Necessity for an Animal Model of Postoperative Pain

EXISTING animal models have not been entirely satisfactory in predicting the ability of new or existing analgesic agents to provide improvements in postoperative analgesia. Part of the problem, obviously, has been the inability of an animal to convey to us that it is experiencing pain. We have to depend on secondary behaviors, such as vocalization, licking, or flinching or on the cessation of normal behaviors, such as eating, sleeping, and ambulation to provide us with indicators of underlying pain. Another part of the problem has been the lack of a model that provides all of the elements associated with surgical trauma that contribute to the production of pain.

There are peripheral and central components to the postoperative pain experience. The peripheral component, which has not been well characterized, is thought to produce sensitization of nociceptors in peripheral tissues by substances released in response to surgical trauma. This sensitization involves the lowering of response threshold and enhancement of the response to suprathreshold stimulation. It is theorized that it is associated with activation of second messenger systems within the nociceptor, triggering of the immune system, and interactions between sympathetic and afferent neurons. The central component, which has been studied fairly extensively, involves sensitization of dorsal horn neurons that are ordinarily activated only by noxious stimuli. After repetitive nociceptor discharge, such neurons can be shown to fire more rapidly and for longer periods of time in response to nociceptor stimulation. In addition, they begin to respond briskly to stimulation of nociceptors that were previously outside their peripheral receptive fields and to stimulation of non-nociceptive afferents such as mechanoreceptors. These peripheral and central changes lead to allodynia (pain in response to a non-noxious stimulus), hyperalgesia (enhancement of the pain intensity evoked by a noxious stimulus), and, if there is ongoing discharge of either peripheral nociceptors or dorsal horn pain projection neurons at rest, spontaneous pain.

Two types of mechanical hypersensitivity have been characterized after injury. Punctate hyperalgesia, as demonstrated by a decrease in pain threshold to von Frey hair stimulation, appears to be associated with activation of nociceptors in the periphery. Allodynia to light touch, on the other hand, is thought to be associated with increased central responses to activation of non-nociceptive afferents such as low threshold mechanoreceptors. Another mechanism that may contribute to light touch allodynia is peripheral mechanoreceptor sensitization, which may occur after injury, and has been shown to be mediated by enhanced sympathetic discharge.

Previous animal models have provided considerable insight into the mechanisms by which tissue injury produces pain, allodynia, and hyperalgesia. The intradermal capsaicin model is a useful research model that produces no tissue injury but induces acute pain by selectively activating nociceptors. It reliably produces an area of primary heat and mechanical hyperalgesia plus a surrounding area of secondary mechanical hyperalgesia and serves as a useful model for testing interventions that affect peripheral and central sensitization mechanisms. It has the distinct advantage of being appropriate for human and animal use, allowing correlation between the pain experience of the human model and the results of peripheral and central recording techniques in animals.

The formalin model is another technique that appears to be useful in assessment of the central sensitization component of tissue injury. The subcutaneous injection of small quantities of dilute formalin into the hindfoot of a rat or mouse produces a several-minute period of flinching and licking. This behavior correlates with intense stinging pain associated with subcutaneous formalin injection in a human (Malmberg A, 1992: personal communication). There follows 10–15 minutes of normal behavior followed by resumption of flinching and licking that lasts for another 40 minutes to 1 hour. Recording from peripheral fibers supplying the area of formalin-induced injury demonstrates a dramatic increase in afferent firing beginning 1 minute after injection and lasting several minutes. Thereafter, there is some ongoing discharge but at a considerably reduced level compared with that seen initially. It is thought that

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this persistent low level peripheral input plus central sensitization initiated by the barrage of afferent activity that occurs shortly after the formalin injection is responsible for the second phase of pain behavior. Drugs that block spinal sensitization, such as N-methyl-D-aspartate (NMDA) antagonists, when given intrathecally before the injection of formalin, do not affect the phase 1 pain behavior, but dramatically lessen the phase 2 response.\(^6\)

The formalin model has shown that certain interventions initiated before but not after the noxious stimulus, such as regional blockade with local anesthetics or opioids, are capable of reducing central sensitization. Unfortunately, such data have not always predicted the ability of similar interventions to provide improved postoperative analgesia. For instance, based on this model, one would anticipate that local anesthetic wound infiltration performed before the incision should be more effective than postoperative wound infiltration.\(^7\) Most clinical studies assessing the effects of pre-versus postincisional wound infiltration have shown little or no difference in postoperative pain or analgesic requirement.\(^8\)\(^-\)\(^10\)

The model presented by Zahn et al. (page 1066) offers some potential advantages over previous acute pain models in animals. The most obvious advantage is that it closely mimics the peripheral and central components of the human postoperative pain experience because it uses essentially the same painful stimulus. Hopefully, it will predict the effect of pharmacologic interventions more accurately than other models. For instance, this model may be better than the formalin or capsaicin models in predicting the ability of spinaly administered agents that block central sensitization to reduce postoperative pain. In addition, the model may be useful in assessing the ability of peripherally acting substances, such as cyclooxygenase inhibitors or agents that interfere with the activity of nerve growth factor, to alter pain behavior. The ability to assess the effects of combined interventions that act at different sites or on different mechanisms also may be a distinct benefit to this model.

The incisional pain model is incapable of assessing the existence of spontaneous pain. Hence, there is no experimental animal measure analogous to the human visual analog pain score at rest. The authors describe a method of assessment for non-evoked pain behavior, consisting of a measurement of the amount of time the animal spends in a weight-bearing versus a non-weight-bearing posture. It is a measure of mechanical sensitivity, not of spontaneous pain. The formalin test is able to evaluate the effect of analgesic interventions on spontaneous, or tonic, pain whose behavioral consequence is flinching and licking. It is likely that the degree of spontaneous pain associated with the incision model is insufficient to produce persistent non-evoked pain behaviors. This is, in a way, fortunate because a model that creates ongoing, spontaneous, inescapable pain sufficient to produce vocalization, flinching, cessation of eating, or complete inactivity for many hours to days would create ethical problems that would probably (and appropriately) preclude approval by animal research committees.

The good news regarding this model is that, in the context of postoperative pain, it is mechanically evoked pain (also known as incident pain or phasic pain) that is most difficult to manage and is more important to study. It is the evoked pain initiated by coughing or deep breathing after upper abdominal or thoracic surgery that leads to potentially devastating consequences: hypoventilation, atelectasis, and hypoxia. Spontaneous, or rest, pain is generally easy to control with opioids or nonsteroidal antiinflammatory drugs. Therefore, interventions that are effective in modifying either the punctate or non-punctate hyperalgesia tested by this model are likely to have a substantial effect on postoperative pain.

This study has shown that mechanically evoked pain is responsive to systemic and intrathecal opioids. It remains to be determined if the model will reliably predict the ability of novel classes of agents that inhibit spinal or peripheral sensitization of pain projection systems to provide effective postoperative analgesia. Of equal or perhaps even greater importance is whether this model will be useful in assessing the effects of surgical trauma on endocrine, immunologic, gastrointestinal, and coagulation function. Because we now have the tools to provide a high degree of patient comfort postoperatively, it is essential that we concentrate much of our future efforts on the adverse physiologic consequences of surgical trauma.

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