Spreading Depolarization
Simon Akerman

Spreading depolarization, first described by Leão in 1944, is a transient wave of neuronal and glial depolarization that is associated with a loss of ion homeostasis, involves vascular and neuronal synaptic changes, and a subsequent depression in electrical activity (spreading depression). It has been observed in a variety of animal models including rodents and cats, and has recently been demonstrated in human studies in injured brains, suggesting its evolutionary conservation (reviewed in Dreier, 2011, Nat Med, 17(4):439-447 and Ayata and Lauritzen, 2015, Physiol Rev, 95:953-993). It is thought that spreading depression within the cortex (CSD) underpins the pathophysiology of the neurological event aura, which is a common neurological phenomenon that can precede headache in migraine (migraine aura). This hypothesis was first described by Lauritzen and Olesen (1984), who suggested the similarity of the blood flow changes during migraine aura with events in Leão’s spreading depolarization. The key components of the neurophysiological and vasomotor events of spreading depolarization that occur within the cerebral cortex, and how these relate to migraine aura, will be reviewed during this presentation. More recent human studies have replicated these initial vascular observations, and animal studies have been conducted to understand the wider role of CSD in migraine pathophysiology. This presentation will include a review of the data from rodents studies, which demonstrate that CSD events mediated by various noxious stimuli can induce activation of dural trigeminovascular neurons, thought to be responsible for mediating the intracranial head-pain during migraine. The potential mechanisms of this process, and the debates surrounding how this might correlate with migraine aura being a potential trigger of headache events during migraine, will also be discussed. I will also review the data which demonstrates that migraine preventive drugs are able to independently inhibit the electrical spreading depression resulting from cortical spreading depolarization, in addition to their actions on dural trigeminovascular neurons, and this is likely a component of their therapeutic mechanism of action. Finally, I will summarize how understanding the mechanisms of CSD, and how it might mediate noxious trigeminovascular activation, has been taken forward to provide opportunities for novel drug development strategies.

Preclinical Insights into Mechanisms of Medication Overuse Headache
Frank Porreca

Medication overuse headache (MOH) is an important risk in the management of episodic migraine. The frequency of attacks in individuals with episodic migraine is predictive of the risk to eventual transformation to chronic migraine. Repeated or frequent activation of nociceptors can result in neural plasticity that increases synaptic strength and amplification of innocuous signals, mechanisms commonly referred to as central sensitization. Central sensitization could contribute to migraine episodes following exposure to normally sub-threshold migraine triggers. Dysfunction of descending pain modulatory circuits may promote the
maintenance of states of central sensitization. It is now appreciated that neural plasticity in these circuits can also arise from overuse of drugs for acute migraine treatment that can produce MOH including opioids or triptans. We modeled MOH preclinically using a “two-hit” priming strategy. In this approach, uninjured rats received a period of morphine or sumatriptan to induce hyperalgesic priming. Following the resolution of hyperalgesia and at a time at which sensory thresholds were at baseline levels, the animals were exposed to a “migraine trigger” (i.e., stress or nitric oxide donor). These normally ineffective stimuli produced a period of delayed and generalized hyperalgesia that was CGRP dependent. Additionally, stress-induced allodynia following priming was associated with a loss of the diffuse noxious inhibitory controls (DNIC) response that may reflect dysregulation of descending pain modulatory pathways. Decreased descending inhibition, or possibly enhanced descending pain facilitation, has been repeatedly observed in patients with functional pain disorders including migraine. Collectively, clinical and preclinical studies suggest that repeated episodic migraine, and medications used to acutely treat migraine, promote dysfunction in central pain modulation to establish or maintain a “pain memory” that may lead to migraine chronification. The hyperalgesic priming model of MOH may allow dissection of descending pain modulatory circuits that promote enhanced responses to migraine triggers and chronification.

**Obesity**

Ana Recober

Our understanding of the mechanisms underlying migraine progression remains incomplete. Obesity is associated with more frequent and more severe migraine attacks (1). Importantly, several studies found that weight loss decreases the frequency and severity of migraine attacks (2), suggesting that obesity may modulate some of the underlying mechanisms of migraine. Despite strong epidemiological evidence, the possible role of obesity in migraine progression remains unknown.

Inflammation, a hallmark of obesity, is a plausible link between the two disorders given its known effects on pain modulation and sensitization of trigeminal nociceptors that contribute to migraine.

Our group pioneered the study of the cellular and molecular mechanisms underlying the link between obesity and migraine (3-7). We have found elevated levels of IL-6 in dura and trigeminal ganglia of obese mice that display migraine-like endophenotypes (photophobia and pain) using novel behavioral assays. Marics et al. have demonstrated that obese rats have enhanced basal and stimulated CGRP release from meningeal afferents (8).

In this lecture I will discuss: a) Recent studies exploring the effects of obesity on trigeminal sensory processing and b) The use of migraine-like endophenotypes (photophobia and affective trigeminal pain) in the study of trigeminal activation and sensitization.

REFERENCES


**Imaging and Headache**

Catherine Chong

Although migraine is clinically well-defined, our understanding of the underlying neuropathology is still developing. Recent neuroimaging results indicate that migraine is associated with structural and functional alterations in a variety of brain regions that are commonly termed the ‘pain-matrix’ and which relate to the sensory, cognitive, emotional and integrative components of the pain experience. Results of imaging studies suggest potential brain biomarkers for migraine but also indicate progressive brain changes in migraine yielding evidence to the notion that the migraine disease process defines the brain. In addition, results from brain structural and functional imaging studies suggest a relationship between brain changes and migraine treatment, potentially indicating the use of imaging for tracking brain recovery patterns. This lecture will introduce brain structural (magnetic resonance imaging, diffusion tensor imaging) and functional (resting-state functional connectivity) imaging techniques and discuss the utility of these imaging methods for elucidating the migraine disease process.

This lecture will discuss 1) the relationship between brain structural and functional alterations and migraine disease factors (ie. years lived with migraine, headache frequency) 2) the relationship between migraine treatments and brain recovery patterns. Lastly, this lecture will highlight imaging findings that specifically investigate the neuro-mechanism associated with medication-overuse headache and post-traumatic headache.