

Endogenous Pain Modulation

From Humans to Animals and Back

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AN important mechanism by which humans and animals process incoming nociceptive information is top-down modulation, either through inhibition or facilitation of the nociceptive input after tissue damage. The net outcome of this endogenous pain modulatory process, in combination with other pain-modulating processes, is a sensory perception that may range from no pain to severe pain. One important example of effective endogenous antinociceptive effect is given by Beecher.¹ Doctor Henry Knowles Beecher served in the U.S. army during World War II and observed that the majority of soldiers that came back from the battlefield with severe injuries reported little pain and refused analgesic treatment. Apparently, the strong emotional experiences of the battlefield produced sufficient endogenous analgesia to effectively block pain perception. Beecher continued his interest in nociception and antinociception by studying placebo responses (another form of endogenous analgesia)² and later became professor of anesthesia research at Harvard University, Boston, Massachusetts.

The recent decade witnessed raised interest in pain modulation in humans, explored by a range of tools, from more simple psychophysical tests to more complex analyses of brain imaging, and applied in a wide range of clinical aspects, from predicting postoperative pain to understanding response to analgesic agents. In this issue of *ANESTHESIOLOGY*, Peters *et al.*³ report the role of endogenous analgesia in the development and resolution of postoperative pain in a rat model of surgical intervention. This is an impressive example of back translation in pain research; human data that described the relations between endogenous pain modulation and postoperative pain provided the practical importance of this line



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pressure measurements on the hind paw.

Important results of Peters *et al.*³ include the discovery that animals with smaller CPM responses displayed a slower recovery from chronic postoperative sensory hypersensitivity. This suggests that the ability to engage the endogenous pain modulatory system is responsible for the recovery of chronic postoperative pain. These findings complement the observation by Yarnitsky *et al.*,⁴ showing that preoperative CPM testing is able to identify patients at risk for chronic postoperative thoracotomy pain; the lesser the ability to activate CPM, the greater the probability of chronic postoperative pain. In addition, Peters *et al.*³ showed the involvement of noradrenaline release in CPM and postoperative hypersensitivity. Ablation of noradrenergic pathways slowed the recovery of postoperative hypersensitivity, an effect that was still

of work⁴; yet, human research is substantially limited in the scope of manipulation that can be performed and, consequently, cannot reach far in understanding the basic mechanisms of the described findings; this is only attainable in the animal lab. In their animals, Peters *et al.*³ used the partial spared nerve ligation as a robust and well-controlled model of chronic postoperative pain. Endogenous modulation was studied using the conditioned pain modulation (CPM) paradigm. CPM is the central inhibition of an intense focal noxious stimulus (the test stimulus) by administration of second noxious stimulus at a remote area (the conditioning stimulus). In humans, CPM is often induced by application of thermal stimuli as test and conditioning stimuli. Peters *et al.*³ applied a short inflammatory pain stimulus on the forepaw (the conditioning stimulus) and tested the resulting diffuse analgesia by paw

Image: Courtesy of Massachusetts General Hospital.

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present 7 weeks after complete recovery had occurred. These findings show an important role for the activity of noradrenergic pathways in the resolution of postoperative pain. Still, noradrenaline is just one of the several neurotransmitter systems involved in endogenous modulation. Others include endogenous opioids and serotonin.⁵

Several questions regarding the endogenous pain modulation and the CPM model remain. For example, the interplay between the noradrenergic and the serotonergic descending tracts in pain inhibition *via* the CPM protocol—which of the neurotransmitters is responsible for pain inhibition? Both? If so, what is the relative contribution of each? Another issue, along the noradrenergic line, is what should we target as possible treatment line—should we augment pain inhibition by increasing noradrenergic tone, for example, by the use of noradrenaline reuptake inhibition *via* agents such as duloxetine, which was found effective for many neuropathic and other pain syndromes, or should we target a decrease in the sympathetic tone, as we do with clonidine, effective in prevention of migraine? Furthermore, should we increase CPM before any expected pain acquisition so that it becomes more efficient and make the patient more resistant to pain? What pharmacological steps should be taken to the end? Maybe the most important point is the lack of ability of clinical studies to isolate the mechanisms of pain inhibition from the many factors involved in the clinical picture of pain, in postoperative pain in our case; there is the stress of surgery, the implications of the underlying diseases which might be life threatening, there are the social and cultural factors, the protocols used for pain protection, the family support, the kind and duration of the rehabilitation phase, and many other factors, all playing a role in generating the pain and

collectively defined as the biopsychosocial model of pain. Peters *et al.*³ provide a platform to answer these and other questions, by allowing a *one-to-one* interaction between the explored and manipulated mechanisms, the behavioral expression, specifically CPM, and the attributes of pain inhibition and pain expression in the postoperative set-up. It is anticipated that this approach of translating and back translating on pain management relevant issues will provide answers to many open questions.

Competing Interests

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