

NEUROPLASTICITY MECHANISMS IN THE PATHOPHYSIOLOGY OF CHRONIC PAIN

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SUMMARY – Chronic pain is a widespread healthcare problem with great impact on mental health, professional and family life of the patient. It can be a consequence of many disorders; however, its pathogenesis has not yet been fully understood. Neuroplasticity is the ability of the nervous system to adapt to different changes and it is present throughout life, not only in prenatal period, infancy and childhood. However, in the pathophysiology of chronic pain, neuroplasticity shows its “dark side”. Due to the central sensitization process, noxious stimuli can produce chronic pain or misinterpretation of non-noxious stimuli (secondary hyperalgesia and allodynia). These changes occur at the level of brain cortex as well at peripheral nerves and receptors. This review summarizes a significant portion of literature dealing with neuroplasticity processes in well known chronic pain conditions such as migraine, chronic posttraumatic headache, low back pain, fibromyalgia, and others. The relevance of this topic lies in providing a new insight in the pathophysiology of chronic pain, while also offering a possibility of new therapeutic approaches including not only pharmacological agents.

Key words: *Chronic pain; Neuroplasticity; Central sensitization; Cortical reorganization*

Introduction

Until a few decades ago, the neuroscientific dogma on the unchangeable human nervous system was common except for degenerative processes. The only periods believed to enable possible brain changes were the prenatal period, childhood and youth. It was considered that after this age, continuous neuron cell death occurs and atrophy of the mammal brain begins. In the years after The Decade of Brain, new discoveries emerged, one of them being neuroplasticity. Comprehensive researches have shown that nervous system is constantly changing due to new neuron connections which are developing in response to new stimulation

or new environment^{1,2}. Results of these studies have revealed that brain can adapt to compensate the disease and disability; it is possible to alter its structure and to generate new neurons³. That adult human brain is not definite and static, was also depicted by Eriksson *et al.* in their study showing that new neurons are generated continuously throughout life from neural stem cells in mammals in the area of dentate gyrus and in the zone next to the walls of lateral ventricles. Their results indicated human hippocampus to retain the ability to generate neurons throughout life⁴. This neurogenesis is believed to be one form of neuroplasticity that enables adaptation of the body to environmental changes.

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such a damage⁵. Nociception implies the process of interaction of noxious stimulus with a receptor, transmission and processing pain re-

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lated signals in the peripheral and central nervous system. Nociceptors are found in all body organs except for the brain and spinal cord. Neuropeptides released from nociceptors are producing sterile inflammation response that enhances nociception, which results in pain hypersensitivity (peripheral sensitization). Nociceptive stimulus travels in peripheral nerves to posterior horn of the spinal cord; at this level, central sensitization processes may lower the nociceptor threshold and promote development of chronic pain.

Through spinothalamic tract and spinoreticular tract, impulses are ascending towards the brain where reticular formation regulates arousal reactions, autonomic reflexes and emotional responses. Thalamus relays and differentiates nociceptive stimuli, while limbic system mediates emotional and motivation aspects of nociception. Somatosensory cortex has the function of pain differentiation and localization, and descending pathways modulate nociception⁶. Prostaglandins, glutamate, enkephalin, endorphin, GABA, serotonin/norepinephrine, substance P and histamine are neurotransmitters and neuropeptides with important role in nociception and pharmacotherapy is targeting these neurochemistry processes⁷. Pain can be of nociceptive type, it arises from actual or potential tissue damage and it is a result of the activation of nociceptors in an intact nervous system. It can be somatic and visceral. Neuropathic type of pain is caused by damage to nerve tissue. Initially, nociceptive pain can transform to neuropathic pain. Chronic pain can be taken as a disorder for itself, but not a single one. It is a consequence of many clinical disorders; it affects a large proportion of population and poses a widespread healthcare problem with negative impact on mental health, professional and family life of the patient. Although studied at different levels, it is not yet completely understood and not enough specifically treated. Current medications (anticonvulsants and antidepressants) are not fully effective because they are not specific substances for chronic pain and another problem is the occurrence of often and significant side effects. Chronic pain can be associated with serious progressive illness (malignancy, etc.), a consequence of static medical condition (amputation, herpes zoster), and often is of unknown etiology, i.e. a consequence of disturbance in neural functioning or complex combination of neural disturbances and psy-

chological disturbances (fibromyalgia, chronic pelvic pain of unknown etiology, chronic tension type headache, etc.)⁸⁻¹⁰.

Neuroplasticity and Pain

Neuroplasticity processes are involved in chronic pain development, but they can also be induced by medications used in the treatment of pain¹¹. Neuroplastic changes can take place in the periphery, spinal cord and in brain centers after injury or inflammation; these changes lead to development of chronic pain syndromes. Central sensitization is one of neuroplastic changes; it is a widespread, persistent hyperexcitability state of central neurons due to repetitive peripheral firing from afferent neurons. The most important consequence of these neuroplastic changes in chronic pain is reduced filtering ability of central sensory neurons in the brain and spinal cord resulting in wrong interpretation of noxious stimuli that can be exaggerated (secondary hyperalgesia) or misinterpreted; non-noxious stimuli are perceived as painful ones (allodynia)¹². If inflammation from injury is treated appropriately and the disease process is controlled, hypersensitivity usually resolves (modulation of primary and secondary neurons in the processes of peripheral and central sensitization is reversible). But if inflammation from injury persists, modification in central neurons occurs and involves even changes in the structure, connectivity and survival of neurons; these changes lead to an increased activity of neurons in the central pain pathway with a fixed central sensitization and chronic pain^{13,14}. Continuous and intense stimuli that lead to neuroplastic changes in the spinal cord and brain result in fixed central sensitization and chronic pain and there is growing evidence that these changes underlie the processes present in a number of pain conditions such as fibromyalgia, low back pain, migraine, temporomandibular disorder and other headaches¹⁵⁻¹⁸. The sequels of neuroplasticity after peripheral nerve injury are disturbed sensation and chronic pain due to the loss of endogenous inhibition mechanisms, which leads to hypersensitivity and pain, as well as due to reorganization of the central nervous system¹⁹. Nerve injury is followed by the processes of re-innervation, collateral branching of undamaged neurons and remodeling of nervous system connections. However, the results of

these processes aimed to compensate for functional deficits can lead to maladaptive changes that lead to neuropathic pain²⁰. The main mechanism is selective death of GABAergic neurons in dorsal horns of the spinal cord that occurs after injury consequently leading to the loss of the GABA mediated inhibition²¹. Peripheral nerve injury also leads to decreased expression of μ -opioid receptors in dorsal root ganglion neurons, which is associated with attenuation of the effects of opioids and other analgesics in neuropathic pain²². Chronic posttraumatic headache develops in up to 15% of patients with whiplash injury. A study performed in 33 patients with posttraumatic headache using magnetic resonance-based voxel-based morphometry discovered neuroplastic, adaptive changes of the central nervous system. Results showed that patients with chronic headache revealed a decrease in gray matter in the anterior cingulate and dorsolateral prefrontal cortex after 3 months. These changes resolved after one year, in parallel to cessation of headache and the same patients showed an increase of gray matter in antinociceptive brainstem centers, thalamus and cerebellum one year after the accident²³. Reorganization in primary somatosensory cortex associated with chronic pain was also revealed in patients with unilateral chronic pain after herpes simplex infection without peripheral nerve injury²⁴. Phantom limb pain is one of the best known consequences of brain plasticity. In this condition, after limb amputation, brain cortex reorganization in motor, but also in somatosensory areas starts. Similar changes can also occur at the level of spinal cord or thalamus. This cortical reorganization can be stopped and reversed by exercises using mental imagery and thus the intensity of pain and exacerbations of pain can be reduced^{25,26}. Fibromyalgia is a central sensitization syndrome. This chronic condition is characterized by musculoskeletal pains all over the body, but without muscle, bone and joint pathology. Disturbed interpretation of the sense of touch is present and touch is perceived as a painful stimulus. In this condition, depression, sleep, immune system, metabolism and endocrine disorders are also involved. All of these factors influence brain changes leading to fibromyalgia. Some studies revealed that the loss of gray matter occurs in fibromyalgia patients. Additional proof that fibromyalgia is a central sensitization syndrome and not a local musculoskeletal

condition is the success of centrally acting drugs in its treatment (pregabalin)²⁷⁻²⁹. Also chronic low back pain can induce reorganization of motor cortical areas³⁰. A promising fact is that motor training can reverse reorganization of neuronal circuits of motor cortex in people with recurrent low back pain, which can be used in nonpharmacological pain treatment³¹.

Except as a response to noxious stimuli and disease, neuroplastic changes develop in response to medications. Repeated exposure to opioids leads to neuroplastic changes in spinal cord at the cellular and intracellular levels and is associated with activation of the NMDA receptors. The interaction of NMDA and opioid receptors can lead to irreversible degenerative neuroplastic changes in spinal cord that are connected to opioid tolerance. Similar changes occur after peripheral nerve injury. These findings may help understand the mechanism of opioid tolerance and difficulties in opioid treatment of neuropathic pain, which poses a major problem because most pain conditions are treated with opiates. In patients with migraine, plastic changes of neurotransmitter receptors that are similar to changes in inflammatory pain states will probably develop during chronic morphine exposure. Calcitonin gene-related peptide levels increase and peripheral and central sensitization develops, with medication overuse headache as the end result^{32,33}. Overuse of triptans can also induce neuroplastic changes in migraineurs, resulting in a state of latent sensitization, which might increase sensitivity to migraine triggers³⁴. Some medication induced neuroplastic changes can also produce benefit in the treatment of pain conditions. One of the hypotheses is that psychoactive drugs that are often used in pain treatment may potentially influence adult neurogenesis and that this effect on neuroplasticity may contribute to the therapeutic effect of antidepressants and antipsychotics. One of the theories proposed is that selective serotonin reuptake inhibitors (SSRI) increase neurogenesis in adult brain^{35,36}.

Conclusion

This review summarizes a significant portion of the recent literature dealing with pain and connection with neuroplastic changes that develop as the result of chronic pain condition or as a causative element of

pain condition. As some studies have shown, medication can also induce neuroplastic changes. Based on this knowledge, the future aims in pharmacotherapy of chronic pain should be to develop a drug targeted to the mechanism of peripheral and central sensitization and other neuroplastic mechanisms, thus to produce disease modifying agents. One of the hypotheses is that a combination of opioid receptor agonists and NMDA receptor antagonists would be effective at this level. Taking into account that neuroplastic changes are induced by a repeated painful stimulus, which leads to central sensitization and chronic pain, guidelines for clinicians should clearly state that acute pain must be vigorously treated.

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Sažetak

MEHANIZMI NEUROPLASTIČNOSTI U PATOFIZIOLOGIJI KRONIČNE BOLI

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Kronična bol je rašireni zdravstveni problem s velikim utjecajem na mentalno zdravlje, profesionalni i obiteljski život bolesnika. Ona može biti posljedica mnogih bolesti, ali njezina patogeneza još nije u potpunosti razjašnjena. Neuroplastičnost je sposobnost živčanog sustava da se prilagodi različitim promjenama i prisutna je tijekom cijeloga života, a ne samo u prenatalnom i dojenačkom razdoblju i djetinjstvu. Međutim, u patofiziologiji kronične boli neuroplastičnost pokazuje svoju „tamnu stranu“. Uslijed procesa središnje senzitivacije štetni podražaji uzrokuju kroničnu bol, a neštetni podražaji se tumače kao bolni (sekundarna hiperalgezija i alodinija). Ove promjene mogu se događati na razini moždane kore, ali i na razini perifernih živaca i receptora. Ovaj pregledni članak obuhvaća značajan dio literature u kojoj su prikazana istraživanja koja su se bavila procesima neuroplastičnosti u čestim kroničnim bolnim stanjima poput migrene, kronične posttraumatske glavobolje, križobolje, fibromijalgije i drugima. Značenje ove tematike je u novom pristupu patofiziologiji kronične boli, odnosno u mogućnosti pronalaženja novih terapijskih opcija u liječenju kronične boli koje ne moraju sadržavati samo farmakološka sredstva.

Ključne riječi: Kronična bol; Neuroplastičnost; Središnja senzitivacija; Kortikalna reorganizacija

