Mediation of chronic pain: Not by neurons alone

There’s no mystery why we have acute pain. Early, immediate, and intense information about actual or imminent tissue damage has saved us all from death and destruction since we were tots. By what is the use of chronic pain? Chronic pain is not simply acute pain pathways stimulated ad infinitum. If it were, then our medications that are so effective at relieving acute pain would be useful in chronic pain as well. Often, chronic pain has no obvious, immediate cause and, even when it does, there is little the organism can do to alter the situation. In fact, behavioral, psychological, and immune responses to chronic pain can often worsen the situation and place the organism at increased risk of injury, infection, or death. In short, acute pain is adaptive, chronic pain is maladaptive. How, then, is chronic pain different from acute pain?

Some interesting clues are given on how chronic pain might be maintained in the article by Gordh et al. (2006). Here, they note three important characteristics in a chronic pain model: (i) astrocytic activation; (ii) increased blood–brain barrier (BBB) permeability; (iii) an altered neuronal architecture. These findings are particularly interesting in that they so well resonant with other work just published in related fields.

Glial activation plays a prominent role in animal models of chronic pain (Wieseler-Frank et al., 2005). Such animal models reveal that, whereas initial pain responses are mediated by neurons relaying information from the site of injury to the brain, more persistent pain involves glial cells as well. Specifically, neuronal signals activate the innate immune system of microglia and astrocytes. These cells have joined the ranks of immune cells in that they are immunocompetent; that is, they become activated when attacked by viruses, bacteria, or are physically traumatized. But glia can also be activated by substances released by neurons, including substance P, ATP, fractalkine, excitatory amino acids, and so on. Activation results in release of various substances, including cytokines. Such activation likely is useful, explaining its existence. Glial activation provides a mechanism that acts as a kind of “volume control” for neuronally mediated pain. But this activation can deteriorate into a positive-feedback loop, resulting in a chronic pain syndrome. This model demonstrates how pain can be propagated long after the original cause is gone and how chronic pain can be mediated by non-neuronal pathways outside the influence of opiates.

But what of the disruption of the BBB? Work from Davis and colleagues has shown that the BBB is disrupted in a hindpaw model of chronic pain (Brooks et al., 2005). Their work also shows that some of the proteins that form the interendothelial tight junctions are altered. Tight junctions cement adjacent endothelial cells together and are one of the cardinal features of the BBB. This work is consistent with the work of Gordh et al. (2006) and provides additional mechanisms for glial activation (Huber et al., 2006). Once the BBB is disrupted, blood-borne substances normally excluded from the CNS have increased access to neurons and glia and could activate them. Cytokines in particular may have increased access, as their BBB transporters are known to be enhanced after insults to the CNS (Pan et al., 1997). Additionally, the brain endothelial cell itself is now known to be a source of cytokines which are secreted both constitutively and after immune stimulants (Verma et al., 2006). Activation of the brain’s endothelial cells also increases their expression of adhesion molecules, resulting in an increased permeability of the BBB to immune cell penetration. Immune cells do not leak across a disrupted BBB, but tunnel through endothelial cells by diapedesis, a process which requires highly orchestrated communication between the immune and brain endothelial cells (Wolburg et al., 2005). In short, BBB disruption provides several mechanisms by which glial-activating substances could find their ways into the CNS.

Welding together the above work suggests that the concept of the neurovascular unit (NVU) is important to an understanding of chronic pain. The NVU emphasizes that the BBB, and by extension the brain endothelial cells which form it, does not act in isolation. It
influences and is influenced by peripheral and CNS events. The dynamic interactions among glia, neurons, brain endothelial cells, afferent nerve stimulation, circulating substances, and immune cells that may underlie the induction and propagation of chronic pain are illustrative of the NVU. The work of Gordh et al. (2006) indicates that the architecture of the NVU may eventually be rearranged in chronic pain.

In summary, the work of Gordh et al. (2006) and that from other investigators offer a new view of how chronic pain could arise and be maintained. This new view emphasizes interactions between diverse types of cells, especially glia and brain endothelial cells, and the ability of these cells to communicate, especially once activated, by the secretion of neuroimmune factors.

References


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