

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.

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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 activation in acute migraine.¹³ Peripherally, adipose tissue has been shown to secrete or modulate several proinflammatory cytokines such as tumor necrosis factor α (TNF- α) and IL-6, as well as adipocytokines (eg, adiponectin, leptin), which are involved in feeding and linked to migraine.^{4,5,10,11,14}

Given the striking similarities between the regulation of feeding and headache, it is likely that our understanding of these links will continue to expand. In the present review, the regulation of feeding is addressed, as are the cytokines and adipocytokines secreted or modulated by adipose tissue. In each section, links to migraine and pain are addressed. 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 hypothalamus), 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 nuclei 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

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other trigeminal autonomic cephalgia).^{13,19,20} The hypothalamic role in migraine was first suggested based on the clinical observations of premonitory symptoms in migraineurs: changes in alertness, thirst, food cravings, and mood or sleep disturbances.¹⁹ More recently, functional imaging data using positron emission tomography supported these clinical observations, with hypothalamic activation being demonstrated during acute migraine attacks.¹³ Thus, it is possible that the hypothalamic peptides activated in feeding are also activated in migraine.

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 ictally.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.

Human globular adiponectin activates the proinflammatory nuclear factor $\kappa\beta$ (NF $\kappa\beta$) pathway and induces the secretion of the proinflammatory cytokines IL-6 and TNF- α .^{26,27} However, under certain conditions, globular adiponectin exerts anti-inflammatory properties and induces self-tolerance to re-exposure of globular adiponectin and tolerance of endotoxin.²⁷

In addition, the different multimers of adiponectin activate different pathways and demonstrate distinct functions. Of the multimers of adiponectin, that of high molecular weight is the only variety shown to activate NF $\kappa\beta$ pathways in humans. Also, while high molecular weight adiponectin induces IL-6 secretion, that of low molecular weight reduces it.^{21,28}

The role of elevated adiponectin levels has been investigated in the context of several inflammatory disorders including arthritis, cardiovascular disease, preeclampsia, and, recently, migraine.⁴ The first study⁴ to evaluate total serum levels of adiponectin and its multimers in headache showed elevated levels of serum total adiponectin as well as high and middle molecular weight adiponectin in chronic daily headache when compared to controls matched for age, sex, and body mass index (BMI). Two important findings stemmed from this study.

First, it suggested that, independent of total body obesity as estimated by BMI, abdominal or visceral obesity was greater for those with chronic daily headache than episodic migraineurs. This finding may be clinically significant as there are multiple differences in the metabolic function of visceral adipose tissue when compared to subcutaneous adipose tissue.²⁹

Second, high molecular weight adiponectin was the multimer most responsible for elevations in serum total adiponectin. In addition, episodic migraineurs showed a similar trend toward higher levels of total and high molecular weight adiponectin though neither measure reached statistical significance.⁴

These data suggest that antagonists of high molecular weight adiponectin, agonists of low molecular weight adiponectin, or both could be potential targets for headache management. Future studies evaluating adiponectin levels inside and outside an acute episode—with adjustments made for the impact of sex hormones or evaluating each sex separately—are warranted.

■ **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 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.¹⁰

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 NF κ B.^{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 flunarazine 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 study^{5,9} noted disease duration in these patients. However, based on the previously mentioned *in vitro*^{21-34,38,39} and animal data,³⁷ the duration of disease was likely long standing.

It is possible that disease duration may affect 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.^{37,38} 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

1. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain*. 2003;106:81-89.
2. Peres MF, Lerário DD, Garrido AB, Zukerman E. Primary headaches in obese patients [published online ahead of print December 15, 2005]. *Arq Neuropsiquiatr*. 2005;63:931-933. Available at: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-282X2005000600005&lng=en&nrm=iso&tlng=en. Accessed June 10, 2009.
3. Tietjen GE, Peterlin BL, Brandes JL, Hafeez F, Hutchinson S, Martin VT, et al. Depression and anxiety: effect on the migraine-obesity relationship. *Headache*. 2007;47:866-875.
4. Peterlin BL, Alexander G, Tabby D, Reichenberger E. Oligomerization state-dependent elevations of adiponectin in chronic daily headache. *Neurology*. 2008;70:1905-1911.
5. Berilgen MS, Bulut S, Gonen M, Tekatas A, Dag E, Mungen B. Comparison of the effects of amitriptyline and flunarazine on weight gain and serum leptin, C peptide and insulin levels when used as migraine preventive treatment. *Cephalalgia*. 2005;25:1048-1053.
6. Sarchielli P, Rainero I, Coppola F, Rossi C, Mancini M, Pinessi L, et al. Involvement of corticotrophin-releasing factor and orexin-A in chronic migraine and medication-overuse headache: findings from cerebrospinal fluid [published online ahead of print May 13, 2008]. *Cephalalgia*. 2008;28:714-722.
7. Holland PR, Akerman S, Goadsby PJ. Orexin 1 receptor activation attenuates neurogenic dural vasodilation in an animal model of trigeminovascular

- nociception [published online ahead of print September 13, 2005]. *J Pharmacol Exp Ther*. 2005;315:1380-1385. Available at: <http://jpet.aspetjournals.org/cgi/content/full/315/3/1380>. Accessed June 10, 2009.
8. Puri V, Chandrala S, Puri S, Daniel CG, Klein RM, Berman NE. Ghrelin is expressed in trigeminal neurons of female mice in phase with the estrous cycle [published online ahead of print January 10, 2006]. *Neuropeptides*. 2006;40:35-46.
 9. Guldiken B, Guldiken S, Demir M, Turgut N, Tugrul A. Low leptin levels in migraine: a case control study [published online ahead of print June 10, 2008]. *Headache*. 2008;48:1103-1107.
 10. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity [review] [published online ahead of print September 22, 2006]. *Nat Rev Immunol*. 2006;6:772-783.
 11. Lago F, Dieguez C, Gómez-Reino J, Gualillo O. The emerging role of adipokines as mediators of inflammation and immune responses [review] [published online ahead of print May 15, 2007]. *Cytokine Growth Factor Rev*. 2007;18:313-325.
 12. Coppola A, Diano S. Hormonal regulation of the arcuate nucleus melanocortin system [review]. *Front Biosci*. 2007;12:3519-3530.
 13. Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. *Headache*. 2007;47:1418-1426.
 14. Sarchielli P, Alberti A, Baldi A, Coppola F, Rossi C, Pierguidi L, et al. Proinflammatory cytokines, adhesion molecules, and lymphocyte integrin expression in the internal jugular blood of migraine patients without aura assessed ictally. *Headache*. 2006;46:200-207.
 15. Valassi E, Scacchi M, Cavagnini F. Neuroendocrine control of food intake [review] [published online ahead of print December 3, 2007]. *Nutr Metab Cardiovasc Dis*. 2008;18:158-168.
 16. Bray GA. Drug insight: appetite suppressants [review]. *Nat Clin Pract Gastroenterol Hepatol*. 2005;2:89-95.
 17. Angelopoulos N, Goula A, Tolis G. Current knowledge in the neurophysiologic modulation of obesity [review]. *Metabolism*. 2005;54:1202-1217.
 18. Crowley VE, Yeo GS, O'Rahilly S. Obesity therapy: altering the energy intake-and-expenditure balance sheet [review]. *Nat Rev Drug Discov*. 2002;1:276-286.
 19. Blau JN. Migraine prodromes separated from the aura: complete migraine. *Br Med J*. 1980;281:658-660. Available at: <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1714112&blobtype=pdf>. Accessed June 10, 2009.
 20. Leone M, Proietti Cecchini A, Mea E, Curone M, Tullo V, Casucci G, et al. Functional neuroimaging and headache pathophysiology: new findings and new prospects [review]. *Neurol Sci*. 2007;28(suppl 2):S108-S113.
 21. Peterlin BL, Bigal ME, Tepper SJ, Urakaze M, Sheftell FD, Rapoport AM. Migraine and adiponectin: is there a connection [review] [published correction appears in *Cephalalgia*. 2007;27:570]. *Cephalalgia*. 2007;27:435-446.
 22. Rozen T, Swidan SZ. Elevation of CSF tumor necrosis factor alpha levels in new daily persistent headache and treatment refractory chronic migraine. *Headache*. 2007;47:1050-1055.
 23. Empl M, Sostak P, Riedel M, Schwarz M, Müller N, Förderreuther S, et al. Decreased sTNF-RI in migraine patients? *Cephalalgia*. 2003;23:55-58.
 24. Munno I, Marinaro M, Bassi A, Cassiano MA, Causarano V, Centonze V. Immunological aspects in migraine: increase of IL-10 plasma levels during attack. *Headache*. 2001;41:764-767.
 25. Combs TP, Berg AH, Rajala MW, Klebanov S, Iyengar P, Jimenez-Chillaron JC, et al. Sexual differentiation, pregnancy, calorie restriction, and aging affect the adipocyte-specific secretory protein adiponectin. *Diabetes*. 2003;52:268-276. Available at: <http://diabetes.diabetesjournals.org/cgi/content/full/52/2/268>. Accessed June 10, 2009.
 26. Haugen F, Drevon CA. Activation of nuclear factor-kappaB by high molecular weight and globular adiponectin [published online ahead of print August 16, 2007]. *Endocrinology*. 2007;148:5478-5486. Available at: <http://endo.endojournals.org/cgi/content/full/148/11/5478>. Accessed June 10, 2009.
 27. Tsatsanis C, Zacharioudaki V, Androulidaki A et al. Adiponectin induces TNF-alpha and IL-6 in macrophages and promotes tolerance to itself and other pro-inflammatory stimuli. *Biochem Biophys Res Commun*. 2005;335:1254-1263.
 28. Neumeier M, Weigert J, Schäffler A, Wehrwein G, Müller-Ladner U, Schölmerich J, et al. Different effects of adiponectin isoforms in human monocytic cells [published online ahead of print January 24, 2006]. *J Leukoc Biol*. 2006;79:803-808. Available at: <http://www.jleukbio.org/cgi/content/full/79/4/803>. Accessed June 10, 2009.
 29. Kissebah AH, Krakower GR. Regional adiposity and morbidity [review]. *Physiol Rev*. 1994;74:761-811.
 30. Tena-Sempere M, Manna PR, Zhang FP, Pinilla L, González LC, Diéguez C, et al. Molecular mechanisms of leptin action in adult rat testis: potential targets for leptin-induced inhibition of steroidogenesis and pattern of leptin receptor messenger ribonucleic acid expression. *J Endocrinol*. 2001;170:413-423. Available at: <http://joe.endocrinology-journals.org/cgi/reprint/170/2/413>. Accessed June 10, 2009.
 31. Lin KC, Sagawa N, Yura S, Itoh H, Fujii S. Simultaneous increases of leptin and gonadotropin-releasing hormone following exogenous estrogen administration in women with normally [sic] menstrual cycle. *Endocr J*. 2005;52:449-454. Available at: http://www.jstage.jst.go.jp/article/endocrj/52/4/52_449/article. Accessed June 10, 2009.
 32. Gunaydin R, Kaya T, Atay A, Olmez N, Hur A, Koseoglu M. Serum leptin levels in rheumatoid arthritis and relationship with disease activity. *South Med J*. 2006;99:1078-1083.
 33. Karmiris K, Koutroubakis IE, Kouroumalis EA. Leptin, adiponectin, resistin, and ghrelin—implications for inflammatory bowel disease [review]. *Mol Nutr Food Res*. 2008;52:855-866.
 34. Tzanela M, Orfanos SE, Tsiarantoni M, Kotanidou A, Sotiropoulou CH, Christophoraki M, et al. Leptin alterations in the course of sepsis in humans. *In Vivo*. 2006;20:565-570.
 35. Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, et al. Leptin regulates proinflammatory immune responses. *FASEB J*. 1998;12:57-65. Available at: <http://www.fasebj.org/cgi/content/full/12/1/57>. Accessed June 10, 2009.
 36. Otero M, Lago R, Gomez R, Dieguez C, Lago F, Gómez-Reino J, et al. Towards a pro-inflammatory and immunomodulatory emerging role of leptin [review] [published online ahead of print May 23, 2006]. *Rheumatology (Oxford)*. 2006;45:944-950. Available at: <http://rheumatology.oxfordjournals.org/cgi/content/full/45/8/944>. Accessed June 10, 2009.
 37. Kutlu S, Canpolat S, Sandal S, Ozcan M, Sarsilmaz M, Kelestimur H. Effects of central and peripheral administration of leptin on pain threshold in rats and mice. *Neuro Endocrinol Lett*. 2003;24:193-196.
 38. Wang B, Trayhurn P. Acute and prolonged effects of TNF-alpha on the expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture [published online ahead of print April 4, 2006]. *Pflugers Arch*. 2006;452:418-427.
 39. Gabay C, Dreyer MG, Pellegrinelli N, Chicheportiche R, Meier CA. Leptin directly induces the secretion of interleukin 1 receptor antagonist in human monocytes. *J Clin Endocrinol Metab*. 2001;86:783-791. Available at: <http://jcem.endojournals.org/cgi/content/full/86/2/783>. Accessed June 10, 2009.