent axons do not have spontaneous electrical activity. The frequency of electrical discharges in these axons increases in proportion to the increase in the intensity of external stimulation. Activation of nociceptors is associated with depolarization of Ca2+ channels. When a certain threshold of stimulation is reached, the distal ak- sonal segment is depolarized due to the entry of Na+ ions into the cell, after which the generated action potential is transferred to the underlying structures. The largest number of nociceptors is found in the skin, muscles, vascular walls, joints, membranes of internal organs, dura mater. The most common subclass of nociceptors is represented by the peripheral endings of thin myelin-free C-fibers. They are non- specialized (polymodal) nociceptors that can be activated by mechanical, chemical or thermal damaging stimuli. Normally, nociceptive afferent axons do not have spontaneous electrical activity. The frequency of electrical discharges in these axons increases in proportion to the increase in the intensity of external stimulation. Activation of nociceptors is associated with depolarization of Ca2+ channels. When a certain threshold of stimulation is reached, the distal ak- sonal segment is depolarized due to the entry of Na+ ions into the cell, after which the generated action potential is transferred to the underlying structures.

Mediators of inflammation and pain A number of inflammatory and pain mediators play an important role in the mechanisms of transduction :

1. Substance P is a neuropeptide released from the terminals of myelin-free primary afferent fibers. The proinflammatory effects of substance P include: vasodilation, plasma extravasation, mast cell degranulation with histamine release , chemoattractive effect on leukocytes and their proliferation, cytokine release . The effects of substance P can be blocked by the neurotoxin capsaicin, which destroys the terminals of afferent nerves.

2. Bradykinin is the main algogenic substance that has a direct activating effect on nociceptors.

3. Histamine is contained in the granules of mast cells, from where it is released under the action of substance P and other mediators. The effects of histamine are vasodilation and edema due to increased permeability of postcapillary venules.

4. Serotonin (or 5-hydroxytryptamine, 5-HT) accumulates in dense granules of platelets, it increases the permeability of micro- vessels.

5. Prostaglandins play an essential role in the initial activation of nociceptors, and also increase inflammation and swelling of tissues in the area of injury. Activation of cyclooxygenase 2 type (COX-2) leads to the rapid formation of prostanoids (prostaglandins and thromboxane A2) from arachidonic acid released from damaged cell membranes.

6. The release of cytokines and interleukins is a component of the peripheral inflammatory response.

Circulating cytokines may contribute to an increase in prostaglandin synthesis in the brain. The accumulation of inflammatory mediators in the injury area leads to persistent stimulation of nociceptors, the formation of new nociceptors and the formation of primary hyperalgesia. Tissue damage caused by infection, inflammation, and ischemia is accompanied by degranulation of mast cells, hyperproduction of inflammatory cells (monocytes and lymphocytes), and also induces the synthesis of a number of enzymes, in particular COX-2. Inflammatory mediators , acting through ligand-dependent ion channels, as well as through metabotropic receptors, activate (sensitize) nociceptors. Endogenous nociception modulators include proteinases, proinflammatory cytokines (TNF, IL-1, IL-6), anti-inflammatory cytokines (IL-10) and chemokines. Activation of the intracellular kinase cascade leads to phosphorylation of channels (in particular, potential- dependent sodium and TRP channels), changes in their kinetics and thresholds, and ultimately to the sensitization of nociceptors. Neuropeptides (substation P and calcitonin-gene-linked peptide) secreted by peripheral nerve endings contribute to the attraction of plasma factors and inflammatory cells to the area of tissue damage (neurogenic edema). Increased sensitivity (decreased pores) within the area of damaged tissues, caused by peripheral mechanisms, is caused by peripheral sensitization and is clinically primary hyperalgesia. NSAIDs are able to modulate the peripheral mechanisms of nociception, inhibiting the synthesis of PGE2.

Transmission. Carrying out nociceptive stimuli from the injury zone to the spinal cord Nociceptive stimuli are carried out from peripheral nociceptors into the posterior horns of the spinal cord (ZRSM) along both myelin-free and myelinated fibers. Nociceptive fibers are classified according to the degree of their myelination, diameter and speed of conduction. A-delta axons are responsible for " primary" or "rapid" pain, i.e. rapid (within 1 sec.) localized perception of pain of short duration, as well as its characteristics (acute, burning, etc.). Myelin-free C-fibers provide a feeling of "secondary" pain with increased latency (from a few seconds to minutes) that exists for a long time. Sodium channels play a major role in conducting neuronal action potentials in the central nervous system. Na+ channels of sensory neurons are the main point of action of local anesthetics, since they are also represented in sympathetic and motor fibers, the effect of MA extends to these fibers. Changes in the kinetics of Na+ channels caused by tissue damage contribute to the formation of hyperexcitability of neurons.

Modulation. In addition to the excitatory mechanisms described above , an important role is played by inhibitory modularization at the level of the eye. Afferent stimuli entering the spinal cord are modulated by inhibitory mechanisms. Braking effects are carried out through local braking interneurons and braking paths descending from supraspinal structures . GABAERGIC

and glycineergic interneurons are involved in tonic inhibition of nociceptive entry.

The death of these neurons leads to the occurrence of chronic neuropathic pain. The inhibitory mode of nociception involves endogenous opioids and noradrenergic inhibitory pathways. Endogenous activation of inhibitory mechanisms limits the responses of neurons to stimulation from C-fibers. Neurotransmitters – enkephalins, endorphins, norepinephrine and serotonin - play a significant role in this. The mechanisms of action of a number of analgesics are associated with the activation of thoracic mechanisms.

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