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This information is current as of August 4, 2012

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Obesity, migraine, and chronic migraine

Possible mechanisms of interaction

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ABSTRACT Migraine and obesity are associated in several ways. First, both are prevalent and disabling disorders influenced by genetic and environmental risk factors. Second, migraine with aura, as obesity, seems to be a risk factor for cardiovascular events. Finally, large population-based studies suggest that obesity is a risk factor for chronic migraine after adjusting for comorbidities. In this article, we discuss plausible mechanisms that may account for this association. Several of the inflammatory mediators that are increased in obese individuals are important in migraine pathophysiology, including interleukins and calcitonin gene-related peptide (CGRP). These mediators may increase the frequency, severity, and duration of migraine attacks per se, which in turn would cause central sensitization. Repeated central sensitization may be associated with permanent neuronal damage close to the periaqueductal gray area, with poor modulation to pain. Obesity is also a state of sympathetic activation, which may contribute to increase in headache frequency. Furthermore, the levels of adiponectin are decreased in obesity. At low but not normal levels, adiponectin is nociceptive. Shared biologic predisposition may also play a major role. Orexins modulate both pain and metabolism. Dysfunction in the orexins pathways seems to be a risk factor for both conditions. Finally, conditions that are comorbid to both states (e.g., depression, sleep apnea) may also make the relationship between both diseases more complex. **NEUROLOGY 2007;68:1851–1861**

Headache and obesity are prevalent and disabling disorders influenced by genetic and environmental risk factors.[1,2] A longitudinal population study showed that persons with episodic headache and obesity develop chronic daily headache (CDH) at more than five times the rate of normal weighted individuals.[3] Subsequently, a large population study confirmed that obesity was a risk factor for CDH, and suggested that this association occurs primarily with chronic migraine (CM) and not with chronic tension-type headache.[4] The prevalence of episodic migraine, however, does not vary significantly with the body mass index (BMI), suggesting that obesity is not a risk factor for migraine.[5] However, among migraineurs, high BMI was associated with more frequent headache attacks.[5] In the three studies, obesity emerged as an independent risk factor, after adjustments for several comorbidities and demographic variables.

Identifying factors and mechanisms that contribute to the onset of CDH, particularly to frequent migraine, now referred to as CM,[6] has emerged as a priority in headache research. Exploring the links between headache and obesity may make a substantial contribution to this effort, and in this article we review those links. We start by highlighting some of the mechanisms of migraine and obesity. We describe the epidemiologic association between the two disorders. Then we provide a framework for understanding the linkages and review overlapping neurochemical mechanisms in both diseases. We stress that many of the putative mechanisms between frequent headaches and obesity are speculative or supported only by animal studies. Finally, although we emphasize the biochemical relations between both conditions, we do not want to suggest that the biobehavioral links are less important. We mention some of these links under the comorbidity section of our article and consider that the behavioral relations between headaches and obesity are beyond the scope of this article.

MIGRAINE AND CHRONIC MIGRAINE: AN OVERVIEW Migraine is a common and often severe disease globally.[7-11] The burden of migraine impacts affected individuals, their family, and society.[12,13] Furthermore, migraine is a disease that sometimes progresses and CM is the result of migraine progression. The former nomenclature of CM was transformed migraine (TM), and both, with different criteria, refer to the same

entity. Since some studies used the TM definition and some studies used the CM definition, herein we refer to CM and TM synonymously. In the United States, the prevalence of CM is 2%.[14]

Migraine is best understood as a primary disorder of the brain[1,15,16] with peripheral consequences.[17] There is abundant evidence that migraine is a familial disorder with genetic foundation.[18] Primary brain dysfunction may drive peripheral neurovascular events with consequent activation of the trigeminovascular system.[17,19,20]

The first neurologic event of migraine is a point of controversy and two non-mutually exclusive hypotheses exist. Migraine may result from a dysfunction of an area of the brainstem that is involved in the modulation of pain, sensory processing, and craniovascular afferents and has also been shown to control trigeminocervical nociceptive inputs.[20,21] According to this view, the pain is understood as a combination of altered perception (due to peripheral or central sensitization) of stimuli, as well as the activation of a feed-forward neurovascular dilator mechanism in the first division of the trigeminal nerve.[1] An alternative theory proposes cortical spreading depression as the first neurologic event, which would explain the migraine aura and would then activate trigeminovascular afferents and induces a series of cortical meningeal and brainstem events consistent with the development of the headache and the associated symptoms.[17,19]

The pathophysiology of migraine progression is less understood. An imaging study identified changes on MRI consistent with iron deposition in the periaqueductal gray (PAG) area in subjects with episodic and CM.[21] The PAG is a crucial component in the modulation of descending inhibitory pathways. It receives input from the trigeminal nucleus caudalis (TNC).[22] Allodynia, perception of pain when a usually nonpainful stimulus is applied, has been reported in about two-thirds of migraineurs during the attack.[23,24] It may be suggested, in a subset of patients, that repeated central sensitization, or alternatively, repetitive activation at the level of the PAG, is associated with high metabolic activity, hyperoxia, high iron turnover, and a progressive free-radical mediated permanent neuronal damage at the level of, or close to, the PAG, with poor modulation to pain and disease progression.[25]

OBESITY: AN OVERVIEW Obesity is a highly prevalent disorder that severely affects health-related quality of life and is a risk factor for hypertension, metabolic syndrome, diabetes, myocardial infarction, and stroke.[26] It has reached epidemic proportions globally[27,28] and in the United States, where 64% of adults are either overweight or obese.[26] Obesity and its associated health problems have a considerable economic impact on the health care system, accounting for 9.1% of total US medical expenditures in 1998 and reaching as high as $92.6 billion in 2002.[29]

Obesity is comorbid with a number of chronic pain syndromes. In fibromyalgia, it is associated with increased pain severity and refractoriness to treatment, while weight loss is followed by improved physical functioning.[30] Obesity is also associated with arthritis, as well as with prevalent and severe back and neck pain in the population.[31]

Discussing the mechanisms of obesity is beyond the scope of this article. Findings that are relevant to headache are discussed below.

CLINICAL RELATIONSHIP BETWEEN MIGRAINE AND OBESITY The link between obesity and the frequency of primary headaches was first demonstrated by Scher and colleagues.[3] In a longitudinal population study, over the course of 1 year, 3% of individuals with episodic headache progressed to CDH. Among the risk factors for progression, obesity figured prominently; the relative odds of CDH were five times higher in individuals with a BMI >30 than in the normal weighted subjects. Overweight individuals (BMI ranging from 25 to 29) had a threefold increased risk of developing CDH. In the cross-sectional component of the study they found that obesity was particularly associated with CDH with migraine features vs with CDH without migraine features. Obesity emerged as a risk factor after adjusting for other comorbidities and demographics.

Following the first study,[3] two large epidemiologic studies further investigated the relationship between BMI, episodic migraine, and CM. The first study focused on the relationship between BMI and episodic migraine.[5] A total of 30,215 participants were interviewed, and 3,791 had migraine. Migraine prevalence, frequency of headache attacks, and headache features were modeled as a function of BMI, adjusting by covariates (age, sex, marital status, income, medical treatment, depressive symptoms, medication use). BMI was not associated with the prevalence of migraine. It was, however, associated with the frequency of headache attacks. In the normal weighted group, just 4.4% of migraine sufferers had 10 to 14 headache days per month. This increased to 5.8% of the overweight group (OR = 1.3, 95% CI = 0.6, 2.8), 13.6% of the obese (OR = 2.9, 95% CI = 1.9, 4.4), and 20.7% of the severely obese (OR 5.7, 95% CI = 3.6, 8.8). Although 6% of the underweight had high frequency of headache at-

## Figure 1   Prevalence of chronic migraine according to the body mass index
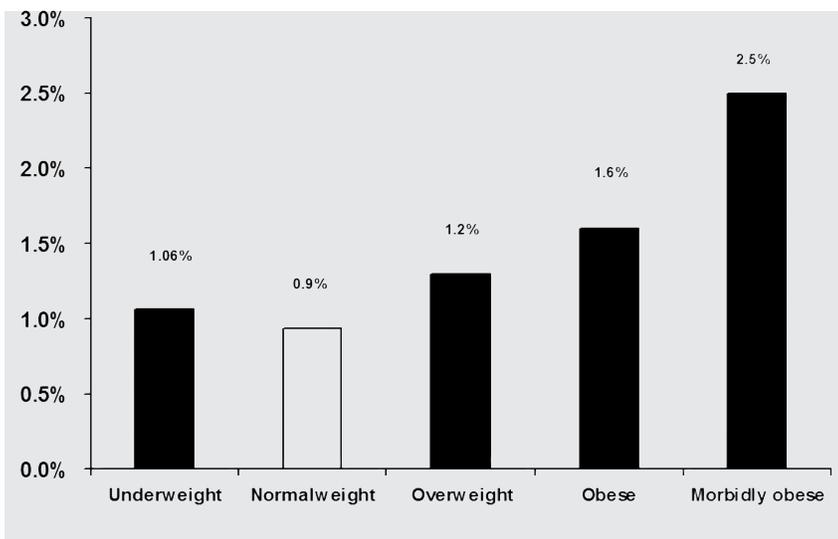
From Bigal and Lipton, 2006.[4] Analyses adjusted by age, gender, socioeconomic income, and depression. OR and CI are described in the text.

Figure 2   Possible links between obesity and chronic migraine

tacks, due to the small sample size in this group, the differences were not significant (OR = 1.4, 95% CI = 0.7, 2.5). In adjusted analyses, obesity correlated with frequency of attacks among migraineurs.

In the obesity-CDH study, similar methods were used to assess the relationship between BMI and CDH, as well as its subtypes, CM and chronic tension-type headache (CTTH).[4] The study confirmed that obesity and CDH are comorbid, after adjusting for several comorbidities and for demographics. It also suggested that obesity is a much stronger risk factor for CM than for CTTH. For CM, the prevalence ranged from 0.9% of the normal weighted (reference group) to 1.2% of the overweight (OR = 1.4 [1.1, 1.8]), 1.6% of the obese (OR = 1.7 [1.2, 2.43]), and 2.5% of the severely obese (OR = 2.2 [1.5, 3.2]). Underweight subjects (prevalence = 1.06%, OR = 1.13 [0.6, 2.1]) did not differ from normal weight (figure 1). The effects of BMI on the prevalence of CTTH were not significant, except in the severely obese group.

Because of the increase in the prevalence of overweight over the past decades,[32] a parallel increment in the prevalence of CM over time could be predicted. However, studies on the prevalence of CM are recent.[3,33] Obesity does not seem comorbid to migraine, just a risk factor to frequent migraine attacks.[5] Furthermore, none of the large prevalence studies conducted in the United States assessed the proportion of migraineurs with frequent attacks as an individualized category.[8,34,35] Nonetheless, most migraineurs in the population have few migraine attacks and even considering that the proportion of individuals with frequent attacks may be increasing following the increase in the prevalence of obesity,
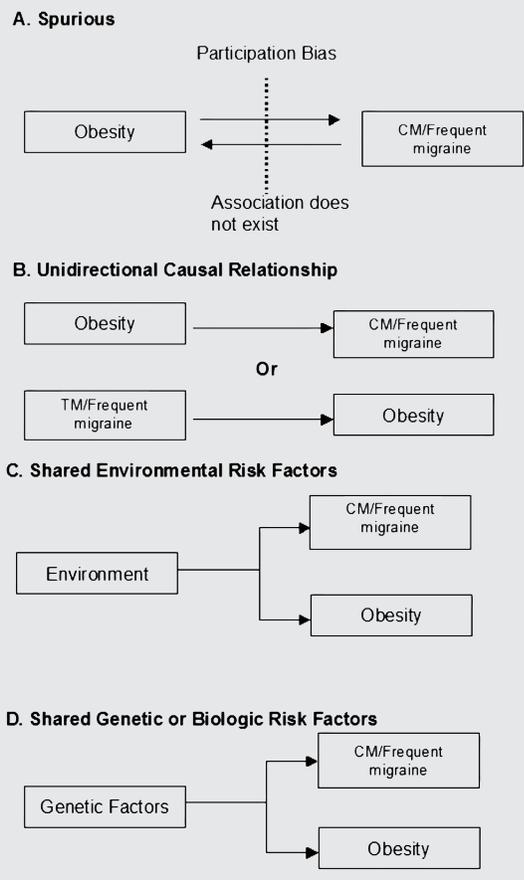
the impact on the overall frequency of attacks should be small.

POSSIBLE LINKS OF MIGRAINE AND OBESITY
Possible reasons for the association between obesity and frequent migraine/CM are summarized in figure 2 and briefly discussed below.

Spurious interaction. It could be that obesity and frequent headaches appeared to be related as a consequence of biased ascertainment. If persons with obesity or migraine/CM were more likely to be in the health care system, individuals with both disorders may be over-represented in clinic-based samples. Another potential source of spurious interaction is the fact that both migraine and obesity are common disorders, potentially leading to a statistically but not pathophysiologically relevant association between the two.

Since the association is supported by two large cross-sectional population studies and a longitudinal analyses adjusted by gender, age, and sociodemographic status, spurious interactions seem to be unlikely.[3,5,6]

Unidirectional causal relationships. Herein, one disease would lead to the other. CM may be a risk factor for obesity, since individuals with daily pain may live more sedentary lives and may use preventive medications that increase weight. Obesity could increase the risk of CM if proinflammatory mediators contribute to headache progression. In the only available longitudinal study,[3] obesity was a risk factor for incident CM. CM has not been studied as a risk factor for obesity.

As detailed in the next section, unidirectional causal relationships may explain some of the relationship between both conditions (e.g., inflammatory mediators that are elevated in obesity and may be of importance in migraine).

Shared environmental risk factors. Comorbid relationships might be explained by shared environmental risks. A sedentary and stressful occupation might contribute to the co-occurrence of these disorders. There is no direct evidence to support this hypothesis.

Shared genetic risk factors. Migraine and obesity may share a common genetic underpinning. Shared genetic risk factors explain several of the comorbidities of migraine.[36,37] Some of the relationship between obesity and migraine may be explained by this model. As discussed below, some neurochemicals, including orexins, are responsible for modulating a number of metabolic and nociceptive processes. Genetic risk factors that lead to dysmodulation in the orexin pathways could lead to both refractory pain and obesity.

In the next section we discuss specific linkage points between both conditions. Although we cannot completely exclude shared environmental risk factors as important, we focus on unidirectional and shared biologic interactions.

POSSIBLE MECHANISMS OF MIGRAINE AND OBESITY RELATIONSHIP

Migraine, inflammation and vascular mediators. The source of pain in migraine headache may involve neurogenic plasma extravasation and consequent vascular meningeal inflammation.[38] Structural changes in the dura mater following trigeminal ganglion stimulation have been demonstrated in animals, specifically mast cell degranulation and changes in post-capillary venules including platelet aggregation.[39] Electrical stimulation of the trigeminal ganglion leads to increases in extracerebral blood flow and local release of both calcitonin gene-related peptide (CGRP) and substance P (SP).[40] SP release is likely to be proinflammatory.[41] Trigeminal ganglion stimulation also causes release of a powerful vasodilator peptide, vasoactive intestinal polypeptide (VIP), through a reflex activation of the cranial parasympathetic outflow.[42]

Other inflammatory promoters are also altered in migraineurs, including several cytokines, and some of these markers are normalized after sumatriptan.[43,44] Transient increase in soluble intracellular adhesion molecule (sICAM-1), interleukin (IL)-6, and tumor necrosis factor (TNF)-alpha can be induced by sensory neuropeptides released from activated trigeminal endings and are seen during migraine attacks.[44]

Migraine is also comorbid to a number of vascular diseases. Migraineurs with aura seem to be at risk of silent cerebellar infarcts.[45] It has been demonstrated that cortical spreading depression (CSD) alters blood–brain barrier (BBB) permeability by activating brain matrix metalloproteinases (MMPs), especially MMP-9.[46] MMP-9 regulates perfusion at the level of the BBB. CSD induces upregulation of MMP-9 which, in turn, opens the BBB and promotes sustained leakage of serum proteins. Barrier disruption may contribute to changes in brain permeability during migraine attacks, as well as neuronal death and an increase in infarct volume in the already compromised brain.[46] It must be borne in mind that most aura is visual, and there seems to be no evidence that this region suffers an undue burden of brain lesions.[47]

Studies also investigated the presence of genetic abnormalities of the protein C system in subjects with migraine, contrasted with controls. In one study, migraineurs had an increased frequency of activated protein C resistance due to Arg506Gln factor V mutation and of protein S deficiency.[48] Additionally, C-reactive protein (CRP) was increased in individuals with migraine with aura in a clinic-based study.[49]

Obesity, inflammation, and vascular mediators. Adipose tissue, previously considered a passive storage depot for fat, is now known to play an active role in metabolism.[50] Adipocytes produce and release inflammatory cytokines, and obesity is considered by some experts as a permanent state of low-grade inflammation.[51] In a population study, overweight and obese individuals were more likely to have elevated CRP levels than their normal-weight counterparts. After adjustment for potential confounders, the odds for elevated CRP were 2.13 for obese men and 6.21 for obese women. Obesity, as well as high levels of CRP, are independent risk factors for leukocytosis.[52] Additionally, adipocytes secrete a wide range of inflammatory molecules including TNF-alpha and IL-6. The adipose tissue is estimated to produce about 25% of the systemic IL-6 in vivo.[51]

Table 1 Selective inflammatory events of importance in obesity and migraine

Biomarker	Obesity	Migraine	Potential linkage
C-reactive protein (CRP)	Increased	Increased	CRP is one of the acute phase proteins that increase during systemic inflammation
			CRP is also associated with cardiovascular disease risk
			Since obesity is a proinflammatory state, it may be associated with enhancement in the inflammatory response in migraine
Tumor necrosis factor (TNF)-α	Secreted by adipocytes	Elevated at the onset of migraine attacks	TNF causes allodynia in animals
			Administration of TNF increases pain states in several models
Interleukin (IL)-6	Secreted by adipocytes	Transient elevation in the onset of migraine attacks	IL-6 induces pain in several models
Mast cells	One of major secretory compartment of adipose tissue	Mast cells can be activated by trigeminal nerve stimulation. Mast cells are also activated by peptides, such as CGRP and substance P	Activated mast cells secrete proinflammatory and neurosensitizing mediators
			Brain mast cells can also secrete proinflammatory and vasodilatory molecules such as IL-6
Macrophages	The fat tissue is infiltrated by macrophages	Macrophage iNOS upregulation and edema formation follow GTN infusion in human models of migraine pain	Macrophages are a major source of locally produced proinflammatory cytokines
			iNOS is implicated in the vasodilatation that happens in migraine pain

CGRP = calcitonin gene-related peptide.

Additionally, the adipose tissue is infiltrated by macrophages, which may also be a major source of locally produced proinflammatory cytokines.[53] Weight loss is associated with a reduction in the macrophage infiltration of adipose tissue.[53] Other substances produced by the adipocytes with inflammatory properties include adiponectin, leptin, and reistin, and are discussed below.

Table 1 summarizes some of the inflammatory abnormalities that happen in obesity and migraine, discussing some of the possible points of interaction.

Calcitonin gene-related peptide (CGRP) and other peptides. CGRP is released into the cranial circulation of humans during acute migraine, and is an important postsynaptic modulator of the trigeminovascular neurotransmission.[54] CGRP receptors in the trigeminocervical complex can be inhibited by CGRP receptor blockade.[55] In models of medication overuse, morphine tolerance in spinal neurons can be reversed by CGRP receptor antagonists.[56] Finally, experimental CGRP receptor antagonists are effective in the acute treatment of migraine.[57,58]

Plasma levels of CGRP are elevated in obese individuals, and fat intake may also be associated with CGRP secretion.[59] In a clinic-based study, CGRP was significantly higher in obese subjects relative to controls. After fat intake, the CGRP levels further increased, and after weight loss, concentrations remain unchanged. It was suggested that CGRP levels may be genetically determined in obese individuals, and that fat intake may be associated with increased CGRP secretion.[59]

Amylin (AM) and adrenomedullin (ADM) are two peptides that share between 25 and 50% sequence homology with CGRP.[60,61] The levels of AM are elevated in obese individuals, probably leading to downregulation of the amylin receptors which, in turn, would lessen the impact of postprandial AM secretion on satiety and gastric emptying.[62] Null amylin mutant mice have reduced pain response in the paw formalin test, suggesting that amylin is pro-nociceptive in primary sensory neurons.[63]

AM is a potent, long-lasting vasoactive peptide. Considerable evidence exists for a wide range of autocrine, paracrine, and endocrine mechanisms for AM which include vasodilatory, antiapoptotic, angiogenic, antifibrotic, natriuretic, diuretic, and positive inotropic.[63] The adipose tissue, especially mature adipocytes, is a major source of AM in the body, and AM might play a pathophysiologic role in obesity.[63]

As with CGRP, ADM is a potent dilatator of human arteries. The vasodilation induced by ADM is mediated through a CGRP1 receptor, suggesting the presence of functional ADM receptors in human astroglial cells.[64] This may be of importance in the pathophysiology of migraine.

Table 2   Calcitonin gene-related peptide (CGRP) and analogous molecules: Importance in obesity and migraine

Biomarker	Obesity	Migraine	Potential linkage
CGRP	Plasmatic CGRP is elevated in obese individuals. Fat intake is associated with increased CGRP secretion	Postsynaptic mediator of the migraine trigemino-vascular inflammation	CGRP is one of the most important peripheral migraine mediators and one target for development of new migraine treatments
Amylin	Elevated in obese individuals	Not tested	Amylin mutant mice display a reduced pain response in the paw formalin test
			Amylin has a pro-nociceptive function in primary sensory neurons
Adrenomedullin (AM)	Adipocytes are a major source of AM in the body	Not tested	ADM is a potent dilatator of human arteries
			The effects of ADM happen trough CGRP1 receptors

ADM = adrenomedullin.

Table 2 summarizes the importance of CGRP and analogous molecules in obesity and migraine.

Substances and pathways important in the regulation of food intake and weight control. *Orexins.* Several peptides have been reported recently to be involved in the modulation of appetite and energy homeostasis, including the orexins (orexin A and B)[65-67] (table 3). The orexins bind to two G-protein coupled receptors, termed OX_1R and OX_2R. Orexin A has an equal affinity for both receptors, whereas orexin B has a 10-fold higher affinity for the OX_2R.[68] The broad projections of the orexinergic system have led to its implication in a variety of functions including feeding, sleep wake cycle, cardiovascular function, hormone secretion,[67] and more recently the modulation of nociceptive processing.[69] Interestingly the orexinergic system has been linked to the sleep disorder narcolepsy with the discovery of a mutation at the OX_2R, being responsible for canine narcolep-

sy,[70] and 90% of narcoleptic patients demonstrating a decreased level of orexin A in their CSF.[71] A link between orexin and migraine can be indirectly postulated by the increased prevalence of migraine in narcoleptic patients.[72] Narcoleptic patients also demonstrate an increased BMI,[73] as do first-degree relatives, suggesting a possible genetic link.[74]

The orexinergic influence on feeding is dependent on circadian processes, with the effect of orexin A administration on feeding varying depending on time of day.[75] Furthermore, the orexins may be important in the modulation of obesity. In a clinic-based study, plasma orexin A concentrations were significantly lower in obese women when compared to control subjects. Plasma orexin B concentrations did not change as a function of BMI.[76]

Recent studies have also linked the orexins with the modulation of nociceptive processing.[77,78] Orexin A receptors have been localized to the spinal

Table 3   Substances important in the modulation of food intake and weight control: Relevance in migraine

Biomarker	Obesity	Migraine	Potential linkage
Orexins	Levels of orexin A are reduced in obese individuals	Injection of orexin A decreased the A- and C-fiber responses to painful stimulation. Orexin A inhibits neurogenic induced vasodilatation	Low levels of orexin, as found in obese individuals, may be related to a proinflammatory state in the trigeminal system
			Orexin plays a key role in regulating the sleep cycle. Sleep disorders are known risk factor for migraine progression
Adiponectin	Decreases with increased BMI	Not tested	Low levels are associated with platelet aggregation, as well as proinflammatory cytokine release
			Adiponectin inhibits IL-6 and TNF-induced IL-8 formation, as well as induction of the anti-inflammatory cytokines, IL-10 and IL-1RA
			Adiponectin levels are inversely correlated with CRP, TNF-α, and IL-6 levels
Leptin	Increases with BMI	Not tested	Leptin induces cytokine release in several models
Resistin	Increases with BMI	Not tested	As leptin, resistin induces cytokine release in several animal models

BMI = body mass index; IL = interleukin; TNF = tumor necrosis factor.

cord and dorsal root ganglion, and orexin-A was shown to be analgesic when given IV and intrathecally.[79] In animals, the efficacy of orexin-A was similar to that of morphine. However, involvement of the opiate system was discounted as the effects were blocked by the OX_1R antagonist SB-334867 but not naloxone.[80]

The orexins have only very recently been linked with a possible role in migraine. In an animal model of trigeminovascular pain, activation of the OX_1R and OX_2R in the posterior hypothalamus has been shown to differentially modulate nociceptive dural input to the TNC.[79] Activation of the OX_1R elicits an antinociceptive effect whereas OX_2R activation elicits a pro-nociceptive effect. This is of importance, since regulation of autonomic and neuroendocrine functions as well as nociceptive processing are closely coupled in the hypothalamus,[80] probably mediated by orexinergic mechanisms.[81] Thus, the orexinergic could be a possible link between the pain of primary neurovascular headaches and the possible hypothalamic dysfunction seen in migraine.[82] In a further study, the effects of orexin A and B on neurogenic dural vasodilation were investigated. Inhibition of neurogenic dural vasodilation has proved successful in predicting antimigraine efficacy with numerous compounds including the triptans.[83] Orexin A, but not orexin B, was able to inhibit neurogenic dural vasodilation, resulting in inhibition of prejunctional release of CGRP from trigeminal neurons. The response was reversed by pretreatment with the OX_1R antagonist SB-334867.[84]

Adipocytokines. Adipocytes also act as endocrine cells, secreting substances called adipocytokines. Some of the adipocytokines have hormonal properties, including adiponectin, resistin, and leptin. They seem to be exclusively produced in the fat cells and placenta.[85]

The better studied of the adipocytokines is adiponectin, a substance that has endocrine effects in the liver, muscle, and vasculature. Adiponectin modulates a number of metabolic processes important in the control of glycemia, as well as fatty acid catabolism. Levels of the hormone are inversely correlated with BMI,[86] which plays a key role in metabolic disorders such as type 2 diabetes, obesity, and atherosclerosis. Plasma concentrations are higher in females than in males.[86] Weight reduction significantly increases circulating levels. At normal levels, the anti-inflammatory activities of adiponectin include inhibition of IL-6 and TNF-induced IL-8 formation, as well as induction of the anti-inflammatory cytokines, IL-10 and IL-1. Adiponectin levels are inversely correlated with C-reactive protein, TNF-α, and IL-6 levels.[85,86] At lower levels, adiponectin induces a proinflammatory state.[85,86]

Beyond their effects on central metabolic functions, leptin, resistin, and adiponectin have profound effects on a number of other physiologic processes, including inflammation.[87] It has been demonstrated that leptin and adiponectin activate proinflammatory cytokine release and phospholipid metabolism in the adipose tissue, and that antiinflammatory agents counteract the induced inflammation.[88] Adiponectin is upregulated in vivo and in vitro in response to inflammatory stimuli. The underlying mechanisms seem to involve a NO-dependent pathway.[89] Finally, it is worth noting that low levels of adiponectin have been recently reported to be associated with platelet aggregation.[89,90]

IMPORTANCE OF COMORBID ASSOCIATIONS
The relationship between chronic migraine and obesity may be at least partially explained by both diseases sharing comorbidities that are also known risk factors for migraine transformation.

Depression and stressful life events have been identified as risk factors for CDH and exemplify this issue.[3] A recent population study showed that, in the United States, obesity was associated with significant increases in lifetime diagnosis of major depression, bipolar disorder, and panic disorder or agoraphobia.[90] Sleep apnea is also a risk factor for migraine progression,[3] and with increased daytime sleepiness in migraineurs.[91]

Medication overuse is a third condition that may be used as an example. It is a known risk factor for CDH.[92] There is increasing evidence that dysfunctioning of the reward and drive circuitry (the frontostriatal-amygdala-midbrain circuit) may play a pivotal role in obesity.[93] The same circuit may also be involved in substance abuse.[94]

It is clear that some of these common comorbidities may contribute to the process of migraine transformation. In two of the studies that found obesity and CDH comorbid,[5,6] analyses were partially adjusted for depression (depression scales were not used, but questions on depression were) and were fully adjusted for acute and preventive medication use and for demographics. In the third[3] analyses were adjusted for stressful life events, sleep apnea, and snoring. In the three studies, obesity emerged as an independent risk factor for transformation. However, it has been suggested that depression may at least partially explain the influence of BMI on CDH prevalence,[95] and none of the mentioned studies used a validated depression scale.

The importance of comorbid associations is ex-

Figure 3 Algorithm summarizing the relationship between obesity and migraine progression
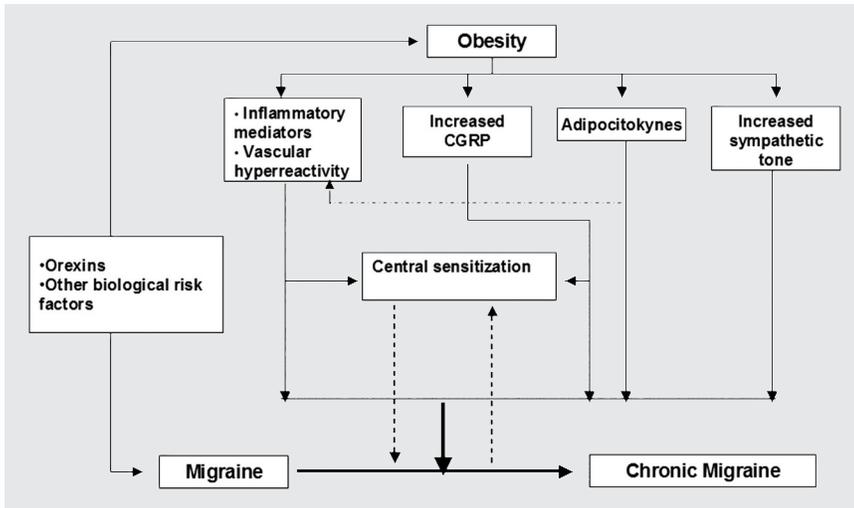
emplified by what is seen in the underweight group. In three population studies (Bigal et al., data in preparation),[4,5] underweight individuals had a higher prevalence of CDH and higher frequency of headache attacks overall. However, after adjusting for covariates (questions on depression and anxiety, for example), the relationship remained true for obesity but not for underweight, suggesting that in the underweight, psychiatric comorbidities mediate at least in part the relationship.

ROLE OF THE AUTONOMIC NERVOUS SYSTEM Obesity may be explained as a disturbance of energy balance, with energy intake exceeding energy expenditure. As the autonomic nervous system has a role in the regulation of both these variables, it has become a major focus of investigation in the fields of obesity pathogenesis.[96] A prospective study in 8,000 obese and nonobese patients revealed a high relative risk to develop type 2 diabetes if autonomic dysfunction is present.[97] It may be suggested that an unbalanced autonomic output develops in obese individuals with increased parasympathetic dominance in the visceral compartment and increased sympathetic tone in the thoracic compartment and muscles. Finally, it is also speculated that the increase in the sympathetic tone, happening under fasting conditions in obesity, may be associated with high cardiovascular morbidity and mortality. At least partially, this dysmodulation is driven by leptin, a proinflammatory molecule.

Autonomic dysfunction has been suggested in migraine.[98] Obesity leads to activation of the sympathetic nervous system, as well as changes in central serotonergic responsiveness (a reduction in central "serotonin tone"), and this might increase the chance of migraine transformation. It may be

hypothesized that, due to sympathetic hypofunction, obese migraineurs are less able to cope with the increased sympathetic tone associated with obesity, and thus would be at a greater risk for frequent headaches.

CONCLUSION In this article, we discussed several hypothetical mechanisms that may account for the association between obesity and frequent migraines, including chronic migraine in epidemiologic studies. Figure 3 summarizes many of these relationships. We propose that unidirectional causality as well as shared biologic mechanisms are important. Obesity increases the levels of several markers that are important in migraine pathophysiology, including interleukins and CGRP. These mediators may increase the frequency, severity, and duration of migraines per se. Increase in the frequency of migraine is associated with central sensitization, which would contribute to self-perpetuating the process. Obesity is also a state of sympathetic activation, which may contribute to increase in headache frequency. The levels of adiponectin are decreased in obesity, and, as exposed, at normal levels, adiponectin has anti-inflammatory properties.[99] Finally, shared biologic predisposition may play a relevant role. Orexins are important, modulating both pain and metabolic pathways. Dysfunction in the orexins pathways seems to be a risk factor for both conditions.

A recent large population in which we interviewed 160,000 individuals supported that obesity was an exacerbating factor for migraine and probable migraine but not for episodic tension-type headache. Therefore it was a risk factor for CM but not for CTTH (Bigal et al., data in preparation). This specificity of association creates opportunity to generate mechanistic hypothesis. Future research should explore the several hypothetical mechanisms of relationship between obesity and CM, as well as the interaction between obesity and other risk factors for migraine progression. For example, based on the obesity data alone, CM should be more frequent in the United States than in Europe, since obesity is more prevalent in the former, which is not the case.[33] It is possible that other known risk factors to migraine transformation (depression, stressful life events, income, head trauma, sleep apnea, frequency of headache attacks, medication overuse) counterbalance the stronger influence of obesity that would be expected in the United States.

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Marcelo E. Bigal, Richard B. Lipton, Philip R. Holland, et al.

Neurology 2007;68;1851

DOI 10.1212/01.wnl.0000262045.11646.b1

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