Take a Closer Look at the CNS Mechanisms that Process Pain

An expert traces the pathophysiology of chronic pain to its destination in the brain.

Pain is a complex biopsychosocial process often involving the peripheral nervous system (PNS) and always involving the central nervous system (CNS). For example, tissue injury may activate the PNS, which may transmit nociceptive signals through the spinal cord to the brain, where pain perception occurs. In other instances, such as in central post-stroke pain, the role of the PNS is minimized. To better understand how pain is perceived in the brain, let’s look at the processes involved in the CNS.

The Nuts and Bolts

Pain is often categorized based upon its duration (acute vs. chronic) as well as its presumed mechanism, e.g., nociceptive, inflammatory, neuropathic. In the first two, the major features triggering pain include significant changes to high-threshold nociceptors (peripheral sensitization), as well as modifications and modulation of the neurons in the PNS. Amplification of the excitability of neurons within the CNS may also occur; this process in often referred to as central sensitization.

Central sensitization has two components: (1) an immediate and transient phase, and (2) a slower onset but longer duration phase. The early phase of central sensitization reflects changes in synaptic connections within the spinal cord, after a nociceptive signal has been received from peripheral nociceptors. The central terminals of these nociceptor release a host of signal molecules, including the excitatory amino acid synaptic transmitter glutamate, neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) and synaptic modulators such as brain derived neurotrophic factor (BDNF). Acting on specific receptors on the spinal cord neurons, these neurotransmitters and neuro-modulating agents activate intracellular signaling pathways that lead to the phosphorylation of various membrane receptors and channels (e.g., NMDA and AMPA receptors) involved in glutamate transmission.

As with peripheral sensitization, these post-translational changes lower the threshold and opening characteristics of these channels, thereby increasing the excitability of the neurons. A later protein transcription-dependent phase of central sensitization is associated with increased levels of protein production. The net effect of these changes is that normally minimal inputs begin to activate the neurons and pain sensitivity is drastically altered, resulting in greater pain sensibility and lowered pain threshold levels. These processes may result in the frequently observed finding of patients with various chronic pain syndromes in which stimuli that ordinarily do not produce pain, such as a touch, clothing, light pressure or a hairbrush, are perceived as if they are painful (allodynia).

An endogenous opioid, dynorphin, is one protein that may be involved in mediating this effect; it is known to be able to increase neuronal excitability. Another such protein is COX-2, the enzyme that facilitates the production of prostaglandin E2. In addition to being involved in peripheral sensitization, prostaglandins can also affect central neurons, and thus can contribute to central sensitization.

Central sensitization may be an important pathophysiological mechanism of the third type of pain syndrome, neuropathic pain. The pathways by which pain is transmitted to the brain are largely the same as the other two; however, the source of the pain signal and the mechanisms involved in transmitting and processing it can differ. Nociceptive and inflammatory pain conditions are frequently self-limiting and often involve identifiable painful stimuli. Neuropathic pain, by contrast, is due to a lesion or dysfunction in the peripheral and/or central nervous system themselves. It is typically persistent and frequently involves perception of spontaneous pain in the absence of an identifiable stimulus as well as exaggerated responses to painful (hyperalgesia) or (normally) non-painful stimuli; both abnormalities of peripheral excitability (peripheral sensitization) and of central pain processing (central sensitization) may be involved.

Clinical examples of neuropathic pain include diabetic peripheral neuropathic pain, post-herpetic neuralgia and neuropathic pain associated with multiple sclerosis. Persistent pain which is neither clearly nociceptive, inflammatory nor neuropathic has been hypothesized as occurring as the result of abnormal central processing. A possible clinical example of this would be the pain associated with fibromyalgia.

The clinician must keep in mind that two or more types of pain may co-exist in the same patient and thus must evaluate and treat the patient accordingly.

Pain in the Brain

What do we know about what role the brain plays in the pain experience? After all, there is no such thing as pain with the brain.
in an analysis to determine commonly activated brain regions during pain conditions in normal subjects (68 studies) and in clinical pain subjects (30 studies) as imaged by hemodynamic methods including PET and fMRI. Six brain regions were consistently and significantly activated across these studies: anterior cingulate cortex (ACC), prefrontal cortex (PFC), insular cortex, somatosensory cortex (primary and secondary cortices), and the thalamus.

A number of factors influence whether or not a brain region is involved in pain processing: genetics, gender and individual differences affect detection of activity in MRI and PET studies. The brain regions involved in processing pain depend on the type of pain experienced (extreme temperature, electrical shock, visceral). Attentional (distraction), emotional, anticipatory, and expectation states also affect pain processing. A key distinction between acute and chronic pain is that brain regions involved in interpreting chronic pain states appear to be activated differentially. In comparing the reaction to pain in normal subjects vs. pain subjects, it was noted that the difference in degree of activation of these regions, except the thalamus, was statistically significant (p < 0.001).8

Another important observation regarding the brain’s role in the experience of pain: the amygdala may play a key role in attaching emotional significance to pain, and the insular cortex is the structure with the largest spectrum of cortical connections. Painful stimulation activates two distinct areas in the insular cortex, one in the anterior-inferior part and a second in the posterior-superior.7,9 In addition, the ACC, one of the most frequently activated areas in pain imaging studies, exerts multiple functions in pain processing and is most often associated with the affective component of pain. The ACC is also involved in pain anticipation, cognitive-attentional and motor responses to pain.8 It doesn’t appear that the entire PFC responds uniformly to pain stimuli—for example, the lateral prefrontal cortex has been activated in conditions such as ongoing neuropathic pain, visceral pain, cluster headaches and cold/allodynia. Inferior (orbital) prefrontal cortex may be activated by both painful and pleasant but not by neutral sensory stimuli, and is thus thought to be involved in the processing of the affective aspects of sensory stimulation.8

Additional investigations have examined whether or not increases or decreases in expectations of pain relief influence pain perception. Functional MRI has been used to measure regional activity in the brain of 10 normal, healthy volunteers under various thermal (48 °C and 50 °C) conditions that were signaled by prior training trials of specific time intervals. Subjects also used a visual analog scale to rate their subjective pain experience in each condition. When subjects were expecting a 48 °C stimulus and decreased pain intensity relative to the higher temperature condition but received exposure to the higher temperature, brain activity was altered to levels intermediate between the two stimulus conditions, suggesting that expectation was able to alter stimulus perception.9 These findings contribute to our appreciation of pain as a extremely complicated condition.

There are therefore a number of cortical and subcortical influences on pain processing. Dorsal horn neurons can synapse on many subcortical areas within the brain: thalamus, hypothalamus and reticular formation. From each, neurons project to different areas of the cortex: the somatosensory cortex (thalamus, spinohypothalamic tract), frontal and insular cortices (hypothalamus, spinohypothalamic tract), and limbic structures (reticular formation, spinoreticular tract).10 This bidirectional system attunes the body to potentially painful stimuli and determines the attention given to sensory stimuli.11

Activation of somatosensory cortices (S1, S2), thalamus, and posterior insula may be associated with the sensory/discriminative aspect of pain. Anterior cingulate cortex and the anterior insula are thought to be associated with the affective aspect of pain while the prefrontal cortex is associated with the cognitive aspects.11

Baliki et al. analyzed the brain regional involvement in a study examining pain in postherpetic neuralgia (PHN) patients and chronic low back pain (CLBP) patients who all had radiculopathy as part of their history (and thus had a neuropathic component to their pain). The brain regions most strongly activated in the PHN patients included the ventral striatum and the amygdala, while CLBP patients showed strong and significant activation of the prefrontal cortex.12