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MIGRAINE (R COWAN, SECTION EDITOR)

How Does Fasting Trigger Migraine? A Hypothesis

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Abstract Fasting or skipping meals are well-characterized migraine triggers. However, mechanisms of the fasting-induced migraine headache are unclear. Here, we review the recent developments on brain glycogen metabolism and its modulation by sympathetic activity and propose that insufficient supply of glycogen-derived glucose at the onset of intense synaptic activity may lead to an imbalance between the excitatory and inhibitory terminals, causing collective depolarization of neurons and astrocytes in a network. This may activate perivascular trigeminal afferents by opening neuronal pannexin1 channels and initiating parenchymal inflammatory pathways. Depending on whether or not network depolarization spreads or remains local, fasting may trigger migraine headache with or without aura.

Keywords Migraine · Headache · Fasting · Hunger · Glucose · Hypoglycemia · Adrenaline · Noradrenaline · Sympathetic nervous system · Insulin · Glucagon · Cortisol · Growth hormone · Glycogen · Glucose transporter · Astrocyte · Brain metabolism

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Introduction

Lifetime prevalence of the fasting-induced headache is about 4 % [1]. The *International Classification of Headache Disorders, 3rd edition* (beta version, ICHD-3beta), describes the headache attributed to fasting as: "diffuse non-pulsating headache, usually mild to moderate, occurring during and caused by fasting for at least 8 hours" [2]. The likelihood of fasting headache increases with the duration of the fast. Migraineurs as well as people with tension-type headache have a higher risk of suffering from headache during fasting [3••, 4••]. A typical example of fasting-induced headache is the Yom Kippur headache observed during the 25-hour fasting practiced by Jews [5, 6]. A prospective study showed that 39 % of the participants observing the Yom Kippur fast developed headache on average 16 h from the start of the fast [5]. A similar headache is also observed during the first day of Ramadan among Muslims. Awada and al Jumah reported that 41 % of 91 prospectively studied patients developed headache with clinical features of migraine (9 %) or tension-type headache (TTH, 32 %) [7]. Of the eight individuals who reported a migraine attack, six had a history of migraine; of the 29 individuals who reported a TTH attack, 26 had a history of TTH. Majority of the attacks exhibited similar features to the headache that they usually experienced. During Ramadan, of the 2,982 patients studied in India, 1,998 (67 %) developed TTH and 407 (14 %) developed migraine [8]. In line with these observations, emergency room admissions for primary headache were reported to be significantly increased during Ramadan in Turkey [9] and migraine days a month of 32 Bedouin Muslims increased from 3.7±2.1 to 9.4±4.3 (mean ± sd) during Ramadan [10]. The frequency and severity of headache attacks were also aggravated during fasting by the monks of Athos, Greece [11]. The above epidemiological data conform with the consensus in the literature that skipping or delaying a meal is a precipitating factor for migraine or TTH attacks [12, 13]. Interestingly, however, although

questionnaires supplied by 1,883 patients for their 2,313 spontaneous attacks showed that fasting was a precipitating factor in 67 % of patients, only 3–5 % of patients perceived fasting as a precipitating factor [14].

Why Does Fasting Trigger Headache?

Despite the general agreement that fasting is an important headache trigger, mechanisms of the fasting-induced headache attacks are currently unclear. Hypoglycemia, dehydration, caffeine withdrawal, free fatty acids (FFAs), sympathetic nervous system activation, hypothalamic dysfunction, insulin and several other hormonal factors have been proposed as a potential trigger for headache [3••, 4••]. In this review, we will focus on potential causes of only the migraine attacks triggered by fasting. Although there is as yet no clear answer, we think that recent developments on brain glycogen metabolism and its modulation by the sympathetic activity are especially worthy of considering among other potential mechanisms of fasting-triggered migraine attacks.

Hypoglycemia

At first glance, hypoglycemia seems to be a reasonable possibility as a trigger for a migraine attack, considering that blood glucose drops toward hypoglycemic levels as hours pass after a meal and that the probability of headache increases with the duration of fasting [3••, 4••]. However, there are counter arguments against this view as clearly stated in ICHD-3beta [2] based on the observations that headache is not a common complaint of patients with symptomatic hypoglycemia [15] and, insulin-induced hypoglycemia does not trigger headache in majority of migraineurs examined [16•]. Nonetheless, these latter observations should be cautiously interpreted because they essentially suggest that there was no causal relationship between insulin-induced hypoglycemia and headache but does not exclude fasting-induced blood sugar decline as a potential migraine trigger. It should also be taken into consideration that triggers of migraine do not always precipitate an attack but increase the probability of an attack. In fact, of the 18 migraine subjects tested, two patients did develop a typical visual aura after insulin administration, which was followed by headache in one patient [16•].

Supporting the role of blood glucose as a trigger for migraine, the prevention of hypoglycemic episodes in migraine patients with diabetes mellitus reduced migraine attacks in five of 36 patients [17]. Hypoglycemia-induced pulsating headaches of a 56-year-old man with unstable diabetes mellitus were reported to improve with orange juice intakes [18]; orange juice was also found to be helpful for a group of patients suffering from fasting-triggered migraine headache [19]. These observations suggest that glucose deficiency directly (as the preferential energy substrate of brain) or indirectly (via hypoglycemia-induced counter regulatory mechanisms such as sympathetic activation or glucagon release) may be the trigger for fasting-induced headache (Fig. 1). Failure of the insulin-induced hypoglycemia to induce a migraine attack in great majority of patients [16•] may be related to central actions of insulin and to accompanying strong sympathetic activation, which might suppress the headache mechanisms triggered by low blood glucose. In fact, insulin-administered migraine patients in the above study reportedly exhibited overt symptoms of sympathetic nervous system activation or neuroglycopenia [16•]. Notwithstanding considerable individual variation, autonomic symptoms (e.g., tremor, pallor, sweating, palpitation) appear below 65 mg/dL blood glucose, whereas symptoms of neural dysfunction (e.g., fatigue, dizziness, syncope, seizures, abnormal mentation and concentration difficulty) appear below 54 mg/dL [20, 21•]. These alarming symptoms are usually not seen in fasting-induced headache in accordance with generally euglycemic blood levels detected in these patients [22, 23]. This is not surprising, because large hepatic glycogen stores can sustain normal blood glucose levels for about one day (Fig. 1). The adult human brain can survive even days lasting starvation by using FFAs when enough glucose, the preferential fuel, is not available [24]. Altogether, these observations suggest that the trigger for a migraine attack cannot simply be insufficient energy supply to the brain. Therefore, insulin-induced profound hypoglycemia appears to be not an appropriate model of fasting-induced migraine. Supporting this idea, insulin-induced hypoglycemia in the mouse did not significantly lower the cortical spreading depolarization (SD) threshold [25], the putative cause of migraine aura and headache [26, 27].

Further support for a role of glucose insufficiency as a trigger for migraine comes from glucose transport protein type 1 (GLUT1) deficiency syndromes. The high glucose requirements of the CNS require facilitated transport of glucose across the blood–brain barrier (Fig. 1). The facilitative glucose transporter GLUT1 is highly expressed on endothelial cells and astrocyte endfeet surrounding vessels [28]. Several heterozygous mutations in the *SLC2A1* gene encoding GLUT1 have been identified. These patients exhibit a transport defect of glucose across the blood–brain barrier and suffer from various neurological disorders including motor-mental retardation, seizures, spasticity, ataxia and dystonia [29]. Interestingly, members of several families also have migraine with or without aura, sometimes associated with hemiplegic attacks [30–34].

Glycogen in Peri-Synaptic Astrocyte Endfeet

It is well documented in experimental studies that brain glycogen increases brain's resistance to hypoglycemia as a

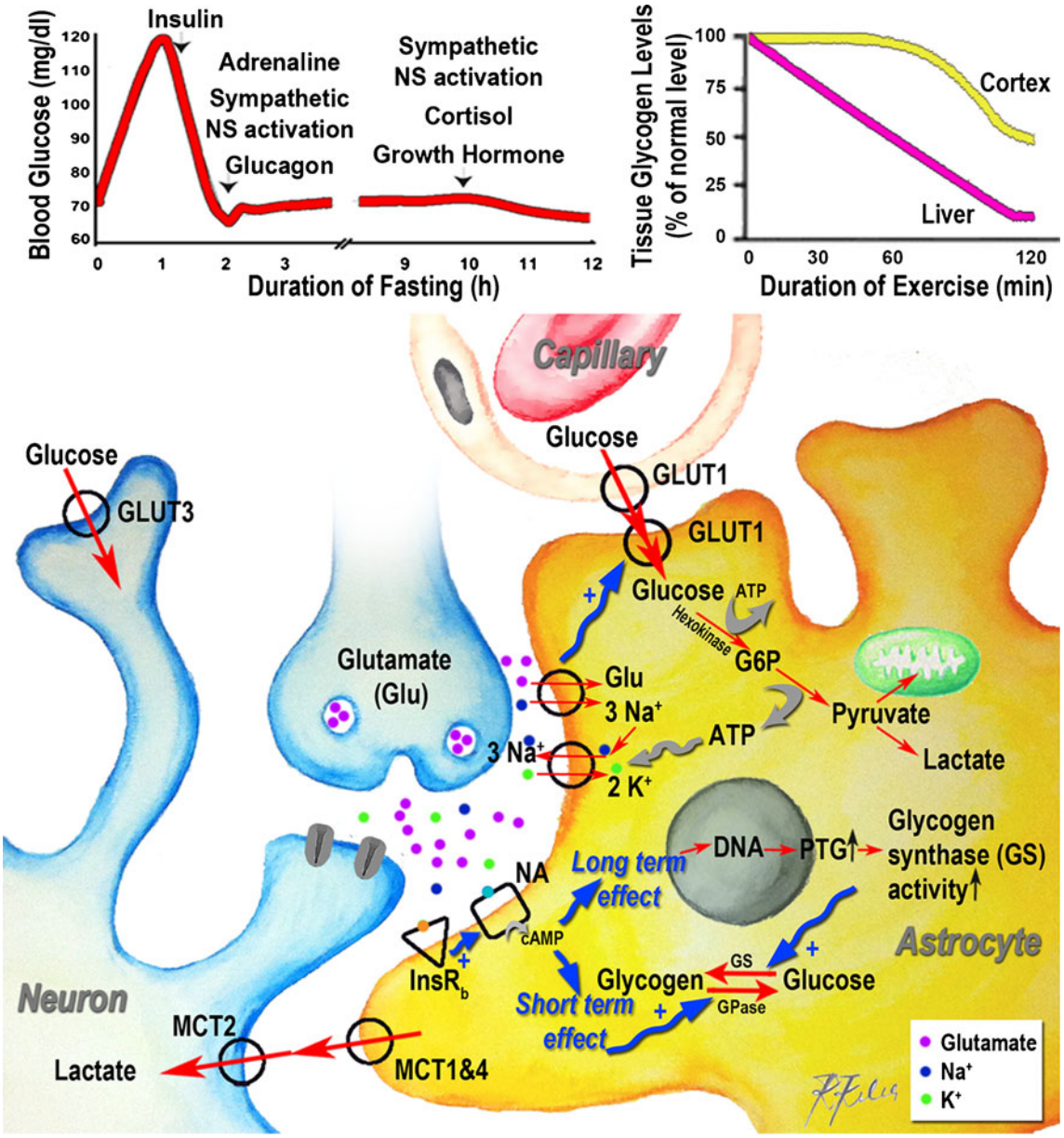

Fig. 1 A surge in blood glucose after a meal induces insulin secretion from pancreas (*top left*, inspired by [3••]). Insulin lowers glucose and a slight undershoot triggers glucagon secretion from pancreas to normalize blood sugar. The adrenergic system is activated by hypoglycemia to maintain euglycemic levels when the blood glucose level falls approximately below 65 mg/dL [3••, 21•]. First, adrenaline is released from the adrenal medulla and then sympathetic nervous system is activated. Growth hormone (GH) and cortisol are secreted at a blood glucose threshold of around 66 and 58 mg/dL, respectively (*top left*). The brain contains glycogen but at low concentration compared with liver and muscle. The levels of brain glycogen change little during fasting while those in liver fall precipitously, suggesting that brain glycogen is needed for local use [35]. After depletion of liver glycogen, cortical glycogen may decrease with intense brain activity as seen, for example, during prolonged exercise (*top right*, adapted from [45]). Glycogen is present only in astrocytes [73] (*bottom*). Glycogen phosphorylase (GPase) breaks down glycogen to glucose to match rapid energy demands in synapses when the pace of glucose transport from circulation cannot cope with this urgent metabolic pressure. Glycogen driven energy is used for uptake of glutamate and potassium building up during intense synaptic activity. The two key enzymes that regulate synthesis and degradation of brain glycogen are glycogen synthase (GS) and glycogen phosphorylase, respectively. Adrenergic stimulation initially promotes glycogen degradation, however, prolonged stimulation upregulates glycogen synthesis [74]. This is mediated by increased expression of PTG protein, which increases glycogen synthase activity. Insulin potentiates noradrenergic activity. Extracellular glucose concentration also determines the glycogen content [75]. Glycogen is rapidly metabolized when glucose falls towards the K_m of hexokinase, the point at which glucose transport becomes rate limiting for glucose metabolism. Glucose is delivered from capillaries to the brain tissue via glucose transporter proteins (GLUTs). GLUT1 is located in the microvascular endothelial cells and astrocyte endfeet surrounding vessels; GLUT3 is located in neurons. Monocarboxylate transporters (MCTs) transport lactate; MCT1&4 are located on the astrocyte plasmalemma and MCT2 is located on neurons [76]. Astrocytes provide lactate as an energy source to neurons during neuronal activity by means of MCTs [43••]

readily available glucose reservoir, although the CNS has a relatively small glycogen pool compared to liver and muscle [35, 36]. A nuclear magnetic resonance (NMR) spectroscopy study on healthy volunteers showed that insulin-induced moderate (non-symptomatic) hypoglycemia (serum glucose level 57.2±9.7 mg/dL) led to a modest but significant drop in total glycogen measured in the occipital lobe [37]. However, NMR detects a relatively stable pool of glycogen in the brain and, is limited by spatial resolution (each voxel is $7\times5\times6$ cm^3). Animal studies have clearly documented that the glycogen pool in peri-synaptic astrocyte endfeet is highly dynamic [38–40, 41••, 42••, 43••]. In fact, the cortical glycogen level has been shown to decrease after 5–10 minutes of vibrissae stimulation [44] or after 2 hours of exercise in rats following consumption of the liver glycogen (Fig. 1) [45]. Glycogen in this compartment is rapidly metabolized to glucose at the onset of intense excitatory synaptic activity to provide energy for uptake of glutamate and K^+ released to the extracellular space by the time glucose is transported from blood to the endfeet (Fig. 1) [42••, 46–48]. Once sufficient glucose reaches to the endfeet, it is used as an energy substrate as well as to restore glycogen [49]. Although not tested, this dynamic pool might be more susceptible to fasting-induced blood glucose decline and accompanying neurohormonal changes. According to a mathematical model developed based on kinetics of GLUT1, glucose flux to the brain starts decreasing as blood glucose decreases toward 54 mg/dL [50]. This moderate drop in glucose supply initially may not have any adverse consequences as astrocyte glycogen stores may provide glucose when needed. Sympathetic activity accompanying fasting may facilitate glycogen degradation at this stage via adrenergic receptors on astrocytes (Fig. 1) [40, 43••, 51]. However, prolonged adrenergic stimulation favors glycogen synthesis over degradation due to cAMP-induced expression of Protein Targeting to Glycogen (PTG) that causes an increased glycogen synthase activity and incorporation of glucose into glycogen [52, 53]. Consequently, a decrease in readily available glycogen in astrocytic endfeet may impose a risk for accumulation of extracellular K^+ and glutamate at the onset of intense excitatory activity reaching to supraphysiological levels. This may induce collective depolarization of a group of neurons and astrocytes within a network and, if severe enough, may trigger an SD wave. Supporting this view, accumulation of glutamate in the synaptic cleft due to unregulated release or uptake in knock-in mice expressing familial hemiplegic migraine 1 and 2 mutations, has been shown to create an imbalance between the excitatory synapses terminating on excitatory and inhibitory neurons, leading to a simultaneous network depolarization and SD [54]. In line with the above arguments, suppressing glycogen use with 1,4-dideoxy-1,4-imino-d-arabinitol (DAB) or by sleep deprivation reportedly lowers cortical SD threshold [55]. Similarly, in acutely prepared hippocampal slices, glycogenolysis inhibitors DAB and 1-deoxynojirimycin increased the propagation rates of potassium chloride and oxygen glucose deprivation (OGD)-induced SDs, whereas L-methionine-DL-sulfoximine increased slice glycogen levels and decreased OGD-SD propagation rates [56].

SD, intense depolarization, high K^+ and glutamate are all known to activate neuronal pannexin1 channels [27, 57, 58]. Opening of pannexin1 channels has recently been shown to activate perivascular trigeminal nociceptors by triggering a parenchymal inflammatory signaling cascade and, hence, to cause headache in mice [27]. A similar mechanism may therefore account for migraine attacks in humans. Depending on whether or not network depolarization spreads or remains local, fasting may trigger a migraine headache with or without aura [59].

Activation of Sympathetic Nervous System

The adrenergic system is activated by hypoglycemia to maintain euglycemic levels when the blood glucose level falls approximately below 65 mg/dL [3••, 21•] First, adrenaline is released from the adrenal medulla and then sympathetic nervous system is activated, which increases the amounts of noradrenaline (NA) at the nerve terminals and adrenaline in the circulation [3••, 21•]. Adrenergic activity not only boost blood glucose levels by various means including increased glycogenolysis at the liver, but also has diverse effects on neurons, astrocytes and microglia [60]. Interestingly, there is considerable evidence suggesting that migraine patients suffer from a benign form of sympathetic nervous system insufficiency [61••]. Compared to controls, interictal serum NA levels and NA increase in response to orthostatic changes were reported to be significantly reduced in migraineurs [62–67]. In line with the idea of a chronic reduced sympathetic activity, arterial blood pressure and pupil response to adrenergic agonists reportedly show adrenergic receptor supersensitivity in migraine patients [68, 69]. Therefore, migraine patients may have a reduced capacity to counter regulate the consequences of a decline in blood sugar, making them more vulnerable to fasting compared to the people without migraine. Perhaps reflecting this regulatory insufficiency, 2–4 hours after 50 g glucose ingestion following an overnight fast, a headache started in six of 12 migraine patients, whose FFA levels rose significantly higher compared to those who did not develop headache [22]. Moreover, unlike short-term adrenergic stimulation that promotes glycogen degradation in astrocytes, sustained adrenergic stimulation as seen during prolonged relative hypoglycemia accompanying fasting, may reduce the available glycogen in astrocytes because prolonged adrenergic activation favors glycogen synthesis over utilization, as discussed above [53].

Glucagon, Cortisol and Growth Hormone

Glucagon is secreted from the pancreas when glucose levels fall slightly below the physiologic range, along with adrenaline release [3••, 21•]. As glucose levels fall further, growth hormone and cortisol are secreted at a blood glucose threshold of around 66 and 58 mg/dL, respectively. Growth hormone and cortisol induce a slow recovery from hypoglycemia by stimulating lipolysis in adipose tissue and ketogenesis and gluconeogenesis in the liver. Unfortunately, there is very little information to implicate that these counter regulatory mechanisms might have a potential role in fasting-induced headache. The most meaningful finding reported is that the hyperglycemic response to glucagon injection was found to be diminished in 19 migraine patients compared to 17 matched controls [23], which may predispose migraineurs to lower than normal blood glucose levels a few hours after food intake. This possibility was not specifically tested in the migraine patients studied, however, their fasting blood glucose levels were not different than control patients. Glucocorticoids promote glycogenolysis in the rat brain during sleep deprivation in response to energy demands [70] whereas, in cultured astrocytes, they decrease glycogen synthesis [71]. Migraineurs were reported to have large variations in plasma cortisol levels when compared to the control group, and a subgroup of migraine patients exhibited abnormal circadian levels of cortisol [72]. However, the significance of these observations with regard to fasting-induced migraine headaches is currently not clear.

Conclusion

Lifetime prevalence of the fasting-induced headache is about 4 %. Fasting-induced headache is more common in patients with migraine. The mechanism of vulnerability to headache created by fasting or skipping meals is currently unclear. Insulin-induced profound hypoglycemia appears to be not an appropriate model to understand fasting as a migraine trigger. Extended periods of low blood glucose, deficient sympathetic activity, or glucagon release at the early hours of fasting as well as prolonged sympathetic activity during long lasting fasting may reduce available glycogen-derived glucose in peri-synaptic astrocyte endfeet at the onset of intense synaptic activity. This may lead to an imbalance between the excitatory and inhibitory terminals, causing collective depolarization of neurons and astrocytes in a network and, hence, may trigger aura and/or headache.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Turgay Dalkara and Dr. Kıvılcım Kılıç reported no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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