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Guest Editorial

Animal models of chronic pain: scientific and ethical issues

Kenneth L. Casey [a,b,c] and Ronald Dubner [d]

Departments of [a] Neurology and [b] Physiology, University of Michigan, Ann Arbor, MI 48105 (U.S.A.), [c] Neurology Research Laboratories, Veterans Administration Medical Center, Ann Arbor, MI 48105 (U.S.A.), and [d] Neurobiology and Anesthesiology Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, MD 20892 (U.S.A.)

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Chronic pain is a major health care problem throughout the world. Available data indicate that acute pain syndromes contribute significantly to health care costs but that chronic or recurrent pain produces an even greater economic burden in addition to social and psychological problems [8,19]. As the medical and scientific community has become aware that chronic pain is different from acute pain and has its own high economic and social costs, there has developed increased interest in research focused on the etiology and treatment of chronic pain. In this paper, we will focus on the implications this interest in chronic pain has for the conduct of basic research in animals.

The importance and nature of the clinical problem have raised questions about the need to develop animal models to study the pathophysiological processes that may be unique to chronic pain. However, the development and use of models in which animals are exposed to persistent painful stimuli present serious and difficult ethical problems that require continuing discussion among scientists [2,3,6].

Some definitions are in order before discussing these issues. We accept the definition of the Taxonomy Committee of the IASP: (pain is) 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [14, p. 217]. However, we prefer not to be limited by an arbitrary definition of 3 months as the dividing line between acute and chronic pain [14]. Experiments using animal models of chronic pain may last only a few days, but the ethical issues are the same as if they lasted much longer. We define nociception as peripheral and central nervous system processing that extracts the sensory features of stimuli that are potentially or actually tissue damaging. These features include the intensity, location, quality and duration of a noxious stimulus. The neural pathways and mechanisms mediating this sensory-discriminative component of pain are uniquely activated by somatic and visceral nociceptive afferents [17,22]. The affective, motivational, and cognitive components of pain are also activated by nociceptive afferents. However, these components can be activated not only by nociceptive input, but by inputs unrelated to pain [13]. For example, mood changes, loss of appetite, inactivity, and inability to sleep can be produced by a multitude of factors that are unrelated to pain. It is reasonable to assume that non-nociceptive input accesses areas of the brain that are not uniquely part of nociceptive pathways. Similarly, when an animal escapes a noxious stimulus by releasing a panel button, complex motor pathways are activated. The same pathways are accessed when the animal learns to avoid noxious stimuli, yet the animal is no longer exposed to noxious stimuli and nociceptive pathways are not activated.

Correspondence to: Kenneth L. Casey, M.D., Chief, Neurology Service (127), Veterans Administration Medical Center, 2215 Fuller Road, Ann Arbor, MI 48105, U.S.A.

Patients with chronic pain fall into 3 broad categories: (1) those with a known or discoverable site of tissue pathology that serves as a chronic or recurrent source of nociceptive input, (2) patients in whom the exact source of nociceptive input is poorly understood, but in whom an organic cause for pain may be inferred because of a characteristic clinical presentation or because of evidence obtained through the history or physical examination, and (3) individuals with behaviors that resemble those of groups 1 and 2, but without any evidence for a source of chronic or abnormal nociceptive input.

The first group includes patients with arthritis, cancer or trauma where there is an identifiable origin of the nociceptive input. Many, but not all, of these patients can be treated effectively with analgesic and anti-inflammatory agents or with opiates. In some cases, surgery is necessary.

The second group is comprised largely of patients with pain caused by neuropathy or CNS disease, certain recurrent or persistent headaches, or with some painful conditions of presumed musculoskeletal origin. In such patients, there is often no clearly recognizable source of nociceptive input. Nerve injury, spinal cord injury and stroke sometimes result in chronic pain and are refractory to treatment. The critical pathophysiology may originate in peripheral or central nociceptive pathways, or both. In the case of headache, the prevalence of several well-defined and easily recognized headache syndromes, such as migraine, leaves little doubt that there is an underlying organic pathology. Patients with lumbosacral or other musculoskeletal disorders may give a history of previous trauma or surgery and may have physical findings that strongly suggest organic pathology, although the exact source of nociceptive input cannot be determined. Why some of these conditions result in chronic pain and are so refractory to treatment is not known.

One clinical feature of these first two groups is especially salient; most patients fortunate enough to have the source of abnormal nociceptive activity eliminated or controlled are free from pain. It is common clinical experience that chronic pain often resolves spontaneously or can be successfully treated. Thus, chronic nociceptive input alone does not necessarily produce an irreversible pathologic change in the CNS that sustains the pain long beyond the time that the nociceptive source is eliminated. There are, however, two reports in the literature suggesting that nociceptive input might induce long-lasting plastic changes in the nervous system and explain some failures of nerve transplants or some features of painful neuropathy [11,16]. This deserves further investigation.

The third group of chronic pain patients is the most troublesome because, as best as can be determined with current diagnostic methods, there is no recognizable nociceptive source to heal or treat — or there is substantial evidence that a previous source has been completely eliminated. Furthermore, there is no evidence that the pain these patients report is due to a pathologic change in the central nervous system. The most prominent feature of these patients is their behavioral, psychological or psychosocial dysfunction. If any neural changes have taken place, they are probably within those structures and pathways that participate in attentional, cognitive, emotional, and motoric functions that are initiated by many different sensory inputs and not by nociceptive input alone.

What implications does the preceding discussion have for the development of animal models of chronic pain? First, a reasonable case can be made for developing animal models of the first two groups of chronic pain patients where there is evidence for increased or abnormal nociceptive input. Models of inflammation or tissue pathology produce persistent increased nociceptive input and there is growing evidence that the excessive neural barrage associated with peripheral tissue injury can lead to altered neural activity in the central nervous system and associated neurochemical changes [4,5,7,9,10,15]. Such changes may result in a hyperexcitable nociceptive system, the persistence of pain, and a need for increased medication. Animal models of nerve injury should be developed [1] because central changes may be important in the persistence of spontaneous pain, hyperalgesia and allodynia associated with neuropathic pain. These models may provide new information that can be applied to the development of new approaches to the control of acute and chronic

pain such as postsurgical pain [12,20], most types of cancer pain, arthritis and painful neuropathy.

Animal models can be used to investigate the peripheral and central pathophysiological processes that may make some of the chronic pain conditions of humans and animals refractory to treatment. Some of these experiments can be performed in animals that are given analgesics, general or local anesthetics, or are surgically rendered insensate. Some experiments, however, will require the use of awake, behaving animals because of evidence that potentially important pathological changes may be prevented by drugs or pain-relieving surgery [21]. Such experiments can be performed within IASP guidelines [23]. The animals should be exposed to the minimal nociceptive input and pain to conduct the experiment. Investigators should evaluate the levels of pain by making a careful assessment of the animal's deviation from normal behavior. Measures of daily activity, food consumption, weight, social interaction, and sleep should be included in such an assessment [18]. The duration of the persistent nociceptive input should be limited to the times required to produce the nociceptive pathophysiological changes as determined in pilot experiments. Analgesic agents should be given if they do not interfere with the aim of the study.

There is at present no clear scientific or ethical rationale for producing persistent pain in animals in order to model the third group of chronic pain patients where pain behaviors persist in the absence of a known source of abnormal or nociceptive input. These animal models may mimic chronic pain behaviors such as loss of appetite and libido, disturbed sleep, reduced behavioral activity and social withdrawal. However, these behaviors represent the persistence of responses that initially may have been produced by antecedent injury or illness and involve neural activity in parts of the brain not associated uniquely with pain. An animal model of reactive depression produced by persistent nociceptive input may involve neural plasticity in the hippocampus, amygdala, frontal cortex or other brain sites that play important roles in emotional and cognitive behavior. However, it is not clear that chronic nociceptive input is necessary to produce these neuronal changes or the behaviors associated with them. Similar changes can be produced by stimuli or conditions that do not involve persistent nociceptive input and pain because the neural systems involved are accessed by multiple environmental stimuli.

The development of animal models to study chronic pain behaviors and their neural correlates should proceed only after a full consideration of the issues we have discussed here. We have emphasized the need to establish carefully the clinical, scientific and ethical rationale for the use of animal models of chronic pain. By so doing, those engaged in these studies will demonstrate their sensitivity to these issues and will retain the public support necessary to make important advances in the treatment of chronic, intractable pain.

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