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Advances in the Study of Microglia in Neuropathic Pain

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Abstract

Neuropathic pain is a kind of chronic pain triggered by nervous system injury or dysfunction, whose mechanism is complex and lacks effective treatment. Recent studies have shown that microglia, as core immune cells in the central nervous system, play a central by role in the development and maintenance of pain). play a central role in the onset and maintenance of pain. In this paper, we systematically reviewed the activation mechanism of microglia and their multi-receptor regulatory network (including in neuropathic painreleasing pro-inflammatory factors (e.g., IL-1β, TNF-α), regulating key signaling pathways (e.g., TLR/NF-κB, NLRP3 inflammatory vesicles, JAK/STAT), and mediating neuron-glia interactions (e.g., BDNF-TrkB, ATP-P2X4P2X4, TLR4, RAGE, GLP-1R, CCR2, KOR, and GPR84) , and elucidated their amplification of pain signals through inflammatory factor release, synaptic plasticity regulation, and neuronal excitability enhancement. Meanwhile, this paper explores the potential value of therapeutic strategies targeting microglia receptors (e.g., antagonists, genetic interventions and electroacupuncture therapy), and looks forward to emerging research directions such as metabolic reprogramming, epigenetic regulation and gender differences, which will provide a theoretical basis for the development of precision analgesic therapies.

Keywords: neuropathic pain, microglia, neuroinflammation, activation mechanisms, receptor-mediated pathways, pro-inflammatory factors, signaling pathways, neuron-glia interactions, synaptic plasticity, therapeutic strategies

1. Introduction

Neuropathic pain is a common chronic pain condition that has a significant impact on quality of lifecaused by damage to nervous system tissues and neuroinflammation[1]. Of the seven diagnostic categories defined by the), neuropathic pain is one of the most common pain conditions, affecting approximately one in ten adults worldwide. 11th revision of the International Classification of Diseases and Related Health Problems (ICD-11[2]. The treatment of neuropathic pain is challenging due to its heterogeneous etiology, lack of objective diagnostic tools, and resistance to classical analgesic drugs. Drugs are now chosen to treat neuropathic pain independent of the cause and symptoms of pain[3]. The mechanism of neuropathic pain is currently unclear, microglia are first responders and major resident immune cells in the central nervous system and have emerged as key players in the development and maintenance of neuropathic pain[4]. Central immune signaling involving microglia plays an important role in neuropathic pain[5]. Recent studies have shown that microglia, as important regulatory cells of the nervous system, are deeply involved in the release and transduction of neuroinflammatory factors and play an important role in the development and maintenance of neuropathic pain[6] Recent research has uncovered that the activation of microglia in neuropathic pain is not a binary switch between pro-inflammatory (M1) and anti-inflammatory (M2) states but rather exists on a continuum of functional phenotypes. This suggests that therapeutic strategies should aim at fine-tuning microglial responses rather than simply suppressing activation. Additionally, single-cell RNA sequencing studies have identified distinct subpopulations of microglia that emerge during neuropathic pain, some of which exhibit transcriptional signatures associated with chronic pain states. These findings emphasize the need for a more nuanced understanding of microglial dynamics in pain pathology. This review explores the mechanisms through which microglia influence neuropathic pain, including their receptor-mediated pathways, interactions with neurons, and potential as therapeutic targets.

2. Cellular Mechanisms in Neuropathic Pain

2.1 Activation of Microglia after Injuryneurologic

Microglia account for the adult mammalian central nervous system (5-10% of all cells in)CNS. Originating from yolk sac cells, microglia maintain a lifelong existence through self-renewal and are highly plastic[7]. Many studies

have shown that healthy mature microglia in thehave a bifurcated morphology, i.e., small cytosolic bodies with fine cellular protrusions, and CNS traumatic brain injury, cerebral ischemia, infections, and degenerative lesions of the CNS in the CNS activate microglia, which migrate and proliferate rapidly from a highly bifurcated resting state, with concomitant changes in morphology and function, such as enlarged soma, increased synapses, and phagocytosis acquisition. , which can be classified according to morphology as branched, perivascular, amoeboid, resting and activated[8]. Traditionally, it is believed that microglia can be categorized as neurotoxic (M1-type microglia) and neuroprotective (M2 microglia), but the traditional categorization does not fully reflect the role of microglia in neuropathic pain, and the protective the balance between may have an important role in neuropathic painand pro-inflammatory phenotypes[9]. In addition to detecting and phagocytosing pathogens, activated microglia release cytokines as well as other inflammatory factors that contribute to neuroinflammation, further modulating the development of neuropathic pain[10, 11]. Recent research highlights that microglial activation is influenced by metabolic reprogramming. Activated microglia shift towards glycolytic metabolism (Warburg effect), which promotes pro-inflammatory responses and sustains chronic pain. Strategies targeting metabolic pathways, such as inhibiting hexokinase-2 (HK2) or lactate transporters, have shown promise in preclinical pain models[12].

2.2 Cytokine and Chemokine Release

Activation of microglia is observed in numerous well-established animal models of peripheral nervous system injury and undergoes morphological changes, proliferation, and upregulation of signaling molecules Suda et al. found that of sciatic nerve injury the level of phosphorylation was significantly elevated and with mechanical p38MAPK in microglia in the dorsal horn of the spinal cord within hours 24 positively correlated hypersensitivity, including nociceptive upregulation of channelsSWELL1[13]. For example, Li et al. co-expressed inflammatory factors with neuroglia by immunofluorescence and found that inflammatory factors (e.g., in neuropathic pain TNF-α, IL-1β) were mainly released by microglia[14]. Activation of microglia via inhibits pro-inflammatory factors the transcription of and activation of inflammasome , which in turn inhibits the NLRP3 the p300-associated NF-κB signaling pathwaymicroglia-mediated inflammatory responses and neuronal death[15]. It has been shown that activation of channels leads to intracellular Piezo1 Ca^{2+} inhibition of microglia activation and pro-inflammatory cytokine-producing signaling, which inhibits M1-type microglia polarization and alleviates neuropathic pain[16].

2.3 BDNF Release and Neural Sensitization

Brain-derived neurotrophic factor (BDNF) serves as a classic example of a neurotrophic factor. It is of great significance in modulating a diverse range of developmental functions within the central nervous system (CNS).This regulation lowers the pain threshold, leading to by altering key receptors, such as TrkB pain hypersensitivity[17]. Huang et al. by constructing conditional knockout in microgliafound that systemic BDNF depletion reduced mechanically abnormal pain. The underlying mechanism may be the activation of microglia to secrete after injury in miceBDNF BDNF , Moreover, the secreted Brain-Derived Neurotrophic Factor (BDNF) binds to neuronal TrkB receptors, thereby triggering the downregulation of potassium chloride co-transporter proteins. This, in turn, diminishes the inhibitory actions mediated by GABAA, ultimately resulting in an amplified excitability of spinal cord neurons[18]. TrkB receptors belong to the tyrosine kinase receptor family (Trk receptors), which are mainly used by brain-derived neurotrophic factor (BDNF) and neurotrophic factor 4/5 (NT-4/5) activation[19]. Upregulation of increases neuronal excitability and triggers P2X4 in microglia of mice in a neuropathic pain model mechanical hypersensitivity[20]. Downstream effects lead to an increased pain response.BDNF binding is able to activate downstream signaling pathways, altering neuronal excitability and further exacerbating pain perceptionto its receptor TrkB[21].

3. Characterization of the Spatiotemporal Dynamics of Microglia Activation

Microglia activation after nerve injury is significantly time-specific. In peripheral nerve injury models (e.g., sciatic nerve chronic compression injury, CCI), microglia in the dorsal horn of the spinal cord show within hours p38 MAPK phosphorylation , accompanied by 24 after injuryup-regulation of expression, and morphology shifts from branching to amoeboid. Peak activation usually occurs after injury Iba1 7-14 days and with mechanical is highly synchronized the development of nociceptive hypersensitivity Allodynia[22]. Notably, different there are differences in the response of microglia inregions: CNS microglia in the dorsal horn of the spinal cord are more sensitive to pain signals, whereas microglia in the prefrontal cortex are more involved in the modulation of pain emotion[23]. Technological advances: Two-photon in vivo imaging reveals that activated microglia through directly remove the synaptic structure of damaged neurons , leading to "synaptic pruning"disinhibition of networks in neuronal the dorsal horn of the spinal cord, which amplifies pain signals[24]. Recent optogenetic studies reveal that microglia can physically contact and engulf inhibitory synapses in the spinal cord, further disrupting pain-

inhibitory circuits. This "synaptic stripping" mechanism provides a new avenue for understanding how microglia exacerbate pain states and suggests that therapies aimed at preserving inhibitory synapses might be beneficial.

4. Microglia and Pain Signaling

Microglia, serving as the immunoregulatory core of the central nervous system, play a pivotal role in the pathological process. Multiple receptors are directly involved in the amplification and maintenance of pain signals by modulating inflammatory factor release, synaptic plasticity, and neuronal excitability. Among them, neuropathic pain (neuro-glial interactionsNPreceptor-mediated inflammatory responses and the P2X4 receptor is one of the most intensively studied targets. Activation of this receptor by triggers calcium inward flow, promotes brain-derived neurotrophic factor (ATP the release of), and inhibits in the spinal cordBDNFthe activity of GABAergic neurons , thereby inducing nociceptive hypersensitivity; by antagonists (e.g., mechanical can be significantly alleviated nociceptive hypersensitivity 5-BDBD) or gene-silencing techniques[25]. The Toll-like receptor 4 (TLR4) receptor plays a crucial role in the sustenance of pain signals by recognizing damage-associated molecular patterns (DAMPs). This recognition activates the nuclear factor-kappa B (NF-κB) signaling pathway, leading to the upregulation of pro-inflammatory mediators such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), and subsequently enhances the excitability of spinal dorsal horn neurons. TAK-242, a specific inhibitor of TLR4, has shown significant anti-inflammatory potential in preclinical investigations[26]. RAGE receptor binding to ligands such as activates HMGB1 the MAPK/ERK pathway, which synergistically TLR4 forming an inflammatory positive feedback loop, and its antagonist sRAGE blocks signaling[27]. In addition, activation of receptors via the GLP-1R inhibits pathwayNF-κB and promotes IL-10 expression , and cAMP/PKA GLP-1 analogs (e.g., liraglutide) have been shown to have analgesic effects in diabetic neuropathy[28]. CCR2 receptors via the chemokine mediate monocyte infiltration and microglial-neuron interactions , and its antagonists (e.g. CCL2RS504393) are effective in reducing pain in nerve injury models[29]. Notably, κ-opioid receptor (KOR) inhibits via electroacupuncture stimulation the TLR4/MyD88 pathway and synergizes with the endogenous opioid system to exert analgesic effects[30], whereas the GPR84 receptor enhances upon medium-chain fatty acid activation NLRP3 inflammatory vesicle activity to further maintain neuroinflammation[31]. These receptor-targeted intervention strategies provide new directions for the precise treatment of neuropathic pain by modulating microglia activation status and inflammatory cascade responses. Emerging evidence suggests that microglia also express cannabinoid receptors (CB2), which exert anti-inflammatory and analgesic effects. CB2 receptor agonists are now being explored as potential non-opioid analgesics for neuropathic pain[32].

5. Summary of the Current Status of Neuropathic Pain Management

Neuropathic pain (NP), a complex and disabling chronic pain condition, faces multiple challenges in its treatment. Its pathophysiology involves a wide range of molecular mechanisms, and its heterogeneous etiology and complex signaling pathways have led to the fact that existing therapeutic strategies, including pharmacological and non-pharmacological interventions, provide only temporary or partial relief of symptoms and are often accompanied by severe side-effects or drug resistance[33]. Pharmacologic treatment remains central to management, but antidepressants, antiepileptics, and opioids have limited efficacy, with inadequate response in most patients and risk of dose-dependent side effects or addictionNP[34]. Non-pharmacological treatments such as neuromodulation techniques (e.g., transcutaneous electrical stimulation), physical therapy, psychological interventions, and acupuncture have shown potential in improving pain symptoms and quality of life, but their efficacy still needs more clinical validation. To address the shortcomings of existing therapies, new drug development focuses on targets such as to enhance efficacy and safetyvoltage-gated sodium channels[35]. In addition, traditional Chinese medicine (e.g., acupuncture) and complementary alternative therapies (CAT) are becoming a due to their role in regulating neuroinflammation and brain functionhot research topic for treatment NP[36]. Epidemiologic data show that the prevalence of reaches in the populationNP 7-10% , but less than 50% of patients can achieve significant remission with existing recommended drugs. Specific types of The high prevalence and under-treatment of (e.g., cancerous neuropathic pain) require multidisciplinary interventions that integrate pharmacological, rehabilitative, and psychosocial support to optimize outcomesNP [22]. In summary, NP treatment research is being continuously advanced through multi-targeted drug development, non-pharmacological innovations, and the integration of Chinese and Western medicine strategies, with the aim of breaking through the bottleneck of efficacy and safety and meeting the unmet clinical needs. The integration of multi-omics approaches (transcriptomics, proteomics, and metabolomics) is expected to provide a deeper understanding of microglial heterogeneity in neuropathic pain. By leveraging artificial intelligence and big data analysis, researchers can identify novel therapeutic targets and optimize drug discovery pipelines.

6. Conclusion

Microglia, as immune sentinels of the CNS, through multiple receptor (e.g., play a central role in the development and chronicity of neuropathic pain neuron-glial interactions. Targeted intervention strategies (e.g., P2X4, TLR4, RAGE)-mediated inflammatory cascade responses and P2X4 antagonists, TLR4 inhibitors, and GLP-1R agonists), although demonstrating analgesic potential in preclinical studies, still need to address the challenges of central permeability, target specificity, and side effects. Future studies need to further focus on microglia polarization (the dynamic balance mechanism of phenotype), the metabolic reprogramming (e.g., glycolysis and oxidative phosphorylation) and epigenetic modifications (e.g., M1/M2 regulation of its function by methylation, histone acetylation), and further explore the effects of sex hormones (e.g., estrogen, androgens) on the activation of microglia, in order to elucidate the molecular basis of the gender differences in pain. Meanwhile, the development of an efficient central targeted DNA drug delivery system, the optimization of biomarker screening technology, and the integration of neuroimmunology and multi-omics approaches to analyze the neuron-glial-immune network will provide a new direction to break through the bottleneck of traditional analgesia, and to promote the clinical translation of precision therapeutic strategies.By bridging the gap between basic science and clinical application, we can develop more effective, mechanism-based treatments that go beyond symptom management to address the root causes of neuropathic pain.

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