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Migraine: A Multi-Modulation Process

Min Su[1,2] and Shengyuan Yu[1]*

[1]Department of Neurology, Chinese PLA General Hospital, Beijing 100853, PR China
[2]School of Medicine, Nankai University, Tianjin 300071, PR China

Abstract

Migraine is a common disabling brain disorder characterized by episodic moderate or severe headache attacks and accompanied by autonomic nervous responses and also other disturbances. It is well established that activation of the trigeminovascular system and neurogenic inflammation play important roles in the pathogenesis of the headache attacks. And our previous work has systematically observed the Fos expression in the brain of conscious rats following electrical stimulation of dura mater surrounding the superior sagittal sinus, and activated neurons were found in the upper cervical spinal cord (UCSC), spinal trigeminal nucleus caudal part (TNC), raphe magnus nucleus (RMg, major part of rostral ventromedial medulla), periaqueductal gray (PAG), ventromedial hypothalamic nucleus (VHM) and mediodorsal thalamus nucleus (MD). In this paper, the involvement of these brain regions in the pathophysiological process of migraine was discussed.

Keywords: Migraine; Neuroregulation

Migraine is one of the most prevalent primary headache disorders, characterized by episodic moderate or severe headache attacks and accompanied by photophobia, phonophobia, gastrointestinal disturbance and other autonomic nervous responses. With a common high prevalence, which is 9.3% in China [1], migraine is ranked as the sixth cause of years lived with disability (YLDs) in the Global Burden of Disease (GBD) 2013 [2]. Besides the nociceptive experience and the accompanied autonomic nervous response, migraine sufferer also report emotional and cognitive disturbances, such as depression, anxiety and slowing of reaction, during both the interictal and postictal phase [3].

Both clinical and preclinical studies have demonstrated that migraine is a multifactorial disease determined by both genetic factors and non-genetic endogenous and exogeneous risk-modulating factors [4]. Currently, once a migraine attack has started, the mechanisms underlying migraine aura and the headache attacks have been well explained. And the activation of the trigeminovascular system is consistently considered the central part in the development of a migraine attack, therefore, kinds of animal models have been constructed targeting the trigeminal nerve-innervating tissues, such as the dura mater, the trigeminal ganglion, the dural arteries and so on [5]. Our team firstly established a migraine animal model by electrical stimulation of dura mater surrounding the superior sagittal sinus in conscious rats [6], which induced nociceptive behavior resembling the clinical facts. Also, the Fos expression in rats' brain was systematically investigated [7] and we found that the Fos-like immunoreactive neurons were distributed mainly in the upper cervical spinal cord (UCSC), spinal trigeminal nucleus caudal part (TNC), raphe magnus nucleus (RMg), periaqueductal gray (PAG), ventromedial hypothalamic nucleus (VHM) and mediodorsal thalamus nucleus (MD), indicating the involvement of these brain regions in the development of migraine.

The three-step trigeminal pathway is pivotal for migraine pathophysiology, including the trigeminal ganglion receiving inputs from both the trigeminal and autonomic systems, the trigeminocervical complex (TCC) and the thalamus [5]. The TCC, composed by UCSC and TNC, is a key point in the transmission of nociceptive information, and the activation of this brain region has always been regarded as a standard for establishing a headache model. The thalamus converges signals from the second-order neurons in the TCC and its' role in nociception has also been well documented. The TCC and thalamus also receive projections from several nociceptive modulatory brain regions, and sensitization of neurons in the two regions has great impacts in the process of headache chronification. Also, the sensitization of TCC and thalamus is believed to be the underlying mechanisms of allodynia [8,9], a common physical sign in migraine patients, featured by increased skin sensitivity in the referred pain area and even the other side of the head or the forearm.

Of all the projections to the TCC and thalamus, the brainstem descending pain control system, especially the PAG and the rostral ventromedial medulla (RVM), is most commonly mentioned and also well documented [10]. Both functional and anatomical studies have verified the modulatory role of the PAG-RVM circuit in the process of pain perception, which is not peculiar to migraine [11]. For many decades, the PAG-RVM system, mainly composed by the noradrenergic and serotonergic pathways, has been regarded as the primary source of descending inhibitory control of pain [12] and also the major target for many analgesic agents such as opioids and cyclooxygenase inhibitors. However, it becomes evident recently that the descending control from the brainstem is bidirectional and there is a dynamic balance between the pain inhibition and facilitation [13], which can be altered in pathological states. Brainstem alterations have been widely discovered in migraineurs [9,14,15], supporting its' modulatory function in the disease.

Currently, much functional imaging studies have indicated the relation between hypothalamic activity and trigeminal autonomic cephalalgias (TACs), the cluster headache for instance [16]. Meanwhile, several researches have been focused on the role of hypothalamus in migraine [17-19], because it influences many aspects of human circadian rhythms such as the wake-sleep cycle, food intake and hormonal

***Corresponding author:** Shengyuan Yu, Professor and Director, Department of Neurology, Chinese PLA General Hospital, Fuxing Road 28, Haidian District, Beijing 100853, P.R. China, Tel: +86-10-55499118; E-mail: yusy1963@126.com

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fluctuations. As an important part of the autonomic and endocrine regulation, the hypothalamus has been implicated in the premonitory phase of migraine attacks such as yawning, fatigue, irritability, sleep disturbances and changes of appetite and thirst [18]. Connectivity between the hypothalamus and the trigeminal nociceptive pathway has been proved in both clinical and preclinical studies [20-22], supporting its' role in nociceptive modulation. What's more, the hypothalamus was found to exhibit altered functional state coupling with the spinal trigeminal nuclei, depending on the state of the migraine cycle [20], indicating the possibility that the hypothalamus initiates an attack. Therefore, the hypothalamus may act either as modulator or trigger of migraine via the integration of nociceptive and autonomic responses.

In summary, migraine is a multifactorial disorder. Activation of the trigeminovascular system is the central part in the initiation and the maintenance of head attacks. The brainstem descending modulation system, mainly including PAG and RVM, has an important role in modifying the pain perception, while the hypothalamus enjoys great impacts in both the pain perception and other aspects of migraine. Despite all the knowledge of modulating mechanisms after the initiation of an attack, little is understood about how migraine is triggered, which is quite important for seeking treatment to prevent migraine attacks and also its' chronification. Therefore, much work is to be done in the future.

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