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Review Article

Migraine, Brain Glucose Metabolism and the "Neuroenergetic" Hypothesis: A Scoping Review

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Abstract: **Increasing evidence suggests that migraine may be the result of an impaired brain glucose metabolism. Several studies have reported brain mitochondrial dysfunction, impaired brain glucose metabolism and gray matter volume reduction in specific brain areas of migraineurs. Furthermore, peripheral insulin resistance, a condition demonstrated in several studies, may extend to the brain, leading to brain insulin resistance. This condition has been proven to downregulate insulin receptors, both in astrocytes and neurons, triggering a reduction in glucose uptake and glycogen synthesis, mainly during high metabolic demand. This scoping review examines the clinical, epidemiologic and pathophysiologic data supporting the hypothesis that abnormalities in brain glucose metabolism may generate a mismatch between the brain's energy reserve and metabolic expenditure, triggering migraine attacks. Moreover, alteration in glucose homeostasis could generate a chronic brain energy deficit promoting migraine chronification. Lastly, insulin resistance may link migraine with its comorbidities, like obesity, depression, cognitive impairment and cerebrovascular diseases.**

Perspective: ***Although additional experimental studies are needed to support this novel "neuroenergetic" hypothesis, brain insulin resistance in migraineurs may unravel the pathophysiological mechanisms of the disease, explaining the migraine chronification and connecting migraine with comorbidities. Therefore, this hypothesis could elucidate novel potential approaches for migraine treatment.***

Key words: *migraine, glucose, brain insulin resistance, postprandial hypoglycemia, insulin sensitivity.*

Migraine is a common neurovascular disorder, characterized by recurrent headache attacks associated with neurological and gastrointestinal symptoms.[54] According to the diagnostic criteria published by the International Headache Society (currently ICHD-3), migraine may be classified into two different forms: migraine with aura (MA) and the most frequent form of migraine, without aura (MO). Although migraine is generally an episodic disorder, it may evolve over time into a chronic condition, with an annual progression rate of 3%.[197] Migraine is a disabling disorder, affecting about 14% of the world's population.[227] Epidemiological data showed a significantly higher prevalence of the disease in women, experiencing a significant burden of migraine symptoms and disability compared to men.[124] According to the *Global Burden of Disease* 2016, it is a worldwide leading cause of disability in all age groups,[227] especially in the under-50s.[213] The economic and societal impact of migraine is enormous, affecting patients' quality of life, impairing work, social activities and family life.[27]

Migraine is a complex disease, explained by an interaction between genetic, epigenetic and environmental factors.[57] However, despite recent progress, the detailed

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pathogenetic mechanisms of the disease are still not fully understood.[26] A growing body of evidence supports the presence of a metabolic dysfunction in migraine, which is mainly related to altered glucose-insulin metabolism.[77]

Glucose and insulin play a fundamental role in the central nervous system (CNS), regulating cerebral bioenergetics, enhancing synaptic viability and modulating the release of several neurotransmitters.[6] The failure of different tissues to respond to normal amounts of insulin is known as "insulin resistance." This phenomenon has been widely investigated in peripheral tissues and there is currently increasing interest in investigating brain insulin resistance. Preliminary studies suggest that brain insulin resistance may well play a role in neurodegenerative diseases, like Alzheimer's disease, and in cognitive vascular impairment.[6] To the best of our knowledge, brain insulin resistance in migraine has never been investigated.

This scoping review focuses on cerebral metabolic aspects of migraine, in an attempt to provide a clearer understanding of the disease pathogenesis, the complex pathophysiological interplay between episodic and chronic migraine and those between migraine and its comorbidities, and, hopefully, to highlight mechanisms that could become potential targets for novel preventive interventions.

Investigation into the pathophysiology of episodic migraine started by revisiting the "*old*" hypoglycemic hypothesis, first proposed in 1935.[76] The role that altered glucose homeostasis plays in migraine was also addressed by Gross EC et al.[77]. These authors suggested the hypothesis that insulin resistance is an adaptive response to migraine that increases energy supply to the brain, rather than a causal factor.[77] Conversely, we investigated into the "neuroenergetic" hypothesis by collecting and analyzing evidence for this new hypothesis, suggesting that postprandial (or reactive) hypoglycemia may well play a major pathophysiological role in episodic migraine and that brain insulin resistance could be a pivotal factor in migraine chronification.

In support of this hypothesis, we report some features associated with the pathophysiology and clinical progression of migraine, ie, brain mitochondrial dysfunction, impaired brain glucose metabolism, a decrease in grey matter volume and neuroinflammation, all of which are related to brain insulin resistance. Comorbidities of migraine, where impaired glucose metabolism and, mainly, insulin resistance are common pathophysiological features, were also identified: obesity, depression and cerebrovascular diseases.[33,160]

We postulated that insulin resistance could be the pivotal pathophysiological feature linking migraine to these comorbidities. Moreover, it has been suggested that insulin resistance may be an underlying factor that increases the risk of migraineurs developing dementia, especially those suffering from migraine with aura.[97,152]

The last paragraph discusses a novel treatment approach based on pathophysiology, ie, a dietary model with no or minimal intake of high glycemic index foods, regular aerobic exercise and Mind-Body Interventions (MBI). It has been reported that these interventions could not only lead to a significant reduction in the frequency and intensity of migraine attacks, but that they may also be able to prevent or, at least delay, some migraine comorbidities, reducing the migraine chronification risk.[126]

From Neuronal Cell Stress to Headache

Although the pathophysiological mechanisms underlying migraine remain to be clarified, a great deal of progress has been made over the past few years. Currently, there is increasing evidence in support of migraine being a compound, multifactorial disorder in the function of the nervous system, rather than merely a vascular headache.[35] Way back in 1984 Moskowitz proposed the first theory involving the vascular system, known as the "trigemino-vascular" theory.[153] This theory has been developed and partly modified over time, on the basis of updated evidence.[31] Recently, it has been hypothesized that altered neuronal excitability, characteristic of migraine, is multifactorial in origin. These include an altered energy homeostasis, mainly due to a defect in mitochondrial oxidative phosphorylation, dysfunction of calcium channels, or reduced plasma magnesium levels.[77] The most intriguing hypothesis is that in migraine with aura, which is underlain by the phenomenon of Cortical Spreading Depression (CSD), neuronal cell stress at a cortical level activates a signal cascade, triggering activation of the trigeminal-vascular system.[104] CSD may activate meningeal nociceptors, inducing an inflammatory cascade through the 'neuronal Pannexin-1 (Panx1) channel' opening and caspase-1 activation, followed by nuclear factor kB (NF-kB) activation in astrocytes.[104] Indeed, experimental studies showed that astrocytes play a pivotal role in this inflammatory response,[209] as most of them show NF-kB pathway activation, followed by the release of cyclooxygenase-2 and inducible nitric oxide synthase (iNOS) in the subarachnoid space.[104] Therefore, as the meninges are densely innervated by pain fibers that activate the trigeminovascular system, this pathway may well be the link between the aura and the algic phase of a migraine attack.[7,26] On the basis of this perspective, the trigeminovascular system could be considered a kind of "signaling mechanism" that alerts us as to alterations in cortical homeostasis.[104]

Cerebral Energy Deficiency: How Does it Come About?

The brain has high energy requirements. In fact, about 20% of the oxygen and 25% of the glucose consumed by the human body are employed in maintaining cerebral functions.[12] Although glucose is the mandatory energy substrate of the adult brain, the brain is capable of using alternative substrates to enable adaptation to certain metabolic conditions such as fasting, eg, by oxidizing ketone bodies, to meet the brain's energy

Table 1. Summary of the Studies Investigating Postprandial Hypoglycemia Incidence at Different Oral Glucose Tolerance Test (OGTT) Times and Different Hypoglycemic Threshold.

First Author	OGTT (hours)	Subject characteristics	Postprandial Hypoglycemia Incidence
Sørensen M.[207]	2	Subjects without diagnosis of abnormal glucose metabolism; 59% had a prior CV complication; mean age 71 years; 214 M, 148 F	12% had 2 h- glycaemia ≤3.9 mmol/L or 2 h-glucose < fasting glucose
Parekh S.[167]	2	Diabetes-free; mean age ≈ 57 years; 3410 F, 3068 M	5.5% had 2 h- glycaemia <3.3 mmol/l
Cai X.[29]	2	Normal glucose tolerance; mean age 40.2 years; 10399 M, 16207 F	0.53% had 2 h-glycaemia < 3.0 mmol/l
Fariss BL.[60]	2	US Army's healthy young men; 17-29 years old; 4928 M	24.4% had 2 h-glycaemia < 3.3 mmol/l
Johnson DD.[101]	5	Normal glucose tolerance; 17% obese; mean age 41 years; 98 F, 49 M	23.8% had 2 h-glycaemia < 2.8 mmol/l
Lev-Ran A.[123]	5	Normal glucose tolerance; mean age ≈ 40 years; 14% overweight; 304 M, 346 F	10% had 5 h-glycaemia < 2.6 mmol/l
	5	Suspected of having hypoglycemia; mean age ≈ 40 years; 13.5% overweight; 83 F, 35 M	13.5% had 5 h-glycaemia < 2.2 mmol/l
Jung Y.[102]	5	Normal weight; 20-45 years old; 122 F	18.8% had 5 h-glycaemia < 3.3 mmol/l
	5	Normal weight; 46-70 years old; 43 F	2.3% had 5 h-glycaemia < 3.3 mmol/l
	5	Obese; 20-44 years old; 58 F	31% had 5 h-glycaemia < 3.3 mmol/l
	5	Obese; 46-70 years old; 62 F	11.3% had 5 h-glycaemia < 3.3 mmol/l
Guiducci L.[80]	> 2	Obese and obesity-prone individuals*	32% had 2 h- glycaemia < 3.9 mmol/L
Altuntas Y.[4]	4	Lean and young PCOS subjects	50% had 4 h- glycaemia < 3.0 mmol/l
Kasim-Karakas SE.[105]	5	Overwheight and obese young PCOS subjects	64% had 5 h- glycaemia < 3.9 mmol/l

Abbreviation. CV, cardiovascular; M, males; F, females; PCOS, Polycystic ovary syndrome.
*(normal weight individuals with a strong family history of obesity).

demands.[136] Lactate also is another main alternative fuel for the brain as both ketone bodies and lactate are able of crossing the blood-brain barrier through monocarboxylate transporters (MCTs) in endothelial cells, astroglia and neurons.[99]

The Role of Postprandial (or Reactive) Hypoglycemia in Episodic Migraine

Hypoglycemia: an "old friend"

Hypoglycemia was considered a precipitating factor in migraine headaches as far back as 1935.[76] In the light of new supportive evidence, particularly studies investigating glucose homeostasis in migraine patients, recent research has brought the hypoglycemic hypothesis back into play.[77] The evidence suggesting that the cerebral energy deficit may characterize people who are particularly susceptible to postprandial (or reactive) hypoglycemia, because of altered insulin sensitivity, will be detailed in the following paragraphs.

In 1998, Bonora et al. estimated that the prevalence of insulin resistance was of 65.9% for subjects with impaired glucose tolerance, 83.9% for non-insulin-dependent diabetes mellitus sufferers, 53.5% for people with hypercholesterolemia, 84.2% for those with hypertriglyceridemia, 88.1% in subjects with low HDL cholesterol, 62.8% in hyperuricemia and 58.0% in hypertension.[19] These percentages are impressive and show how prevalent insulin resistance is in the general population. Indeed, about one third of American adults have impaired glycemic homeostasis[41,44] and young people are not spared either. This can be seen in a 2006 population-based study on non-diabetic US adolescents (12-19 years old), which reported that about 13% of them were insulin resistant.[120] Postprandial hypoglycemia in insulin resistant subjects is associated with impaired first phase glucose-stimulated insulin response and a compensatory increased late insulin response.[4,50,156] Half a century ago, it was hypothesized that an increase in insulin sensitivity might also underlie postprandial hypoglycaemia,[131] and this was later demonstrated with the hyperinsulinemic normoglycemic glucose clamp technique.[218] Nowadays, it is scientific knowledge that subjects with high insulin sensitivity have an increased glucose absorption which leads to postprandial hypoglycaemia.[22,218] Moreover, this altered insulin sensitivity leads to postprandial hypoglycemia, which, in turn, causes increased food intake and weight[22,72,73] – in particular if high insulin sensitivity is combined with a high acute insulin response to glucose (high AIRg)[73,169,204] – and may represent an event preceding insulin resistance.[73,80] Postprandial hypoglycemia is not uncommon, both in the general population and in those with diseases that alter the glucose metabolism. Table 1 reports some significant studies on the incidence of postprandial hypoglycemia and shows that a 2-h OGTT does not suffice to fully understand the real prevalence of those suffering from postprandial hypoglycemia, but that a 4- or 5-hour (OGTT) may be required.[132,157,167]

As described in Table 1, three studies carried out OGTTs and observed that subjects with diseases characterized by insulin resistance, ie, polycystic ovary syndrome and obesity, had high incidence of reactive hypoglycemia: 32%,[80] 50%[4] and 64%.[105] Noteworthy, was the high incidence of postprandial hypoglycemia

reported also in young, normal weight (on average) subjects, without a diagnosis of abnormal glucose metabolism: 24.4%,[60] 23.8%,[101] 10%[123] and 18.8%.[102] Other studies reported in Table 1,[29,167,207] carried out OGTTs to identify reactive hypoglycemia in thousands of diabetes-free subjects or subjects with normal glucose tolerance.

No association was observed between reactive hypoglycemia at the 2-h OGTT and insulin resistance. Conversely, a glycemia of < 3.3 mmol/l detected at the 2-h OGTT, was associated with a younger age, higher insulin sensitivity and a lower body mass index. This is further evidence supporting that both high insulin sensitivity and insulin resistance may lead to the development of postprandial hypoglycemia. Moreover, high insulin sensitivity appears to be the most frequent cause of postprandial hypoglycemia, being probably implicated in 50 to 70% of all cases.[22,23]

Episodic Migraine and Postprandial (or Reactive) Hypoglycemia: Clinical Evidence

Clinical evidence suggests that migraine can, to a large extent, be generated by postprandial hypoglycemia. Indeed, data from clinical practice has taught us that the most frequent triggering factor reported by migraineurs is fasting and that migraine is more likely to occur in susceptible persons when there is insulin resistance.[142,187] Hockaday et al. carried out a study where 50g of glucose was given to 10 migraineurs whose attacks were associated with fasting, after a 10-hour fast. A total of 6 of 10 of them had a migraine attack within 8 hours of the glucose test,[90] as the hyperglycemic effect of cortisol requires a few hours to appear.[218] Luyckx et al. observed that 30 of 47 patients who had reactive hypoglycemia had reported signs of a so-called "*neuroglycopenia*" occurring from 2 to 4 hours after a meal in their everyday life. They had signs and symptoms which included weakness, faintness, headache, irritability, anxiety, nervousness, palpitations, inward trembling, vertigo, hunger, and syncope. In another study, 74 migraineurs who reported that fasting had triggered their attacks, had a 5-h OGTT with 100g of glucose. A curve, consistent with reactive hypoglycemia values, was observed in 56 of 74 (76%) of them.[52] Wilkinson reported that 11 of 13 (85%) subjects, who seemed to have '*headaches of a migrainoid nature*' had induced headaches during a 5-hour OGTT. The headache began 3-4 h into the test when the glucose level dropped to its lowest (ie, < 3.3 mmol/L).[232] A serum glucose level below 3.3 mmol/L within a few hours of glucose ingestion is considered to be a sign of reactive hypoglycemia.[167] A review of international literature indicates that, more often than not, there are two main specific dietary factors, ie, fasting and a relatively mild reactive hypoglycemia, which may follow large (ie, 100 g) carbohydrate ingestions, which induce migraine in sufferers and more generalized headaches in the general population.[94]

The classical signs of hypoglycemia include: blurred vision, headache, confusion, depression, tremors, anxiety, hunger, palpitations, sweating, nausea, dizziness and weakness.[22,101,218] Similar symptoms have been observed in subjects with insulinoma,[34,93,119,180,203] a rare condition that can lead to postprandial hypoglycemia. The patients enrolled into these studies complained of typical hypoglycemia symptoms, such as dizziness, sweating, confusion, irritability and blurred vision, 2 hours after a meal. All the symptoms reported by people with insulinoma may be attributed to an insufficient supply of glucose to the brain. Their comorbidities were epilepsy, anxiety, depression and, interestingly, migraine. The hypoglycemia symptoms match most of the non headache symptoms of migraine, including tiredness and/or weariness, difficulty in concentration, blurred vision, light sensitivity, intolerance and/or irritability, hunger and/or food craving and dizziness.[71] Moreover, estro-progestinic drugs induce hyperinsulinism and hypoglycemia, which might explain the frequent worsening of migraine in patients on these drugs.[107] In line with this, Granella et al. reported a more severe migraine in 25% of patients without aura and in 56% of those with aura on estro-progestinic drugs.[75]

Intriguingly, an experimental study[141] demonstrated that administration of insulin as well as glucagon, a peptide hormone produced by alpha cells of the pancreas that counteracts insulin actions, significantly modulate the neuronal firing in the trigeminocervical-complex, a key structure in the pathogenesis of the migraine attack. This suggests that there is a potential neurobiological link between migraine and altered glucose homeostasis.

Metabolic Similarities Between a Migraine Attack and the Hypoglycemic State

Biochemical studies highlight similarities in the metabolism observed during a migraine attack and a hypoglycemic state. Indeed, it was observed that the levels of free fatty acid, ketone bodies, glycerol and cortisol, were increased in the venous blood samples of migraineurs during an attack.[202] The same metabolic pattern was observed during fasting or glucoprivation, in the general population.[2] Several studies reported a higher frequency of altered insulin sensitivity in both episodic migraine (EM) and chronic migraine (CM).[174] Bhoi et al. observed that insulin resistance correlated with the duration of migraine attacks.[17] A case-control study identified a significant insulin resistance prevalence in CM with a three-fold higher probability of having insulin resistance than the EM group, where an insulin resistance prevalence similar to that of the control group was observed.[61] This association remained constant also after adjustment for the confounding variables commonly associated with a higher insulin resistance status.

Glucose-Insulin Metabolism and the Brain

There is an increasing amount of data on insulin and brain insulin resistance, which evidence important

features of migraine, dementia and other neurodegenerative disorders.[6,221] Under physiological conditions, the regulatory mechanisms in the blood-brain barrier, astrocytes and neurons provide an efficient supply of energy during neuronal activation.[103]

Current literature reports that the human brain is an insulin sensitive organ and, as such, may become insulin resistant.[89,210] Indeed, some researchers suggests that peripheral insulin resistance can extend to the brain, triggering brain insulin resistance.[145,190,210]

Similarly, to the mechanism that takes place in peripheral insulin resistance, brain insulin resistance occurs when the brain cells fail to respond to insulin. The following paragraphs will focus on the main metabolic pathways involved in brain glucose homeostasis which may be altered by insulin resistance and, consequently, fail to provide an adequate energy supply during neuronal activation (Fig 1).

Insulin Resistance and the Brain

Insulin resistance is generally defined as a reduced sensitivity in body tissues to the action of insulin.[9] Therefore, insulin resistance is a state where a normal amount of insulin produces a subnormal physiological response. Similarly, brain insulin resistance can be defined as the failure of brain cells (neurons and glial cells) to respond to insulin.[148] Systemic and brain insulin resistance may be closely related. In patients with type 2 diabetes (T2DM), systemic insulin resistance may lead to brain insulin resistance and brain dysfunction, whilst abnormal insulin signaling in the brain may have systemic effects, impairing metabolism regulation.[6,192,211] Currently, it is not yet clear whether peripheral and brain insulin resistance can exist independently or not.

The reduced response to insulin could be related to various mechanisms, including a downregulation of insulin receptors, the inability of insulin receptors to bind insulin or an abnormal activation of the insulin signaling cascade.[6] At the cellular level, this dysfunction might manifest as an impairment of neurotransmitter release, altered receptor regulation in neurons and glial cells, or dysfunction of processes more directly related to insulin metabolism, such as neuronal glucose uptake in neurons or homeostatic or inflammatory responses to insulin.[112,114]

The most efficacious method to measure insulin resistance in humans is considered to be the use of a hyperinsulinemic-euglycemic (HI-EG) clamp, that infuses insulin at a constant rate and a variable infusion of dextrose to maintain euglycemia.[217] However, HI-EG is demanding and costly. The oral glucose tolerance test (OGTT) is a valid alternative for the evaluation of insulin resistance as it provides information on insulin secretion and action, even if it does not directly yield a measure of insulin sensitivity. Several indexes of insulin resistance have been suggested on the basis of the data derived from OGTTs and some of these had a highly significant correlation with the clamp.[139,173] The study of brain insulin resistance requires intranasal administration of insulin. This approach delivers insulin directly to the CNS, bypassing the BBB, with a minimal insulin increase in the periphery. The direct effects of insulin on CNS activity can be assessed by neuropsychological, neurophysiological and neuroimaging investigations.[161,238]

Insulin Receptors

It has been demonstrated that insulin receptors and the related insulin signaling cascade are pivotal factors in brain metabolism, both in neurons and astrocytes.[13] The insulin receptor (IR) in mammals occurs in two isoforms, IR-A and IR-B, which are expressed in different relative proportions in various organs and tissues. Moreover, it has been observed that their expression varies during development, aging and disease states.[208] On binding to IR-A, insulin triggers the classical mitogenic signaling cascade (non-metabolic effects), whilst if it binds to IR-B it activates the metabolic phenotype pathway.[13,170,208]

The IR−B/IR−A mRNA ratio is predominant in human tissues like the liver, adipose tissue, skeletal muscle and kidney and is associated with the metabolic effects of insulin. Conversely, insulin acts as a mitogenic agent in fetal and cancer tissues where, the IR−A/IR−B mRNA ratio prevails.[13,18,231] Although the expression of both IR-A and IR-B in human astrocytes had been previously described,[69] Spencer et al. used an innovative, investigative method (in situ RT-PCR/ FISH assay) and was the first to demonstrate that both IR-A and IR-B are expressed in the neurons of the adult human frontal cortex brain tissue.[208] These IR-A and IR-B receptors have distinct activation and regulation mechanisms. There is a downregulation of IR-B in chronically high levels of insulin, without it affecting the brain IR-A.[69] Indeed, animal studies have demonstrated that an increased IR-A/IR-B ratio is related to insulin resistance[13] and glucose intolerance in mice.[208] Moreover, IR-A is favored in diabetic or pre-diabetic subjects in a state of peripheral hyperinsulinism, whilst IR-B metabolic processes are reduced.[13]

Alterations in insulin receptor signaling have been associated with dementia[11] and, interestingly, it has been reported that an IR-B analogue, discovered in C. elegans, is involved in learning and memory.[162] Therefore, as postulated by Spencer et al., IR-A and IR-B may have distinct functions in neurons.[208]

Glucose Transporters in the Brain

Neurons

The uptake of glucose by neurons is mainly provided by the insulin-independent high-affinity glucose transporter GLUT3.[112] However, insulin-sensitive GLUT4 is also co-expressed with GLUT3 in some brain regions which are particularly reactive to insulin[114] and related to cognitive behavior and tasks. These regions include the basal forebrain, the hippocampus, the amygdala, the cerebral cortex and the cerebellum.[6,100] GLUT4 improves glucose influx into neurons during high metabolic demand tasks, like learning.[6,210] It has been proven that insulin induces the incorporation of GLUT4 from intracellular stores into the plasma membrane via an

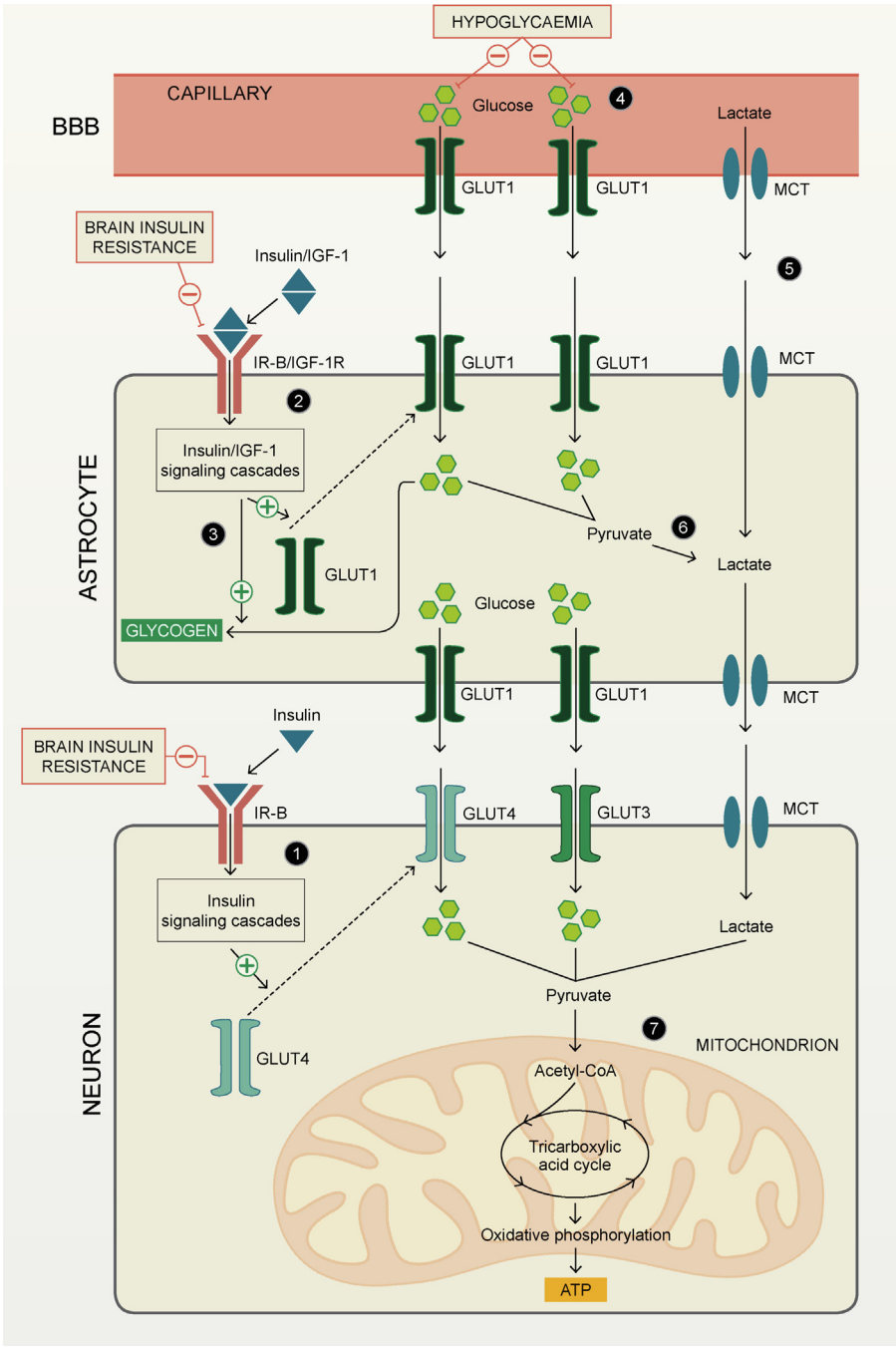

Figure 1. Cerebral metabolic abnormalities that might be implicated in migraine pathophysiology. Insulin induces incorporation of GLUT4 from intracellular stores into the plasma membrane in neurons, binding to insulin receptor isoform B (IR-B), during a period of high metabolic demand, especially in brain regions related to cognitive behavior (step 1). The increased abundance of GLUT4 and maybe also GLUT3 in the membrane increases the glucose influx into neurons. The membrane GLUT1 abundance and glycolysis are upregulated in astrocytes during neuronal activation, leading to an interstitial decrease in glucose and an upregulation of GLUT1 in the plasma membranes of capillary endothelial cells. The combined action of insulin and insulin-like growth factor-1 (IGF-1), achieved by the binding to IR-B and IGF-1 receptor (IGF-1R) respectively, lead to the translocation of GLUT1 from intracellular compartments to the cell membrane in astrocytes, stimulating glucose uptake (step 2). Insulin and IGF-1 also stimulate glycogen synthesis in astrocytes (step 3). Glucose crosses the blood-brain barrier (BBB) via glucose transporter 1 (GLUT1), expressed by capillary endothelial cells. Hypoglycemia, which can occur after a glucidic meal (ie, postprandial hypoglycemia), reduces the amount of glucose available for brain metabolism (step 4). In brain insulin resistance, IR-B could be downregulated, triggering an alteration of glucose metabolism in neurons and astrocytes. Lactate is an alternative fuel for the brain and is capable of crossing the BBB through monocarboxylate transporters (MCTs) in endothelial cells, astrocytes and neurons (step 5). Lactate may be also generated by pyruvate, which is generated by astrocytes through a non-oxidative glucose metabolism and shuttled to neurons through monocarboxylate transporters (step 6), as proposed by the astrocyte-lactate-neuron shuttle hypothesis. In neurons and specifically in the mitochondria, glucose and lactate produced pyruvate is converted into acetyl-coenzyme A (Acetyl-CoA), which, via the tricarboxylic acid cycle and oxidative phosphorylation, leads to energy production in the form of ATP (step 7).

AKT-dependent mechanism.[6,112] Indeed, Wortmannin, a specific phosphatidylinositol 3-kinase (PI3K) inhibitor (AKT is a significant downstream effecter of PI3K signaling[127]) totally abolishes insulin-dependent GLUT4 translocation and glucose uptake.[14] Benomar et al. observed in an experimental model that cultivated human neuronal cells decreased GLUT4 incorporation into the plasma membrane after chronic insulin treatment.[14] Some authors have hypothesized that protracted changes in glucose and insulin concentrations in the brain and a reduced insulin receptor sensitivity during diabetes, could influence the GLUT4 expression and function in the brain.[112] This was supported by an in vivo experiment on an animal model which demonstrated a reduced GLUT1, GLUT3 and GLUT4 density in mouse brains, after a 3-month diet rich in fat and sugar.[68]

Astrocytes

Astrocytes are the brain reservoir of glucose storage in the form of glycogen[55] and inadequate brain glycogen reduces the threshold for CSD in vivo.[106] The high affinity glucose transporter GLUT1, the main glucose transporter in astrocytes, is also responsible for glucose transport in the endothelial cells of the blood-brain barrier[77,151] and is highly expressed in the dendritic endfeet of astrocytes that wrap around brain capillaries.[112] On the basis of the fact that an expression of the insulin-sensitive glucose transporter GLUT4 was observed in astrocytes,[154] it was speculated that insulin may stimulate glucose uptake into astrocytes through GLUT4.[154] Further experimental studies reported a co-operative mechanism where insulin stimulates glucose uptake through forebrain astrocytes that work in conjunction with insulin-like growth factor-1 (IGF-1), through the synergistic activation of mitogen-activated protein kinases (MAPKs) and protein kinase D (PKD), ie, the MAPK/PKD pathway.[64]

The combined action of insulin and IGF-1 leads to the translocation of GLUT1 from intracellular compartments to the cell membrane.[64] Moreover, Heni et al. demonstrated that insulin stimulates glucose uptake and glycogen synthesis in astrocytes through IR-B.[88] Muhič et al. have demonstrated that insulin and IGF-1 enhance glycogen levels in single isolated astrocytes through the PI3K/AKT pathway.[154] This evidence supports the hypothesis that a dysfunction in insulinoid signaling could trigger an inadequate replenishment of glycogen stores.

Interestingly, the lack of a short-term energy buffer may be pivotal in neurodegenerative and psychiatric disorders.[154]

Migraine Features Potentially Related to Brain Insulin Resistance

Brain Mitochondrial Dysfunction

It has been suggested that brain mitochondrial dysfunction takes place in association with brain insulin resistance[210] and recent evidence in support of a mitochondrial dysfunction in migraine has also been reported.[77] Neuroimaging studies have demonstrated a lower adenosine triphosphate (ATP) and 'mitochondrial phosphorylation potential' in the brain of migraineurs without aura during the interictal period, than in controls.[179] Interestingly, the lowest ATP concentrations were observed in the most severely affected migraine patients.[77] Several studies have described that the lowest ATP concentrations in the migraineurs' brains, evaluated by phosphorus magnetic resonance spectroscopy and compared to controls, are associated with a reduced glucose metabolism in the parietal, temporal and frontal lobes, as reported in Table 2.[108,143,176,198,199,229] However, further research is required to elucidate whether brain insulin resistance could be implicated in brain mitochondrial dysfunction.

Impaired Brain Glucose Metabolism in Migraine

Specific areas of the brain, like the Brodmann areas 10 and 47, seem to suffer from glucose hypometabolism, both in subjects with insulin resistance and those with chronic migraine (Table 2). This evidence strengthens our hypothesis that brain insulin resistance, stemming from peripheral insulin resistance extending to the brain and impairing a correct astrocytes and/or neurons glucidic metabolism, may well trigger the neuronal cell stress implicated in migraine chronification. This hypothesis is supported by other experimental evidence. Firstly, GLUT4 is mainly expressed by the cerebral areas that regulate memory, learning, emotional and cognitive functions, ie, the hippocampus, the amygdala and the cerebral cortex.[6,86,195] This suggests that the insulin signaling pathway may well play a key role in the utilization of glucose in these areas.[86] Noteworthy is the fact that all these areas are affected both in subjects with insulin resistance and those with migraine (Table 2). Moreover, it has been observed in rats that insulin activation of GLUT4 improves glucose flux into neurons during periods of high metabolic demand, like during learning or other cognitive tasks.[146,147,168]

Therefore, we hypothesize that, if this increased glucose demand is not satisfied – in subjects with episodic migraine partly due to postprandial hypoglycemia, and in subjects with chronic migraine partly due to brain insulin resistance – and if the brain is not able to use ketone bodies efficiently,[77] as should happen during fasting or carbohydrate restriction[164] (conditions unlikely in Western countries with a carbohydrate-laden diet[77]), then this would lead to an energy deficit, which would, in turn, trigger a migraine attack.

Arnold et al. also observed that alterations in insulin levels might affect neuronal glucose uptake and metabolism via GLUT4 translocation in response to insulin-IRS1-AKT signaling in the brain regions involved in cognitive and emotional function.[6] Moreover, data from a study on normal weight young women with mild insulin resistance (suffering from Polycystic ovary syndrome-PCOS) strengthens the hypothesis that insulin resistance could be a primary cause of cerebral glucose

Table 2. Comparison Between Brain Areas Affected by Reduced Glucose Metabolism, Volume and Energy Metabolism in Insulin Resistance and Migraine.

	Reduced regional cerebral glucose metabolism in subjects with insulin resistance	*Reduced regional cerebral volume in migraine subjects*	*Reduced regional cerebral energy metabolism in migraine subjects* ‡	*Reduced regional cerebral glucose metabolism in migraine subjects*
The insular lobe		Insular cortex (CM)[117,*] Valfrè W, et al.[225,‖]		Insular cortex (EM)[108]. Insular cortex (CM)[143]
The parietal lobe	Left parietal cortex[30,‡‡]. Lateral parietal lobe[234]. Brodmann areas 7 and 40[10]	Parietal lobe (CM)[117]. Left parietal operculum (CM)[225,‖]	PCr/Pi ↓, Pi/Tp ↓[229]. $[Mg^{+2}]$ ↓[176]. PCr/Pi ↓, Pi/ATP ↑[198]. PCr/Pi ↓[199]	Parietal cortex (CM)[143]
The anterior cingulate cortex		Yu Y, et al. (EM, CM)[236,†] Valfrè W, et al. (CM)[225,‖]		Kim JH, et al. (EM)[108] Mathew NT. (CM)[143]
The posterior cingulate cortex	Baker LD, et al.[10]			Kim JH, et al. (EM)[108]
The temporal lobe	Left middle temporal cortex[30,‡‡]. Lateral and medial temporal lobes[234]. Temporal/angular gyri (BA 39)[10]		PCr/Pi ↓, Pi/Tp ↓[229]. $[Mg^{+2}]$ ↓[176]. PCr/Pi ↓, Pi/ATP ↑[198] PCr/Pi ↓[199]	
The prefrontal cortex	Anterior and inferior prefrontal cortices (BA 10, 45, **47**)[10]. Bilateral prefrontal cortex[234]	Inferior frontal gyrus (BA 44, 45, **47**)[¶] (CM).[225,‖] Lateral orbital gyrus (BA **47**)** (CM)[39,††]		Left prefrontal cortex (EM)[108]. Orbitofrontal cortex (BA 10, 11 and **47**)[§] (CM)[143]
The frontal lobe	Right superior frontal cortex, right and left middle frontal cortex[30,‡‡]	Caudal middle frontal gyrus (CM)[117]. Precentral gyrus (CM)[117]. Right frontal pole (CM)[39,††] Medial frontal lobes (CM)[39,††]	PCr/Pi ↓, Pi/Tp ↓[229]. $[Mg^{+2}]$ ↓[176]. PCr/Pi ↓[199]	
The hippocampus	Castellano CA, et al.[30]	left hippocampus (CM)[236]		
The amygdala	Castellano CA, et al.[30]	left amygdala[225,‖]		

Abbreviation. BA, Brodmann area; EM, episodic migraine; CM, chronic migraine; PCr, phosphocreatine; Pi, inorganic phosphate; TP, total phosphorus signal; ATP, adenosine triphosphate.
*Lai KL et al. enrolled patients with CM without medication overuse headache, major depression or prior preventive treatment.
†A higher headache frequency was associated with smaller grey matter volume in the anterior cingulate cortex and hippocampus in EM and CM.
‡According to current literature, most studies have chosen the occipital cortex as the region of interest, as aura, most commonly with visual symptoms, is attributed to this area in patients suffering from this type of migraine.[179]
§The orbitofrontal cortex includes the Brodmann areas 10, 11 and 47.[113]
¶The inferior frontal gyrus includes the Brodmann areas 44, 45 and 47.[78]
‖Valfrè et al. observed that CM patients had significantly more grey matter reductions in these areas than EM patients.
**The lateral orbital gyrus includes the Brodmann area 47.[134]
††Chronic migraine patients had smaller frontal regions than episodic migraine patients.
‡‡This study[30] on young women with Polycystic Ovary Syndrome reported a direct association between mild insulin resistance and brain glucose hypometabolism, which was independent of overweight or obesity.

hypometabolism itself. Indeed, a direct association was observed between mild insulin resistance and brain glucose hypometabolism, whether the subjects were overweight and/or obese or not.[30] The same authors studied women with PCOS by fluorodeoxyglucose (FDG)-positron emission tomography (PET) and observed that they had a lower cerebral metabolic glucose rate and volumetric magnetic resonance imaging (MRI) evidenced a reduced volume of the frontal and parietal cortex.[30]

Brain Morphometric Studies: a Decrease in Grey Matter Volume

There is increasing evidence supporting an association between grey matter volume and chronic pain conditions.[144] Indeed, based on MRI-morphometry, some studies demonstrated grey matter reductions in samples of patients with chronic back pain,[5,67] fibromyalgia[24,184] or osteoarthritis.[185] Although most of these studies reported that pain is the main cause of grey matter volume reduction, other non-painful conditions do involve the presence of a grey matter reduction, often in the same brain areas, major depression[235] and PCOS[30] (Table 3).

Moreover, differently to migraine headache a recent study observed that there is no reduction in grey matter volume in tension-type headache,[38] suggesting that the metabolic alterations typical of migraine may play a role in these morphometric changes.

Other studies suggest that the reduction in grey matter volume depends mainly on two features shared by chronic migraine, major depression, chronic back pain, polycystic ovary syndrome, fibromyalgia and osteoarthritis, ie, a higher incidence of insulin resistance and systemic inflammation, than what is observed in healthy controls.[30,43,62,66,87,95,128,177,186,201] Interestingly, research data confirmed the efficacy of metformin in obtaining chronic pain relief.[8] This was further supported by evidence showing that a grey matter volume reduction is related to obesity[114] and that hippocampal atrophy can be observed in individuals with impaired glucose tolerance and insulin resistance.[114] Furthermore, a relationship between the metabolic syndrome and chronic pain was also observed.[128]

All brain regions affected by a grey matter volume reduction in the aforementioned pathologies are dedicated to higher cognitive functions (mood regulation, memory, the regulation of affective states, emotion, awareness of bodily states and cognitive processing).[39,46,182,215,222,235] Interestingly, the Brodmann area 47, part of the prefrontal cortex, is affected by a reduction in grey matter volume in 4/7 diseases listed in Table 3, ie, chronic migraine, major depression, chronic back pain and fibromyalgia. This area is related to memory and emotion[215] and in particular, to empathy.[223]

As aforementioned, GLUT4 is predominantly expressed in the areas of the brain responsible for higher cognitive functions.[6,100] As a reduction in GLUT4 activity, along with a decreased glucose uptake and glycogen synthesis in astrocytes, would reduce the neuronal function, it is reasonable to hypothesize that this process could lead to brain atrophy and a reduction in grey matter volume.[6] Patients with chronic migraine had smaller frontal regions than those with episodic migraine. A correlation analysis revealed a negative correlation between headache frequency and the volume of the right frontal pole, right lateral orbital gyrus and the medial frontal lobes.[39] This evidence seems to further support our hypothesis that a proportion of the subjects with episodic migraine have an altered insulin sensitivity which, when insulin resistance develops over time, would favor the chronification of migraine due to the extension of insulin resistance from the periphery to the brain. Accordingly, people with chronic migraine are more likely to have insulin resistance than those with episodic migraine.[61]

Neuroinflammation in Migraine

Inflammatory processes are associated with the pathophysiology and clinical progression of migraine.[42,122] Indeed, a large amount of literature data report that inflammation may play a pathophysiological role, both before and after the neuronal cell stress, in a migraine attack:

Inflammation hinders insulin action

Some data suggest that pro-inflammatory cytokines play a key role in the development of insulin resistance by the suppression of insulin receptor activity and downregulation of the GLUT4 expression.[85,92,188,214] Therefore, in line with our initial hypothesis, inflammation may well be pivotal in migraine pathophysiology involving the downregulation of GLUT4 and, in turn, may lead to a reduction in brain glucose metabolism, inducing neuronal cell stress. Moreover, there may be a vicious circle between inflammation and insulin resistance. Experimental diabetic neuropathy study[159] has reported that NF-κB regulates neuroinflammation by increasing oxidative damage and insulin resistance. It has already been established that there is a strong link between insulin resistance and neuroinflammation in the pathophysiology of Alzheimer's disease.[48,226] Indeed, some peripherally produced pro-inflammatory cytokines, eg, TNF-α, IL-6 and IL-12, are capable of crossing the blood-brain barrier.[135] Their subsequent activation through receptor binding would then hinder the insulin effects and promote the progression of Alzheimer's disease[1] and it is reasonable to presume that there may well be a similar process involved in the pathogenesis of migraine.

Neuronal cell stress triggers inflammatory response

Karatas et al. described a previously unknown signaling pathway between 'stressed neurons'[104] – which we hypothesized to be due to an energy deficiency – and trigeminal afferents during CSD, that was proposed to link the aura to the migraine headache attack.[36]

Table 3. The Brain Areas Affected by a Decrease in Grey Matter Volume in Different Pathologies.

	Chronic migraine	*Major depression*	*Chronic back pain*	*PCOS*	*Fibromyalgia*	*Osteoarthritis*
The insular lobe	Insular cortex[117,*]	Bilateral insula[235]	Anterior insula[67]		Left mid insula[184]	Right insular cortex[185]
The parietal lobe	Lai KL, et al.[117] Left parietal operculum[225,†]			Left supramarginal cortex (BA 40)[30]. Right superior parietal cortex[30]		
The anterior cingular cortex	Yu Y, et al.[236,†] Valfrè W, et al.[225,§]	Wise T, et al.[235]		Unlu E, et al.[224]	Burgmer M, et al.[24] Robinson ME, et al.[184]	Rodriguez-Raecke R, et al.[185]
The temporal lobe		Superior temporal gyrus[235]				
The hippocampus	Left hippocampus[236]	Left hippocampus[235]				
The frontal lobe	Caudal middle frontal gyrus[117]. Precentral gyrus[117]. Right frontal pole[39,**]. Medial frontal lobes[39,**]			Left superior frontal cortex[30]		
The prefrotal cortex	Inferior frontal gyrus (BA 44, 45, **47**)[‡,225,§]. Lateral orbital gyrus (Brodmann area **47**)[‖,39,**].	Medial prefrontal cortex[235]. Orbitofrontal cortex[235]. Inferior frontal gyrus (BA 44, 45, **47**)[‡,235].	Ventromedial prefrontal cortex (BA 10, 11)[‡,67]. Ventrolateral prefrontal cortex (BA **47**)[67]. Dorsomedial prefrontal cortex (BA 10)[67]	Dorsomedial prefrontal cortex[224]. Dorsolateral prefrontal cortexes[224]	Inferior frontal gyrus (BA 44, 45, **47**) [‡,24]	Dorsolateral prefrontal cortex[185]
The amygdala					Burgmer M, et al.[24]	Rodriguez-Raecke R, et al.[185]

Abbreviation. BA, Brodmann area; CM, chronic migraine; EM, episodic migraine.
*Lai KL et al. enrolled subjects with CM without medication overuse headache, major depression, or prior preventive treatment.
†A higher headache frequency was associated with a smaller grey matter volume in the anterior cingulate cortex and hippocampus in EM and CM.
‡The inferior frontal gyrus includes the Brodmann areas 44, 45 and.[78]
§Valfrè et al. observed that CM patients had significantly more grey matter reductions in these areas than EM patients.
‖The lateral orbital gyrus includes the Brodmann area 47.[134]
**CM patients had smaller frontal regions than episodic migraine patients.
‡BA 10 also shows a reduced glucose metabolism in subjects with insulin resistance and migraine.

Therefore, the inflammatory response may occur in parallel with a migraine attack and may well be pivotal in the chronification of migraine through trigeminal sensitization, probably due to the release of inflammatory cytokines.[56] A population-based prospective study investigated the influence high-sensitivity C-reactive protein (hs-CRP) at baseline had on the risk of developing migraine 11 years later. The results reported that the group with the highest hs-CRP levels had an almost three-fold higher risk of developing chronic migraine.[83] Another recent large-scale population-based study reported that elevated hs-CRP was associated with headache $\geq$ 7 days/month, especially for migraine with aura.[82] A summary of recently published studies concluded that migraineurs had higher hs-CRP levels than controls,[125] which suggests that systemic inflammation may be a major etiopathogenetic factor in migraine.

The "Neuroenergetic" Hypothesis

The fact that currently available evidence underlying the pathophysiology of migraine suffices to propose a novel "neuroenergetic" hypothesis, was taken into consideration. We suggest that both episodic and chronic migraine are caused, at least partially, by an energy deficit (ie, a mismatch between the brain's energy reserve and expenditure). Postprandial hypoglycemia leading to an episodic mismatch between the brain's energy reserve and workload could well be a pivotal pathophysiological mechanism in episodic migraine.[52,90,94] Indeed, similarities between non headache symptoms of migraine and those of hypoglycemia have been observed.[34,71,93,119,180,203] Moreover, levels of free fatty acid, ketone bodies, glycerol and cortisol increase during a migraine attack.[202] The same metabolic pattern has been observed during fasting or glucoprivation.[2,164] There is evidence that, over time, insulin resistance may extend to the brain, leading to brain insulin resistance.[145,190,210] We suggest that migraine chronification could originate, at least partly, from a chronic mismatch between the brain's energy reserve and expenditure caused, at least in part, by a dysfunction of insulinoid signaling in neurons and astrocytes, due to insulin resistance, in particular in the nervous tissue, ie, brain insulin resistance.

Astrocytes are structural intermediates between blood vessels and neurons, delivering blood-derived glucose to neurons, thus supporting neuronal needs on demand.[63,77]

The IR-B – the receptor, used by insulin to manifest its metabolic effects – may be downregulated both in neurons and astrocytes in brain insulin resistance. Therefore, some regulatory mechanisms in astrocytes and neurons that allow an efficient supply of energy during neuronal activation may be inhibited, ie,

- glycogen synthesis in astrocytes;
- glucose uptake in astrocytes through the translocation of GLUT1 from intracellular compartments to the cell membrane;
- the incorporation of GLUT4 from intracellular stores into the plasma membrane via an AKT-dependent mechanism, in particular in neurons in brain regions related to cognitive behavior during periods of high metabolic demand, such as during learning.

Further evidence supports the hypothesis that brain insulin resistance may underlie the downregulation of IR-B and the resulting defect in the brain glucose metabolism. Indeed, an increased IR-A/IR-B ratio after bariatric surgery is corrected at about 17 post-surgical months, suggesting that improved insulin sensitivity may, in turn, also improve the IR-B expression.[15]

Garwood et al. treated human astrocytes with 1 μM insulin and 1 mM fructose for 4 days and assessed the impact on the insulin signaling pathway. There was a significantly higher reduction in mature IR-B (probably due to a receptor degradation/internalization) than in controls.[69]

A time response study on the development of cognitive deficits in an experimental model on peripheral insulin resistance, induced by a high fructose diet for 7 weeks, led to lasting symptoms of cognitive dysfunction, as from week 20.[190]

Kilic et al.'s data on inhibited glycogen phosphorylation in mice support our hypothesis, as they demonstrated that the suppression of a glycogen breakdown in astrocytes can activate neuronal pannexin-1 channels and the downstream inflammatory pathway and also lead to a drop in the CSD threshold.[106] Other findings are in agreement with our hypothesis, i.e., several subjects with glucose transporter type 1 deficiency syndrome (GLUT1 DS), a rare genetic brain energy failure syndrome,[111] have been reported to suffer from migraine with and without aura.[47,150] Noteworthy is also the fact that patients with GLUT1 DS and migraineurs have been successfully treated by ketogenic diet therapies.[77,111]

Could Insulin Resistance be the Metabolic Link Between Migraine and its Comorbidities?

Clinical and epidemiological studies have frequently associated migraine to depression, T2DM, cerebrovascular diseases and obesity.[33,59,160] Moreover, there is increasing evidence in supporting the hypothesis that migraineurs, in particular those with aura, are more likely to develop dementia (Table 4) and that central insulin resistance is involved, to varying degrees, in obesity,[37] T2DM,[114] Alzheimer's disease[49,53,170] and depression.[86,158] Some authors have suggested that an impaired peripheral glucose metabolism may account for the association between depression and dementia,[138,181] on the basis of the connection between T2DM with depression and dementia. Indeed, there seems to be a close clinical and epidemiological link between dementia and depression, ie, depressed patients run a higher risk of

developing late-onset Alzheimer's disease (AD) and about 1 of 4 AD patients are co-diagnosed with major depression.[196] Some authors suggest that late-onset depression, mild cognitive impairment and dementia might well represent a clinical continuum.[165]

It is known that migraine and depression have a bidirectional relationship, where each pathology increases the risk of developing the other.[239] The most commonly reported association is between chronic migraine with aura and major depression.[20,21,61,216] Moreover, some epidemiological studies demonstrated that comorbidity for depression is a risk factor for migraine chronification.[28]

Others have hypothesized a common underlying serotoninergic dysfunction in migraine and depression.[65] However, the exact mechanism linking migraine and depression still remains a question of debate. There is current evidence that insulin modulates central levels of neurotransmitters, eg, acetylcholine, serotonin or norepinephrine.[70] Some literature data have demonstrated bidirectional effects of insulin and serotonin in the median hypothalamus.[70] That is, previous experimental studies have evidenced that the administration of insulin into the median hypothalamus increases hypothalamic serotonin release, whereas central stimulation of the serotonergic system increases the extracellular hypothalamic insulin concentration.[166] Although, to date, the cross-talk between serotonin and insulin signaling pathways has received little attention, we are of the opinion that it would be important to investigate into the central mechanisms involved in insulin-serotonin interplay, also in the light of the following evidence that:

- frequent consumption of sweetened beverages may increase the risk of depression;[81,193]
- Metformin favors serotonergic neurotransmission in the hippocampus and promotes antidepressant-like effects in mice;[237]
- there is a high rate of comorbidity between brain insulin resistance and depression.[86]

However, further research may lead to a better understanding of whether brain insulin resistance plays a role in the serotonergic dysfunction involved in depression and in the comorbidity between migraine and depression.

There is evidence that high blood sugar may be a risk factor for dementia, even amongst people without diabetes.[45] A recent prospective cohort study reported that suffering from migraine increases the risk of developing Subjective Memory Complaints more than older age and coronary heart disease.[171] It has been proposed that migraine, mainly migraine with aura, is a risk factor for cardiovascular disease in general, as well as for stroke.[115] Several studies, including reviews and meta-analyses, have reported up to a 2-fold increased risk for ischemic stroke and cardiovascular disease among migraineurs.[79,118]

Moreover, there is an increasing amount of evidence in support of an association between insulin resistance and vascular disease[200] and it seems that insulin resistance may also increase the risk of ischemic stroke,[51] meaning it may well play a role in the comorbidity between migraine and vascular diseases.[175,219] Moreover, numerous studies suggest that an impaired glucose metabolism and insulin resistance are common pathophysiological features in T2DM, obesity, depression and dementia.[138,181]

Therefore, we are of the opinion that insulin resistance may be an important metabolic link between migraine and these comorbidities. However, only further research can confirm the appealing hypothesis that insulin resistance is a central pathophysiological feature linking migraine to these comorbidities.

Migraine and Type 2 Diabetes Mellitus: a Peculiar Relationship

Glucose dysregulation begins at least 20 years before a diagnosis of T2DM in most patients. Moreover, it has

Table 4. Summary of the Studies Investigating the Epidemiological Relationship Between Migraine and Dementia.

First author	*Year*	*Method*	*Country*	*Observations*
Chuang CS[40]	2013	Retrospective cohort study - data from the National Health Insurance Research database in Taiwan.	Taiwan	After adjusting the covariates, migraine patients had a 1.33-fold higher risk of developing dementia. Young adults have a higher association between migraine and dementia than older adults.
Islamoska S[97]	2020	62578 individuals, 10857 with migraine. Follow-up 6.9 years.	Denmark	207 individuals with migraine developed dementia. Individuals without aura had a 19% higher rate of dementia, and individuals with aura had a 2-fold higher rate of dementia.
Lee SY[121]	2019	Retrospective cohort study - 11438 dementia participants, 45752 controls.	Korea	7.7% of patients in the dementia group and 6.3% of those in the control group had a history of migraine. The crude and adjusted odds ratios for migraine with dementia was 1.22 and 1.13, respectively.
Morton RE[152]	2019	Prospective cohort study - 679 community-dwelling participants 65+ years, follow up 5 years.	Canada	A history of migraines was significantly associated with both all-cause dementia (odds ratio [OR]=2.97; 95% confidence interval [CI]=1.25-6.61) and AD (OR=4.22; 95% CI=1.59-10.42).

been reported that higher fasting plasma glucose levels can be observed at least 10 years before the diagnosis of T2DM.[191]

Although migraine has been associated with some factors implicated in diabetes, such as obesity and insulin resistance, to date little is known about the relationship between migraine and T2DM. Interestingly, Fagherazzi et al. recently reported[59] a linear decrease in the prevalence of migraine during the 24 years prior to T2DM diagnosis. They also observed a plateau of migraine prevalence of around 11% 22 years after diagnosis and hypothesized that the migraine prevalence may decrease, due to the fact that there is a rise in plasma glucose concentrations over time, until T2DM occurs.[59]

According to our hypothesis, the higher plasma glucose concentration may partly prevent the cerebral energy deficit caused by hypoglycemia and brain insulin resistance.

Summary

In summary, considering that:

- postprandial hypoglycemia (subsequent to OGTT) is not an uncommon event, both in the general population and in subjects with diseases that alter glucose metabolism (Table 1); - both high insulin sensitivity (particularly in young, normal weight subjects) and insulin resistance may generate postprandial hypoglycemia;[4,23,50,80,156]
- high insulin sensitivity, leading to postprandial hypoglycemia triggers increased food intake and weight gain[22,72,73,169,204] and may well be an event that precedes insulin resistance;[73,80]
- there is evidence that the reactive hypoglycemia that occurs in migraineurs following an OGTT triggers headaches in a high percentage of them,[52,90,94,232]
- migraineurs are more prone to have altered insulin sensitivity than other headache types or asymptomatic individuals (Table 5);
- there is evidence that chronic migraine subjects are more likely to have insulin resistance than episodic migraine subjects (Table 5);
- all but 1 of the studies we found in international literature reported a significant association with insulin resistance for CM subjects, but not EM subjects (a summary of the studies investigating insulin sensitivity in migraine is provided in Table 5). Noteworthy is the study by Cavestro et al., 2007, as it demonstrated that migraineurs with an average of 12.1 attacks per month, ie, on the borderline between EM and CM, had a higher incidence of both increased sensitivity to insulin and insulin resistance than the control group;[32]
- brain mitochondrial dysfunction,[77,179] decrease in grey matter volume in specificareas,[39,117,225,236] impaired brain glucose metabolism[143] and neuroinflammation are main features of chronic migraine which could be caused, at least in part, by brain insulin resistance;[10,155,210,234]
- insulin resistance may well be a pivotal pathophysiological feature, linking migraine with its major comorbidities: obesity, depression and cerebrovascular diseases;
- brain insulin resistance may be a pathophysiological mechanism behind migraineurs' increased risk of developing dementia, especially those with aura (Table 4).

Based on this evidence, we would like to propose a novel hypothesis (illustrated in Fig 2) that we deem may, at least partially, provide the missing pathophysiological link between episodic and chronic migraine. According to this hypothesis, postprandial hypoglycemia may be the leading cause of the episodic brain energy deficit underlying episodic migraine. Indeed, it is most likely that postprandial hypoglycemia is generated mainly by high insulin sensitivity and, to a lesser extent, by insulin resistance. A high insulin sensitivity would increase the risk of developing peripheral insulin resistance, which may eventually extend to the brain, leading to brain insulin resistance. In brain insulin resistance, the downregulation of IR-B in astrocytes and neurons could impair glucose uptake and glycogen synthesis in astrocytes, as well as glucose uptake in neurons during periods of high metabolic demand, such as during learning. This, in turn, could reduce the metabolic processes in the brain, by hindering the proper functioning of astrocytes – which are the main players in glucose metabolism in the brain, supporting neuronal needs on demand – and by reducing the preferred fuel for neuronal metabolism. This sort of a chronic, self-maintaining mismatch between the brain's energy reserve and functional expenditure may well be the final mechanism underlying the metabolic abnormalities which promote migraine chronification.

Neuroinflammation could also play a key role in migraine chronification, which in turn, could increase brain insulin resistance. Indeed, although they are produced peripherally, the pro-inflammatory cytokines TNF-α, IL-6 and IL-12 are capable of crossing the blood-brain barrier[135] and therefore, of hindering the action of insulin in the brain.[1] Interestingly, there is evidence that migraineurs have higher hs-CRP levels than controls[125] and that there is a stronger association with chronic migraine.[83]

Although, currently, whether or not migraine is primarily a "metaboloendocrine" disorder[174] remains a question of debate, the growing evidence herein reviewed supports the intriguing new hypothesis that impaired glucose homeostasis and insulin resistance are pivotal factors in migraine pathophysiology and, above all, in the chronification process.

Potential Treatment Regimes

The aforementioned pathophysiological evidence poses the rationale for interventional strategies which

Table 5. Summary of the Studies Investigating Insulin Sensitive in Migraine.

First author	Year	No. days/month migraine attacks	Migraine duration (years)	Results	Comments
Cavestro[32]	2007	12.1	22.6	After glucose loading (2h OGTT), among migraineurs 20 patients (24%) had a normal pattern, 9 (11%) showed insulin sensitivity and 55 (65%) insulin resistance. In the control group, 20 (77%) had a normal pattern, 1 (4%) showed insulin sensitivity and 5 (19%) insulin resistance.	Migraineurs show either insulin sensitivity or insulin resistance more commonly than other headache types or asymptomatic individuals. Given the increased susceptibility to both profiles in migraineurs, the metabolic disorder associated with migraine cannot simply be explained by the insulin resistance theory.
Bhoi[17]	2012	Migraineurs with insulin resistance: 16.00 ± 12.27. Migraineurs without insulin resistance: 13.53 ± 10.7.	Migraineurs with insulin resistance: 9.98 ± 6.30. Migraineurs without insulin resistance: 8.40 ± 7.48.		It can be concluded that migraine is associated with metabolic syndrome in 31.9% and insulin resistance in 11.1% of migraineurs.
Sacco[189]	2014	MwA: < 4 (66%), 4 to 8 (22%), > 8 (12%) MwoA: < 4 (58%), 4 to 8 (28%), > 8 (14%).	MwA:17 .4 ± 10.9. MwoA: 15.8 ± 11.3.	No difference in insulin, HOMA-IR, HOMA-B and QUICKI was observed.	In contrast to that observed in most of the available studies, their results do not support an association of migraine with insulin resistance.
Fava[61]	2014	CM ≥ 15 /month. EM < 15/month.	CM: 24.7. EM: 16.2.	EM and healthy controls had a similar HOMA-IR value. A significant prevalence of insulin resistance in CM was observed.	This may suggest that CM is associated with insulin resistance status.
Siva[205]	2018	CM ≥ 15 /month. EM < 15/month.		Patients with chronic migraine were more insulin resistant than episodic migraine or healthy controls.	The major metabolic alteration innon-obese, non-diabetic female migraine patients was increased insulin resistance.
Rainero[175]	2005	MwA: 6.05 ± 4.65. MwoA: 4.28 ± 3.0.	MwA: 14.4 ± 7.63. MwoA: 14.2 ± 8.0.	Patients with migraine (episodic) were more insulin resistant than healthy controls.	Insulin sensitivity is altered in migraine. During the OGTT, glucose plasma concentrations in nonobese, nondiabetic, normotensive migraine patients resulted significantly higher than in controls.

Abbreviation. MwA, migraine with aura; MwoA; migraine without aura; CM, chronic migraine (at least 15 days per month); EM, episodic migraine; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-B, homeostatic model assessment of β-cell function; QUICKI, quantitative insulin sensitivity check index.

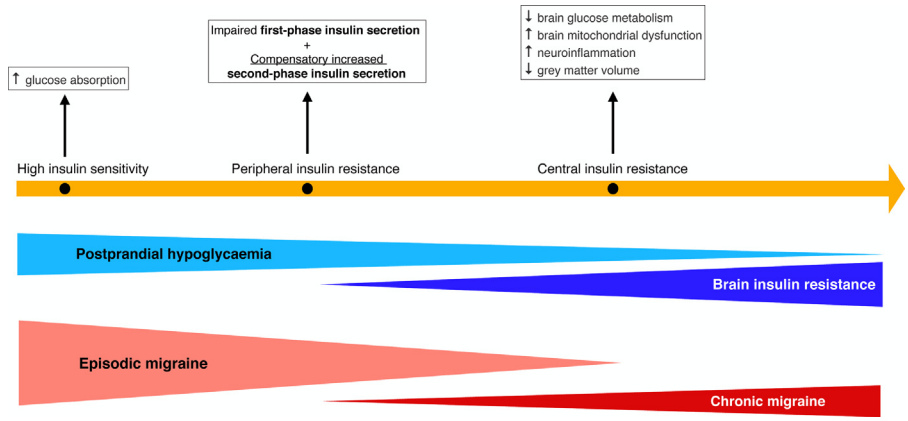

Figure 2. The novel neuroenergetic hypothesis and altered brain glucose and insulin homeostasis. The conditions related by a time and pathophysiological continuum are marked with an orange arrow, ie, high insulin sensitivity, peripheral insulin resistance and central insulin resistance. Both high insulin sensitivity and peripheral insulin resistance can lead to postprandial hypoglycemia – the former to a higher extent than the latter. Subjects with high insulin sensitivity have an increased glucose absorption which may lead to postprandial hypoglycemia. Whereas, peripheral insulin resistance is characterized by an impaired first phase glucose-stimulated insulin response and a compensatory increased late insulin response, which may lead to postprandial hypoglycemia. Postprandial hypoglycemia may be a leading cause of the brain energy deficit that underlies episodic migraine. Moreover, peripheral insulin resistance can, over time, extend to the brain, leading to brain insulin resistance. Central insulin resistance is related to brain mitochondrial dysfunction, impaired brain glucose metabolism, a decrease in grey matter volume, neuroinflammation and, according to our novel neuroenergetic hypothesis, also to the chronification of migraine, triggering a chronic mismatch between the brain's energy reserve and functional expenditure.

are very likely to be beneficial in the prophylaxis of migraine, ie, diet, aerobic exercise and mind-body interventions.

A Dietary Model With no or Minimal Intake of High Glycemic Index Foods

(ie, foods that strongly raise blood sugar level[178,220]). Although well-conducted RCTs on reducing or avoiding high glycemic index foods have not been conducted in migraine patients, this dietary model has been proposed to prevent, at least partially, postprandial hypoglycaemia[130,183] not only in predisposed individuals (with impaired glucose metabolism), but also in non-predisposed individuals. Furthermore, the optimal dietary pattern should reduce systemic inflammation,[178] have no adverse effects and be sustainable at long-term. We have identified a dietary pattern that meets all four of these requirements in the traditional Mediterranean diet.[58,130,233]

There is evidence[3,84,149] that diets similar to the traditional Mediterranean one, ie, the Healthy Eating Plate and the Dietary Approaches to Stop Hypertension (DASH), are efficacious in reducing the frequency and intensity of migraine and its associated disability. Moreover, randomized control trials (RCTs), meta-analyses and systematic reviews that, over the past 11 years, have evaluated the role diet plays in the treatment and prevention of depression[98,172,194] and dementia[109,110,129,137,140] have suggested that a higher adherence to the Mediterranean diet and similar ones (DASH and the Healthy Nordic diet) is associated with higher remissions and a lower incidence of depression, slower cognitive decline and a reduction in the risk of developing dementia.

Regular Aerobic Exercise

The two most recent systematic reviews and meta-analyses on the relationship between exercise and migraine demonstrated that aerobic exercise programmes may have beneficial effects on the frequency, intensity and duration of migraine pain.[116,133] This could partly be due to an improved glucose tolerance in response to regular endurance training and an increased mitochondrial biogenesis.[91,228] Indeed, an increase in mitochondria was observed not only in the muscles, but also in the brain of mice who did regular exercise (8 weeks of treadmill running for 1 h/day, 6 days/week).[212]

Mind-Body Interventions (MBIs)

To date, the most recent and largest RCT investigating the use of Mindfulness-based stress reduction (MBSR) in the treatment of migraine,[230] showed that MBSR reduced disability, enhanced the quality of life, self-efficacy, pain catastrophizing and depression at 36 weeks, with a decrease in experimentally induced pain, suggesting a potential shift in pain appraisal. There is evidence that mind-body interventions decrease the expression of pro-inflammatory genes (eg, NF-kB).[16,25,96,163] Moreover, studies have reported the efficacy of MBIs in the prevention and treatment of the most common comorbidity of migraine, ie, depression,[74,206] with a bidirectional relationship, as aforementioned.

Conclusions

Although it remains a matter of debate whether or not migraine is primarily a "metaboloendocrine"

disorder,[174] growing evidence supports the intriguing new neuroenergetic hypothesis where impaired glucose homeostasis and insulin resistance would be the pivotal factors. We argue that brain insulin resistance could be a *metabolic bridge* between episodic and chronic migraine. Moreover, insulin resistance may be a central pathophysiological feature linking migraine to some of its major comorbidities. Hopefully, this novel "neuroenergetic" hypothesis will promote further research and new approaches for the prophylactic treatment of a neurological disorder that, despite extensive effort, is still a leading cause of disability worldwide.

We consider that further research aimed at completing the puzzle of the "neuroenergetic" hypothesis should focus on 5-hour observation oral glucose tolerance tests in age, gender, BMI and waist circumference matched migraineurs and healthy controls to further investigate postprandial hypoglycemia. Although there has been a scarcity of OGTT studies on migraine sufferers for the last 15 years or so, the current heightened interest and research in this area is promising. Another line of research which would be welcome is the use of the hyperinsulinemic normoglycemic glucose clamp technique in episodic migraine subjects to assess the status of their insulin sensitivity. It would also be helpful if the potential treatment options outlined in the last paragraph, in particular a dietary model with no or minimal intake of high glycemic index foods sustainable at long-term (eg, the traditional Mediterranean diet), were investigated by further RCTs. Lastly, we are of the opinion that further research should be aimed at clarifying which areas of migraineurs' brains are more affected by insulin resistance.

Author contributions

LDM and EP conceived the presented idea. LDM and ER researched evidence for the article, revised and corrected the manuscript. LDM, ER and EP made substantial contributions to the discussion of content and writing of the article. IR made a substantial contribution to the discussion of content, reviewed and edited the manuscript before submission. All authors contributed to the final manuscript and approved it.

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