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Calcitonin gene-related peptide (CGRP): a molecular link between obesity and migraine?

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Abstract

Epidemiological studies have begun to suggest obesity is a risk factor for chronic migraine, although no causal relationship has been established, and risk factors for progression from episodic to chronic migraine remain unknown. The neuropeptide calcitonin gene-related peptide (CGRP) plays a important role in the pathophysiology of migraine. Here the potential role of CGRP as a molecular link between obesity and migraine is reviewed. A mechanistic association is supported by several lines of evidence: a) common markers are elevated in obesity and migraine, b) adipose tissue secretes pro-inflammatory cytokines and adipocytokines that have been implicated in migraine pathophysiology and c) elevated plasma levels of CGRP have been found in obese individuals. We propose that CGRP released from trigeminal neurons may represent a biological link between obesity and migraine. Enhanced trigeminal CGRP production in obese susceptible individuals may lower the threshold necessary to trigger migraine attacks, leading to more frequent episodes and eventually to chronic migraine.

1. Introduction

Migraine is a common (1), disabling (2), and complex neurological disorder. It is characterized by recurrent attacks of moderate or severe head pain, that is frequently unilateral, throbbing, aggravated by movements, and associated with symptoms such as nausea, and sensitivity to light and sound (3). Episodic migraine attacks, although at times disabling (2), may be well controlled with acute anti-migraine medications, but between 2.5 and 14% of patients with episodic migraine develop chronic migraine over the course of one year (4,5). Chronic migraine is defined as fifteen or more days with headache per month for more than three months with particular features, such as nausea, photophobia and phonophobia, or triptan/ergotamine treatment, on a proportion of those days (6). The progression from episodic to chronic migraine is sometimes referred to as migraine transformation (7) or “chronification”. Chronic migraine is frequently regarded as refractory to medical management by headache experts, and has a significant impact on the patient’s life and society. The mechanisms underlying the change

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from episodic to chronic migraine are not well understood and multiple culprits have been proposed. Obesity has been identified as one of the conditions associated with chronic migraine, based on several large population-based studies, although a causal relationship has not been established (8).

2. Relationship between Obesity and Migraine Progression: Epidemiology

Scher *et al* were the first to report a link between chronic daily headache (CDH), headache on fifteen days or more for more than three months, and obesity (9). In a large population based study they found the prevalence of chronic daily headache was higher in obese subjects defined as those with a body mass index (BMI) of 30 or higher. Prospective follow-up a year later led to the observation that obesity was a risk factor for the evolution from episodic headache to CDH. The risk of progression from episodic to CDH was threefold higher in the overweight group (BMI 25–29), and fivefold higher in the obese group, compared to individuals with normal weight.

The higher prevalence of CDH in obese and morbidly obese subjects was confirmed by Bigal *et al* in another large population based study (10). Furthermore, obesity was found to be associated with *transformed* migraine, as well as headache every day, and more severe and disabling headache, but not with chronic tension-type headache (10). Importantly, although obesity was not found to be associated with the prevalence of episodic migraine by Bigal *et al*, a BMI of greater than thirty was associated with higher number of attacks (10–14 attacks/month) and severe migraine attacks that cause more disability (11). This suggests obesity may exacerbate the underlying mechanisms involved in eliciting a migraine attack and perhaps also enhance its intensity.

Keith *et al* evaluated the association between obesity and headache among women in a cross-sectional analysis of 11 epidemiologic datasets and found that increased BMI was associated with higher risk of headache (non-migraine headaches and possibly undiagnosed migraine), but not diagnosed migraine (12). Whereas the final size sample was very large, 220,370 women, the headache-related questions varied considerably among the datasets making difficult to differentiate between respondents with migraine and other headaches. Similarly, Ford *et al* found that obesity was associated with a higher prevalence of self-reported “severe headaches or migraine” during the previous 3 months, but unfortunately not further information about the headache was obtained and subjects with episodic and chronic headaches were analyzed together (13).

Another study of middle-aged and older women found no association between migraine and obesity (14). Strengths of this study are that all subjects were interviewed by the same neurologist as opposed to lay interviewers and BMI was measured and not based on self-reports of weight and height. A major limitation is that only 22 of the migraineurs were obese and only 3 women had more than eight days with headache per month. In contrast, Horev *et al* found in an admittedly small study including only morbidly obese women (BMI >35) that almost half of them had episodic migraine and, interestingly, a high proportion of them, 77%, reported auras (15).

An important question remaining unanswered is the lack of an impact of the epidemic of obesity on the prevalence of chronic migraine in the U.S. over the last twenty years. Data from the National Health and Nutrition Examination Surveys shows that among adults aged 20–74 years the prevalence of obesity increased from 15.0% in the 1976–1980 survey (16), to 32.2% in the 2003–2004 survey (17). An important consideration is that obesity is defined as a threshold, hence a small increase in the average weight has a disproportionate effect in the incidence of obesity (18). Therefore, a plausible explanation is that the mean weight of the population may have been high enough to increase the prevalence of chronic migraine even before it reached

the threshold of overweight or obesity that has now reached epidemic proportions. On the other hand, we may have inaccurate information regarding the exact prevalence of chronic migraine. Lack of diary data with the consequence of having to rely exclusively on patients' memory reporting their headache frequency, may interfere with accurate diagnosis of chronic migraine. Furthermore, in the recent past, the lack of consensus regarding the nomenclature used makes studies results difficult to interpret and compare. Some use the diagnostic criteria for transformed migraine (19), even while the entity of chronic migraine was hotly debated and indeed not represented in the first edition of the International Classification of Headache Disorders (20).

3. Potential Mechanistic Link between Obesity and Migraine

In addition to the epidemiological link between obesity and chronic migraine, a mechanistic link is supported by the following lines of evidence: a) inflammatory markers are elevated in obesity and migraine, b) adipose tissue secretes pro-inflammatory cytokines and adipocytokines that have been implicated in migraine pathophysiology and c) elevated plasma levels of CGRP have been found in obese individuals.

The possible mechanisms of interaction between obesity and chronic migraine have been recently reviewed in detail by Bigal *et al* (8). The authors suggest a unidirectional causality, as well as shared biological mechanisms, but a potential spurious interaction or shared environmental risk factors have not been systematically studied (8). Here we will focus on the potential role of CGRP as a molecular link between migraine and obesity.

3. 1. CGRP and its Role in the Pathophysiology of Migraine

The neuropeptide calcitonin gene-related peptide (CGRP) plays an important role in migraine. CGRP is a multifunctional peptide, a major modulator of the cardiovascular system (21–23) and a key promoter of neurogenic inflammatory pain (24), as well as modulating nociceptive input via central pathways (25).

CGRP has been found to be elevated in the jugular outflow during migraine attacks (26), and levels of CGRP were normalized parallel to pain resolution following treatment with sumatriptan in both spontaneous (27) and nitroglycerin-induced attacks (28). Two sets of clinical studies have solidified the importance of CGRP in migraine. Lassen *et al* demonstrated that CGRP injected intravenously caused a delayed moderate or severe headache in eight out of nine migraine sufferers (29). In several cases, the headache met the criteria for migraine. In contrast, non-migraineurs did not have a delayed headache after intravenous CGRP, and only reported an immediate mild sensation of head fullness (30). The exact mechanism underlying this difference in susceptibility to CGRP remains unexplained. Furthermore, in clinical trials the efficacy of selective non-peptide CGRP receptor antagonists, first olcegepant (BIBN-4096BS; Boehringer Ingelheim GmbH) (31), and later telcagepant (MK-0974; Merck) (32) provide proof for the importance of CGRP in migraine.

This evidence supports the concept of CGRP being important in the induction as well as in the perpetuation of the migraine attack. It has also been suggested that migraineurs may have an increased sensitivity to CGRP, and that this may be due to differences in expression of the functional rate limiting subunit of the CGRP receptor, the receptor activity modifying protein 1 (RAMP1) (33).

3. 2. CGRP as a Potential Molecular Link between Obesity and Migraine

The pathophysiology of migraine is not completely understood. However, activation, or the perception of activation, of the trigeminovascular system leading to trigeminally-mediated CGRP release is likely to play a role (3,34). Despite the significant advances that the field has

experienced in the last decades, we still do not have a good understanding of the pathophysiology of chronic migraine or the mechanisms that lead to transformation from episodic to chronic migraine.

Obesity, an emerging risk factor for chronic migraine, is recognized to be, among other things, a state of low grade systemic inflammation (35). There is strong evidence suggesting that CGRP has immunomodulatory effects *in vivo* (36,37). CGRP has shown potent anti-inflammatory effects in several animal models of inflammation, including endotoxemia (38), delayed-type hypersensitivity (39), and inflammatory bowel injury (40). In humans, CGRP has been reported elevated in conditions where inflammation is implicated, such as sepsis (41), acute exacerbation of asthma (42) and psoriasis (43).

While little is known about the role of CGRP in obesity, it is plausible for this important mediator of neurogenic inflammation, and indeed widespread neuropeptide, to be a player in the association between obesity and chronic migraine. Based on the interaction among obesity, inflammation and CGRP, we could speculate that chronically elevated circulating levels of CGRP, or increased sensitivity to otherwise normal levels of CGRP, may decrease the trigeminovascular activation threshold. This would lead to increased frequency of migraine attacks by making the patient more susceptible to their usual triggers. Furthermore, CGRP effects on other unidentified pathways may, indirectly, play an important role triggering migraine attacks. Conversely, other mediators or neuromodulators present or elevated in obesity may activate nociceptive pathways upstream of CGRP.

3. 2. a. Common inflammatory markers in obesity and migraine—Several inflammatory markers are elevated in migraine and obesity. C-reactive protein (CRP), a established marker of inflammation, is elevated in obese subjects (44) as well as in young migraineurs interictally (45). Interestingly, CRP has also been associated with depression (46). Depression is a co-morbidity for migraine (47) and obesity (48,49), and it has been reported to be a modifier of the strength of the relationship of obesity with migraine attacks frequency and disability (50). Moreover, a study including only women confirmed that serum levels of CGRP are elevated in depression and also showed that this group have more pain symptoms in several scales (51). High levels of CGRP have also been reported in cerebrospinal fluid in depressed individuals (52).

Plasma levels of pro-inflammatory cytokines have been studied in migraineurs during and outside migraine attacks. Inconsistent findings may be due to differences in study designs, time elapsed from headache onset, site of blood extraction or a lack of a true relationship. Kemper *et al* have carried out a comprehensive review that suggests an interaction between the immune system and migraine (53). TNF-alpha and interleukin 6 (IL-6) are transiently elevated in jugular blood at the onset of a migraine attack (54). TNF-alpha increases CGRP promoter activity and CGRP secretion in rat trigeminal ganglion neurons (55). Additionally, CGRP is known to inhibit TNF-alpha synthesis *in vivo* (56) and secretion of TNF-alpha is up-regulated in obesity (57,58), which could lead to higher levels of CGRP, lower threshold for migraine attacks, or both.

It will be important to determine if baseline, or interictal, levels of TNF-alpha are higher in obese than non-obese migraineurs. A plausible theory is that persistently elevated levels of pro-inflammatory cytokines may increase the frequency of migraine attacks, but this has yet to be investigated. Furthermore, elucidating the mechanism of interaction between CGRP and cytokines will shed light on the immunomodulatory role of CGRP.

Additional research on the effects of migraine preventive drugs on these pro-inflammatory cytokines will clarify the role of cytokines in chronic migraine or migraine chronification, and will improve our understanding of the mechanisms of action of these drugs.

3. 2. b. A role for adipose tissue?—Increasing evidence support the role of adipose tissue as a dynamic endocrine organ that secretes a number of factors that contribute to systemic and vascular inflammation (59).

Cells in the human adipose tissue matrix and stromovascular cells, and to a lesser degree, adipocytes, secrete pro-inflammatory cytokines, including TNF-alpha and IL-6 (60), which have been found elevated in migraine attacks as previously discussed (54). Mast cells, another major secretory compartment of adipose tissue, are also implicated in the pathophysiology of migraine (61). CGRP receptors have been identified in rat dura mast cells (62) where CGRP has been shown to trigger mast cell degranulation and release of histamine (63).

Most recently, adipocytokines, such as adiponectin and leptin, have been implicated in the association of migraine and obesity (64). These proteins are secreted primarily by the adipose tissue and have an important role in energy homeostasis among other functions. Peterlin *et al* found higher levels of total serum adiponectin in women with chronic daily headaches compared with episodic migraine and healthy controls, which appears to be due to higher levels of high and middle-molecular-weight but not low-molecular-weight oligomers of adiponectin (65). While most evidence suggests that adiponectin protects against headache, there is data supporting a potential pro-headache role (66). Guldiken *et al* found lower levels of leptin interictally and lower fat mass in patients with episodic migraine compared with healthy controls despite having similar BMI (67). Studies analyzing possible interactions between CGRP and adipocytokines, either directly or indirectly (for example through their effects on other cytokines), are likely to provide more insight into the influence of obesity in migraine.

3. 2. c. Plasma levels of CGRP in obese individuals—Only one published study has analyzed the relationship between obesity and plasma levels of CGRP in humans (68). Zelissen *et al* measured plasma levels of CGRP in 24 obese women and 15 healthy normal-weight female volunteers. Their main finding was that obese women have higher plasma levels of CGRP. They also studied the effect of two different meals on levels of CGRP in a control group with normal BMI. While the two meals were isocaloric, plasma levels of CGRP increased significantly after the high-fat meal, but not after the high-carbohydrate meal. No significant effect of weight loss on levels of CGRP was observed, but subjects were still obese despite losing more than 10% of their initial weight (68). Nevertheless, these results need to be replicated in a larger study including males and subjects across different age groups to confirm that, indeed, plasma levels of CGRP are elevated in obese individuals.

In an animal study, plasma levels of CGRP were found to be elevated in pre-obese Zucker rats prior to the onset of severe obesity (69). This raises the possibility of CGRP having a role in the development of obesity instead of being elevated as a consequence of the low grade inflammation state of obesity. Nonetheless, further studies are required to conclude that.

Circulating plasma levels of CGRP in obese and normal weighted migraineurs with episodic versus chronic migraine have not been investigated. Studies addressing plasma levels of CGRP in migraineurs, to this date, have focused on differences between interictal levels and during the attack or in response to acute treatment of a migraine attack. It might be revealing to address potential differences between subgroups of migraine patients, including the sub-type of migraine, specific symptoms, gender and age to name a few. Much harder to examine will be any possible differences in CGRP receptors availability or function in the previously mentioned subjects.

4. CONCLUSIONS

The relationship between CGRP, obesity and migraine remains elusive. There are important questions that need to be answered from clinical studies to give clues for future mechanistic studies: Do elevated plasma levels of CGRP precede obesity or are they secondary to the weight gain? To address this, lengthy and carefully designed prospective studies will be necessary. What is the effect of weight loss in the frequency of migraine attacks and levels of CGRP? The difficulties of such studies are obvious. Likewise, some questions will need to be addressed at the bench and then translated to the clinic: What are the effects of diet-induced obesity on CGRP and other pro-inflammatory mediators? What are the effects of a high-fat or high-carbohydrate diet in genetically obese animals? Are there changes in the trigeminovascular system in any of these models, or perhaps a lower threshold of activation?

In this review, we have proposed some ways in which CGRP may be important in the biological association between migraine and obesity. It is crucial to keep in mind that two complex disorders such as migraine and obesity are predicted to interact in an intricate way. Therefore, it will be very unlikely for CGRP to be the only molecular link between migraine and obesity. Nevertheless, we feel that the current evidence points towards CGRP being an important player in this association. There is an imperative need for future mechanistic studies addressing the role of CGRP, and other molecules, in the association between obesity and migraine. This will advance the current understanding of both disorders and result in the identification of novel therapeutic targets and tools that will have a great impact in patients and in our society.

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