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Participations of Glias and Immune Cells in Neuropathic Pain

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Abstract

Nowadays, one cannot but recognize a key role of the peripheral and central glial cells for generation of clinical neuropathic pain. Many cytokines are released from glial cells, immune cells and nociceptive primary afferent central or peripheral terminals by injury, bacterial or viral infection, and envenomation by bee venom or scorpion. Released cytokines mutually affect by paracrine or autocrine manner among glias, immune cells and neurons, thereby produce and transmit the exaggerating pain information to the brain. Indeed, suppression of activated glia and immune cells by chemical agents or antibodies can relief abnormal pain caused by various experimental neuropathies. Thus, abnormal exaggerated pain cannot be explained without the role of glia and immune cells. Many investigators emphasized that therapeutic use of inactivating agents to glial and immune cells but not to neurons is available for alleviation of clinical pain. Thermo-TRP channels, TRPV1, TRPA1 and TRPM8 could not sense neuropathic pain by themselves without close interactions between glias, immune cells and TRP channels. The removal of persistent clinical pain will be rescued by treatment with inactivating chemicals to glias and immune cells. In addition, physiological noxious heat could be sensed by unknown sensor other than thermo-TRP channels, TRPV1, TRPA1 and TRPM8

Introduction

Pathological pain (hyperalgesia: acute or persistent exaggerated pain induced by peripheral or central nerve injury, allodynia: pain induced by innocuous touch or thermal stimuli under normal conditions) is caused by infections, tissue damage, envenomation, and injury (including experimental neurotomy) to the peripheral nerves or spinal cord. Peripheral sensitization involves the activation of peripheral nerve nociceptors (capsaicin receptor, TRPV1) and glial cells within dorsal root ganglion (DRG), and a phenotypic change in primary sensory neurons after intraplantar injection of algogens (i.e., larger DRG neurons switch to express substance P (SP) [1] or TRPV1 [2]). On the other hand, central sensitization involves the activation of microglia and astrocytes mainly in the spinal superficial dorsal horn underlying the interaction of immune cells and intrinsic neurons via cytokines and neurotransmitters.

Recently, we reported the role of central and peripheral glia, and thermo-TRP channels (TRPV1, TRPA1 and TRPM8) in pathological pain [3]. It was demonstrated that many kinds of cytokines mutually acting between glias, immune cells and nociceptive sensory neurons have crucial role in generation of neuropathic pain after experimental neuropathy. In the present review, further literature survey was undertaken to enhance the interaction between glial cells and sensory neurons in neuropathic pain, especially focused on the role of glia.

Several Factors Participating in Neuropathic Pain

Another aspect of sensitization in the superficial dorsal horn (substantia gelatinosa: SG), anatomical reorganization in the SG, purinergic (P2X) receptors, and glial and immune cells are referred as several factors relevant to the induction of abnormal pain.

Central sensitization also includes the activation of brain stem inhibitory neurons which descends to the spinal dorsal horn from the rostral ventromedial medulla (RVM), and the indirect stimulation of secondary nociceptive neurons via the inactivation of inhibitory interneurons (disinhibitory sensitization) [4]. Accordingly, since this descending pathway tonically facilitates the spinal nociceptors, spinal cord transection and inactivation of the neurons in the RVM can reduce central sensitization (pain relief) [4]. Spinal disinhibition resulting in hyperalgesia was suggested due to down-regulation of inhibitory neurotransmitters (GABA or glycine) and their receptors, and the inhibitory neuronal cell death after constriction injury of peripheral nerves [5].

Moreover, central sensitization may occur through the sprouting of large Aβ myelinated fibers into lamina II (anatomical reorganization) in the spinal dorsal horn after nerve damage [6-8] or the topical application of

capsaicin [9]. Thus, progressive tactile hypersensitivity in inflamed animals was thought to be due to sprouting of low threshold Aβ fibers which normally do not sense nociception [10]. Nerve growth factor (NGF) immunoreactive activation of microglia, a subset of astrocytes and putative Schwann cells (peripheral nerve glia) in dorsal entry zones, was demonstrated in the injured area 1 to 2 weeks after spinal cord transection [11]. NGF released from these cells was assumed to promote the sprouting of primary afferents in the spinal dorsal horn after injury [11].

Besides, activation of P2X receptors [a subfamily of P2 (purinergic) receptor for ATP] expressed in the nociceptive neurons (P2X3), dorsal horn interneurons (P2X3) and spinal cord microglia (P2X4) is thought to contribute to the generation of neuropathic pain after peripheral nerve injury [12, 13].

Several reviews [14-16] specifically infer how central and peripheral glia is involved in the induction or propagation of neuropathic pain (other related reviews are cited in the reference [3]). The importance of interactions between immune cells (T-lymphocytes, macrophages, neutrophils and dendritic cells) including central glias (microglias and astrocytes) and peripheral glias (satellite cells and Schwann cells), endothelium, fibroblasts and mast cells (immune and inflammatory cells), and central and peripheral neurons was repeatedly referred by Watkins and Maier [16]. Glia and immune cells release inflammatory cytokines (tumor necrosis factor: TNF, interleukin: IL-1, 6) in response to pathological conditions [16]. Thus, neuro-immune interactions were stressed to participate in the development of peripheral neuropathies [17, 18]. Immune suppressant such as cyclosporine A is considered to reduce neuropathic pain [16]. Complex regional pain syndrome (CRPS) I (reflex sympathetic dystrophy) and CRPS II (causalgia), mirror image (uninjured side) pain and extraterritorial pain changes, and clinical back pain are explained by immune or autoimmune effects on the peripheral (PNS) and central nervous system (CNS) [16]. Being confronted with these mounting evidences, the authors suggested that the available drugs for clinical pain must target glias but not neurons [19].

Glial Activation in Experimental Neuropathy

Spinal dorsal horn glias are now well known to be activated in response to subcutaneous (s.c.) inflammation, s.c. yeast cell walls, intraperitoneal (i.p.) bacteria, peripheral nerve and spinal cord trauma (neuropathic conditions after nerve constriction or transection), bone cancer, and immune activation in the spinal cord, all of which are able to generate hyperalgesia [20]. Namely, glial activation affects pathological pain rather than normal acute pain [20]. Activated glia (also mast cells) release IL-1, IL-6 and TNF and these receptors are expressed in both neurons and glia [14, 21]. These proinflammatory cytokines are thought to reinforce pain in the spinal cord [20].

Watkins et al. [22] studied the effects of several glial metabolic inhibitors [fluorocitrate (inhibitor of astrocyte activation), CNI-1493 (tetravalent guanylhydrazone compound, inhibitor of nitric oxide synthesis and cytokine), and TNF-bp (binding protein, antagonist of TNF)] in hyperalgesic conditions after formalin injections using the rat spinal cord. They found that fluorocitrate and CNI-1493 but not TNF-bp inhibited formalin-induced hyperalgesia, suggesting the participation of glia in the mediation of hyperalgesia. The role of IL-1, TNFα, and NO produced by glia was emphasized [22]. Allodynic behavior was closely associated with an enhancement of the immune reactivity of complement receptor C3bi (OX42, marker of microglia), major histocompatibility complex II (OX6, marker of microglia) and glial fibrillary acidic protein (GFAP, marker of astroglia) in the superficial dorsal horn [23].

A neurotrophic virus, HIV-1 can cross the blood- brain barrier and activate microglia and astrocytes. Microglia and astrocytes recognize a glycoprotein, gp 120, expressed on the surface of HIV-1 [24]. Intrathecal (i.t.) application of gp 120 induced mechanical allodynia and hyperalgesia. Thus, the importance of spinal cord microglia and astrocytes to hyperalgesia and allodynia was stressed [24]. HIV gp120 application into the sciatic nerve up-regulated the TNF α, suggesting the release from the activated astrocytes or microglia in the spinal dorsal horn and DRG [binding of gp120 with CXCR4 on Schwann cells releases RANTES (regulated upon activation, normal T-cell expressed, and secreted) or chemokine ligand 5 (CCL5)], followed by leading to TNFα production by DRG neurons [25]. Furthermore, mechanical allodynia induced by gp120 application was lost by knockdown of TNFα with siRNA or recombinant TNFα receptor [25]. Thus, the role of TNFα by glial and DRG cell activation was emphasized in the HIV-sensory neuropathy [25].

Cytokines, cyclooxygenase (COX) products, and NO released from activated microglia were suggested as serious inducers of neuropathic pain [26]. IL-1β -dependent COX2 induction and PGE2 release were demonstrated in the CNS of rats injected with complete Freund's adjuvant (CFA) into the hind paw [27].

Tight ligation of the lumbar spinal nerve induced an increase of fibroblast growth factor (FGF)-2 and FGF-2 mRNA expression in the ipsilateral dorsal horn astrocytes [26]. The activated astrocytes and increase of FGF-2 in the dorsal horn paralleled the induction of mechanical allodynia 2 weeks after surgery, suggesting that FGF-2 is involved in the central sensitization after peripheral nerve injury [28]. It was demonstrated in rats that ipsilateral glial cells (microglia and astroglia) in the medullary superficial dorsal horn (MDH, lamina I-II) were activated following inferior alveolar and mental nerve transection (IMANT) associated with hyper tactile sensitivity [29]. Since the number of trigeminal ganglion (TG) neurons did not show a decrease, the authors concluded that the glial activation is due to degenerative effects of the TG neurons but to the release of substances from the central terminals of the primary afferent neurons. Minocycline (inhibitor of microglial activation) reduced pain hypersensitivity after trigeminal nerve transection in parallel with a decrease in the phosphorylation of p38 MAP (mitogen activated protein) and microglial activation [29]. Substances released from nociceptive central afferent terminals and /or MDH neurons were presumed to be cause of glial activation (neuronal effects on central glia) [29].

AV411(ibudilast:3-isobutyryl)1-2-isopropylpyrazole-pyridine, inactivation chemicals for glial cells) reduced mechanical allodynia induced by chronic constriction injury (CCI) of sciatic nerve and tight spinal nerve ligation (SNL) in rats [30]. The efficacy of AV 411 was closely related to the decrease in immunoreactivity for GFAP in the lumbar spinal dorsal horn on the operated side [30]. The authors proposed to use AV 411 for the clinical regulation of chronic pain.

Intraplantar injection of Asian scorpion Butus martensi Karsch (BmK) into the rat hind paw induced thermal and bilateral mechanical hyperalgesia and early and late activation of microglia and astrocyte, respectively, suggesting the share of microglia and astrocyte in BmK envenomation-induced pain [31]. From the available time difference, astrocyte was considered to contribute the persistence of bilateral mechanical hyperalgesia. The activation of microglia and astrocytes in the ipsilateral superficial dorsal horn and pain-related behavior were reduced by the i.t. injection of fluorocytrate or i.p. injection of minocycline. The therapeutic potential of glial inhibition was stressed for the treatment of patients stung by scorpions [31].

Relationships between Sensory Neurons and Glia

Upon stimulation with supernatant of damaged sensory neurons by repeated freezing and thawing (SDSN), the mRNA expression of TNF-α, IL-1β, IL-6 and inducible nitric oxide synthetase (iNOS) increased in the wild-type microglia, but almost completely disappeared in the toll-like receptor 2 (TLR2) knock-out cells [32]. These results indicate that TLR 2 mediates the effects of nerve injury factors (for instance, SDSN), leading to mechanical allodynia and thermal hyperalgesia [32]. Although the chemicals of SDSN are not known, unknown substances from damaged neurons were predicted as important inducers of neuropathic pain.

Inhibition of glutamate recycling (accumulation of glutamate) in DRG cells caused by a decrease of glutamate transporters in the satellite glial cells (SGC) after nerve injury and activation of macrophages were emphasized to explain the chronic neuropathy [33]. Thus, the role of SGC in neuropathic pain was proposed.

Protein kinase (PKs) sensitizes TRPV1 to agonists (acid, heat, exogenous or endogenous vanilloids) by potentiating the channel opening and leads to activation of primary afferent neurons by inflammatory mediators (bradykinin, mast cell tryptase and histamine) [34]. The anatomical and biochemical interaction between primary afferent nerve terminals and mast cells (immune and inflammatory cells) is thought to ensure a key role of TRPV1 in neuro-immune interaction responsible for neuropathic pain [34].

Release of the chemokine CCL2 [chemokine (c-c motif) ligand 2] from the central terminals of the nociceptive primary afferents, predominantly P2X3 expressing small DRG neurons, activated the microglia which in turn generated the neuropathic pain behavior [35]. Interaction between DRG neurons and spinal microglia via CCL2 was suggested in inducing mechanical allodynia [35]. However, the mechanisms of neuron-glia communication and of the release of ATP, glutamate and other chemical mediators from glia underlying the pathophysiological conditions are yet to

be defined [36].

As noted above, it is becoming steady evidence that induction of neuropathic pain is dependent on the activated glia and interactions between glias and neurons in the PNS and CNS. However, the acute physiological noxious heat can be sensed without TRPV1 channel irrespective of tissue inflammation [3, 37, 38]. In fact, noxious heat was normally sensed despite the profound loss of capsaicin-sensitive DRG neurons and inflammation induced by carrageenan in mice treated with capsaicin on 2 days after birth [39]. Thus, the pathways of transduction for pathological and physiological noxious heat pain were separately illustrated in Fig. 1.

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Illustrations

Illustration 1

1

Fig.1. Interrelationships among glial cells, immune cells, and nociceptive primary sensory neurons (PNS) and secondary sensory neurons in the superficial dorsal horn (CNS). Various inflammatory mediators [ATP, Bradykinin, CGRP (calcitonin-gene related peptides), Glutamate, Histamine, IL-6, IL-1β, NGF, NO, Prostanoid, Protease, SP, TNFα, CCL5 etc.] called inflammatory soup are released from peripheral or central nociceptive primary afferent terminals, immune cells (dendritic cells, endothelial cells, T-lymphocytes, mast cells, macrophage, microglia etc.) by environmental or internal pathophysiological stresses, and mutually influence the activation or inactivation of the release the substances. Therefore, various kinds of receptors are concomitantly up-regulated on glias, neurons and immune cells. The signals of neuropathic (clinical) pain are conducted from injured site to (*via* nociceptive neurons; TRPV1, TRPA1 or TRPM channels: peripheral sensitization) to the spinal dorsal horn where the signals are more potentiated (central sensitization). As a result,

exaggerated pain (hyperalgesia or allodynia) will be produced (pathways indicated by red arrows). Neither glias and immune cells alone nor TRP thermo-sensors alone can sense the exaggerated pain. In contrast, the acute physiological noxious heat may be sensed by an unknown sensor without *via* TRP thermo-channels, and glial and immune cells (pathway indicated by yellow arrows).

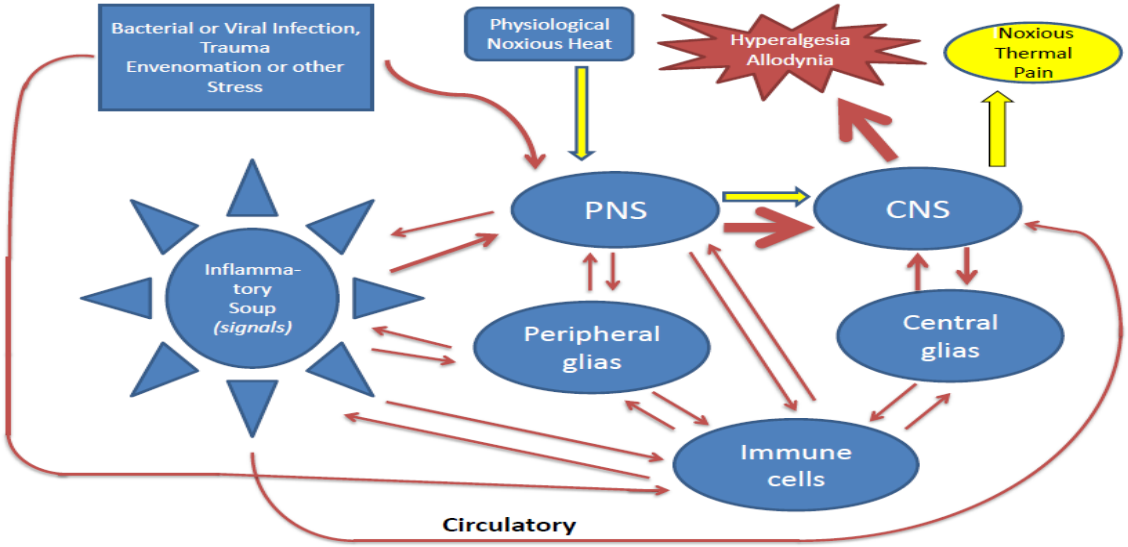

Fig. 1

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