A New “Kine” of Pain: MCP-1 and Sensory Neuron Excitability. Focus on “MCP-1 Enhances Excitability of Nociceptive Neurons in Chronically Compressed Dorsal Root Ganglia”

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In 1998, Hu and Xing (1998) developed a method for nerve injury by chronically compressed dorsal root ganglia (CCD). Robert LaMotte and his colleagues at Yale have utilized this technique to explore the consequences of injury on nociception and excitability of primary sensory neurons. This elegant model closely resembles common compressive injuries that occur in people and allows investigations in the whole animal (Song et al. 1999), in situ (Hu et al. 2001; Zhang et al. 1999), and in vitro (Ma and LaMotte 2005; Tan et al. 2006; Yao et al. 2003). In this issue of the Journal of Neurophysiology (p. 2189–2199), Dr. LaMotte and his colleagues investigate the direct actions of the inflammatory chemokine, monocyte chemotactic protein-1 (MCP-1), on sensory neurons subjected to CCD (Sun et al. 2006).

For a long time, inflammatory cytokines and chemokines were thought to be specifically involved in the hematological system and in immune responses. Now it is clear that a growing number of these compounds have significant actions on neurons in the central and peripheral nervous systems. One such example, MCP-1, is a member of the β or C-C chemokine family and a ligand for the β chemokine receptor 2, CCR2 (Gu et al. 1999). The levels of MCP-1 production are increased in various inflammatory conditions, including rheumatoid arthritis (Koch et al. 1992). Last year, White et al. (2005) demonstrated that mRNA levels of CCR2 and immunofluorescent staining for MCP-1 were increased in neurons of the dorsal root ganglia (DRG) subjected to CCD injury. When MCP-1 was applied to these intact ganglia, neuronal depolarization was observed. These interesting results raised two questions. First, does MCP-1 cause depolarization through a direct action on sensory neurons as opposed to indirect mechanisms mediated by surrounding nonneuronal cells? Second, if the actions of MCP-1 on sensory neurons are direct, which ionic currents are involved in this response? These questions have been answered by the new work of Sun et al. (2006).

Sun et al. demonstrate that MCP-1 depolarizes sensory neurons acutely isolated from previously compressed ganglia. The small-diameter sensory neurons treated with MCP-1 also exhibit a decreased rheobase and prolonged action potential duration. These findings demonstrate a direct action of MCP-1 on small-diameter sensory neurons, neurons that presumably have increased CCR2 receptor expression and increased production of endogenous MCP-1 (White et al. 2005). MCP-1 causes a dose-related increase in an inward current in these small-diameter neurons with properties consistent with activation of nonselective cation channels. In addition, MCP-1 inhibits a voltage-dependent outward current of the type associated with delayed-rectifier potassium channels. These data suggest two ionic mechanisms underlying the increased excitability of small-diameter sensory neurons from the CCD injury model exposed to MCP-1.

The observation that the magnitude of MCP-1-induced depolarization is larger in the isolated small-diameter neurons compared with the neurons of the intact ganglia is intriguing and raises questions about the interactions between different subtypes of sensory neurons in the ganglia or between nonneuronal cells and neurons. Was the response of the isolated small-diameter neurons more pronounced because of the absence of paracrine influences from larger-diameter, nociceptive neurons or nonneuronal cells? Although Sun et al. focused on the small-diameter neurons in this investigation, previous studies using the intact ganglia (White et al. 2005) demonstrated that after CCD, both medium- and large-diameter neurons as well as those classified as nonnociceptive were responsive to MCP-1. Was the depolarization of nonnociceptive and large-diameter neurons after treatment of CCD ganglia with MCP-1 mediated by the actions of MCP-1 on nearby nociceptive neurons? Additional characterization of how different subgroups of sensory neurons respond to direct MCP-1 administration should help to answer these questions and add to our understanding of neuropathic pain processes.

Two mechanisms are proposed for the increased excitability of CCD injured sensory neurons exposed to MCP-1: increased activation of a nonselective cation channel and inhibition of voltage-gated potassium channels. It will be interesting to see if these channels are similar to those altered by other inflammatory mediators. The receptor for MCP-1, CCR2, is a G-protein-linked receptor and, therefore, the intracellular transduction cascades activated by MCP-1 are potentially diverse. Again, one would suspect significant overlap of the intracellular changes caused by MCP-1 and other inflammatory mediators known to alter the excitability of nociceptive neurons.

The overall significance of this work by Sun et al. is that there are growing levels of complexity to the process of injury-induced pain. The list of inflammatory mediators with direct actions on nociceptive sensory neurons continues to grow. By understanding the unique as well as the common mechanisms by which MCP-1 and other inflammatory substances alter the excitability of nociceptive sensory neurons, we will begin to understand the broader pathophysiology of neuropathic pain. Sun et al. take us further into the complexity of neuropathic pain, but it is in trying to make sense of the
complexity that we will come closer to developing rational treatments to relieve chronic pain.

REFERENCES


