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MINIREVIEWS

Contributions of aversive environmental stress to migraine chronification: Research update of migraine pathophysiology

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Abstract

Clinical studies have suggested that internal and/or external aversive cues may produce a negative affective-motivational component whereby maladaptive responses (plasticity) of dural afferent neurons are initiated contributing to migraine chronification. However, pathophysiological processes and neural circuitry involved in aversion (unpleasantness)-producing migraine chronification are still evolving. An interdisciplinary team conducted this narrative review aimed at reviewing neuronal plasticity for developing migraine chronicity and its relevant neurocircuits and providing the most cutting-edge information on neuronal mechanisms involved in the processing of affective aspects of pain and the role of unpleasantness evoked by internal and/or external cues in facilitating the chronification process of migraine headache. Thus, information presented in this review promotes the understanding of the pathophysiology of chronic migraine and contribution of unpleasantness (aversion) to migraine chronification. We hope that it will bring clinicians' attention to how the maladaptive neuroplasticity of the emotion brain in the aversive environment produces a significant impact on the chronification of migraine headache, which will in turn lead to new therapeutic strategies for this type of pain.

Key Words: Migraine chronification; Aversive environmental stress; Migraine pathophysiology; Migraine headache; Roles of unpleasantness; Emotion brain

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Core Tip: In this article, neuronal plasticity for developing migraine chronicity and relevant neurocircuits were reviewed and discussed. Specifically, we focused on providing the most cutting-edge information on neuronal mechanisms involved in the processing of affective aspects of pain and the role of unpleasantness evoked by internal and/or external cues in facilitating the chronification process of migraine headache. New information collected from both preclinical and clinical studies on these aspects may advance our understanding on the chronic migraine pain mechanisms and lead to new strategies for pain treatment.

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INTRODUCTION

Migraine is the third most prevalent disease and the second most severe disabling disorder worldwide[1]. In the United States, it is estimated that over 45 million people are actively afflicted by migraine. Of these, about 4% of them develop chronic migraine annually[2]. The International Headache Society clinically characterizes chronic migraine as recurrent unilateral throbbing headache attacks of moderate to severe intensity and associated symptoms (including facial allodynia, nausea, vomiting, phonophobia and photophobia) occurring episodically for more than 15 d every month for 3 consecutive months[3]. Before or at the same time as a headache, migraineurs could have aura, *i.e.* a transient visual, sensory, or other central nervous system symptoms[3]. Clinical retrospective data show that the development of chronicity (chronification) is frequently related to a wide variety of internal and external triggers, such as physical and/or mental stress, hormonal fluctuations, sleep disturbances, meal skipping, sensory overload, *etc.*[1,3]. Also, such a chronic disorder is associated with greater psychiatric and medical comorbidities[4]. Pathophysiologically, maladaptive responses (plasticity) of dural afferent neurons of the ophthalmic division in the trigeminal ganglia are evident to be an underlying mechanism for migraine headache. This plasticity is modulated by descending pathways from the higher brain centers[5]. Thus, it is proposed that internal and/or external aversive cues produce a negative affective-motivational component whereby maladaptive responses are initiated contributing to migraine chronification. However, our understanding of pathophysiological processes and neural circuitry involved in aversion (unpleasantness)-producing migraine chronification is still evolving. In this article, neuronal plasticity for developing migraine chronicity and relevant neurocircuits were reviewed and discussed. Specifically, we focused on providing the most cutting-edge information on neuronal mechanisms involved in the processing of affective aspects of pain and the role of unpleasantness evoked by internal and/or external cues in facilitating the chronification process of migraine headache. New information collected from both preclinical and clinical studies on these aspects may advance our understanding on the chronic migraine pain mechanisms and lead to new strategies for pain treatment.

LITERATURE REVIEW

An interdisciplinary team conducted this narrative review. MEDLINE and Cochrane databases were reviewed to identify publications relevant to chronic migraine pathophysiology, unpleasantness (aversion), and synaptic plasticity. Publications were selected based on author expertise to summarize our current understanding of the impact of aversive environmental stress on chronic migraine.

MIGRAINE PATHOPHYSIOLOGY

It is well established by a great deal of research work that migraine pathophysiology involves altered excitability of many brain regions, intracranial arterial dilatation, recurrent activation (sensitization) of the trigeminovascular pain pathway, and consequential structural and functional changes in genetically susceptible individuals[6]. The headache of a migraine attack is the major complaint from the migraine sufferers and is thought to originate from activation of nociceptors innervating meninges, large cerebral arteries, and sinuses. Activation of these structures by mechanical, electrical, or chemical (inflammatory "soup" or infectants) stimulation contributes to migraine headache and its most common associated symptoms including nausea, throbbing pain, photophobia, and phonophobia[6,7]. The nociceptive innervation of the meninges and intracranial vasculature consists of unmyelinated and thinly myelinated axons (C- and Aδ fibers) that contain vasoactive neuropeptides, mainly substance P and calcitonin gene-related peptide contributing to neurogenic inflammation. These peripheral nociceptive terminals originate in the trigeminal ganglion and reach the dura mainly through the ophthalmic branch of the trigeminal nerve (V1) and, to a lesser extent, through the maxillary (V2) and mandibular (V3) divisions[8,9]. Innervation of the dura is also supplied by neurons in the upper cervical dorsal root ganglia[10]. Central processes of meningeal sensory afferents enter the brainstem *via* the trigeminal tract and at the same time sends out collaterals that terminate in the spinal trigeminal nucleus caudalis (Sp5C) and upper cervical spinal cord (C1-3), called trigeminocervical pathway. The projections of intracranial (visceral) and extracranial (somatic) primary afferents onto Sp5C neurons are involved in the perception of referred pain in the periorbital and occipital regions (orofacial allodynia)[11]. Ascending projections of Sp5C neurons to several cortical and subcortical areas contribute to a wide variety of symptoms like migraine headache, phonophobia, photophobia, osmophobia, nausea, irritability, fatigue, sleepiness, and exaggerated emotional responses[6,11-13].

Development of neural plasticity in the trigeminovascular pain pathway has been evidently shown to be the underlying migraine pathophysiology. Brief chemical stimulation with inflammatory agents on the dura of rodents can lead to peripheral sensitization of the primary afferent neurons in the trigeminal ganglion and dorsal root ganglia of C2/C3 and central sensitization of the second order neurons in the Sp5C (known as trigeminocervical complex)[11,14]. Central sensitization may extend to the thalamic (third order) neurons. This is proven clinically by finding an exaggerated activation of the cortical and subcortical areas during ictal period of migraine attack in human migraineurs triggered by nitroglycerin and experimentally by finding the increased responses of sensitized thalamic neurons of rats to cephalic and extracephalic skin stimuli after exposing their dura receptive field to inflammatory soup[6,15]. These strongly support there are endogenous inflammatory mediators released during migraine attacks to activate and sensitize peripheral and central trigeminovascular neurons by the mechanism of neurogenic inflammation[16,17].

Peripheral sensitization mediates the throbbing perception of the headache, whereas sensitization of second-order neurons in the Sp5C mediates cephalic allodynia as well as muscle tenderness[18]. In most chronic migraineurs, episodic attacks are associated closely with the triggering of sensitization of the trigeminovascular pain pathway. These neural plastic responses to episodic attacks are initially adaptive and physiological but later become maladaptive and pathological, which would eventually create a vicious cycle leading to the chronicity of migraine headache[7]. However, it still remains debatable how episodic attacks are triggered and initiated. So far the most widely accepted view is that migraines are preceded by visual, motor, or somato-sensory symptoms known as aura that is characterized by a visual perception of light flashes moving across the visual field.

Aura has been suggested to be closely linked to a reversible, transient cortical event, called cortical spreading depression (CSD)[19]. Electrophysiologically, CSD is a slowly propagating wave (2-6 mm/min) from membrane depolarization of neurons and glia followed by a prolonged inhibition (15-30 min) of cortical activity[20]. This distinctive electrophysiological phenomenon has been correlated with the visual aura that precedes the onset of headache in migraine[21,22]. Neurochemically, triggering of CSD has been shown to lead to the local release of ATP, glutamate, potassium, hydrogen ions, calcitonin gene-related peptide, and nitric oxide by neurons, glia, or vascular cells[23]. These molecules in turn diffuse toward the surface of the cortex to irritate persistently (activate) dural nociceptors, triggering a consequential neurogenic inflammation (vasodilatation, plasma protein extravasation, and mast cell degranulation). The release of pro-inflammatory molecules in the meninges due to

nociceptor activation contribute to the pain of migraine[16,17]. Further, the plastic changes in the trigeminocervical pathway by CSD was suggested by showing that CSD induces an increase of c-fos expression in the Sp5C and that neural firing of meningeal nociceptors and central trigeminocervical neurons in the Sp5C are enhanced by CSD[24]. One of the molecular mechanisms has been proposed by the finding that CSD propagation induces the opening of neuronal Panx1 megachannels leading to a downstream cascade of events that include the release of pro-inflammatory molecules in the meninges[25]. These would serve as the triggers of episodic attacks of migraines. Thus, abnormal cortical excitability plays a pivotal role in the predisposition to develop neural plasticity contributing to the recurrent trigeminovascular and/or dural nociceptor activation. These pathophysiological processes are likely associated with the transition of migraine from acute to chronic disorder (chronification).

CONTRIBUTION OF THE UNPLEASANTNESS (AVERSION) TO MIGRAINE PAIN

A number of internal and external cues are suggested to be triggers of episodic attacks of migraines in approximately 75% of patients. These include physical and/or mental stress, menstruation, hormonal fluctuations, sleep disturbances, noise, odors, heat, head/neck movement, neck pain, and sensory overload[26,27]. However, whether these factors are the causes of CSD causing migraine attacks remains to be investigated. It has long been known that negative emotions-induced unpleasantness produces a significant impact on pain perception[28]. Patients experiencing pain caused by many diseases often reported a higher degree of unpleasantness (or aversion) that are reflected as varying degrees of affective symptoms, such as fear, anxiety, anger, depression, and aversion to pain associated environments. Moreover, the negative affect or "bothersome"-like pain significantly impacts the quality of life of the sufferers and leads to the common comorbidities of psychiatric disorders such as depression[29,30]. Clinical studies have provided important evidence that pain-related aversion experiences seem to be not related to pain intensity but to be significantly influenced by the psychological environment in which pain is perceived[31].

UNPLEASANTNESS COMPONENT OF MIGRAINE PAIN

Migraine is a subjective multidimensional conscious experience, and the pain processing and perception are significantly affected by negative emotions. In addition to cephalic allodynia and/or hyperalgesia perceived as headache, a negative unpleasant affective-motivational component (aversion) is clinically very important and named as pain aversion[31]. A number of clinical retrospective data seem to support etiologically that migraine pain is associated with adverse affective and emotional states. For example, the high comorbidity of migraine and depression highlights the importance of negative affect[32]. Also, migraine patients have been identified to be significantly associated with suicide, and literature has proven that migraine patients have a higher suicide risk (about 2.5 times) than patients without migraine[33]. It is widely accepted that stress contributes to the severity and frequency of migraine attacks[26,27]. In laboratory studies using animal models, the reward- and/or penalty-conditioned paradigms, such as conditioned place preference (CPP) and/or conditioned place aversion (CPA), are the common procedures to assess the affective component of pain and then analyze its mechanisms[34]. Animals are conditioned with CPA paradigm where aversive stimuli (like varieties of stress) can "teach" animals to avoid environments (or objects) that are associated with aversive stimuli by psychologically producing negative, unpleasant affect[31] and by behaviorally inducing avoidance or escape[35]. Using CPP paradigm, the conditioned animals learn to differentiate the pain-alleviating environment from pain-producing environment. For example, in animals with migraine-like pain induced by inflammatory mediators applied to the dural membrane, administration of lidocaine elicited animals to develop a CPP[36]. Thus, both CPP and CPA paradigms are demonstrated experimentally to be a useful, effective tool to reveal affective pain and are therefore available to study the psychological mechanisms of affective dimension of pain.

BRAIN REGIONS AND RELEVANT NEURAL CIRCUITRY RESPONSIBLE FOR MIGRAINE PAIN AVERSION

It is well known that pain is processed in discrete but interacting brain structures, which help to produce multidimensional experiences composed of sensory, cognitive, and emotional (subjective) components[37]. However, our understanding of the neural circuitry that mediates the negative affective component of pain is still very limited. The anterior cingulate cortex (ACC) is the region of the brain that has been frequently reported to mediate consistently pain affects and unpleasantness in many types of pain, particularly chronic pain[31,37,38]. The ACC, along with the insular cortex and orbitofrontal cortex, is part of a salience network. This network circuit has a central role in the detection of behaviorally relevant salient stimuli (including pain) and in the coordination of neural resources[39]. Thus, aberrant salience processing in the salience network may contribute to chronic pain. When brain salience systems become dysregulated or disrupted, they may overly respond to certain types of stimuli because they cannot properly filter and process information[40,41]. Thus, the dysfunction of the salience network would be a critical mechanism contributing to chronic pain. Functional imaging analysis has firstly been used to capture the activity of the brain in a migraine cycle that includes preictal, ictal, and postictal phases for migraine attacks[42,43]. Secondly, increasing neuroimaging studies have investigated the brains of migraine patients in responses to painful and other stimuli during interictal periods. Studies have consistently observed increased activation of a network of brain regions collectively known as the "painmatrix" including the primary and secondary somatosensory cortices, ACC, insula, prefrontal cortex, amygdala, thalamus, and others. Also, decreased activation can be observed in areas responsible for pain inhibition (*e.g.*, pons and ventral medulla), thereby suggesting an imbalance between facilitation and inhibition, likely resulting from maladaptive neural plasticity[15,43,44]. Some of these brain regions, like the ACC, prefrontal cortex, amygdala, *etc.*, have been shown to specifically contribute to psychological and/or aversive processing of migraine headache[43]. It is evident that migraine patients viewing pain-related words exhibited enhanced activation in the insular cortex and orbitofrontal cortex compared to healthy control subjects. Further, there is a report of structural deficits in the orbitofrontal cortex and increased functional connectivity between the orbitofrontal cortex and ACC in migraineurs[45]. In an animal model of migraine pain induced by application of inflammatory mediators to the dural membrane, lesions of the ACC prevented the acquisition for place preference produced by injection of lidocaine into the rostral ventral medulla[46]. The important role of the ACC in the integration of the aversive component of pain was also demonstrated by the evidence that a CPA to formalin-induced pain was absent following the lesion of the ACC[47,48]. Migraineurs were identified to have structural and functional cerebral abnormalities (*e.g.*, reduced cortical thickness) in the prefrontal cortex, the rostral ACC, the somatosensory cortex, the orbitofrontal cortex, and insular cortex[45]. In addition to cortical thinning, the functional activity of both the ACC and the insular cortex was significantly reduced in patients with chronic migraine[49].

The amygdala is another important brain region contributing to the mediation of the aversive component of pain because there is overwhelming evidence demonstrating the comorbidity of psychiatric illness with migraine[50]. Also, more than 47% of migraineurs are comorbid with mood and anxiety disorders[51]. The development of disease comorbidity and the progression to chronic migraine are proposed to be a result of stress-induced neuronal plasticity heavily integrated with stress, affect, and pain[28]. An interesting finding by Akcali *et al*[52] suggests that synaptic plasticity within the amygdala may contribute to migraine pain. Their study demonstrated that (1) topical application of N-methyl-D-aspartate to the central amygdala led to a high expression of c-fos in the amygdaloid neurons and CSD; and (2) sumatriptan attenuated c-fos expression that was thought to result from the induction of CSD. An *in vitro* electrophysiological recording on the amygdala-hippocampus-cortex slices further indicated that CSD modulates synaptic transmission of the lateral amygdala producing synaptic plasticity[53]. Human imaging data showed that migraine patients during spontaneous and untreated attacks had significantly higher blood oxygen level-dependent signal intensities in the limbic structures (amygdala and insular cortices)[54]. These findings suggest strongly a pathophysiological mechanism how the CSD is linked to negative emotions-induced unpleasantness, which in turn contributes to migraine pain. Since there is broad transmission from the amygdala to other brain structures facilitating stress and pain response, it is proposed that the sensitization of the amygdala may underlie the progression of migraine symptoms that are comorbid

with mood disorders.

THE ROLE OF UNPLEASANTNESS (AFFECTIVE) IN THE CHRONIFICATION OF MIGRAINE HEADACHE

The transition from acute migraine to chronic status of migraine is called "migraine chronification". It is estimated that approximately 4% of patients with acute migraine develop and become chronic migraineurs[2]. So far the pathophysiology of migraine chronification still remains elusive. Some mechanisms have been proposed including (1) altered trigeminal and cranial autonomic system function; (2) thalamic contribution to central sensitization; (3) dysfunction of the descending pain-modulating network; and (4) medication-associated central sensitization[55]. These proposed views share a common mechanism, *i.e.* sensitization of migraine pain related pathways. As mentioned above, sensitization of trigeminovascular system and higher brain centers contributes to the neuronal plasticity that should be the key to the progression of migraine. Therefore, it is proposed that frequent or persistent exposure to unpleasant (affective) events leads to a synaptic plasticity in these pain pathways, leading to chronicity. Nevertheless, the exact pathophysiological mechanism remains to be clarified, because this sensitization is affected by multiple internal and external triggers. Patients with migraine often show a "lack of habituation", *i.e.* no decrease or even an increase in response following frequent or persistent stimulation[56]. Clinically, this habituation deficit seen in migraine patients has been demonstrated using several tests, including visual evoked potentials, somatosensory and auditory evoked potentials, blink reflex, and laser evoked potentials[56,57]. This migraine-related deficit in the normal habituation phenomenon is suggested to be one of the mechanisms underlying interictal deficits in habituation and the associated changes accompanying migraine chronification. Clinical observations on patients with chronic migraine showed that the habituation pattern during interictal periods is similar to that during a migraine attack. This should explain such chronic disorder as a status of never-ending migraine[58].

Studies at cellular and molecular levels using animal models have provided insights into the mechanisms that lead to and sustain chronic pain. Synaptic plasticity has been reported in several cortical and sub-cortical regions that are known to be involved in the processing of pain aversion. Of these higher centers, synaptic plasticity has been most extensively studied in the ACC[59,60]. Hyperactivation of the ACC is involved in signaling the unpleasantness associated with pain, especially individuals with neuropathic pain and chronic pain conditions[61]. Further, activation of the ACC has also been linked to emotional or psychological pain. For example, experimentally induced sadness, social exclusion, or rejection led to an increase in activity in this cortical region[62]. Thus, the ACC mediates various negative effects, including the unpleasantness of pain in the course of pain chronification.

Long-lasting synaptic plasticity mostly seen in the form of long-term potentiation (LTP) and mediated by excitatory amino acid receptors and their relevant downstream signaling molecules is the major pathophysiological change responsible for chronic pain. Increasing evidence suggests that LTP recorded in the ACC is causally associated with chronic pain[60,63]. Pharmacological studies on the ACC synaptic plasticity by using *in vitro* electrophysiological recordings reveal that LTP exists in at least four different forms: N-methyl-D-aspartate receptor-dependent, L-type voltage-gated calcium channel-dependent, late-phase LTP, and presynaptic LTP[63]. Some of these LTPs may coexist to be involved in chronic pain or affective (*e.g.*, fear) memory[59,60]. The development of pain chronicity seems to be encoded temporally by LTP in the ACC: (1) Synaptic responses in the ACC are potentiated at the time that allodynia develops seen in rodent models of chronic inflammatory pain, neuropathic pain, bone cancer pain, and chronic visceral pain, and LTP is persistently expressed when pain symptom develops[64]; and (2) Although acute nociception is short-lasting, it can trigger persistent synaptic changes associated with the formation of affective memory[65]. Thus, acute pain may engage synaptic plastic mechanisms in the ACC to encode physiologically relevant information about pain-evoked cognitive impairment, which might contribute to the chronification of pain. With the known widespread connectivity among the ACC, as well as other subcortical limbic regions known as "emotion brain" and nociceptive pathways, it may be presumed that the ACC would integrate the processing of pain with the associated emotional and affective events, contributing to the migraine chronification[31]. Internal and/or external environmental stressors would serve as aversive triggers to stimulate these limbic brain areas and

cause a negative affective state that significantly changes pain sensation, which is the main source of pain aversion. When aversive stimuli become frequent or persistent, the emotional brain may develop sensitization, *i.e.* hyper responsiveness. It thus is proposed that central sensitization of emotional brain will be generated through affective learning of aversive environment, which can trigger recurrence of migraine and contributes to the development of migraine chronicity.

SIGNIFICANCE OF STUDYING THE ROLE OF AVERSIVE ENVIRONMENTS IN MIGRAINE CHRONIFICATION

Insights into the plasticity of emotion brain induced by aversive environment are prerequisites to the understanding of the neural basis of chronic migraine headache and how this chronic event develops due to the maladaptive changes in mood and cognitive function caused by environmental stress. Traditionally, the trigeminal ganglia are trigeminovascular structures and are still seen as "gold" targets for controlling migraine pain. However, when the pain becomes chronic, the situation does not always seem to be the case, because more and more evidence shows that some central changes will occur in the course of chronification. Just like aversion memory and other affective learning processes, it is too late to interfere at the periphery if such "bad" memory takes place in the brain. Therefore, clinicians and laboratory researchers should pay more and more attention to how the maladaptive neuroplastic changes of the emotion brain in aversive environment promote the development of the chronic pain state. The results of this study may provide potential new targets for the treatment of this chronic disorder.

CONCLUSION

Migraine pathophysiology in the transition from acute to chronic pain is complex and multifactorial and involves altered excitability of many brain regions, intracranial arterial dilatation, recurrent activation (sensitization) of the trigeminovascular pain pathway, and consequential structural and functional changes in genetically susceptible individuals. Chronic migraine is closely associated with adverse affective and emotional states. Frequent or persistent exposure to unpleasant (affective) events leads to a synaptic plasticity in these pain pathways, leading to chronicity. The achievements from clinical and laboratory studies may provide potential new targets for the treatment of this chronic disorder.

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