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Nerve Injury-Induced Plasticity in the Nociceptive Pathways

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Context: Neuropathic pain is a common and disabling complication. To develop a better treatment of the neuropathic pain, a comprehensive understanding is essential. In this paper, we review pathophysiological principles of neuropathic pain, focusing on synaptic plasticity and long-term potentiation (LTP) in the nociceptive circuits. Finally, the role of glial cells on the synaptic plasticity in neuropathic pain is discussed.

Evidence Acquisition: We searched the Cochrane and PubMed databases using the following terms: neuropathic pain, dorsal horn, LTP, synaptic plasticity, nociceptive circuits, glial cells, nerve injury, allodynia, hyperalgesia, nociceptive neurons, and rat. All of searches were limited to the animal studies in English articles. Full-text copies were obtained when the studies had possible relevance.

Results: Analysis of our research showed that nerve injury-induced LTP decreased pain threshold and increased pain hypersensitivity to sub-threshold stimuli. In addition, cross talk between dorsal horn neurons and glial cells are pivotal for the induction of spinal synaptic plasticity and LTP.

Conclusions: It seems that LTP in the spinal nociceptive pathways constitutes cellular mechanisms that explains how acute pain may become chronic.

Keywords:-

1. Context

Neuropathic pain is a common and severely disabling complication that impairs quality of life. The treatment of neuropathic pain is problematic because it is very complex, and the underlying mechanisms are not clearly understood (1). In recent years, attention was focused on synaptic plasticity in the dorsal horn as an important mechanism for neuropathic pain. One important type of the synaptic plasticity is LTP in the spinal neural system (2). Therefore, targeting maladaptive neuronal plasticity and LTP in the spinal pathways is an important way for the treatment of neuropathic pain. Moreover, recently it has been reported that glial cells are critical for the development and maintenance of synaptic plasticity (3). The aim of this review is to investigate recent progress in the neuropathic pain pathophysiology. We focus on the synaptic plasticity and LTP in nociceptive circuits. Finally, the cross talk between neuronal and glial cells in neuropathic pain is discussed.

2. Evidence Acquisition

We searched the Cochrane and PubMed database without date limitation, using the following terms: neuropathic pain, dorsal horn, LTP, synaptic plasticity, nociceptive circuits, glial cells, nerve injury, allodynia, hyperalgesia, nociceptive neurons, and rat. Following this search, we conducted a backward search by examining reference lists of all obtained articles. The searches were limited to the animals in English language. We checked all titles and abstracts. Full-text copies were obtained when the studies had possible relevance.

3. Results

3.1. Neuropathic Pain

Clinical pain can arise from damage to the nervous system (neuropathic pain), inflammation, or tissue injury (inflammatory pain). Etiology of neuropathic pain is different and includes nerve injury (e.g. amputation, spinal cord injury) or diseases that affect peripheral nerve function (e.g. metabolic disorders, viral infection and cancer). The most distinctive signs of neuropathic pain are hyperalgesia (an exaggerated response to painful stimuli), allodynia (the presence of pain in response to normally non-painful tactile stimuli) and spontaneous pain (stim-

ulus independent pain) (4-6). The dorsal horn of the spinal cord is the first and major site for the integration and modulation of the pain signals. In neuropathic conditions, nerve injury induces ectopic firing of action potentials (ongoing activity) in the site of injury that develops to the dorsal horn, leading to synaptic plasticity. Ectopic action potentials also develope in uninjured fibers, and increased sensitivity to the pain (7-9). All of these states have important roles in the development and maintenance of neuropathic behaviors such as allodynia and hyperalgesia (10-14).

3.2. Short-Term and Long-Term Plasticity in Spinal Synapses

Recent studies have increasingly shown that synaptic strength is not fixing and vary in response to the changes of transmitter release from presynaptic terminals and the postsynaptic neuron activity. The variation of synaptic strength constitutes a mechanism known as synaptic plasticity (15, 16). Depending on the type of synapse and the intensity, frequency, and duration of the stimulus, both increase (potentiation or facilitation) and decrease (depression) in synaptic strength can be induced. In the animal model studies, nociceptive spinal connections exhibit short-term potentiation (STP or wind-up), long-term potentiation (LTP) and long-term depression (LTD) (2, 17). Wind-up is characterized by a progressive potentiation in the number of action potential from dorsal horn neurons during a train of repeated low frequency stimulation of C-fiber (16 stimuli, 5Hz). Second type of the synaptic plasticity is long-term potentiation (LTP). LTP is defined as a long-lasting responsiveness of dorsal horn neurons (18).

LTP was first detected at the hippocampus synapses as a model of learning and memory formation (19). Subsequent studies showed that LTP can also be induced in spinal pain pathways and may contribute to the neuropathic behaviors such as hyperalgesia and allodynia (20-22). LTP can induce in the superficial dorsal horn by field potentials recording (21) or patch clamp techniques (23), and even in the deep single WDR neurons by in vivo single-unit recording (24, 25). Ikeda et al. have shown that electrical high-frequency stimulation (HFS, 100Hz) of dorsal root induces LTP in the NK1-expressing neurons in laminae I (26). Moreover, low frequency stimulation (LFS, 2Hz) induces LTP in the laminae I neurons (27). In addition, LTP can be induced in the deep laminae of the spinal cord (e.g. in laminae IV-VI), where mainly WDR neurons are located (24, 25). The contribution of the WDR neurons in the nociceptive plasticity is less clear; however, many studies reported that these neurons have a pivotal role in the LTP.

For the first time, Svendsen et al. showed that electrical HFS of the sciatic nerve induces LTP in the evoked C-fiber responses from single WDR neurons in the deep spinal dorsal horn using in vivo extracellular single-unit recording (24, 25, 28). It seems that spinal LTP, injury-induced hyperalgesia and allodynia share common signaling pathways, time course and pharmacological profiles (21, 29). Taking together, LTP can be induced throughout the dorsal horn (superficial and deep lamina) and is an attractive model for injury-evoked painful behaviors such as allodynia and hyperalgesia. At least two different stages of LTP, depending upon its duration and signaling pathways, can be identified. Early phase LTP only required post translational modifications and lasted up to three hours. Late phase LTP required gene transcription and probably lasted up to the life span of an animal (30).

3.3. Cellular Mechanisms of the LTP in Spinal Cord

Some studies have shown that activation of the N-methyl-D-aspartate (NMDA) receptors is critical for the induction of LTP in the dorsal horn. Application of NMDA receptor antagonists like ketamine suppresses induction of spinal LTP (23, 31). NMDA receptors are activated by several mechanisms following nerve injury, including:

1) Nerve injury reduced the glutamate transporter expression in the spinal cord, leading to elevation of synaptic glutamate concentration (32).

2) Nerve injury reduced the inhibitory GABAergic and serotonergic input onto dorsal horn neurons, leading to facilitation of synaptic strength (33, 34).

In addition to NMDA receptor, induction of LTP in the spinal cord requires activation of NK1 receptors, opening of T-type voltage-gated Ca^{2+} channels, and activation of group I metabotropic glutamate receptors (26, 27, 35). Activation of NK1 receptors by substance P directly increases activation of NMDA receptor in the laminae I neurons and so increases postsynaptic intracellular Ca^{2+} level (36). Several signaling pathways modulate Ca^{2+} concentration in neuropathic pain such as activation of protein kinase A (PKA), protein kinase C (PKC), phospholipase C (PLC), inositol triphosphate-3 (IP3) receptors, calcium/calmodulin-dependent protein kinase II (CaMKII), nitric oxide synthase (NOS), mitogen-activated protein kinase (MAPK), and extracellular signal regulated kinase (ERK) (37-39). Studies using voltage sensitive dyes have shown that the potentiation of the electrical activity in the primary afferents after induction of LTP is partially sensitive to an mGluR group I antagonist (LY367385), iNOS inhibitor (AMT), an inhibitor of glial metabolisms (MFA) and protein synthesis inhibitors (cycloheximide or anisomycin) (40, 41). Interestingly, the same signal transduction pathways is required for the initiation and development of neuropathic signs like hyperalgesia in animal models of neuropathic pain (42).

3.4. Role of Glial Cells in the Neuropathic Pain

Glial cells are generally divided into three main categories: (1) oligodendrocytes, located in the white matter and constitute the myelin sheath around axons; (2) astrocytes, which have an important role in metabolism of the neurons; and (3) microglial cells, which do not have a neural origin and are referred to as the immune cells of

the brain (43). The oligodendrocytes, astrocytes and microglia are being activated in neuropathic pain, leading to neuronal hypersensitivity. It is reported that knock out of glial fibrillary acidic protein (GFAP) gene in the astrocytes and Bergmann glial cells (a type of the astrocyte in the cerebellum) impairs eye blink conditioning and LTD in the cerebellum (44). However, in the hippocampus, the lack of GFAP in the astrocytes induces an increase of LTP (44, 45). Moreover, the lack of GFAP in GFAP-null mice decreases the number of glutamate transporters both in the neurons and astrocytes (46). Thus, signaling pathways of the glial cells can modulate the synaptic strength. Several studies have shown that overexpression of S100b (a type of astrocytic calcium-binding protein) impaired spatial exploration and therefore, synaptic plasticity (47-50). Additionally, application of the fluoroacetate (an inhibitor of the glial metabolism) suppresses induction of LTP in the spinal cord. However, the role of glial cells in the synaptic potentiation is still not well understood.

4. Discussion

Neuropathic pain is a highly complex disorder, which requires more studies. LTP is considered as a cellular mechanism for neuropathic pain. Pain memory in dorsal horn is a suitable explanation for maintenance of hyperalgesia and allodynia even after complete nerve healing. We conclude that LTP in the spinal nociceptive system constitutes cellular mechanisms to explain how acute pain may become chronic. It seems that the synaptic memory in the nociceptive system is a principle topic for pain researchers.

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Authors' contributions

Acquisition of data: Zahra Bahari, and Gholam Hossein Meftahi Drafting of the manuscript: Zahra Bahari, Seyed Shahabeddin Sadr, Maedeh Ghasemi, Alireza Mohammadi, and Nasrin Mehranfard; and Critical revision of the manuscript for important intellectual content: Homa Manaheji.

Role of the sponsor

Electrophysiology Research Center of Medical Sciences, Tehran, Iran, had effective contribution in preparation and review of this manuscript.

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