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 elsewhere[3]) 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 attack[4].

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 migraine[7] 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.

misinterpreted[8]. 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 effect[9], 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 stress[10]. For instance, intense physical[11,12] or psychological stress can increase oxidative stress in the CNS[13]. In healthy people, one night of sleep deprivation is enough to substantially reduce levels of glutathione, ATP, cysteine and homocysteine[14]. Intense sensory stimuli, including odours[15], perfumes containing phthalates[16], blue light[17] and loud noises[18], can increase oxidative stress. Experimental hypoxia can trigger migraine headaches[8,19] (less so migraine aura[19]), even in most healthy people[20], and in line with this observation, migraine prevalence is higher in populations that live at high altitude[21].

In animals, alcohol-induced oxidative or nitrosative stress alters mitochondrial membrane properties in the brain[22]. 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 CSD[24], and influence oxidative metabolism in the rat brain[25]. Furthermore, oestrogen, which greatly modulates the course of migraine in females, is involved in insulin sensitivity, the regulation of insulin secretion and nutrient homeostasis[26]. 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 responsivity, 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 severity[6].

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 ^{31}P-MRS has shown that mitochondrial oxidative phosphorylation is impaired in the brain of patients with migraine during[27] 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 ^{31}P-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 controls[38]. 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 ^{31}P-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 ^{1}H-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 group[40]. An important consideration is that stimulus-induced increases in cortical lactate levels are physiological[46] and are explained by the astrocyte-to-neuron lactate shuttle[47], 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 abnormal[48]. 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 ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET. This procedure involves measuring positron emission from the systemically administered, radiotracer-labelled glucose analogue ^{18}F-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 ^{18}F-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 controls[49]. 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 interictally[68]. 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 stress[67] and nitric oxide[68] are elevated during migraine attacks, but not interictally.

Another possible marker of oxidative stress is heavy metals, levels of which can be increased in migraine[69]. For example, free iron is highly pro-oxidant and accumulates in the brainstem of patients with migraine in proportion to disease duration[70].

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 hypoglycaemia[73] 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 activation[73].

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 response[77] 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 craving[79]. 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 patients[79]. 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 nitroglycerin[80], 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 aura[81] 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 elsewhere[84]), although this association was not seen at all in one study[85] and only in women with migraine in another[86]. 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 severity[87].

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 aura[93] and with chronic migraine in women[94]. 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 prevalence[95].

Elevated interictal cortisol levels have been observed in episodic[86,96] and chronic migraine[97], as well as during migraine attacks[81], although a review of the evidence published in 2017 concluded that the results are mixed overall[98]. High catecholamine levels have also been associated with early morning migraine[99]. 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 glycogenolysis[100], 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 trigger[101], 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 controls[102]. 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 data[103]. Low leptin levels were identified in patients with episodic migraine in one study[104] 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 review[108], 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 men[109], and maternal transmission of the condition is more common than paternal transmission[110], 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 prolonged[113]. 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 migraine[115]. 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 mitochondriopathies, 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 episodes[123].

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 haplogroups[126] (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 U[127], as well as in migraine without aura and in cyclic vomiting, a childhood equivalent of migraine[128]. 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 polymorphism[129]. A high prevalence of these two polymorphisms has also been associated with chronic fatigue syndrome and depression[130]. 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 replicated[118].

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 attention[131]. 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 demethylation[132]. 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 aura[133]. 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 controls[134]. Both enzymes act in concert to reduce ROS accumulation, and the polymorphisms reported in this study are thought 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 rats[137], although in a Finnish population of patients with migraine with aura, the association between MTHFR and migraine could not be replicated[138]. 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 damage[139].

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 aura[144].

Genome-wide associated loci

Genome-wide association studies (GWAS) have identified 38 gene loci that are associated with migraine[145]. 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 pathophysiology[146]. 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 migraine[146]. Similarly, genes related to mitochondrial function are differentially expressed in adolescent patients with menstrual migraine compared with healthy controls[147].

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 migrainosus[148]. Caffeine (>100 mg), on the other hand, has a beneficial (though small) analgesic effect, at least when used in conjunction with common analgesics[149]. Besides its suppression of transient receptor potential A1 (TRPA1) activity[150], caffeine also stimulates cortisol secretion[151,152] and, consequently, gluconeogenesis[153]. In addition, caffeine increases levels of free fatty acids and decreases insulin responses[152], effects that are similar to the metabolic changes that occur during a migraine attack[81]. 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 resistance[154] and migraine chronification[155], whereas caffeine discontinuation is associated with higher efficacy of acute migraine treatment[156].

Prophylactic nutraceuticals

Several nutraceuticals[157] have been shown to be beneficial in migraine prevention[158], and most of these can be linked to energy metabolism and/or mitochondrial function[159]. 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 prevention[168]. A systematic review published in 2017 showed that high-dose riboflavin (400 mg daily) is well tolerated, inexpensive and effectively reduces migraine headache frequency[169]. In one study, mtDNA haplogroup influenced the therapeutic response to riboflavin[126]: 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 placebo[176], but did have beneficial preventive effects in paediatric patients with migraine and low CoQ10 blood levels in an open-label study[177].

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 severity[180]. In an open-label trial of ALA in patients with migraine and insulin resistance, a 50% response was seen in 69% of participants[181]. In another study, combined treatment with topiramate and ALA for 1 month was more effective for migraine prevention than either drug alone[182].

Other B vitamins. In double-blind randomized placebo-controlled trials, a 2 mg daily dose of folic acid (vitamin B_9) combined with 25 mg pyridoxine (vitamin B_6) and 400 µg cobalamin (vitamin B_{12}) 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 reductase[184]. The same vitamin B combination with a 1 mg dose of folic acid was not superior to placebo[185]. According to a systematic

review[186] in which nine open studies were identified, niacin (nicotinic acid or vitamin B_3) 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

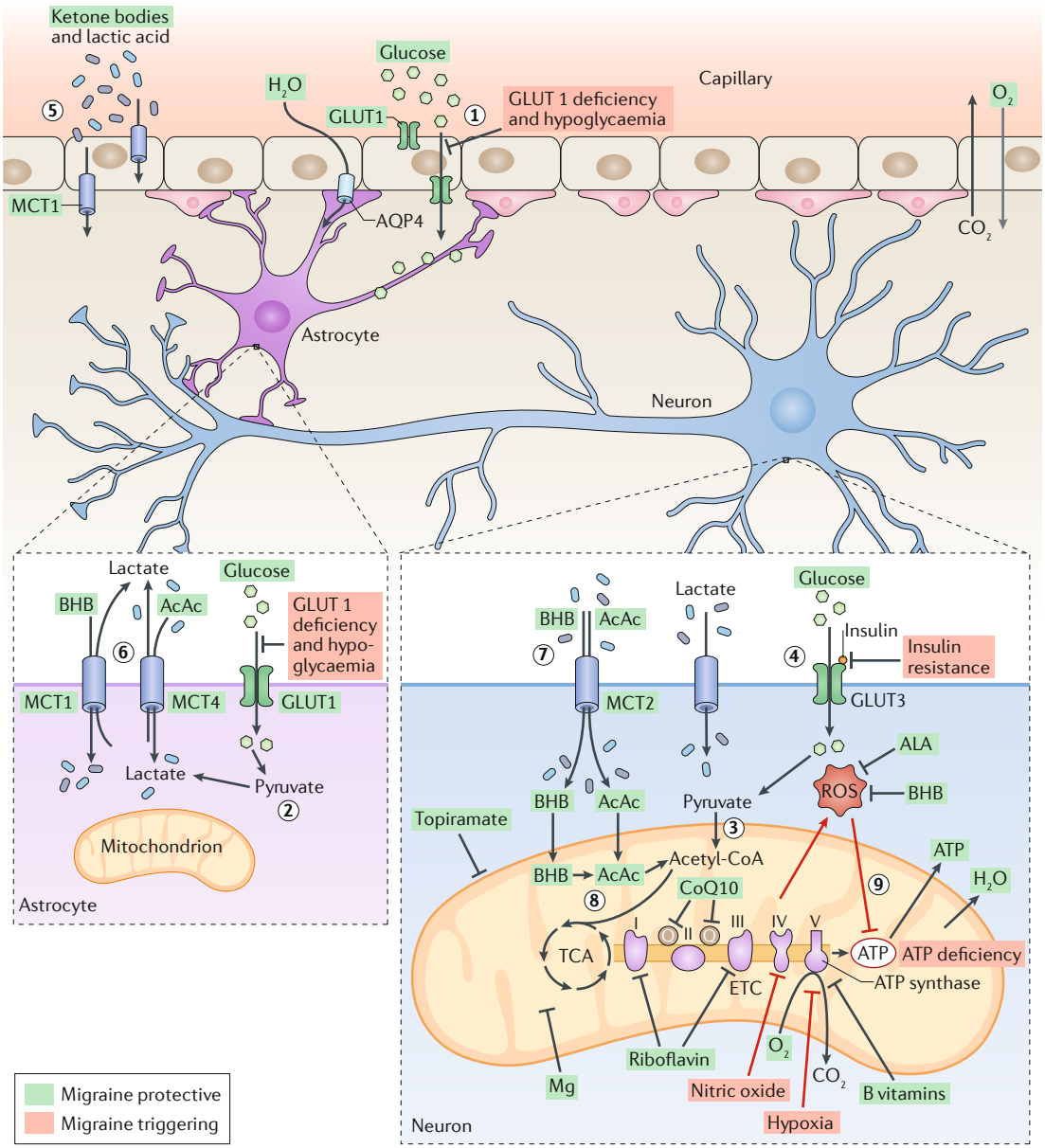

Fig. 1 | **Cerebral metabolomics that might be involved in migraine pathogenesis and therapeutic targets.** Glucose crosses the blood–brain barrier via insulin-independent glucose transporter 1 (GLUT1) (step 1), deficiency of which can contribute to migraine, as can insufficient glucose, oxygen, water 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 intensity[188]. 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 daily[189].

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 treatment[190]. Migraine attacks and days decreased significantly in all patient groups, although this decrease was greater among patients who received magnesium oxide alone[190]. 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 placebo[191]. 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 period[175].

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 generation[194] (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 responses[200]. 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 migraine[201]. 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 trial[202].

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 efficacy[203]. 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 turnover[204]. Furthermore, in mice, exercise training increases the number of mitochondria not only in muscle but also in the brain[205].

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 reactivity[206] 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, inflammation[207] and mitochondrial membrane depolarization[208], prolongs mitochondrial survival[208], slightly increases lipolysis in children[209] and increases the sensitivity of adipocytes to insulin in female rats[210].

Other drugs used for prevention of migraine treatment have clear metabolic effects. Amitriptyline also reduces markers of oxidative stress and increases antioxidant capacity[65]. Valproate attenuates nitroglycerin-induced trigeminovascular activation by preserving mitochondrial function in a rat model of migraine[211] and increases mitochondrial biogenesis[212]. Amitriptyline and flunarizine increase serum levels of leptin and insulin and increase BMI after 12 weeks of therapy in patients with migraine[213]. Gabapentin, atenolol, verapamil, valproate, pizotifen and amitriptyline all increase body weight in a substantial number of patients after 6 months of use[214]. Beta-blockers decrease the whole-body metabolic rate and body fat[215], thereby theoretically leaving more energy for the brain. In addition, beta-blockers reduce rebound headache that often follows stress in patients with migraine[216], and this effect could result from regulation of noradrenaline-mediated consumption of energy reserves[100] 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 trigeminovascular 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 amygdala[79]. 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 brainstem[217]. 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 upregulated[218].

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 CSD[219] and inhibition of cerebral glycogen reduces the threshold for CSD in vivo[220]. Hyperglycaemia protects against induction of CSD[219]. 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 CSD[221].

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 stores[224]. When hypoxia is preceded by pharmacological mitochondrial inhibition, hypoxia-induced CSD in rat hippocampal slices is greatly facilitated[222]. This observation suggests a mechanism by which genetic or acquired mitochondrial dysfunction could exacerbate the impact of a metabolic stressor.

Trigeminovascular system

In experimental animals, CSD can activate the trigeminovascular system[225]. 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 nociceptors[227] (FIG. 2). In addition, CSD and subsequent restoration of ion homeostasis have an extremely high energy demand[228]. Moreover, in mice, CSD causes tissue hypoxia[223,229] and increases expression of mitochondrial uncoupling proteins, which decreases ATP synthesis and increases thermogenesis[230]. 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 system[231]. 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 attack[235], as they can be directly activated by various exogenous and endogenous agents that are associated with migraine, and their activation induces the release

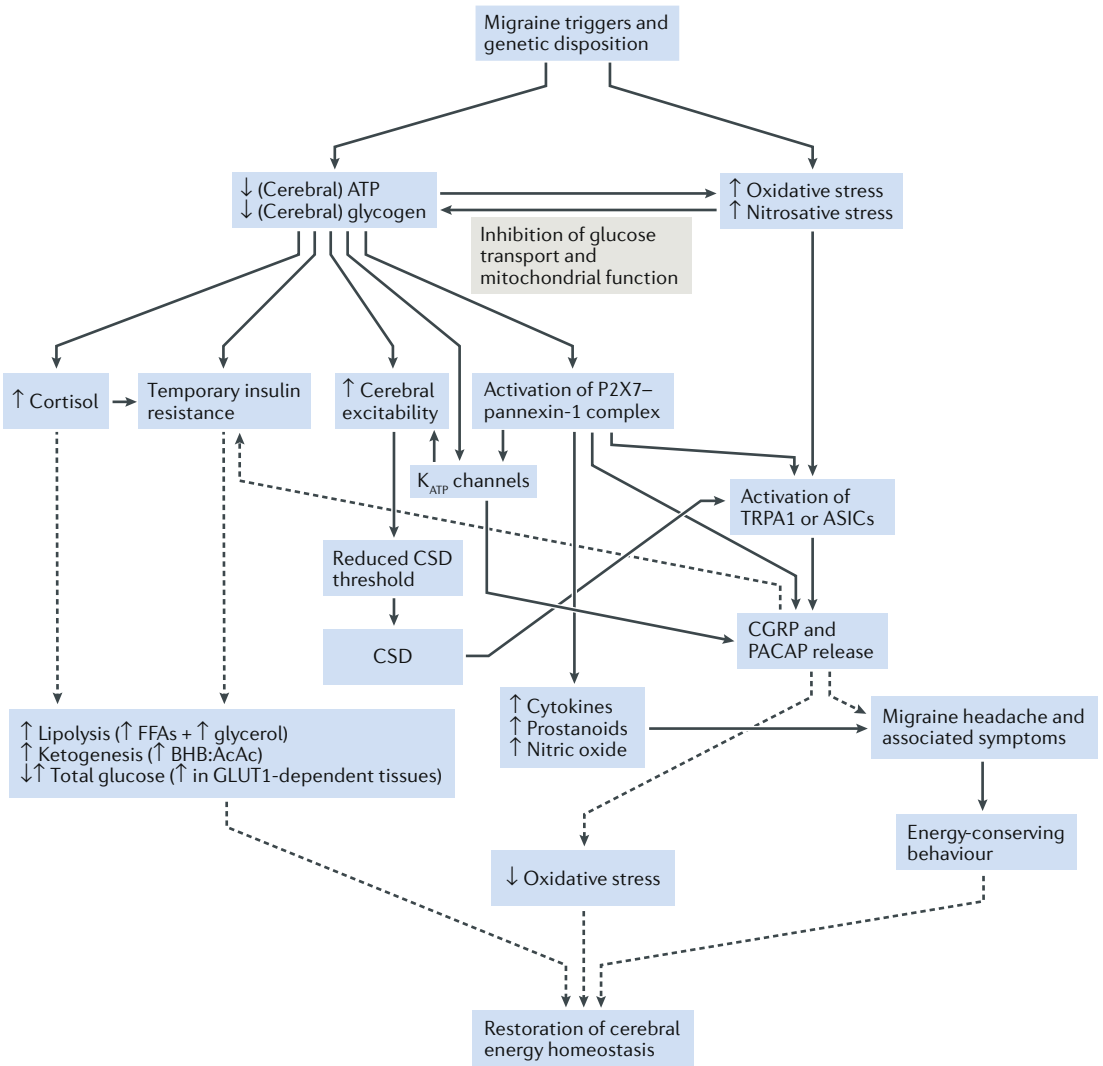

Fig. 2 | **Metabolic face of migraine attack generation and resolution.** In genetically predisposed individuals, migraine triggers can increase oxidative and nitrosative stress and/or reduce cerebral ATP and glycogen levels. These processes ignite a cascade of events that assists restoration of cerebral 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 CGRP[234]. TRP channels are also inhibited or desensitized by abortive migraine drugs[235]. These channels can also sense reactive species indirectly through second messengers or directly via oxidative modification of cysteine residues[236], 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 neurons[220], which leads to activation of meningeal nociceptors[227]. 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 nucleus[237]. 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 levcromakalim induced migraine headache in 16 of 16 patients with migraine, whereas placebo treatment did so in only 1 of these 16 patients[194] (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 bodies[238] or a decrease in extracellular glucose levels[239] 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 receptors[239] (FIG. 2).

High nitric oxide concentrations stimulate CGRP release and activate the trigeminovascular system, and nitric oxide can also modulate mitochondrial activity via various mechanisms[240]. The mitochondrial effects of nitric oxide could, therefore, explain the headache experienced by patients with migraine upon administration of nitric oxide donors[241]. Examples of the mitochondrial effects of nitric oxide in animals include inhibition of the mitochondrial respiratory chain in cultured astrocytes[242]. By contrast, use of ^{1}H-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, changes[243].

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 attacks[246], CGRP triggers attacks in patients with migraine[247], and blocking the action of CGRP transiently (with CGRP antagonists) or durably (with monoclonal antibodies) aborts attacks or reduces attack frequency, respectively[248]. 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 aura[249], and CGRP does not elicit premonitory symptoms[114]. 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 transport[254], decreased tolerance to glucose in the GTT without altering plasma insulin levels[255], inhibited muscle glycogen synthesis and caused insulin resistance upon activation of skeletal muscle sensory nerves[256]. In addition, intravenous injections of CGRP in the rat increased plasma glucose concentrations[255], 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 modality[262]. 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 controls[49]. 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 space[227], 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 aura[220]. Similarly, metabolic distress lowers the threshold for cortical spreading depression[220], which can aggravate metabolic alterations and cause migraine with aura. Alternatively, diencephalic and brainstem chemosensitive neurons[217] could sense metabolic changes and sensitizes 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 deficient[177].
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 glasses[263], 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 homeostasis[257]. 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 visceroautonomic 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 elsewhere[257]). In rats, PACAP stimulated glucose production via sympathetic hepatic innervation, indicating the PACAP release could also be an adaptive response to restore energy homeostasis[258].

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 account[259]. 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 response[77] 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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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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