The Role of the Adipocytokines Adiponectin and Leptin in Migraine

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Although it has long been known that fasting or the consumption of certain foods can trigger headaches, abdominal and total body obesity have only recently been linked to migraine. Several adipocytokines appear to play an integral role in feeding and obesity—and have also been linked to pain. Among these proteins are adiponectin and leptin. The author reviews the regulation of adipose tissue and feeding and provides an in-depth examination of adiponectin and leptin and their association with migraine.


Although the role of fasting and certain foods have long been known to trigger headaches, total body and abdominal obesity have only recently been linked to migraine.1-4 Recent data4-9 have shown that several adipose-tissue–derived proteins, including adiponectin and leptin, play an integral role in feeding and obesity and are linked to migraine. To understand why these proteins may be linked to migraine, the physiology of adipose tissue and the central and peripheral regulation of feeding must be understood.

Adipose tissue is a functioning, active endocrine organ with important physiologic and pathophysiologic roles. In addition to regulating energy homeostasis, adipose tissue is important in regulating lipid and glucose metabolism as well as autoimmunity and inflammatory processes.1,10,11

Centrally, the role and function of feeding and adipose tissue is modulated by the hypothalamus and its connections.12 Likewise, functional imaging has implicated the hypothalamic role in migraine was first suggested based on the clinical

Areas for future research are also noted.

Central Regulation of Feeding

Several hypothalamic nuclei are involved in regulating energy balance. This regulation occurs through a complex pathway via afferent signals from the periphery to the hypothalamus. These signals are dependent on nutrient status as well as via efferent pathways from the sympathetic and parasympathetic systems.12,15 While the sympathetic system promotes energy expenditure and decreases feeding, the parasympathetic system promotes energy storage and increases feeding.

In addition, feedback regulation of the central and peripheral signals are involved in achieving feeding and energy balance. For example, signals from adiponectin and leptin act on the arcuate nucleus to produce reciprocal activation or inhibition of the proopiomelanocortin and cocaine- and amphetamine-regulated transcript neurons while also inhibiting or activating the neuropeptide Y and agouti-related peptide neurons.16,17

Proopiomelanocortin activation from peripheral signals triggers the release of α-melanocyte–stimulating hormone (α-MSH) from axon terminals. Alpha-MSH activates the melanocortin 4 receptor, resulting in suppression of food intake. Signals from the arcuate nucleus neurons are subsequently transmitted to several other hypothalamic nuclei (eg, paraventricular nucleus and lateral hypothalamicus), which also play a role in energy regulation.12,17

In the lateral hypothalamus, two groups of neurons participate in the regulation of feeding; the orexin and melanin-concentrating hormone neurons. The orexin neurons stimulate feeding while the melanin-concentrating hormone neurons inhibit food intake. Neurons project from these hypothalamic neurons to brainstem nuclei (ie, solitary nucleus and tract, dorsomotor nucleus of the vagus nerve) where the descending hypothalamic inputs are integrated with peripheral inputs from the liver and gastrointestinal tract.12,15,18

Hypothalamic involvement in several headache disorders has been well described (eg, migraine, cluster headache, and other trigeminal autonomic cephalalgia).13,19,20 The hypothalamic role in migraine was first suggested based on the clinical

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Peripheral Role of Adipose Tissue
Expansion of adipose tissue during weight gain leads to the recruitment of macrophages as well as the synthesis of various mediators by adipocytes, including cytokines, such as TNF-α and IL-6, and adipocytokines, such as adiponectin and leptin.17

Cytokines
Alterations in cytokines have been reported in several pain disorders including migraine.21-24 Specifically, among patients with chronic daily headache, TNF-α is elevated in cerebrospinal fluid.22 Among episodic migraineurs, serum TNF-α, IL-1, and IL-6 are increased icterically.14

Less soluble tumor necrosis factor receptor type 1 has been noted in migraineurs,23 suggesting that these patients may lack sufficient antagonistic soluble tumor necrosis factor receptor type 1 to neutralize the effects of TNF-α.

In addition to abnormal proinflammatory cytokine levels, abnormal levels of the anti-inflammatory cytokine IL-10 have been observed in migraineurs.24 Specifically, decreased IL-10 levels were recorded when acute migraine was managed with sumatriptan succinate.24

Adipocytokines
Cytokines that are primarily, though not exclusively, produced by adipose tissue are known as adipocytokines. Adiponectin and leptin are two such adipocytokines.21 Both provide an important link between obesity and inflammatory disorders.11 And, like other cytokines, adiponectin and leptin may be altered in patients with headache disorders.4,5,9

Adiponectin—Primarily secreted from adipocytes, adiponectin is a 30-kDa protein.10,11 It exhibits a sexual dimorphism, with girls having higher levels than boys by puberty.25 Human plasma adiponectin can exist as a full-length form; a smaller fragment of the full-length form (ie, formed by cleavage of full-length adiponectin by proteases), termed globular adiponectin; or as one of several characteristic oligomers or multimers—including high, middle, or low molecular weight adiponectin.21

Based on the observations that serum total adiponectin levels are reduced in obesity, the metabolic syndrome, and diabetes mellitus, the anti-inflammatory properties of adiponectin are most often emphasized in the literature. However, adiponectin can exert either pro- or anti-inflammatory properties depending on the form and multimer of adiponectin involved.

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Leptin—As a 16-kDa adipocytokine, leptin has a demonstrated role in energy homeostasis, appetite suppression, and modulation of immune and inflammatory processes.11 Like adiponectin, leptin is primarily produced by adipocytes, but it is also produced by several other tissues including the stomach, muscle, bone marrow, and the brain.10,12

Leptin receptors are abundantly expressed in the arcuate nucleus and dorsomedial hypothalamus.12 Leptin is inhibited by testosterone and increased by ovarian sex steroids.30,31 Serum leptin concentrations are up to three times higher in women than in men, even when results are adjusted for age and BMI.11

In mice and humans, serum leptin reflects the amount of adiponectin and leptin, which can be used as biomarkers for the diagnosis and management of various diseases, including obesity, diabetes, and inflammatory disorders.
of energy stored in adipose tissue and remains proportional to overall adipose mass. Mice with a mutation in the gene encoding leptin (ie, ob/ob) or in the leptin receptor (ie, db/db) express an obese phenotype and have defects in cell-mediated and humoral immunity.

Further, though elevated serum leptin is associated with an increase in the anorexigenic proopiomelanocortin expression and a decrease in orexigenic neuropeptide Y and agouti-related peptide expression, serum leptin levels are increased in obesity as a result of leptin resistance.12 Thus, leptin deficiency and resistance frequently occur in obesity.

In addition to its role in energy homeostasis, leptin modulates inflammation. Specifically, in experimental models of acute inflammation, circulating leptin levels are promptly and highly increased. Acute infection, sepsis, and rheumatoid arthritis have all been associated with increased leptin synthesis.32-34

Leptin also induces the production of nitric oxide and several cytokines, including TNF-α and IL-6, in monocytes and macrophages.35,36 Similarly, leptin increases IL-6 production in microglia via several pathways, most notably in proinflammatory NFκβ.35,36 In addition to the activation of the proinflammatory cytokines implicated in migraine, intraperitoneal injections of leptin in mice have also been associated with increased pain sensitivity.37

Although the majority of data suggest a proinflammatory role for leptin, it has also been suggested that leptin has an anti-inflammatory effect.38,39 In human adipocytes, chronic stimulation with proinflammatory cytokines suppresses leptin production. Experiments38 using preadipocytes treated with TNF-α and monitored for 24 hours showed a reduction in leptin release after 8 hours that continued for study duration. In addition, a potential anti-inflammatory role for leptin is suggested by its ability to reduce the secretion of IL-1ra in human monocytes.39

Differences among study results may be due to the variety of cell cultures used by each set of investigators. Alternatively, the form of leptin receptor activated may affect study outcomes. Further research in this area using uniform human cell lines (ie, monocytes or macrophages) may help elucidate the seemingly conflicting roles in the inflammatory process attributed to leptin.

The first study5 to evaluate leptin levels in migraineurs evaluated pre- and posttreatment serum leptin levels in 19 patients given amitriptyline hydrochloride and 20 patients given fluoxetine hydrochloride. In both study groups, serum leptin levels were higher at 4- and 12-week follow-up when compared to baseline levels.5 This finding suggests that serum leptin levels may have been low at baseline in these patients.

This hypothesis is further supported by a recent study9 that specifically compared interictal serum leptin in age- and sex-matched episodic migraineurs. When unadjusted for fat mass, lower levels of leptin were seen in migraineurs than controls. However after adjusting for fat mass, no significant difference in leptin levels was noted between groups. Neither study5,9 noted disease duration in these patients. However, based on the previously mentioned in vitro21-34,38,39 and animal data,37 the duration of disease was likely long standing.

It is possible that disease duration may effect serum leptin levels in migraineurs, given the data suggesting that extended exposure to inflammation may be associated with decreased leptin levels while short-term exposure is associated with increased levels.27,28 If so, then leptin levels may be low in migraineurs with long disease duration and elevated in those with a more recent onset—and during acute attacks. Future studies evaluating disease duration and serum leptin levels in sex-, race-, and BMI-matched migraineurs ictally and interictally are warranted.

Conclusion

Adipose tissue is a dynamic neuroendocrine organ with multiple possible links within the pain system. The hypothalamus regulates feeding centrally and is activated in acute migraine.12 Peripherally, adipose tissue has been shown to secrete or modulate several proinflammatory cytokines and adipocytokines, several of which have already been linked to migraine.4,6,9

Thus, migraine pathophysiology is closely linked to the central and peripheral pathways involved in feeding and obesity. Further research in regard to the role of obesity-related neuroendocrine peptides and proteins, such as adiponectin and leptin, may further elucidate migraine disease mechanisms—as well as identify diagnostic biomarkers and new therapeutic drug targets.

References


