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Neuroendocrine signaling modulates specific neural networks relevant to migraine

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ABSTRACT

Migraine is a disabling brain disorder involving abnormal trigeminovascular activation and sensitization. Fasting or skipping meals is considered a migraine trigger and altered fasting glucose and insulin levels have been observed in migraineurs. Therefore peptides involved in appetite and glucose regulation including insulin, glucagon and leptin could potentially influence migraine neurobiology. We aimed to determine the effect of insulin ($10\ U \cdot kg^{-1}$), glucagon ($100\ \mu g \cdot 200\ \mu l^{-1}$) and leptin (0.3, 1 and 3 $mg \cdot kg^{-1}$) signaling on trigeminovascular nociceptive processing at the level of the trigeminocervical-complex and hypothalamus. Male rats were anesthetized and prepared for craniovascular stimulation. In vivo electrophysiology was used to determine changes in trigeminocervical neuronal responses to dural electrical stimulation, and phosphorylated extracellular signal-regulated kinases 1 and 2 (pERK1/2) immunohistochemistry to determine trigeminocervical and hypothalamic neural activity; both in response to intravenous administration of insulin, glucagon, leptin or vehicle control in combination with blood glucose analysis. Blood glucose levels were significantly decreased by insulin ($p < 0.001$) and leptin ($p < 0.01$) whereas glucagon had the opposite effect ($p < 0.001$). Dural-evoked neuronal firing in the trigeminocervical-complex was significantly inhibited by insulin ($p < 0.001$), glucagon ($p < 0.05$) and leptin ($p < 0.01$). Trigeminocervical-complex pERK1/2 cell expression was significantly decreased by insulin and leptin (both $p < 0.001$), and increased by glucagon ($p < 0.001$), when compared to vehicle control. However, only leptin affected pERK1/2 expression in the hypothalamus, significantly decreasing pERK1/2 immunoreactive cell expression in the arcuate nucleus ($p < 0.05$). These findings demonstrate that insulin, glucagon and leptin can alter the transmission of trigeminal nociceptive inputs. A potential neurobiological link between migraine and impaired metabolic homeostasis may occur through disturbed glucose regulation and a transient hypothalamic dysfunction.

1. Introduction

Migraine is a severe and disabling brain condition (Goadsby et al., 2002), characterized by attacks of unilateral throbbing head pain, with hypersensitivity to movement, visual and auditory inputs (Headache Classification Committee of the International Headache Society, 2013). Approximately one-third of migraine patients suffer attacks that are associated with cortical perturbations, namely migraine aura (Charles, 2013). Additional symptoms in the premonitory phase, such as changes of appetite, thirst, tiredness, irritability and reduced concentration, can precede the headache by up to 48 h (Giffin et al., 2003).

Migraine pathophysiology is thought to involve activation and sensitization of trigeminovascular nociceptive pathways that innervate the cranial vasculature, and activation of hypothalamic and brain stem nuclei (Akerman et al., 2011). In addition, some studies report that

Abbreviations: ARC, hypothalamic arcuate nucleus; BBB, blood brain barrier; CNS, central nervous system; CSD, cortical spreading depression; DMN, hypothalamic dorsomedial nucleus; DMH, dorsomedial hypothalamic area; ERK1/2, extracellular signal-regulated kinase 1/2; LRP1, lipoprotein receptor-related protein 1; MAP, mitogen-activated protein; MMA, middle meningeal artery; ObRb, long form of the leptin receptor; pERK1/2, phosphorylated extracellular signal-regulated kinase 1/2; PVN, hypothalamic paraventricular nucleus; TCC, trigeminocervical complex; TNC, trigeminal nucleus caudalis; VMH, ventral medial hypothalamic area; WDR, wide dynamic range.

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inducing cortical spreading depression (CSD), the animal correlate of aura in humans, can also activate the trigeminovascular system and therefore, the authors suggest migraine can originate outside the TCC (Moskowitz and Cutrer, 1993; Zhang et al., 2011). Migraine attacks can start centrally in the brain as evidenced by hypothalamic changes (Denuelle et al., 2007; Maniyar et al., 2014) and trigeminocervical complex (TCC) alterations (Stankewitz et al., 2011) during the pre-ictal phase. The migraine brain is extremely susceptible to perturbations of internal and external cues and their alteration likely leads to activation of the pain processing trigeminovascular system that includes the pseudounipolar trigeminal ganglion and its afferent projections to the trigeminal nucleus caudalis (TNC) and C1 and C2 regions in the medullary and cervical spinal cord (the TCC), and its peripheral afferent projections mainly from the ophthalmic division of the trigeminal nerve to the cranial blood vessels including the pain-sensitive dura mater (Akerman et al., 2011).

Fasting or skipping meals is one of the most consistently reported migraine triggers in susceptible individuals and appetite change is reported during the premonitory phase (Blau and Cumings, 1966; Giffin et al., 2003; Kelman, 2007). The hypothalamus is a major appetite center and imaging studies in humans show activations in the region of the hypothalamus before (Maniyar et al., 2014) and during migraine headache (Denuelle et al., 2008). Several studies and clinical observations highlight a clear association between migraine, feeding behavior and metabolic disorders. Clinically, some patients report loss of appetite during attacks, potentially via hypothalamic mechanisms (Malick and Burstein, 2001); and common premonitory symptoms and/or migraine triggers include hunger or skipping meals (Giffin et al., 2003), suggesting disruption of common regulatory networks early in the attack phase. Obesity is a risk factor for migraine chronification (Bigal et al., 2006) and attack frequency and severity increase with body mass index (Bigal et al., 2006). Moreover, a higher migraine prevalence in metabolic syndrome patients was demonstrated comparing to the general population (Guldiken et al., 2009). On the other hand, there is also a potential association with eating disorders, with a high prevalence of migraine in woman affected by anorexia or bulimia nervosa (D'Andrea et al., 2012). In rodents, neuropeptides like orexin and neuropeptide Y involved in the regulation of feeding have been proposed to regulate the trigeminovascular system (Hoffmann et al., 2015; Holland et al., 2006; Martins-Oliveira et al., 2016). Therefore, the gut-brain pathway that enables the communication between the endocrine system and CNS may underlie the observed interaction of appetite regulation, glucose homeostasis and migraine (Fig. 1).

Insulin is a dipeptide hormone secreted by the β-cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism (Wilcox, 2005). The insulin-secreting β-cells, which respond to a rise in extracellular glucose with membrane depolarization, are the best understood glucose-sensing excitable cells (Burdakov et al., 2005). Headache is associated with high fasting glucose blood levels and migraine is specifically associated with higher insulin levels, after fasting and after the oral glucose tolerance test (Bernecker et al., 2010; Cavestro et al., 2007; Rainero et al., 2005). In addition, a significant prevalence of insulin resistance has been observed in chronic migraineurs (Fava et al., 2014). Glucagon is a polypeptide synthesized and secreted from pancreatic α-cells, the levels of which increase during meals creating postprandial satiety (Geary, 1990). Glucagon has been previously administered in migraineurs resulting in a lowered hyperglycemic effect compared to controls (De Silva et al., 1974), suggesting a defect or failure of mechanisms which normally counteract hypo- and hyperglycemia in migraineurs. Leptin, a peptide hormone mainly secreted by white adipocytes, crosses the blood-brain barrier (BBB) (Friedman and Halaas, 1998) and activates neurons in the paraventricular nucleus (PVN), arcuate nucleus (ARC), ventromedial hypothalamic (VMH) and dorsomedial hypothalamic (DMH) areas. Of particular interest lipoprotein receptor-related protein 1 (LRP1),

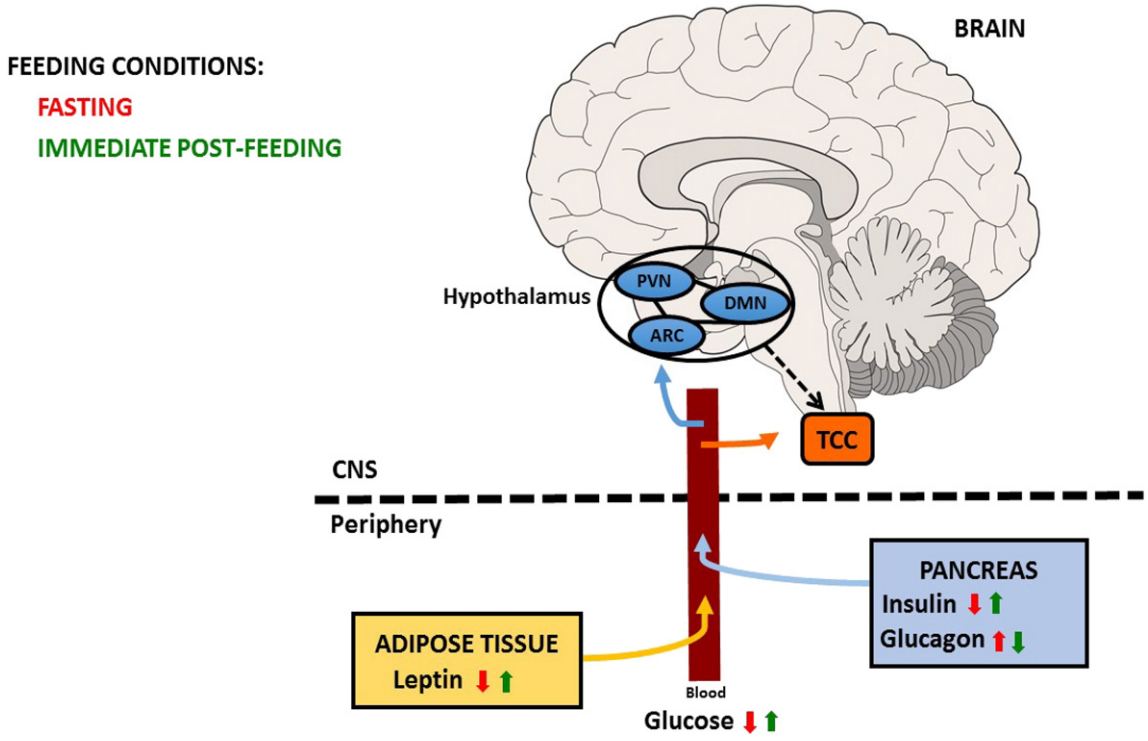

Fig. 1. Schematic representation of neuroendocrine signaling in healthy individuals during two different feeding conditions (fasting and immediate post-feeding). Leptin is released from adipose tissue and insulin and glucagon are release by the pancreas into the blood circulation. These peptides are able to cross the blood brain barrier (BBB) and act in the hypothalamus to regulate appetite and blood glucose levels. There is a potential hypothalamic output (dashed arrow) towards the trigeminocervical complex (TCC) and these peptides may additionally act directly at the TCC, modulating nociceptive trigeminovascular activation. PVN: hypothalamic paraventricular nucleus; ARC: hypothalamic arcuate nucleus; DMN: hypothalamic dorsomedial nucleus; CNS: Central nervous system.