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Review

Spinal glial activation contributes to pathological pain states

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ABSTRACT

Chronic pain, a pathological state, affects millions of people worldwide. Despite decades of study on the neuronal processing of pain, mechanisms underlying the creation and maintenance of enhanced pain states after injury or inflammation remain far from clear. In the last decade, however, the discovery that glial activation amplifies pain has challenged classic neuronal views of "pain". This review focuses on recent developments in understanding that spinal cord glia are involved in pathological pain. We overview the action of spinal glia (both microglia and astrocytes) in several persistent pain models, and provide new evidence that spinal glia activation contributes to the development and maintenance of arthritic pain facilitation. We also attempt to discuss some critical questions, such as how signals are conveyed from primary afferents to spinal glia following peripheral nerve injury and inflammation. What causes glia to become activated after peripheral/central injury/inflammation? And how the activated glia alter neuronal sensitivity and pain processing? Answers to these questions might open a new approach for treatment of pathological pain.

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1. Introduction

Pain consists of physiological pain and pathological or clinical pain. Physiological pain (also called acute pain, sometimes referred to as "good" pain) is adaptive, transient, and has a protective role

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that warns of potential tissue damage in response to a noxious stimulus. This pain initiates from the peripheral nerve terminals of the nociceptors. The activation of transduction molecules, such as transient receptor potential ion channel TRPV1 (also called vanilloid receptor 1, VR1) and TRPM8 (also called cold and menthol receptor 1, CMR1), Purinoreceptor P2X3, and mechanoreceptor DEG (degenerin), leads to the generation of action potential. The action potential generated in the peripheral nociceptor terminal is conducted via thin unmyelinated C fibers and myelinated Aδ fibers, to a specialized region of spinal cord called the dorsal horn. The dorsal horn neurons convey this message to cortex neurons via a relay in thalamus, inducing pain.

Pathological pain, or clinic pain (also called chronic pain, "bad" pain) is usually maladaptive, persistent, and serves no meaningful defensive, or other helpful purpose. This pain is mainly divided into neuropathic pain, a pain associated with damage or dysfunction of the peripheral nervous system (PNS) and central nervous system (CNS), and inflammatory pain, a pain related to peripheral tissue damage/inflammation (e.g. arthritic pain). In addition, there are other types of pathological pain, such as cancer pain, and pain elicited by continuous infusion of morphine, which share some features with inflammatory and neuropathic pain but also have their distinct characteristics (Brennan et al., 1996; Mantyh et al., 2002). Pathological pain is typically characterized by hyperalgesia (increased responsiveness to noxious stimuli) and allodynia (painful responses to normally innocuous stimuli), as well as by spontaneous pain (Ji and Wen, 2006). The pain hypersensitivity is not only produced in the injured tissue or territory (innervated by the injured nerve), but also spread to the adjacent non-injured regions or the extraterritory (extraterritorial pain) and contralateral body (mirror-image pain) (Woolf and Mannion, 1999; Woolf and Salter, 2000). This exaggerated pain is thought to result from peripheral sensitization (increase in sensitivity of nociceptive primary afferent neurons) and central sensitization (hyperexcitability of nociceptive neurons in the central nervous system, CNS) (Ji and Woolf, 2001).

In the spinal cord, microglia, oligodendrocytes and astrocytes form a large group of glial cells. Microglia are the immune system's ambassadors to the CNS, closely related to macrophages. They fight infections, but in response to injury, release a slew of compounds that may stimulate or damage neurons. Oligodendrocytes provide the fatty myelin sheaths that insulate axons, and the long extensions that convey signals from one end of a neuron to the other. When they die off, neural communication breaks down. Astrocytes are the most mysterious glia, and have many roles in the CNS. For example, they are integral parts of synapse, where they regulate many molecules important for communication between neurons; they release neural growth factors; and in response to injury, they take on vastly different personae. Thus, in addition to providing physical support and housekeeping for neurons, glia are accepted to contribute to the modulation of neuronal excitability and synaptic transmission (Araque et al., 1999; Laming et al., 2000). Recently, glial–neuronal interactions have been studied in the context of enhanced nociception. Studies from our and other laboratories have demonstrated that spinal cord microglia and astrocytes are integral to the initiation and maintenance of pathological pain (Hains and Waxman, 2006; Hashizume et al., 2000; Ledeboer et al., 2005b; Milligan et al., 2003; Raghavendra et al., 2003; Sun et al., 2006, 2007b, 2008). Given the reports on the involvement of oligodendrocyte in pathological pain are quite few, we are referring to microglia and astrocytes when referring to glia below. In the present review, we summarize the roles of spinal microglia and astrocytes in the processing of pain information in several pathological pain models, and further discuss how these pain modulators alter pain processing.

2. Pathological pain and glial activation

2.1. Peripheral events in relation to the generation of pathological pain states

As mention above, pathological pain mainly includes neuropathic pain and inflammatory pain. Neuropathic pain arises as a result of many forms of damage to the nervous system, including diabetic neuropathy, HIV neuropathy, post-herpetic neuralgia, drug-induced neuropathy and traumatic nerve injury. There are several animal models of neuropathic pain, most of which involve partial injury of the sciatic nerve in rodents (see below). Nerve damage exposes the peripheral nerve proteins P0 and P2, which are responded to as nonself by the immune system, hence initiates an immune response similar to that triggered by pathogens (Watkins and Maier, 2002). Nerve injury also leads to Wallerian degeneration that characterized by demyelination and denervation followed by remyelination and renervation (Stoll et al., 2002; Wagner et al., 1998). In this process, various cell types are activated and recruited to the injury site, including mast cells, macrophages, fibroblasts, neutrophils, and Schwann cells, these cells release ATP, proinflammatory cytokines, chemokine ligand 2 (CCL2), prostaglandins (PGs), and nerve growth factor (NGF), which contribute to abnormal pain sensitivity in periphery. The signs and symptoms of inflammation include cell migration, edema, fever, erythema, pain and hyperalgesia. Various events precipitate the inflammatory pain, including exposure to microbial cell wall fragments or toxins (lipopolysaccharide, LPS) from bacterial and zymosan from yeast cell walls, HIV-1 envelope glycoprotein gp120, irritant chemicals, and autoimmune reactions. After tissue inflammation, mast cells, macrophages, and some blood-borne immune cells (neutrophils, T and B cells) may be recruited. Various immune mediators are released, such as proinflammatory cytokines, nitric oxide (NO), bradykinin, NGF, and PGs (Marchand et al., 2005). The sensitizing reagents from nerve terminals and inflammatory cells exert their algesic effects by activating multiple intracellular signaling pathways and increasing the sensitivity and excitability of nociceptors (Ji, 2004; Julius and Basbaum, 2001). Many types of ion channels such as TRPV1, TRPV2, TRPM8, DEG, P2X3, acid-sensitive channel (ASIC), and TTX-resistant channels Nav 1.8 and 1.9, are expressed in primary sensory neurons in dorsal root ganglion (DRG) or trigeminal ganglion. For example, PGE2 results in potentiation of TRPV1 and Nav 1.8/1.9 via PKA activation. TRPV1 is also sensitized by many other factors including protons, NGF, and bradykinin (Julius and Basbaum, 2001). Several protein kinases such as PKA, PKC, PI3K (phosphatidylinositol 3-kinase), and ERK (extracellular signal-regulated kinase) are also implicated in TRPV1 sensitization (Ji et al., 2007).

2.2. Spinal glial activation in pathological pain models

Activation of peripheral nociceptors also results in a series of changes in plasticity in the CNS. The plasticity modifies the performance of nociceptive pathway by enhancing and prolonging the responses to subsequent peripheral stimuli. These changes in the spinal cord, as well as in the brain are referred to central sensitization. Recently, it has become clear that spinal glial cells (referred to astrocytes and microglia) importantly contribute to the development and maintenance of central sensitization in pathological pain states (Deleo and Yezierski, 2001; Marchand et al., 2005; Watkins et al., 2001; Wieseler-Frank et al., 2004). Microglial activation occurs in response to CNS injury, microbial invasion and some persistent pain states (Kreutzberg, 1996; Tsuda et al., 2005; Vila et al., 2001). Activated microglia exhibit amoeboid morphology, increased proliferation, upregulated cell-surface molecules, such as the complement receptor 3 (CR3; also know