EDITORIAL

Novel Therapies for the Control and Prevention of Neuropathic Pain

The development of animal models has facilitated scientific advances in the field of neuropathic pain. Allan Basbaum was the first to report, in 1974,[1] a preclinical model of experimental neuropathic pain in which rats with unilateral transections of several adjacent lumbar dorsal roots began to bite and gnaw the deafferented hind paw. Avulsion of dorsal roots in humans frequently results in severe pain that is felt in the deafferented region; therefore, Basbaum inferred that the rats were responding to a similar pain. Five years later, Patrick Wall and his colleagues[2] reported that similar self-injurious behavior (autotomy) occurred after a much simpler surgery: unilateral transection of the rat's sciatic and saphenous nerves, which results in a complete sensory denervation of the hind paw. Similar lesions in humans generally produce complete anesthesia in the nerve territory, but a small number of patients nevertheless develop severe pain that is felt to arise from the anesthetic region. This condition is called anesthesia dolorosa, and it is akin to the phantom pain that occurs when the nerves are transected via an amputation. Researchers working on analgesics did not adopt the autotomy model, and it is rarely used today for three primary reasons. First, the assumption that autotomy is due to pain may be fundamentally indeterminable.[3] Second, autotomy lacks face validity because comparable self-injurious behavior is very rare in humans (and when it does occur may be due to neuropathic itch rather than pain).[4,5] Third, the model's endpoint, autotomy, can not be scheduled; it begins several days after the lesion and continues fitfully for weeks thereafter. Thus, to test a putative analgesic's effects on autotomy would require about two weeks of observation.

Advances in the field of neuropathic pain accelerated following a report in 1988 that described a model of post-traumatic painful peripheral neuropathy produced via a simple surgical procedure that creates a partial injury to the rat's sciatic nerve (chronic constriction injury [CCI]).[6] Because the injury does not completely denervate the hind paw and relevant motor responses are preserved such that the rat is able to respond to paw stimulation and allodynia and hyperalgesia, common complaints in nerve-damaged patients, could be assayed. Using the stimulus-evoked pain abnormalities as endpoints, it was now possible to test the effects of a putative analgesic in one hour. This and other preclinical models of post-traumatic painful peripheral neuropathy, described in this issue of *Neurotherapeutics*, have provided most of the data for our current understanding of the pathophysiological mechanisms of neuropathic pain. However, most clinical cases of painful peripheral neuropathy may be due to other factors and may involve other mechanisms. Thus, data generated from the more recent preclinical models of painful diabetic neuropathy, postherpetic neuralgia, and the toxic neuropathies caused by cancer chemotherapeutics are likely to be of very great importance.

Seven years after the introduction of the CCI model, anecdotal reports appeared suggesting that gabapentin had an analgesic action in neuropathic pain patients, and it was quickly demonstrated that it was antihyperalgesic in CCI rats.[7-9] The availability of a practical animal model, the agreement between clinical and animal data concerning gabapentin, and gabapentin's extraordinary commercial success gave rise, in large part, to the intensive drug discovery programs that characterize the field today. The current and future status of these programs is the subject of this issue of *Neurotherapeutics*.

Myriad factors contribute to the failure of a drug to yield a clinically meaningful effect in patients, including the ability of the compound to reach the target site.[10] In fact, the last decade has shown that the animal models are excellent predictors of analgesic efficacy.[10,11] There are now several U.S. Food and Drug Administration-approved drugs for the treatment of distinct neuropathic pain conditions, whereas, prior to the development of preclinical neuropathic pain models, only carbamazepine for the treatment of idiopathic trigeminal neuralgia (tic douloureux) had been confirmed in a controlled clinical trial.[12] Despite this success, we are far from finished. Our current drugs give a useful degree of pain relief in only about one half of the patients, and very few patients obtain the complete pain relief that is their (and our) goal. As shown in the pages that follow, new insights from basic science, improvements in clinical diagnosis, and improvements in clinical trials methodology hold great promise for the future.

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