Animal Models of Nociception and Pain

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ABSTRACT

Research on the neurobiological bases of nociception and pain and related investigations of potential therapies require great reliance on animal models. There are unique challenges in the development of well-validated models in this field because of the distinction between nociception, the processing and response to potentially pain producing stimuli by lower levels of the nervous system, and pain, the conscious result of nociceptive stimulus processing by the cerebral cortex. The most frequently used models actually represent tests of nociception only and are appropriate for investigating diverse pathophysiological processes that cause nociceptive activity in peripheral tissues, nerves, the spinal cord, or subcortical regions. However, because human pain is a complex end result of nociception and consciousness-dependent processes, models intended to address pain must be validated for this purpose. Models assessing processes related to pain are relatively rare and more difficult to validate and use than those relevant only for nociception. A failure to recognize the pain–nociception distinction has significant practical consequences for successful extrapolation of results from laboratory to clinical practice.

Key Words: Nociception–pain dichotomy, Construct validity, Neocortex, Nocifensive behavior, Neural substrate.

THE NEED FOR ANIMAL MODELS OF NOCICEPTION AND PAIN

Pain research with human subjects is productive on many fronts, as shown by the large and diverse literature surveyed in the most recent edition of Wall and Melzack’s Textbook of Pain. A particularly prominent area of progress is in the use of brain imaging methods such as positron emission tomography and functional magnetic resonance imaging to advance our understanding of the higher brain processes that underlie pain. However, there are great limitations on the use of humans in experimental studies of pain and animal models continue to be vital. In vivo models are particularly important because pain and its underlying mechanisms are emergent processes of a whole nervous system; these processes cannot be fully simulated in highly reduced cell or tissue systems. In addition to bettering our understanding of nociception and pain, these models are valuable out of welfare concerns for achieving a better understanding of pain–nociception processes in animals. In spite of great recent progress in deciphering the neurobiological basis of nociception and pain, this knowledge has yet to see large-scale translation into effective pain therapies. A limiting factor has been the often unsuccessful extrapolation from animal models to human clinical practice, as exemplified by recent attempts to develop new pharmacological treatments for migraine headache. Beneficial applications from animal models could be fostered by rigorous examination of the validity and limits of these models. This goal also hinges on a better understanding of the similarities and differences between nociception and pain in humans and in the animal models, an understanding that would make model selection and interpretation more valid for human applications.

This chapter’s principal objectives are to clarify distinctions between nociception and pain to improve the interpretation and validity of animal models and to discuss and evaluate commonly used and important models. There are several recent reviews, some highly detailed, on animal models in nociception–pain research that should be consulted by readers wishing further information.

DEFINING PAIN IN HUMANS: IMPLICATIONS FOR ANIMAL MODELS

A valid working definition of pain is vital for efforts to explain its underlying mechanisms or develop therapeutic interventions. To this end, the International Association for the Study of Pain defines human pain as follows: (1) pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage; (2) pain is always subjective; and (3) pain is sometimes reported in the absence of tissue damage and the definition of pain should avoid tying pain to an external eliciting stimulus. One of the most critical conceptual advances in the understanding of pain is the distinction between nociception and pain. As Wall emphasized, nociception that is “activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state.” It is also critical to understand that the pain experience requires conscious awareness. In the usual course of events, tissue-damaging forms of stimuli excite nociceptors and this activity is conducted through peripheral nerves, the spinal cord, and subcortical brain structures to the cerebral cortex. If a person is conscious when nociception-related activity arrives in the cortex, further processing by extensive cortical regions results in pain.

From: Sourcebook of Models for Biomedical Research (P. M. Conn, ed.), © 2008 Humana Press Inc., Totowa, NJ.
The separateness of pain and nociception is seen in diverse ways. First, nociceptive processes do not always lead to pain. People can sustain severe injuries in warfare, sports, or everyday life and either not report pain or report it differently than the extent of an injury would suggest. Second, people with “functional” pain syndromes experience chronic, disturbing pain without any demonstrable tissue damage or pathology. Third, pain can be reduced by psychological manipulations such as a visual illusion or hypnotic suggestion. Fourth, pain has a strong social learning component and depends greatly on prior experience with it and interpersonal interactions that accompany this experience.

THE NEUROLOGY OF NOCICEPTION AND PAIN

There has been great progress in identifying the functional neuroanatomy underlying nociception and pain. We will present a brief account of the neural structures and systems implicated in nociception and pain as it pertains to the use and interpretation of animal models. Numerous excellent reviews provide more detailed information.

Studies of diverse mammals have shown that nociceptive stimuli activate two types of nociceptor receptors in body tissues: those that appear to respond exclusively to noxious mechanical, thermal, or chemical stimuli and those that respond to combinations of these stimuli (polymodal nociceptors). Activity is conducted from these receptors to the spinal cord through both myelinated (Aβ and Aδ) and unmyelinated (C) axons. These axons synapse on dorsal horn spinal neurons, principally in the more superficial laminae, where extensive processing occurs. Ascending projections arise from neurons in diverse dorsal horn laminae, principally lamina I and V, and travel through the contralateral lateral and ventral spinal pathways.

The ascending pathways have synaptic terminations in diverse regions of the brainstem, mainly catecholamine neuron groups, parabrachial nuclei of the pons, midbrain periaqueductal gray, and diverse sites through the brainstem reticular formation. The thalamus receives multiple direct spinal projections to topographically organized lateral and nontopographically organized medial nuclei. There are significant differences between mammalian species at this level, particularly in the existence of a posterior ventromedial nucleus that seems to exist only in primates and is greatly enlarged in humans. Functional imaging studies in humans have consistently shown a diverse array of cortical structures to be activated specifically in association with perceived pain, including the first and second somatosensory areas, anterior cingulate gyrus, insula, and prefrontal cortex. Diverse evidence indicates that the somatosensory cortical zones are critical for the sensory-discriminative dimension of pain, that pain intensity is related to activation of multiple zones, especially involving both hemispheres, and that the emotional-evaluative (suffering) component depends on the anterior cingulate gyrus, insula, and prefrontal cortex. In addition, it is now well established that in humans, pain experience is absolutely dependent on the functioning of these neocortical and limbic cortical areas. The dependence of pain on these cortical regions makes sense also when it is considered that pain depends on the concurrent existence of another function: consciousness. Extensive evidence shows that the cortical regions known to be essential for pain greatly overlap with those vital to the existence of consciousness.

In addition to the ascending pathways is a network of descending modulatory controls, centered in the periaqueductal gray and rostral ventromedial medulla, that exerts both antinociceptive and pronociceptive actions on ascending nociceptive signaling.

THE ADAPTIVENESS OF NOCIFENSIVE BEHAVIORS

Nociceptors form a common underlying thread throughout the evolutionary history of multicellular organisms. Nociceptors have been observed in all bilaterally symmetrical multicellular organisms that have been examined, with the notable exception of elasmobranch fishes. Even the leech has nociceptive neurons, many of which display close similarity to the polymodal nociceptor population that has been so well characterized in mammals.

Although nociceptors are common in the animal kingdom, the existence of nocifensive behaviors, the unconscious protective responses to noxious stimuli, is even more widespread and not specifically tied to possession of nociceptors. The single-celled paramecium (absent any possibility of a nervous system) exhibits protective responses to adverse environmental stimuli. Likewise, sponges with no nervous system and jellyfish with simple nerves have simple, but functional nocifensive behaviors. In these and more advanced bilaterally symmetrical invertebrate organisms as well as vertebrates, the nociceptive system and nocifensive behaviors constitute an essential component to survival. Importantly, the suite of responses to nociceptive stimuli does not end simply with withdrawal reflexes, but in advanced multicellular organisms also includes complex arrays of endocrine and autonomic responses that help prepare the organism for a defense of disturbed homeostasis. Species with nociceptors showing properties in common with those of mammals could serve as useful models for investigating peripheral nociception.

DISTINGUISHING NOCICEPTION FROM PAIN: WHY IT MATTERS

As explained above, nociception and pain are distinctly different things, with differing underlying mechanisms. Unless one is studying the processes that specifically mediate the conscious experience of pain or a behavioral response that is specific to such processes, nociception is being studied and the term pain should not be used. Unfortunately, these terms are frequently used in ambiguous or inconsistent ways, with significant practical costs in the use and interpretation of animal models and theoretical costs in understanding of mechanisms.

The Nociception–Pain Dichotomy in Clinical Neurology

The behavioral separateness of nociception and nocifensive responses from pain is commonly seen in humans with severe neurological injury such as a spinal cord transection. Noxious stimulation of a limb below the level of the transection excites nociceptive sensory receptors and nocifensive pathways within the spinal cord. This spinal activity produces a nocifensive limb withdrawal response, but because nocifensive pathways are interrupted between the spinal cord and the cortex, no pain is felt. The pain–nociception distinction does not stop at this level.

Humans with massive damage or dysfunction of the cerebral cortex are unconscious, but can be awake and show grimacing, vocalization, and organized avoidance reactions in response to a nociceptive stimulus. The importance of understanding the nociception–pain distinction was shown by the confusion and contentiousness surrounding the recent tragic case of Terri Schaivo, who in 1990 experienced a prolonged period of anoxia. Although examining neurologists agreed that she was unconscious, in an irreversible, persistent vegetative state, Mrs. Schaivo was awake, was quite reactive to noxious stimuli, and exhibited nocifensive and emotion-like behaviors, which led to claims by some that Ms. Schaivo’s behaviors had to be consciously mediated. After a pro-

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