NOCECEPTIVE SYSTEM:
FEATURES OF PHYSIOLOGICAL BASES OF FUNCTIONING

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Abstract. This article is devoted to the features of the physiological functioning of
the nociceptive system. Nociception is a neurophysiological term that describes the totality
of the perception, conduct, and processing of signals about processes or effects. Accordingly,
the system itself, which implements the translation of such signals, is called nociceptive.
The concept of pain reflects a kind of subjective experience accompanying nociception. In addition,
there are reactions to nociceptive irritation in the depressed mind. This article reflects
the hypotheses that form the concept of a nociceptive system and the physiological mechanisms
of perception, analysis and response to nociceptive information. Over the past decade, there has been
tremendous progress in the study of the molecular features of phenomena and processes.
Multicomponent reactions initiated by the reception of pain, develop according to certain
algorithms, referring to the parameters of nociceptive signals, where the study of molecular markers
is particularly promising. In the body there is also a specialized response to nociceptive information,
which is called the antinociceptive system. The results of many years of research have revealed
correlation parallels and significantly significant differences in the neurophysiological and
neurochemical mechanisms of pain in a given pathological condition.

Аннотация. Данная статья посвящена особенностям физиологического
функционирования ноцицептивной системы. Ноцицепция — нейрофизиологический термин,
который характеризует совокупность восприятия, проведения и обработки сигналов о
процессах либо воздействиях. Соответственно сама система, реализующая трансляцию
объектных сигналов, получила название ноцицептивной. Понятие боль отражает некое субъективное переживание, сопровождающее ноцицепцию. Помимо того, встречаются реакции на ноцицептивное раздражение при угнетенном сознании. В данной статье отражены гипотезы, формирующие концепцию ноцицептивной системы и физиологические механизмы восприятия, анализа и реагирования на ноцицептивную информацию. За последнее десятилетие наметился огромнейший прогресс в изучении молекулярных особенностей явлений и процессов. Мультicomponentные реакции, инициируемые рецепторами боли, развиваются по определенным алгоритмам, обращаясь к параметрам ноцицептивных сигналов, где особенно перспективным выступает изучение молекулярных маркеров. В организме присуществует и специализированная реакция на ноцицептивную информацию, которая обеспечивается наличием антinoцицептивной системы. Результаты многолетних исследований выявили корреляционные параллели и достоверно значимые отличия в нейрофизиологических и нейрохимических механизмах возникновения боли при том или ином патологическом состоянии.

**Keywords:** nociception, nociceptive system, physiological basis.

**Ключевые слова:** ноцицепция, ноцицептивная система, физиологические основы.

Perhaps, one of the main functions of the nervous system, with all its species specificity [1, p. 1236], is the common feature of signalling the threat of damage and mobilizing the whole complex of protective and adaptive mechanisms [3, p. 1133].

Nociception is a neurophysiological term that describes the totality of the perception, conduct, and processing of signals about processes or effects [5, p. 10655]. Accordingly, the system itself [2, p. 350], which implements the translation of such signals, is called nociceptive.

The proven fact is that pain is a reflection of the subjective state of the nociceptive system. Subsequently, multicomponent reactions initiated by pain arise depending on the intensity, strength and, accordingly, other characteristics of the nociceptive flow and the realization of the peripheral response.

Thus, in accordance with the recommendations of the IASP (International Association for the Study of Pain), it is necessary to clearly distinguish between pain and nociception [4, p. 5437; 9, p. 772].

Pain is often a negative and negative physiological process, but it also warns about the presence of failures in the body.

The concept of pain reflects a kind of subjective experience accompanying nociception. In addition, there are reactions to nociceptive irritation in the depressed mind, for example, during anaesthesia. Many scientists note that the intensity of pain does not always correspond to the degree of metabolic disorders. Thus, the literature describes cases when pain serves as a precursor to the severity of the injury, for example, it has been established that pain cannot serve as a predictor of injury since the body's adaptive reserves are in direct correlation with age and the level of blood biochemical parameters.

Historically, there are 3 hypotheses, which in turn form the concept of a nociceptive system: Specificity hypothesis — there is a cascade of species-specific nociceptors that respond exclusively to the most powerful superthreshold stimuli [10, p. 334]. The hypothesis of intense irritation is as follows: any receptor complex is capable of producing pain impulses due to prolonged stimulation. The distribution hypothesis is based on the coding of biological damage signals. It is well known that the reticular formation is a zone of perception and interpretation of nociceptive signals.
The body's response to damage is formed as follows: first, there is the initiation of pain impulses (nociception); due to the integration of nociceptive signals, pain is formed; the occurrence of stress is manifested in the form of anxiety, anxiety, and suffering, this is precisely what causes the motor–behavioural response of the organism.

Somatic pain is determined by the irritation of the mechanic–nucleoceptors or thermoreceptors, Hemon–receptors realize the acceptance of the signal associated with the effects of biologically active substances, which are produced during tissue ischemia with the development of energy–deficient states.

Actually, the fight against pain lies at the basis of the therapeutic action of all medical specialities, but above all in anesthesiology, where the control of pain and stress, i.e. antinociception is the main specificity of the work. Unresolved pain is not only a frequent cause of unstable hemodynamics during surgical interventions but also a factor preventing recovery.

The study of the processes and phenomena occurring in the nervous system, caused by exposure to nociceptive stimuli, fully begins with research C. Bell (1811), & F. Magendie (1822) and I. M. Sechenov (1863) in the era of establishing the relationship of the reflex influence of the spinal cord and brain on the organism as a whole [6, p. 45].

Since 1894, the first hypotheses were put forward reflecting the mechanisms of pain perception [7, p. 1744], and the confrontation between supporters of these theories continues to this day. According to the theory put forward by M. Frey, pain is not a physical sensation, and there are no special receptors that perceive only pain irritation. The feeling of pain is associated with receptor irritation, provided that the strength of receptor stimulation is super–threshold. According to the hypothesis of A. Goldscheiders, there are special pain receptors that are excited only by stimuli of the “destructuring” intensity of specialized stimuli.

Today, nociception represents a chain of successively interconnected processes — transduction, transmission, modulation and perception, and also touch sensory pain unit, in the modern sense — is a nociceptor consisting of a receptor apparatus in a cascade with afferent nerve fibres.

Thanks to modern achievements of science, the initiation component of the process of nociception are practically studied in detail. Various chemicals can be used as this component (substance P, NO₂, immunoreactive substances, etc.).

Synthesis of these substances is observed in the case of alteration of cellular structures, a distinctive feature is their ability to bind with receptors on nociceptor membranes with minimal titers and activating the process of excitation.

Damaged membranes act as a trigger for the immuno–inflammatory response, so under the influence of hydrolases, arachidonic acid derivatives begin to be synthesized and metabolized to biologically active components, among which prostaglandins, namely, prostaglandin E₂, the level of which is correlated to the intensity of the immune–inflammatory response, are most significant; syndrome Nociceptors are distinguished by their different sensitivity to heterogeneous stimuli/stimuli. Some nociceptors respond exclusively to stimuli of a chemical nature, others only to temperature or mechanical stimuli. There are also nociceptors that, under physiological conditions, do not respond to any known stimulus, and the process of excitation occurs in them only in cases of violation of the integrity of cellular structures.

Activation of nociceptors can also be carried out retrograde due to irritation of peripheral nerves or sensory roots. In this case, substance P, neuropeptide A, calcitonin–gene–reactive peptide, which not only have a vasodilating effect [11, p. 349] but also increase the permeability of the vascular wall for plasma algogens are secreted from the terminals of C–nociceptors.
At the same time, they promote the release of immunoreactive substances from mast cells and leukocytes, which leads to the development of aseptic neurogenic inflammation and initiates the activation of nociceptors [12, p. 1270].

The received signals along the A1 and C fibres are carried to the spinal cord and brain stem [4, p. 5437], where they are switched to the central neurons through synapses, and taking the form of motor and vegetative impulses, are sent partially efferently to the executive organs, and partially afferently, through the ascending paths, transmitted further to the brain. At the spinal level, the inhibitory effect on pain also begins to form. In the brain from the thalamus, the ascending information is distributed in the limbic system, the hypothalamus, the pituitary gland and the somatosensory cortex. Nociceptive impulses are analyzed using the total cortical potential and are transformed into psychosomatic reactions.

The body has a special physiological mechanism for responding to nociceptive information, which is commonly called the endogenous antinociceptive system. This system is capable of triggering compensatory and adaptive metabolic mechanisms. During surgical aggression in the regulation of these mechanisms, the leading role belongs to $\alpha$-aminobutyric acid (GABA) [10, p. 334]. In response to stress, GABA inhibits excessive release of catecholamines and corticosteroids and also provides additional energy production. Another important element of the endogenous antinociceptive system is the opioid mechanism, the essence of which is the release of secretory granules and cells localized in the brain [11, p. 349], endorphins and enkephalins in response to the activation of catecholamines, which inhibits their extraordinary activity and also increases the resistance of tissues to hypoxia. Along with GABA and opioids, a number of other metabolic mechanisms regulated by serotonin, histamine, substance P, catecholamines and other neurohormonal factors are involved in the antinociceptive system [12, p. 1275].

Knowledge of the physiological mechanisms of nociceptive processes in the body is constantly deepening. However, over the past 20 years, there has been a marked increase in interest in the fundamental mechanisms of pain [4, p. 5438; 8, p. 2]. It should also be borne in mind that recent studies have found significant differences in the neurophysiological and neurochemical mechanisms of pain in various pathological conditions. On the basis of etiopathogenesis, all pain syndromes are divided into 3 main groups: somatogenic (nociceptive), neurogenic (neuropathic) and psychogenic pain syndromes.

It has long been known that a nerve impulse is a propagating action potential, which is caused by multidirectional flows of ions (primarily Na⁺ and K⁺) through the lipid neuronal membrane through ion channels, which are a protein complex. These channels can be open, closed or inactivated. The driving force behind the movement of ions through the open channel is the concentration gradient and the electric potential difference.

In cells of the spinal ganglia, the afferent signal causes the formation of neuropeptides (mainly substance P is a peptide of 11 amino acid residues [5, p. 10660], calcitonin gene–reactive peptide CGRP, and glutamate and other amino acids), which enter both the spinal cord and the brainstem, and in the peripheral nerve endings. Thus, neuropeptides play the role of neuromodulators of pain reactions (modulation), also taking part in the processes of CNS excitability [3, p. 1133] and the regulation of blood circulation along with the sympathetic nervous system. At the same time, neuropeptides, in contrast to sympathetic vasoconstriction, cause vasodilation, extravasation and increase the sensitivity of nociceptors, which is manifested by «neurogenic oedema» and hyperalgesia [1, p. 1236]. This leads to a further increase in the release of neuropeptides, closing the vicious circle.

Under normal conditions, a neuron receives from the innervated organ a variety of signalling substances that ensure tropism of nerve cells, the so-called neurotrophins. These substances reach
the cell nucleus and control the transcription of genes so that the protein necessary for the special function of the neuron is synthesized on site.

Under pathological conditions, there is a shortage of signalling substances from the target organ and is synthesized or a typical regenerative protein GAP (growth associated protein) required for nerve regeneration, or cell death (apoptosis) is programmed if regeneration is impossible [4, p. 5449]. In the spinal ganglion neuron, the choice is one of the two directions to regeneration or apoptosis — occurs with the help of the rapidly inducing c–jun gene [7, p. 1750]. The phosphorylation of c–jun by jun–kinase is an early signal of the path to regeneration.

Recently, our understanding of the effects of pain in the chemical–physiological direction has expanded. In particular, it became possible to explain the physiology of pain at the gene level, which led to the creation of pharmacogenetics. It is believed [2, p. 360] that at present it is impossible to do without knowledge of pharmacogenetics in opioid therapy, not only in surgery but also in the outpatient clinic.

It has been established that with prolonged nociceptive stimulation, fast–inducing genes (IEG — immediate early genes) are activated, for example, the c–jun gene. Its encoded c–jun protein, being a transcription factor, controls many other genes: c–Fos, jun–D, Krox-24 [10, p. 335]. These nuclear proteins are transcription factors that control, by binding on the promoter region of the DNA, the expression of other nerve cell genes. As a consequence, there may be changes in transcription and, thus, the target gene, which, with continuous action, causes changes in the biochemistry and function of the nervous system. Such plasticity is considered as a biologically rational adaptive process, compensating for the harmful loss of sensitization. Today, mediator systems have been established that, through the association of IEG with the DNA chain, induce or enhance the expression of a large number of other genes, which intensifies pain (NO synthetase, galanin, dynorphin) or decreases it (GABA, opioid receptors).

A cascade of intracellular signals reaching the intracellular nucleus is involved in the described transcription mechanisms. Many of these signals are already known, such as high–energy phosphatases, calcium ions, phospholipase and protein kinase. In addition, neurotransmitters, cytokines, growth hormones or oxidative stress–like activating factors act in various cellular systems. At the same time, the pain–specific intracellular signalling cascades or IEG samples have not yet been found. It follows that all potentially damaging stimuli activate pain [12, p. 1273]. Nociceptive processes, causing deep biochemical changes in the functions of the nervous system, lead to a further increase in the lack of neuronal function of the vicious circle.

Modern ideas suggest that pathological pain is the result of dysregulation processes in nociception systems that affect both the intracellular mechanisms regulating the excitability of neurons and the mechanisms of interneuronal interaction [9, p. 778]. The concept of the antinociceptive system, along with the concept of the antiepileptic system, represents the development of the general biological principle of antagonistic regulation [3, p. 1133]. The concept of antinociceptive anaesthesia arose, which would not only prevent or limit the nociceptive effects of operational stress by blocking nociceptive information but would also stimulate the activity of the antinociceptive system and defensive reactions aimed at eliminating the energy structural deficit [12, p. 1271].

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