REVIEW

Central Sensitization in Migraine: A Narrative Review

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Abstract: Central sensitization (CS) is an increase in the responsiveness of nociceptive neurons in the central nervous system to their normal afferent input. As a result, even minor irritation can induce severe pain, leading to the chronicity and severity of various diseases, such as neurological disorders. CS is associated with migraine, which is a major neurological disorder that inflicts a high disability in daily life. Specifically, CS is thought to be involved in the pathogenesis of cutaneous allodynia as well as chronification of migraine. In this article, we reviewed the association between CS and migraine, including pathophysiological aspects and evidence from clinical studies. We suggest that appropriate screening and management of CS in migraine could further improve the quality of life of migraine patients.

Keywords: migraine, central sensitization, cutaneous allodynia, restless legs syndrome

Introduction

Central sensitization (CS) occurs when the function of circuits in nociceptive pathways is enhanced and results in abnormal sensitivity; it is defined as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" according to the International Association for the Study of Pain.[1] An original work by Woolf[2] showed that a peripheral injury-induced increase in the excitability of spinal cord neurons profoundly modifies the gain of the somatosensory system. While peripheral sensitization is an increase in the sensitivity of the local peripheral terminals of sensory fibers that innervate injured tissue, CS involves the central nervous system. Moreover, CS can occur due to tissue damage after peripheral nerve injury but also in diseases without any peripheral pathology, such as migraine, fibromyalgia, temporomandibular joint disease, and irritable bowel syndrome.[3] A multicenter case–controlled study showed higher central sensitization inventory (CSI) scores in patients with various neurological, psychological, and pain disorders, including migraine, than in healthy controls. Additionally, CS-related symptoms were associated with pain severity, interference of pain with daily activities, and depressive symptoms in the patient group.[4] Therefore, the management of CS-related pain and symptoms in various pain-related diseases is urgent. Migraine is a major neurological disorder that inflicts a high disability in daily life, and many patients suffer from intractable pain. Although genetic predisposition and activation of the trigeminal vasculature are considered the main pathophysiological factors for migraine,[5] CS is thought to be involved in the pathogenesis of cutaneous allodynia (CA) and chronicity in migraine. In this article, we provide a narrative review of CS in people with migraine.

Methods

We performed a literature search of MEDLINE, a PUBMED database, and Web of Science to retrieve articles published in the English language between March and May 2022 using a combination of keywords such "migraine" and "central sensitization" or "central sensitization syndrome". The important literature that was retrieved by handsearching was also included in this review.

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Definition and Diagnosis of Central Sensitization

CS clinically manifests as CA (a reduction in the pain threshold of the skin), hyperalgesia (an increase and prolonged responsiveness to noxious stimuli) and secondary hyperalgesia (a spread of sensitivity outside of the region of injury into noninjured tissue).[3,6] To diagnose pain due to CS, three major criteria are recommended: 1) experiencing pain disproportionate to the nature and extent of injury or pathology; 2) a diffuse pain distribution and the presence of allodynia and hyperalgesia; and 3) hypersensitivity of senses unrelated to the musculoskeletal system.[7] People suffering pain due to CS show hypersensitivity to bright lights, touch, noise, pesticides, mechanical pressure, medication and temperature (low and high), and these symptoms may also be associated with fatigue, sleep disturbances, unrefreshing sleep, concentration difficulties, a feeling of swelling in the limbs, tingling and numbness.[7] These characteristics are important in differentiating pain due to CS from neuropathic pain.

Screening Tools for Diagnosing Central Sensitization

The CSI is a widely used self-administered questionnaire for assessing CS-related symptoms in clinical studies.[8] Part A of the CSI comprises 25 CS-related items with total scores ranging from 0 to 100. A Part A score≥40 contributes to CS diagnosis and can be used as an alternative to the aforementioned third criterion (hypersensitivity of senses unrelated to the musculoskeletal system).[7] Part B of the CSI assesses whether seven CS-related diseases (fibromyalgia, chronic fatigue syndrome, temporomandibular joint disorder, irritable bowel syndrome, migraine or tension headaches, multiple chemical sensitivities and restless legs syndrome (RLS)) were previously diagnosed.[9] Additionally, quantitative sensory testing (QST) is a noninvasive method for evaluating the function of the A delta and C fibers.[10] By detecting mechanical hyperalgesia and mechanical allodynia, pain due to CS can be evaluated.

As later described, cutaneous allodynia (CA), a skin hypersensitivity often seen in patients with migraine, is believed to be related to the pathogenesis of CS. The Allodynia Symptom Checklist (ASC) consists of 12 questions that inquire about the frequency of various allodynia symptoms associated with headache attacks. The ASC has been validated for usefulness and validity. In a study of 88 patients with migraine, ASC was used to correctly identify 84.8% of patients classified as allodynic by QST.[11] In a large survey of 16,573 headache sufferers, the ASC showed that the prevalence of severe CA (ASC score ≥9) was highest in patients with transformed migraine (28.5%) followed by those with migraine (20.4%), probable migraine (12.3%), other chronic daily headaches (6.2%), and severe episodic tension-type headache (5.1%).[12] Additionally, for patients with migraine, CA is associated with female sex, headache frequency, increased body mass index, disability, and depression.

A self-rated pain sensitivity questionnaire (PSQ) has been developed to assess pain intensity in daily life as an alternative to experimental pain testing. In a validation study, the results of comprehensive experimental pain testing, including different modalities such as heat, cold, pressure and pinprick, were compared on the PSQ. PSQ scores were significantly correlated with experimental pain intensity ratings, suggesting that PSQ could be a useful, alternative tool for experimental procedures on rating pain intensity in healthy subjects.[13] In addition, the validity of the PSQ has been tested in patients with chronic pain. In that study, patients with chronic pain had significantly higher PSQ scores than healthy controls, and PSQ scores were significantly correlated with both experimental pain intensity ratings and experimental pain thresholds.[14] The PSQ can be used to directly measure the sensory facilitation involved in CS, whereas the CSI can be used to assess CS in a broader context and the characteristics of CS-related conditions.[15]

Central Sensitization-Related Diseases

Table 1 shows CS-related diseases.[6,9] Patients with restless legs syndrome (RLS) showed decreased pain thresholds and enhanced temporal summation of thermal pain, indicating involvement of spinal levels and supraspinal processes.[16] A study comprising 11 RLS patients showed static mechanical hyperalgesia to puncture stimuli, which was reversed by long-term dopaminergic treatment. This observation suggests that RLS is associated with CS of spinal cord neurons due to abnormal peripheral input or altered spinal cord ascending inhibitory dopaminergic control.[17] The symptoms of chronic fatigue syndrome (CFS) and fibromyalgia (FM) overlap in that both cause debilitating fatigue and chronic widespread pain. In patients with FM, abnormal pain modulation has been attributed to dysregulation of thalamic activity and hypoperfusion of the

Table 1 Central Sensitization-Related diseases[6,9]

Restless legs syndrome
Chronic fatigue syndrome
Fibromyalgia
Temporomandibular joint disorder
Migraine
Tension type headaches
Irritable bowel syndrome
Multiple chemical sensitivity

caudate nucleus according to imaging studies.[18] When pain is induced in FM patients, there is no observation of significant activation of the thalamus, but bilateral activation of the somatosensory cortex and right anterior cingulate is observed,[19] which is characteristic of patients with allodynia. Patients with CFS have been reported to have lower pain thresholds and hyperalgesia at various sites compared to controls.[20] As with FM, the absence of peripheral tissue damage together with the lack of a clear localization of pain in patients with CFS suggests that CS may be the cause of chronic widespread pain.[18]

Widespread bilateral mechanical and thermal pain sensitivity was reported in female patients with temporomandibular disorders compared to age-matched controls,[21] suggesting that CS has a role. The relationship between migraine and CS will be later discussed in detail. During headache attacks in patients with tension-type headache, muscle tenderness was increased in the temporal region and thermal pain thresholds were decreased, but were normal in the hands, indicating that a segmental central sensitization may contribute to pain in patients with frequent tension-type headache.[22]

Most patients with irritable bowel syndrome (IBS) show both rectal and somatic sensitivity;[6] recurrent sigmoid colon stimulation in patients with IBS leads to rectal hyperalgesia and visceral somatic reactions.[23] In contrast, rectal local anesthesia decreases rectal and somatic pain in patients with IBS, suggesting CS involvement in IBS patients. Multiple chemical sensitivity (MCS) is a condition in which chemical intolerance or toxicant-induced loss of tolerance is triggered by exposure to multiple chemical substances. MCS is frequently induced by olfactory stimuli. Compared to controls, patients with MCS reported greater perceived odor intensity and discomfort following exposure to odorants.[24] Compared to healthy controls, patients with MCS showed significantly higher bilateral olfactory cortex metabolism at rest.[25] These observations suggest that CS is involved in sensory hypersensitivity in patients with MCS.

Imaging Data for Central Sensitization

A functional magnetic resonance imaging (fMRI) study of capsaicin-induced CS in humans revealed activation of the brainstem and thalamus;[26] moreover, these were the only areas where activity remained elevated in the hyperalgesic state compared with the normal state, suggesting that brainstem activity contributes to the maintenance of CS. Additionally, a study of capsaicin-induced CS observing somatosensory evoked potentials showed increased excitability in the somatosensory cortex.[27] In patients with fibromyalgia, region-specific changes in the gray matter volume of the prefrontal cortex, anterior cingulate cortex, insula, thalamus, pons and left precuneus, altered functional connectivity in the descending pain-modulating system, and increased activity in the pain matrix related to CS, such as the dorsolateral prefrontal cortex, periaqueductal gray and anterior cingulate cortex, have been reported.[28] In patients with chronic fatigue syndrome, the white matter volume in the midbrain[29] and left inferior fronto-occipital fasciculus are decreased[30] and this volume correlated with disease duration. CS also plays a role in chronic lower back pain, a common musculoskeletal disorder. In a study that utilized fMRI, after equal pressure was applied to the thumb nail, patients with chronic lower back pain showed significantly more activation in pain-associated areas, such as the primary and secondary contralateral somatosensory cortex, inferior parietal lobule, cerebellum, and ipsilateral somatosensory cortex, than healthy subjects.[31]

Migraine

Migraine is a disabling neurological disorder affecting over 1 billion people worldwide, with a one-year prevalence of 15%. Its prevalence peaks in those aged 35–39, and it is the leading cause of disability in people younger than 50 years old, particularly women.[32] Migraine is characterized by a recurrent unilateral, pulsating headache, with moderate to severe intensity, accompanied by nausea, vomiting, and sensory hypersensitivity symptoms such as photophobia and phonophobia.[33] This disorder can be classified as migraine without aura and migraine with aura. Aura, marked by transient focal neurological symptoms that last 5–60 minutes and usually precede or accompany the headache, is present in one-third of migraine patients. Chronic migraine (CM) is defined as headaches that occur 15 or more days per month for at least 3 months, while episodic migraine (EM) refers to headaches that occur 14 days or less per month. Patients with migraine develop changes in brain activity in association with concomitant symptoms before the headache attack, and these symptoms persist after the attack. Migraine involves multiple phases: the premonitory, aura, headache, postdrome, and interictal phases.[34] Hypothalamic activation develops during the premonitory phase, followed by dorsal pontine activation in the headache phase.[5,35] During the aura phase, changes in the visual cortex consistent with cortical spreading depression (CSD) have been observed.[36] CSD, first described by Leao, is a slowly propagating (2-5 mm/min) state of altered electrocortical activity accompanied by vasodilation and followed by prolonged inhibition; it is thought to be the neural correlate of the migraine aura.[37] A neuroimaging study showed a slowly spreading area of abnormal blood flow, a CSD-like phenomenon, in the occipital lobe during the aura phase of migraine, supporting this concept.[36] CSD sensitizes peripheral and central trigeminovascular neurons as shown by stimulating the cortex with pinpricks or potassium chloride (KCl) granules.[38] However, whether CSD can trigger migraine headaches is debatable because approximately 70% of migraine patients do not experience an aura, and migraine patients have not usually experienced the trauma that triggers CSD, as in animal studies.

Migraine Pathophysiology is Related to Central Sensitization

Peripheral sensitization is the pain that develops when sensitized nociceptors begin to stimulate the spinal cord with increasing intensity, resulting in further pain amplification known as CS.[39] Peripheral sensitization is clinically observed in migraine patients because their migraine headaches are exacerbated by physical activity. CS is associated with abnormal neuronal excitability in the trigeminal nucleus caudalis.[39] An animal study showed that astrocytic activation of the trigeminal nucleus caudalis contributed to CS in CM.[40] Peripheral sensitization of dural and meningeal trigeminovascular nociceptors is involved in the throbbing nature of migraine headaches. In contrast, CA is considered a manifestation of CS during migraine attacks and could be a marker of CS.[39,41]

Thus, although CS is thought to be more involved in pain amplification and the chronification of CM than in EM, CS is observed during and between attacks, suggesting that CS may have a role in EM and not only in CM. Plasma glutamate levels, which could be a marker for CS, were significantly higher in patients with CM and EM than those in controls, but they were not significantly different between participants with EM and CM.[42] In a study in which researchers used an experimental protocol based on slowly repeated evoked pain (SREP), characteristic patterns were observed in patients with EM, but not in controls, therefore indicating CS in patients with EM.[43] A dynamic evoked pain index based on the application of SREP could be used as a CS marker in patients with migraine. In a study consisting of 136 patients with migraine, compared with patients with low-frequency EM (1–8 headache days a month), patients with high-frequency EM (9–14 headache days a month) and CM (>14 headache days a month) had similar severe degrees of headache-related disability and CS-related symptoms.[44] A comparison of migraine patients with 15 or more headaches per month and those with 8 to 14 or more headache days per month showed no differences in parameters such as depression, anxiety, and pain scores between the two groups.[45] Becerra et al[46] investigated differences in brain metabolite in the anterior cingulate cortex during the interictal phase in EM patients using magnetic resonance spectroscopy, and concluded that the brain in EM patients is hyperexcitable during the interictal state based on the findings of alterations of metabolites, such as aspartate /Cre, N-acetyl aspartate /Cre and glutamine /Cre.

The hypothalamus is a possible origin of migraine attacks as the trigeminovascular system, innervating the dura mater and of the major brain blood vessels, is activated during the headache phase.[34,47] Some studies have suggested that patients with migraine exhibit subtle differences in brain structures related to pain processing or in the trigeminovascular

system during the interictal phase.[41] Calcitonin gene-related peptide (CGRP), abundant in trigeminal ganglion neurons, has an important role in generating migraine headaches. This peptide is secreted in the trigeminal ganglion and may perpetuate peripheral sensitization by interacting with adjacent neurons and satellite glial cells to promote CS of second-order neurons.[37] Photophobia, phonophobia and osmophobia are common sensory hypersensitivity symptoms in migraine. More severe symptoms of photophobia, phonophobia, osmophobia and nausea are associated with greater intensity of migraine headaches.[48] In fact, patients with migraine exhibit atypical brain activation in response to painful, olfactory, and visual stimuli and atypical functional connectivity in the sensory-discriminative processing of pain, affective emotional processing, cognitive processing, and pain modulation.[49] In migraine patients, activation of the limbic and rostral pons has been reported following exposure to odors,[50] and activation of the visual cortex has been reported following visual stimulation.[51]

Clinical Studies on Migraine and Central Sensitization

Table 2 shows clinical studies on CS in patients with migraine. In a case–control study, the rate of CS in 186 patients with migraine was higher than that of 186 age- and sex-matched healthy controls (21.0% vs 8.6%). The determinants of CS in patients with migraine were the presence of RLS and interference of headache pain with daily activities, suggesting a potential role of comorbid migraine and RLS in CS.[52] A significant association between RLS and migraine has been confirmed by many population-based and clinical studies,[53] and CS may also be involved in this association. For example, in a cross-sectional study including 164 patients with migraine, CS was observed in 53 patients (32.3%).[54] CS is associated with cranial parasympathetic symptoms such as lacrimation, aural fullness, nasal blockage, and rhinorrhea, suggesting that both trigeminovascular systems and the cranial parasympathetic system contribute to persistent CS in patients with migraine. MCS is reported to overlap with fibromyalgia, a disease known to be associated with CS.[55] Similarly, there is a report suggesting a link between MCS and migraine. A cross-sectional study that included 95 patients with migraine found that 20% had MCS. Migraine patients with MCS had higher rates of photophobia, osmophobia, visual aura, sensory aura, and CS as well as higher migraine-related disability and Kessler Psychological Distress scores than those without MCS.[56] This study showed a possible association of MCS with CS and hypersensitivity-related symptoms, such as photophobia and osmophobia, in migraine patients.

Table 2 Clinical Studies on Central Sensitization in Patients with Migraine

Authors (Years)	Sample	Methods for CS Evaluation	Conclusion
Suzuki et al,[4] (2021)	551 patients with neurological, psychological, and pain disorders including 234 patients with migraine or tension-type headache	A case-controlled study using CSI	CSI score was associated with pain severity, pain interference with daily activities, and depressive symptoms.
Suzuki et al,[52] (2021)	186 patients with migraine and 186 age- and sex-matched healthy controls	A case-controlled study using CSI	CS was more prevalent in migraine patients than in controls (21.0% vs 8.6%). The determinants of CS in migraine patients were restless legs syndrome and interference of headache pain with daily activities.
Danno et al,[54] (2022)	164 patients with migraine	A cross-sectional study using CSI	CS was observed in 32.3% of migraine patients and was related to cranial parasympathetic symptoms such as lacrimation, aural fullness, nasal blockage, and rhinorrhea,
Suzuki et al,[56] (2022)	95 patients with migraine	A cross-sectional study using CSI and QEESI	Multiple chemical sensitivity was found in 20% of migraine patients and was related to CS, photophobia, osmophobia, visual aura, sensory aura, higher migraine-related disability and Kessler Psychological Distress scores.

Note: CSI scores ≥ 40 were defined as having CS.
Abbreviations: CS, central sensitization; CSI, central sensitization inventory; QEESI, the quick environment exposure sensitivity inventory.

In a cross-sectional study, photophobia, phonophobia and osmophobia were observed in 75.4%, 76.5% and 55.1% of patients with migraine, respectively; these hypersensitivities exhibited substantial overlap, as the proportions of patients with 2 and 3 coexisting sensory hypersensitivities were 33.2% and 41.7%.[57] In the same study, the migraine Disability Assessment score was found to be higher in patients with 3 sensory hypersensitivities than in those with 0–2 sensory hypersensitivities. These results, which illustrate the burden of multiple hypersensitivity symptoms, may support the contribution of CS to migraine. In patients with chronic but not episodic migraine, a clear relationship between photophobia and CA was noted, suggesting that light stimulation may contribute to CS and subsequent chronicity.[58]

Cutaneous Allodynia and Central Sensitization

CA is a condition defined as perceptions of pain elicited by the application of nonpainful stimuli to normal skin; it has been observed in 60% of patients with migraine[59] and is even more prevalent in patients with chronic migraine (up to 90%).[60] The CS of trigeminovascular neurons has been implicated in the development of CA.[41] CA may be evoked by thermal or dynamic/static mechanical stimulation and may be localized to the head (cephalic) or generalized (extra-cephalic). In particular, CA in the head and face during a migraine attack is thought to be the result of sensitization at the level of the trigeminospinal tract nucleus, which is connected to the periaqueductal gray.[61] In a study consisting of a random sample of 24,000 headache sufferers, CA was more common and more severe in patients with transformed migraine and migraine than in other primary headaches.[12] In patients with migraine, the presence of CA was associated with female sex, depression, disability, an increase in headache days and increased body mass index. The authors suggest that recurrent activation of trigeminovascular neurons and modulatory pain pathways involving the periaqueductal gray plays an important role in the progression of migraine. Other risk factors for CA include acute medication overuse and early age of migraine onset.[59] Longitudinal data over 2 years showed that CA is an independent risk factor for migraine chronification.[62] A study of resting-state functional connectivity showed that compared to migraine patients without ictal CA, migraine patients with ictal CA showed stronger functional connectivity of the periaqueductal gray and nucleus cuneiformis to other brainstem, thalamic, insular and cerebellar regions that participate in discriminative pain processing as well as higher order pain-associated regions, such as the frontal and temporal cortices.[63] Rosso et al[64] reported that abnormalities in the functional connectivity of the default mode network and central executive network as well as microstructural changes predicted CA incidence. In an fMRI study, increased activation of the contralateral pons, insula and thalamus in the ictal versus interictal state were observed in the generalized allodynia group but not in the no allodynia group.[62]

The complication rate of both CA and osmophobia is higher in patients with chronic migraine than in those with episodic migraine.[65] Additionally, sound aversion thresholds were lower in migraine patients with allodynia than in those without allodynia, suggesting a link between phonophobia and CA.[66] These observations indicate that CS evoked by recurrent headaches may cause hypersensitivity to olfactory, visual, and auditory stimuli in parallel with CA.

Implications for Treating Central Sensitization in Migraine

CS may be involved in the pathogenesis of migraine, including migraine chronicity and CA; thus, CS intervention may be important for treating migraine. In a retrospective study that included 1100 patients with migraine aged 18–75 and investigated the effect of preventive drugs, low headache frequency and absent or mild CA predicted better outcomes.[67] Migraine patients who never developed allodynia were more likely to be made pain-free by triptan therapy at any time after the onset of pain.[68] However, the role of CA in the triptan response is not conclusive.[59] Interestingly, the presence of CA predicted responsiveness to erenumab, a calcitonin gene-related peptide (CGRP) receptor monoclonal antibody, along with male sex and baseline migraine frequency.[69] In contrast, a subanalysis of a double-blind, randomized, placebo-controlled study, showed that the efficacy of erenumab in reducing monthly migraine days and acute migraine-specific medication days in chronic migraine patients was not affected by the presence of moderate to severe CA.[70] In a rodent model of migraine, noninvasive stimulation of the vagus nerve inhibited mechanical nociception and down-regulated expression of proteins associated with peripheral sensitization and CS of trigeminal neurons.[71] Moreover, in patients with chronic migraine, severe CA is associated with a decreased response to treatment with occipital transcu-taneous electrical stimulation.[72] A preliminary study showed that an intravenous infusion of ketorolac, a central-acting

COX1/COX2 inhibitor, effectively reversed CS induced by application of inflammatory soup to the dura of rats; intravenous administration of the same drug to migraine patients with CA who missed the critical period for triptan therapy provided a rescue therapy, possibly by suppressing CS.[73]

Because the release of CGRP may be involved in the enhancement of CS,[37] it would be interesting to determine whether CGRP antagonists can alleviate CS. Melo-Carrillo et al[74] demonstrated sensitization of central trigeminovascular neurons by CSD in high-threshold neurons of rats; this sensitization was prevented by administering the CGRP-monoclonal antibody fremanezumab. Clinically, fremanezumab not only significantly reduced the number of headache days in patients with episodic and chronic migraine but also significantly reduced the number of days with photophobia/phonophobia.[75] This result would be even more interesting if there is a clear pathophysiologic relationship between photophobia/phonophobia and CS.

Botulinum toxin type A inhibits the release of glutamate and CGRP from primary nociceptive fibers, and one possible mechanism for its therapeutic effect on migraine is inhibition of peripheral and central trigeminal sensitization.[76] Another topic of interest is the appropriate treatment of migraine comorbidities. For example, RLS is a CS-related condition, and in one study, the presence of RLS was a determinants of CS in migraine.[52] The presence of RLS also predicted headache-related disability in migraine patients 7 years later.[77] Although not yet proven, the management of sleep disturbances in migraine, especially RLS, may improve CS in migraine.

Conclusion

We described the involvement of CS in migraine, including various pathophysiological aspects and evidence from clinical studies. CS is associated with the chronification of migraine and CA; moreover, we believe clinical assessment and appropriately management of CS could further improve the quality of life of migraine patients. The limitations of this narrative review include selection bias, a subjective search and literature acquisition. Further placebo-controlled studies in which researchers evaluate changes in CS using brain imaging are needed to clarify the role of CS in the pathogenesis of migraine.

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Disclosure

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