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CENTRAL SENSITIZATION: THE UNRECOGNIZED EXPRESSION OF AUTONOMIC DYSREGULATION

Peter Behel[1]

[1] *Faculty member, Sonoma State University, Veteran, Hospital-Based Multidisciplinary Chronic Pain Treatment Programs, Kaiser Permanente, USA*

Abstract

Central sensitization is a condition that is usually associated with chronic pain, and refers to a heightened level of spinal cord neuron excitability compared to normal activation levels. In addition to this hyperexcitability resulting in a disproportionately elevated pain response, the accompanying sensory receptor field expansion can also increase responsiveness to non- painful stimulation. Recent studies have examined the role that autonomic nervous system dysfunction plays in the development of central sensitization (1). These findings underscore the potentiality that mediating autonomic output provides as an effective means of moderating central sensitization.

Keywords

Central Sensitization, Pain, Stimulation, Autonomic, Symptoms, Glutamatergic

The phenomenon of central sensitization is characterized by the amplified responsiveness of spinal cord neurons that results in hypersensitivity to stimulus not normally considered to be painful. The increased reactivity that defines this condition is potentiated by autonomic nervous system dysfunction at its point of inception. Elevated autonomic arousal is considered to be the principle neural response pathway associated with stress. To the degree that mediating stress is classically accompanied by reductions in autonomic output, targeted autonomic regulation provides a basis for modifying central sensitization where it is generated.

To the extent that anxiety has been involved with predicting the magnitude of central sensitization symptoms in various instances (2), it remains puzzling why stress isn‟t more routinely associated with the development of central sensitization, particularly in consideration of the well-documented high comorbidity between central sensitization and PTSD (3). This may be due to the relationship between central sensitization and glutamate, a neurotransmitter not always appreciated for its relationship with stress (4). As it turns out however, glutamate functions as the most prominent excitatory neurotransmitter in the nervous system of adult mammals, and is principally involved in regulating neuroplasticity (5). While the presence of cortisol remains the biomarker most commonly associated with long-term stress, it remains less than plausible to expect heightened stress responses to take place over time without the ongoing involvement of excitatory neurotransmission.

The synaptic plasticity that defines central sensitization is the result of excitatory glutamatergic synapses in the spinal cord that produce pain hypersensitivity (6). Remarkably, in some instances central sensitization is said to occur independently of any sort of peripheral injury (7). Classically however, the increased synaptic excitability that represents the defining characteristic of central sensitization is facilitated by a process known as long-term potentiation (LTP), a lasting increase in synaptic strength resulting from intense barrages of pain signal sensory inflow that serve to lower the threshold of synaptic transmission in central pain pathways (8).

The effects of LTP are extensive, and consist of increased synaptic transmission resulting in a reduction of pain threshold, subsequent pain response amplification and the spread of pain sensitivity to non-injured areas. Elevated neuronal activation increases synaptic efficacy, recruits previously subthreshold synaptic inputs and generates an augmented action potential output. The threshold changes in pain sensibility produce pain hypersensitivity, and the changes in neuron properties result in pain that is no longer correlated with its original source. Instead, the heightened neuronal activation elevates the response to sensations that would normally register as benign, or innocuous (9).

Generally this abnormal hypersensitivity emerges from pain signaling neurons in the periphery known as nociceptors. When nociceptive sensory neurons become activated following intense or repeated stimulation, their terminals are exposed to inflammatory mediators during the release of neuropeptides that include substance P, a proinflammatory mediator that is co- released with glutamate. Calcitonin gene-related peptide

(CGRP) is a second neuropeptide that potentiates the effects of substance P and facilitates nociceptive transmission. Research has determined that CGRP is involved in the development of neurogenic inflammation, and upregulated in conditions involving inflammatory or neuropathic pain (10).

When pain becomes chronic, the ensuing flare response can produce an enhanced sensitivity to heat and touch that is referred to as primary hyperalgesia. This occurs as an outcome of inflammatory mediator-initiated sensory neuron signaling (11). Additional inflammatory substances such as bradykinin, histamines, and neurokinin A typically become released as a result, and this process potentiates thermal sensitivity and produces what is described as primary or peripheral sensitization (12). Although peripheral sensitization is commonly regarded as the process responsible for initiating hyperexcitability of nociceptive neurons in the central nervous system (13), nociceptive pain is said to emerge from the overlapping influences of both peripheral and central sensitization (14). While peripheral sensitization is responsible for conducting the release of the inflammatory mediators that induce central sensitization, this process is classically activated in response to some level of tissue injury. What is particularly noteworthy is that peripheral injury, pathology or tissue damage is not *necessarily* required for the inflammatory triggering sequence to become engaged. Instead, sensory neuron-initiated inflammatory signaling may be based on either "actual or *potential* tissue damage" (italics mine), which ends up meaning that inflammatory cascading might be more appropriately regarded as a stress response (15).

This adds a dimension to stress that isn"t routinely accounted for, in that the inflammatory release is stimulated by nociceptive pain signaling transmission. The induced inflammatory cascade amounts to an undetected stress response structured to mobilize in response to physical damage, yet it also becomes triggered as a result of the *threat* of damage. When one factors in the propensity for this process to cycle without resolution, an entire category of stress-related pain afflictions emerges that often prove to be clinically challenging to resolve.

Sympathetically maintained pain for example refers to a spectrum of disorders said to be produced by abnormal autonomic nervous system activity. These conditions include complex regional pain syndrome (CRPS) and postherpetic neuralgia (16). Fibromyalgia is another affliction associated with unrelenting sympathetic hyperactivity (17), and elevated sympathetic arousal is also reported to play a role in complex neuropathic pain (18). The nociceptive pain generated in these conditions is characterized as a maladaptive response to actual or imminent tissue damage that is reported to be sympathetically maintained (19). Absent of actual physical damage, the development of these symptoms is associated with the nociceptive inflammatory cascade programmed to respond to the threat of tissue damage.

Another example of sympathetically mediated pain involves small fiber neuropathy (SFN), a peripheral pain disorder associated with autonomic dysregulation (20). In this condition sensory abnormalities involving the small diameter fibers that mediate pain and temperature sensations are also linked to autonomic dysfunction (21). Abnormal interactions between sympathetic innervation and inflammatory responses in these instances are connected with altered neuronal excitability and increased pain sensitivity (22). Intriguingly, early research findings have indicated that various long COVID symptoms overlap with small fiber peripheral neuropathy and dysautonomia (23).

Inasmuch as peripheral neuropathy has been linked to the presence of hyperalgesia, central sensitization has been implicated as the principle pathophysiological mechanism underlying the development of neuropathic pain (24). Perhaps even more ubiquitously, following *acute* injury, visceral nociceptors exposed to inflammation increase the excitability of centralized nociceptors during the actual repair process itself. Research has indicated that centralized hypersensitivity in these cases is wholly dependent on afferent barrages from sensitized peripheral nociceptors (25). Small wonder then that reducing peripheral nociceptive input has been presented as a viable approach for decreasing hyperexcitability in central sensitization sufferers (26).

To the extent that central sensitization is initiated by inflammatory cascading generated from the periphery, accounting for neurogenic inflammation effectively alters the makeup of what a stress response is said to contain. Neuroinflammation involves the sustained release of cytokines and chemokines responsible for producing widespread chronic pain that effects multiple body sites (27).

Centralized pain sensitivity is associated with a multitude of chronic pain conditions, from whiplash (28) to temperomandibular disorders (29). This list includes pelvic pain (30), sleep disturbances (31), bladder pain (32) and rheumatoid arthritis (33). Central sensitization is a fundamental component of neuropathic and inflammatory pain, fibromyalgia, irritable bowel syndrome (IBS) and migraine (34). The extent to which autonomic dysregulation is responsible for inducing centralized sensitivity may partially explain why standard approaches aimed at ameliorating chronic pain only seem to last for an abbreviated period of time.

When defective autonomic response patterning becomes reflexive, blocking pain receptors pharmaceutically does not address the cause of the pain signaling disruption itself. Long-term medication management may only serve to temporarily mask the outcome, and this approach is not immune to suffering from diminished effectiveness over time, irrespective of any of the various accompanying side effects.

Along these lines, the Center for Disease Control and Prevention (CDC) has declared the United States to be in the midst of an opioid overdose epidemic that is resulting in 40 fatalities per day; and 165,000 total since 1999. The CDC reports that while the amount of opioids prescribed and sold has quadrupled since 1999, the overall amount of

reported pain has not changed during that time (35).

In view of these developments, CDC on February 10, 2022 proposed updating opioid prescribing guidelines to recommend non-opioid therapies as a first line approach for treating chronic pain, and found there is "insufficient evidence to determine the long-term benefits of opioid therapy for chronic pain beyond 1 year" (36). As circumstances would have it, various researchers have determined non-pharmaceutical, functionally-based chronic pain approaches to be efficacious (37); and associated with an improved quality of life (38).

Central sensitization represents the outcome of ongoing pain signaling inputs from the periphery becoming increasingly excited within the spinal cord, a condition that potentiates when primary sensory neurons are exposed to inflammatory mediators. The increased neuronal responsiveness is the result of reflexive interactions between nociceptive pain signal transmission and autonomic functioning (39). Accounting for the impact that autonomic, nociceptive and inflammatory influences exert collectively serves to expand the magnitude of what a stress response is generally thought to consist of.

Research has established the relationship between central sensitization and generalized pain (40), and substantiated the association between exaggerated pain sensitivity and autonomic dysregulation (41). Clinical findings indicate that modifying sympathetic hyperactivity through targeted autonomic regulation can mediate pain signal transmission with none of the attendant side effects (42). Perhaps CDC"s recommended opioid prescribing guidelines will usher in an era where functionally-based applications become prioritized as the recommended first line approach for treating chronic pain.

Works Citation

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