Pain: new insights, new treatments?

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THE ABILITY TO PERCEIVE PAIN and avoid further contact with noxious stimuli is important for survival. Pain originating in injured tissues (tissue damage, inflammation, etc.) is valuable because it limits use of the injured area and allows it to rest and heal. The plasticity of the nervous system is demonstrated under conditions of prolonged pain, which may be associated with sensitization. Minor stimuli may then lead to severe pain. The hypersensitivity of sunburned skin areas is a familiar example. In chronic pain conditions, such as metastatic bone cancer or neuropathic pain, the increase in pain perception may become unbearable.

Within the last few years, significant advances have been made in the understanding of pain. The identity of a number of receptors and transmitters has been unraveled at the molecular level, and it has become clear that pain itself, by inducing release of nerve growth factor, may induce significant changes in the pain transduction pathways and thereby contribute to hyperalgesia.

Pain is perceived in the peripheral tissues by pain receptors—nociceptors—that come in separate types responding to stimulation by heat, cold, or pressure and mechanical stress. Local inflammation increases the nociceptor activity by, e.g., acidosis and release of ATP, serotonin, and prostaglandin E2, which interact with ion channels on the nociceptors (e.g., the vanilloid receptor and the sensory nerve-specific sodium channel) or by bioactive peptides, including bradykinin and nerve growth factor, which bind to metabotropic receptors (3). The nerve fibers of the nociceptors are of two general types: lightly myelinated axons (A fibers) conduct action potentials rapidly and mediate the fast, pricking quality of pain, whereas unmyelinated axons (C fibers) conduct more slowly and mediate the slower, dull, burning quality of pain (6).

Pain has sensory (discriminative) and affective (unpleasantness, intensity) dimensions, which have been suggested to be transmitted to the brain by two separate parallel pathways by second-order neurons originating in the spinal dorsal horn. The sensory signals seem to be transmitted to the brain via the spinothalamic pathway, which originates from neurons in the neck of the dorsal horn and ends in the ventrobasal and ventroposterior thalamus, which then projects to the cortex. The intensity of pain is probably transmitted through the spinothalamic pathway, which originates primarily from lamina I neurons of the dorsal horn and terminates in the parabrachial area and the periaqueductal gray. These areas project on the hypothalamus and amygdala that modulate the affective dimensions of pain and control autonomic activity. Pain-induced anxiety and depression may follow this pathway (2). In keeping with this, selective destruction of the spinothalamic pathway in rats alleviates hyperalgesia induced by inflammation and by manipulation of the peripheral nerve without affecting the discriminative dimension of pain (2). In theory, therefore, ablation of these neurons may block the unwanted pain without interfering with the useful discriminative type of pain.

The synapses of C fibers that form the beginning of the spinothalamic tract are located in lamina I and in the outer part of lamina II. They are rich in substance P, which is released upon noxious stimulation and acts on postsynaptic neurokinin 1 (NK1) receptors, which are internalized after binding of the ligand. This internalization process opens the possibility of specifically introducing substance P-coupled toxic substances, such as saporin, pseudomonas exotoxin, or diphtheria toxin, into the cells, thereby ablating the spinothalamic pathway. In the rat, lamina I expressing the NK1 receptor is located very superficially in the spinal cord and lamina I neurons have been ablated by infusion of substance P-coupled saporin into the intrathecal space of the spinal cord. This ablation results in attenuation of responses to highly noxious stimuli and to mechanical and thermal hyperalgesia (4).

On the basis of these promising animal experiments, NK1-positive neurons in lamina I have become a potential target for intervention in humans. However, in humans, lamina I is located deeper within the spinal cord and is not accessible by intrathecal infusion. Therefore, the substance P-coupled toxin needs to be infused directly into the spinal cord. For ethical reasons, neurotoxic substances cannot be infused into human spinal cords by trial and error, and mathematical models that can simulate the outcome of the experiments are strongly warranted. The study by Sartinoranont et al. (5) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology provides one such model. The authors simulate what happens on infusion of substance P-coupled toxin directly into the nerve tissue of the spinal cord. They take into consideration how fluid distributes in white matter, where flow tends to be more rapid along the axis of the myelinated fibers, and in gray matter, where fluid distribution is isotropic. In addition, their model includes extracellular breakdown of the substance P-coupled toxin, the uptake process in

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the NK₁-expressing cells, as well as estimations of the toxin level necessary to kill the cells. The authors show that there is a very steep gradient of toxin in the tissue when infused close to lamina I, and they test the model with different model parameters, including infusion rates, concentrations, and localization of the catheter. Test of the model predictions in actual infusion experiments will be important to validate the model. As for the clinical usefulness of the principle, there are a few caveats. One is whether ablation of NK₁-expressing neurons is as efficient a painkiller in humans as it is in rats. A less complete intervention in the pain transduction pathway by NK₁ receptor antagonists has not yet proven efficient as an analgesic in humans (1). Another practical consideration is that the infusion catheter needs to be placed with great precision (submillimeter) to be close enough to lamina I to cause efficient ablation, without risking admittance of the toxin to the motoneurons of the anterior spinal horn, which also express NK₁ receptors, as pointed out by the authors.

In conclusion, this model and the results it has produced are likely to become useful tools for the future development of this exciting potential modality for treatment of chronic pain in humans.

REFERENCES