congenital myopathy, especially when neonatal hypotonia with breathing and swallowing difficulties is present. This study also establishes the existence of null alleles for NaV1.4 in humans and illustrates the differential consequences of inheriting a hypomorphic loss-of-function allele versus a complete null.

Stephen C. Cannon M.D, PhD, Department of Physiology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

E-mail: sccannon@mednet.ucla.edu

doi:10.1093/brain/awv400

### Hypoxia, a turning point in migraine pathogenesis?

This scientific commentary refers to ‘Migraine induced by hypoxia: an MRI spectroscopy and angiography study’, by Arngrim et al. (doi:10.1093/brain/awv359).

Experimental models of human diseases are vital for pathophysiological and therapeutic research. In migraine, animal models have contributed greatly to better understanding of causal mechanisms and to the development of novel therapies, but they do not allow comprehensive analysis of the entire clinical phenotype. Human models are more suitable for this purpose, particularly because there are no insurmountable ethical barriers to inducing migraine attacks as they produce no sequelae and are treatable. The nitroglycerin test is the best studied human model for inducing attacks in migraine patients, although various other compounds have a similar effect (Olesen, 2008). The sensitivity of the nitroglycerin test is up to 80% in migraine without aura. However, nitroglycerin only rarely induces a migrainous headache in patients with migraine with aura and almost never an aura (Sances et al., 2004). A human model for the induction of migraine with aura attacks is thus still missing. In this issue of Brain, Arngrim and co-workers demonstrate that exposure to hypoxia may be one such model (Arngrim et al., 2016).

There are several reasons why normobaric hypoxia might be suitable. First, there is evidence that migraine (with aura) attacks may be triggered when blood oxygen saturation decreases. High-altitude headache occurs frequently with ascent above 2500 m, has at least some migrainous features and is more prevalent in mountaineers with a history of migraine (ICHD-3b, code 10.1.1 2013). Moreover, sleep apnoea-induced migraine attacks improve after bariatric surgery (Kallweit et al., 2011). Second, it has been known for more than two decades from studies in vitro and in vivo that hypoxia can induce spreading depression (Somjen et al., 1992), the most likely cortico-subcortical generator of the migrainous aura, thought to be favoured by increased brain glutamate levels. Third, mitochondrial energy metabolism may be deficient in migraine with and without aura between attacks, a frequently neglected facet of migraine pathophysiology that could sensitize migraineurs to hypoxia (Paemeleire and Schoenen, 2013). That metabolic failure might play a crucial role in migraine was hypothesized by Amery in 1982, before the first experimental data supporting the hypothesis were obtained by studies using MRS. The most recent of these used improved methodology and found that ATP is decreased by 16% and phosphorylation potential by 39% in migraine patients between attacks (Reynoudt et al., 2011). Interestingly, experimental mitochondrial poisoning also induces cortical spreading depression and facilitates hypoxia-induced spreading depression in rat hippocampal slices. Fourth, the...
hypoxia-induced cerebral vasodilatation is mediated in part by nitric oxide (Van Mil et al., 2002), to which migraine patients are thought to be hypersensitive (Olesen, 2008). There is thus a convincing rationale for testing the effects of hypoxia in migraine with aura, as in the sham-controlled, blinded study by Arngrim and co-workers.

Arngrim et al. explored whether 3 h of breathing air containing 11% O$_2$, which is equivalent to 4700 m altitude and which reduced capillary oxygen saturation (SpO$_2$) to 72%, was able to induce attacks in 15 patients suffering exclusively from migraine with aura and in 14 healthy volunteers. In addition, they obtained invaluable information on possible pathophysiological mechanisms by determining glutamate and lactate levels in visual cortex (1H-MRS) and venous blood, and by measuring the circumference of cranial arteries (3 T high-resolution magnetic resonance angiography). The results are highly interesting and thought-provoking (Fig. 1).

**Is hypoxia an adequate human model for migraine with aura?**

First, the clinical results show that 8 of 15 (53%) patients with migraine with aura developed migraine headache-like attacks during hypoxia, compared to one after sham hypoxia and one healthy volunteer. Headache without typical migraine features occurred in 13 patients and 11 volunteers. Three patients (20%) reported typical ICHD3b auras, one after sham exposure, while seven patients with migraine with aura and two volunteers had ‘atypical auras’ during hypoxia, mainly blurred vision. Using a strict definition, the hypoxia test has a 100% specificity for aura, the hallmark of the migraine subtype studied here, but a low (20%) sensitivity. For comparison, infusion of calcitonin gene-related peptide (CGRP) induced migraine-like headache in 57% of a group of patients with migraine with aura and aura in 28% (Hansen et al., 2008), while sublingual nitroglycerin produced headache but no aura in 13.6% of patients (Sances et al., 2004). Sensitivity for aura increases to 67% if ‘atypical’ auras are included at the expense of a decrease in specificity (86%). The precise nature of such ‘atypical’ auras is not certain, however, as blurred vision and difficulty in ocular fixation are quite common during the whole course of severe migraine without aura attacks. By the same token, the
border between ‘migraine-like headaches’ and non-migrainous headaches is fuzzy. This is illustrated in the headache classification shown in Supplementary Table 1 of Arngrim et al. (2016). Migraine with aura Patient 7, for instance, was considered to have a ‘migraine-like’ attack induced by hypoxia, although he had no associated symptoms and a moderate headache aggravated by exertion, which can be tested only after the hypoxia. By contrast, during placebo Patients 5 and 13 had a moderate headache that mimicked their usual migraine, but which was nevertheless classified as ‘non-migraine-like’. More surprisingly, during hypoxia, Patient 13 also developed bilateral, severe, throbbing headache, aggravated by movement and associated with photophobia that he considered similar to his usual attacks, but again this was not classified as ‘migraine-like’. It is likely that several headaches during both hypoxia and placebo were ‘probable’ migraine without aura attacks (ICHD3B 1.5.1) with one missing diagnostic criterion. Finally, patients were still included in the study with ‘tension-type headache’ for 5 days per month. As tension-type headaches can mimic mild migraine without aura attacks, this opens the door for inclusion of patients suffering from both migraine with and without aura, who are highly prevalent in clinical practice, and hence for a bias toward a higher frequency of hypoxia-induced migraine without aura attacks.

Schoonman et al. (2006) were the first to investigate the attack-inducing effect of normobaric hypoxia in a mixed group of eight patients with migraine without aura and eight patients with migraine with aura and to compare it with that of intravenous nitroglycerin or placebo in a double-dummy design. They found that hypoxia induced migraine attacks without aura in 6 of 14 patients (43%) who underwent the three provocations, while the incidence after nitroglycerin was surprisingly low (21%). Overall, three patients with migraine with aura (37.5%) and four patients with migraine without aura (50%) developed a migraine attack during hypoxia, but no aura was reported. The lower incidence in migraine with aura patients compared to that seen by Arngrim et al. could be due to the fact that the hypoxia was less severe (SpO2 75–80%), although on the other hand it was of longer duration (5 h).

The metabolic and vascular studies performed by Arngrim et al. failed overall to find a difference between patients with migraine with aura and controls. Intracranial and extracranial arteries dilated slightly (10–15%) during hypoxia in both groups of subjects, confirming that vasodilatation has no major role in migraine generation, and there was no correlation with the migraine headache. Instead, the authors suggest that patients with migraine with aura may be supersensitive to NO or other chemicals influenced by hypoxia, such as cyclic guanosine monophosphate (cGMP) or adenosine. While there are no data available for the latter, NO supersensitivity, as demonstrated for migraine without aura in many studies with the exception of that by Schoonman et al., is unlikely to be prevalent in migraine with aura patients, who rarely develop migraine-like headache after nitroglycerin provocation (Sances et al., 2004).

Brain glutamate levels were normal at baseline in patients with migraine with aura and not increased after hypoxia. This does not a priori support the ‘glutamatergic hyperexcitability’ model of migraine with aura pathophysiology, although glutamate and glutamine may be difficult to distinguish on 31P-MRS and glutamate is undoubtedly an important factor in cortical spreading depression.

In contrast to previous reports, Arngrim et al. also found no abnormality of baseline lactate in visual cortex. As expected, brain and blood lactate levels rose during hypoxia, but on average to a similar extent in patients with migraine with aura and healthy volunteers. The authors thus conclude, and rightly so, that these findings are not consistent with a mitochondrial abnormality in migraine with aura, as suggested by the 31P MRS studies cited above. It is worth mentioning nonetheless that

**Glossary**

**Cortical spreading depression (CSD):** A neuroglial phenomenon initially described by Leão (1944) and characterized by a brief neuronal depolarization followed by inhibition of neuronal activity for long periods. CSD can be induced in the cerebral cortex by mechanical, chemical or electrical triggers and is favoured by hypoxia and hypoglycaemia. There is strong evidence that CSD causes the aura symptoms in migraine.

**Migraine with aura:** Headache attacks preceded or accompanied by transient neurological disturbances of which the most frequent and characteristic are scintillating scotomata (ICHD 3beta-code 1.2.1)

**Nitric oxide (NO):** A gaseous neuromodulator that plays a role in cerebral blood flow regulation and in nociception, in particular in the trigeminovascular (TGV) system. NO interacts with calcitonin-gene related peptide (CGRP), a vasodilating neuropeptide that plays a seminal role in TGV nociception. NO donors, like nitroglycerin, are able to induce a migrainous headache in the majority of migraine without aura patients.
venous blood lactate was significantly increased in patients with migraine with aura at the 1-h post-hypoxia time point. Whether this is due to the decreased phosphorylation potential observed in the muscles of patients with migraine with aura (Barbirori et al., 1992) remains unclear. Moreover, Arngrim and co-workers’ data in their Fig. 2 might suggest that patients with migraine with aura who developed migraine-like headaches after hypoxia tended to have higher brain lactate levels than those who did not, and that the groups were too small for this difference to reach statistical significance. In fact, one can speculate that lactate may not be the optimal marker to detect subtle impairments of mitochondrial energy metabolism because of its complex role in neurono-glial functions (Magistretti and Pellerin, 1999).

Future studies could use the combination of hypoxia and visual stimulation for increased sensitivity, and/or measurement of brain pH changes with T1ρ MRI mapping (Heo et al., 2015).

To conclude, the study by Arngrim et al. is important because it provides important data about the pathophysiology of migraine with aura and suggests that hypoxia could be a valuable model for this subtype of migraine, although it induces migrainous headache more consistently than aura. The results set the scene for future studies that should aim to increase the sensitivity of the model, and also take into account the genetic heterogeneity of migraine, the presence of oxygen-sensing neurons in the CNS (Neubauer and Sunderram, 2004) and of meningeal TRPA1 channels able to transduce oxidative stress and to trigger neurogenic inflammation.

Jean Schoenen
University of Liège,
Department of Neurology,
Headache Research Unit, 4000 Liège,
Belgium

E-mail: jschoenen@ulg.ac.be
doi:10.1093/brain/awv402

References

Inflammatory changes in very early Alzheimer’s disease: friend, foe, or don’t know?

This scientific commentary refers to ‘Diverging longitudinal changes in astrocytosis and amyloid PET in autosomal-dominant Alzheimer’s disease’, by Rodriguez-Vieitez et al. (doi:10.1093/brain/awv404).

Whilst a definitive diagnosis of sporadic Alzheimer’s disease still rests on pathological confirmation, the emergence of biomarkers capable of revealing different aspects of pathology in vivo has led to a paradigm shift in how we conceptualize the disease. PET imaging using ligands that bind fibrillar amyloid-β or CSF measures of amyloid-β1-42 allow for the demonstration of amyloid pathology in life; MRI allows for cerebral and...