

The metabolic face of migraine — from pathophysiology to treatment

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Abstract | Migraine can be regarded as a conserved, adaptive response that occurs in genetically predisposed individuals with a mismatch between the brain's energy reserve and workload. Given the high prevalence of migraine, genotypes associated with the condition seem likely to have conferred an evolutionary advantage. Technological advances have enabled the examination of different aspects of cerebral metabolism in patients with migraine, and complementary animal research has highlighted possible metabolic mechanisms in migraine pathophysiology. An increasing amount of evidence — much of it clinical — suggests that migraine is a response to cerebral energy deficiency or oxidative stress levels that exceed antioxidant capacity and that the attack itself helps to restore brain energy homeostasis and reduces harmful oxidative stress levels. Greater understanding of metabolism in migraine offers novel therapeutic opportunities. In this Review, we describe the evidence for abnormalities in energy metabolism and mitochondrial function in migraine, with a focus on clinical data (including neuroimaging, biochemical, genetic and therapeutic studies), and consider the relationship of these abnormalities with the abnormal sensory processing and cerebral hyper-responsivity observed in migraine. We discuss experimental data to consider potential mechanisms by which metabolic abnormalities could generate attacks. Finally, we highlight potential treatments that target cerebral metabolism, such as nutraceuticals, ketone bodies and dietary interventions.

As early as 1935, migraine — which now affects >15% of the population worldwide — was referred to as a 'hypoglycaemic headache'¹. Despite this early connection between migraine and energy metabolism, clinical and basic research in migraine largely focused on the vasculature, neurovasculature and neurotransmission until Willem Amery revived the idea that metabolism is involved in the pathogenesis of migraine in his hypothesis-generating review in 1982 (REF.²). Since then, accumulating evidence — much of it clinical — indicates that migraine is at least partially an energy deficit syndrome with mitochondrial dysfunction. Technological advances (for example, in neuroimaging and genetics) have enabled examination of different aspects of cerebral metabolism in patients with migraine, and complementary animal research has deciphered possible links between metabolic factors and trigeminovascular activation in migraine pathophysiology. Evidence that cortical responsivity and sensory processing are abnormal in patients with migraine between attacks (reviewed elsewhere³) led to the suggestion that a combination of sensory overload and lowered energy reserve ignites the major pain-signalling system of the brain, the trigeminovascular system, leading to the migraine attack⁴.

In this Review, we describe the abnormalities of energy metabolism observed in migraine with a particular focus on clinical data, including phenotypic, biochemical, genetic and therapeutic studies. We also discuss experimental data to elaborate on the potential role of such metabolic abnormalities in migraine attack generation. Finally, we highlight therapeutic approaches to targeting of cerebral metabolism (antioxidants, nutraceuticals, pharmaceuticals and dietary ketogenesis).

Triggers and metabolic dysfunction

Two systematic reviews^{5,6} and a study of 1,207 patients with migraine⁷ have identified that the most common migraine trigger factors are stress or subsequent relaxation, fasting or skipping a meal, sleep changes (too much or too little), ovarian hormone changes (including menstruation and oral contraception), weather changes (including certain winds, hypoxia and high altitude), physical exercise (including sexual activity), alcohol, strong odours (especially perfume or cigarette smoke), intense light (especially bright or blue light) and loud noises. The distinction between trigger factors and premonitory symptoms of migraine attacks is not always easy, as some premonitory symptoms might be

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Key points

- Prevalent triggers of migraine attacks can all be linked to unbalanced cerebral energy metabolism and/or oxidative stress.
- Magnetic resonance spectroscopy studies have shown that mitochondrial phosphorylation potential and ATP are decreased in the brains of people with migraine between attacks. Glucose (and lipid) metabolism and mitochondrial functions are abnormal in the peripheral blood.
- Among patients with migraine, various single nucleotide polymorphisms are present in non-coding mitochondrial DNA and nuclear-encoded mitochondrial proteins; common variants associated with migraine are functionally involved in mitochondrial metabolism.
- Metabolic enhancers, such as riboflavin and coenzyme Q10, and dietary or pharmacological ketogenesis improve migraine but novel, more efficient metabolic strategies are needed.
- Experimental studies indicate a link between cerebral energy disequilibrium and cortical spreading depression and/or trigeminovascular system activation; calcitonin gene-related peptide and pituitary adenylate cyclase-activating peptide could also help restore energy homeostasis.
- Migraine can be regarded as a conserved, adaptive response that occurs in individuals with a genetic predisposition and a mismatch between the brain's energy reserve and workload.

misinterpreted¹⁸. For example, premonitory photophobia could lead to interpretation of light as a trigger. Similarly, as a result of premonitory craving for sweets, chocolate is frequently mistaken as a trigger. Nevertheless, individual triggers seem to have an additive effect⁹, leading to an attack only when a threshold has been reached. This observation suggests that trigger factors act on common pathways.

Some triggers — such as skipping a meal or fasting, exercise, dehydration, hypoxia and lack of sleep — have a clear link to metabolism. However, many other triggers, including hormonal changes, also have a potential common metabolic denominator: changes in mitochondrial metabolism and/or oxidative stress¹⁰. For instance, intense physical^{11,12} or psychological stress can increase oxidative stress in the CNS¹³. In healthy people, one night of sleep deprivation is enough to substantially reduce levels of glutathione, ATP, cysteine and homocysteine¹⁴. Intense sensory stimuli, including odours¹⁵, perfumes containing phthalates¹⁶, blue light¹⁷ and loud noises¹⁸, can increase oxidative stress. Experimental hypoxia can trigger migraine headaches^{8,19} (less so migraine aura¹⁹), even in most healthy people²⁰, and in line with this observation, migraine prevalence is higher in populations that live at high altitude²¹.

In animals, alcohol-induced oxidative or nitrosative stress alters mitochondrial membrane properties in the brain²². In rodents, oestrogen and, to a lesser extent, progesterone increase susceptibility to cortical spreading depression (CSD)²³, the cause of migraine aura. These hormones also modulate the ability of 5-hydroxytryptophan (the precursor of serotonin) to inhibit CSD²⁴, and influence oxidative metabolism in the rat brain²⁵. Furthermore, oestrogen, which greatly modulates the course of migraine in females, is involved in insulin sensitivity, the regulation of insulin secretion and nutrient homeostasis²⁶. In combination, these observations show that most migraine triggers or aggravating factors have a link to energy metabolism and oxidative stress.

Biochemical studies

A large number of biochemical studies in migraine point towards a variety of different metabolic abnormalities, discussed below, all of which are related to energy homeostasis (Supplementary Tables 1 and 2). A combination of metabolic and endocrinological abnormalities, possibly together with abnormal cerebral responsiveness, are likely to determine the migraine attack threshold of an individual. The cumulative number of abnormalities, in combination with unfavourable environmental factors, is likely to determine disease severity⁶.

Oxidative phosphorylation, ATP and lactate

Magnetic resonance spectroscopy (MRS) enables non-invasive measurement of numerous substances in various tissues. Some of these substances, such as lactate, magnesium and ATP, provide pivotal information about energy metabolism, and this approach has been used in studies of migraine (Supplementary Table 1).

The use of ³¹P-MRS has shown that mitochondrial oxidative phosphorylation is impaired in the brain of patients with migraine during²⁷ and between migraine attacks^{28–34}. This impairment is seen as increased levels of ADP, decreased levels of organic phosphate and a decreased phosphorylation potential. Similar patterns have been observed in skeletal muscles^{28,35,36}, suggesting a generalized rather than brain-specific alteration (reviewed in detail elsewhere^{33,37}). Subsequently, a modified ³¹P-MRS methodology was used to directly quantify brain ATP, which was found to be decreased by 16% between attacks in patients with migraine without aura compared with healthy controls³⁸. The lowest ATP concentrations were detected in the most severely affected patients, a finding that agrees in part with those of other studies showing modest associations between brain hypometabolism and attack frequency^{31,35,38}. Magnesium is often also measured in ³¹P-MRS studies of neural metabolism because it is a crucial cofactor for ATP production. These measurements have shown that, in line with alterations in oxidative phosphorylation, cytosolic free magnesium is reduced in the occipital lobes of patients with migraine^{30,31,39}.

The more widely available ¹H-MRS technique can be used to determine concentrations of lactate, a key cellular metabolite. Variability in methodologies and patient selection criteria in studies of brain lactate levels in patients with migraine mean that strong conclusions cannot be drawn^{33,37}. Elevated levels of brain lactate have been found in patients with migraine with aura^{40,41} but not in those with migraine without aura^{42–45}. Occipital baseline lactate levels were increased in patients who had strictly visual aura compared with healthy controls but not in those who had complex neurological auras; lactate levels increased considerably during photic stimulation in the latter group of patients but not in the former group⁴⁰. An important consideration is that stimulus-induced increases in cortical lactate levels are physiological⁴⁶ and are explained by the astrocyte-to-neuron lactate shuttle⁴⁷, the mechanism by which astrocytes provide energy to neurons when they become activated. Hence, the absence of a stimulus-induced increase in lactate levels in patients with migraine could be considered pathological, as it

might render them vulnerable to an energy crisis, particularly because neuronal activation is likely to have a higher energy demand in patients with migraine than in healthy individuals because their sensory information processing is abnormal⁴⁸. A study that combines quantification of lactate in the cortex and electrophysiological testing of brain-evoked responses would be able to clarify this relationship between function and metabolism.

Another useful method for assessing energy dynamics in the brain is ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET. This procedure involves measuring positron emission from the systemically administered, radiotracer-labelled glucose analogue ¹⁸F-FDG that is taken up by metabolically active tissue, although this technique does not allow glucose uptake by neurons to be distinguished from that by non-neuronal cells such as astrocytes. In a study published in 2018, the use of ¹⁸F-FDG-PET to compare glucose uptake at rest with that during interictal neuronal activation (visual evoked potentials) showed that glucose uptake during interictal neuronal activation exceeded glucose uptake in visual processing areas in 90% of patients with migraine without aura, but in only 15% of healthy controls⁴⁹. Given that at least 50% of glucose taken up in the brain goes to the astrocytes, where energy is stored in the CNS, this observation suggests that energy reserves are reduced in patients with migraine, thereby supporting our hypothesis that a mismatch between brain activation and glucose metabolism is a cornerstone of migraine pathophysiology. Further studies are needed to confirm this hypothesis.

Peripheral metabolic abnormalities

Several metabolic abnormalities in peripheral tissues have been described (Supplementary Table 2). These abnormalities include alterations in mitochondrial enzyme function, oxidative stress and glucose metabolism.

Mitochondrial enzyme function. Evidence that generalized metabolic dysfunction is a feature of migraine comes from studies showing that activity of mitochondrial enzymes, such as monoamine oxidase, succinate dehydrogenase, NADH dehydrogenase, cyclooxygenase and citrate synthetase, is reduced in the platelets of patients with migraine with or without aura^{50,51}. Interestingly, these biochemical changes are restricted to enzymes of the respiratory chain that are encoded by mitochondrial DNA (mtDNA), which is more vulnerable than nuclear DNA to oxidative stress and is, like migraine, chiefly maternally inherited. This observation suggests that both inherited and acquired mtDNA abnormalities play a role in migraine pathophysiology (see Genetic studies below). Elevated lactate and pyruvate levels in the plasma provide further evidence for mitochondrial abnormalities in migraine, although these abnormalities are mostly found in patients with migrainous stroke^{52,53}.

Oxidative and nitrosative stress and antioxidant capacity. As discussed above, all common migraine triggers are likely to increase levels of oxidative stress. This link is supported by studies in which markers of increased oxidative or nitrosative stress and/or decreased antioxidant

capacity have been directly examined^{54–67} (Supplementary Table 2). All studies of oxidative stress and/or antioxidant capacity in migraine have demonstrated that at least one marker is abnormal^{54–67}. Of all biomarkers examined, superoxide dismutase activity seems to be the only one that is consistently reduced in patients with migraine, including interictally⁶⁸. Inconsistent results for other markers could be due to differences in methodology, patient selection criteria (for example, low-frequency versus high-frequency migraine, or migraine with aura versus migraine without aura) and variations related to the migraine cycle — for example, nitrosative stress, oxidative stress⁶⁷ and nitric oxide⁶⁸ are elevated during migraine attacks, but not interictally.

Another possible marker of oxidative stress is heavy metals, levels of which can be increased in migraine⁶⁹. For example, free iron is highly pro-oxidant and accumulates in the brainstem of patients with migraine in proportion to disease duration⁷⁰.

Glucose metabolism. The human brain is highly dependent on energy sources from the circulation owing to limited glycogen stores, high energy needs and the exclusion of large, energy-dense molecules by the blood–brain barrier, so is particularly vulnerable to their shortages. Hypoglycaemia has been associated with migraine for almost a century^{1,71,72}, and a simple comparison between migraine-associated symptoms — premonitory symptoms in particular — and symptoms of hypoglycaemia⁷³ reveals several similarities. Shared symptoms include dizziness, pale skin, cold hands and feet, binge eating and/or sugar cravings, yawning, nausea, low blood pressure, shaking, cognitive difficulties, tiredness, fatigue, visual dysfunction and slurred speech. All of these symptoms can be caused by an insufficient supply of glucose to the brain and/or by release of catecholamines as a result of sympathetic activation⁷³.

The hypothalamus controls homeostasis and is activated early during the premonitory phase of triggered and spontaneous migraine attacks^{74–76}. This activation could represent the underlying physiological correlate of premonitory symptoms or could be part of an adaptive behavioural response⁷⁷ to a hypoglycaemic or energy-compromised brain that initiates increased yawning (to increase brain levels of oxygen), craving (to restore energy balance), fatigue, sickness and hypersensitivity (all energy-conserving behaviours) and other symptoms.

Circumstantial evidence from early experimental studies suggests that metabolic changes induced by fasting or administration of glucose or insulin can trigger migraine attacks. Although insulin-induced hypoglycaemia elicited an attack in only 2 of 20 patients during an observation time of 2 h (REF.⁷⁸), a 50 g glucose tolerance test (GTT) after 10 h of fasting initiated an attack within an 8-h test period in 6 of 10 patients with migraine whose attacks were associated with fasting or craving⁷⁹. Interestingly, the metabolic responses in patients who developed an attack differed substantially from those in patients who did not: in those who developed an attack, free fatty acid and ketone body levels increased substantially before headache onset and increased further

during the attack, despite similar food intake by all patients⁷⁹. No differences in glucose and glycerol levels were apparent between patients who developed attacks and those who did not. These findings suggest that, similar to attacks triggered by nitroglycerin⁸⁰, attacks triggered by metabolic stress develop after a latency of several hours, which is probably needed for activation of the trigeminovascular system.

Abnormal metabolic responses have been observed in several studies in which the GTT has been used (Supplementary Table 2). Comparison of responses to an intravenous GTT during and outside attacks in patients with migraine with aura⁸¹ showed that, during an attack, glucose tolerance was impaired, levels of free fatty acid, ketone bodies, glycerol and cortisol were increased, and the ratio of β -hydroxybutyrate to acetoacetate (both ketone bodies) was increased. However, insulin levels were decreased, which was considered to be an ictal stress response that was accompanied by increased lipolysis and ketogenesis. These increases in lipolysis and ketogenesis can also be interpreted as counter-regulatory responses to a cerebral energy deficit. Given that ketone bodies are an efficient alternative fuel for the brain when glucose availability is low, their elevation would be expected to restore brain energy homeostasis. However, the Western carbohydrate-laden diet means that in most people in Western countries the brain is not keto-adapted so does not have the enzymatic composition and transporters to make use of ketone bodies produced during an energy crisis.

Interictal impairments of glucose tolerance and insulin resistance have been found in various other studies of migraine^{82,83} (Supplementary Table 2). Insulin is the key regulator of glucose homeostasis, promoting absorption of glucose from the blood into predominantly fat and muscle cells with the help of insulin-sensitive glucose transporters (GLUTs), in particular GLUT4. Insulin also blocks carnitine transporters and, consequently, penetration of free fatty acids into cells. In the endothelial cells of the blood–brain barrier and in astrocytes and oligodendrocytes, insulin-independent GLUT1 is responsible for glucose transport under basal conditions. Multiple studies have provided evidence for an association between migraine and insulin resistance (reviewed elsewhere⁸⁴), although this association was not seen at all in one study⁸⁵ and only in women with migraine in another⁸⁶. One study has shown that β -cell function, and therefore insulin production, is normal in patients with migraine but that the degree of insulin resistance correlates with disease severity⁸⁷.

Rather than being directly involved in migraine pathogenesis, reduced insulin sensitivity could be part of a temporary adaptive response to ensure that the brain's energy needs are met. Such a 'glucose-sparing' effect is typically observed when glucose availability is low (for example, during fasting or carbohydrate restriction)^{88–90}. Some evidence suggests that diabetes mellitus protects against migraine^{91,92}, and this finding supports the hypothesis that insulin resistance is an adaptive response to migraine that increases energy supply to the brain rather than a causal factor. In the long-term, however, chronic insulin resistance might contribute to

metabolic diseases, such as the metabolic syndrome that is associated with migraine with aura⁹³ and with chronic migraine in women⁹⁴. Whether metabolic derangements are risk factors for or consequences of migraine, however, remains unclear. Findings in relation to BMI, for instance, have shown that this measure is associated with frequency of attacks but not with migraine prevalence⁹⁵.

Elevated interictal cortisol levels have been observed in episodic^{86,96} and chronic migraine⁹⁷, as well as during migraine attacks⁸¹, although a review of the evidence published in 2017 concluded that the results are mixed overall⁹⁸. High catecholamine levels have also been associated with early morning migraine⁹⁹. The observed increases in cortisol and catecholamines were not accompanied by the increase in glucose that would be expected, indicating that prior glucose levels were low but corrected by a hypoglycaemia-induced stress response. The body's physiological reaction to hypoglycaemia does involve secretion of cortisol, adrenaline and noradrenaline, which protect cells by increasing gluconeogenesis and glycogenolysis¹⁰⁰, stimulating protein catabolism and blocking the action of insulin. These mechanisms ensure that prolonged hypoglycaemia is avoided at all costs, even if this requires constant elevation of stress hormone levels. For this reason, and because a migraine attack can take several hours to develop, hypoglycaemia might not be detectable as a trigger¹⁰¹, unless blood glucose levels are monitored over a long time period.

The body's response to hypoglycaemia also involves the release of glucagon, the antagonist of insulin. In one study, increases in blood glucose levels in response to glucagon injection were less pronounced in patients with migraine than in healthy controls¹⁰². This reduced response to glucagon could lead to a deficiency in energy compensation that partly explains migraine attacks that are induced by fasting.

Investigation of other hormones involved in energy homeostasis, such as leptin and adipocytokines, in migraine has produced conflicting data¹⁰³. Low leptin levels were identified in patients with episodic migraine in one study¹⁰⁴ and could exacerbate a cellular energy deficit. However, another study showed that levels of leptin and adiponectin are increased in migraine, and these increases could increase inflammation^{103,105}.

Genetic studies

Genetic studies (Supplementary Table 3) directly and indirectly support the hypothesis that people with migraine have an increased vulnerability to oxidative stress, suboptimal mitochondrial functioning and/or altered metabolism. In contrast to nuclear DNA, mtDNA is particularly sensitive to reactive oxygen species (ROS)^{106,107}. However, whether accumulation of mtDNA damage as a result of oxidative stress over time has a role in migraine chronification and increased vascular risk remains to be determined. As pointed out in a previous review¹⁰⁸, epigenetic mechanisms, particularly mitochondrial methylation, could be a new avenue of investigation for exploring the underpinnings of mitochondrial dysfunction in migraine, as the mtDNA epigenetic status

of healthy individuals differs from that of individuals with complex neurological disorders.

Coding mitochondrial DNA

Migraine is approximately threefold more prevalent among women than men¹⁰⁹, and maternal transmission of the condition is more common than paternal transmission¹¹⁰, suggesting that either an X-linked form of inheritance is involved or that mtDNA has a role. The prevalence of migraine among people with mitochondrial disorders (29–35.5% of patients) is more than double that among the general population^{111,112} and migraine-like attacks in mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) are especially severe and prolonged¹¹³. Furthermore, the lifetime prevalence of migraine among healthy carriers of the Ala3243Gly mutation in coding mtDNA that causes MELAS is significantly higher than among the general population (58% versus 18%; $P < 0.001$)¹¹⁴. Among patients with the mitochondrial Ala8344Gly mutation in the *MTTK* gene, which causes myoclonic epilepsy with ragged red fibres (MERRF), 52% also have migraine¹¹⁵. These findings suggest a clinical association between a monogenic inherited disorder of mtDNA and susceptibility to migraine.

In contrast to these studies of migraine prevalence in mitochondrialopathies, most genetic studies in patients with migraine have not identified the classic mutations in coding mtDNA^{116–122} (Supplementary Table 3). However, such mutations have been associated with migrainous stroke episodes¹²³.

Non-coding mitochondrial DNA

Mitochondrial function could be impaired in migraine as a result of single nucleotide polymorphisms (SNPs) in the non-coding portion of mtDNA, which could influence mitochondrial metabolism. Specific mitochondrial haplogroups, defined by specific combinations of highly conserved polymorphisms in non-coding mtDNA, are associated with specific metabolic profiles. For example, haplogroup H confers an advantage in oxidative phosphorylation function^{124,125} and is associated with a poorer response to metabolism-stimulating treatment with riboflavin than that associated with other haplogroups¹²⁶ (Supplementary Table 3). A high prevalence of specific SNPs in non-coding mtDNA has been seen in patients with migraine and occipital stroke associated with haplogroup U¹²⁷, as well as in migraine without aura and in cyclic vomiting, a childhood equivalent of migraine¹²⁸. In a similar patient population, the prevalence of the common Cys16519Thr polymorphism in non-coding mtDNA was greater than in healthy controls, and the difference from controls was even greater for the combination of this polymorphism with the less common Gly3010Ala polymorphism¹²⁹. A high prevalence of these two polymorphisms has also been associated with chronic fatigue syndrome and depression¹³⁰. As is the case when studying nuclear DNA, large cohort studies of cases and controls are needed to detect small to moderate associations between mtDNA variants and a complex disease such as migraine; a lack of such studies might explain why some results have not been replicated¹¹⁸.

Nuclear-encoded mitochondrial proteins

Given that most proteins involved in mitochondrial function are encoded by nuclear DNA, the role of genes that encode nuclear-encoded mitochondrial proteins (NEMPs) in migraine susceptibility is a promising line of investigation, yet has received little attention¹³¹. A gene-centric association analysis of NEMPs within the genetically isolated Norfolk Island population revealed an association between migraine and three genes that encode NEMPs involved in phosphorylation, fatty acid metabolism and oxidative demethylation¹³². This finding provides further evidence for a link between mitochondrial function and migraine susceptibility.

Non-mitochondrial genes

Some evidence suggests that genetic predisposition can lead to reduced antioxidant capacity or increased oxidative stress in migraine. For example, a polymorphism (the rs4880 TT (Val/Val) genotype) in the gene that encodes superoxide dismutase 2 (SOD2), a crucial enzyme in the clearance of mitochondrial ROS, has been associated with unilateral cranial autonomic symptoms in patients with migraine with aura¹³³. In paediatric patients with migraine, the C–T genotype and C allele at position 16 of *SOD2* and the A–A genotype and A allele at position 21 of *CAT* (which encodes catalase) were more frequent among patients with migraine with or without aura than among healthy controls¹³⁴. Both enzymes act in concert to reduce ROS accumulation, and the polymorphisms reported in this study are thought to be associated with reduced transcriptional and/or enzyme activity, meaning people with migraine are more vulnerable to oxidative stress.

Other genetic variants that affect oxidative stress have also been identified in migraine. For example, migraine, particularly migraine with aura, has been associated with the Cys677Thr mutation in the gene that encodes methylenetetrahydrofolate reductase (MTHFR)^{135,136}. This mutation diminishes the enzyme's capacity to remethylate homocysteine to form methionine^{135,136}, and increased homocysteine levels favour vascular pathologies in humans and induce oxidative stress and reduce antioxidant capacity in rats¹³⁷, although in a Finnish population of patients with migraine with aura, the association between MTHFR and migraine could not be replicated¹³⁸. Next-generation nuclear DNA sequencing has also revealed an association between cyclic vomiting syndrome, which is considered to be a migraine equivalent, and variants in *RYR2*, which encodes a stress-induced calcium channel; this association could favour ROS-mediated mitochondrial damage¹³⁹.

Further genetic findings that indicate alterations in metabolism in migraine include associations of the condition with polymorphisms in insulin-related genes^{140–143}. Similarly, GLUT1 deficiency syndrome, a genetic condition of impaired glucose transport to the brain, has been linked to hemiplegic migraine and migraine with aura¹⁴⁴.

Genome-wide associated loci

Genome-wide association studies (GWAS) have identified 38 gene loci that are associated with migraine¹⁴⁵. In a study published in 2016, data from GWAS were integrated

with high-resolution spatial gene expression data from normal adult brains to identify specific brain regions and molecular pathways that might be involved in migraine pathophysiology¹⁴⁶. Genes associated with mitochondrial function were enriched in migraine-associated loci identified by GWAS, a finding that establishes a genetic link between mitochondrial function and migraine¹⁴⁶. Similarly, genes related to mitochondrial function are differentially expressed in adolescent patients with menstrual migraine compared with healthy controls¹⁴⁷.

Therapeutic studies

A large number of metabolic treatments have already been investigated in migraine (Supplementary Table 4) and most therapeutic agents used in migraine prevention can influence metabolism and mitochondrial functioning via several possible mechanisms of action (FIG. 1). The fact that some of these treatments are effective in migraine does not prove that migraine is primarily a disorder of brain energetics, but reinforces the idea that migraine is a multifactorial disorder in which the predominant pathophysiology can vary between patients. Nevertheless, the observed benefits do strongly suggest that these metabolic treatments act by improving brain energetics in some patients, although assessment of brain metabolism before and after treatment is needed to enable definitive conclusions to be drawn.

Acute treatment

Only two abortive migraine treatments have a proven link to energy metabolism. Corticosteroids that stimulate gluconeogenesis, are amongst the most effective drugs for abortion of prolonged migraine attacks and status migrainosus¹⁴⁸. Caffeine (>100 mg), on the other hand, has a beneficial (though small) analgesic effect, at least when used in conjunction with common analgesics¹⁴⁹. Besides its suppression of transient receptor potential A1 (TRPA1) activity¹⁵⁰, caffeine also stimulates cortisol secretion^{151,152} and, consequently, gluconeogenesis¹⁵³. In addition, caffeine increases levels of free fatty acids and decreases insulin responses¹⁵², effects that are similar to the metabolic changes that occur during a migraine attack⁸¹. This similarity supports the idea that the ictal metabolic abnormalities reflect counter-regulatory effects rather than pathogenic changes. Long-term use of excess caffeine, however, is associated with insulin resistance¹⁵⁴ and migraine chronification¹⁵⁵, whereas caffeine discontinuation is associated with higher efficacy of acute migraine treatment¹⁵⁶.

Prophylactic nutraceuticals

Several nutraceuticals¹⁵⁷ have been shown to be beneficial in migraine prevention¹⁵⁸, and most of these can be linked to energy metabolism and/or mitochondrial function¹⁵⁹. The level of evidence, however, is variable (TABLE 1), and not all of them are included in international guidelines for migraine prevention. They are almost devoid of adverse effects, in contrast to most classic preventive drugs.

Riboflavin. Riboflavin has an important role in the metabolism of carbohydrates, proteins and fats and in the recycling of oxidized glutathione, and is a precursor

of flavin nucleotides, which are necessary for activity of flavoenzymes that participate in the electron transport chain^{160,161}. Furthermore, riboflavin has neuroprotective properties, as it alleviates oxidative stress, mitochondrial dysfunction, neuroinflammation and glutamate excitotoxicity^{161,162}. Several studies have demonstrated the efficacy of high-dose (200–400 mg daily) riboflavin for migraine prevention in adults and children^{163–166}, but not of a low dose (50 mg daily)¹⁶⁷. In a single-blind, comparative, parallel group study ($n = 90$), 400 mg riboflavin daily was as effective as 500 mg sodium valproate daily for migraine prevention¹⁶⁸. A systematic review published in 2017 showed that high-dose riboflavin (400 mg daily) is well tolerated, inexpensive and effectively reduces migraine headache frequency¹⁶⁹. In one study, mtDNA haplogroup influenced the therapeutic response to riboflavin¹²⁶: most patients who responded had non-H haplogroups, whereas most patients who did not respond had haplogroup H with the best oxidative phosphorylation function.

Coenzyme Q10. Coenzyme Q10 (CoQ10; known as ubiquinone in its oxidized form and ubiquinol in its reduced form) is an essential cofactor of the electron transport chain with strong antioxidant properties^{170,171}. In four placebo-controlled double-blind trials and two open-label studies, CoQ10 treatment (400 mg capsules or 300 mg liquid suspension daily) reduced migraine frequency in adults^{172–175}. In another randomized controlled trial in children and adolescents with migraine, a 100 mg dose of CoQ10 was not superior to placebo¹⁷⁶, but did have beneficial preventive effects in paediatric patients with migraine and low CoQ10 blood levels in an open-label study¹⁷⁷.

Alpha-lipoic acid. Alpha-lipoic acid (ALA; also known as thioctic acid) is a water-soluble and fat-soluble antioxidant that can reduce oxidative stress directly by removing reactive species, or indirectly by chelating transition metal ions^{178,179}. Results of a randomized placebo-controlled trial of 600 mg ALA daily for 3 months indicated a trend towards reduction of attack frequency, number of headache days and headache severity¹⁸⁰. In an open-label trial of ALA in patients with migraine and insulin resistance, a 50% response was seen in 69% of participants¹⁸¹. In another study, combined treatment with topiramate and ALA for 1 month was more effective for migraine prevention than either drug alone¹⁸².

Other B vitamins. In double-blind randomized placebo-controlled trials, a 2 mg daily dose of folic acid (vitamin B₉) combined with 25 mg pyridoxine (vitamin B₆) and 400 µg cobalamin (vitamin B₁₂) reduced migraine-related disability and the frequency and severity of migraine with aura^{183,184}. In this trial, the greatest clinical effects and reductions in homocysteine levels were seen in carriers of the C allele of the *MTHFR* Cys677Thr variant and of the A allele of the Ala66Gly variant of the gene that encodes methionine synthase reductase¹⁸⁴. The same vitamin B combination with a 1 mg dose of folic acid was not superior to placebo¹⁸⁵. According to a systematic

review¹⁸⁶ in which nine open studies were identified, niacin (nicotinic acid or vitamin B₃) might also have a prophylactic effect in migraine, but randomized controlled trials are lacking.

Magnesium. Magnesium acts as a cofactor for as many as 300 enzymes and has a vital role in energy metabolism. Blood levels of magnesium are reduced in migraine^{31,39,187} and a meta-analysis of randomized controlled trials

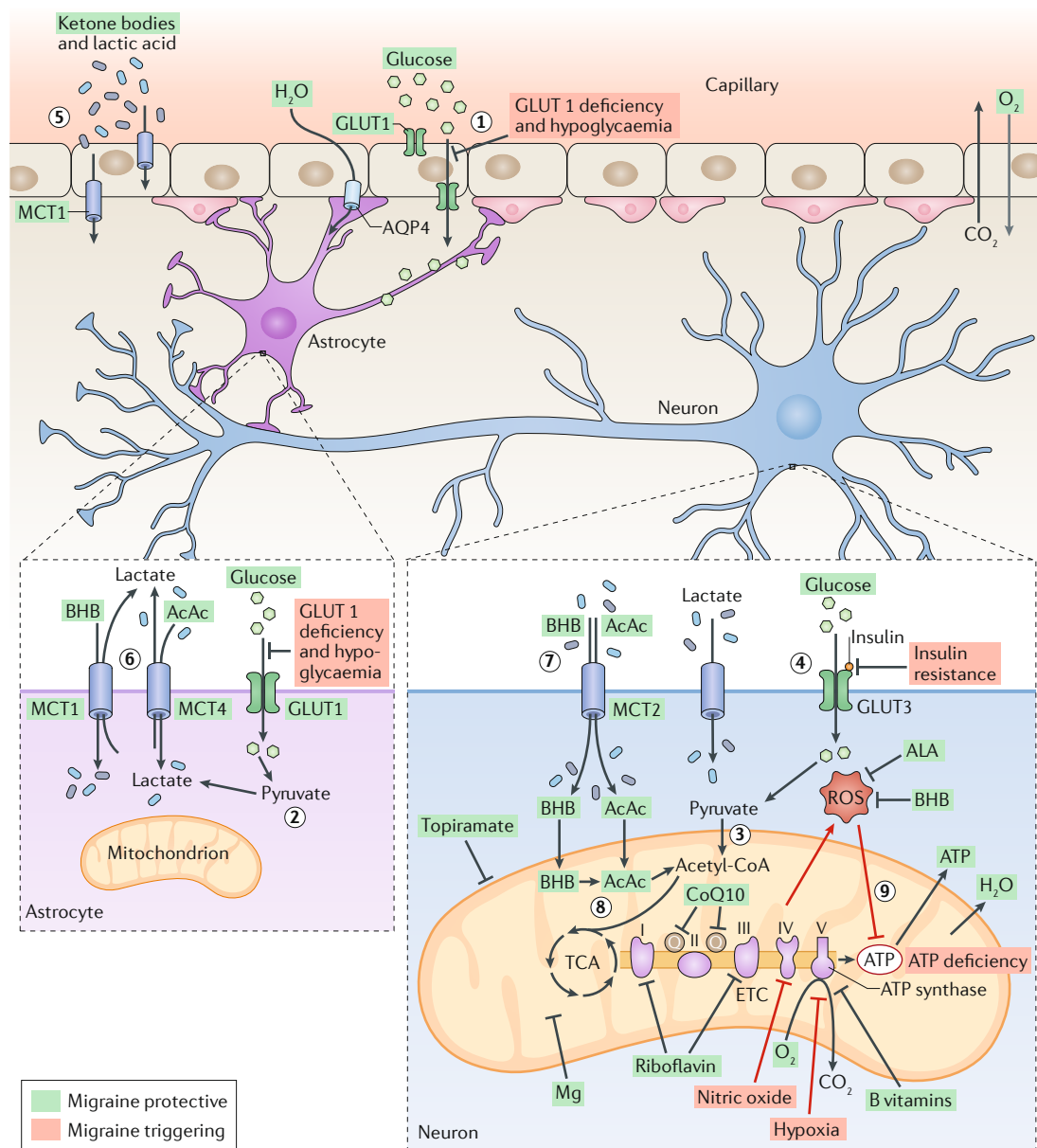


Fig. 1 | **Cerebral metabolomics that might be involved in migraine pathogenesis and therapeutic targets.** Glucose crosses the blood–brain barrier via insulin-independent glucose transporter 1 (GLUT1) (step 1), deficiency of which can contribute to migraine, as can insufficient glucose, oxygen, water or minerals. GLUT1 is expressed by capillary endothelial cells and astrocytes. Non-oxidative glucose metabolism produces pyruvate (step 2), which is converted to lactate and shuttled to neurons through monocarboxylate transporters (MCTs; mainly MCT1 and MCT4 in astrocytes and MCT2 in neurons). In neurons, this lactate can be used as an energy substrate following its conversion to pyruvate, which can be converted into acetyl-coenzyme A (Acetyl-CoA) and fed in turn into the tricarboxylic acid cycle (TCA) (step 3). Neurons can also take up glucose via neuronal GLUT3 (step 4), which is insulin-dependent and can be influenced by insulin resistance. Ketone bodies (β -hydroxybutyrate (BHB) and acetoacetate (AcAc) cross the blood–brain barrier via MCT1 transporters (step 5), and penetrate astrocytes via MCT1 or MCT4 (step 6) and neurons via MCT2 (step 7). BHB provides an alternative to glucose as a substrate for oxidative phosphorylation; it is converted to AcAc and, subsequently, acetyl-CoA, which enters the TCA to produce ATP (step 8). BHB also has antioxidant properties and, compared with glucose, its conversion to ATP produces fewer reactive oxygen species (ROS) per oxygen molecule consumed. Increased ROS, nitric oxide, lack of energy substrates or lack of necessary co-enzymes inhibit mitochondrial function and reduce ATP levels (step 9). Antioxidants and co-enzymes, such as riboflavin, other B vitamins, coenzyme Q10 (CoQ10), magnesium, α -lipoic acid (ALA), L-carnitine and the anticonvulsant topiramate, support mitochondrial function and protect against migraine. AQP4, aquaporin 4; ETC, electron transport chain.

Table 1 | Evidence levels for treatment of migraine with nutraceuticals and steroids and classic preventive drugs

Treatment	Recommendation and evidence level		
	European Headache Federation ²⁶⁴	American Academy of Neurology and American Headache Society ^{265–268}	Canadian Headache Society ²⁶⁹
Nutraceuticals and steroids			
Riboflavin	Drug of third choice (level C, possibly effective)	Should be considered (level B, probably effective)	Strong recommendation, low-quality evidence
Coenzyme Q10	Drug of third choice (level C, possibly effective)	May be considered (level C, possibly effective)	Strong recommendation, low-quality evidence
Magnesium	Drug of third choice (level C, possibly effective)	Should be considered (level B, probably effective)	Strong recommendation, low-quality evidence
Caffeine	Level A (effective) (aspirin + paracetamol + caffeine)	Level A (aspirin + paracetamol + caffeine)	Not specified
Steroids	Expert consensus but not evidence-based (for status migrainosus)	Level C, possibly effective	Limited evidence; limit to short courses
Classic preventive drugs			
Antiepileptic drugs (topiramate, valproate)	Drug of first choice (level A, effective)	Should be offered (level A, established efficacy)	Strong recommendation, high-quality evidence for topiramate; weak recommendation for valproate
Beta-blockers (metoprolol, propranolol)	Drug of first choice (level A, effective)	Should be offered (level A, established efficacy)	Strong recommendation, high-quality evidence
Flunarizine	Drug of first choice (level A, effective)	Not available	Weak recommendation, high-quality evidence
Amitriptyline	Drug of second choice (level B, probably effective)	Should be considered (level B, probably effective)	Strong recommendation, high-quality evidence
Gabapentin	Drug of third choice (level C, possibly effective)	Level U, inadequate or conflicting data to support or refute medication use	Strong recommendation, moderate-quality evidence

provides evidence that intravenous magnesium has a modest beneficial effect on acute migraine attacks and that oral magnesium reduces attack frequency and intensity¹⁸⁸. A randomized controlled trial published in 2019 showed that 500 mg magnesium oxide daily had a similar preventive effect in migraine as 400 mg sodium valproate daily¹⁸⁹.

L-Carnitine. L-Carnitine transports fatty acids into the mitochondria for lipid oxidation and energy production. Trials of L-carnitine for migraine prevention have been conducted, but results are conflicting. In a large (133 patients) but single-blinded study the effects of daily administration of 500 mg L-carnitine, 500 mg magnesium oxide or both for 3 months were compared with each other and with routine treatment¹⁹⁰. Migraine attacks and days decreased significantly in all patient groups, although this decrease was greater among patients who received magnesium oxide alone¹⁹⁰. By contrast, in a randomized crossover trial with successive 3-month treatment periods separated by a 4-week washout, the effect of 3 g acetyl L-carnitine daily was not significantly different from that of placebo¹⁹¹. In a randomized controlled trial published in 2019, a combination of 500 mg L-carnitine and 30 mg CoQ10 daily was significantly more effective than placebo in reducing headache severity, frequency and duration during an 8-week treatment period¹⁷⁵.

Ketogenic diet and exercise

A ketogenic diet mimics, to some extent, the state of fasting and promotes hepatic production of an alternative to glucose as an energy substrate for the brain.

Ketone body transport is not GLUT1-dependent and ketosis has a variety of other effects that are potentially beneficial in migraine pathophysiology, including: increased mitochondrial biogenesis; increased antioxidant capacity; upregulation of GLUT1 and ketone body transporters; increased GABA but inhibition of glutamate transport and, therefore, reduced excitatory synaptic transmission pain and inflammation (reviewed in detail elsewhere^{192,193}). Ketone bodies can also stabilize neuronal excitability by inhibiting ATP-sensitive potassium channels (K_{ATP}) that might play a crucial role in migraine attack generation¹⁹⁴ (see below). Several case studies have shown that ketosis can protect against migraine^{195–200}. In addition, in a 1-month observational study of the ketone diet in 96 patients with migraine as part of a weight-loss programme, attack frequency, attack severity and acute medication use were reduced by up to 80%¹⁹⁹. Similarly, in a study of 18 patients with episodic migraine, the same intervention reduced migraine days by 62.5%, and this reduction was accompanied by normalization of interictal deficits in habituation of visual evoked responses²⁰⁰. In a double-blind study published in 2019, a very low-calorie ketogenic diet and a very low-calorie non-ketogenic diet were compared in a 2-month crossover study in a population of 35 overweight individuals with episodic migraine²⁰¹. The ketogenic diet was superior to the non-ketogenic diet for reducing monthly migraine days, and the 50% response rate was much higher (74.3% of patients on the ketogenic diet and 8.6% of patients on the non-ketogenic diet)²⁰¹. The potential for supplementation with the ketone body β -hydroxybutyrate without a strict dietary

change to prevent migraine is currently being examined in a randomized controlled trial²⁰².

Aerobic exercise is often recommended in migraine management, and a randomized study showed that regular aerobic exercise is associated with a decrease in migraine frequency comparable to that achieved with topiramate, a prophylactic drug with level A evidence for efficacy²⁰³. The metabolic effects of aerobic exercise mimic those of ketosis and include upregulation of multiple proteins that are involved in brain energy metabolism, such as enzymes involved in glucose catabolism, ATP synthesis and hydrolysis, and glutamate turnover²⁰⁴. Furthermore, in mice, exercise training increases the number of mitochondria not only in muscle but also in the brain²⁰⁵.

Prophylactic pharmaceuticals

The level of evidence for the classic preventive migraine drugs is higher overall than that for nutraceuticals (TABLE 1). The precise mechanisms of action of most drugs used in migraine prophylaxis are not known, but many downregulate neuronal reactivity²⁰⁶ and might, therefore, reduce the energy demands of the brain. Certain prophylactic agents can also have direct metabolic effects. For instance, topiramate protects against oxidative stress, inflammation²⁰⁷ and mitochondrial membrane depolarization²⁰⁸, prolongs mitochondrial survival²⁰⁸, slightly increases lipolysis in children²⁰⁹ and increases the sensitivity of adipocytes to insulin in female rats²¹⁰.

Other drugs used for prevention of migraine treatment have clear metabolic effects. Amitriptyline also reduces markers of oxidative stress and increases antioxidant capacity⁶⁵. Valproate attenuates nitroglycerin-induced trigemino-vascular activation by preserving mitochondrial function in a rat model of migraine²¹¹ and increases mitochondrial biogenesis²¹². Amitriptyline and flunarizine increase serum levels of leptin and insulin and increase BMI after 12 weeks of therapy in patients with migraine²¹³. Gabapentin, atenolol, verapamil, valproate, pizotifen and amitriptyline all increase body weight in a substantial number of patients after 6 months of use²¹⁴. Beta-blockers decrease the whole-body metabolic rate and body fat²¹⁵, thereby theoretically leaving more energy for the brain. In addition, beta-blockers reduce rebound headache that often follows stress in patients with migraine²¹⁶, and this effect could result from regulation of noradrenaline-mediated consumption of energy reserves¹⁰⁰ during stress. Together, the findings suggest that the double action of prophylactic drugs — on neurons and metabolism — favours the equilibrium between metabolic needs and available energy that is necessary to maintain cerebral homeostasis.

Metabolism and migraine pathophysiology

Above, we highlight the clinical evidence that suggests a role for energy metabolism and mitochondrial function in migraine pathophysiology. In this section, we examine how such abnormalities could lead to a migraine attack. We consider these changes in relation to three hallmarks of the pathophysiological migraine cascade: hypothalamic and brainstem activation (which is thought to initiate and modulate the attack),

CSD (which is responsible for the aura) and trigemino-vascular activation (which causes the headache and associated symptoms). For this purpose, we mainly draw upon experimental data obtained in rodents.

Hypothalamic and brainstem activation

The hypothalamus is activated early in migraine attack initiation, during the premonitory phase^{75,76}. What activates the hypothalamus is not known; possibilities include an intrinsic biorhythm, an environmental trigger or stimulation from a CNS centre that is highly connected to the hypothalamus, such as the amygdala⁷⁹. The hypothalamus can sense a metabolic disequilibrium in the brain, owing to the presence of chemosensitive neurons, and in the periphery, partly because some hypothalamic areas lack a fully functional blood–brain barrier. Chemosensitive neurons, notably those that detect oxygen, form a network that extends from the thalamus to the brainstem²¹⁷. Therefore, we hypothesize that metabolic changes in the brain and/or in the blood might activate these neuronal systems and ignite a migraine attack.

Involvement of the amygdala in activation of the hypothalamus in migraine, as suggested above, could provide a link between mitochondrial function and the sexual dimorphism of migraine. In the human and mouse basolateral amygdala, mitochondrion-related biological pathways are the most strongly associated with sexual dimorphism and, in females, genes related to mitochondrial function are downregulated whereas genes related to regulation of the circadian rhythm are upregulated²¹⁸.

Cortical spreading depression

CSD is the pathophysiological cause of migraine aura. Susceptibility to CSD is strongly modulated by metabolic factors. For example, cerebral glucose availability modulates induced CSD^{219,220}. Hypoglycaemia prolongs CSD²¹⁹ and inhibition of cerebral glycogen reduces the threshold for CSD *in vivo*²²⁰. Hyperglycaemia protects against induction of CSD²¹⁹. In rats, supply of an energy substrate other than glucose via short-term and long-term treatment with a medium-chain triglyceride-enriched ketogenic diet has a similar protective effect against CSD²²¹.

Hypoxia negatively influences energy metabolism and can trigger CSD^{222,223}. Its effects in mice and rats include inhibition of astroglial mitochondrial respiration, leading to mitochondrial depolarization, production of free radicals, lipid peroxidation and release of calcium ions from intracellular stores²²⁴. When hypoxia is preceded by pharmacological mitochondrial inhibition, hypoxia-induced CSD in rat hippocampal slices is greatly facilitated²²². This observation suggests a mechanism by which genetic or acquired mitochondrial dysfunction could exacerbate the impact of a metabolic stressor.

Trigemino-vascular system

In experimental animals, CSD can activate the trigemino-vascular system²²⁵. One mechanism of this process is the opening of pannexin 1 large-pore channels in neurons,

which are associated with the ligand-gated ion channels P2X7 (REF.²²⁶), leading to downstream activation of the inflammatory pathway in astrocytes and — via cytokines and prostanoids — to sensitization of meningeal nociceptors²²⁷ (FIG. 2). In addition, CSD and subsequent restoration of ion homeostasis have an extremely high energy demand²²⁸. Moreover, in mice, CSD causes tissue hypoxia^{223,229} and increases expression of mitochondrial uncoupling proteins, which decreases ATP synthesis and increases thermogenesis²³⁰. These changes could create a vicious circle in which the metabolic disequilibrium that favours or triggers CSD, and hence trigeminovascular system activation, is perpetuated. CSD also induces oxidative stress in the trigeminal nociceptive system²³¹.

For example, hydrogen peroxide production can activate TRPA1 and acid-sensing ion channels (ASICs), thereby promoting release of calcitonin gene-related peptide (CGRP) from meningeal nociceptors, which is known to be pivotal in mediating the headache of the migraine attack^{232–234} (FIG. 2).

Clinically, most patients with migraine never experience an aura. Therefore, triggers of the trigeminovascular system other than CSD must exist. TRP channels, which are expressed in meningeal nociceptive nerve terminals, might contribute to generation of a migraine attack²³⁵, as they can be directly activated by various exogenous and endogenous agents that are associated with migraine, and their activation induces the release

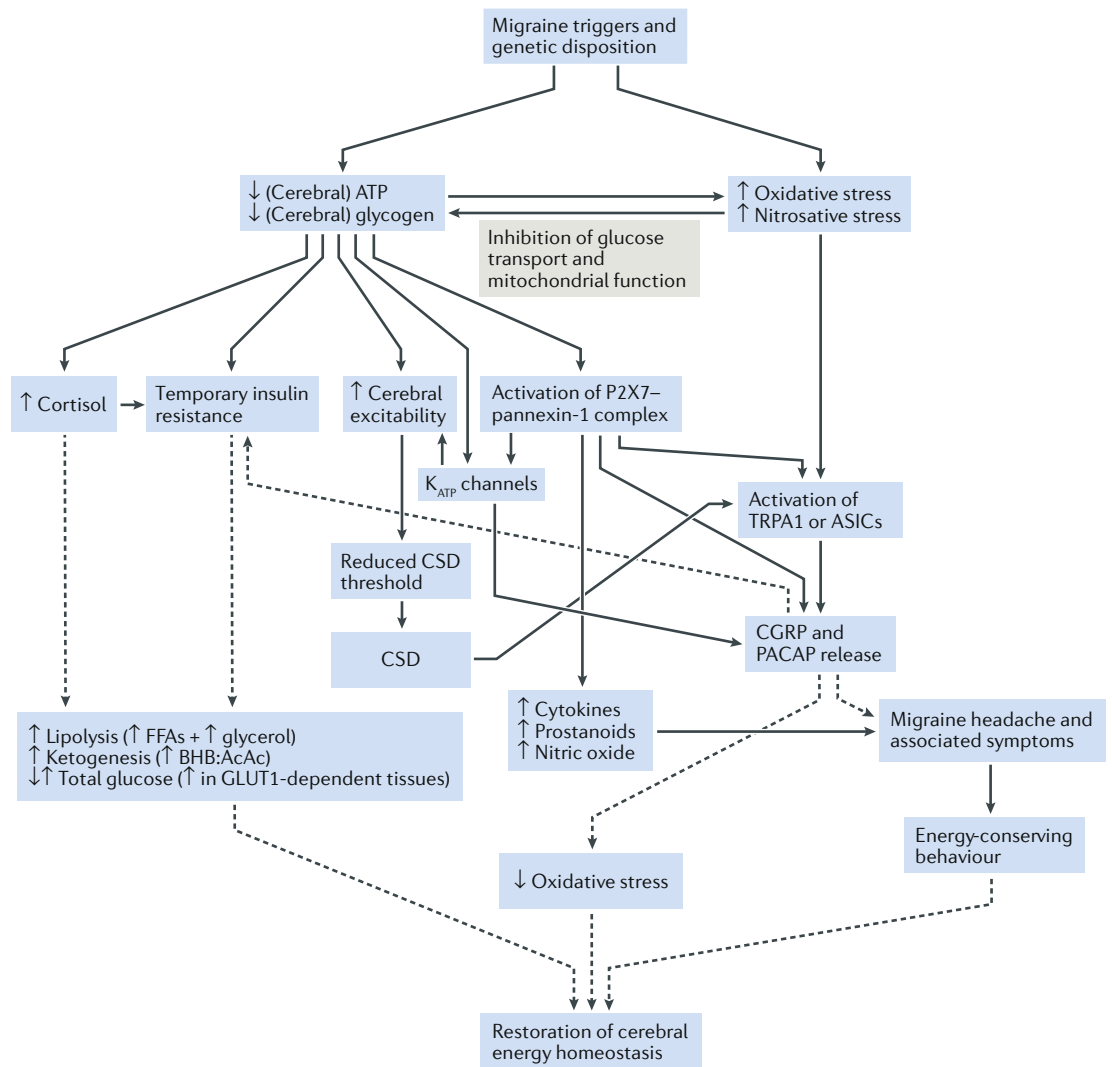


Fig. 2 | **Metabolic face of migraine attack generation and resolution.** In genetically predisposed individuals, migraine triggers can increase oxidative and nitrosative stress and/or reduce cerebral ATP and glycogen levels. These processes ignite a cascade of events that assists restoration of cerebral energy homeostasis but also favours cortical spreading depression (CSD), trigeminovascular activation via activation of transient receptor potential channel A1 (TRPA1), acid-sensing ion channels (ASICs) and the pannexin-1–P2X7 pore complex, which leads to release of calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating peptide (PACAP) and opening of ATP-sensitive potassium channels (K_{ATP}). Together, this molecular cascade can produce the symptoms of migraine. In this way, the factors that are known to participate in generation of migraine attacks might also be involved in its resolution. Dashed lines indicate mechanisms by which metabolic homeostasis may be restored. AcAc, acetoacetate; BHB, β-hydroxybutyrate; FFA, free fatty acid; GLUT1, glucose transporter 1.

of CGRP²³⁴. TRP channels are also inhibited or desensitized by abortive migraine drugs²³⁵. These channels can also sense reactive species indirectly through second messengers or directly via oxidative modification of cysteine residues²³⁶, and the subchannel TRPA1 is strongly activated by oxidative, nitrosative and electrophilic stress^{235,236}. In combination, these observations suggest a mechanism by which known migraine trigger factors that increase oxidative stress could lead to migraine pain.

Cerebral energy deficiency caused by inhibition of glycogen use in the brain was recently shown to cause CSD-independent opening of pannexin 1 large pore channels in neurons²²⁰, which leads to activation of meningeal nociceptors²²⁷. Furthermore, a study published in 2017 showed that metabolic changes can directly modify activity of central trigeminovascular nociceptors — changes in blood glucose levels after injection of insulin, glucagon or leptin were associated with changes in baseline firing of dural responsive nociceptive neurons in the spinal trigeminal nucleus²³⁷. Recent evidence indicates that K_{ATP} channels link metabolic stress with activation of trigeminovascular nociceptors. These channels are located in cranial arteries and the trigeminal ganglion and are modulated by the intracellular ratio of ATP to ADP and levels of cAMP and cGMP. In a study published in 2019, intravenous infusion of the K_{ATP} channel opener levromakalim induced migraine headache in 16 of 16 patients with migraine, whereas placebo treatment did so in only 1 of these 16 patients¹⁹⁴ (BOX 1). The role of K_{ATP} channels in the metabolic aspects of migraine pathophysiology might not, however, be restricted to cranial vessels and the

trigeminovascular system. In slice preparations of rodent cerebrum, ketone bodies²³⁸ or a decrease in extracellular glucose levels²³⁹ can open K_{ATP} channels and decrease the excitability of central neurons. This process is thought to be mediated by pannexin 1 hemichannel-mediated ATP release and activation of adenosine receptors²³⁹ (FIG. 2).

High nitric oxide concentrations stimulate CGRP release and activate the trigeminovascular system, and nitric oxide can also modulate mitochondrial activity via various mechanisms²⁴⁰. The mitochondrial effects of nitric oxide could, therefore, explain the headache experienced by patients with migraine upon administration of nitric oxide donors²⁴¹. Examples of the mitochondrial effects of nitric oxide in animals include inhibition of the mitochondrial respiratory chain in cultured astrocytes²⁴². By contrast, use of ¹H-MRS in rats has shown that cortical lactate increases as early as 10 min after intraperitoneal injection of nitroglycerin, suggesting that the widely used nitroglycerin model of migraine involves metabolic, in addition to vascular, changes²⁴³.

Finally, limited evidence from animal experiments suggests that the migraine attack itself can affect mitochondrial energy metabolism in the trigeminal ganglion. In a rat model of chronic migraine in which an inflammatory soup is applied to the dura mater, abnormal mitochondrial dynamics and impaired mitochondrial biogenesis were observed in the trigeminal ganglion^{244,245}.

Metabolic functions of CGRP and PACAP

CGRP is known to play a role in spontaneous and triggered migraine headache^{232,233}. Blood levels of CGRP are elevated during attacks²⁴⁶, CGRP triggers attacks in patients with migraine²⁴⁷, and blocking the action of CGRP transiently (with CGRP antagonists) or durably (with monoclonal antibodies) aborts attacks or reduces attack frequency, respectively²⁴⁸. As a consequence, CGRP is overwhelmingly considered to be the ‘villain’ in migraine pathophysiology. However, in CGRP-triggered migraine attacks, only 28% of patients with migraine with aura experience an aura²⁴⁹, and CGRP does not elicit premonitory symptoms¹¹⁴. These observations suggest that CGRP does not trigger a complete migraine attack, but is the physiological correlate of the headache pain and the headache-related behaviour.

Some evidence suggests that CGRP release is a response to oxidative stress or cerebral energy disequilibrium and might be part of an adaptive response, thereby challenging the perception that CGRP is the pathophysiological trigger of migraine. For example, CGRP has antioxidant and anti-inflammatory actions^{250–253}, supporting the hypothesis that its release mediates an adaptive response to oxidative stress and/or energy deficiency. The idea that CGRP increases endogenous energy availability for the brain is also supported by rodent studies in which CGRP inhibited insulin-stimulated glucose transport²⁵⁴, decreased tolerance to glucose in the GTT without altering plasma insulin levels²⁵⁵, inhibited muscle glycogen synthesis and caused insulin resistance upon activation of skeletal muscle sensory nerves²⁵⁶. In addition, intravenous injections of CGRP in the rat increased plasma glucose concentrations²⁵⁵, an effect that could help to restore energy homeostasis.

Box 1 | The link between altered bioenergetics and trigeminovascular activation

Numerous studies have provided evidence for alterations in energy metabolism at the cortical level in patients with migraine (discussed in this Review). Similarly, vast research has shown that patients with migraine exhibit increased cerebral reactivity to sensory stimuli in almost every sensory modality²⁶². Together, this evidence suggests that in patients with migraine, the brain not only has reduced energy supplies but also has increased energy needs. This possibility has been assessed in one study in which the ratio between the magnitude of visually evoked cortical responses and cerebral glucose uptake in the visual cortex in patients with migraine was compared with that in healthy controls⁴⁹. The ratio was almost threefold higher in patients with migraine, suggesting that their metabolic reserves are barely sufficient to meet high energy needs, a scenario that renders them vulnerable to disruption of cortical homeostasis. However, one link seems to be missing: how can alterations in cortical homeostasis trigger migraine headache?

The most plausible answer involves pannexin channels. These megachannels in neurons open under conditions of distress, acting as sensors of cortical homeostasis, and form a pore complex with the ligand-gated ion channel P2X7 (REF.²²⁵). Their opening triggers a cascade of biochemical events involving molecules of the alarmin family. The final result of this cascade is trigeminovascular activation and calcitonin gene-related peptide release in the extradural space²²⁷, which leads to headache. Reduction of metabolic substrates available for neurons in the cortex directly activates pannexin 1 channels, which could explain the pathogenesis of migraine without aura²²⁰. Similarly, metabolic distress lowers the threshold for cortical spreading depression²²⁰, which can aggravate metabolic alterations and cause migraine with aura. Alternatively, diencephalic and brainstem chemosensitive neurons²¹⁷ could sense metabolic changes and sensitize the trigeminovascular system, either directly or via descending pathways. Therefore, the downstream molecular events activated by pannexin channel opening could be the missing link between energy disequilibrium at the cortical level and the migraine attack.

Box 2 | Suggested approach to improving mitochondrial function and energy metabolism in migraine

1. **Individualize supplementation of micronutrients.** To ensure that all micronutrients needed for mitochondrial function are available, laboratory tests can be used to individualize supplementation with minerals, hydrophobic and lipophilic vitamins and trace minerals that are deficient¹⁷⁷.
2. **Reduce oxidative stress and increase antioxidants.** Measurement of oxidative and/or nitrosative stress levels and antioxidant status in individuals could detect a potential mismatch between oxidative stress levels and antioxidant capacity and enable therapeutic adjustments to be made, although studies are needed to prove that such an approach improves migraine management. Strategies to reduce oxidative stress could include elimination or reduction of processed food, food with a high glycaemic index and alcohol, use of green or blue light filtering glasses²⁶³, interruption of hormone-based contraception, lifestyle changes and addition of antioxidants, such as polyphenols, coenzyme Q10, α -lipoic acid or β -hydroxybutyrate mineral salts, to the diet.
3. **Stabilize blood glucose levels.** An oral glucose tolerance test should be undertaken in patients with migraine and clinical features that suggest glucose intolerance or a family history of glucose intolerance. Patients with reactive hyperinsulinaemia and reactive hypoglycaemia are likely to benefit from stabilization of blood glucose levels, which can often be achieved with dietary adjustments.
4. **Provide an alternative energy substrate for the brain.** For patients with compromised energy metabolism, an alternative source of fuel for the brain, in addition to glucose and lactate, might be beneficial. This source can be generated with a ketogenic diet^{196,199,200} and/or use of exogenous ketogenic substances, such as medium-chain triglycerides or exogenous ketone body salts. Further placebo-controlled trials are needed to validate ketogenic therapies in migraine.

Moreover, CGRP is widely distributed in the brainstem and diencephalon, including a network that includes hypothalamic nuclei, the locus coeruleus, the area postrema and the nucleus tractus solitarius, and is involved in energy homeostasis²⁵⁷. Several of these nuclei do not have a functional blood–brain barrier and are therefore accessible to CGRP therapies that are administered systemically.

Pituitary adenylate cyclase-activating peptide (PACAP) is also released during migraine attacks and induces migraine-like headache when administered to patients with migraine. Consequently, PACAP is another promising molecular target for migraine treatment. PACAP is present in the trigemino-parasympathetic visceromotoric circuit, where it contributes to headache pain and associated autonomic symptoms, but it also has a role in the hypothalamus, where it modulates circadian rhythms and food anticipatory behaviour (reviewed elsewhere²⁵⁷). In rats, PACAP stimulated glucose production via sympathetic hepatic innervation, indicating the PACAP release could also be an adaptive response to restore energy homeostasis²⁵⁸.

Summary

Cerebral energy deficiency and/or increased oxidative stress decrease the threshold for CSD and activate TRP channels and ASICs, thereby stimulating CGRP and PACAP release. These peptides are pivotal in eliciting the migraine headache and associated symptoms, but we hypothesize that they also induce an antioxidant response and various metabolic changes that, together with energy-conserving behavioural changes, decrease oxidative stress levels and increase glucose and ketone body availability for the brain to help restore energy homeostasis (FIG. 2).

Future research

Studies that combine assessments of brain and mitochondrial metabolism with those of sensory processing are necessary to disentangle the disequilibrium between metabolic reserve and brain activity in migraine. In these studies, age-related adaptive increases in glucose uptake

in the brainstem and in visual areas must be taken into account²⁵⁹. Similarly, studies to examine the role of specific alterations in mitochondrial function and/or energy metabolism in migraine subgroups are needed. More data are also needed to determine whether therapeutic interventions that improve mitochondrial function lead to changes in sensory processing and cerebral energy availability that correlate with treatment responses.

Despite the need for more data, the findings described in this Review already have several potential therapeutic implications. We suggest a four-step approach to improve mitochondrial function and energy metabolism in migraine (BOX 2).

Conclusion

The evidence discussed in this Review indicates that, from a metabolic perspective, migraine is a conserved adaptive response⁷⁷ that helps to reduce harmful oxidative stress levels and restore brain energy homeostasis, a concept that was proposed by Edward Liveing as early as 1873 (REF.²⁶⁰). Given the high prevalence of migraine and the fact that it is associated with common gene polymorphisms, a migraine-prone nervous system might be, or at least might have been, associated with reproductive or survival advantages^{77,261} from an evolutionary perspective. Over time, possibly owing to changes in nutrition, our environment might have become inadequate or suboptimal for the conserved adaptive genetic response patterns. Alternatively, migraine could be the price the human species has to pay for having a developed, high-performing and energy-consuming brain.

Commonly reported migraine trigger factors can be linked to energy disequilibrium and oxidative stress, and numerous biochemical and genetic studies point towards a variety of different metabolic abnormalities in migraine. Most preventive migraine treatments can improve metabolic functioning in addition to their effects on brain responsiveness and excitability. Disruption of cerebral metabolic homeostasis is a plausible trigger of the trigeminovascular system and its limbic connections via induction of CSD, stimulation of chemosensitive brainstem neurons or direct activation of TRP channels

and/or ASICs that stimulate CGRP and PACAP release by meningeal nociceptive fibres, or modulation of K_{ATP} channels, which might be the final common pathway in activation of trigeminal nociceptors. These neuropeptide pathways are the likely culprits for the migraine headache and associated symptoms, but they could also participate in an antioxidant response and various metabolic changes that help restore energy homeostasis.

Looking at the metabolic face of migraine has several potential therapeutic implications (BOX 2). Some progress

has been made in developing anti-migraine therapies that target metabolism, and novel strategies, such as ketone body supplementation, are being explored. More research is needed on different metabolic subtypes, the association between metabolic phenotypes and genotypes and treatment responses to metabolic agents, interactions between the sensory system and metabolism, and metabolic nutraceutical treatments for migraine.

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1. Gray, P. A. & Burtner, H. I. Hypoglycemic headache. *Endocrinology* **19**, 549–560 (1935).
2. Amery, W. K. Brain hypoxia: the turning-point in the genesis of the migraine attack? *Cephalalgia* **2**, 83–109 (1982).
This article is the first to have drawn attention to the possible role of brain hypoxia in migraine pathogenesis.
3. Schoenen, J., Ambrosini, A., Sándor, P. S. & Maertens de Noordhout, A. Evoked potentials and transcranial magnetic stimulation in migraine: published data and viewpoint on their pathophysiological significance. *Clin. Neurophysiol.* **114**, 955–972 (2003).
4. Schoenen, J. Pathogenesis of migraine: the biobehavioural and hypoxia theories reconciled. *Acta Neurol. Belg.* **94**, 79–86 (1994).
This article presents the hypothesis that the conjunction of abnormal energy metabolism and information processing in the brain may be able to generate migraine attacks.
5. Pavlovic, J. M., Buse, D. C., Sollars, C. M., Haut, S. & Lipton, R. B. Trigger factors and premonitory features of migraine attacks: summary of studies. *Headache* **54**, 1670–1679 (2014).
6. Peroutka, S. J. What turns on a migraine? A systematic review of migraine precipitating factors. *Curr. Pain Headache Rep.* **18**, 454 (2014).
7. Kelman, L. The triggers or precipitants of the acute migraine attack. *Cephalalgia* **27**, 394–402 (2007).
8. Schoonman, G. C., Evers, D. J., Terwindt, G. M., van Dijk, J. G. & Ferrari, M. D. The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. *Cephalalgia* **26**, 1209–1213 (2006).
9. Spierings, E. L. H., Donoghue, S., Mian, A. & Wöber, C. Sufficiency and necessity in migraine: how do we figure out if triggers are absolute or partial and, if partial, additive or potentiating? *Curr. Pain Headache Rep.* **18**, 455 (2014).
10. Borkum, J. M. Migraine triggers and oxidative stress: a narrative review and synthesis. *Headache* **56**, 12–35 (2016).
11. Pingitore, A. et al. Exercise and oxidative stress: potential effects of antioxidant dietary strategies in sports. *Nutrition* **31**, 916–922 (2015).
12. Powers, S. K., Radak, Z. & Ji, L. L. Exercise-induced oxidative stress: past, present and future. *J. Physiol.* **594**, 5081–5092 (2016).
13. Schiavone, S., Jaquet, V., Trabace, L. & Krause, K.-H. Severe life stress and oxidative stress in the brain: from animal models to human pathology. *Antioxid. Redox Signal.* **18**, 1475–1490 (2013).
14. Trivedi, M. S., Holger, D., Bui, A. T., Craddock, T. J. A. & Tartar, J. L. Short-term sleep deprivation leads to decreased systemic redox metabolites and altered epigenetic status. *PLOS ONE* **12**, e0181978 (2017).
15. Angelucci, F. L. et al. Physiological effect of olfactory stimuli inhalation in humans: an overview. *Int. J. Cosmet. Sci.* **36**, 117–123 (2014).
16. Franken, C. et al. Phthalate-induced oxidative stress and association with asthma-related airway inflammation in adolescents. *Int. J. Hyg. Environ. Health* **220**, 468–477 (2017).
17. Nakamura, M., Kuse, Y., Tsuruma, K., Shimazawa, M. & Hara, H. The involvement of the oxidative stress in murine blue LED light-induced retinal damage model. *Biol. Pharm. Bull.* **40**, 1219–1225 (2017).
18. Demirel, R. et al. Noise induces oxidative stress in rat. *Eur. J. Gen. Med.* **6**, 20–24 (2009).
19. Arngim, N. et al. Migraine induced by hypoxia: an MRI spectroscopy and angiography study. *Brain* **139**, 723–737 (2016).
In this study, normobaric hypoxia induced migraine headache, but not aura in patients with migraine.
20. Broessner, G. et al. Hypoxia triggers high-altitude headache with migraine features: a prospective trial. *Cephalalgia* **36**, 765–771 (2016).
21. Arregui, A. et al. High prevalence of migraine in a high-altitude population. *Neurology* **41**, 1668–1668 (1991).
22. Reddy, V. D., Padmavathi, P., Kavitha, G., Saradamma, B. & Varadacharyulu, N. Alcohol-induced oxidative/nitrosative stress alters brain mitochondrial membrane properties. *Mol. Cell. Biochem.* **375**, 39–47 (2013).
23. Chauvel, V., Schoenen, J. & Multon, S. Influence of ovarian hormones on cortical spreading depression and its suppression by L-kynurenine in rat. *PLOS ONE* **8**, e82279 (2013).
24. Chauvel, V., Multon, S. & Schoenen, J. Estrogen-dependent effects of 5-hydroxytryptophan on cortical spreading depression in rat: modelling the serotonin-ovarian hormone interaction in migraine aura. *Cephalalgia* **38**, 427–436 (2018).
25. Irwin, R. W. et al. Progesterone and estrogen regulate oxidative metabolism in brain mitochondria. *Endocrinology* **149**, 3167–3175 (2008).
26. Mauvais-Jarvis, F., Clegg, D. J. & Hevener, A. L. The role of estrogens in control of energy balance and glucose homeostasis. *Endocr. Rev.* **34**, 309–338 (2013).
27. Welch, K. M., Levine, S. R., D'Andrea, G., Schultz, L. R. & Helyer, J. A. Preliminary observations on brain energy metabolism in migraine studied by in vivo phosphorus 31 NMR spectroscopy. *Neurology* **39**, 538–541 (1989).
A pioneering study that showed that mitochondrial energy metabolism is abnormal in the brain of patients with migraine.
28. Barbiroli, B. et al. Abnormal brain and muscle energy metabolism shown by 31P magnetic resonance spectroscopy in patients affected by migraine with aura. *Neurology* **42**, 1209–1214 (1992).
29. Kim, J. H. et al. Interictal metabolic changes in episodic migraine: a voxel-based FDG-PET study. *Cephalalgia* **30**, 53–61 (2010).
30. Lodi, R. et al. Deficit of brain and skeletal muscle bioenergetics and low brain magnesium in juvenile migraine: an in vivo 31P magnetic resonance spectroscopy interictal study. *Pediatr. Res.* **42**, 866–871 (1997).
31. Lodi, R. et al. Deficient energy metabolism is associated with low free magnesium in the brains of patients with migraine and cluster headache. *Brain Res. Bull.* **54**, 437–441 (2001).
32. Montagna, P. et al. 31P-magnetic resonance spectroscopy in migraine without aura. *Neurology* **44**, 666–669 (1994).
33. Reyngoudt, H., Achten, E. & Paemeleire, K. Magnetic resonance spectroscopy in migraine: what have we learned so far? *Cephalalgia* **32**, 845–859 (2012).
34. Schulz, U. G. et al. Association between cortical metabolite levels and clinical manifestations of migrainous aura: an MR-spectroscopy study. *Brain J. Neurol.* **130**, 3102–3110 (2007).
35. Lodi, R. et al. Quantitative analysis of skeletal muscle bioenergetics and proton efflux in migraine and cluster headache. *J. Neurol. Sci.* **146**, 73–80 (1997).
36. Barbiroli, B. et al. Complicated migraine studied by phosphorus magnetic resonance spectroscopy. *Cephalalgia* **10**, 263–272 (1990).
37. Cevoli, S., Favoni, V. & Cortelli, P. Energy metabolism impairment in migraine. *Curr. Med. Chem.* <https://doi.org/10.2174/0929867325666180622154411> (2018).
Excellent comprehensive review of energy metabolism in migraine highlighting the pivotal contribution of the Bologna group initiated by the late Pasaquale Montagna.
38. Reyngoudt, H., Paemeleire, K., Descamps, B., De Deene, Y. & Achten, E. 31P-MRS demonstrates a reduction in high-energy phosphates in the occipital lobe of migraine without aura patients. *Cephalalgia* **31**, 1243–1253 (2011).
This study showed that absolute brain levels of ATP are reduced interictally in patients with migraine without aura.
39. Ramadan, N. M. et al. Low brain magnesium in migraine. *Headache* **29**, 416–419 (1989).
The first study to show that magnesium is low in the brain of patients with migraine.
40. Sandor, P. S. et al. MR-spectroscopy imaging during visual stimulation in subgroups of migraine with aura. *Cephalalgia* **25**, 507–518 (2005).
This study revealed that resting and stimulation-induced levels of lactate in the occipital cortex differ among phenotypic subtypes of patients with migraine with aura.
41. Watanabe, H., Kuwabara, T., Ohkubo, M., Tsuji, S. & Yuasa, T. Elevation of cerebral lactate detected by localized 1H-magnetic resonance spectroscopy in migraine during the interictal period. *Neurology* **47**, 1093–1095 (1996).
42. Reyngoudt, H. et al. Does visual cortex lactate increase following photic stimulation in migraine without aura patients? A functional (1)H-MRS study. *J. Headache Pain* **12**, 295–302 (2011).
43. Prescott, A. et al. Excitatory neurotransmitters in brain regions in interictal migraine patients. *Mol. Pain* **5**, 34 (2009).
44. Mohamed, R. E., Aboelsafa, A. A. & Al-Malt, A. M. Interictal alterations of thalamic metabolic concentration ratios in migraine without aura detected by proton magnetic resonance spectroscopy. *Egypt. J. Radiol. Nucl. Med.* **44**, 859–870 (2013).
45. Becerra, L. et al. A 'complex' of brain metabolites distinguish altered chemistry in the cingulate cortex of episodic migraine patients. *Neuroimage Clin.* **11**, 588–594 (2016).
46. Sappey-Marinié, D. et al. Effect of photic stimulation on human visual cortex lactate and phosphates using 1H and 31P magnetic resonance spectroscopy. *J. Cereb. Blood Flow Metab.* **12**, 584–592 (1992).
47. Magistretti, P. J. & Pellerin, L. Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. *Phil. Trans. R. Soc. Lond. B* **354**, 1155–1163 (1999).
This is a review of brain energy metabolism, in particular of the "neuron-astrocyte lactate shuttle" by the authors who first described this important phenomenon.
48. Gantenbein, A. R. et al. Sensory information processing may be neuroenergetically more demanding in migraine patients. *Neuroreport* **24**, 202–205 (2013).
49. Lisicki, M. et al. Evidence of an increased neuronal activation-to-resting glucose uptake ratio in the visual cortex of migraine patients: a study comparing 18FDG-PET and visual evoked potentials. *J. Headache Pain* **19**, 49 (2018).
This study showed that in patients with migraine there is a mismatch between neuronal activation and glucose uptake in the visual system between attacks.
50. Littlewood, J. et al. Low platelet monoamine oxidase activity in headache: no correlation with phenolsulphotransferase, succinate dehydrogenase, platelet preparation method or smoking. *J. Neurol. Neurosurg. Psychiatry* **47**, 338–343 (1984).
51. Sangiorgi, S. et al. Abnormal platelet mitochondrial function in patients affected by migraine with and without aura. *Cephalalgia* **14**, 21–23 (1994).

52. Montagna, P. et al. Mitochondrial abnormalities in migraine. Preliminary findings. *Headache* **28**, 477–480 (1988).
53. Okada, H., Araga, S., Takeshima, T. & Nakashima, K. Plasma lactic acid and pyruvic acid levels in migraine and tension-type headache. *Headache* **38**, 39–42 (1998).
54. Alp, R., Selek, S., Alp, S. I., Taşkın, A. & Koçyigit, A. Oxidative and antioxidative balance in patients of migraine. *Eur. Rev. Med. Pharmacol. Sci.* **14**, 877–882 (2010).
55. Aytac, B. et al. Decreased antioxidant status in migraine patients with brain white matter hyperintensities. *Neurol. Sci.* **35**, 1925–1929 (2014).
56. Bernecker, C. et al. Oxidative stress is associated with migraine and migraine-related metabolic risk in females. *Eur. J. Neurol.* **18**, 1233–1239 (2011).
57. Bolayir, E. et al. Intraerythrocyte antioxidant enzyme activities in migraine and tension-type headaches. *J. Chin. Med. Assoc.* **67**, 263–267 (2004).
58. Ciancarelli, I., Tozzi-Ciancarelli, M., Massimo, C. D., Marini, C. & Carolei, A. Urinary nitric oxide metabolites and lipid peroxidation by-products in migraine. *Cephalalgia* **23**, 39–42 (2003).
59. Ciancarelli, I., Tozzi-Ciancarelli, M., Spacca, G., Massimo, C. D. & Carolei, A. Relationship between biofeedback and oxidative stress in patients with chronic migraine. *Cephalalgia* **27**, 1136–1141 (2007).
60. Eren, Y., Dirik, E., Neşelioglu, S. & Erel, Ö. Oxidative stress and decreased thiol level in patients with migraine: cross-sectional study. *Acta Neurol. Belg.* **115**, 643–649 (2015).
61. Geyik, S., Altunşik, E., Neyal, A. M. & Taysi, S. Oxidative stress and DNA damage in patients with migraine. *J. Headache Pain* **17**, 10 (2016).
62. Gumusayla, S. et al. A novel oxidative stress marker in migraine patients: dynamic thiol-disulphide homeostasis. *Neurol. Sci.* **37**, 1311–1317 (2016).
63. Shimomura, T. et al. Platelet superoxide dismutase in migraine and tension-type headache. *Cephalalgia* **14**, 215–218 (1994).
64. Tozzi-Ciancarelli, M. et al. Oxidative stress and platelet responsiveness in migraine. *Cephalalgia* **17**, 580–584 (1997).
65. Tripathi, G. M., Kalita, J. & Misra, U. K. A study of oxidative stress in migraine with special reference to prophylactic therapy. *Int. J. Neurosci.* **128**, 318–324 (2018).
66. Tuncel, D., Tolun, F. I., Gokce, M., Imrek, S. & Ekerbiçer, H. Oxidative stress in migraine with and without aura. *Biol. Trace Elem. Res.* **126**, 92–97 (2008).
67. Yılmaz, G., Sürer, H., Inan, L. E., Coskun, O. & Yücel, D. Increased nitrosative and oxidative stress in platelets of migraine patients. *Tohoku J. Exp. Med.* **211**, 23–30 (2007).
68. Neri, M. et al. A meta-analysis of biomarkers related to oxidative stress and nitric oxide pathway in migraine. *Cephalalgia* **35**, 931–937 (2015).
69. Gonullu, H. et al. The levels of trace elements and heavy metals in patients with acute migraine headache. *J. Pak. Med. Assoc.* **65**, 694–697 (2015).
70. Welch, K. M., Nagesh, V., Aurora, S. K. & Gelman, N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? *Headache* **41**, 629–637 (2001).
71. Blau, J. N. & Cumings, J. N. Method of precipitating and preventing some migraine attacks. *Br. Med. J.* **2**, 1242–1243 (1966).
72. Roberts, H. J. Migraine and related vascular headaches due to diabetogenic hyperinsulinism. Observations on pathogenesis and rational treatment in 421 patients. *Headache* **7**, 41–62 (1967).
73. Binder, C. & Bendtsen, I. Endocrine emergencies. Hypoglycaemia. *Baillieres Clin. Endocrinol. Metab.* **6**, 23–39 (1992).
74. Denuelle, M., Fabre, N., Payoux, P., Chollet, F. & Geraud, G. Hypothalamic activation in spontaneous migraine attacks. *Headache* **47**, 1418–1426 (2007). **This study was the first to demonstrate activation of the hypothalamus during attacks of migraine without aura.**
75. Maniyar, F. H., Sprenger, T., Monteith, T., Schankin, C. & Goadsby, P. J. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain J. Neurol.* **137**, 232–241 (2014). **This study showed that the hypothalamus is activated during the premonitory phase of migraine attacks.**
76. Schulte, L. H. & May, A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain J. Neurol.* **139**, 1987–1993 (2016). **Daily recordings in a patient with migraine confirmed that the hypothalamus is activated hours before the migraine headache starts.**
77. Montagna, P., Pierangeli, G. & Cortelli, P. The primary headaches as a reflection of genetic darwinian adaptive behavioral responses. *Headache* **50**, 273–289 (2010).
78. Pearce, J. Insulin induced hypoglycaemia in migraine. *J. Neurol. Neurosurg. Psychiatry* **34**, 154–156 (1971).
79. Hockaday, J. M., Williamson, D. H. & Whitty, C. W. M. Blood-glucose levels and fatty-acid metabolism in migraine related to fasting. *Lancet* **297**, 1153–1156 (1971). **An early study of metabolic responses and migraine attack generation after a glucose tolerance test; 6 of 10 patients developed an attack and increases in free fatty acids and ketone bodies.**
80. Christiansen, I., Thomsen, L. L., Daugaard, D., Ulrich, V. & Olesen, J. Glyceryl trinitrate induces attacks of migraine without aura in sufferers of migraine with aura. *Cephalalgia* **19**, 660–667 (1999). discussion 626.
81. Shaw, S. W., Johnson, R. H. & Keogh, H. J. Metabolic changes during glucose tolerance tests in migraine attacks. *J. Neurol. Sci.* **33**, 51–59 (1977).
82. Dexter, J. D., Roberts, J. & Byer, J. A. The five hour glucose tolerance test and effect of low sucrose diet in migraine. *Headache* **18**, 91–94 (1978).
83. Cavestro, C. et al. Insulin metabolism is altered in migraineurs: a new pathogenic mechanism for migraine? *Headache* **47**, 1436–1442 (2007).
84. Rainero, I., Govone, F., Gai, A., Vacca, A. & Rubino, E. Is migraine primarily a metaboloendocrine disorder? *Curr. Pain Headache Rep.* **22**, 36 (2018).
85. Sacco, S. et al. Insulin resistance in migraineurs: results from a case-control study. *Cephalalgia* **34**, 349–356 (2014).
86. Kokavec, A. Effect of sucrose consumption on serum insulin, serum cortisol and insulin sensitivity in migraine: evidence of sex differences. *Physiol. Behav.* **142**, 170–178 (2015).
87. Siva, Z. O. et al. Determinants of glucose metabolism and the role of NPY in the progression of insulin resistance in chronic migraine. *Cephalalgia* **38**, 1773–1781 (2018).
88. Brand-Miller, J. C., Griffin, H. J. & Colagiuri, S. The carnivore connection hypothesis: revisited. *J. Obes.* **2012**, 258624 (2012).
89. Issad, T. et al. Effects of fasting on tissue glucose utilization in conscious resting rats. Major glucose-sparing effect in working muscles. *Biochem. J.* **246**, 241–244 (1987).
90. Stepien, M. et al. Increasing protein at the expense of carbohydrate in the diet down-regulates glucose utilization as glucose sparing effect in rats. *PLOS ONE* **6**, e14664 (2011).
91. Wang, X. et al. Are glucose and insulin metabolism and diabetes associated with migraine? A community-based, case-control study. *J. Oral Facial Pain Headache* **31**, 240–250 (2017).
92. Antonazzo, I. C. et al. Diabetes is associated with decreased migraine risk: a nationwide cohort study. *Cephalalgia* **38**, 1759–1764 (2018).
93. Streel, E. et al. Screening for the metabolic syndrome in subjects with migraine. *Cephalalgia* **37**, 1180–1188 (2017).
94. He, Z. et al. Metabolic syndrome in female migraine patients is associated with medication overuse headache: a clinic-based study in China. *Eur. J. Neurol.* **22**, 1228–1234 (2015).
95. Bigal, M. E., Liberman, J. N. & Lipton, R. B. Obesity and migraine: a population study. *Neurology* **66**, 545–550 (2006). **A population study that revealed an association between obesity and chronic migraine.**
96. Ziegler, D. K., Hassanein, R. S., Kodanaz, A. & Meek, J. C. Circadian rhythms of plasma cortisol in migraine. *J. Neurol. Neurosurg. Psychiatry* **42**, 741–748 (1979).
97. Peres, M. F. et al. Hypothalamic involvement in chronic migraine. *J. Neurol. Neurosurg. Psychiatry* **71**, 747–751 (2001).
98. Lippi, G. & Mattiuzzi, C. Cortisol and migraine: a systematic literature review. *Agri* **29**, 95–99 (2017).
99. Hsu, L. K. et al. Early morning migraine. Nocturnal plasma levels of catecholamines, tryptophan, glucose, and free fatty acids and sleep encephalographs. *Lancet* **1**, 447–451 (1977).
100. Coggan, J. S. et al. Norepinephrine stimulates glycolysis in astrocytes to fuel neurons with lactate. *PLOS Comput. Biol.* **14**, e1006392 (2018).
101. Jacome, D. E. Hypoglycemia rebound migraine. *Headache* **41**, 895–898 (2001).
102. De Silva, K. L., Ron, M. A. & Pearce, J. Blood sugar response to glucagon in migraine. *J. Neurol. Neurosurg. Psychiatry* **37**, 105–107 (1974).
103. Peterlin, B. L., Sacco, S., Bernecker, C. & Scher, A. I. Adipokines and migraine: a systematic review. *Headache* **56**, 622–644 (2016).
104. Guldiken, B., Guldiken, S., Demir, M., Turgut, N. & Tugrul, A. Low leptin levels in migraine: a case control study. *Headache* **48**, 1103–1107 (2008).
105. Dominguez, C. et al. Role of adipocytokines in the pathophysiology of migraine: a cross-sectional study. *Cephalalgia* **38**, 904–911 (2018).
106. Van Houten, B., Hunter, S. E. & Meyer, J. N. Mitochondrial DNA damage induced autophagy, cell death, and disease. *Front. Biosci. Landmark Ed.* **21**, 42–54 (2016).
107. Yang, J.-L., Weissman, L., Bohr, V. A. & Mattson, M. P. Mitochondrial DNA damage and repair in neurodegenerative disorders. *DNA Repair* **7**, 1110–1120 (2008).
108. Roos-Araujo, D., Stuart, S., Lea, R. A., Haupt, L. M. & Griffiths, L. R. Epigenetics and migraine: complex mitochondrial interactions contributing to disease susceptibility. *Gene* **543**, 1–7 (2014).
109. MacGregor, E. A. Oestrogen and attacks of migraine with and without aura. *Lancet Neurol.* **3**, 354–361 (2004).
110. Lemos, C. et al. Assessing risk factors for migraine: differences in gender transmission. *PLOS ONE* **7**, e50626 (2012).
111. Kraya, T., Deschauer, M., Joshi, P. R., Zierz, S. & Gaul, C. Prevalence of headache in patients with mitochondrial disease: a cross-sectional study. *Headache* **58**, 45–52 (2018).
112. Vollono, C., Primiano, G., Della Marca, G., Losurdo, A. & Servidei, S. Migraine in mitochondrial disorders: prevalence and characteristics. *Cephalalgia* **38**, 1093–1106 (2018).
113. Montagna, P. et al. MELAS syndrome: characteristic migrainous and epileptic features and maternal transmission. *Neurology* **38**, 751–754 (1988).
114. Guo, S. et al. Prevalence of migraine in persons with the 3243A>G mutation in mitochondrial DNA. *Eur. J. Neurol.* **25**, 175–181 (2016).
115. Altmann, J. et al. Expanded phenotypic spectrum of the m.8344A>G “MERRF” mutation: data from the German mitoNET registry. *J. Neurol.* **263**, 961–972 (2016).
116. Buzzi, M. G. et al. mtDNA A3243G MELAS mutation is not associated with multigenerational female migraine. *Neurology* **54**, 1005–1007 (2000).
117. Cevoli, S. et al. High frequency of migraine-only patients negative for the 3243 A>G tRNA^{Leu} mtDNA mutation in two MELAS families. *Cephalalgia* **30**, 919–927 (2010).
118. Fachal, L. et al. No evidence of association between common European mitochondrial DNA variants in Alzheimer, Parkinson, and migraine in the Spanish population. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **168B**, 54–65 (2015).
119. Haan, J. et al. Search for mitochondrial DNA mutations in migraine subgroups. *Cephalalgia* **19**, 20–22 (1999).
120. Klopstock, T. et al. Mitochondrial DNA in migraine with aura. *Neurology* **46**, 1735–1738 (1996). **A negative search for mtDNA mutations associated with migraine with aura.**
121. Rozen, T. D. et al. Study of mitochondrial DNA mutations in patients with migraine with prolonged aura. *Headache* **44**, 674–677 (2004).
122. Russell, M. B., Diamant, M. & Norby, S. Genetic heterogeneity of migraine with and without aura in Danes cannot be explained by mutation in mtDNA nucleotide pair 11084. *Acta Neurol. Scand.* **96**, 171–173 (1997).
123. Ojaimi, J., Katsabanis, S., Bower, S., Quigley, A. & Byrne, E. Mitochondrial DNA in stroke and migraine with aura. *Cerebrovasc. Dis.* **8**, 102–106 (1998).
124. Larsen, S. et al. Increased intrinsic mitochondrial function in humans with mitochondrial haplogroup H. *Biochim. Biophys. Acta* **1837**, 226–231 (2014).
125. Martínez-Redondo, D. et al. Human mitochondrial haplogroup H: the highest VO₂max consumer—is it a paradox? *Mitochondrion* **10**, 102–107 (2010).
126. Di Lorenzo, C. et al. Mitochondrial DNA haplogroups influence the therapeutic response to riboflavin in migraineurs. *Neurology* **72**, 1588–1594 (2009). **A pharmacogenetic study that showed that patients with migraine who have non-H mtDNA haplogroups respond better to high-dose riboflavin than those with the H haplogroup.**

127. Majamaa, K., Finnilä, S., Turkka, J. & Hassinen, I. E. Mitochondrial DNA haplogroup U as a risk factor for occipital stroke in migraine. *Lancet* **352**, 455–456 (1998).
128. Wang, Q. et al. Mitochondrial DNA control region sequence variation in migraine headache and cyclic vomiting syndrome. *Am. J. Med. Genet. A* **131**, 50–58 (2004).
129. Zaki, E. et al. Two common mitochondrial dna polymorphisms are highly associated with migraine headache and cyclic vomiting syndrome. *Cephalalgia* **29**, 719–728 (2009).
A study that showed that childhood migraine and cyclic vomiting are associated with a high prevalence of two mtDNA polymorphisms.
130. Boles, R. G. et al. Increased prevalence of two mitochondrial DNA polymorphisms in functional disease: are we describing different parts of an energy-depleted elephant? *Mitochondrion* **23**, 1–6 (2015).
131. Stuart, S. & Griffiths, L. R. A possible role for mitochondrial dysfunction in migraine. *Mol. Genet. Genomics* **287**, 837–844 (2012).
132. Stuart, S. et al. Gene-centric analysis implicates nuclear encoded mitochondrial protein gene variants in migraine susceptibility. *Mol. Genet. Genomic Med.* **5**, 157–163 (2017).
The first evidence that polymorphisms in genes that encode nuclear-encoded mitochondrial proteins might play a role in migraine.
133. Palmirotta, R. et al. Is SOD2 Ala16Val polymorphism associated with migraine with aura phenotype? *Antioxid. Redox Signal.* **22**, 275–279 (2015).
134. Saygi, S. et al. Superoxide dismutase and catalase genotypes in pediatric migraine patients. *J. Child Neurol.* **30**, 1586–1590 (2015).
135. Kowa, H. et al. The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. *Am. J. Med. Genet.* **96**, 762–764 (2000).
136. Lea, R. A., Ovcarić, M., Sundholm, J., MacMillan, J. & Griffiths, L. R. The methylenetetrahydrofolate reductase gene variant C677T influences susceptibility to migraine with aura. *BMC Med.* **2**, 3 (2004).
137. Bhattacharjee, N. & Borah, A. Oxidative stress and mitochondrial dysfunction are the underlying events of dopaminergic neurodegeneration in homocysteine rat model of Parkinson's disease. *Neurochem. Int.* **101**, 48–55 (2016).
138. Kaunisto, M. et al. Testing of variants of the MTHFR and ESR1 genes in 1798 Finnish individuals fails to confirm the association with migraine with aura. *Cephalalgia* **26**, 1462–1472 (2006).
139. Lee, J., Wong, S. A., Li, B. U. K. & Boles, R. G. NextGen nuclear DNA sequencing in cyclic vomiting syndrome reveals a significant association with the stress-induced calcium channel (RYR2). *Neurogastroenterol. Motil.* **27**, 990–996 (2015).
140. Curtain, R., Tajouri, L., Lea, R., MacMillan, J. & Griffiths, L. No mutations detected in the INSR gene in a chromosome 19p13 linked migraine pedigree. *Eur. J. Med. Genet.* **49**, 57–62 (2006).
141. Kaunisto, M. A. et al. Chromosome 19p13 loci in Finnish migraine with aura families. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **132B**, 85–89 (2005).
142. McCarthy, L. C. et al. Single-nucleotide polymorphism alleles in the insulin receptor gene are associated with typical migraine. *Genomics* **78**, 135–149 (2001).
143. Netzer, C. et al. Replication study of the insulin receptor gene in migraine with aura. *Genomics* **91**, 503–507 (2008).
144. Mohammad, S. S., Coman, D. & Calvert, S. Glucose transporter 1 deficiency syndrome and hemiplegic migraines as a dominant presenting clinical feature. *J. Paediatr. Child Health* **50**, 1025–1026 (2014).
145. Gormley, P. et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat. Genet.* **48**, 856–866 (2016).
A large meta-analysis of genome-wide association studies, which showed that a great number of loci are each responsible for a very small proportion of the genetic risk of migraine.
146. Eising, E. et al. Gene co-expression analysis identifies brain regions and cell types involved in migraine pathophysiology: a GWAS-based study using the Allen Human Brain Atlas. *Hum. Genet.* **135**, 425–439 (2016).
147. Hershey, A., Horn, P., Kabbouche, M., O'Brien, H. & Powers, S. Genomic expression patterns in menstrual-related migraine in adolescents. *Headache* **52**, 68–79 (2012).
148. Woldeamanuel, Y., Rapoport, A. & Cowan, R. The place of corticosteroids in migraine attack management: a 65-year systematic review with pooled analysis and critical appraisal. *Cephalalgia* **35**, 996–1024 (2015).
149. Derry, C. J., Derry, S. & Moore, R. A. Caffeine as an analgesic adjuvant for acute pain in adults. *Cochrane Database Syst. Rev.* **11**, CD009281 (2014).
150. Nagatomo, K. & Kubo, Y. Caffeine activates mouse TRPA1 channels but suppresses human TRPA1 channels. *Proc. Natl Acad. Sci. USA* **105**, 17373–17378 (2008).
151. Lovallo, W. R. et al. Caffeine stimulation of cortisol secretion across the waking hours in relation to caffeine intake levels. *Psychosom. Med.* **67**, 734–739 (2005).
152. Wu, B. H. Dose effects of caffeine ingestion on acute hormonal responses to resistance exercise. *J. Sports Med. Phys. Fit.* **55**, 1242–1251 (2015).
153. Khani, S. & Tayek, J. A. Cortisol increases gluconeogenesis in humans: its role in the metabolic syndrome. *Clin. Sci.* **101**, 739–747 (2001).
154. Pagano, G. et al. An in vivo and in vitro study of the mechanism of prednisone-induced insulin resistance in healthy subjects. *J. Clin. Invest.* **72**, 1814–1820 (1983).
155. Bigal, M. E. & Lipton, R. B. Concepts and mechanisms of migraine chronification. *Headache* **48**, 7–15 (2008).
156. Lee, M. J., Choi, H. A., Choi, H. & Chung, C.-S. Caffeine discontinuation improves acute migraine treatment: a prospective clinic-based study. *J. Headache Pain* **17**, 71 (2016).
157. Kalra, E. K. Nutraceutical—definition and introduction. *AAPS PharmSci* **5**, 27–28 (2003).
158. Rajapakse, T. & Pringsheim, T. Nutraceuticals in migraine: a summary of existing guidelines for use. *Headache* **56**, 808–816 (2016).
159. Shaik, M. M. & Gan, S. H. Vitamin supplementation as possible prophylactic treatment against migraine with aura and menstrual migraine. *Biomed Res. Int.* **2015**, 469529 (2015).
160. Barile, M., Giancaspero, T. A., Leone, P., Galluccio, M. & Indiveri, C. Riboflavin transport and metabolism in humans. *J. Inher. Metab. Dis.* **39**, 545–557 (2016).
161. Büttin, A., Naziroglu, M., Demirci, S., Çelik, Ö. & Uğuz, A. C. Riboflavin and vitamin E increase brain calcium and antioxidants, and microsomal calcium-ATPase values in rat headache models induced by glyceryl trinitrate. *J. Membr. Biol.* **248**, 205–213 (2015).
162. Marashly, E. T. & Bohlega, S. A. Riboflavin has neuroprotective potential: focus on Parkinson's disease and migraine. *Front. Neurol.* **8**, 333 (2017).
163. Boehnke, C. et al. High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. *Eur. J. Neurol.* **11**, 475–477 (2004).
164. Condò, M., Posar, A., Arbizzani, A. & Parmeggiani, A. Riboflavin prophylaxis in pediatric and adolescent migraine. *J. Headache Pain* **10**, 361–365 (2009).
165. Gaul, C., Diener, H.-C. & Danesch, U., Migravent® Study Group. Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-blind, multicenter trial. *J. Headache Pain* **16**, 516 (2015).
166. Schoenen, J., Jacquy, J. & Lenaerts, M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology* **50**, 466–470 (1998).
A placebo-controlled trial that showed that 400 mg riboflavin daily is effective for migraine prevention.
167. Bruijn, J. et al. Medium-dose riboflavin as a prophylactic agent in children with migraine: a preliminary placebo-controlled, randomised, double-blind, cross-over trial. *Cephalalgia* **30**, 1426–1434 (2010).
168. Rahimdel, A., Mellat, A., Zeinali, A., Jafari, E. & Ayatollahi, P. Comparison between intravenous sodium valproate and subcutaneous sumatriptan for treatment of acute migraine attacks; double-blind randomized clinical trial. *Iran. J. Med. Sci.* **39**, 171–177 (2014).
169. Thompson, D. F. & Saluja, H. S. Prophylaxis of migraine headaches with riboflavin: a systematic review. *J. Clin. Pharm. Ther.* **42**, 394–403 (2017).
170. Pranthip, P., Kettawan, A., Posuwan, J., Okuno, M. & Okamoto, T. An improvement of oxidative stress in diabetic rats by ubiquinol-10 and ubiquinol-10 and bioavailability after short- and long-term coenzyme Q10 supplementation. *J. Diet. Suppl.* **13**, 647–659 (2016).
171. Yang, X. et al. Neuroprotection of coenzyme Q10 in neurodegenerative diseases. *Curr. Top. Med. Chem.* **16**, 858–866 (2016).
172. Dahri, M., Hashemilar, M., Asghari-Jafarabadi, M. & Tarighat-Esfanjani, A. Efficacy of coenzyme Q10 for the prevention of migraine in women: a randomized, double-blind, placebo-controlled study. *Eur. J. Integr. Med.* **16**, 8–14 (2017).
173. Dahri, M., Tarighat-Esfanjani, A., Asghari-Jafarabadi, M. & Hashemilar, M. Oral coenzyme Q10 supplementation in patients with migraine: effects on clinical features and inflammatory markers. *Nutr. Neurosci.* **22**, 607–615 (2019).
174. Sándor, P. S. et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology* **64**, 713–715 (2005).
175. Hajhashemi, P., Askari, G., Khorvash, F., Reza Maracy, M. & Nourian, M. The effects of concurrent coenzyme Q10, L-carnitine supplementation in migraine prophylaxis: a randomized, placebo-controlled, double-blind trial. *Cephalalgia* **39**, 648–654 (2019).
176. Slater, S. K. et al. A randomized, double-blinded, placebo-controlled, crossover, add-on study of coenzyme Q10 in the prevention of pediatric and adolescent migraine. *Cephalalgia* **31**, 897–905 (2011).
177. Hershey, A. D. et al. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. *Headache* **47**, 73–80 (2007).
178. Müller, U. & Kriegelstein, J. Prolonged pretreatment with α -lipoic acid protects cultured neurons against hypoxic, glutamate-, or iron-induced injury. *J. Cereb. Blood Flow Metab.* **15**, 624–630 (1995).
179. Packer, L., Witt, E. H. & Tritschler, H. J. α -lipoic acid as a biological antioxidant. *Free Radic. Biol. Med.* **19**, 227–250 (1995).
180. Magis, D. et al. A randomized double-blind placebo-controlled trial of thioctic acid in migraine prophylaxis. *Headache* **47**, 52–57 (2007).
181. Cavestro, C. et al. Alpha-lipoic acid shows promise to improve migraine in patients with insulin resistance: a 6-month exploratory study. *J. Med. Food* **21**, 269–273 (2018).
182. Ali, A. M., Awad, T. G. & Al-Adl, N. M. Efficacy of combined topiramate/thioctic acid therapy in migraine prophylaxis. *Saudi Pharm. J.* **18**, 239–243 (2010).
183. Lea, R., Colson, N., Quinlan, S., Macmillan, J. & Griffiths, L. The effects of vitamin supplementation and MTHFR (C677T) genotype on homocysteine-lowering and migraine disability. *Pharmacogenet. Genomics* **19**, 422–428 (2009).
184. Menon, S. et al. Genotypes of the MTHFR C677T and MTRR A66G genes act independently to reduce migraine disability in response to vitamin supplementation. *Pharmacogenet. Genomics* **22**, 741–749 (2012).
185. Menon, S. et al. The effect of 1 mg folic acid supplementation on clinical outcomes in female migraine with aura patients. *J. Headache Pain* **17**, 60 (2016).
186. Prousky, J. & Seely, D. The treatment of migraines and tension-type headaches with intravenous and oral niacin (nicotinic acid): systematic review of the literature. *Nutr. J.* **4**, 3 (2005).
187. Facchinetti, F., Sances, G., Borella, P., Genazzani, A. R. & Nappi, G. Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. *Headache* **31**, 298–301 (1991).
188. Chiu, H.-Y., Yeh, T.-H., Huang, Y.-C. & Chen, P.-Y. Effects of intravenous and oral magnesium on reducing migraine: a meta-analysis of randomized controlled trials. *Pain Physician* **19**, E97–E112 (2016).
189. Karimi, N., Razian, A. & Heidari, M. The efficacy of magnesium oxide and sodium valproate in prevention of migraine headache: a randomized, controlled, double-blind, crossover study. *Acta Neurol. Belg.* <https://doi.org/10.1007/s13760-019-01101-x> (2019).
190. Tarighat-Esfanjani, A. et al. The effects of magnesium, L-carnitine, and concurrent magnesium-L-carnitine supplementation in migraine prophylaxis. *Biol. Trace Elem. Res.* **150**, 42–48 (2012).
191. Hagen, K. et al. Acetyl-L-carnitine versus placebo for migraine prophylaxis: a randomized, triple-blind, crossover study. *Cephalalgia* **35**, 987–995 (2015).
192. Yang, H., Shan, W., Zhu, F., Wu, J. & Wang, Q. Ketone bodies in neurological diseases: focus on neuroprotection and underlying mechanisms. *Front. Neurol.* **10**, 585 (2019).
193. Gross, E. C., Klement, R. J., Schoenen, J., D'Agostino, D. P. & Fischer, D. Potential protective mechanisms of ketone bodies in migraine prevention. *Nutrients* **11**, 811 (2019).
A comprehensive review of the various potential mechanisms by which ketone bodies might protect against migraine.
194. Al-Karaghali, M. A.-M., Hansen, J. M., Guo, S., Olesen, J. & Ashina, M. Opening of ATP-sensitive potassium channels causes migraine attacks: a new

- target for the treatment of migraine. *Brain J. Neurol.* awz199 (2019).
- A demonstration that a K_{ATP} channel opener induces migraine headache in patients with migraine.**
195. Strahman, R. S. Can ketosis help migraine sufferers? A case report. *Headache* **46**, 182 (2006).
 196. Di Lorenzo, C. et al. Diet transiently improves migraine in two twin sisters: possible role of ketogenesis? *Funct. Neurol.* **28**, 305–308 (2013).
 - The first clinical indication that a ketogenic diet can improve migraine.**
 197. Maggioni, F., Margoni, M. & Zanchin, G. Ketogenic diet in migraine treatment: a brief but ancient history. *Cephalalgia* **31**, 1150–1151 (2011).
 198. SCHNABEL, T. G. An experience with a ketogenic dietary in migraine. *Ann. Intern. Med.* **2**, 341 (1928).
 199. Di Lorenzo, C. et al. Migraine improvement during short lasting ketogenesis: a proof-of-concept study. *Eur. J. Neurol.* **22**, 170–177 (2015).
 200. Di Lorenzo, C. et al. Cortical functional correlates of responsiveness to short-lasting preventive intervention with ketogenic diet in migraine: a multimodal evoked potentials study. *J. Headache Pain* **17**, 58 (2016).
 201. Di Lorenzo, C. et al. A randomized double-blind, cross-over trial of very low-calorie diet in overweight migraine patients: a possible role for ketones? *Nutrients* **11**, 1742 (2019).
 202. Gross, E. et al. Efficacy and safety of exogenous ketone bodies for preventive treatment of migraine: a study protocol for a single-centred, randomised, placebo-controlled, double-blind crossover trial. *Trials* **20**, 61 (2019).
 203. Varkey, E., Cider, A., Carlsson, J. & Linde, M. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. *Cephalalgia* **31**, 1428–1438 (2011).
 204. Ding, Q., Vaynman, S., Souda, P., Whitelegge, J. P. & Gomez-Pinilla, F. Exercise affects energy metabolism and neural plasticity-related proteins in the hippocampus as revealed by proteomic analysis. *Eur. J. Neurosci.* **24**, 1265–1276 (2006).
 205. Steiner, J. L., Murphy, E. A., McClellan, J. L., Carmichael, M. D. & Davis, J. M. Exercise training increases mitochondrial biogenesis in the brain. *J. Appl. Physiol.* (1985) **111**, 1066–1071 (2011).
 206. Silberstein, S. D., Latsko, M. & Schoenen, J. in *Multidisciplinary Management of Migraine: Pharmacological, Manual, and Other Therapies* (eds Fernandez-de-las-Penas, C., Chaitow, L., & Schoenen, J.) 91–102 (Jones & Bartlett Learning, 2013).
 207. Motaghinejad, M., Motevalian, M. & Shabab, B. Neuroprotective effects of various doses of topiramate against methylphenidate induced oxidative stress and inflammation in rat isolated hippocampus. *Clin. Exp. Pharmacol. Physiol.* **43**, 360–371 (2016).
 208. Kudin, A. P., Debska-Vielhaber, G., Vielhaber, S., Elger, C. E. & Kunz, W. S. The mechanism of neuroprotection by topiramate in an animal model of epilepsy. *Epilepsia* **45**, 1478–1487 (2004).
 209. Franzoni, E. et al. Topiramate: effects on serum lipids and lipoproteins levels in children. *Eur. J. Neurol.* **14**, 1334–1337 (2007).
 210. Wilkes, J. J., Nelson, E., Osborne, M., Demarest, K. T. & Olefsky, J. M. Topiramate is an insulin-sensitizing compound in vivo with direct effects on adipocytes in female ZDF rats. *Am. J. Physiol. Endocrinol. Metab.* **288**, E617–E624 (2005).
 211. Li, R. et al. Valproate attenuates nitroglycerin-induced trigeminovascular activation by preserving mitochondrial function in a rat model of migraine. *Med. Sci. Monit.* **22**, 3229–3237 (2016).
 212. Sitarz, K. S. et al. Valproic acid triggers increased mitochondrial biogenesis in POLG-deficient fibroblasts. *Mol. Genet. Metab.* **112**, 57–63 (2014).
 213. Berilgen, M. S. et al. Comparison of the effects of amitriptyline and flunarizine on weight gain and serum leptin, C peptide and insulin levels when used as migraine preventive treatment. *Cephalalgia* **25**, 1048–1053 (2005).
 214. Maggioni, F., Ruffatti, S., Dainese, F., Mainardi, F. & Zanchin, G. Weight variations in the prophylactic therapy of primary headaches: 6-month follow-up. *J. Headache Pain* **6**, 322–324 (2005).
 215. Lamont, L. S. Beta-blockers and their effects on protein metabolism and resting energy expenditure. *J. Cardiopulm. Rehabil.* **15**, 183–185 (1995).
 216. Lipton, R. B. et al. Reduction in perceived stress as a migraine trigger: testing the “let-down headache” hypothesis. *Neurology* **82**, 1395–1401 (2014).
 217. Neubauer, J. A. & Sunderram, J. Oxygen-sensing neurons in the central nervous system. *J. Appl. Physiol.* (1985) **96**, 367–374 (2004).
 218. Lin, L.-C., Lewis, D. A. & Sibille, E. A human-mouse conserved sex bias in amygdala gene expression related to circadian clock and energy metabolism. *Mol. Brain* **4**, 18 (2011).
 219. Hoffmann, U., Sukhotinsky, I., Eikermann-Haerter, K. & Ayata, C. Glucose modulation of spreading depression susceptibility. *J. Cereb. Blood Flow Metab.* **33**, 191–195 (2013).
 220. Kilic, K. et al. Inadequate brain glycogen or sleep increases spreading depression susceptibility. *Ann. Neurol.* **83**, 61–73 (2018).
 - A pivotal study that showed that in rodents, glucose shortage and sleep deprivation increase susceptibility to cortical spreading depression and open pannexin-1 megachannels, enabling activation of the trigeminovascular system.**
 221. de Almeida Rabello Oliveira, M. et al. Effects of short-term and long-term treatment with medium- and long-chain triglycerides ketogenic diet on cortical spreading depression in young rats. *Neurosci. Lett.* **434**, 66–70 (2008).
 222. Gerich, F. J., Hepp, S., Probst, I. & Müller, M. Mitochondrial inhibition prior to oxygen-withdrawal facilitates the occurrence of hypoxia-induced spreading depression in rat hippocampal slices. *J. Neurophysiol.* **96**, 492–504 (2006).
 223. Takano, T. et al. Cortical spreading depression causes and coincides with tissue hypoxia. *Nat. Neurosci.* **10**, 754–762 (2007).
 224. Angelova, P. R. et al. Functional oxygen sensitivity of astrocytes. *J. Neurosci.* **35**, 10460–10473 (2015).
 225. Chen, S.-P. et al. Inhibition of the P2X7-PANX1 complex suppresses spreading depolarization and neuroinflammation. *Brain* **140**, 1643–1656 (2017).
 226. Bolay, H. et al. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat. Med.* **8**, 136–142 (2002).
 - The first study to show that CSD in rats can activate the trigeminovascular system.**
 227. Karatas, H. et al. Spreading depression triggers headache by activating neuronal Panx1 channels. *Science* **339**, 1092–1095 (2013).
 - This study showed that CSD-induced trigeminovascular activation is mediated by the opening of neuronal pannexin-1 channels.**
 228. Feuerstein, D. et al. Regulation of cerebral metabolism during cortical spreading depression. *J. Cereb. Blood Flow Metab.* **36**, 1965–1977 (2016).
 229. Yuzawa, I. et al. Cortical spreading depression impairs oxygen delivery and metabolism in mice. *J. Cereb. Blood Flow Metab.* **32**, 376–386 (2012).
 230. Viggiano, E. et al. Cortical spreading depression produces a neuroprotective effect activating mitochondrial uncoupling protein-5. *Neuropsychiatr. Dis. Treat.* **12**, 1705–1710 (2016).
 231. Shatillo, A. et al. Cortical spreading depression induces oxidative stress in the trigeminal nociceptive system. *Neuroscience* **253**, 341–349 (2013).
 232. Diener, H.-C. et al. CGRP as a new target in prevention and treatment of migraine. *Lancet Neurol.* **13**, 1065–1067 (2014).
 233. Durham, P. L. Calcitonin gene-related peptide (CGRP) and migraine. *Headache* **46** (Suppl. 1), S3–S8 (2006).
 234. Holland, P. R. et al. Acid-sensing ion channel 1: a novel therapeutic target for migraine with aura. *Ann. Neurol.* **72**, 559–563 (2012).
 235. Benemei, S., Fusi, C., Trevisan, G. & Geppetti, P. The TRPA1 channel in migraine mechanism and treatment. *Br. J. Pharmacol.* **171**, 2552–2567 (2014).
 236. Kozai, D., Ogawa, N. & Mori, Y. Redox regulation of transient receptor potential channels. *Antioxid. Redox Signal.* **21**, 971–986 (2014).
 237. Martins-Oliveira, M. et al. Neuroendocrine signaling modulates specific neural networks relevant to migraine. *Neurobiol. Dis.* **101**, 16–26 (2017).
 - An experimental study that showed that systemic metabolic changes can modulate firing of nociceptors in the spinal trigeminal nucleus.**
 238. Ma, W., Berg, J. & Yellen, G. Ketogenic diet metabolites reduce firing in central neurons by opening K(ATP) channels. *J. Neurosci.* **27**, 3618–3625 (2007).
 239. Kawamura, M., Ruskin, D. N. & Masino, S. A. Metabolic autocrine regulation of neurons involves cooperation among pannexin hemichannels, adenosine receptors, and KATP channels. *J. Neurosci.* **30**, 3886–3895 (2010).
 240. Ghasemi, M., Mayasi, Y., Hannoun, A., Eslami, S. M. & Carandang, R. Nitric oxide and mitochondrial function in neurological diseases. *Neuroscience* **376**, 48–71 (2018).
 241. Kruse, C., Thomsen, L. L., Birk, S. & Olesen, J. Migraine can be induced by sildenafil without changes in middle cerebral artery diameter. *Brain J. Neurol.* **126**, 241–247 (2003).
 242. Bolaños, J. P., Peuchen, S., Heales, S. J., Land, J. M. & Clark, J. B. Nitric oxide-mediated inhibition of the mitochondrial respiratory chain in cultured astrocytes. *J. Neurochem.* **63**, 910–916 (1994).
 243. Abad, N. et al. Metabolic assessment of a migraine model using relaxation-enhanced 1H spectroscopy at ultrahigh field. *Magn. Reson. Med.* **79**, 1266–1275 (2018).
 244. Dong, X. et al. Abnormal mitochondrial dynamics and impaired mitochondrial biogenesis in trigeminal ganglion neurons in a rat model of migraine. *Neurosci. Lett.* **636**, 127–133 (2017).
 245. Fried, N. T., Moffat, C., Seifert, E. L. & Oshinsky, M. L. Functional mitochondrial analysis in acute brain sections from adult rats reveals mitochondrial dysfunction in a rat model of migraine. *Am. J. Physiol. Cell Physiol.* **307**, C1017–C1030 (2014).
 246. Goadsby, P. J., Edvinsson, L. & Ekman, R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann. Neurol.* **28**, 183–187 (1990).
 - By showing that CGRP levels in the blood in the jugular vein are increased during migraine attacks, this study paved the way for the novel migraine therapies that block CGRP neurotransmission.**
 247. Lassen, L. H. et al. CGRP may play a causative role in migraine. *Cephalalgia* **22**, 54–61 (2002).
 248. Khan, S., Olesen, A. & Ashina, M. CGRP, a target for preventive therapy in migraine and cluster headache: systematic review of clinical data. *Cephalalgia* **39**, 374–389 (2019).
 249. Hansen, J. M., Hauge, A. W., Olesen, J. & Ashina, M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. *Cephalalgia* **30**, 1179–1186 (2010).
 250. Bai, Y.-X., Fang, F., Jiang, J.-L. & Xu, F. Extrinsic calcitonin gene-related peptide inhibits hyperoxia-induced alveolar epithelial type II cells apoptosis, oxidative stress, and reactive oxygen species (ROS) production by enhancing notch 1 and homocysteine-induced endoplasmic reticulum protein (HERP) expression. *Med. Sci. Monit.* **23**, 5774–5782 (2017).
 251. Dang, H.-X. et al. CGRP attenuates hyperoxia-induced oxidative stress-related injury to alveolar epithelial type II cells via the activation of the Sonic hedgehog pathway. *Int. J. Mol. Med.* **40**, 209–216 (2017).
 252. Holzmann, B. Antiinflammatory activities of CGRP modulating innate immune responses in health and disease. *Curr. Protein Pept. Sci.* **14**, 268–274 (2013).
 253. Smillie, S.-J. et al. An ongoing role of α -calcitonin gene-related peptide as part of a protective network against hypertension, vascular hypertrophy, and oxidative stress. *Hypertension* **63**, 1056–1062 (2014).
 254. Hothersall, J. S., Muirhead, R. P. & Wimalawansa, S. The effect of amylin and calcitonin gene-related peptide on insulin-stimulated glucose transport in the diaphragm. *Biochem. Biophys. Res. Commun.* **169**, 451–454 (1990).
 255. Morishita, T. et al. Effects of islet amyloid polypeptide (amylin) and calcitonin gene-related peptide (CGRP) on glucose metabolism in the rat. *Diabetes Res. Clin. Pract.* **15**, 63–69 (1992).
 256. Leighton, B. & Foot, E. A. The role of the sensory peptide calcitonin-gene-related peptide(s) in skeletal muscle carbohydrate metabolism: effects of capsaicin and reseriferatoxin. *Biochem. J.* **307**, 707–712 (1995).
 257. Holland, P. R., Saengjaroentharn, C. & Vila-Pueyo, M. The role of the brainstem in migraine: potential brainstem effects of CGRP and CGRP receptor activation in animal models. *Cephalalgia* **39**, 390–402 (2019).
 258. Yi, C.-X. et al. Pituitary adenylate cyclase-activating polypeptide stimulates glucose production via the hepatic sympathetic innervation in rats. *Diabetes* **59**, 1591–1600 (2010).
 259. Lisicki, M. et al. Age related metabolic modifications in the migraine brain. *Cephalalgia* **39**, 978–987 (2019).
 260. Liveing, E. O. *Megrim, Sick-headache, and Some Allied Disorders: A Contribution to the Pathology of Nerve-storms.* (Churchill, 1873).
 - The formulation of the concept that the migraine attack results from a disruption of brain homeostasis that the attack itself resolves.**

261. Loder, E. What is the evolutionary advantage of migraine? *Cephalalgia* **22**, 624–632 (2002).
262. de Tommaso, M. et al. Altered processing of sensory stimuli in patients with migraine. *Nat. Rev. Neurol.* **10**, 144–155 (2014).
263. Nosedà, R. et al. Migraine photophobia originating in cone-driven retinal pathways. *Brain J. Neurol.* **139**, 1971–1986 (2016).
264. Evers, S. et al. EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force. *Eur. J. Neurol.* **16**, 968–981 (2009).
265. Holland, S. et al. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* **78**, 1346–1353 (2012).
266. Marmura, M. J., Silberstein, S. D. & Schwedt, T. J. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache* **55**, 3–20 (2015).
267. Silberstein, S. D. et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* **78**, 1337–1345 (2012).
268. Tfelt-Hansen, P. C. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* **80**, 869–870; correction 871 (2013).
269. Pringsheim, T. et al. Canadian Headache Society guideline for migraine prophylaxis. *Can. J. Neurol. Sci.* **39**, S1–S59 (2012).

Author contributions

E.C.G. was responsible for the literature search and the main composition of the manuscript, including the majority of display items. M.L. edited the manuscript and provided additional text and display items. D.F. and P.S.S. edited the manuscript. J.S. was responsible for the design of the

manuscript, edited in depth the manuscript and display items and provided additional text and citations. All authors proofread the final manuscript prior to submission.

Competing interests

E.C.G. is the founder of KetoSwiss. E.C.G. and D.F. are the inventors of patent WO/2018/115158 held by the University Children's Hospital Basel (UKBB) and the University of Basel for the use of β -hydroxybutyrate in migraine prevention. M.L., P.S.S. and J.S. declare no competing interests.

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