Centralization, Central Sensitization and Neuropathic Pain. Focus on “Sciatic Chronic Constriction Injury Produces Cell-Type-Specific Changes in the Electrophysiological Properties of Rat Substantia Gelatinosa Neurons”

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Admiral Lord Nelson lost his right arm in a sea battle some years before his successful encounter with the forces of Napoleon at the Battle of Trafalgar (1805). Like virtually all amputees Lord Nelson continued to feel his right arm as if it were still there. And like many, for the rest of his life, he suffered from pain in the missing arm. Referring to this phantom limb pain, in his case, the sensation of fingernails digging into his absent palm, he famously declared that his phantom fingers were the best possible proof of the existence of the eternal soul. Maybe so.

Nerve injury, like a severed telephone cable, ought to result in sensory silence. But in fact, it frequently yields ongoing paresthesias and pain and an augmented response to applied stimuli. It is widely held that such “neuropathic pain” results from nerve injury-triggered pathophysiological changes in both the peripheral and the central nervous systems (PNS, CNS). Indeed, electrophysiological recordings in the spinal cord of animals (and humans) with neuropathic pain show elevated spontaneous discharge and other signs of neural hyperexcitability (Laird and Bennett 1993; Loeser et al. 1968). But does this activity reflect changes in the intrinsic properties of central neurons or excessive drive from hyperexcitable peripheral afferents? The answer to this question is important not only for theoretical reasons but also for practical ones. To relieve neuropathic pain, should we be looking for therapeutic targets in the PNS or in the CNS?

There is no doubt that nerve injury can trigger intrinsic hyperexcitability in peripheral sensory neurons. For example, hyperexcitability can be documented in primary afferents isolated from the skin and spinal cord and in dissociated afferent neurons maintained in vitro (Devor 2006b). In contrast, there is little evidence one way or the other concerning nerve injury-evoked changes in the intrinsic electrogenticity of second-order sensory neurons in the spinal cord as very few studies have ever directly addressed the matter. In this issue of the Journal of Neurophysiology (p. 579–590), Balasubramanyan, Stemkowski, Stebbing, and Smith (2006) have taken the bull by the horns by comparing the electrical properties of substantia gelatinosa neurons in spinal cord slices from normal and nerve-injured rats. They looked for changes in excitability after a form of peripheral nerve injury that causes behavioral signs of spontaneous pain and hypersensibility, and abnormal spontaneous and evoked spiking in spinal cord neurons in vivo. Sure enough, changes were detected, but they were surprisingly modest. In certain types of substantia gelatinosa neurons, the authors observed an increase in the amplitude and frequency of ongoing subthreshold synaptic currents, whereas in others, there was a decrease. Overall, changes seen in the intrinsic biophysical properties of these neurons were not nearly as prominent as one might have guessed would be required to account for the behavioral and electrophysiological agitation seen in the whole animal. For example, there was no indication of a depolarizing shift in the resting membrane potential, no sign of the massive spontaneous impulse discharge that occurs in vivo, and not even much change in the tendency of the neurons to fire spike trains when artificially depolarized.

The subtle changes observed by the authors may well reflect true postsynaptic alterations in the properties of the spinal neurons studied, changes that are independent of ongoing synaptic drive from the periphery. However, even this cannot be stated with certainty as central terminals of the injured peripheral afferents are still present in the slice preparation. It is possible that the observed alterations in the mini-synaptic currents are due to changes in spontaneous synaptic release from the presynaptic terminals of peripheral afferents. What is certain is that these neurons did not undergo the substantial increase in centrally generated firing called for by many current theories of neuropathic pain (Devor 2006a). So where does that leave us in terms of the CNS’s contribution to neuropathic pain? First, it is possible that the subtle changes observed by Balasubramanyan et al. (2006) are in fact enough to cause a lifetime of pain. Or perhaps the cause of neuropathic pain rests in neurons that reside in the marginal zone or in deeper layers of the spinal gray. Finally, it is possible that nothing of much consequence actually changes in the intrinsic properties of spinal neurons and that the elevated firing seen in intact preparations simply reflects abnormal neural activity generated in the periphery. That is, the elevated central firing could be due to: excess drive by spikes that originate in active primary afferents and/or dynamic short-term changes in the response of spinal neurons due to the ongoing release of neurotransmitters and peptide neuromodulators from peripheral afferent terminals. This latter phenomenon is termed peripheral activity-maintained “central sensitization.” Changes in descending modulatory controls could also contribute (Burgess et al. 2002).

The classical explanation of phantom limbs and other refractory neuropathic pain states is that pain signals originating in the periphery migrate centrally, “burn their way” into the CNS and in time create a permanent trace that is independent of peripheral drive (Kalso 1997; Melzack 1989). This putative
process, “pain centralization,” likens pain to a raging river that over time carves a deep canyon out of solid rock. But the idea of pain centralization has always been more poetry than physiology. Consider cases of intense and long-standing pains where the source is clearly peripheral and is eventually removed; total hip replacement surgery in osteoarthritis, for example, or release of an entrapped nerve, passage of a kidney stone or childbirth. Pain tends to cease abruptly after the peripheral source is removed, leaving no obvious permanent trace. Pain signals per se do not appear to induce centralization. But that having been said, it remains possible that peripheral neuropathy could occasion the emergence of painful sources of impulse generation from within the CNS proper. The most we can say at present is that the data of Balasubramanyan et al. (2006) do not point strongly in this direction.

REFERENCES


