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A Role for Cyclooxygenase-1 in Neuropathic Pain?

CYCLOOXYGENASES (COX) and prostaglandins are key players in inflammatory diseases and contribute significantly to the accompanying pain sensitization. More than 10 yr of research have shown that, in particular, those prostaglandins that are produced by the inducible COX-2 isoenzyme trigger inflammatory reactions in the tissue. Two articles in this issue of the *Journal* now suggest that the constitutively expressed COX-1 might be similarly important for the development of neuropathic pain—at least in animal models. Zhu and Eisenach¹ show that spinal COX-1 expression increases early in experimental neuropathy. Hefferan *et al.*² provide data suggesting that inhibition of COX-1 during early stages prevents the development of two typical symptoms of painful neuropathies: allodynia, which describes a state of increased pain sensation in response to stimuli that are usually not sensed as painful, such as light touch; and hyperalgesia, which is an increased sensitivity to noxious (painful) stimuli.

Both studies were conducted in closely related standard animal models of neuropathic pain. Zhu and Eisenach¹ used the partial peripheral nerve transection³ and Hefferan *et al.*² the peripheral nerve ligation model.⁴ Because both of these models involve surgical proce-

dures, they are associated with tissue damage and trigger some inflammatory response. They are therefore not universally accepted as “good models” resembling the most frequent forms of neuropathic pain in patients, which occur in the course of metabolic diseases such as diabetes or renal failure.⁵ Nevertheless, both groups have performed reasonable controls to show that the inflammatory component was, at least, not dominating.

If we assume that the results of both groups can be transferred to the clinical situation of patients, *e.g.*, after traumatic nerve injury, their results bear important consequences for the treatment or prevention of neuropathic pain. Unlike inflammatory pain, neuropathic pain is difficult to treat. Classic cyclooxygenase inhibitors as well as opioids are only marginally effective, and physicians often use anticonvulsants and drugs with unknown mechanisms of action, such as gabapentin, with variable success. The present studies may provide a rational basis for an early, or possibly even prophylactic, treatment of neuropathic pain. In light of the short time period, such a prophylactic intervention will not be possible in metabolic neuropathies. However, the present results may promote clinical studies in patients with acute nerve injuries. One might speculate that cyclooxygenase inhibitors might be given as premedication before elective surgery when the patient is at risk for the development of painful neuropathies (*e.g.*, before amputation). Cyclooxygenase inhibitors might therefore find a place in so-called preemptive analgesia in neurosurgery.

What COX inhibitor, then, should be used to prevent the development of painful neuropathies? Selective COX-2 inhibitors have gained enormous publicity over the past years as a novel class of antiinflammatory and analgesic drugs with a largely reduced risk of upper gastrointestinal bleeding, which often limits the long-term use of classic (nonselective) cyclooxygenase inhibitors.⁶ The work by Hefferan *et al.*² points to selective

This Editorial View accompanies the following articles: Zhu X, Eisenach JM: Cyclooxygenase-1 in the spinal cord is altered after peripheral nerve injury. *ANESTHESIOLOGY* 2003; 99:1175-9; and Hefferan MP, O' Rielly DD, Loomis CW: Inhibition of spinal prostaglandin synthesis early after L5/L6 nerve ligation prevents the development of prostaglandin-dependent and prostaglandin-independent allodynia in the rat. *ANESTHESIOLOGY* 2003; 99:1180-8.

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COX-1 inhibitors, which, by the way, may also exhibit reduced gastrointestinal toxicity.⁷ This question, however, is far from being settled. In the spinal cord dorsal horn, and in a number of other organs, including the kidney, COX-2 is already expressed at low levels under physiologic conditions but becomes dramatically increased after peripheral tissue inflammation. It is not clear why only COX-1 should contribute to painful neuropathy. In fact, if one looks carefully at the results by Hefferan *et al.*,² it is clear that the selective COX-1 inhibitor SC-560 was less effective than the nonselective S-ibuprofen. Because no dose-response relationship has been performed, this interpretation must be made with caution. If it turns out to be true, one would therefore expect that a significant inhibition would also be likely after treatment with a selective COX-2 inhibitor. So, in a prospective trial, we would suggest comparing all three classes of COX inhibitors.

Two other unresolved questions are related to the pathophysiology of neuropathic pain. How do prostaglandins promote the development of painful neuropathies, and why are they only effective early in the course of the disease? Two recent publications have shed light on the molecular mechanisms of prostaglandin E₂ in the spinal cord. Baba *et al.*⁸ showed that prostaglandin E₂ directly depolarizes wide dynamic range neurons in the deep dorsal horn, and Ahmadi *et al.*⁹ demonstrated that prostaglandin E₂ reduces the inhibitory tone of the neurotransmitter glycine onto neurons in the superficial layers of the dorsal horn, thereby causing a disinhibition

of spinal nociceptive transmission. Both mechanisms can explain why prostaglandin E₂ facilitates pain sensation. In addition, they may both contribute to plastic changes in neurotransmission between dorsal horn neurons, which may become prostaglandin-independent and largely irreversible during the disease course. In any case, the novel results point to a new possibility to prevent neuropathic pain, which, if already established, is largely refractory to current treatment options.

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