

Here Today and Not Gone Tomorrow: The Curse of Chronic Pain and Other Central Sensitization Syndromes

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Issue: *Pain may perpetuate pain if it triggers an irreversible sensitization process within the central nervous system.*

Adding Insult to Injury or Insult Added to No Injury?

Acute pain can be caused by mechanical, thermal, chemical, and inflammatory inputs from the periphery and also from various types of tissue injury. The CNS pathways and many of the neurotransmitters that mediate acute pain, also known as “nociception,” are increasingly being clarified.¹⁻³ What remains an enigma, however, is the pathophysiology of various common *chronic* pain states, as well as how best to meet the challenge of treating the numerous, difficult-to-manage clinical conditions associated with chronic pain.

Many chronic pain conditions have no apparent ongoing peripheral injury once a precipitating injury is healed. The insult that may be added to the

injury, however, is that in some cases, despite recovery from an initial painful condition, pain starts to be generated from within the CNS, a process now known as “central sensitization.”^{4,5} This insult may even occur when no peripheral injury has ever been detected and may underlie the pathophysiology of a wide range of conditions known as functional somatic syndromes and characterized by diffuse and distressing somatic symptoms that are often painful and fatiguing.⁴⁻⁸

Pain Begets Pain

Pain travels into the CNS from peripheral terminals in pain neurons, then up the spinal cord to the thalamus, and finally to the cortex.^{1,2} Various descending pathways from brain centers down the spinal cord can both facilitate and inhibit this input.^{3,9} It is now known that continuous activation of peripheral neurons in the pain pathway causes molecular changes in the spinal cord called activity-dependent or use-dependent neuronal plasticity.^{5,10} These changes result in exaggerated or prolonged responses to noxious inputs—sometimes referred to as “wind-up”—as well as painful responses to normally innocuous

inputs.⁸ This process may explain pathologic pain states that arise from either tissue injury induced by inflammation or nerve injury–induced neuropathic pain.^{1,4,5,8} Phosphorylation of key membrane receptors and channels appears to increase synaptic efficiency and thus trip a master switch that turns on central sensitization, best characterized at the spinal level.^{5,10} Here, a veritable soup of neurotransmitters acting at their receptors regulates pain and includes well-known messengers such as γ -aminobutyric acid, glutamate, serotonin, and norepinephrine, as well as some more exotic players such as neurokinin-1, nitric oxide, substance P, glycine, bradykinin, and CGRP (calcitonin gene related peptide).^{1,8,11} Further up the pathway, opioids, cannabinoids, and other messengers are involved in regulating pain, but it is not yet clear what molecular events may be occurring in the brain of patients with central sensitization syndromes.^{1,11}

Can the Pain Gates Be Opened From the Inside and Cause Functional Somatic Syndromes?

The notion of central sensitization has now expanded into areas where

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the triggering experience that becomes amplified and enduring is one that may be internal in nature. Thus, an event occurring within the CNS rather than one arising from a peripheral painful input could theoretically open the gate to activity-dependent functional plasticity in patients with functional somatic syndromes such as fibromyalgia, noncardiac chest pain, or irritable bowel syndrome. Such patients may have become sensitized by an emotional event or by residual somatic symptoms of depression or anxiety rather than from a peripheral painful input.^{7,12} Furthermore, patients with addictions could have become sensitized by chemical events resulting from actions within central mesolimbic dopamine pleasure centers.¹³ Stress may sensitize patients' fear pathways and emotional centers, such as amygdala and limbic cortex, to precipitate anxiety and affective disorders

that are amplified and endure long after the stress has abated.¹⁴⁻¹⁶

Fagedaboudid (Forget About It)

It is as though the brain "learns" from its experience of pain and decides not only to keep the pain process going but also to enhance it and make it permanent. Interrupting this process and getting the CNS to "forget" its molecular memories may be one of the greatest unmet needs in psychopharmacology today, not only because it may be a therapeutic strategy for various chronic inflammatory and neuropathic pain conditions,¹¹ but also because it may be a viable approach to treating the hypothesized molecular changes that may underlie functional somatic syndromes, stress-induced anxiety and affective disorders, and addictive disorders.^{7,13,15,16} Early innovative approaches to this problem include experimental strategies to prevent pain before it predictably

occurs by administering analgesics *before* surgery to reduce the need for analgesics postoperatively. In the meantime, prior to the development of specific treatments to reverse central sensitization, it would be common sense to try to prevent its development whenever possible with the pharmacologic tools at hand, including antidepressants, anti-inflammatory agents, and ion channel-inhibiting anticonvulsants.^{7,15} Logically, treating pain aggressively early in the onset of a chronic pain condition could theoretically prevent the development of angry and sensitized central pain pathways. It might even extend to treating psychiatric disorders in general to the point of remission of all symptoms whenever possible in the hope that by relieving these theoretical proxies of central sensitization, the patient will experience less symptom generation and more symptom relief in the future. ♦

Take-Home Points

- ♦ Acute pain may indicate one type of CNS activity that causes suffering in the here and now.
- ♦ Chronic pain may indicate another type of CNS activity, namely that a vicious cycle has been triggered in which progressive and potentially irreversible molecular changes eventually lead to progressive and potentially irreversible symptoms.
- ♦ Activity-dependent functional plasticity within the CNS may be the cause of "central sensitization syndromes" of ongoing symptoms that occur not only long after painful triggering events are over but perhaps even in the absence of identifiable triggering events.
- ♦ This pathophysiology may extend beyond chronic pain conditions and serve as a hypothesis for explaining the amplification and enduring nature of symptoms in functional somatic syndromes, addictive disorders, stress disorders, and numerous other CNS conditions.

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