Pains, gains, and midbrains

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One of the main aims of neuroscience is to understand how the CNS deals with and adapts to external inputs and internal events. The altered molecular and cellular events form a basis for abnormal processing that underlies physiopathological events. Understanding these events can allow translation from bench science to the patient, and a key step in this process is using models of a clinical condition in animals and human volunteers. Pain is an example of an area where this process has reached a high level of sophistication and where the route from the bench to the patient is starting to be mapped out. The article by Iannetti et al. in this issue of PNAS (1) is a wonderful example of how an imaginative and well planned imaging study can build on findings from animals to help explain the complex mechanisms of pain and its modulation in humans.

Sensory and Affective Events in Pain

Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Key to this definition is the recognition that both the perception and experience of pain are multifactorial. Detection of a noxious stimulus begins with nociceptors that are expressed on primary afferent fibers distributed throughout the body. These afferents, thinly myelinated Aδ fibers and small diameter unmyelinated C fibers, transduce stimulus energy into electrical signals (action potentials) that are conducted along neurones to the spinal cord and brain. There is no dependable relationship between the intensity of the stimulus and the pain that is eventually perceived; instead, the relationship is subject to individual variation and is influenced, at least in part, by the condition of the tissue and the environmental context in which the stimulus is received, as well as the cognitive and affective states of the individual. Imaging pain in healthy volunteers and patients has revealed areas of the CNS activated by this stimulus, the so-called “pain matrix,” where areas involved in the sensory, affective, and motor components of the stimulus can be visualized (2).

However, very few studies have looked at midbrain and brainstem mechanisms and how active drugs can influence the transmission and modulatory regions. A very useful surrogate model is the use of capsaicin, the pungent ingredient of chili peppers that activates the TRPV1 receptor; this peripheral stimulus triggers CNS mechanisms, including central sensitization that generate allodynia (pain to a previously innocuous stimulus), hyperalgesia (exaggerated transmission of a noxious stimulus), and ongoing pain.

Abnormal Pain States

Damage to tissues and peripheral nerves can lead to peripheral and central sensitization, characterized by lowered thresholds for nociceptor activation, spontaneously generated activities in the absence of peripheral input, expansion of receptive fields, and increased spinal activity (3). In addition, mechanisms such as wind-up and long-term potentiation enhance peripheral inputs in conjunction with molecular changes that occur over longer time courses. After nerve injury, for example, there is increased expression and function of N-type calcium channels (4–6), which are critical for governing neurotransmitter release, and an up-regulation of the α-2 δ subunit (7), which is the main site of action of the drug used in the present study, gabapentin (8). Changes in these peripheral, spinal, and supraspinal circuits are likely contributors for the behavioral manifestation of allodynia and/or hyperalgesia. There are, in addition, other higher-order cognitive and emotional processes that can influence perceived pain, including anxiety, mood, and attention. Such phenomena are enabled by the convergence of somatic and limbic systems into a descending modulatory system, providing a way by which the cognitive and emotional states can influence pain processing at the level of the spinal cord (9, 10). In short, it allows the brain to have some control over pain. Areas in the midbrain and brainstem, such as the periaqueductal gray and the rostroventral medial medulla (RVM), are key structures in the descending modulatory repertoire, allowing the bidirectional control of spinal cord activity through descending facilitatory and inhibitory networks (11–16). Ergo, whereas the RVM may serve a protective role during some pain states by increasing its inhibitory output (e.g., inflammatory pain), it may become maladaptive and permit long-lasting abnormal pain (e.g., neuropathic pain). In the latter case, acute pain that has a probable limited duration may progress to chronic pain and outlast the time it takes for the injury to heal.

Imaging the Brain in Pain

The present randomized double-blind study (1) uses a highly sophisticated approach, integrating functional MRI imaging with sensory pain testing, pharmacology, and measurement of plasma drug levels. Of great interest are two key findings: that in the presence of hyperalgesia, the brain exhibits marked deactivation, and that the drug gabapentin not only blocks this deactivation but, in the presence of hyperalgesia, also selectively reduces brainstem stimulus-evoked activation. The deactivation has rarely been studied and is suggested to represent the general “housekeeping” activity of the brain being turned down so that attention to the pain is enhanced. Indeed, this points to ways in which not only can internal and external events cause changes in CNS activity but also how the brainstem, one of the phylogenetically old parts of the brain, can integrate and alter this activity in a top-down manner. The article by Iannetti et al. (1) sheds light on the multiple mechanisms of abnormal pain located in the periphery and CNS, and how this can influence the outcome of treatment.

In animals and humans, the actions of gabapentin are state-dependent, in that it modulates only abnormal pain function without effect on acute noxious physiological activity. How action on a ubiquitous target channel translates to this highly selective action is unknown. The observations of the Iannetti et al. study reveal exactly this, that gabapentin has a mild antinociceptive action; however, in the presence of central sensitization, a powerful antihyperalgesic drug effect could be induced. The site of action of the drug has yet to be determined, because it could act spinally (and animal studies suggest this can be the case), supraspinally, or both. Success with attempts to image activity in the spinal cord, although fraught with problems because of size, cardiovascular issues, and cerebrospinal fluid flow, will shed light on spinal contributions.

Conflict of interest statement: No conflicts declared.
See companion article on page 18195.
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Drug Effects on Pain Circuits

Recent evidence has demonstrated a reliance of gabapentin efficacy on serotoninergic and noradrenergic influence from the brainstem, suggesting that gabapentin analgesia may involve interactions with descending monoaminergic (NA/5-HT) circuits (17, 18). The state dependency of gabapentin actions could be induced by changes in these circuits induced by capsaicin in this study (1) and also by nerve injury. One speculation would be that gabapentin efficacy relates to activity in the spinal–brainstem circuits, which in turn could be influenced not only by peripheral and spinal events but also by the affective state of the patient (e.g., stress, anxiety, and fear), impacting on complex mechanisms relating to attention as revealed by drug effects on deactivation. The elegant findings of Iannetti et al. (1) illustrate beautifully how such a hypothetical model (derived from animal studies) could indeed be applied to a human model of central sensitization. Marked activation of the brainstem after mechanical punctate stimulation on capsaicin-treated skin could reflect the engagement of descending influences during central sensitization. Only under such circumstances of “heightened excitability” could gabapentin exert its antihyperalgesic effects (i.e., inhibition of stimulus-evoked brainstem activity), confirming its state-dependent actions. This state-dependent or permissive interaction may explain why only one in three neuropathic patients achieve >50% pain relief after gabapentin in clinical practice (19). Similar figures are seen with other primarily drug therapies, such as the use of antidepressants, which presumably are also interacting with these brainstem monoamine systems. This leads to the idea that the same circuits (spinal and supraspinal) that alter the gain in this sensory system, thereby producing hyperalgesia, also permit certain drugs to treat the pain. This appears to be true for both acute experimental pain, such as that induced by capsaicin, and physiological pain, such as that seen after nerve injury. In states of chronic pain, feedback onto this descending modulatory circuitry from higher centers such as the amygdala and anterior cingulate cortex (20, 21) could further amplify spinal nociception, so that the perceived pain is greater. It may also be that, even in cases of relatively normal peripheral activity, abnormal central activity may lead to diffuse, widespread pain, as seen in fibromyalgia, migraine, and irritable bowel syndrome. Extensions of these studies in patients with chronic pain should shed light on the role of descending pathways in pathological pain states and reveal how such circuits impact upon treatment efficacy.

This research is supported by The Wellcome Trust and The London Pain Consortium.