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Hypothalamic inflammation and gliosis in obesity

Mauricio D. Dorfman and **Joshua P. Thaler**

Diabetes and Obesity Center of Excellence, Department of Medicine, University of Washington, Seattle, WA, 98109, USA

Structured Abstract

Purpose of review—Hypothalamic inflammation and gliosis are recently discovered mechanisms that may contribute to obesity pathogenesis. Current research in this area suggests that investigation of these CNS responses may provide opportunities to develop new weight loss treatments.

Recent findings—In rodents, hypothalamic inflammation and gliosis occur rapidly with high-fat diet consumption prior to significant weight gain. In addition, sensitivity or resistance to diet-induced obesity in rodents generally correlates with the presence or absence of hypothalamic inflammation and reactive gliosis (brain response to injury). Moreover, functional interventions that increase or decrease inflammation in neurons and glia correspondingly alter diet-associated weight gain. However, some conflicting data have recently emerged that question the contribution of hypothalamic inflammation to obesity pathogenesis. However, several studies have detected gliosis and disrupted connectivity in obese humans, highlighting the potential translational importance of this mechanism.

Summary—There is growing evidence that obesity is associated with brain inflammation in humans, particularly in the hypothalamus where its presence may disrupt body weight control and glucose homeostasis. More work is needed to determine whether this response is common in human obesity and to what extent it can be manipulated for therapeutic benefit.

Keywords

obesity; hypothalamus; inflammation; gliosis

INTRODUCTION

Over the past 3 decades, the increased consumption of high calorie “Western” diets along with an ever-more sedentary lifestyle has led to over two-thirds of US adults being currently overweight or obese (body mass index > 25 kg/m^2). This trend is particularly concerning

Address for correspondence: Joshua P. Thaler, UW Medicine at South Lake Union, 850 Republican St, N248, Box 358055, Seattle, Washington, 98109, USA. Phone: (206) 897-1802 Fax: (206) 897-5293, jpthaler@u.washington.edu.

Conflicts of interest

None.

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due to the strong association of obesity with serious chronic health conditions including diabetes, hypertension, and cardiovascular disease. Few pharmacologic therapies are available that show success in sustaining weight loss over the long term (1), and gastric bypass surgery is an effective but risky procedure that can be offered realistically to only a small number of obese individuals. Thus, new strategies to combat the obesity epidemic are urgently needed, but gaps in our understanding of body weight control continue to limit progress toward this goal.

Body weight is maintained in homeostatic equilibrium by balancing changes in fat mass with compensatory alterations in energy balance (2). This system of energy homeostasis critically depends on the action of leptin, a hormone secreted from adipose tissue in proportion to body fat content. Leptin signals in the brain largely at the level of the hypothalamus, modulating the activity of specific neuronal subsets (including the orexigenic Agouti-related peptide (AgRP) and anorexigenic proopiomelanocortin (POMC) neurons) to reduce appetite and increase energy expenditure (3). This allows lean individuals to maintain stable body weights over many years (4) but fails to protect obese individuals from the deleterious effects of highly palatable, calorie-dense foods and sedentary lifestyles. This differential susceptibility results not from leptin deficiency in obese individuals but rather from an acquired insensitivity to leptin action (5), akin to the central pathogenic role of insulin resistance in type 2 diabetes. In this light, investigations into the potential origins of leptin resistance have drawn inspiration from several decades of research into the mechanisms underlying insulin resistance, focusing particularly on the link between inflammation and impaired hormonal signaling. Beginning with the discovery of hypothalamic inflammation in obese rodents 10 years ago (6••), this area of investigation has led to the hypothesis that obesity progression involves a complex multicellular pathology involving inflammatory signaling, neuronal stress, and reactive gliosis. In this review, we will summarize recent findings on hypothalamic inflammation, the specific CNS cell types involved in this process, the relevance of injury and inflammation to obesity pathogenesis, and the evidence for similar mechanisms in human obesity.

HYPOTHALAMIC INFLAMMATION

An association between obesity and low-grade peripheral inflammation was discovered two decades ago with the identification of increased TNFα expression in the adipose tissue of obese rodents and humans (7). Subsequent work demonstrated that this response includes numerous cytokines and chemokines beyond TNF, is required for obesity-associated insulin resistance, and is propagated by infiltrating macrophages and a variety of other recruited leukocyte cell types (8, 9). Based on these findings, the group of Lício Velloso at the State University of Campinas in Brazil was the first to identify a similar inflammatory response in the hypothalamus (6••). Long-term feeding of a lard-based high fat diet (HFD) to rats increased mediobasal hypothalamic activation of the inflammatory signaling intermediates c-Jun N-terminal kinase (Jnk) and nuclear factor-κB (NF-κB), resulting in the production of proinflammatory cytokines (TNFα, IL-1β, and IL6) and impairment in insulin and leptin signaling. This initial description of hypothalamic inflammation has been reproduced by many other investigators, with extension of the finding to obese mice and non-human primates (10–18); models of neonatal overfeeding, type 1 diabetes, and aging (19–22); and

other hypothalamic nuclei and the hippocampus (19, 23, 24). In addition, HFD-induced inflammation has been associated with hypothalamic resistance to growth hormone and ghrelin signaling (25, 26) and the development of obesity-associated diseases including cognitive dysfunction (27, 28), hypertension (29), hepatic steatosis (30), beta cell dysfunction (31), and, through non-canonical TGF-β signaling, glucose intolerance (32•). Thus, hypothalamic inflammation represents a unifying mechanism of diet-induced obesity (DIO) and metabolic disease.

DIETARY AND CELLULAR MEDIATORS OF HYPOTHALAMIC INFLAMMATION

As mentioned above, the mediobasal hypothalamus is a primary CNS center of metabolic control. Remarkably, the presence of fenestrated capillaries and specialized tanycytes in the median eminence enable this area of the brain to sense and respond rapidly to circulating nutrient and hormonal mediators (33•). This has led to the suggestion that specific macronutrient components—in particular, free fatty acids derived from dietary lipid—are responsible for triggering the inflammatory process. With HFD feeding, mice accumulate a number of fatty acid species in the hypothalamus, including triacylglycerols, diacylglycerols and ceramides (34). Furthermore, acute intracerebroventricular (icv) infusion of lipids such as the saturated fatty acid palmitate and the ω-6 polyunsaturated arachidonate induces inflammatory signaling (11, 35–37), alters autophagic protection from cellular stress (38), increases the unfolded protein response in the endoplasmic reticulum (39, 40••), promotes insulin and leptin resistance (11, 41) and possibly triggers apoptosis (42). Likewise, lipid ingestion via milk fat gavage or butter-based HFD consumption increases the hypothalamic levels of saturated fatty acids and proinflammatory gene expression without evidence of systemic inflammation (15••, 17). In addition to fatty acids, several recent studies have suggested that hyperglycemia and fructose exposure can also induce hypothalamic inflammation (21, 43), raising the possibility that nutrient excess itself may be the primary driver of the inflammatory process. Translating these findings to humans is challenging, however, as diet composition, dietary metabolism, and immune function differ greatly between species (44, 45•).

As described above, HFD-induced inflammation in peripheral tissues is tightly associated with infiltration of leukocytes—most notably, classically activated (M1) proinflammatory macrophages (8). In contrast, whether a similar process occurs in the CNS is controversial. In theory, leukocytes cannot enter the brain due to BBB impermeability to diapedesis. Nevertheless, several groups have reported increased numbers of M1-type macrophages in the brains of HFD-fed rodents (46, 47). However, these studies used irradiation-induced myeloablation and bone marrow transplantation to provide tagged donor macrophages, an approach known to compromise the BBB and allow inappropriate ingress of circulating monocytes (48, 49). More recent approaches that included head shielding during irradiation demonstrated the near-complete absence of donor-derived macrophages (15••), indicating that CNS resident cells must be responsible for HFD-induced hypothalamic inflammation. Indeed, the cellular response to HFD in the hypothalamus involves reactive gliosis (15••, 18••, 50), the CNS-specific process of recruitment, proliferation, and morphological

transformation of astrocytes and microglia (CNS macrophages) in response to brain injury (51). These changes can be observed as early as 24 hours after the initiation of hypercaloric feeding (18••) and are maintained during prolonged HFD consumption (15••, 18••, 50). Interestingly, hypothalamic gliosis reverses with diet switch, resolving 4 weeks after restarting normal chow feeding (52•); in contrast, caloric restriction of HFD-fed animals does not ameliorate microglial accumulation and activation (53•)(MDD and JPT, unpublished observation), suggesting diet composition is an important determinant of gliosis development. As in other neurodegenerative, infectious, and vascular diseases, HFD-induced reactive gliosis represents an active response to neuron injury (18••), altering neuronal POMC neurovascular coupling through ensheathment of synapses (54), modifying neurotransmitter dynamics through altered astrocyte expression of glutamate and glucose transporters (55), and changing the firing activity of POMC and NPY neurons (56•). Eventually, HFD exposure results in loss of POMC neurons (18••), reduced hypothalamic neurogenesis (57), and impaired synaptic plasticity (54), all potential contributors to excess weight gain. Together, these studies suggest the possibility that glial cells play a primary role in obesity pathogenesis.

Though a new area of investigation, a number of studies have pointed to an active role of glial cells in the control of energy homeostasis. Both astrocyte leptin signaling and overall astrocyte activation can regulate feeding behavior under basal and ghrelin-stimulated conditions (58•, 59•). Tanycytes—specialized glial cells of the median eminence that contribute to blood-brain barrier (BBB) transport and can serve as neural progenitors—promote weight gain during HFD feeding both by limiting leptin access to the mediobasal hypothalamus (33•) and by producing new neurons that increase food intake and decrease energy expenditure (60). Likewise, the oligodendrocyte progenitor cell (OPC) functions through its proliferation/maturation proteoglycan NG2 to increase body weight and fat mass (61). Finally, microglia are critical mediators of HFD-induced inflammatory signaling, modulating hypothalamic neuronal activity and food intake both during basal and HFD feeding (15••, 46, 56•) (MDD and JPT, unpublished data). These data notwithstanding, it should be noted that obesogenic diet consumption is associated with nearly instant glutamate release in the mediobasal hypothalamus, likely stimulated by orosensory perception of food (62), suggesting that glutamatergic neurons themselves may be the primary responders to HFD.

CONTRIBUTION OF HYPOTHALAMIC INFLAMMATION TO OBESITY PATHOGENESIS

Hypothalamic inflammation is a robust and reproducible response to HFD feeding in rodent models, but its relevance as an obesity mechanism is still unclear. In favor of a causative role, hypothalamic inflammation occurs prior to obesity onset within the first few days of HFD feeding (18••). Moreover, blocking the NF-κB pathway in all CNS neurons, only hypothalamic neurons, or AgRP neurons exclusively, reduces levels of HFD-induced leptin resistance and weight gain (40••, 63). Similarly, preventing Toll-like receptor 4 (TLR4) signaling with blocking antibodies or through deletion of MyD88, a TLR and IL-1 signaling intermediate, improves hypothalamic leptin and insulin sensitivity and limits DIO (35, 41).

Conversely, deletion of GABA B receptors from POMC neurons results in obesity and increased hypothalamic inflammation (64). Likewise, infusion of low dose TNF-α or viral activation of neuronal NF-κB signaling promotes hyperphagia and weight gain (40••, 65). These data collectively suggest that in some contexts, hypothalamic inflammation is both necessary and sufficient for DIO.

Glial cell inflammation may also contribute to DIO. Use of a virally-expressed dominant negative blocker of NF-κB signaling in astrocytes prevents the acute astrocytosis response induced by HFD (66) while depletion of microglia with a colony stimulating factor-1 receptor (CSF-1R) antagonist reduces food intake in the setting of excess saturated fat ingestion (15••). However, not all forms of obesity require hypothalamic inflammation and gliosis. For example, leptin-deficient *ob/ob* mice become extremely obese on regular chow without gliosis (53•). Nevertheless, exposing *ob/ob* mice to HFD feeding increases leptin resistance, weight gain, microglial activity, and hypothalamic inflammation (53•, 67), suggesting that DIO sensitivity correlates with hypothalamic inflammation and gliosis. As another example, HFD-fed male C57BL6 mice are highly DIO sensitive due to increased hypothalamic inflammation from reduced estrogen signaling in neurons and astrocytes (14•). Conversely, female C57Bl6 mice and other DIO resistant models (e.g. DIO-R rats) lack central inflammatory and gliosis responses (14•, 46, 68, 69). Recently, we discovered a sex-specific microglial switch for DIO susceptibility using a mouse model that lacks the fractalkine/CX3CL1 receptor CX3CR1 (MDD and JPT, unpublished data). CX3CL1, a chemokine secreted by neurons to maintain microglial quiescence, increases in the hypothalamus of females exposed to HFD. Remarkably, HFD-fed female *Cx3cr1* knockout mice develop hypothalamic microglial activation and obesity compared to their heterozygous littermates. Conversely, HFD-fed males treated with a CNS CX3CL1 infusion have reduced microgliosis and weight gain in a CX3CR1-dependent manner, suggesting that HFD-induced microglial inflammatory activation contributes to obesity pathogenesis.

CONFLICTING DATA

While substantial evidence suggests that hypothalamic inflammation and gliosis are associated with HFD-induced obesity, recent studies cast doubt on their causal role in the pathogenesis of DIO. First, it has long been known that total-body proinflammatory cytokine and cytokine receptor knockout models (e.g., IL-1, IL-6, IL-1 receptor, and TNF receptors) display obesity phenotypes rather than being protected from DIO. Second, several studies have demonstrated dissociation between weight changes and alterations in hypothalamic inflammation. In the first, DIO-sensitive HFD-fed rats switched back to regular chow for 8 weeks lose their excess weight despite sustained elevations in hypothalamic inflammatory gene expression (69). Similarly, chronic ghrelin treatment increases adiposity while reducing hypothalamic inflammation and gliosis (70). Conversely, neuronal peroxisome proliferator–activated receptor-δ and growth hormone receptor knockout mice are resistant to HFD-induced hypothalamic inflammation and gliosis yet more susceptible to DIO than wild-type controls (71). Finally, a stereological analysis of the hypothalamus in HFD-fed mice revealed minimal evidence of neuronal loss and sustained gliosis though the diet composition and duration were different than prior studies (72•). Thus, the evidence supporting a direct role of hypothalamic inflammation and gliosis in

promoting weight gain is clearly mixed. These considerations highlight the importance of determining whether hypothalamic inflammation and injury occurs in humans and contributes to obesity pathogenesis.

HYPOTHALAMIC PATHOLOGY IN HUMANS?

Although the extent to which obesity and/or HFD feeding impacts hypothalamic structure and function in humans remains uncertain, translational insights using brain imaging are beginning to support this type of neuropathologic model. A retrospective analysis of MRIs from 34 subjects (BMI range: 17.7–44.1 kg/m^2) revealed evidence of gliosis in the mediobasal hypothalamus that correlated with BMI (18••), and recently the findings were replicated in a prospective cohort showing an additional link between gliosis and insulin resistance (Ellen Schur, personal communication). A separate MRI study in 44 overweight/obese subjects reported an inverse correlation between systemic inflammation (measured as serum fibrinogen) and the integrity of brain structures involved in food reward and feeding behavior (73). Most recently, diffusion tensor imaging (DTI) was used to screen for hypothalamic damage in 44 obese patients and controls (74••). In the obese cohort, lower axon diffusivity (i.e. increased damage) was correlated with increased BMI and impaired cognitive performance. Finally, a few studies of structural alterations in the brains of obese subjects have shown reduced connectivity through the corpus callosum (75, 76), reduced hypothalamic volume in obese females with insulin resistance (77), and greater connectivity between the hypothalamus and reward-related brain areas than homeostatic areas (78•). Together, these data support the hypothesis that humans develop hypothalamic pathology akin to that of rodents with gliosis and injury potentially promoting weight gain, insulin resistance, and cognitive impairment.

SUMMARY

The causes and consequences of hypothalamic inflammation and gliosis remain incompletely understood, but the field is progressing rapidly. Hypothalamic inflammation shares several common features with obesity-associated peripheral inflammation, but the involvement of unique CNS cell types identifies it as a fundamentally distinct process. Though there is considerable experimental support for a pathologic role of hypothalamic inflammation and gliosis, recent conflicting data have muddied the waters. Nevertheless, the preponderance of evidence in humans and animal models to date points to structural damage of the hypothalamic energy homeostasis center as a central deleterious consequence of diet-induced inflammation and gliosis and suggests an opportunity to reverse weight gain through manipulation of this complex multicellular process.

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Key Points

1. High-fat diet feeding is associated with hypothalamic inflammation, reactive gliosis, and neuron injury in rodents.
2. Interventions that increase or decrease inflammatory pathways in the hypothalamus have corresponding effects to promote or prevent diet-induced obesity.
3. Glial cells play an important role in transmitting diet-related inflammatory signals and can modulate neuronal regulation of energy balance.
4. Obese humans show signs of hypothalamic gliosis and impaired connectivity possibly contributing to weight gain, metabolic disease, and cognitive dysfunction.