Acutely Dissociated Sensory Neurons: Normal or Neuropathic? Focus on: “Dissociation of Dorsal Root Ganglion Neurons Induces Hyperexcitability That Is Maintained by Increased Responsiveness to cAMP and cGMP”

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The cell body of the primary nociceptive neuron, located in a ganglion, has an axon that bifurcates, one branch extending to the periphery, the other to the CNS. The cell body (soma) is big relative to the tiny size of its terminal axonal endings. Unlike its terminal ending, it is easily recorded electrophysiologically. Furthermore, when separated from its axon and cellular neighbors by the process of enzymatic and mechanical dissociation and placed in culture, the soma exhibits many functional processes that are similar to those assumed or known to occur at the distal or the proximal terminal ending. The soma has long been used as a model of sensory transduction and sensitization and transmitter release in nociceptive neurons (Richardson and Vasko 2002 for review).

But do the functional processes occurring in the isolated soma represent those occurring at the terminal ending or even in the cell body, in vivo? More realistically, they may represent a mixture of the normal and the abnormal (neuropathic).

In this issue of the Journal of Neurophysiology (p. 15–25), Zheng, Walters, and Song describe at least three exciting and important observations. Their findings support the notion that different kinds of stress applied to the soma, one by axotomy, the other by compression, produce very similar changes in two different signaling pathway contributing to enhanced neuronal excitability. And because the excitatory changes occur very quickly after dissociation, there is support for the idea that the dissociated dorsal root ganglion (DRG) neuron, commonly used in studies of normal pain processing, is an injured neuron with “neuropathic” properties.

The first observation: the authors show that small-diameter DRG neurons from control (sham-operated) rats rapidly became hyperexcitable—within 2 h or so of dissociation. Patch-clamp recordings indicated that the cells were more excitable (e.g., lower current threshold and less accommodation) than those in the control (sham-operated) intact DRG. This confirms and extends our recent observations using sharp electrode recording (Ma and LaMotte 2005). In both studies, these small cells from control were as hyperexcitable after dissociation as they were in an intact ganglion that had been injured by a chronic compression of the DRG (CCD model of neuropathic pain). The importance of these findings is that the acutely dissociated “nociceptive” small-diameter neuron is sensitized and perhaps more a model for studies of neuropathic as opposed to normal nociceptive processing.

The second observation: Zheng et al. found that the hyperexcitability of small diameter neurons, whether produced by dissociation or CCD, appeared to be maintained by activity in two signaling pathways—one involving adenylyl cyclase/cAMP/PKA and the other, guanylyl cyclase/cGMP/PKG. The hyperexcitability was increased by activators of either cyclase or by analogues of cAMP or cGMP or reduced by inhibitors of either cyclase or kinase. However, the inhibitors did not completely block the hyperexcitability and return it to normal (as it was in the control DRG), raising the question of whether simultaneous inhibition of both pathways would have done so.

A possible reason for the excitatory effects of cyclase inhibitors after CCD or dissociation in the present study might be an increase in substances, released in a paracrine or auto- crine manner that continually activate G-protein-coupled receptors that, in turn, maintain a heightened level of adenylyl and guanylyl cyclase. Alternatively, there may be a normal amount of receptor agonist present but the injury somehow induces a higher level of cyclases. In any case, the novel implication is that either type of “stress” to these neurons, a CCD injury or an acute dissociation, produced a similar state of excitability maintained in part by activity in these two signaling pathways.

The third observation: the same activators and inhibitors did not significantly modulate the excitability of small diameter neurons in the intact, control DRG. The fact that previous laboratories have shown that they do so in dissociated neurons (and that certain inflammatory mediators activate the protein kinase A and G (PKA and PKG) pathways in these neurons) (see Zheng et al. 2007 for references) is attributed to the fact that the dissociated neurons are hyperexcitable whereas those in intact, control DRGs are not. Explanations can also be offered for other seemingly contradictory results, such as our finding that an inflammatory soup of four inflammatory mediators, two of which activate the cAMP/PKA pathway, had the same excitatory effect on small as well as larger-sized neurons regardless of whether the neurons were in the intact DRG or dissociated (Ma et al. 2006). The effects of the soup are likely to be more complex and potent than any single ingredient. Still, it is a mystery as to the mechanisms that somehow prevent PKA/PKG activation from decreasing the current threshold in the intact soma but then makes it possible within a very short time, as shown by Zheng et al., after the dissociation injury. Does the injury result, for instance, in a rapid increase in the availability of ion channels to be phosphorylated? Does the injury prime other pathways (resulting in phosphorylation of existing channels) via novel cross talk with PKA/PKG?
In addition to the question of how different stresses can have a common effect of linking two signaling pathways to neuronal excitability, there is the question as to long-term consequences. For instance, the authors raise the intriguing possibility that the hyperexcitability may endure if the alterations in signaling lead to gene transcription and protein synthesis as can occur in spinal neurons, during persistent central sensitization, or in the hippocampus during the formation of long term memory (Ji et al. 2003). If so, there is the exciting possibility of uncovering, in the primary sensory neuron, a mechanism that is responsible for transforming acute pain into chronic.

REFERENCES


