European Journal of Pharmacology ■ (■■■■) ■■■–■■■

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

Importance of glial activation in neuropathic pain

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ARTICLE INFO

Keywords:
Neuropathic pain
Astroglia
Microglia
Opioids
Glial inhibitors

ABSTRACT

Glia plays a crucial role in the maintenance of neuronal homeostasis in the central nervous system. The microglial production of immune factors is believed to play an important role in nociceptive transmission. Pain may now be considered a neuro-immune disorder, since it is known that the activation of immune and immune-like glial cells in the dorsal root ganglia and spinal cord results in the release of both pro- and anti-inflammatory cytokines, as well as algesic and analgesic mediators. In this review we presented an important role of cytokines (IL-1alfa, IL-1beta, IL-2, IL-4, IL-6, IL-10, IL-15, IL-18, TNFalpha, IFNgamma, TGF-beta 1, fractalkine and CCL2); complement components (C1q, C3, C5); metaloproteinases (MMP-2,-9) and many other factors, which become activated on spinal cord and DRG level under neuropathic pain. We discussed the role of the immune system in modulating chronic pain. At present, unsatisfactory treatment of neuropathic pain will seek alternative targets for new drugs and it is possible that anti-inflammatory factors like IL-10, IL-4, IL-1alpha, TGF-beta 1 would fulfill this role. Another novel approach for controlling neuropathic pain can be pharmacological attenuation of glial and immune cell activation. It has been found that propentofylline, pentoxifylline, minocycline and fluorocitrate suppress the development of neuropathic pain. The other way of pain control can be the decrease of pro-nociceptive agents like transcription factor synthesis (NF-kappaB, AP-1); kinase synthesis (MEK, p38MAPK, JNK) and protease activation (cathepsin S, MMP9, MMP2). Additionally, since it is known that the opioid-induced glial activation opposes opioid analgesia, some glial inhibitors, which are safe and clinically well tolerated, are proposed as potential useful ko-analgesic agents for opioid treatment of neuropathic pain. This review pointed to some important mechanisms underlying the development of neuropathic pain, which led to identify some possible new approaches to the treatment of neuropathic pain, based on the more comprehensive knowledge of the interaction between the nervous system and glial and immune cells.

1. Introduction

Pain plays an important reflex/defense role in physiological conditions. This is changed upon development of chronic pain, which is considered a disease per se, and is associated by dramatic reduction in the quality of life, inducing many accompanying symptoms such as anxiety, depression or insomnia, etc. (Dworkin et al., 2010; Kalso et al., 2004). Chronic pain may be divided into inflammatory pain, associated with the development of tissue inflammation that lowers the nociceptive excitation threshold, and neuropathic pain, developing as the result of central or peripheral nervous system damage (Dworkin et al., 2010; Kalso et al., 2004). Neuropathic pain, leading to extensive secondary changes in the entire nervous system continues to be an important clinical problem. The term neuropathic pain is used to describe various pain syndromes that do not share common etiology and are not due to a single particular anatomical injury. The clinical neuropathic pain syndrome develops both as a result of mechanical nerve damage and in the course of cancer, diarrhea, herpes zoster, complex regional pain syndrome, multiple sclerosis, hypoxia or stroke (Dobrogowski et al., 1996; Dworkin et al.,. 2010; Kalso et al., 2004). Such damage results not only in hyperalgesia, i.e. increased sensitivity to pain stimuli, but also to increased sensitivity to sensory stimuli, i.e. allodynia. Currently used drugs are effective in inflammatory pain, but their efficacy in neuropathic pain symptoms is limited. Treatment of neuropathic pain is difficult due to the weaker efficacy of opioids (Dworkin et al. 2010; Kalso et al., 2004; McMahon, 2002). Coanalgesics used in the treatment of chronic pain include anticonvulsants, antidepressants, cellular membrane stabilizers, *N*-methyl-D-aspartate (NMDA) receptor antagonists and corticosteroids, while isolated attempts suggested possible use of immunomodulators such as propentophylline or pentoxifylline. Understanding the mechanisms of neuroimmune activation is therefore very important for effective treatment.

However, despite numerous studies, the molecular mechanism of development and persistence of chronic pain remains unknown (Weihe et al., 1991; Woolf and Mannion, 1999). Studies involving

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http://dx.doi.org/10.1016/j.ejphar.2013.01.072

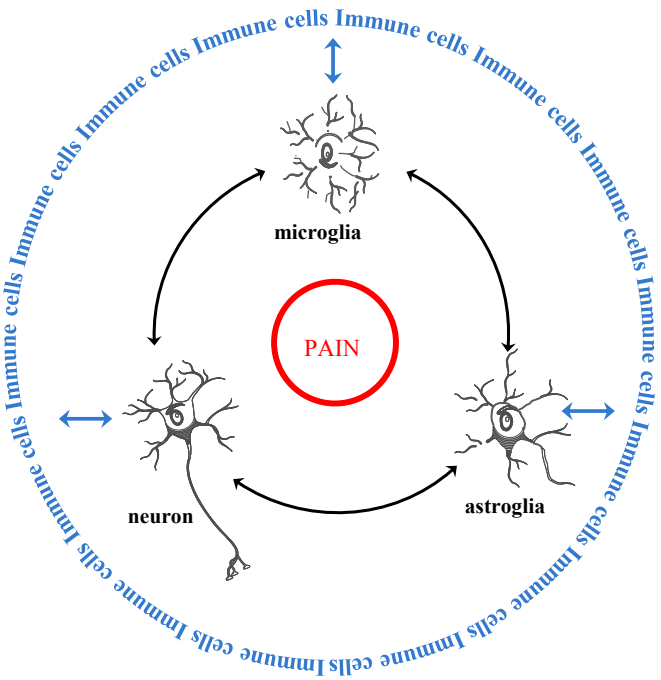

Fig. 1. Interactions of neurons, astrocytes and microglia participate in the development and persistence of chronic pain.

gene expression profiling and mass spectrometry suggest that chronic pain is associated with strong activation of certain neuronal genes, as well as genes associated with immune cell responses, including microglial activation (Dreger et al., 2005; Mika et al. 2008, 2009a, 2009b, 2010, 2011; Rodriguez Parkitna et al., 2006). Moreover, besides reports regarding numerous endogenous initiators and regulators of neuropathic pain, recent studies suggested a significant contribution of neuroimmune interactions in the loss of opioid analgesics efficacy (DeLeo and Yezierski, 2001; Jin et al., 2006; Lee et al., 2004; Mika, 2008a, 2008b; Watkins et al., 2003; Woolf and Mannion, 1999). Understanding the mechanisms of chronic pain with particular focus on neuroimmune interactions (Fig. 1) should lead to identification of novel targets for more effective pharmaceutical treatment of pain, being the objective of many ongoing studies.

2. Involvement of glia in central nervous system on the neuropathic pain development

Glial cells account for 70% of central nervous system cells; in normal conditions, resting microglia accounts for only 5–20% of cells (Nakajima and Kohsaka, 2001; Watkins et al., 2007). Central nervous system includes two main types of glial cells—the microglia and the macroglia, consisting of astrocytes, oligodendrocytes and radial cells including Bergmann cells and Müller cells.

Recent studies suggest a significant role of glia in the maintenance of homeostasis within the central nerveous systems (Kreutzberg, 1996; Nakajima and Kohsaka, 2001; Stoll and Jander, 1999; Watkins et al., 2005). Besides neurons, glial cells are the second main element of neural tissue, not transmitting nerve impulses like neurons but altogether playing an important role in the synthesis, release and uptake of neurotransmitters. In addition, glial cells play a protective role by their involvement in the blood–brain barrier formation and the development of myelin sheath, contribute to the nutrition of neurons and engage in defense mechanisms (Watkins et al., 2005, 2007). Peripheral nerve injury, central nervous system hypoxia and neurodegradation are associated with strong activation of Schwann cells around the damaged peripheral nerves, satellite cells within the dorsal root ganglia, and astrocytes and microglia at the spinal level (Mika et al., 2008, 2009a, 2009b, 2010, 2011; Nakajima and Kohsaka, 2001; Nakagawa et al., 2007; Stoll and Jander, 1999). First reports suggesting the involvement of glia in neuropathic pain were published in the mid-1990s (Colburn et al., 1997, 1999), but it was only recently that the relationship between activated glia and pain behavior was demonstrated. Literature data show that peripheral nerve damage is followed by microglial activation in dorsal horns 24 h after the damage, while astrocyte activation was demonstrated to occur as late as on day 3 after the injury. Activation of the microglia lasts not longer than 3 months and then subsides. Currently, it is known that it is associated with the onset of neuropathic pain symptoms such as allodynia or hyperalgesia (Coyle, 1998; Ledeboer et al., 2005; Zhuang et al., 2005). The last decade formulate new concepts regarding the role of activated glia in synaptic transmission, based on the presence of similar receptors, ion channels, transporters and intracellular signaling pathways on the surface of both neurons and glial cells. Glial cells are also capable of active communication with the neighboring neurons by direct junctions (Nedergaard, 1994; Roh et al., 2010; Zündorf et al., 2007) and synapses (Haber et al., 2006; Oliet et al., 2008). Today, it is known that spinal damage and peripheral nerve damage lead to physiological and morphological activation of glial cells, particularly astrocytes and microglia (Colburn et al., 1999; Fujiki et al., 1996; Tzeng et al., 1999; Woolf and Mannion, 1999). Neuroanatomical and neurochemical transformations of glial cells lead to very important changes in the dorsal horns of the spinal cord in the course of neural trauma-associated disorders (Fig. 2).

2.1. Glia

2.1.1. Macroglia

Astrocytes are the most abundant macroglia cells in the central nervous system. Through expression of numerous transport proteins, astrocytes are capable of maintaining homeostasis by means of regulation of extracellular levels of ions, proteins and neurotransmitters in their surrounding environment. Activation of astrocytes leads to morphological changes, such as hypertrophy and increased production of GFAP (astrocyte marker) and functionally increased production of diverse substances, including pro-inflammatory substances (Watkins and Maier, 2003).

Garrison et al. (1991) were the first to observe increased activation of astrocytes on the damaged side of the spinal cord in rats following sciatic nerve injury. The authors demonstrated that astrocytes are subject to structural and functional modifications. These cells are capable of switching their resting phenotype into the active phenotype, leading to systemic release of cytokines (e.g. TNFα and IL-1β) at the spinal level. Once activated, astrocytes release a high number of factors such as nitric oxide (NO) (Liu et al., 2000), prostaglandines (PGs) (Dirig and Yaksh, 1999; Ghilardi et al., 2004), excitatory amino acids (Duan et al., 2003), cytokines (Milligan et al., 2001) and ATP (Queiroz et al., 1997). What's more, these cytokines mediate pain hypersensitization. Intrathecal administration of IL-1β and TNFα antagonists as well as of the IL-6 neutralizing antibody attenuates pain behavior in neuropathic models (Mika et al., 2008; Milligan et al., 2001; Schoeniger-Skinner et al., 2007).

Many studies were initiated after the first report by Garrison et al. (1991), associating the astrocyte response with pain. Increased expression of astrocyte markers (e.g. GFAP and S100β) was observed in many neuropathic pain models such as sciatic nerve ligation (chronic constriction injury; CCI), (Stuesse et al., 2001), partial sciatic nerve ligation (PSNL) (Coyle, 1998) or tibial nerve ligation (spared nerve injury, SNI) (Vega-Avelaira et al., 2007). Activation of spinal astrocytes was also observed in the models of inflammatory pain induced e.g. by formalin or zymosan injection (Sweitzer et al., 1999). In their studies in the rat bone

Please cite this article as: Mika, J., et al., Importance of glial activation in neuropathic pain. Eur J Pharmacol (2013), http://dx.doi.org/10.1016/j.ejphar.2013.01.072