

Brain structure and function related to headache

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Primary headaches range among the most common and disabling neurological disorders. Migraine alone affects a billion people worldwide and represents the leading cause of years lost to disability (1). In contrast, cluster headache, despite being much less common, is one of the most painful conditions a human being can experience. These two examples highlight the burden primary headaches cause for patients and the vast socio-economic impact it has on the society.

Given this significant burden, there is a major need to determine the pathophysiological mechanisms that underlie the susceptibility, initiation and cessation of these disorders, as only by doing so will novel disease-modifying targets be identified. Our understanding of primary headaches has advanced significantly in the past 20 years, facilitated by a detailed disease classification (2) and advances in clinical and preclinical research.

In this special issue we will focus on our current understanding of the structural and functional role of specific peripheral and central nervous system regions as they relate to headache and its related non-pain symptoms. While individual regions are discussed, it is clear that headache is a system-wide disorder, which involves both peripheral head pain processing trigeminal afferents and dysfunctional CNS networks that lead to hypersensitivity to multisensory inputs (3). The hypothalamus has emerged as a key hub that demonstrates abnormal activity and circuit connectivity during the earliest attack phases (4–6), with important roles in attack rhythmicity and clustering (7). In this issue, Arne May and Rami Burstein set out the preclinical and clinical evidence supporting a critical role for the hypothalamus in the pathophysiology of migraine and cluster headache (8). Laura Schulte and Kuan-Po Peng further explore the role of the hypothalamus and its related neuronal networks in the generation of migraine-related premonitory symptoms (9). Interestingly, hypothalamic connectivity is altered temporally across individual attacks with important consequences for attack initiation and chronification (10,11). The circadian and circannual periodicity of

several headache subtypes (7) suggests an important role for the biological clock, which is located within the suprachiasmatic nucleus of the hypothalamus. The suprachiasmatic nucleus regulates the rhythmic release of melatonin from the pineal gland, which is altered in several headache syndromes (12,13). Despite this link, the role of the pineal gland has been largely neglected in studies on headache pathophysiology. Herein, Mario Peres et al. review the available evidence on its role in primary headache including its potential to modulate neuropeptide release (14).

While the hypothalamus has been linked to the initiation of attacks, the thalamus is central to multisensory integration (15), highlighting its potential importance in the diverse symptomatology of headaches. This relationship is reviewed by Samaira Younis et al. (16) and Rodrigo Nosedá et al. (17) further building on this with a focus on the thalamic integration of light and pain signals that are proposed to underlie photophobia and photoallodynia.

The above diencephalic nuclei form reciprocal connections with several cortical regions that have important implications for the modulation and integration of headache-related pain signals. The role of cortical perturbations in the form of cortical spreading depression (CSD), which is considered to underlie migraine aura, is discussed by Else Toner et al., highlighting key pathophysiological consequences of and the genetic influence on CSD and their relationship to migraine with aura (18).

Focusing on the role of the brainstem, Marta Vila-Pueyo et al. (19) review the neuroanatomical and functional consequences of dysfunctional brainstem circuits, including the trigeminocervical complex as they

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relate to trigeminal pain processing. These powerful modulatory structures can elicit bidirectional control over peripheral sensory inputs from the trigeminal primary afferents, the role of which is discussed by Karl Messlinger and Andrew Russo (20), who review the role of trigeminal sensory afferents arising in the trigeminal ganglion as a key integrator of head pain and a potential site of action of novel CGRP-targeted therapies (21–24). Finally, Dan Levy and colleagues (25) expand on the peripheral innervation of the meninges and cerebral vasculature, the role they play in head pain and their potential as therapeutic targets.

The current special issue represents a concise review of our current understanding of the key peripheral and central nervous system structures involved in the pathophysiology of headache, with a particular focus on the neural circuitry that underlies the functional dysregulation of trigeminal sensory inputs and related multisensory integration. We currently sit at an important crossroads for headache, with recent therapeutic advances (26); however, there remains a critical need to enhance our understanding of the complexity of headaches. Herein, the progress over the past 20 years is expertly laid out and several of the future challenges identified. It is hoped that this special issue will serve as both a summary of the current knowledge, and a stimulus to encourage further research on primary headaches to target many of the unanswered questions that the readers will no doubt encounter.

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