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Review

Modulating the delicate glial–neuronal interactions in neuropathic pain: Promises and potential caveats

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ABSTRACT

During neuropathic pain, glial cells (mainly astrocytes and microglia) become activated and initiate a series of signaling cascades that modulate pain processing at both spinal and supraspinal levels. It has been generally accepted that glial cell activation contributes to neuropathic pain because glia release proinflammatory cytokines, chemokines, and factors such as calcitonin gene-related peptide, substance P, and glutamate, which are known to facilitate pain signaling. However, recent research has shown that activation of glia also leads to some beneficial outcomes. Glia release anti-inflammatory factors that protect against neurotoxicity and restore normal pain. Accordingly, use of glial inhibitors might compromise the protective functions of glia in addition to suppressing their detrimental effects. With a better understanding of how different conditions affect glial cell activation, we may be able to promote the protective function of glia and pave the way for future development of novel, safe, and effective treatments of neuropathic pain.

Contents

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1. Introduction

Injury to the somatosensory nervous system can produce chronic neuropathic pain characterized by abnormal sensations such as allodynia (pain produced by normally non-painful stimuli) and hyperalgesia (excessive pain from noxious stimuli) (Sorge et al., 2012). Chronic pain can persist for several months and can be very difficult to manage or treat. In fact, only 40–60% of patients achieve even partial relief (Dworkin et al., 2007; Finnerup et al., 2010). Pain processing is a dynamic system that can be modulated at multiple levels of the nervous system (Milligan and Watkins, 2009). For many decades, most research on neuropathic pain has revolved around neuronal mechanisms. However, recent studies have demonstrated that neighboring astrocytes and microglia also act as powerful modulators of pain (Milligan and Watkins, 2009; Ji et al., 2013).

Glia are non-neuronal cells that maintain homeostasis, form myelin, and provide support and protection to neurons in both central and peripheral nervous systems (Jessen and Mirsky, 1980; Clarke et al., 2013). They also play an important role in the synthesis, release, and uptake of various neurotransmitters (Watkins et al., 2007). Glia account for 70% of central nervous system (CNS) cells (Nakajima and Kohsaka, 2001; Watkins et al., 2007) and consist mainly of two types, the microglia and the macroglia. Macroglia include astrocytes, oligodendrocytes, and radial cells.

For over a century, it was believed that the glial cells did not play a role in neurotransmission. However, it is now known that they indeed play important roles in physiological processes and in assisting neurons to form synaptic connections (Gourine et al., 2010). The involvement of glia in neuropathic pain was first suggested in the mid-1990s (Colburn et al., 1997, 1999). It is now well established that nerve damage leads to activation of glial cells, particularly astrocytes and microglia, and that this activation can cause neuroanatomical and neurochemical transformations in the CNS that result in neuropathic pain (Colburn et al., 1999; Woolf and Mannion, 1999).

Both astrocytes and microglia play important roles in mediating neuropathic pain by releasing proinflammatory cytokines and chemokines and other factors known to facilitate pain signaling, such as calcitonin gene-related peptide (CGRP), substance P, and glutamate (Wieseler-Frank et al., 2005; Milligan and Watkins, 2009; Ji et al., 2013). In preclinical studies, mechanical allodynia and hyperalgesia have been associated with early increased levels of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, and delayed expression of IL-10 (Chiang et al., 2007; Vallejo et al., 2010). Cytokines are very potent small proteins produced by immune (macrophages or helper T cells) and non-immune cells (endothelial cells or Schwann cells). They function as cellular communicators. Under normal conditions, the production of both pro- and anti-inflammatory cytokines aids the immune system in destroying pathogens and healing damaged tissue. However, release of proinflammatory cytokines for prolonged periods may lead to pathological conditions such as chronic pain (Kawasaki et al., 2008).

Recent studies suggest that activation of glia can also have beneficial effects, including release and maintenance of anti-inflammatory factors that protect against neurotoxicity and restore normal pain signaling (Milligan and Watkins, 2009). Despite the extensive research in this field, preclinical findings have not translated into improved therapeutic strategies for patients with chronic pain. Thus, an understanding of the mechanisms involved in both beneficial and pathological roles of activated glia is necessary for the development of novel, safe, and effective pain therapies.

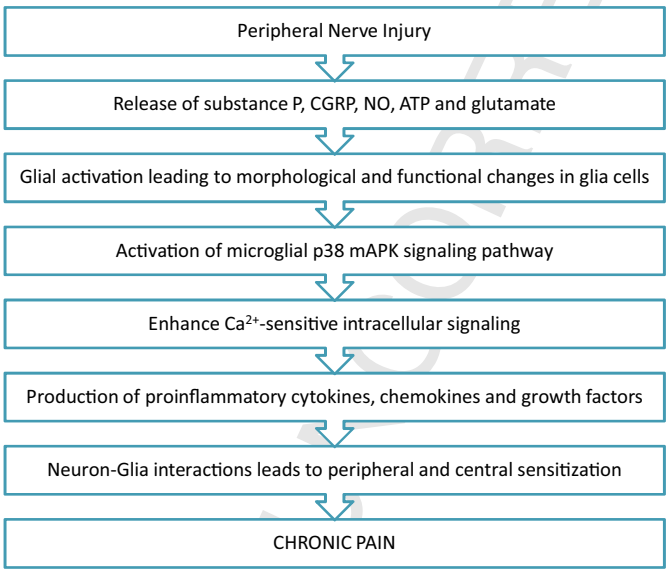

Fig. 1. Flow chart depicting how peripheral nerve injury leads to chronic pain. ATP: adenosine triphosphate; CGRP: calcitonin gene-related peptide; NO: nitric oxide; mAPK: mitogen-activated protein kinase.

2. Neuron–glia interactions in neuropathic pain

Neuron–glia interactions play critical roles in the development and maintenance of neuropathic pain (Scholz and Woolf, 2007; Watkins et al., 2007; Ji et al., 2013). Some fundamental questions about neuron–glia interactions in pain have been addressed, such as the signals that lead to glial activation after injury and how glial cells affect neuronal activity and promote hyperalgesia (Ren and Dubner, 2008). For example, Coull et al. (2005) proposed that ATP-stimulated microglia send signals to pain-projection neurons in the dorsal horn of the spinal cord. Neuron-derived ATP then activates purinergic ionotropic receptors (P2X4) on microglia, causing further release of microglial ATP and brain-derived neurotrophic factor in spinal lamina neurons (Fig. 1). Another factor that contributes to neuropathic pain is the activation of microglial p38 mAPK (mitogen-activated protein kinase), which enhances Ca^{2+}-sensitive intracellular signaling and thereby leads to production of proinflammatory cytokines. TNFα and matrix metalloproteinases (MMPs) also trigger p38 mAPK activation of microglia in the dorsal horn of spinal cord during neuropathic pain (Svensson et al., 2005). During the onset and early stages of neuropathic pain, MMP-9-induced pro-IL-1β cleavage leads to p38 mAPK activation in microglia, whereas during the ongoing and later stages of neuropathic pain, MMP-2 induces pro-IL-1β cleavage that leads to astrocyte activation (Kawasaki et al., 2008) (Fig. 2). These findings suggest that glial activation can be initiated by neurotransmitters and neuromodulators through neuron-to-glia signaling (Fig. 3).

Chemokines play important roles in neuron–glia signaling during neuropathic pain. Expression of chemokines and their receptors is not limited to peripheral immune cells and glia; neurons can also express these factors (Tran and Miller, 2003). Studies have suggested that CCL2 (*i.e.*, monocyte chemoattractant protein 1 [mCP1]) and its receptor, CCR2, are significantly upregulated in dorsal root ganglia and spinal cord after peripheral nerve injury (Zhang and De Koninck, 2006). CCL2 was reported to modulate thalamic nociceptive processing after spinal cord injury through remote activation of thalamic microglia (Zhao et al., 2007). Further, injection of CCL2 into the thalamus induced pain-related behavior in rats (Zhao et al., 2007). Spinal cord dorsal horn also expresses the lysosomal cysteine protease cathepsin S, an enzyme that may activate and induce

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