Introduction

Neuron Glia Biology has dedicated this Special Issue to the role of glial–neuronal interactions in the etiology of chronic pain states by assembling eight papers that span from in vitro glial mechanisms to treatment options for chronic pain. This is a timely issue considering the exponential growth of research in this field over the past ten years. Unfortunately, what has often been missing in the profusion of data is an adequate explanation of how glial activation following injury causes downstream effects of either enhanced neuronal firing or decreased thresholds to firing and, therefore, produces heightened responses to noxious and non-noxious stimuli. In rodent models of persistent pain, these heightened responses are measured routinely using hyperalgesia and mechanical allodynia as behavioral endpoints that represent pain in humans. The synaptic involvement of glia in the pathogenesis of central sensitization draws on concepts that glial biologists have proposed previously for homeostasis and disease states such as neurodegenerative disorders.

In the first paper of this issue, an astrocytic–neuronal mechanism is postulated via progesterone-mediated modulation of neurotransmission through the regulation of astrocyte-derived neuregulin 1. Modulation of gonadal steroids has profound actions on both basal nociception and in chronic pain syndromes. LaCroix-Fralish et al. (see p. 227) demonstrate a unique astrocytic interaction between progesterone and neuregulin as a mechanism to explain sex differences in chronic pain. These findings support a novel glial–neuronal signaling pathway that is involved in the modulation of steroid activity in the CNS.

Inflammation and cytokines have been common themes in pain research in the past decade. The role of innate immunity in the CNS has gained increased attention with the finding that Toll-like receptor 4 (TLR 4) has a key role in initiating chronic neuropathic pain. The tyrosine phosphatase SHP-1 is a crucial regulator of cytokine signaling and inflammation. SHP-1-knockout mice have severe inflammation and are exquisitely sensitive to the TLR 4 ligand lipopolysaccharide (LPS). Hudson et al. (see p. 235) discovered that heterozygous SHP-1-deficient mice display increased thermal sensitivity and LPS-induced fear/anxiety-like behaviors. Interestingly, SHP-1-deficient mice have constitutively higher levels of TLR 4 in the CNS. Furthermore, in the CNS of SHP-1-deficient mice, a type 2 innate immune response is associated positively with behaviors that are usually linked to type 1 proinflammatory cytokines. This forces us to question if therapeutically inducing type 2 immunity in order to treat CNS inflammation processes is always beneficial.

The role of dorsal root ganglion (DRG) satellite cells has not been characterized extensively in the context of the pathophysiology of persistent pain. These cells are often referred to as ‘contaminants’ in DRG culture systems because they are difficult to remove from neuronal cell-culture systems. Therefore, data generated are influenced directly by these glial cells without acknowledgement of their presence. There is also controversy regarding whether these cells express either peripheral or central glial markers, and their function in modulating neuronal transmission. Vit et al. (see p. 247) hypothesize that a change in the expression of gap junctions in satellite cells might alter the excitability of sensory neurons and demonstrate that specific knockdown of Cx43 results in spontaneous pain behavior. They also show, for the first time, that glial fibrillary acidic protein (GFAP), a specific intermediate filament marker for astrocytes, increases in the trigeminal ganglion after an injury that results in behaviors suggestive of chronic pain.

Classically, GFAP has been studied in the spinal cord and brain in relation to either injury to peripheral nerves or central CNS injury. It has been hypothesized that microglia have a role in initiating pain and that astrocytes maintain central sensitization because of their close functional contact with neurons. Ji et al. (see p. 259) advance a novel concept in which the bFGF/JNK pathway serves as a signaling mechanism in spinal astrocytes to drive chronic pain. Further investigation into glial signaling pathways might lead to the discovery of novel molecular targets for the treatment of chronic pain.

The majority of pain studies have focused on glial activation following nerve injury. Saab et al. (see p. 271) apply what we know related to glia after nerve injury to visceral nociception. They show that fractalkine, a chemokine that is a neuron-to-glial signal, facilitates EMG responses to noxious visceral stimulation and that minocycline, a tetracycline with inhibitory effects on microglia, inhibits these effects. Therefore, microglia and the neuron-to-microglial signal fractalkine might be involved in both somatic and visceral nociceptive processing.

A natural transition to elucidating glial–neuronal mechanisms in nociception is how the information can be directed to the discovery of novel drug targets for the treatment and/or prevention of chronic pain syndromes. Therapeutic drug treatments specifically targeted at glia and/or immune mechanisms have been limited to date. AV411 (ibudilast) is a nonselective phosphodiesterase inhibitor that suppresses proinflammatory cytokines in activated glia in vitro. Ledeboer et al. (see p. 279) report that AV411 attenuates mechanical allodynia in rat models of neuropathic pain, possibly through a direct mechanism on activated glial cells in vivo. In another paper, Milligan et al. (see p. 293) utilize a novel gene-therapy approach to target the spinal cord with polymer-based interleukin–10. This concept relies on the administration of an anti-inflammatory cytokine to counteract the increase in inflammatory cytokines that occurs in persistent pain states. In the final contribution, Barcia et al. (see p. 309) caution that systemic infection with adenovirus either before or after the delivery of therapeutic gene via adenoviral vector might significantly affect the levels of transgene expression and, thus, the efficacy of therapy.

We would like to thank Doug Fields, MD, as Editor-in-Chief of Neuron Glia Biology for the opportunity to undertake this special issue on the role of glial–neuronal interactions in chronic pain, and hope that this issue spurs new ideas and attracts additional investigators to this exciting
field. We anticipate that further elucidation of how glia and neurons communicate after nervous system injury will translate into novel drug therapies to treat and to prevent chronic pain states.

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REFERENCES


