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Pain - Pathophysiological Basis

Lizaveta I. Bon*, and N.V. Kokhan

Assiatant Professor of Pathophysiology, Grodno State Medical University, 80, Gorkogo St., 230009, Grodno, Republic of Belarus

***Corresponding Author:** Lizaveta I. Bon, Assistant Professor of Pathophysiology, Grodno State Medical University80, Gorkogo St., 230009, Grodno, Republic of Belarus*

E-mail: asphodela@list.ru

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ABSTRACT

Pain is a complex psycho-emotional unpleasant sensation, realized by a special system of pain sensitivity and higher parts of the brain. It signals influences that cause tissue damage or already existing damage resulting from the action of exogenous factors or the development of pathological processes. The study of the mechanisms of the occurrence of pain will serve as a fundamental basis for the development of new directions for its relief.

Keywords: Pathological pain, Nociceptive system, Antinociceptive system, Neurons

INTRODUCTION

Pain is a complex psycho-emotional unpleasant sensation, realized by a special system of pain sensitivity and higher parts of the brain. It signals influences that cause tissue damage or already existing damage resulting from the action of exogenous factors or the development of pathological processes. The system of perception and transmission of the pain signal is also called the nociceptive system. Pain signals cause a corresponding adaptive effect–reactions aimed at eliminating either the nociceptive effect or the pain itself if it is excessive. Therefore, under normal conditions, pain plays the role of the most important nervous regulation and contributes to the implementation of these influences [1-3].

Treatment aimed only at normalizing the altered function of the internal organ is not pathogenetic, but symptomatic. Its result is usually short-lived, and when maintenance therapy is stopped, a relapse may occur, since there are main parts of the pathological system that, under conditions of treatment withdrawal or new pathogenic influences, become more active and acquire a new outlet to the target organ. Pathogenetic treatment should consist of the elimination of the pathological system, in the normalization of the altered apparatus of nervous regulation, i.e., in the elimination of the pathological determinant. It is very important to use complex pathogenetic therapy in the form of a combined effect on the altered regulatory apparatus, other parts of the pathological system, and the target organ. Etiological therapy should be to eliminate the factors that arise and support disorders of nervous regulation [4-6].

People with congenital or acquired (for example, injuries, infectious lesions) pathology of the nociceptive system, deprived of pain sensitivity, do not notice damage, which can lead to serious consequences. Different types of pain (acute, dull, localized, diffuse, somatic, visceral, etc.) are carried out by different structures of the nociceptive system [7].

Pathological pain. In addition to the physiological pain described above, there is pathological pain. The main biological feature that distinguishes pathological pain from physiological pain is its maladaptive or direct pathogenic significance for the body. It is carried out by the same nociceptive system, but changed under conditions of pathology and is an expression of a violation of the measure of the processes that realize physiological pain, the transformation of the latter from a protective into a pathological mechanism. The pain syndrome is an expression of the corresponding pathological (Algic) system [1,3-5].

Pathological pain causes the development of structural and functional changes and damage in the cardiovascular system and internal organs, tissue degeneration, impaired autonomic reactions, changes in the activity of the nervous, endocrine, and immune

systems, psycho-emotional sphere, and behavior. Severe and prolonged pain can cause severe shock, and uncontrollable chronic pain can cause disability. Pathological pain becomes an endogenous pathogenic factor in the development of new pathological processes and acquires the significance of an independent neuropathological syndrome or even a disease. Pathological pain is poorly corrected, and the fight against it is very difficult. If pathological pain occurs secondarily (with severe somatic diseases, malignant tumors, etc.), then often, causing excruciating suffering to the patient, it obscures the underlying disease and becomes the main object of therapeutic interventions aimed at reducing the patient's suffering [1,5,8,9].

LITERATURE REVIEW

Pathological pain of peripheral origin

This type of pathological pain occurs with chronic irritation of pain receptors (nociceptors), with damage to nociceptive fibers, spinal ganglia, and posterior roots. These structures become a source of intense and often constant nociceptive stimulation. Nociceptors can be intensively and for a long time activated during chronic inflammatory processes (for example, with arthritis), under the action of tissue decay products (for example, with tumors), etc. Chronically damaged (for example, when squeezing scars, overgrown bone tissue, etc.) and regenerating sensitive nerves degeneratively altered (under the action of various hazards, with endocrinopathies), and demyelinated fibers are very sensitive to various humoral influences, even to those to which they do not respond under normal condi-tions (for example, to the action of adrenaline, K^+ ions, etc.). Areas of such fibers become an ectopic source of constant and significant nociceptive stimulation [6,10-12].

A particularly significant role of such a source is played by a neuroma – a formation of chaotically overgrown, intertwined sensory nerve fibers, which occurs during their disordered and difficult regeneration. These endings are very sensitive to various mechanical, thermal, chemical, and endogenous influences (for example, to the same catecholamines). Therefore, attacks of pain (causalgia) with neuromas, as well as with nerve damage, can be triggered by various factors and changes in the state of the body (for example, during emotional stress) [13].

Nociceptive stimulation from the periphery can cause an attack of pain if it overcomes the so-called "gate control" in the posterior horns, which consists of an apparatus of inhibitory neurons (neurons of the gelatinous substance play an important role in it), which regulates the flow of passing and ascending nociceptive stimulation. Such an effect can occur with intense stimulation or with insufficient inhibitory mechanisms of "gate control" [6,14,15].

Pathological pain of central origin

This type of pathological pain is associated with the hyperactivation of nociceptive neurons at the spinal and supraspinal levels. Such neurons form aggregates, which are generators of pathologically enhanced excitation (GPEE). According to the theory of genera-tor mechanisms of pain, GPEE is the main and universal pathogenetic mechanism of pathological pain. It can be formed in various parts of the nociceptive system, causing the occurrence of various pain syndromes. With the formation of GPEE in the posterior horns of the spinal cord, a pain syndrome of spinal origin occurs, in the nuclei of the trigeminal nerve - trigeminal neuralgia, in the nuclei of the thalamus - thalamic pain syndrome. The clinical picture of central pain syndromes and the nature of their course depend on the structural and functional features of those parts of the nociceptive system in which the GPEE arose, and on the characteristics of the GPEE activity [10,16,17].

Following the stages of development and mechanisms of GPEE activation in the early stages of the pathological process, an attack of pain caused by the activation of the GPEE is provoked by nociceptive stimuli from a certain receptive field directly related to the GPEE (pain projection zone), in the later stages, the attack is provoked by stimuli of different intensity and different modality, from different receptor fields, and can also occur spontaneously. The peculiarity of an attack of pain (paroxysmal, continuous, short-term, prolonged, etc.) depends on the features of the functioning of the GPEE. The nature of the pain itself (dull, acute, localized, diffuse, etc.) is determined by what formations of the nociceptive system, realizing the corresponding types of pain sensitivity, have become parts of the pathological (Algic) system underlying this pain syndrome. The role of the pathological determinant, which forms the pathological system of this syndrome, is played by the hyperactive formation of the nociceptive system, in which the primary GPEE arose. For example, in pain syndrome of spinal origin, the role of the pathological determinant is played by the system of hyperactive nociceptive neurons of the posterior horn (I–III or/and V layers) [17].

GPEE in the central apparatus of the nociceptive system is formed under the influence of various factors. It can occur with prolonged nociceptive stimulation from the periphery. Under these conditions, pain originally of peripheral origin acquires a central component and becomes a pain syndrome of spinal origin. This situation occurs with chronic neuromas and damage to the afferent nerves, with neuralgia, in particular with trigeminal neuralgia [17,18].

GPEE in the central nociceptive apparatus can also occur during deafferentation, due to an increase in the sensitivity of deafferented nociceptive neurons and a violation of inhibitory control. Deafferentation pain syndromes can appear after amputation of limbs, transection of nerves and posterior roots, and after a break or transection of the spinal cord. In this case, the patient may feel pain in a devoid of sensitivity or a non-existent part of the body (for example, in a non-existent limb, in parts of the body below the spinal cord transection). This type of pathological pain is called phantom pain (from the phantom - ghost). It is due to the activity of the central GPEE, the activity of which no longer depends on nociceptive stimulation from the periphery [17,19].

GPEE in the central parts of the nociceptive system can occur with infectious damage to these parts (herpetic and syphilitic lesions,

trauma, toxic effects) [19].

In the experiment, such GPEE and the corresponding pain syndromes are reproduced by introducing into the corresponding parts of the nociceptive system substances that either causes a violation of inhibitory mechanisms or directly activate nociceptive neurons (tetanus toxin, penicillin, K^+ ions, etc.) [2,17].

In the central apparatus of the nociceptive system, secondary GPEE can form. So, after the formation of GPEE in the posterior horns of the spinal cord, after a long time, a secondary GPEE may occur in the thalamus. Under these conditions, the primary GPEE may even disappear, however, the projection of pain to the periphery may remain the same since structures of the same nociceptive system are involved in the process. Often, when the primary GPEE is localized in the spinal cord, to prevent the receipt of impulses from it to the brain, a partial (break in the ascending tracts) or even complete transection of the spinal cord is performed. This operation, however, has no effect or causes only short-term relief of the patient's suffering [17, 19,20].

Antinociceptive system

The nociceptive system has its functional antipode – the antinociceptive system, which controls the activity of the structures of the nociceptive system [21].

The antinociceptive system consists of a variety of nerve formations belonging to different departments and levels of organization of the CNS, starting from the afferent input in the spinal cord and ending with the cerebral cortex. Each relay switch in the nociceptive system has its control apparatus for the activity of its constituent nociceptive neurons. The regulatory activity of the antinociceptive system is carried out by various specialized neurophysiological and neurochemical mechanisms. The nociceptive and antinociceptive systems constitute a common system of pain sensitivity, which determines the nature of the nociceptive signaling, the degree of its perception, and the reaction to it [21,22].

The antinociceptive system plays an essential role in the mechanisms of prevention and elimination of pathological pain. Being included in the reaction with excessive nociceptive stimuli, weakens the ascending flow of nociceptive stimulation and the intensity of pain, so that pain remains under control and does not acquire pathological significance. When the activity of the antinociceptive system is disturbed, nociceptive stimuli of even low intensity cause excessive pain. Such an effect occurs, for example, in congenital or acquired insufficiency of the antinociceptive mechanisms of the spinal cord, in particular, in the insufficiency of the "gate control", in violation of the conduction of excitation through thick fibers that activate this control, in trauma, infectious lesions of the central nervous system, etc. It is known that with the loss of localized epicritic pain sensitivity, diffuse protopathic pain may be extremely intensified [21-23].

In all cases of insufficiency of the antinociceptive system, its additional and special activation is necessary. The latter is carried out in various ways. Effective direct electrical stimulation of antinociceptive structures of the brain can cause the suppression of even severe pathological pain. This method is used in the clinic. Thus, electrical stimulation of the raphe nuclei with the help of chronically implanted electrodes is often the only way to suppress pain attacks. Many analgesics, in particular opioid ones, exert their effect not only through a direct suppressive effect on nociceptive neurons and blockade of synaptic transmission of excitation but also through the activation of structures of the antinociceptive system. Through the activation of the antinociceptive system, non-drug means of pain suppression (for example, acupuncture) also act. Electrical stimulation of thick fibers, which activates "gate control" and other mechanisms of the antinociceptive system, is used in the clinic to suppress many types of pain, especially of peripheral origin [22].

At the same time, hyperactivation of the antinociceptive system can cause inadequate hypoalgesia and even profound suppression of pain sensitivity. Such effects occur during the formation of GPEE in the structures of the antinociceptive system. Hysterical loss of pain sensitivity, analgesia that occurs during severe stress, and some psychoses are also associated with increased activity of the antinociceptive system [21, 22].

Neurochemical mechanisms of pain

Functional neurophysiological mechanisms of the activity of the pain sensitivity system are implemented by neurochemical pro-cesses at various levels of the nociceptive and antinociceptive systems [21,24].

Peripheral nociceptors are activated under the influence of many endogenous biologically active substances – histamine, substance P, kinins, prostaglandins, etc. Substance P plays an important role in conducting excitation in primary nociceptive neurons. It is considered a pain mediator. Capsaicin (a substance found in red peppers) causes impaired synthesis of substance P; the introduction of capsaicin intrathecally in the spinal cord region causes prolonged analgesia; the analgesic effect of pepper patch may be related to the action of capsaicin. In the overlying levels of the nociceptive system, there is also substance P, however, excitation in them is carried out mainly by those neurotransmitters that are inherent in the neurons of these levels. Various neuropeptides take part in the processes of conducting excitation in different parts of the nociceptive system, which, like in other parts of the CNS, play the role of neuromodulators [6,11,24,25].

The neurochemical mechanisms of the activity of the antinociceptive system are implemented by endogenous neuropeptides and the so-called classical neurotransmitters. Analgesia is caused, as a rule, by the combined or sequential action of several transmitters [22].

Very common and effective endogenous analgesics are opioid neuropeptides (enkephalins, endorphins, dynorphins). They have a depressing effect on the transmission neurons and an activating effect on the neurons of the antinociceptive system, stimulate the system of diffuse nociceptive inhibitory control (DNIC), change the activity of neurons in the higher parts of the brain that perceive nocicep-

tive stimulation and participate in the formation of pain; their effects are also realized through the action of serotonin, norepinephrine and other neurotransmitters. Other neuropeptides also cause analgesia (neurotensin, cholecystokinin, bombesin, angiotensin-II, vasopressin, etc.). Substance P can also cause analgesia and suppression of even pathological pain when it acts on antinociceptive structures, for example, on the dorsal raphe nucleus. Its fragments can cause opposite effects – enhance hyperalgesia or algesia. The final aspect of substance P depends on which fragment of it and on which structures of the pain sensitivity system it acts. Since neuropeptides, as modulators of neuronal activity, can enhance and weaken various neuronal reactions (the polyfunctional action of neuropeptides), they can activate the structures of both nociceptive and antinociceptive systems [22,23, 25,26].

Of the classic neurotransmitters, serotonin, norepinephrine, dopamine, and GABA play an important role in the implementation of analytical effects. Serotonin is a mediator of the antinociceptive system at the spinal level. At the same time, one of the parts of the serotonergic system takes part in the activity of the nociceptive system, expanding the fields of nociceptive sensitivity [22,26].

Norepinephrine is also a mediator of the descending antinociceptive system; it suppresses the activity of nociceptive neurons of the posterior horns of the spinal cord and the nuclei of the trigeminal nerve. In addition, norepinephrine suppresses pain mechanisms at the supraspinal level. Its analgesic effect is associated with the activation of α-adrenergic receptors, as well as with the involvement of the serotonergic system. Therefore, the activator of central α-adrenergic receptors clonidine causes a pronounced analgesic effect [22, 26, 27].

GABA is involved in the suppression of the activity of nociceptive neurons and pain at the spinal level. Violation of GABAergic inhibitory processes (for example, by exposing the posterior horns to tetanus toxin, penicillin, etc.) causes the formation of HPUV in them and a severe pain syndrome of spinal origin. At the same time, GABA can inhibit the neurons of the antinociceptive structures of the midbrain and medulla oblongata and, thus, weaken the pain relief mechanisms that occur at this level. Endogenous enkephalins can weaken the GABAergic inhibition of these neurons and thereby enhance the descending antinociceptive effects, which is one of the mechanisms of endogenous opioid analgesia [22,26].

Principles of treatment of pathological pain

The main principle of the treatment of pathological pain is to suppress the hyperactivity of nociceptive neurons and the GPEE formed by them and to eliminate the pathological (Algic) system underlying the corresponding pain syndrome [17,28].

This goal is achieved by a combination of two kinds of influences: 1) influence on nonspecific, standard basic processes of neuronal hyperactivation, formation, and activity of GPEE, which are fundamentally the same in different parts of the CNS; 2) influence on specific neurochemical processes associated with the activity of different nociceptive neurons, different GPEE and different nociceptive pathological systems [29].

Correction of the basic processes of hyperactivation of neurons and the formation of GPEE can be carried out with the help of anticonvulsants (antiepileptic drugs). Thus, the use of the antiepileptic drug carbamazepine (Tegretol, finlepsin) for the treatment of trigeminal neuralgia and other pain syndromes, especially acute paroxysmal nature, gives a high therapeutic effect. Suppress some pain syndromes and other anticonvulsants. Of paramount importance for suppressing the hyperactivity of nociceptive neurons is the blockade of Ca^{2+} entry into them, which is carried out with the help of Ca-antagonists. Activation of the antinociceptive system is essential for regaining control and suppression of hyperactive nociceptive neurons and GPEE [17, 28,29].

Since nociceptive and antinociceptive effects are realized at different levels and not by one, but by several mediators, it is advisable to use complex pathogenetic therapy in the form of a combined effect on different links of the pathological (Algic) system to suppress it and the antinociceptive system to activate it. In addition, it is also important to influence the psycho-emotional, vascular, and other vegetative and tissue components of pathological pain. It is necessary to eliminate the effect of the etiological factor that supports pathological changes in the nociceptive system [29,30].

CONCLUSION

Thus, the study of the mechanisms of pain will serve as a fundamental basis for detailing the pathogenesis of various diseases, as well as for the creation of new analgesics.

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