บทความปริทัศน์
(Review article)

พยาธิกำเนิดของโรคปวดศีรษะไมเกรน

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บทคัดย่อ

ไมเกรนเป็นโรคปวดศีรษะที่พบบ่อยโดยเกิดขึ้นเป็นครั้งคราวซึ่งเกิดจากการกระตุ้นเซลล์ประสาทไทรเจมมินัลและหลอดเลือดโดยอาการปวดจะมีความรุนแรงปานกลางถึงมาก อย่างไรก็ตาม พยาธิกำเนิดของไมเกรนยังไม่เป็นที่ทราบแน่ชัด ลักษณะอาการปวดศีรษะเป็นไปตามการเต้นของหลอดเลือดในสมอง แนวคิดในปัจจุบันได้มีการสนับสนุนบทบาทของระบบประสาทไทรเจมมินัลในการพัฒนาของโรคปวดศีรษะไมเกรน ซึ่งสมมุติฐานนี้ไมเกรนเกิดจากการถูกกระตุ้นและภาวะไวต่อการรับความรู้สึกเจ็บปวดของระบบประสาทส่วนปลายในปมประสาทไทรเจมมินัลที่รับความรู้สึกบริเวณเยื่อหุ้มสมองและส่งผลถึงระบบประสาทส่วนกลางที่อยู่บริเวณไทรเจมมินัลนิวเคลียสคอดาลิสบริเวณไขสันหลังระดับคอที่ 1 และ 2 โดยข้อมูลนี้จะทำให้สามารถเข้าใจพยาธิกำเนิดของโรคปวดศีรษะไมเกรนและนำไปสู่การพัฒนาและเพิ่มประสิทธิภาพของยาที่ใช้ในการรักษาต่อไปในอนาคต

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Pathogenesis of migraine

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Abstract

Migraine is a common neurovascular disorder characterized by chronic episodic attacks of moderate to severe primary headache involving activation of trigeminal neurons. Despite its prevalence, the pathogenesis of migraine is not clearly understood. The pulsating nature of the headache suggests the involvement of the cranial vasculature in headache pathogenesis. However, current hypotheses emphasize the role of the trigeminal nociceptive system in the development of migraine, and other forms of primary headache. In these hypotheses, migraine pain is driven by the activation and sensitization of central trigeminal neurons driving the activation and sensitization of peripheral trigeminal neurons that innervate the meninges forming the trigeminocervical complex, which includes the caudal extension of trigeminal nucleus in the upper spinal cord. A better understanding of headache pathogenesis will pave the way for the development of more effective treatments.

Keywords: migraine, trigeminovascular, cortical spreading depression, sensitization

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Introduction

Migraine is a highly prevalent and complex disorder. Migraine has an annual worldwide prevalence of about 6% in men and 16% in women that varies slightly across populations and cultures[1]. A survey of a community in Bangkok, Thailand found slightly higher one-year prevalence[2]. Although migraine does not cause permanent neurological damage, its symptoms are troublesome and can cause high burden in terms of socioeconomic cost. In 2005 it was estimated that the economic lost in European countries is about 27 billion Euro per annum for 41 million patients. Migraine is ranked as the seventh highest cause of disability[3, 4]. In China, where costs are perhaps more aligned with those in Thailand, the total estimated annual cost in 2011 of primary headache disorders, including migraine, tension-type headache, and chronic daily headache is Yuan 672.7 billion, accounting for 2.24% of gross domestic product (GDP) (direct cost: Yuan 108.8 billion, 0.36% of GDP; indirect cost: Yuan 563.9 billion, 1.88% of GDP)[5]. With a 2011 GDP of THB 10.54 trillion (Office of the National Economic and Social Development Board, 17 July 2012), by analogy with China, this puts the total monetary cost of headache in Thailand at around THB 236 billion. This is without mentioning the unaccountable social costs of the pain and suffering of headache sufferers and their families. A better understanding of migraine is certainly warranted.

Migraine is characterized by the episodic recurrence of the associated headache. The duration of the headache ranges from 4 to 72 hours. Headache can be unilateral, as consistent with ancient observations by Galen of Pergamon used the term hemicrania (half-head) for migraine, and may spread to another side. In some patients, headache is preceded by transient neurological deficits including visual alterations, altered somatic sensations, and dysphasia. This phase is called 'aura'. Based on the presence or absence of aura, migraine can be classified as migraine with aura (MA) or migraine without aura (MO)[6]. Recent evidence suggests that migraine is the result of a complex interaction between environmental and genetic factors. The brains of migraineurs, or migraine sufferers, have shown abnormality in structure and function, which may lead to abnormality in sensory processing[7, 8]. Several mechanisms such as neurogenic inflammation, sensitization of the trigeminal nociceptive system, and dysfunction of the endogenous pain control system may be involved in the pathogenesis of migraine.

Pathogenesis of migraine

In the 17th century, an early hypothesis for migraine was proposed by Thomas Willis with a vascular theory that "megrim" was the result of dilatation of blood vessels within the head. This hypothesis was supported in part by the observation that migraine intensity could sometimes be reduced by superficial temporal artery compression[9]. Towards the end of the 19th century, ergot, a potent vasoconstrictor agent, was introduced by W.H. Thomson as an effective remedy for migraine[10].

Harold G. Wolff was attributed with being the first to place migraine on a scientific basis in the early 20th century. He found that during migraine attacks, the temporal branches of the external carotid artery could be demonstrated by their pulsations. The vascular pulsation and headache was reduced either by superficial temporal artery compression or by injection of ergotamine (the first pure ergot alkaloid[11]). This finding further supported the role of cranial vessels in migraine pathogenesis. The so-called "vascular theory" proposed that migraine attack is characterized by initial constriction of intracranial vessels resulting in transient neurological deficits. Then, the process is followed by the vasodilation, which causes headache. However, some clinical features of migraine cannot be explained by the vascular theory. For example, the slowly progressive character of migraine aura does not comply with ischaemic process, and the spatial pattern of the neurological deficit cannot be explained by neurovascular distribution.

Modern experiments have suggested the role of nervous system as primary process in migraine generation. For instance, cerebral blood flow changes can be induced by brainstem electrical stimulation[12]. This finding supported a "neurogenic theory" and stimulated researchers to investigate the relationship between the trigeminal nerve and the intracranial vasculature. The trigeminal nerve has strong anatomical relationship

with the cranial vessels[13]. Moskowitz and colleagues described that activation of trigeminovascular axons causes a release of vasoactive peptides from their terminals. An inflammatory reaction and activation of trigeminal nociceptive terminals surrounding the cranial vessels was observed in their animal subjects[14]. This response is called "trigeminal vascular reflex" and was believed to play an important role in migraine pathogenesis.

Neurogenic inflammation

Neurogenic inflammation was described in 1910 by Bruce, who showed that application of mustard oil into the conjunctiva sac in animal models induced inflammation that could be inhibited by sensory nerve ablation[15]. This observation was consistent with the antidromic sensory vasodilatation observed by others. Neurogenic inflammation was recognized as a physiological process of inflammation produced by the nervous system. In the context of migraine, vasoactive neuropeptides, such as calcitonin gene related peptide (CGRP), substance P (SP), and neurokinin A (NKA), were released from trigeminal and parasympathetic perivascular fibers, and evoked vasodilatation, plasma protein extravasation, and the release of other proinflammatory mediators. Neurogenic inflammation consists of two distinct and independent physiological components, namely neurogenic plasma protein extravasation and neurogenic vasodilatation[16]. Plasma protein extravasation is a phenomenon that allows macromolecules, including albumin, to pass through the endothelial gaps in postcapillary venules into the interstitial space and produces an inflammatory edema[17]. The leakage occurs following stimulation of peripheral sensory nerves. Direct stimulation of sensory nerves in rodents elicits the peripheral release of vasoactive neuropeptides[18]. The effects of SP and NKA are mediated by G-protein-coupled receptor, NK1 receptor, expressed on the endothelial cells of postcapillary venules and collecting vessels. NK1 receptor is associated with Gq/11 proteins and its stimulation results in the mobilization of Ca^{2+} ions into the cytosol, where it activates intracellular contractile elements. Within seconds of NK1 receptor activation, endothelial gaps form because of the contraction of the endothelial cells. This allows plasma proteins to leak out of the blood vessels. The gaps are located at the intracellular junctions of endothelial cells and are reversible[19].

Although experiments in rodent models of migraine suggest that plasma protein extravasation (PPE) in the meninges could by an important mechanism in migraine pathogenesis, various antagonists with a good pharmacodynamics and pharmacokinetic profile were not effective in clinical trials[20,21]. The embarrassing lack of clinical effectiveness of these antagonists demonstrated that even if SP and NKA were released from human sensory neurons, they did not produce the PPE commonly observed in rodents, and thus PPE probably does not play any role in migraine. On the other hand, the role of the other components of neurogenic inflammation, the neurogenic vasodilatation, in mediating migraine pain has received much more attention in the recent years[22]. This process is mediated via the activation of CGRP receptors expressed on vascular smooth muscle cells.

Trigeminovascular sensitization: the role of cortical spreading depression

Pain receptors, or nociceptors, in facial and intracranial structures receive input from trigeminal innervation and send nociceptive signals to higher brain centres. Although activation of the trigeminal nociceptive system and release of CGRP and SP from trigeminal nociceptor are known to be essential steps in development of migraine pain, little is known about the way these processes are activated. Because headache is preceded by an aura in some patients, the mechanism underlying aura may have roles in trigeminal activation. It is generally accepted that transient neurological symptoms occurring during aura phase are likely to be explained by an experimentally observed electrophysiological phenomenon called cortical spreading depression that may be a homologue of aura in experimental animals.

Cortical spreading depression (CSD) is a surge of electrophysiological cortical activity and followed by its inhibition. This wave-like surge usually starts in the

occipital cortex and gradually propagates forward over the cortex at about 3-5 mm per minute and disappears at the central sulcus. Based on the propagation of this phenomenon, CSD is consistent with the development of aura in migraine patients. CSD is caused by a transient disturbance of mechanisms maintaining ionic homoeostasis. These perturbations in ionic homoeostasis are characterized by extracellular negative direct current potential, indicating a cell depolarization. CSD can be induced in animals with non-noxious stimuli, and is frequently referred to in the literature as the "spreading depression of Leão"[23]. Although CSD was first demonstrated in lissencephalic brains of rodents, it can also occur in gyrencephalic brains. Using in vitro studies, CSD has been observed in human cortical brain tissue[24], and in human hippocampus and striatum in vivo[25].

Accumulating evidence suggests that CSD can account for the pathogenesis of the migraine aura. However, the initiation of the migraine attack phase and CSD is not clearly understood. Previous experiments show that during CSD, several physiological measurements, including cortical blood flow, neurotransmitter levels, and extracellular ionic concentration can change. For instance, blood flow is increased in various brain areas such as cerebral cortex, hippocampus, and brainstem. The level of neurotransmitters such as glutamate, glycine, and nitric oxide (NO) have been shown to be increased in cerebral cortical tissue[26,27]. These chemical messengers may induce perivascular inflammation and activate or sensitize perivascular nociceptors during CSD. On the other hand, these chemical messengers may direct activate nociceptors and produce headache. This hypothesis is supported by work published in 2004 by Maneesri and coworkers, who found that CSD can induce c-fos expression in the trigeminal nucleus caudalis (TNC) without perivascular inflammation[28].

Dysfunction of the endogenous pain control system

It is known that the excitability of TNC neurons is strongly influenced by supraspinal controls. Positron emission tomography (PET), and other brain imaging studies have demonstrated activation of the dorsal midbrain including the periaqueductal gray (PAG) and the locus coeruleus, thalamus, rostroventral medulla (RVM), and raphe nuclei, in migraine patients[29,30,31,32]. These brain areas exert their nociceptive modulation effect via downward projection to the trigeminocervical complex[33]. A derangement of this system at any level or a complex mechanism may decrease the sensitivity of pain perception and may increase the chance of generating a migraine headache. Experiments in animals showed that the development of long-term potentials in the dorsal horn synapse, a condition comparable to central sensitization, is facilitated when this endogenous antinociceptive system is impaired[34]. The clinical evidence indicates possible relationship between PAG dysfunction and headache pathogenesis. The PAG is a brain area with a descending antinociceptive function that has a strong influence on the trigeminocervical complex. Migraine-like headache sometimes occurs in the patients with electrodes implanted into the PAG for pain relief[35].

Serotonin (5-HT) plays an important role in the endogenous pain modulating system. It is known that migraine pathogenesis is associated with 5-HT depletion. A decrease of 5-HT concentration in platelets and an increase in plasma 5-HT correlated with migraine attacks in patients. However, the mechanism by which 5-HT depletion predisposes the brain to migraine attack is not well understood. Experimental evidence from animal models of migraine shows that 5-HT depletion increases the frequency of CSD and that CSD induced c-fos expression in the second order neurons in the trigeminocervical complex[36]. Pretreatment with NO blockers can modulate cortical hyperexcitability and trigeminal nociception[37]. Other studies show that 5-HT depletion can increase NR1 phosphorylation of the NMDA receptor and c-Fos expression in the TNC induced by dural inflammation[38]. Dysfunction of this neurotransmitter system may induce changes including an increase in cortical excitability, disinhibition of the descending pain control system, and activate the trigeminal nociceptive system in second order neurons in trigeminocervical complex.

Conclusions

This review describes some of the current knowledge regarding role of trigeminal system in migraine pathogenesis. The data from clinical and preclinical research indicates trigeminovascular sensitization and the derangement of endogenous pain control system as being important in the pathogenesis of migraine. The current concept regards migraine as a genetic predisposing condition. Various genetic abnormalities have been reported to contribute to migraine development especially in the forms with strong genetic predisposition such as familial hemiplegic migraine. The genes include CACNA1A (for P/Q calcium channel) SCN1 (for voltage controlled sodium channel) and ATP/A2 (for ion pump). Since most of these genes control the expression of protein involved in the control of membrane potential, their alterations may change the cellular excitability and increase the susceptibility of having CSD. CSD then activates the trigeminal system resulting in headache.

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