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SCIENTIFIC COMMENTARIES

Holes in the leaky migraine blood–brain barrier hypothesis?

This scientific commentary refers to 'Increased brainstem perfusion, but no blood-brain barrier disruption, during attacks of migraine with aura', by Hougaard *et al.* (doi:10.1093/brain/awx089).

Disruption of the blood–brain barrier (BBB) and inflammation are important contributors to the pathogenesis of neurological disorders. Although inflammation has been implicated in migraine pathogenesis, it is not known whether barrier integrity is compromised during attacks. It has been posited by Harper and colleagues (1976) that a leaky barrier may allow noxious chemicals within the blood to trigger pain, and explain the pattern of changes in cerebral blood flow during attacks. BBB penetration may also provide a route by which abortive drugs used for acute treatment and normally excluded from the brain (e.g. triptans) access binding sites in the CNS to achieve their therapeutic effects. Furthermore, leakage of plasma protein and upregulation of matrix metalloproteinases has been observed within rat cortex for 24 h after cortical spreading depression (CSD), the biological substrate for migraine aura (Gursoy-Ozdemir *et al.*, 2004). In this issue of *Brain*, Hougaard and colleagues use high resolution imaging techniques in human patients to study the integrity of the BBB within specific brain regions during attacks of migraine with aura (Hougaard *et al.*, 2017).

Their bottom line finding is that the BBB is not compromised during headache in migraine attacks. To reach this conclusion, Hougaard *et al.* used a sensitive and validated technique, dynamic contrast-enhanced high-field MRI coupled with gadolinium tracer, to measure BBB function during the headache of migraine aura. They assessed multiple regions including visual cortex and cortical territories within the anterior, middle and posterior cerebral arteries and brainstem. They found no correlation between permeability change and time of symptom onset or intensity of pain. The data appeared consistent across 19 subjects within the time window identified on the basis of CSD in an animal model. However, an important next step would be to test the possibility that barrier disruption may occur transiently and early during an attack.

The link between aura and headache

So, if BBB disruption is not a contributing mechanism, then what may link aura and headache? Preclinical experimental studies support the importance of CSD. CSD is well established as a propagating depolarization of neurons and glia that spreads slowly (3–5 mm/min) and contiguously within grey matter structures followed by many minutes of depression of electrical activity (Pietrobon and Moskowitz, 2014). CSD has been documented in damaged human brain. The evidence implicating it in migraine aura is strong (Hadjikhani *et al.*, 2001) but there is no evidence of accompanying tissue injury. CSD imposes severe tissue stress and extends and expands tissue damage but does not appear to initiate it, except within already compromised tissue. It imposes a severe metabolic demand for ATP, which is required to restore ionic gradients in the presence of constrained blood flow (and hence delivery of oxygen and glucose), so called flow/metabolism mismatch (Dreier and Reiffurth, 2015).

Although there is no evidence for brain damage in otherwise normal humans or experimental models after a single spontaneous or evoked attack (and there need not be), it turns out that CSD is noxious and activates/discharges trigeminal axons (Pietrobon and Moskowitz, 2013). Trigeminal axons innervate primarily the ipsilateral meninges (Mayberg *et al.*, 1981) as well as midline structures bilaterally, and contain neuromediators such as calcitonin gene-related peptide (Uddman *et al.*, 1986). Activation of the trigeminovascular (TV) system following CSD has been reported by four different laboratories using six different experimental paradigms in two species (Pietrobon and Moskowitz, 2013). Hence, it may not be coincidental that 16 of 18 patients studied by Hougaard *et al.* experienced headache on the same side of the head (and 13 of 18 strictly on the same side) as the CSD generating the aura.

Although auras are understudied, there have been no other candidate events proposed or identified ipsilateral to the affected cortex that trigger trigeminal afferents and generate headache unilaterally, like the headache after stroke for example. Hence, the anatomy helps to predict the sidedness of the headache. Contralateral headache would be an expectation if thalamus and cortex on the same side as the CSD were processing transmitted pain signals. CSDs that are less intense or that are limited in spatial distribution (Zandt *et al.*, 2015), and/or reflect more efficient tissue clearance of nociceptive molecules may explain why some people with migraine do not experience headache after aura. Consistent with the above formulation, trigeminal axons and cell bodies are known to express multiple 5-HT1 receptor subtypes plus CGRP and its cognate receptor, which figure prominently as therapeutic targets (see below).

Is drug translocation to brain tissue target sites important to abort acute attacks?

Sumatriptan, a 5-HT1 receptor agonist and the first triptan abortive agent, reportedly does not cross the BBB but does diminish headache significantly when given within the average MRI scanning period (especially the earlier time point reported in the Hougaard *et al.* study). Furthermore, recent studies have concluded that occupancy of brain CGRP receptors is not essential for relief of acute migraine headache. Telcagepant, a small molecule CGRP receptor antagonist, did not penetrate the brain further (i.e. displace more radiolabelled ligand from its central binding sites) when given at clinically effective doses (Hostetler *et al.*, 2013). Similar findings were reported for dihydroergotamine during a drug-induced attack.

Questions need to be asked about the therapeutic importance of CNS targets, especially the activity of drugs that do not penetrate the brain (triptans and ergot alkaloids). Furthermore, the same might be said for high molecular weight antibodies directed against neutralizing CGRP or blocking its receptor that diminish attack frequency. What all this means is that expression of a receptor or drug target within brain (even within primary pain processing networks) does not by itself ensure its relevance to a therapeutic effect, especially if the drug does not reach target sites at sufficient concentrations to modulate target cell signalling.

In other words, the evidence to date suggests that drug penetration into CNS is not facilitated by BBB disruption during a migraine aura attack. There may be exceptions. A disrupted barrier and brain oedema were reported in a migraine genetic variant with aura (Dreier, 2016) that may suggest a counterpart to matrix metalloproteinase upregulation and barrier disruption following multiple CSDs in an animal model (Gursoy-Ozdemir *et al.*, 2004). The greater degree of tissue stress and inflammatory signalling in a multiple CSD animal model may explain why humans with typical migraine aura do not also show BBB disruption. These exceptions notwithstanding, the findings by Hougaard and colleagues suggest that candidate tissues and cells outside the BBB merit investigation to help identify therapeutically relevant target sites.

Cerebral blood flow alterations and migraine with aura

Harper took their leaky brain formulation one step further by suggesting that noxious circulating molecules normally excluded from brain and cerebrovascular smooth muscle contribute to brain perfusion changes observed in people with migraine during and after attacks (Harper *et al.*, 1976). The literature over the past two decades contradicts this notion. From animal and a few human studies, it seems clear that deviations in cerebral blood flow during migraine aura are caused by CSD, at least early on. Blood oxygen level-dependent signal changes in functional MRI during a visual aura reveal slowly propagating hypoperfusion, characteristic of the blood flow changes observed in rats during CSD (Hadjikhani *et al.*, 2001). Low blood flow usually persists for many minutes or longer, and as first described in humans, is sometimes followed by hyperperfusion (Hougaard *et al.*, 2017). However, decreases in blood flow during aura are usually modest (10–25%) and above ischaemic thresholds, so that if hyperperfusion develops afterwards, it may reflect an integral of prolonged and persistent plus mild blood flow reductions rather than ischaemia-reperfusion, *per se*.

Hougaard *et al.* also reported increases in pontine blood flow bilaterally, a finding noted previously. Pontine activation may reflect the processing of pain and its autonomic accompaniments associated with nausea, vomiting, diaphoresis, changes in heart rate and blood pressure, bladder/bowel disturbance, anxiety, changes in wakefulness, among other characteristics of an altered physiological state; some of these were experienced by patients studied by Hougaard *et al.* (Table 1). Sorting this out will be difficult without the development of new techniques with higher spatial resolution for imaging brainstem anatomy and improvements in deep phenotyping of migraine patients.

In summary, brain imaging is a powerful tool to interrogate the underlying mechanisms of migraine headache and inform us about what may or may not be important. Although still in its formative stages, MRI in patients has informed us about the role of CSD and helped us characterize attendant blood flow changes that occur during headache. It has also informed us that brainstem activation is a consistent, albeit poorly understood feature of attacks, whereas BBB disruption does not appear to characterize the sustained headache.

Glossary

Calcitonin gene related peptide (CGRP): An effective therapeutic target in migraine, CGRP is a neuromediator within the trigeminovascular system as well as within rostrally projecting central pain pathways.

Matrix metalloproteinases: A family of at least nine extracellular matrix-degrading enzymes that impact tissue function after cleaving matrix proteins to reshape the extracellular space.

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Cortical areas needed for choosing actions based on desires

This scientific commentary refers to 'Selective impairment of goal-directed decision-making following lesions to the human ventromedial prefrontal cortex', by Reber *et al.* 2017 (doi:10.1093/brain/awx105).

Lesions to prefrontal cortex lead to disinhibition, altered preferences and behavioural inflexibility. These clinical problems can be viewed as deficits in goal-directed behaviour. Goals enable coordinated planning of actions, and crucially, they can change depending on circumstances, permitting flexible behaviour. In this issue of *Brain*, Reber and co-workers (2017) demonstrate that patients with damage to ventromedial prefrontal cortex (vmPFC) show a specific deficit in flexibly adjusting behaviour to reflect a change in goal.

The study examines six patients with vmPFC lesions, and compares them to a control group with temporal lobe lesions and to a healthy group. The authors adapted a well-studied behavioural paradigm from the animal learning literature, termed outcome devaluation. Devaluation studies aim to test what a subject learns when they learn to perform an action to obtain a reward. Do they simply learn that the action is valuable, or do they learn that it leads to a specific outcome, the subjective value of which might vary depending on current goals? In the devaluation paradigm, the subject learns to perform two different actions to obtain two different rewarding outcomes, typically different foods. One of them is then devalued, for example by satiation or pairing with illness, so that it becomes subjectively less desirable. Finally, the tendency to perform both actions is assessed. If the subject has learned the specific outcomes that follow the actions, then devaluing one outcome should reduce the tendency to perform its corresponding action. If instead the subject has learned only whether an action is valuable, then subsequently devaluing its outcome will have no effect.

In Reber *et al.*'s study, participants learned to press two different keys to