International Journal of Trend in Scientific Research and Development (IJTSRD)
Special Issue on Modern Trends in Science, Technology and Economy
Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Pathophysiological Mechanisms of Pain Syndromes

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ABSTRACT

Pain is the most common symptom that causes suffering to millions of people and for a doctor, pain treatment is one of the first tasks. Thanks to numerous electrophysiological, morphological, neurochemical and clinical studies, significant material has been accumulated to date on the study of pain mechanisms. Experimental data on the role of free nerve endings in the perception of damaging stimuli were obtained, a clear connection was revealed between the A-delta and C-afferent fibers of peripheral nerves with pain sensations in humans, the main ascending pathways and nerve structures of the spinal cord, brain stem, visual tubercle and cerebral cortex, which transmit and process pain information, were traced. Neurotransmitters mediating pain reactions have been identified. The structures of the spinal cord and brain, chemicals and their receptors providing pain suppression have been established. Subtle mechanisms of interneuronal interaction in changing pain sensitivity in inflammation, trauma, ischemia, and damage to nerve structures are shown. And finally, the important role of the psychological state of a person in the perception of pain is clearly demonstrated. Understanding the essence of pain, the mechanisms that regulate pain sensitivity, and a clear understanding of the etiopathogenesis of pain syndromes are the key to their successful treatment.

KEYWORDS: *Zakharyin-Ged zone, somatogenic pain, reflected pain, nociceptive pain, neurogenic pain, psychogenic pain*

Currently, there are several classifications of pain. Depending on the location of the injury, the pain is divided into: somatic superficial (in case of damage to the skin), somatic deep (in case of damage to the musculoskeletal system), visceral (in case of damage to internal organs). The pain that occurs when peripheral nerves are damaged is referred to as neuropathic pain, and when the structures of the central nervous system are damaged, it is referred to as central pain. Often, the pain felt by a person does not coincide with the place of injury. In this case, we can talk about projection pain and reflected pain. Projection pain occurs as a result of irritation or damage to nerve structures that provide pain signals to the central structures of the brain. For example, when the spinal roots are compressed, pain is felt in the area of the body innervated by them. Reflected pain occurs due to damage to internal organs and is localized in remote surface areas of the body. It is often felt in those parts of the body that are innervated by the same segment (segments) of the spinal cord as the affected internal organ. In other words, in relation to the skin surface, the pain is reflected on the corresponding dermatome. Many organs are innervated by more than one spinal segment, in such cases, the pain is reflected in several dermatomes. Together they represent the Zakharyin-Ged zone for this body. According to the time parameters, acute and chronic pain are distinguished. Acute pain is a new, recent pain that is inextricably linked to the damage that caused it and, as a rule, is a symptom of some disease. Such pain disappears when the damage is eliminated. Chronic pain often acquires the status of an independent disease, lasts for a long period of time even after the elimination of the cause that caused acute pain. In some cases, the cause of chronic pain may not be determined at all. Nevertheless, such pain is not a "figment of the imagination", but arises as a result of violations in the work of systems that regulate pain sensitivity. In the clinic, etiological classification is used to focus on the causes of pain. Examples of such pains are: postoperative pain, oncological pain, arthritis pain, etc. The pathogenetic classification of pain syndromes is based on the identification of the main, leading mechanism in the formation of pain, which significantly affects the choice of therapeutic agents. There are three main types of pain syndromes: somatogenic (nociceptive), neurogenic and psychogenic. Pain syndromes resulting from the activation of nociceptors in trauma, inflammation, ischemia, stretching of tissues are referred to as somatogenic pain syndromes. In turn, somatogenic pain is divided into somatic and visceral. Clinically, among them are: post-traumatic and postoperative pain syndromes, pain with inflammation of joints, muscles, pain in cancer patients, pain with cholelithiasis and many others. The development of neurogenic pain syndromes is associated with damage to the structures of the peripheral or central nervous systems involved in conducting nociceptive signals. The most typical examples of neurogenic pain syndromes are neuralgia (trigeminal), complex regional pain syndrome, phantom pain syndrome, painful mono- or polyneuropathies, deafferentation pains (with traumatic avulsion of the brachial plexus), thalamic pains. A special group consists of psychogenic pains or pains of a psychological nature, which occur regardless of somatic, visceral or neuronal injuries and are largely determined by psychological and social factors. Determining in the mechanism of the occurrence of psychogenic pain is the mental state of a person caused by depression, hysteria or psychosis. Etiopathogenesis of somatogenic pain syndromes. As already mentioned, somatogenic pain syndromes occur as a result of the activation of nociceptors in damaged tissues. When the surface tissues are damaged, patients experience acute pain. In the case of involvement in the pathological process of muscles or bones, there is a feeling of dull, aching pain. This pain increases with movement and weakens at rest. Somatic pain is well localized and clearly felt in the affected area. The pain that occurs when visceral organs are damaged is usually poorly localized and is perceived as deep, compressive, cramping. It can be combined with nausea, vomiting, changes in heart rate and breathing depth, accompanied by profuse sweating. In the pathology of visceral organs, along with deep pain, areas of reflected surface and muscle pain appear. For example, with coronary insufficiency, along with chest pain, pain is often felt in the shoulder or little finger of the left hand, with cholelithiasis,

pain radiates to the area of the right shoulder blade. It should be remembered that the radiating pain can be much stronger than the pain in the area of the affected organ. Somatogenic pain syndromes are characterized by the appearance of areas of constant soreness and/or increased pain sensitivity at the site of injury. Over time, the zone of increased pain sensitivity can expand and cover healthy tissues. Areas with increased pain sensitivity or reduced pain perception thresholds are called hyperalgesia zones. Primary and secondary hyperalgesia are distinguished. Primary hyperalgesia develops in the area of damaged tissues, secondary hyperalgesia is localized outside the area of damage, spreading to healthy tissues. The zone of primary skin hyperalgesia is characterized by a decrease in pain thresholds and pain tolerance to damaging mechanical and thermal stimuli. Secondary hyperalgesia zones have a normal pain threshold and reduced pain tolerance only to mechanical stimuli. The pathophysiological basis of primary hyperalgesia is the sensitization of nociceptors - non-encapsulated nerve endings A δ (delta) and C-afferents. Sensitization (increased excitability) of nociceptors occurs as a result of the action of algogens - substances released from damaged cells (histamine, serotonin, ATP, leukotrienes, interleukin-1, tumor necrosis factor, endothelins, prostaglandins, nitric oxide, etc.) formed in blood plasma (bradykinin) and released from the terminals of C-afferents (substance P, neuro-kinin A). Substance P and neurokinin A, being released from the peripheral terminals of C-afferents and increasing the permeability of the vascular wall, can lead to the development of neurogenic inflammation. In addition, they promote the release of prosta-glandin E2, cytokines (interleukins, tumor necrosis factor) and biogenic amines from mast cells and leukocytes, which, acting on the membrane of nerve endings, trigger metabolic processes that increase the excitability of nociceptive afferents. The efferents of the sympathetic nervous system increase neurogenic inflammation, which also contributes to the sensitization of nociceptors and the development of primary hyperalgesia. At the same time, it must be remembered that under normal conditions nociceptors are not sensitive to catecholamines. The activating effect of sympathetic efferents is observed only in conditions of inflammation or tissue damage, when there is already sensitization of nociceptors. It is very important that the presented mechanisms of sensitization are characteristic of nociceptors localized in any tissue, and the development of primary hyperalgesia is noted not only in the skin, but also in muscles, joints, bones and internal organs. An essential point is the ability of nociceptors to change their phenotype during the prolonged course of the inflammatory process in the surrounding tissues. Under these conditions, the increased sensitivity of nociceptors to damaging stimuli is determined not only by algogens, but also by a change in the nociceptor membrane of an ensemble of receptors interacting with the corresponding ligands. In particular, an increase in the number of μ- and a decrease in γ- and κ-opioid receptors has been shown. These plastic changes of nociceptors are caused by activation of early response genes (immediate-early genes), such as c-Jun, JunD. These genes express transcription factors, through which effector genes encoding the formation of receptors and peptides involved in the mechanisms of excitation of nociceptor inhibition are controlled. The appearance of secondary hyperalgesia zones after tissue damage is associated with the sensitization of central nociceptive neurons and mainly neurons located in the dorsal horns of the spinal cord. The area of secondary hyperalgesia can be located not only around the injury area, but also be removed from the injury site or even located on the opposite side of the body. The term sensitization of nociceptive neurons is understood as an increase in their excitability, which is characterized by an increase in spontaneous activity of neurons and an increase in their sensitivity to mechanical stimuli. Sensitized neurons in response to stimuli not only generate discharges with increased frequency, but also maintain increased activity for a longer time. One of the mechanisms underlying the sensitization of nociceptive neurons is the phenomenon of "wind-up" or a progressive increase in the frequency of action potentials generated by nociceptive neurons in response to repeated stimulation of C-afferents. This increased excitability of nociceptive neurons persists for several seconds after the last stimulation of C-fibers. It is believed that short-term pain stimuli cause short-term excitation of nociceptive neurons in the dorsal horns of the spinal cord due to the interaction of glutamate secreted by A-delta and C-afferents with α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptors of nociceptive neurons. In the case of repeated or longer stimulation of C-fibers, only an increase in the release of glutamate occurs, but also the secretion of neuropeptides - substance P, neurokinin A, calcitonin gene-related peptide, which, interacting with the corresponding receptors, independently excite nociceptive neurons and simultaneously potentiate the excitatory effect of glutamate through NMDA receptors (N-methyl-O-aspartate). Neurokinins, depolarizing the cell membrane, eliminate the blockade of NMDA-regulated channels by Mg2+ ions, after which the interaction of glutamate with NMDA receptors leads to the active entry of Ca2+ into the cell and the development of prolonged depolarization of nociceptive neurons. It should also be emphasized that the sensitization of nociceptive neurons, both in animals and in humans, develops even if the damaging effect is applied under general anesthesia. In other words, the phenomenon of central sensitization is also observed in the unconscious state and largely depends on the intensity of the nociceptive flow coming from the periphery to the central nervous system. As a rule, the sensitization of nociceptive neurons caused by damage to peripheral tissues persists for several hours or even days. This is largely due to the mechanisms of central neuroplasticity. Under conditions of increased intake of Ca2+ into neurons through NMDA-regulated channels, early response genes such as c-fos, c-jun, junB and others are expressed, which, through effector genes, change not only the metabolism of nociceptive neurons, but also the receptor ensemble on the neuronal membrane, as a result of which neurons remain hyperexcited for a long time. Activation of early response genes and, as a consequence, neuroplastic changes occur within 15 minutes after tissue damage. In addition to sensitization of nociceptive neurons of the dorsal horn, tissue damage initiates an increase in excitability of nociceptive neurons in the overlying centers, including the thalamus nuclei and the somatosensory cortex of the large hemispheres. Thus, peripheral damage can trigger a cascade of pathophysiological and regulatory processes affecting the entire nociceptive system from tissue receptors to cortical neurons, causing persistent changes in excitability in them, leading to the development of primary and secondary hyperalgesia. It should be particularly noted that an increase in the excitability of nociceptive neurons in the structures of

the central nervous system inevitably causes reflex activation of motor neurons in the corresponding segments of the spinal cord and muscle contraction. Prolonged muscle tension initiates the mechanisms of neurogenic inflammation in them. Loci of painful muscle seals appear, which further enhances the afferent flow of nociceptive impulses into the structures of the central nervous system and, as a result, a greater number of central nociceptive neurons are excited. This vicious circle plays an important role in prolonging somatogenic pain and the development of chronic pain syndromes. At the same time, the damage triggers not only the mechanisms of sensitization of nociceptive neurons, but also activates antinociceptive systems that control the transmission of nociceptive signals to the central nervous system. It has been experimentally confirmed that with inflammation or damage to peripheral tissues during the first 3 hours, there is a compensatory increase in the activity of not only the opioid system, but also other inhibitory spinal systems that realize their effects through GABA and GABA receptors, α2-adrenoreceptors, etc. Activation of inhibitory presynaptic receptors restricts the secretion of glutamate and neurokinins from the central terminals of C-afferents. Inhibitory postsynaptic receptors hyperpolarize the membranes of neurons of the spinothalamic tract, which together leads to a decrease in NMDA-conditioned sensitization of neurons. And accordingly, in case of violation of the control mechanisms of nociceptive signals or in the case of severe damage to peripheral tissues, the inhibition efficiency of nociceptive neurons decreases and their persistent sensitization is formed. Clinical and experimental neuropathophysiological studies have convincingly proved that neurogenic pain syndromes occur when peripheral or central structures associated with nociceptive signals are involved in the pathological process. One of the proofs of this position is clinical observations indicating a deterioration of pain and/or temperature sensitivity in patients with neurogenic pain syndromes. Thus, in patients with mono- or polyneuropathies in the area of constant soreness, in addition to paresthesia and dysesthesia, there is an increase in pain thresholds for injection and nociceptive electrical stimulus. In patients with syringomyelia, pronounced pains appear when the pathological process spreads to the dorsal horns of the spinal cord, while there is a decrease in temperature and pain sensitivity. In patients with multiple sclerosis, attacks of pain paroxysms occur when nociceptive afferents of the trigeminal complex nuclei or afferents of the spinothalamic tract are involved in the pathological process. Patients with post-stroke pain note a decrease in temperature and pain sensitivity. In clinical practice, the term "thalamic pain" is often used as a synonym for central pain. At the same time, modern diagnostic methods, such as magnetic resonance imaging, reveal foci of damage in the "thalamic syndrome" not only in the nuclei of the thalamus, but also in the structures of the brain stem, midbrain, subcortical white matter and cerebral cortex. At the same time, the greatest probability of pain syndrome is observed in patients with damage to the structures of the somatosensory system - the lateral part of the medulla oblongata (Wallenberg-Zakharchenko syndrome), the ventrobasal complex of the thalamus, the posterior femur of the inner capsule, the postcentral gyrus of the cerebral cortex (1st somatosensory region) and the insular region (2nd somatosensory region). All this indicates that neurogenic pain syndrome can occur when any of the structures of the pain-conducting system are damaged. The most common causes of central pain are traumatic injuries of the spinal cord and brain, ischemic and hemorrhagic strokes, leading to a deficiency of somatosensory sensitivity, multiple sclerosis. At the same time, the development of central pains is noted not only in conditions of persistent focal damage to the structures of the central nervous system. So, about 2-3% of patients suffering from epilepsy experience pain during aura or partial seizures. The clinical picture of neurogenic pain syndromes is characterized by polymorphism of pain sensations, which is determined by the nature, degree and location of damage. Patients may experience persistent or paroxysmal pain. With incomplete, partial damage to peripheral nerves, plexuses or dorsal spinal roots, in most cases, acute periodic paroxysmal pain occurs, similar to an electric shock, lasting several seconds. In conditions of complete damage, pain in the denervated area is more often permanent. In the area of pain in patients with neurogenic pain syndromes, as a rule, changes in tactile, temperature and pain sensitivity are also detected in the form of paresthesia, dysesthesia, hyperpathy, allodynia, hyperesthesia and hypesthesia. Spontaneously arising sensations of tingling, numbness or crawling goosebumps belong to paresthesia. The perversion of the perception of stimuli when tactile or thermal stimuli are felt as painful or cold is called dysesthesia. A painful sensation that occurs in response to a slight mechanical irritation of the skin areas with a brush is defined as allodynia. Hyperpathy is a violation of sensitivity in the form of enhanced perception of ordinary stimuli and characterized by long-lasting unpleasant painful sensations after the cessation of irritation. Hyperesthesia and hypesthesia are respectively an increase or decrease in sensitivity to various types of irritation. In addition, the clinical picture of neurogenic pain syndromes may reveal muscle weakness or local autonomic disorders in the form of tissue swelling, changes in dermography, skin color and temperature. Trophic changes of the skin, subcutaneous tissue, hair and nails may be observed. The severity of pain in patients with neurogenic pain syndromes largely depends on various internal processes and external influences. Pain can be provoked by noise, bright light, changes in ambient temperature, emotional experiences, bowel movements, filling of the bladder, etc. Unlike somatogenic pain syndromes, pain caused by damage to the structures of the nociceptive system can be delayed and occur with a delay of up to 2-3 years. The variety of clinical symptoms in neurogenic pain syndromes suggests the existence of serious changes in the peripheral and central mechanisms of pain sensitivity regulation. Trophic changes of the skin, subcutaneous tissue, hair and nails may be observed. The severity of pain in patients with neurogenic pain syndromes largely depends on various internal processes and external influences. Pain can be provoked by noise, bright light, changes in ambient temperature, emotional experiences, bowel movements, filling of the bladder, etc. Unlike somatogenic pain syndromes, pain caused by damage to the structures of the nociceptive system can be delayed and occur with a delay of up to 2-3 years. The variety of clinical symptoms in neurogenic pain syndromes suggests the existence of serious changes in the peripheral and central mechanisms of pain sensitivity regulation. Ectopic discharges have an increased amplitude and duration of the signal, which can lead to cross-excitation in nerve fibers. Such cross-excitation of fibers or efaptic signal transmission is observed only in conditions of pathology and can serve as a basis for

dysesthesia and hyperpathy. The causes of spontaneous ectopic activity in damaged nerves can also include the appearance of mechanosensitivity of nerve fibers and an increase in their sensitivity to algogens. Normally, the axons of peripheral nerves are not sensitive to mechanical stimuli. In conditions of damage, the appearance of mechanosensitivity in them increases the range of stimuli that can cause the generation of action potentials. For example, a slight stretching of the nerve during movement or tremors from a pulsating artery can cause painful paroxysms. An increase in the excitability of nerve fibers in case of damage is noted already on the first day and largely depends on axonal transport. The sprouting (overgrowth) of the endings of damaged axons is accompanied by an increase in their sensitivity to prostaglandins and cytokines (interleukins, tumor necrosis factor), which also contributes to the generation of pathological activity in nerve fibers. Experimental studies have shown that subcutaneous injection of tumor necrosis factor (TNF) or its application to the surface of the sciatic nerve of a healthy rat leads to structural changes in the nerve, the appearance of ectopic discharges in A-delta and C-afferent fibers and the development of hyperalgesia. Other pro-inflammatory cytokines (IL-1, IL-6, IL-8) have a similar effect. Damaged nerve fibers become sensitive to catecholamines. It has been shown that intra-arterial administration of norepinephrine, application of α2-adrenergic receptor agonists or electrical irritation of the sympathetic ganglion in animals with a neuropathic pain model causes excitation of C-nociceptors and enhances hyperalgesia. At the same time, the mechanism of development of sensitivity to catecholamines of C-nociceptors in damaged nerves has not been fully elucidated. It is believed that the activation of C-afferents by sympathetic terminals is due to the formation (de novo) of a2-adrenergic receptors on the membrane of nerve fibers and neurons of dorsal ganglia. An important role in the mechanisms of increasing the excitability of nociceptors in nerve damage is assigned to the synthesis of "new" neuropeptides that are not typical for this nerve. It has been proved that the neurons of the dorsal ganglia, after damage to their axons, express the production of galanine, vasoactive intestinal polypeptide, neuropeptide Y, cholecystokinin. At the same time, the synthesis of substance P, calcitonin gene-related peptide and somatostatin decreases. The number of c-opioid receptors on the membrane of neurons of the dorsal ganglia also decreases. Thus, the change in the phenotype of nociceptors caused by nerve damage leads to an expansion of the list of stimuli capable of activating C-afferents, and consequently, to form a signal perceived by CNS structures as nociceptive. Phenotypic changes resulting from damage to peripheral nerves affect not only the cells of the dorsal ganglia and their peripheral axons, but also neurons in the central nociceptive structures, which leads to increased excitability and reactivity of neurons of the dorsal horns of the spinal cord and overlying structures of the somatosensory system. Patterns of pachinal activity of neurons were recorded in the dorsal horns of the spinal cord, in the thalamic nuclei, in the somatosensory cortex of the large hemispheres in animals with models of neuropathic pain, as well as in patients with deafferentiation pain syndromes. It is believed that such activity of neurons is not associated with peripheral stimuli, but is due to the phenomenon of deafferential hypersensitivity, which leads to disinhibition of neurons and increased signal transmission to the overlying levels of the central nervous system. This mechanism differs significantly from the mechanisms underlying the sensitization of nociceptive neurons in somatogenic pain. The development of the phenomenon of deafferential hypersensitivity is accompanied by the death of a part of nociceptive neurons in the structures of the spinal cord and brain with damage to peripheral nerves. The death of neurons in these conditions is caused by a "glutamate shock", i.e. excessive secretion of excitatory amino acids and neurokinins from the central terminals of nociceptors when they are damaged. The resulting trans-synaptic degeneration is observed not only in the dorsal horns of the spinal cord, but also in the nuclei of the thalamus and the somatosensory cortex of the large hemispheres. Deafferential hypersensitivity in the overlying structures also develops with ischemic damage to neurons or non-infectious inflammatory processes (multiple sclerosis, syringomyelia). As a rule, the replacement of dead neurons with glial cells leads to an increase in the concentration of extracellular K+ and contributes to the emergence of stable depolarization of neurons in the structures of the central nervous system, which is manifested by an increase in their activity. Another important reason contributing to the disinhibition of nociceptive neurons during peripheral denervation is a decrease in the number of opioid receptors in the dorsal ganglia and dorsal horns of the spinal cord. These receptors play an important role in the mechanisms of regulation of pain sensitivity, carrying out pre- and postsynaptic inhibition of nociceptive neurons. In rats with a model of pain neuropathy, the maximum decrease in opioid receptors in the spinal cord coincided with the development of hyperalgesia, and in patients suffering from neuropathic pain, an inverse correlation was found between the content of met-enkephalin in the cerebrospinal fluid and the degree of pain syndrome. In the mechanisms of inhibitory reactions suppression in neurogenic pain syndromes, glycine and GABAergic inhibition deficiency is of significant importance. GABAergic interneurons are present mainly in the II-V plates of the dorsal horn. Glycine co-exists with GABA in many, but not all, GABAergic neurons. GABA- and glycine-containing neurons are activated by peripheral thick myelinated fibers, as well as descending supraspinal afferents. As a result of GABA secretion and activation of presynaptic GABA- and partly GABA-receptors, there is a decrease in the release of neurotransmitters from the central terminals of primary afferents. By activating postsynaptic GABA receptors and glycine receptors, hyperpolarization and inhibition of the activity of neurons of a wide dynamic range of the horn is carried out. In animals with models of neuropathic pain, a decrease in the number of GABAergic neurons in the dorsal horns of the spinal cord was found. A deficiency of spinal glycine and GABAergic inhibition also occurs in local spinal cord ischemia (a model of central pain syndrome), leading to the development of neuronal hyperexcitability and allodynia. Intra-spinal (subarachnoid) administration of GABA receptor antagonists (bicuculin) or glycine receptors (strychnine) causes the development of pain syndrome in animals, accompanied by significant hyperactivation of neurons of the dorsal horns of the spinal cord. Conversely, the use of GABA- and GABA-receptor agonists with neurogenic pain syndromes showed their high therapeutic efficacy. At the same time, it should be emphasized that the introduction of agonists to GABA receptors under normal conditions does not cause analgesia. This suggests that glycine and GABAergic spinal interneurons more control the activity of neurons excited by low-threshold afferents, and violation of

this control leads to disinhibition of a WIDE DYNAMIC RANGE -neurons receiving inputs from low-threshold A-beta fibers and high-threshold C fibers. Hyperactivity of a WIDE DYNAMIC RANGE of neurons can serve as the pathophysiological basis of allodynia, since in this case consciousness perceives an enhanced and prolonged discharge of a WIDE DYNAMIC RANGE of neurons activated by low-threshold afferents as pain. Thus, the data presented allow us to conclude that the development of neurogenic pain syndromes is accompanied by a whole complex of structural changes at different levels of the nociceptive system, in which conditions there is a steady depolarization of neurons and a deficiency of opioid and GABAergic inhibition, resulting in impaired interneuronal interactions, neuronal disinhibition occurs and long-term self-sustaining activity is formed. At the same time, the reasons underlying such disinhibition of neurons are not clear enough. Clinical experience and extreme studies indicate that neurogenic pain does not occur in all cases of damage to the structures of the nociceptive system. Thus, cutting of the sciatic nerve leads to the appearance of painful behavior only in 40-70% of rats Spinal cord injury with symptoms of hyperalgesia and temperature hypesthesia is accompanied by central pain in 30% of patients. No more than 8% of stroke patients with somatosensory sensitivity deficiency experience neurogenic pain. These data indicate that damage to the structures of the nociceptive system is not enough for the development of neurogenic pain, but a number of conditions are required that lead to disruption of integration processes in the regulation of pain sensitivity. The most frequently cited hypothesis about the nature of neurogenic pain is the concept of a violation of the inhibitory effect of the lemniscus somatosensory system on the ascending paleospinothalamic system (Head H., Holmes G., 1911). Later hypotheses about the mechanisms of neurogenic pain formation are essentially details of the concept of Head and Holmes about the interaction of "specific" lateral and "non-specific" medial structures of the brain. For example, L. A. Orbeli (1935) attached great importance to the imbalance between the lemniscal and extralemniscal systems of the brain in the mechanisms of the development of pathological pain. In the hypothesis of R. Melzak and P. D. Wall (1968), a significant place is given to the violation of afferent interaction between the flow of epicritical pain sensitivity and the flow of protopathic pain. Electrophysiological studies conducted in patients with central pain syndromes suggested that hyperactivation of neurons of the medial thalamus with damage to the lateral thalamic nuclei occurs through the reticular thalamic nucleus (Jeanmonod et al., 1993). According to the hypothesis of limiting the thermosensory input (Craig, 1999), central pain occurs due to a decrease in the cold inhibitory effect on the processing of pain information. The author's assumption is based on the fact that with central pain syndromes, a decrease in temperature sensitivity occurs earlier than pain, and in some cases is the only sensory deficiency. In most cases, patients with central pain syndrome experience burning or chilling pains in the area of reduced temperature sensitivity, while the degree of pain is proportional to temperature hypesthesia. However, none of the hypotheses presented reveals the mechanisms that contribute to or hinder the development of pain syndrome when nociceptive structures are damaged. In our opinion, the concept of G. N. Kryzhanovsky (1980, 1997) on the generative and systemic mechanisms of the formation of neuropathological syndromes most fully reveals the mechanisms of the development of neurogenic pain. According to G. N. Kryzhanovsky, the pathophysiological basis of pathological pain is an aggregate of interacting hyperactive neurons with impaired inhibitory mechanisms and increased excitability. Such aggregates arise as a result of the deafferentation of structures that conduct and process nociceptive signals at different levels of the spinal cord and brain. Their formation is carried out by synaptic and non-synaptic mechanisms. In conditions of insufficient inhibitory mechanisms and increased excitability of neurons, synaptic interneuronal interactions are facilitated, "silent" inactive synapses are activated and nearby hyperactive neurons are combined into a single aggregate. The morphological basis for the aggregate of hyperactive neurons can serve as collaterals of axons of neurons of a wide dynamic range, which, combining neurons with each other, form a single network-type generator capable of developing long-term and self-sustaining excitation. The formation of aggregates of hyperactive neurons occurs in conditions of violation of the mechanisms that regulate the excitation and inhibition of neurons. The occurrence of stable depolarization of neurons with damage to neuronal structures as a result of increased release of excitatory amino acids, neurokinins and nitric oxide from the presynaptic terminals of C-afferents promotes the unification of neurons into a single aggregate. Deep neuroplastic transformations that occur during the development of neurogenic pain syndromes affect not only the primary nociceptive relay, but also the higher structures of the pain sensitivity system. Under the influence of the impulses produced by the generator in the dorsal horns, changes occur in the higher parts of the nociceptive system - in the thalamus and sensorimotor cortex, as well as in the structures of the antinociceptive system. Dysregulation processes change the activity of these systems so much that stimulation of the antinociceptive structures of the brain, in particular the central gray matter, not only does not stop, but aggravates the course of neurogenic pain syndrome, which is accompanied by increased activity of nociceptive neurons of the dorsal horn. The combination of neuroplastic changes in the system of pain sensitivity regulation leads to the formation of a new pathodynamic state - the pathological algic system, which is the pathogenetic basis of neurogenic pain syndrome.

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