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Activity-triggered tetrapartite neuron–glial interactions following peripheral injury

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Recent studies continue to support the proposition that non-neuronal components of the nervous system, mainly glial cells and associated chemical mediators, contribute to the development of neuronal hyperexcitability that underlies persistent pain conditions. In the event of peripheral injury, enhanced or abnormal nerve input is likely the most efficient way to activate simultaneously central neurons and glia. Injury induces phenotypic changes in glia and triggers signaling cascades that engage reciprocal interactions between presynaptic terminals, postsynaptic neurons, microglia and astrocytes. While some responses to peripheral injury may help the nervous system to adapt positively to counter the disastrous effect of injury, the net effect often leads to long-lasting sensitization of pain transmission pathways and chronic pain.

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Introduction

Most recent studies continue to support the proposition that non-neuronal components of the nervous system, mainly glial cells and associated chemical mediators, contribute to the development of neuronal hyperexcitability that underlies persistent pain conditions. As microglia are considered innate immune cells of the so-called immune-privileged brain, their responses to peripheral injury with collaborative involvement of astroglia and cytokines are considered a type of neuroinflammation [1,2]. This type of neuroinflammation, however, is remote from the site of injury and characteristically distinct from the conventional meaning of 'inflammation'. It is generally devoid of cardinal signs of inflammation in the brain and spinal cord, not necessarily deleterious to neurotransmission as seen in other degenerative neurological diseases, and most importantly, it depends upon enhanced afferent neuronal activity after peripheral injury. Thus, the central 'neuroinflammation' induced by peripheral injury is deemed 'neurogenic' [2–4], which consists of a plethora of mutual signaling between neurons and glia *via* chemical mediators and their receptors. While some of these responses to peripheral injury may help the central nervous system (CNS) to adapt positively to counter the disastrous effect of injury, the net effect often leads to long-lasting sensitization of pain transmission pathways and chronic pain. We will briefly discuss some recent literature on injury-induced central neuron–glial interactions and their significance in persistent pain.

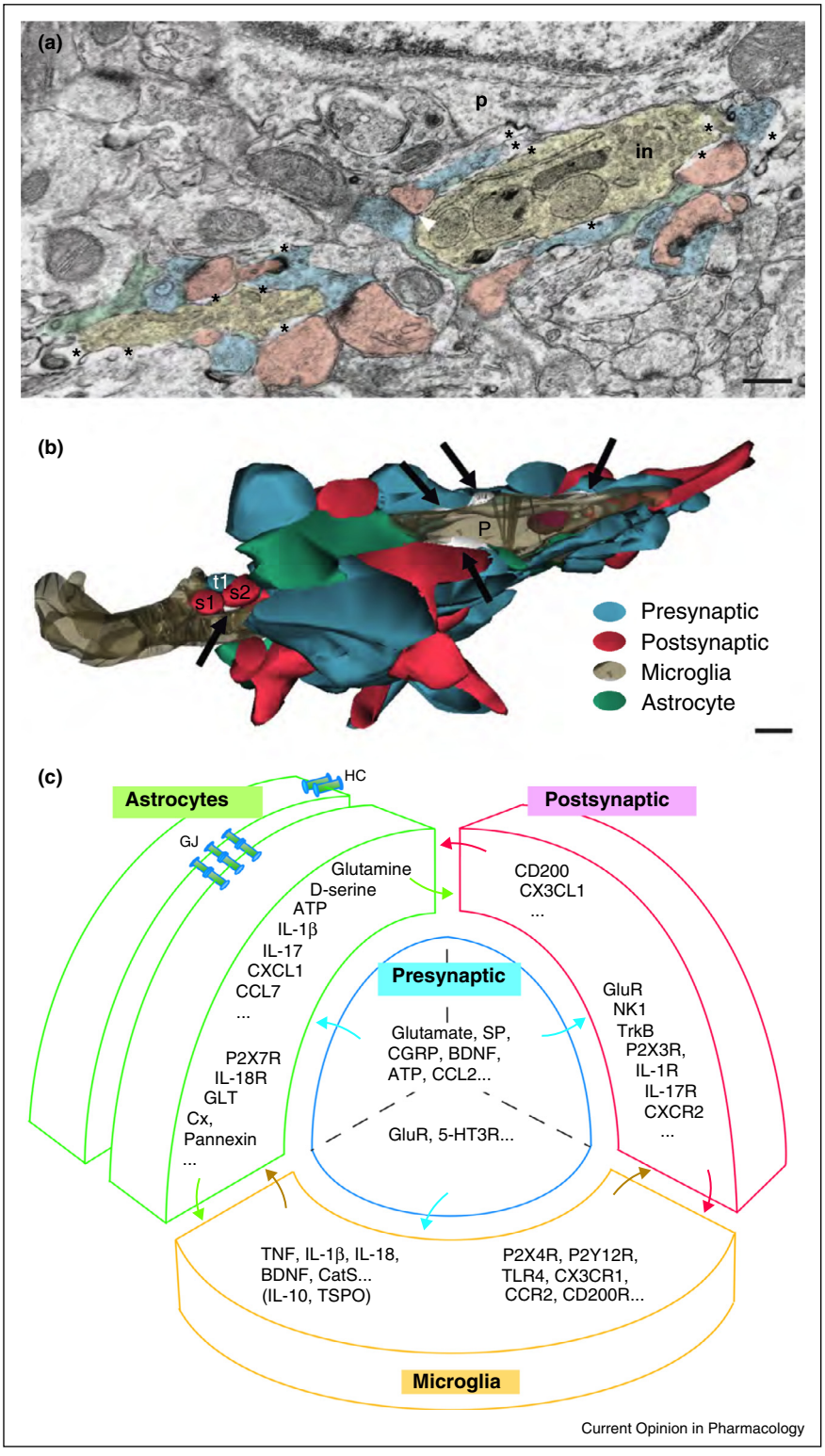
Glial response to peripheral injury in humans

Despite ample evidence from animal studies, it has been a challenge to directly demonstrate the involvement of glia in human chronic pain conditions [(see 5)]. Indirect evidence suggests that humans also exhibit glial response to injury. Increased levels of astroglial marker glial fibrillary acidic protein (GFAP) and S100β were observed in postmortem spinal cord dorsal horn tissues from Human Immunodeficiency Virus (HIV) patients with chronic pain [6]. Increased CNS inflammatory cytokine levels in chronic pain patients have been observed [(see 7)].

Utilizing an improved *in vivo* marker of glial activation with integrated positron emission tomography (PET)-magnetic resonance imaging (MRI), Loggia *et al.* [8••] have recently provided the first observation suggesting brain glial activation in chronic pain patients. They imaged the translocator protein (18 kDa) (TSPO) through its specific binding to a newly developed PET radio ligand ^{11}C-PBR28 in patients suffering from chronic low back pain. The TSPO was first described as the peripheral-type benzodiazepine receptor or recognition site [9]. It was found later that TSPO was also expressed in microglia, astrocytes and neurons [(see 10, 11)]. Interestingly, TSPO has been selectively upregulated in spinal astrocytes and microglia, but not in neurons, following L5 spinal nerve injury in rats [11] and has been used as a marker of increased glial activity after CNS injury in imaging studies [(see 8)]. Peripheral immune challenge with lipopolysaccharide (LPS) induced an increased TSPO binding in the mouse brain with another TSPO PET ligand ^{18}F-PBR06 [12].

In comparison between matched pairs controlling TSPO polymorphism, age and sex, the levels of TSPO, assessed

Figure 1



The tetrapartite model of the neuron–glial interactions. (**a**) Electron microscope image showing oppositions between the presynaptic axon terminals (blue), postsynaptic dendritic spines (pink), microglia (beige) and perisynaptic astrocytes (green). Note a microglia contiguous to a neuronal perikaryon (p) with its associated extracellular space (asterisks) and contacted synapse-associated elements in, cellular inclusion. Scale = 250 nm. (Adapted from [21], Figure 2B.) (**b**) Partial 3-D reconstruction of the microglial proximal process (P) cut in transverse. Note that microglial processes directly contact multiple presynaptic axon terminals (blue), postsynaptic dendritic spines (red), and perisynaptic astrocytic