Center Stage for Targeting Migraine and its Treatment

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Migraine is not a fatal disorder but can ruin a life and a family. Migraine is very common, afflicting 15 percent of the population. It ranks among the top 10 causes of years lived with disability, and women are 3 times more likely to be affected. Its manifestations include a prodrome (early symptoms indicating onset), the headache and the postdrome. The headache phase is sometimes anticipated by a punctuated focal neurological event called an aura. Being complex, migraine varies clinically from patient to patient and reflects a highly choreographed interplay between the brain and its environment.

Despite exciting treatments in development, we still know little about the brain mechanisms or biological substrates that generate different attack phases or even what terminates an attack. The prodrome begins hours to days before the headache begins. It is likely due to limbic system disturbance (e.g., hypothalamus) giving rise to mood, appetite and autonomic dysfunction. Auras are somewhat better understood and are characterized by a neurophysiological event called cortical spreading depression (CSD). Auras may be visual but also can involve other sensory modalities, cause motor weakness or produce language difficulty usually lasting less than an hour. During the headache phase, migraineurs complain of throbbing headaches, nausea, vomiting, malaise, as well as sensitivity to light, sound and smell. Acute attacks may last up to 72 hours. A chronic subtype with 15 or more headache days per month occurs in about 1 percent of the population and is particularly difficult to treat. But hope may be on the horizon with developing treatment options awaiting the final stages of testing.[1]

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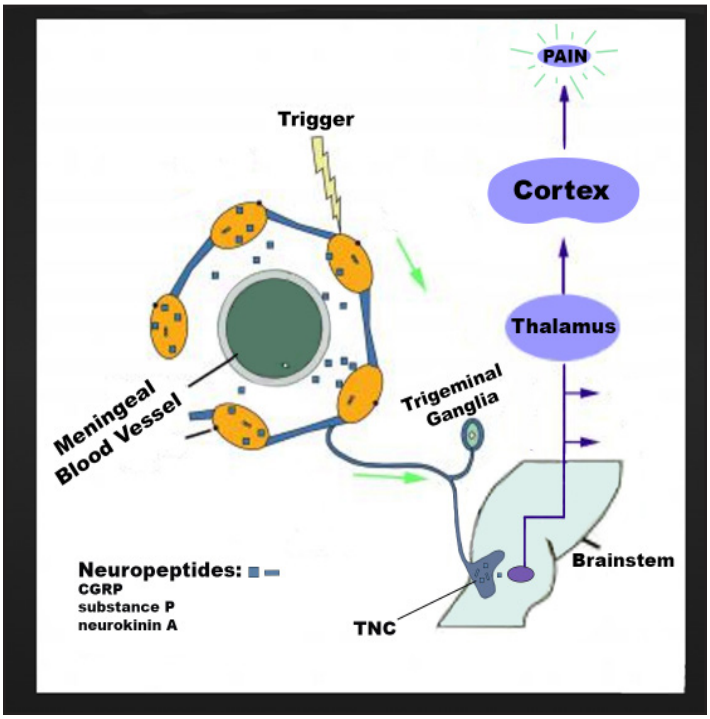
Historically, migraine has been viewed primarily as a vascular disorder. The evidence was based in part on the vasoconstrictor actions of signature drugs used to treat acute attacks such as the ergot alkaloids and the triptan family, plus the notion that vasodilation caused the headache. Although it made for a plausible theory, the evidence was meager and went unchallenged for many decades. We now know that vasodilation does not cause migraine pain and that vasoconstriction is neither necessary nor sufficient to abort headaches.[2] Furthermore, there is no evidence for tissue damage in migraine, and vascular injury from extreme vasodilation is an unlikely cause. In fact, vessels may dilate or constrict during the headache accounting for the heterogeneous blood flow patterns observed in many human studies. The best evidence so far is that pain is more likely due to an inflammatory trigger reflecting recently described molecular signaling between neurons, astrocytes (glial cells), the layers of meninges (membranes covering the brain and spinal cord), and meningeal sensory fibers.[3] However, multiple causes seem likely.

The Trigeminovascular System (TV) Emerges

The evidence against simple theories of constriction and dilation began with the recognition that meningeal blood vessels receive a rich trigeminal innervation known as the trigeminovascular system (TV).[4] (Trigeminal nerve cells send one of their axonal projections to blood vessels and surrounding tissues of the meninges and the other into the trigeminal nucleus caudalis within the brain stem.) The brain itself is insensate. These trigeminal nerve fibers contain vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), substance P and neurokinin A.[5] They are stored within meningeal axons and free nerve endings as well as central nerve endings within the trigeminal nucleus caudalis (TNC). Upon activation or nerve discharge, signals from meningeal fibers are transmitted to the trigeminal ganglia and then to TNC as well as to brain stem and thalamic nuclei and distribute to regions of the cortex and the subcortex, where the signals are processed and may

be registered as pain.[6,7] (See Figure 1) In these brain regions and within TNC, the response to incoming signals may become excessively amplified during an attack giving rise to a state called sensitization, which identifies a notoriously difficult migraine population to treat.[8]

Figure 1



So the focus on the trigeminal nerve and its peripheral and central connections (a final common pathway for headache) did cause a paradigm shift.[9] This shift ushered in more than three decades of research to better understand the pathophysiology of migraine and to develop new treatment options. Unfortunately, efforts to reliably trigger full-blown migraine attacks in patients and experimental animals have been largely unsuccessful. So the approach to investigation until recently has been to deconstruct a full-blown attack. This approach divided an attack into the two phases easiest to study in both animal models and humans: aura and headache. Both are important parts of an incomplete puzzle.

Aura and Cortical Spreading Depression

The aura and its biological substrate cortical spreading depression are significant because they strongly implicate ion channels and ion pumps in the migraine story. Evidence also supports a role for cortical spreading depression in triggering the headache and as a target for prevention.[10] The aura, which occurs in 30 percent of migraineurs, is due to a slowly propagating intense depolarization of neurons and glia in grey matter known as cortical spreading depression. Cortical spreading depression has been validated using brain imaging studies. Specifically, high resolution functional imaging studies have shown many shared characteristics between a migraine visual aura and blood flow patterns during cortical spreading depression evoked in experimental animals.[11]

Chronic treatments with drugs used in migraine prevention elevate the threshold for cortical spreading depression in experimental animals. How this disparate group of drugs with multiple pharmacological signatures (e.g. antidepressants, anticonvulsants, beta-blockers, etc.) raise the threshold is still a mystery. Equally relevant, cortical spreading depression can activate the trigeminovascular system in an otherwise normal brain. Cortical spreading depression may still not qualify as a universal headache trigger (if one does exist) because an aura develops in only a subpopulation of migraineurs and is only followed by headache most but not all of the time. In other words, we still need to identify upstream candidates that can reliably trigger or activate the trigeminovascular system in humans.

CSD and Genes

Genes confer susceptibility to migraine headaches. Studies of a familial monogenic variant called Familial Hemiplegic Migraine (FHM) have been particularly revealing. These studies have helped to unravel key elements of cortical spreading depression and to understand the basis of migraine aura.[12] In these FHM patients, attacks are characterized by typical and sometimes multiple auras and headache. Hemiplegia, which is weakness or paralysis on one side of the body is due to aura involving motor cortex. Three subtypes of familial hemiplegic migraine identified to date exhibit mutations expressed either on:

- synaptic membranes containing a key subunit of a voltage gated calcium channel (Type 1)
- the alpha-2 subunit of Na/K+ ATPase (Type 2)
- an axonal membrane sodium channel NaV1.1 (Type 3).

These molecular entities underscore the importance of neuronal and glial ion channels and transporters that contribute to attack susceptibility.

For example, expressing either Type 1 or Type 2 mutations in mice lowers the threshold for cortical spreading depression. These mutations are thought to cause an imbalance between excitation and inhibition largely related to the synaptic fate of glutamate, the primary excitatory neurotransmitter in the brain, that favors excitation as well as periodic and seemingly spontaneously evoked cortical spreading depression.[13] Potassium clearance has also been implicated. Migraine susceptibility loci implicated in Genome Wide Association Studies in more typical types of migraine headaches are also consistent with this formulation.[14] Although still a topic for investigation, it is possible that stress, sex hormones, as well as oxygen availability and brain glucose levels (for example) may unfavorably impact this delicate balance in genetically susceptible individuals to provoke or contribute to an attack.

CGRP and its Receptor: an Important Therapeutic Target

Perhaps the most exciting story evolving at this time is the emergence of a new class of drugs based on targeting CGRP (calcitonin gene related peptide) and its receptor. CGRP is a 37 amino acid neuropeptide. To a large extent the focus on CGRP was inspired by earlier studies examining the actions of ergots and triptans. These studies underscored the importance of the trigeminovascular system including its ganglion as the most coherent (but perhaps not the only) therapeutic target for established or promising anti-migraine drugs.[9] These targets today include 5-HT1B/D and 5-HT1F (both are serotonin receptor subtypes) and CGRP and its receptor. The triptans inhibit neuropeptide release including CGRP, block neurotransmission within TNC, and suppress meningeal neuroinflammatory changes. They attenuate elevated CGRP blood levels during experimental trigeminal stimulation[15,16] or during an attack[17], suggesting a relation between CGRP release and the attack as well as inhibition of CGRP release and its therapeutic effect.

CGRP emerged as a challenging target for the pharmaceutical industry. Five different CGRP receptor antagonists were effective in clinical trials with a success rate approaching the triptans. The trials established proof of principle for targeting CGRP and like many of the effective triptans (and like the monoclonal antibodies noted below), they were brain impenetrant and suggest that sites outside the central nervous system may be the relevant therapeutic target (e.g., a subpopulation of trigeminal ganglion cells). However, development of these small molecule receptor antagonists was halted because of liver toxicity. Following a different approach, four humanized monoclonal antibodies were recently developed to neutralize CGRP or its target receptor.[18] Clinical results from phase 2 prevention trials in test populations of high frequency episodic migraine and chronic migraine appear promising. Major safety or tolerability issues have not been reported to date. The impact of treatment was consistent, albeit small-modest (1-2.5 median days per month less headache than placebo). Rather impressively, all four antibodies achieved a near headache-free response rate in about 15 to 30 percent of subjects. Phase 3 trials are now ongoing. We can learn a lot about the biology of migraine from this subpopulation of super responders, and perhaps now develop biomarkers that distinguish super-responsive individuals to advance a more personalized approach to migraine treatment. As first proposed nearly 40 years ago[19], neuropeptides and key modulating molecules within the trigeminovascular system have now become very effective drug targets for migraine.

Finally, the critical question remains: can monoclonal antibodies be extended as a treatment platform for other painful disorders or is the migraine promise so far a one-off? Too early to say. But identifying signature molecules or receptors expressed by distinct signaling pathways could provide a promising roadmap from the migraine experience.

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