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Current and novel insights into the neurophysiology of migraine and its implications for therapeutics

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ABSTRACT

Migraine headache and its associated symptoms have plagued humans for two millennia. It is manifest throughout the world, and affects more than 1/6 of the global population. It is the most common brain disorder, and is characterized by moderate to severe unilateral headache that is accompanied by vomiting, nausea, photophobia, phonophobia, and other hypersensitive symptoms of the senses. While there is still a clear lack of understanding of its neurophysiology, it is beginning to be understood, and it seems to suggest migraine is a disorder of brain sensory processing, characterized by a generalized neuronal hyperexcitability. The complex symptomatology of migraine indicates that multiple neuronal systems are involved, including brainstem and diencephalic systems, which function abnormally, resulting in premonitory symptoms, ultimately evolving to affect the dural trigeminovascular system, and the pain phase of migraine. The migraineur also seems to be particularly sensitive to fluctuations in homeostasis, such as sleep, feeding and stress, reflecting the abnormality of functioning in these brainstem and diencephalic systems. Implications for therapeutic development have grown out of our understanding of migraine neurophysiology, leading to major drug classes, such as triptans, calcitonin gene-related peptide receptor antagonists, and 5-HT_{1F} receptor agonists, as well as neuromodulatory approaches, with the promise of more to come. The present review will discuss the current understanding of the neurophysiology of migraine, particularly migraine headache, and novel insights into the complex neural networks responsible for associated neurological symptoms, and how interaction of these networks with migraine pain pathways has implications for the development of novel therapeutics.

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Abbreviations: CGRP, calcitonin gene-related peptide; CSD, cortical spreading depression; GON, greater occipital nerves; iNOS, inducible nitric oxide synthase; LD, lateral dorsal thalamic nuclei; LP, lateral posterior thalamic nuclei; NRM, nucleus raphe magnus; NTG, nitroglycerin; PACAP, pituitary adenylate cyclase-activating peptide; PO, posterior thalamic nuclei; PVN, paraventricular hypothalamic nucleus; RVM, rostral ventromedial medulla; TCC, trigeminocervical complex; TG, trigeminal ganglion; tDCS, transcranial direct current stimulation; TNC, trigeminal nucleus caudalis; SPG, sphenopalatine ganglionp; sTMS, single-pulse transcranial magnetic stimulation; SuS, superior salivatory nucleus; VIP, vasoactive intestinal peptide; vlPAG, ventrolateral periaqueductal gray; VNS, vagus nerve stimulation; VPM, ventropostermedial thalamic nuclei.

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1. Introduction

Migraine is a severe and hugely debilitating brain disorder, ranked the most disabling of all neurological disorders, and the 6th most disabling globally (Murray et al., 2012; Global Burden of Disease Study, 2015). It affects 15–18% of people worldwide each year (Lipton, Stewart, Diamond, Diamond, & Reed, 2001; Lipton et al., 2007), and it is also thought to cost the US economy nearly $20 billion a year (Stewart, Ricci, Chee, & Morganstein, 2003). Migraine is characterized by attacks of unilateral throbbing head pain, with increased sensitivity to movement, touch, light, sounds, smells, and even foods, which can last 4–72 h (Headache Classification Committee of the International Headache Society, 2013). Additionally, both before (by up to 48 hours (Giffin et al., 2003); during the premonitory phase) and during their headache, patients can experience autonomic, affective and cognitive symptoms. These symptoms can include nausea, vomiting, yawning, lacrimation, nasal congestion (all autonomic), depression and irritability (affective), and reduced concentration (cognitive). Most attacks are followed by hours or a day of feeling unwell, usually associated with tiredness, called the postdrome (Giffin et al., 2003; Kelman, 2004; Giffin, Lipton, Silberstein, Olesen, & Goadsby, 2016). In approximately one-third of migraine patients, their attacks are associated with neurological deficits, including focal cortical perturbations, collectively termed migraine aura (Rasmussen & Olesen, 1992), which can occur just before or during the headache. This symptomatology reflects the complex nature of migraine as a neurological disorder that affects multiple cortical, subcortical and brainstem areas involved in the regulation of autonomic, affective, cognitive, as well as sensory functions. This suggests that the migraine brain is somehow different from the non-migraine brain, and as such responds to inputs differently.

While the exact pathophysiology of migraine headache and its associated symptoms are not fully understood, we are beginning to understand its neurophysiology with knowledge of the brain anatomy, physiology and pharmacology involved, and how this impacts therapeutic discovery efforts. Furthermore, we are beginning to understand that migraine pathophysiology should not just be thought of as the neurophysiology of these pain pathways. We need to consider how complex neural networks relative to homeostatic stressors, such as stress, loss of sleep, skipping meals, specific light and noise, specific foods and alcohol, and hormonal fluctuations, interact with each other to influence pain processing and also produce the complexity of neurological symptoms in migraine. These homeostatic stressors have a huge influence on the migraine brain and how it processes sensory information. Sometimes these stressors can result in triggering a migraine attack, and then removing the potential causes of this disrupted homeostasis, such as through eating or sleeping, can provide relief from symptoms. However, it has also been shown that it is the removal, or recovery from stress, when migraine is triggered, rather than during the stress itself.

In this review we will outline the accepted anatomy of the pain pathways involved in migraine, concentrating predominantly on the neurophysiology related to migraine headache, and discuss the therapeutic implications of this neurophysiology. We will also consider the recent insights into the complex neural networks thought responsible for the many associated neurological symptoms, and their interaction with pain pathways, and discuss how these might open novel opportunities for therapeutic development.

2. Neurophysiological mechanisms of migraine headache

It is acknowledged now that migraine is a brain disorder most likely driven by changes that occur centrally. However, these central changes have a huge impact on peripheral cranial structures and neural mechanisms, including the peripheral projections to the craniovasculature via sensory trigeminal neurons and the parasympathetic nervous system. Together, these central and peripheral changes result in premonitory symptoms, aura, other associated symptoms, as well as migraine headache. It is still not fully clear what the peripheral and central mechanisms are that cause activation of pain pathways that result in headache in migraine. However, our understanding of the anatomy and physiology of these pain pathways has advanced greatly over the last 25 years, and are well described elsewhere (Akerman, Holland, & Goadsby, 2011; Noseda & Burstein, 2013).

2.1. Anatomy of trigeminovascular pain pathways

2.1.1. Peripheral and central afferent projections

The severe and throbbing head pain associated with a migraine attack, localized to frontal, temporal, parietal, occipital and high cervical regions, is thought to be the consequence of activation of the trigeminovascular system (Fig. 1). A rich plexus of nociceptive nerve fibers that originate in the trigeminal ganglion (TG) innervate the pial, arachnoid and dural blood vessels, including the superior sagittal sinus and middle meningeal artery, as well as large cerebral arteries (Penfield & McNaughton, 1940; Ray & Wolff, 1940; McNaughton & Feindel, 1977). This nociceptive innervation is via non-myelinated (C-fibers) and thinly myelinated (Aδ-fibers) axonal projections, mainly through the ophthalmic (V1) division of the trigeminal nerve. To a lesser extent it is also through the maxillary (V2) and mandibular divisions (V3). In addition, there is neuronal innervation of the dura mater provided by the upper cervical dorsal root ganglia (Marfurt, 1981). The nerve endings of these collected nociceptive fibers contain vasoactive neuropeptides, some of which have been implicated in migraine pathophysiology. These include calcitonin gene-related peptide (CGRP), substance P, neurokinin A and pituitary adenylate cyclase-activating peptide (PACAP) (Uddman, Edvinsson, Ekman, Kingman, & McCulloch, 1985; Edvinsson, Brodin, Jansen, & Uddman, 1988; Uddman & Edvinsson, 1989; Uddman, Goadsby, Jansen, & Edvinsson, 1993). They are thought to be released upon stimulation of the trigeminal nerve causing vasodilation of dural and pial vessels (Williamson, Hargreaves, Hill, & Shepheard, 1997; Ebersberger, Averbeck, Messlinger, & Reeh, 1999; Petersen, Birk, Doods, Edvinsson, & Olesen, 2004). Studies from the 1940s clearly demonstrate that activation of intracranial structures, particularly the dura mater, with mechanical, chemical or electrical stimulation, results in headache pain very similar to the pain in migraine, localized to specific head regions depending on the site of stimulation, as well as causing other symptoms associated with migraine, including nausea and photophobia (Penfield & McNaughton, 1940; Ray & Wolff, 1940; McNaughton & Feindel, 1977). Interestingly, stimulation of sites away from these blood vessels is much less nociceptive, with correspondingly less severe symptoms of headache.

Central projections of dural nociceptive primary afferent Aδ- and C-fibers enter the caudal medulla of the brainstem, via the trigeminal tract, terminating predominantly in the superficial laminae, I and IIo, as well as deeper laminae V-VI of the spinal trigeminal nucleus caudalis (TNC; Sp5C), and also the upper cervical spinal cord (C1-C2) (Kaube, Hoskin and Goadsby, 1993; Kaube, Keay, Hoskin, Bandler and Goadsby, 1993; Goadsby & Hoskin, 1997; Burstein, Yamamura, Malick, & Strassman, 1998; Hoskin, Zagami, & Goadsby, 1999; Millan, 2002; Liu, Broman, & Edvinsson, 2004; Liu, Broman, & Edvinsson, 2008). These dural-nociceptive neurons converge on trigeminal neurons that receive additional inputs from facial skin and muscle, including the greater occipital nerve (Davis & Dostrovsky, 1988a, 1988b; Bartsch & Goadsby, 2002; Bartsch & Goadsby, 2003). These data suggest that the trigeminal nucleus extends beyond its caudalis boundary to the dorsal horn of the higher cervical region in a functional continuum that includes the cervical extension – together known as the *trigeminocervical complex* (TCC). The convergence of primary afferent inputs from intracranial and extracranial structures relayed through the TCC (Kaube, Hoskin, et al., 1993; Kaube, Keay, et al., 1993; Goadsby & Hoskin, 1997; Hoskin et al., 1999) probably accounts for the distribution of pain perception in migraine over the frontal and temporal regions,