Neuromodulation for the Management of Chronic Pain in SCI: Is it a Better Approach to the Problem than Other Treatments?

Philip Siddall

University of Sydney Pain Management & Research Centre,
Royal North Shore Hospital, Sydney, NSW, Australia

Pain has been viewed in the past as a sensation that is transmitted along anatomical pathways that are fixed and constant. Much of early pain research was therefore devoted to determining the origins and destinations of these pathways to try to understand how pain is processed by our nervous system. Identification of these pain pathways then led to the surgical approach to pain management in which nerves, spinal cord tracts and brain regions were severed or destroyed in order to alleviate pain. Unfortunately, it did not work. Although helpful for many in the short term and some in the long term, pain relief was often temporary. Some people even developed pain that was worse than the pain that was present initially.

The failure of surgical procedures to remove pain was one observation that stimulated pain research and the development of new concepts of pain. There is now abundant evidence that the nervous system is far from static or hard-wired. Neither is it a passive carrier of information. Rather, the nervous system is constantly changing in response to its environment and the information it carries. These changes can occur with either loss of inputs or increased inputs. For example, amputation and spinal cord injury (SCI) are associated with both short and long term changes as the nervous system attempts to adapt to the loss of sensory information. On the other hand, a barrage of sensory information such as occurs following surgery or trauma also results in changes in the way that the nervous system processes subsequent information. The demonstration of these changes has had a major impact on our approach to the management of pain and opens the possibility for new approaches in the future.

Neuropathic pain is a well recognised problem associated with SCI. Although well recognised, management of the problem is difficult. Many people with this type of pain have severe, persistent pain that fails to respond to all of our currently available treatments. This difficulty in treating neuropathic pain following SCI highlights our lack of understanding of how the nervous system reacts to damage. In the last couple of decades we have been fortunate to see a large increase in the funding available for the investigation of SCI-related problems and much of this money has been expended on trying to find a cure for SCI and trying to restore function.

Regeneration and restoration of function are undoubtedly good things for those with SCI. However, the pain community has for many years been warned of the problems associated with nervous system reorganisation. Although there are still doubts about the applicability of the findings to humans, one of the most widely quoted findings in the pain literature is a study that was published in the journal *Nature* just over ten years ago (Woolf et al., 1992). This paper reported that nerve injury in rats was associated with sprouting of the terminals of incoming primary afferent fibres from the periphery. Following nerve injury, the terminations of some large myelinated fibres were no longer in the deeper dorsal horn in regions normally associated with transmission of innocuous information. Instead, they sprouted so that their terminations could be found in the superficial dorsal horn, a region normally associated with the transmission of noxious information. This reorganisation was believed to underlie the problem of pain and hypersensitivity to touch that occurs with nerve injury.

Of interest to the problem of neuropathic pain and SCI, almost the reverse situation has been observed in animals following hemisection (Christensen and Hulsebosch, 1997). These investigators found that a hemisection SCI results in sprouting of fine diameter primary afferents which normally conduct noxious information into the deeper dorsal horn. This would theoretically provide a substrate for the transmission of noxious information into a region of the cord which normally subserves the transmission of innocuous
information. Once again they propose that this reorganisation may result in pain and sensitivity, in this case following SCI.

Since then, a number of other studies have reported the adverse effects of the body's own attempts at reorganisation. Damaged primary afferent fibres can also send out signals that result in sprouting of sympathetic fibres around the dorsal root ganglia of these damaged afferent fibres (McLachlan et al., 1993). It has been suggested that this aberrant connection between the sympathetic nervous system and primary afferent fibres may underlie the phenomenon of causalgia or complex regional pain syndrome, as it is now termed.

As well as these changes at a peripheral and spinal level, changes at higher levels of the nervous system have been reported. For example, deafferentation of the thalamus in humans results in abnormal bursting activity of thalamic neurons which appears to correspond with the presence of neuropathic pain (Lenz et al., 1987). This abnormal activity may be the result of chemical changes that occur with the loss of inputs that follow nervous system damage (Rausell et al., 1992). These chemical changes include a reduction in inhibitory neurotransmitters such as GABA that normally regulate the transmission of sensory information. A reduction of inhibition subsequent to loss of inputs may result in exaggerated responses and either spontaneous pain or an increased responsiveness to sensory inputs. These changes can occur rapidly following deafferentation and a reorganisation of receptive fields following amputation can occur within minutes (Calford and Tweedale, 1988).

This fast functional reorganisation and its relationship to the presence of neuropathic pain have also been demonstrated by some elegant work by Flor and her colleagues. They have demonstrated using brain imaging techniques that amputation in humans is associated with a reorganisation of the somatosensory cortex. Furthermore, the extent of reorganisation appears to correspond with the presence of pain (Flor et al., 1995).

Thus, there is abundant evidence that the nervous system quickly attempts to reorganise following damage. These changes include both anatomical and biochemical changes that can result in fast changes in synaptic efficacy or relatively slow structural changes that result in inappropriate re-routing of information. However our own body's often feeble attempts to repair itself may be responsible for further problems including the development of pain.

What does this mean for the problem of pain following SCI? And what does it mean for the application of stimulation techniques in both SCI and pain? At present, the effectiveness of stimulation techniques for the management of neuropathic SCI pain has not been tremendously successful. For people with at level neuropathic pain in the segments close to the level of injury, the results have been more promising. A proportion of patients will achieve some relief of their pain. However, for people with below level neuropathic pain, the results are disappointing. Very few achieve adequate relief of this type of pain with the use of stimulation technologies.

Does this mean that stimulation techniques are of little value in the treatment of neuropathic pain following SCI? Certainly the way that they are currently used suggests that only a minority of patients will achieve substantial relief of their pain. However, there are several pieces of enticing information that suggest that stimulation techniques could have an important role in relieving neuropathic pain following SCI and other types of nervous system damage.

Firstly, stimulation of the nervous system is clearly linked to nervous system plasticity. Strong tetanic inputs are linked with plastic changes that are associated with a long lasting increased responsiveness of spinal cord neurons (Ikeda et al., 2003). Thus, peripheral stimulation can result in changes that may underlie persistent pain states including those following nerve and spinal cord injury. However, a change in the parameters of peripheral stimulation can also result in the opposite changes. Instead of the long-term potentiation of responses induced by stimulation of small diameter afferents, stimulation of A fibres can result in long term depression of spinal responses (Sandkuhler et al., 1997). Thus it may be possible to reverse changes by changing the parameters of stimulation.
Secondly, it has been demonstrated that these plastic changes are reversible (Knecht et al., 1998). The group that demonstrated a link between cortical reorganisation following amputation and the presence of pain performed a subsequent study investigating the effects of peripheral inputs on pain and reorganisation. They found that the use of a myoelectric prosthesis appeared to be associated with less pain (Lotze et al., 1999). Thus it was hypothesised that peripheral inputs that are applied to a region that has previously lost its input can result in a subsequent "good" reorganisation that is associated with less pain. Thus it may be that peripheral or central inputs provided by stimulation, if the right parameters are used, can result in a reversal of the "bad" reorganisation associated with the presence of pain.

Although not definitive, these studies suggest that stimulation technologies may have an important role in the reversing the changes associated with pain and nervous system damage. Inputs have a strong influence on the organisation of the central nervous system and identification of the optimal parameters to induce "good" reorganisation or to reverse central hyperexcitability may be a powerful therapeutic tool.

References