# Hypothalamic Inflammation in the Control of Metabolic Function

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## Keywords

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## Abstract

Diet-induced obesity leads to devastating and common chronic diseases, fueling ongoing interest in determining new mechanisms underlying both obesity and its consequences. It is now well known that chronic overnutrition produces a unique form of inflammation in peripheral insulin target tissues, and efforts to limit this inflammation have met with some success in preserving insulin sensitivity in obese individuals. Recently, the activation of inflammatory pathways by dietary excess has also been observed among cells located in the mediobasal hypothalamus, a brain area that exerts central control over peripheral glucose, fat, and energy metabolism. Here we review progress in the field of diet-induced hypothalamic inflammation, drawing key distinctions between metabolic inflammation in the hypothalamus and that occurring in peripheral tissues. We focus on specific stimuli of the inflammatory response, the roles of individual hypothalamic cell types, and the links between hypothalamic inflammation and metabolic function under normal and pathophysiological circumstances. Finally, we explore the concept of controlling hypothalamic inflammation to mitigate metabolic disease.

## INTRODUCTION

**MBH:** mediobasal hypothalamus

**ARC:** arcuate nucleus of the hypothalamus

**ME:** median eminence of the hypothalamus

**TNF-α:** tumor necrosis factor α

The prevalence of obesity, in the context of dietary excess and sedentary lifestyles, has risen dramatically in recent decades, and it is now estimated that up to 36% of adults in the United States are obese [body mass index (BMI) $\geq$ 30 kg/m$^2$] and that another 33% are overweight (BMI $\geq$ 25 kg/m$^2$) (1). Particularly alarming is the increase in obesity among certain ethnicities, in highly populous emerging nations, and among children (2). Moreover, obesity is closely associated with devastating diseases such as type 2 diabetes, cardiovascular disease, steatohepatitis, neurodegeneration, and certain forms of cancer (3). Given this scenario, there has never been a greater need to determine the mechanistic underpinnings leading to both obesity and its consequences.

It is now well accepted that overnutrition in susceptible individuals results in metabolic inflammation, or metaflammation, which is a form of chronic, low-grade, sterile inflammation in the absence of any demonstrable systemic or local microbial infection (3, 4). This diet-induced activation of inflammatory pathways—which has been observed in a variety of insulin-responsive peripheral tissues, including white adipose (5, 6), liver (7), and skeletal muscle (8, 9) tissues—is implicated in driving aspects of metabolic dysfunction, including the development of insulin resistance. Interestingly, genetically deleting key aspects of inflammatory function in mice is protective against both diet-induced metabolic inflammation in these tissues and the development of insulin resistance. These findings highlight the idea that inflammatory pathways may play a causative role in metabolic dysfunction. Nutrient overload also stimulates metabolic inflammation in the pancreatic islets, promoting β cell apoptosis and reducing insulin secretion that leads to full-blown diabetes (10, 11). These data demonstrate that metabolic inflammation is not limited to glucose-consumptive insulin target tissues.

In addition to being activated in peripheral tissues, inflammatory pathways are also activated in brain areas that exert central control over peripheral glucose, fat, and energy metabolism. In particular, inflammation in the mediobasal hypothalamus (MBH), which contains the arcuate nucleus (ARC) and median eminence (ME), occurs in the context of diet-induced obesity (DIO) (12–14). However, critical questions need to be answered before determining the value of targeting mechanisms underlying diet-induced hypothalamic inflammation to prevent or treat metabolic disease. In this review, we discuss progress in the field of diet-induced hypothalamic inflammation and draw distinctions between metabolic inflammation in the hypothalamus and that occurring in peripheral tissues. We also discuss the impact of hypothalamic inflammation on metabolism, under both normal physiological and pathophysiological circumstances, and explore potential strategies to mitigate hypothalamic inflammation to control metabolic disease.

## THE ASSOCIATION BETWEEN DIET-INDUCED OBESITY AND HYPOTHALAMIC INFLAMMATION

Obesity-associated hypothalamic inflammation was initially described in 2005 after it was discovered that inflammatory pathways were activated in the hypothalami of rats fed a high-fat diet (HFD) for 16 weeks (15). This work revealed a diet-induced upregulation of the inflammatory cytokines tumor necrosis factor α (TNF-α), interleukin (IL)-1β, and IL-6. In conjunction with these proinflammatory transcriptional changes, the hypothalamic actions of insulin, which normally acts under euglycemic conditions to acutely reduce food intake, were impaired. Since this earlier study, diet-induced hypothalamic inflammation has also been observed in mice and reconfirmed in rats (16–18).

One of the key distinctions between diet-induced metabolic inflammation in peripheral tissues and that occurring in the hypothalamus relates to latency. Studies show that inflammatory

responses to overnutrition develop much more rapidly in the hypothalamus compared with peripheral tissues. Indeed, metabolic inflammation in the white adipose tissue is marked by the accumulation of macrophages and CD8 effector T cells and by a reduction in the numbers of cells that exert restraining effects on inflammation, including eosinophils and regulatory T cells (19). These changes are induced by chronic obesity over, for example, weeks to months in rodents consuming a high-calorie HFD or by chronic hyperphagia in the context of specific genetic models (6, 20). By contrast, diet-induced metabolic inflammation in the hypothalamus—as marked by, for example, the increased transcription of inflammatory cytokines—can occur quickly over 24–72 h after initiation of a HFD in rodents (16).

Therefore, hypothalamic inflammation induced by dietary excess precedes the onset of overt obesity and occurs much earlier than inflammation or metabolic disturbances in peripheral tissues. This primacy suggests that hypothalamic inflammation plays an acute role in modulating normal metabolic physiology and is an early driver of the pathophysiology associated with overnutrition.

**NPY:** neuropeptide Y

**AgRP:** agouti-related peptide

**POMC:** pro-opiomelanocortin

**α-MSH:** α-melanocyte-stimulating hormone

## HYPOTHALAMIC CONTROL OF METABOLIC FUNCTION

### Hypothalamic Neurocircuitry and Feedback Regulation

The MBH is a critical regulator of food intake, energy expenditure, body weight, and glucose metabolism (21–23). The ARC, which sits adjacent to the third ventricle in the MBH and is the best-understood hypothalamic area in this regard, contains two interconnected groups of neurons. One group is orexigenic and releases the neurotransmitters neuropeptide Y (NPY) and agouti-related peptide (AgRP). The other is anorexigenic and contains neurons expressing pro-opiomelanocortin (POMC). When bound to its cognate receptor, NPY is a potent stimulator of food intake and reducer of basal energy expenditure (24). In contrast, POMC neurons release α-melanocyte-stimulating hormone (α-MSH), which binds to melanocortin receptors (MCRs) 3 and 4 and exerts anorectic effects. AgRP is an inverse agonist at both the MC3R and MC4R and prevents the anorectic effects of α-MSH (25). Therefore, NPY/AgRP neurons and POMC neurons reciprocally regulate one another to form an elegant neuronal circuit. Due to their interconnectedness and reciprocal actions, these two groups of neurons allow the hypothalamus to exert fine-tuned control over other groups of neurons and ultimately on efferent CNS outputs that regulate energy balance and fuel homeostasis in the rest of the body. The neuronal circuitry of the hypothalamus, and its impact on metabolic regulation, has been extensively reviewed elsewhere (26).

This hypothalamic circuit of energy balance is amenable to feedback regulation by circulating metabolic signals, including those from nutritional hormones such as leptin and insulin. As is the case for local neurotransmitters, these two hormonal signals also exert reciprocal actions on one another in the MBH, revealing another layer of competing inputs that can finely modulate CNS-dependent metabolic control (21, 27).

### Hypothalamic Nutrient Sensing in Metabolic Control

Finally, AgRP and POMC neurons are also able to sense nutrients, and there is evidence for reciprocal regulation in this regard as well. For example, increasing extracellular levels of glucose inhibits the firing of AgRP/NPY neurons and stimulates firing among POMC neurons (28, 29). As a result of this hypothalamic glucose-sensing capacity, peripheral glucose infusions can increase CNS-induced sympathetic activity (30) and can consequently stimulate thermogenesis

LPL: lipoprotein lipase

even when the effects of insulin are controlled for (31). The specific thermogenic effects of glucose are probably also mediated by other groups of hypothalamic glucose-sensing neurons, including those residing in the ventromedial hypothalamus (VMH). Evidence for VMH control over thermogenesis comes from classical work showing that injections of glucose directly into the VMH of rats are sufficient to increase the activity of sympathetic efferent fibers that eventually stimulate brown adipose tissue (BAT) activation, as measured by recording the firing rates of sympathetic neurons innervating the BAT (32).

Beyond its control of basal thermogenesis, hypothalamic glucose sensing is also part of the feedback regulatory mechanism that maintains whole-body glucose homeostasis in mammals. For example, changes in hypothalamic glucose concentrations modulate the output of vagal efferents that regulate hepatic glucose production. As such, increasing hypothalamic glucose levels markedly reduces hepatic glucose production. In addition to responding to glucose, hypothalamic neurons respond to lactate. For example, administering lactate directly into the ARC of mice is sufficient to inhibit hepatic glucose production, and the effects of lactate in the hypothalamus are blocked by coinfusion of the $K_{ATP}$ channel blocker glibenclamide (33).

The sensing of both glucose and lactate by the hypothalamus also modulates CNS control over hepatic lipid metabolism, as intracerebroventricular (ICV) administration of glucose or lactate lowers circulating lipid concentrations and hepatic triglyceride synthesis. Although the molecular sensors of central glucose and lactate have yet to be fully defined, hypothalamic $K_{ATP}$ channel activity appears important for mediating the effects of both centrally acting glucose and lactate on hepatic lipid metabolism (34).

Hypothalamic neurons detect and respond to changes not only in carbohydrates and glycolytic by-products but also in circulating lipid levels. To date, no molecular sensors of hypothalamic lipids have been identified. However, one set of studies suggests that long-chain fatty acid (FA)-CoA molecules alter the activity of hypothalamic neurons via mechanisms regulating intracellular patterns of lipid flux. For example, ICV administration of the monounsaturated FA oleic acid inhibits food intake and decreases hepatic glucose production in mice (35, 36). The effects of central oleate infusion are essentially duplicated by ICV administration of etomoxir; this drug inhibits hypothalamic carnitine palmitoyltransferase, an enzyme that catalyzes the rate-limiting step in the intracellular β-oxidation of FAs.

The importance of intracellular FA sensing within the hypothalamus is further bolstered by work focusing on lipoprotein lipase (LPL), an enzyme that catalyzes the hydrolysis of triacylglycerols present within lipoproteins. This enzyme facilitates the intracellular uptake, storage, and utilization of FAs (37). Deleting neuronal LPL in mice produces significant hyperphagia and increases CNS levels of two orexigenic neuropeptides, AgRP and NPY, leading to obesity (38). The metabolic changes associated with LPL deficiency were coupled to deficiencies in essential and long-chain FAs within the hypothalamus, pointing to a potential role of hypothalamic LPL in regulating intracellular lipid content.

## HYPOTHALAMIC INFLAMMATION AND METABOLIC DYSFUNCTION IN OBESITY

### Comparing Metabolic Inflammation in the Hypothalamus and Peripheral Tissues

Although nutrients, fluctuating within normal physiological parameters, are important regulators of hypothalamic neurocircuitry, the excess consumption of these same nutrients is implicated in triggering metabolic inflammation in the MBH. For example, acute administration of glucose in

the third ventricles of mice increases the activity of NF-κB (nuclear factor κ–light-chain enhancer of activated B cells), a master transcriptional activator of inflammation that is critical for the cellular response to a variety of proinflammatory molecular patterns, in the hypothalamus but not in peripheral tissues (18).

Acute increases in the hypothalamic levels of specific lipids also exert proinflammatory effects within the MBH. For example, ICV administration of long-chain saturated FAs (SFAs) in rats induces the expression of several inflammatory cytokines within the hypothalamus (39). The concept that this inflammatory response is caused by nutrient excess rather than by associated changes in body weight (obesity) is supported by work showing that hypothalamic inflammation is induced within a few hours to 3 days following either glucose or lipid infusion, a time course that is too rapid to be reflective of diet-induced weight gain, which happens much more slowly (16). Similarly, recent work showed that hypothalamic inflammation in response to feeding mice a HFD was still evident even after the mice were switched back to a low-fat diet and lost the excess weight that they had previously gained (40). Therefore, diet-induced metabolic inflammation in the hypothalamus can happen rapidly, in a body weight–independent manner that precedes overt obesity, and may persist after the loss of excess body weight.

Interestingly, in accordance with the persistent nature of hypothalamic inflammation that is induced by the intake of excess dietary fat, evidence also suggests that recovery from the impairment of hypothalamic function induced by a HFD is slow. For example, resistance of hypothalamic neurons to the actions of the adipokine leptin, a phenomenon that occurs in mice with DIO in parallel with hypothalamic inflammation (39, 41), is not reversible until mice chronically fed a HFD are returned to a low-fat diet for 20 weeks (42).

Because diet-induced hypothalamic metabolic inflammation precedes or occurs simultaneously with hypothalamic dysfunction, there is growing interest in the notion that hypothalamic inflammation is a cause rather than a consequence of diet-induced metabolic disease. This concept is distinct from findings in peripheral tissues such as the white adipose, where both acute physiological stimuli (for example, fasting) and chronic overnutrition (obesity) increase the number of macrophages in the tissue. Interestingly, under these two conditions, the phenotypes of macrophages recruited into the white adipose tissue are quite different; fasting promotes the accumulation of anti-inflammatory M2 macrophages, and obesity is associated with the accumulation of relatively inflammatory M1-like macrophages. Unlike for peripheral tissues, the phenotypic nature of diet-induced metabolic inflammation in the brain is not understood. Further studies are needed to dissect the role of specific hypothalamic inflammatory pathways in acute versus chronic regulation of hypothalamic neuronal function. Additionally, further work is needed to determine the role of metabolic inflammatory activation in the regulation of normal hypothalamic physiology and in the pathophysiological effects on feeding, energy expenditure, and fuel metabolism that are seen under conditions of overnutrition. Finally, sex differences are important in directing hypothalamic development and in the hypothalamic regulation of energy homeostasis and body composition. In this regard, a recent study indicates that regulation of estrogen receptor signaling in the brain may be a determinant in the susceptibility of mice to diet-induced hypothalamic inflammation (43). Future work will need to fully determine the extent to which metabolic inflammation in the brain is sexually dimorphic.

**NF-κB:** nuclear factor κ–light-chain enhancer of activated B cells

**SFA:** saturated fatty acid

## Functional Consequences of Hypothalamic Metabolic Inflammation

Recent work has gone beyond describing the rapid onset of diet-induced hypothalamic metabolic inflammation and has begun to delve into its functional impact on tissues throughout the body. These efforts show that the inflammatory activation in the MBH exerts broad effects on peripheral

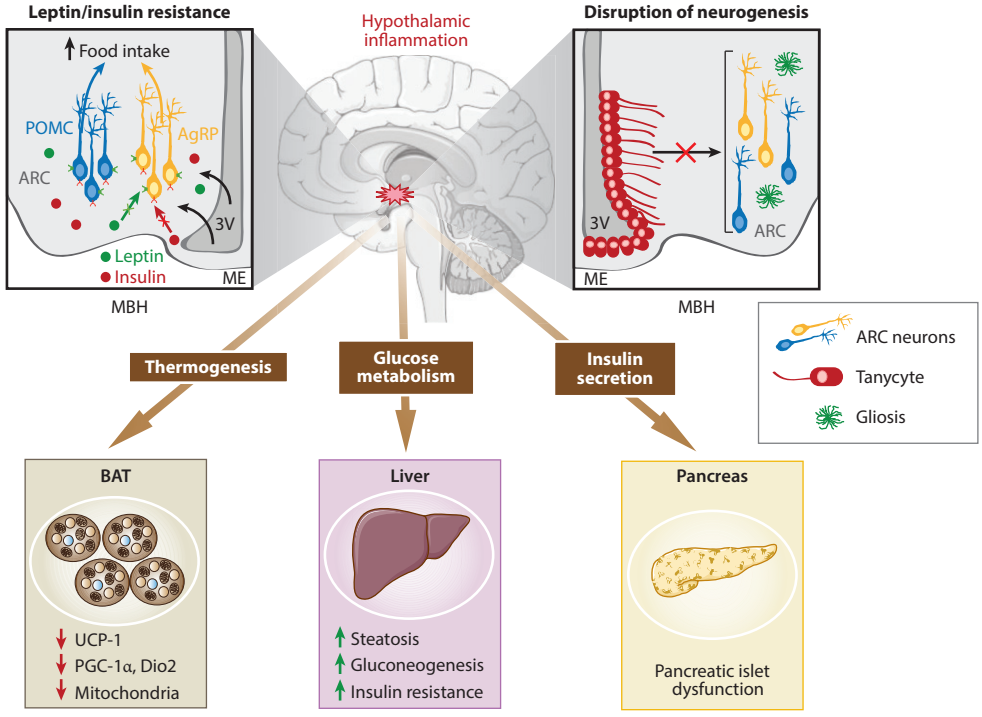



**Figure 1**

The impact of metabolic inflammation in the MBH on the neurocircuitry controlling energy balance and processes that maintain hypothalamic architecture. Specifically, diet-induced hypothalamic inflammation is associated with reduced responsiveness of POMC and AgRP neurons in the ARC to the physiological actions of leptin and insulin. Hypothalamic inflammation is also linked to a reduction in the capacity of tanycytes and other potential progenitor cell types lining the wall of the 3V to give rise to new neurons and glia. Leptin resistance is associated with increased food intake and reduced energy expenditure, exacerbating obesity. Disrupted neurogenesis is associated with enhanced aging. Also shown are hypothalamic control mechanisms regulating thermogenesis, hepatic metabolism, and pancreatic insulin secretion. Hypothalamic metabolic inflammation is implicated in altering these control mechanisms to result in BAT, liver, and pancreatic islet dysfunction. Abbreviations: 3V, third ventricle; AgRP, agouti-related peptide; ARC, arcuate nucleus of the hypothalamus; BAT, brown adipose tissue; Dio2, type 2 deiodinase; MBH, mediobasal hypothalamus; ME, median eminence of the hypothalamus; PGC-1α, peroxisome proliferator–activated receptor gamma coactivator 1 alpha; POMC, pro-opiomelanocortin; UCP-1, uncoupling protein 1.

tissues (**Figure 1**). For example, hypothalamic inflammation, independently of body weight, is associated with impaired insulin release by pancreatic β cells, with insulin action in target tissues, and with the development of renovascular dysfunction leading to hypertension (44–46).

There is also evidence to suggest that peripheral metabolic disturbances lead to cellular stress in hypothalamic neuronal subsets (16). For example, Hsp72, a heat shock protein induced in response to many forms of cellular stress (47), is rapidly induced in neurons within both the ARC and ME of rats consuming a HFD (16). In particular, Hsp72 expression is prominently induced in POMC neurons involved in satiety signaling. This neuronal stress response gives way to apoptosis of hypothalamic neurons when the HFD is chronic in nature. Moreover, ICV administration of the proinflammatory cytokine TNF-α at low doses in rats is also sufficient to induce apoptosis of hypothalamic neurons (48, 49), indicating that soluble inflammatory factors may play a role in promoting neuronal demise in the setting of overnutrition.

Recent work suggests that, beyond modulating the regulation of hunger and satiety, low-grade hypothalamic inflammation also reduces adaptive thermogenesis (50, 51). For example, ICV administration of TNF-α provided at low doses is sufficient to reduce the expression of genes encoding uncoupling protein 1, peroxisome proliferator–activated receptor gamma coactivator 1 alpha, and type 2 deiodinase, all of which are upregulated in BAT under conditions favoring thermogenesis, such as cold and fasting (50). Moreover, mice lacking a critical TNF-α receptor [TNF-α type 1 (p55) receptor (TNFR1)] have increased BAT activation and are accordingly resistant to obesity in response to consuming a HFD (52).

**NSC:** neural stem cell

**IKKβ:** inhibitor of nuclear factor κ-B kinase subunit β

The effects of hypothalamic inflammation on glucose and energy metabolism may have strong health and disease consequences. For example, a recent study demonstrated that the predisposition of mice lacking insulin receptor substrate 2 (IRS-2) [a well-studied murine model of diabetes (53)] to develop overt hyperglycemia occurs in association with the activation of inflammatory hypothalamic pathways in parallel with antecedent changes in feeding, body weight, and systemic glucose intolerance (54). In summary, work in rodent models indicates that strategies aimed at ameliorating diet-induced hypothalamic inflammation may have translational potential in preventing metabolic disease.

Despite these intriguing correlations linking hypothalamic inflammation and positive energy balance associated with weight gain, a vexing paradox remains: Hypothalamic inflammation can also be associated with negative energy balance and anorexia (as is the case under conditions promoting cachexia). An interesting example of this paradox is the finding that, in contrast to the antithermogenic effects of low-dose TNF-α, delivering high doses of TNF-α into rat brains stimulates the release of thermogenic neurotransmitters, including thyroid-releasing hormone and corticotropin-releasing hormone, and reduces hypothalamic levels of NPY and melanin-concentrating hormone; the net effect is enhanced thermogenesis (51). Two of the key challenges in the field of hypothalamic metabolic research, therefore, are to determine the neuroanatomical determinants of these differences and to elucidate what inflammatory signals are involved in stimulating and modulating these disparate responses (55).

Beyond metabolic diseases, neurodegenerative diseases are another devastating category of diseases that attack people as they age and that are potentiated by DIO. In this regard, the MBH and adjacent third ventricular wall are niches for multipotent neural stem cells (NSCs) with the capacity to differentiate into astrocytes, oligodendrocytes, and new neurons both in vivo and in vitro (56). This neogenic capacity of the adult hypothalamus may help to preserve normal CNS control over food intake and energy balance as human beings age (57). Thus, impairing the putative NSC-dependent remodeling in the hypothalamus by dietary excess is hypothesized to set up a vicious cycle that increases the susceptibility of individuals to further DIO and consequent metabolic diseases with advancing age (58).

As such, determining how hypothalamic inflammation impinges on the viability and neogenic capacity of NSCs residing in the hypothalamus becomes important. For example, cultured hypothalamic NSCs from obese mice overproduce the proinflammatory cytokines TNF-α and IL-1β (56). Also, hypothalamic inflammation, induced by manipulating the IKKβ/NF-κB pathway, promotes obesity-associated hypothalamic neurodegeneration in mice (56). Similar findings are well known in other brain areas. For example, previous work showed that NF-κB-mediated inflammation, induced by activation of Toll-like receptor 4 (TLR4), myeloid differentiation primary response gene 88 (MyD88), or IL-1 receptor–dependent pathways (59), impairs hippocampal neurogenesis in the context of age-dependent cognitive decline and mood disorders. Therefore, diet-induced neuroinflammation can promote the degeneration of circuits beyond those impacting energy homeostasis to include those governing processes fundamental to aging, such as learning, memory, and mood.

## EXPLORING THE TRIGGERS AND MEDIATORS OF HYPOTHALAMIC METABOLIC INFLAMMATION

**MUFA:** monounsaturated fatty acid

**PUFA:** polyunsaturated fatty acid

### Saturated Fatty Acids

Long-chain SFAs are emerging as a potential nutritional trigger of hypothalamic metabolic inflammation; they exert effects in the brain analogous to those documented for peripheral tissues. In the course of developing DIO, individuals experience a progressive elevation in circulating levels of free FAs. These FAs flux into ectopic, nonadipose tissue sites (e.g., liver, skeletal muscle, pancreas) within the body and contribute to nonadipose tissue steatosis. Once in these tissues, FAs and their glycerolipid, phospholipid, and sphingolipid metabolites can trigger proinflammatory pathways in tissue-resident macrophages and infiltrating immune cells. In insulin target tissues, triggering these pathways alters patterns of PKC, IRS-1, and AKT phosphorylation, leading to the development of insulin resistance (60). SFAs, including palmitic and stearic acid, can activate TLR2- and TLR4-dependent signaling pathways, whereas monounsaturated FAs (MUFAs) and polyunsaturated FAs (PUFAs), particularly *n*-3 PUFAs, do not do so and may instead protect against SFA-induced TLR activation (61, 62).

Long-chain palmitoyl and stearoyl (SFA)-CoA species also accumulate within the hypothalamus in response to high-fat feeding, and this accumulation is emerging as a driver of hypothalamic inflammation and of both leptin and insulin resistance (63). The propensity for SFAs to accumulate may stem, at least in part, from the fact that long-chain SFAs (>C:12) are less efficiently oxidized than are unsaturated species and therefore flux into compartments that experience less turnover.

The idea that SFAs act locally in the brain to stimulate hypothalamic inflammation is supported by studies employing ICV injection in mice. ICV injections of stearic acid increase inflammatory cytokines, including TNF-α, IL-1β, and IL-6, and activate JNK and NF-κB in the hypothalamus (45). Moreover, consumption of an excess amount of dietary SFAs is more obesogenic than isocaloric consumption of a diet rich in other FA species (64). The negative impact of excess dietary SFA on energy balance and body weight regulation therefore correlates well with an increase in the hypothalamic inflammatory response. The concept that SFA-induced hypothalamic inflammation alters hypothalamic function is further underscored by the observation that DIO in mice is partially reversed when saturated fats are replaced by unsaturated fats (65). More importantly, this reversal was associated with lowered hypothalamic inflammatory responses and with the restoration of leptin and insulin sensitivity (65).

The specificity of dietary SFAs as inducers of inflammation within the MBH has been assessed in several ways. First, MBH-focused inflammation that is induced by feeding mice a diet rich in SFAs is reproduced within days after administering SFAs via enteric gavage. By contrast, enteric administration of isocaloric MUFAs, PUFAs, or short-chain SFAs does not produce such an effect (66). Additionally, hypothalamic inflammation can be specifically induced by ICV infusion of SFAs (18, 39, 41). Moreover, inflammation induced by CNS administration of SFAs (*a*) promotes the impairment of hypothalamic leptin and insulin signaling and (*b*) increases body weight and disturbs other metabolic parameters (18).

To better define the links between hypothalamic lipid flux, lipotoxicity, inflammation, and neuronal dysfunction, investigators have begun performing lipidomic analyses on hypothalamic tissue under various conditions (67). Such approaches have revealed that consuming a HFD produces a specific accumulation of dietary lipids in the hypothalami of mice, although whether there are differences across individual hypothalamic nuclei is unknown. This finding is of interest given that some of these dietary lipids, such as diacylglycerols and ceramides, are already known to impair insulin signaling in peripheral tissues (17, 68). Furthermore, profiles of hypothalamic FAs

closely mirror the profiles of dietary FAs when consumed in excess; this is not true for other brain regions, highlighting the unique ability of the hypothalamus to sense changes in dietary fat intake (69). Focusing on the hypothalamus in conjunction with new, high-resolution mass spectrometric methods therefore has the potential to identify unrecognized lipids that may trigger or modulate metabolic inflammation in the hypothalamus.

**NLRP:** Nod-like receptor protein

**DAMP:** danger-associated molecular pattern

## Inflammatory Cytokines

The role of inflammatory cytokines in hypothalamic inflammation has been explored, and the data are mixed. On one hand, hypothalamic levels of activated IKKβ and several inflammatory cytokines become relatively high in response to dietary excess (18). Pharmacological activation of the IKKβ/NF-κB pathway or introduction of a constitutively active IKKβ into hypothalami of mice also causes obesity and both leptin and insulin insensitivity. By contrast, inhibiting NF-κB maintains leptin and insulin sensitivity and protects against obesity in the face of dietary challenge (18). On the other hand, forced activation of the IKKβ/NF-κB pathway in hypothalamic neurons is not associated with an increase in hypothalamic expression of proinflammatory cytokines (18), suggesting that, whereas neuronal NF-κB signaling may be important in regulating hypothalamic function, activation of the NF-κB pathway in nonneuronal cell types may play a key role in the elaboration of inflammatory cytokines in the setting of hypothalamic metabolic inflammation.

Recent evidence targeting individual cytokine receptor pathways within the hypothalamus suggests strongly that inflammatory cytokines act directly in the hypothalamus to promote diet-induced metabolic disease. For example, ICV administration of TNF-α at low doses increases food intake, decreases energy expenditure (50, 70), and increases blood pressure (46), thus recapitulating the effects of overnutrition. In addition, ICV injection of TNF-α also affects pancreatic function by impairing insulin secretion and altering pancreatic expression of genes involved in cellular energy metabolism, mitochondrial function, and apoptosis (45). Consistent with these findings, genetic ablation of TNF-α (13, 71) or TNFR (50, 52) in mice lessens the impact of overnutrition. Interestingly, ICV injection of stearic acid (SFA) mimics that of TNF-α and leads to proapoptotic signaling and dysfunctional insulin secretion in pancreatic islets, indicating that SFAs and TNF-α modulate the same or parallel hypothalamic pathways involved in metabolism (45).

Whereas the secretion of cytokines such as TNF-α and IL-6 in myeloid cells is stimulated by NF-κB activation, another highly regulated protein complex termed the Nod-like receptor protein 3 (NLRP3) inflammasome integrates NF-κB-dependent signaling with separate inflammatory signals resulting from the detection of pathogen- and danger-associated molecular patterns. Interestingly, lipids such as cholesterol, in crystal form, and SFAs induce NLRP3 activation, leading to consequent activation of caspase-1, and induce the processing and secretion of two cytokines, IL-1β and IL-18. Several studies showed that the NLRP3 inflammasome is important in the pathogenesis of diet-induced metabolic inflammation in peripheral tissues, insulin resistance, and obesity (72–76). More recently, *Nlrp3*- and *Casp1*-deficient mice were shown to be resistant to diet-induced hypothalamic inflammation (73). An emerging area of active research is focused on what MBH cell types mediate the NLRP3 inflammasome activation; what DAMPs are sensed by these MBH cells in dietary excess; and what role the NLRP3 inflammasome, IL-1β, and IL-18 play in diet-induced hypothalamic dysfunction.

Cytokines acting in the brain do not always stimulate processes leading to weight gain or insulin resistance. For example, recent work suggests that IL-6 and IL-10 are involved in the exercise-induced suppression of hyperphagia and in reducing both IKKβ/NF-κB activity and endoplasmic reticulum (ER) stress in the brain (77). Indeed, IL-6 can promote proinflammatory or

anti-inflammatory effects, depending on the environmental circumstances. In addition, the infusion of recombinant IL-6 into the third hypothalamic ventricle reduced food intake, hypothalamic ER stress, and IKKβ activation in obese mice. Similarly, infusion of recombinant IL-10 into the third ventricle promoted the restoration of energy homeostasis in obese mice by abrogating ER stress, blocking IKKβ activation, and restoring insulin-simulated Akt phosphorylation and leptin-induced STAT3 phosphorylation (77). Recently, investigators showed that spleen-derived IL-10 was decreased in rats with DIO compared with levels in lean counterparts and that splenectomy accelerated DIO-induced hypothalamic inflammation (78). These data suggest that the original source of IL-10 in modulating hypothalamic inflammation comes from a peripheral location, such as the spleen. Whether IL-10 crosses the blood-brain barrier (BBB) freely or whether its transport into the brain is actively regulated remains to be determined. In any case, splenic IL-10 may be emerging as a potential target to quell diet-induced hypothalamic inflammation and its deleterious impact on metabolic function.

**BBB:** blood-brain barrier

**ROS:** reactive oxygen species

CNS administration of IL-4 also exerts anti-inflammatory effects, which have been associated with beneficial disease-modifying outcomes in mouse models of neuroinflammation, including experimental autoimmune encephalomyelitis (79) and Alzheimer's-like dementia (80). However, IL-4 unexpectedly enhanced the proinflammatory effects of high-fat feeding in the hypothalami of mice, suggesting that the role of IL-4 in the pathogenesis of diet-induced hypothalamic inflammation may differ importantly from its role in other models of brain inflammation (81).

## Endoplasmic Reticulum Stress

The inflammatory pathways linked to the development of insulin resistance are also closely linked to ER stress in multiple cell types (82). For example, activation of the unfolded protein response (UPR) to ER stress can lead to activation of NF-κB signaling via the ability of UPR sensors [e.g., ATF-6 (transcription factor 6), IRE1 (inositol-requiring enzyme 1), and PERK (protein kinase RNA-like ER kinase)] to modulate positive and negative regulators of the IKKβ/NF-κB pathway (83–85). Moreover, overnutrition in mice has revealed a positive feedback mechanism in which hypothalamic IKKβ/NF-κB activation promotes the induction of neuronal ER stress (18, 46), setting up a potentially vicious cycle. Indeed, mice that genetically lack the IRE1-dependent transcription factor Xbp1 (X-box-binding protein 1) are susceptible to hypothalamic leptin resistance and to associated body weight gain (86).

## Oxidative Stress

Oxidative stress is also being explored as a factor in initiating and maintaining hypothalamic metabolic inflammation in the setting of overnutrition. Oxidative stress results from an ongoing imbalance between the production and disposal of reactive oxygen species (ROS). The precedent for focusing on oxidative stress comes from work in peripheral tissues such as the liver and white adipose tissue, where local ROS generation and oxidative stress precede severe metabolic inflammation and the onset of insulin resistance induced by DIO (87).

Recently, mitochondrial ROS generation was directly linked to inflammation. For example, the NLRP3 inflammasome in macrophages is activated by chemical and genetic manipulations that induce mitochondrial dysfunction and promote ROS. NLRP3 is also induced by pharmacological or genetic inhibition of mitophagy (a form of autophagy in which defective mitochondria are selectively degraded), leading to the accumulation of damaged, ROS-producing mitochondria (88–91).

The human brain accounts for approximately 2% of total body weight but utilizes approximately 20% of the oxygen and calories consumed by the body (92). The brain's metabolic

demand confers a vulnerability to excess ROS generation and oxidative stress in the setting of high rates of oxidative phosphorylation and electron transport chain flux (93). Mitochondria generate considerable amounts of ROS as a result of both glucose and fat oxidation. As such, the finding that orexigenic AgRP neurons in the hypothalamus utilize intracellular lipids for energy, particularly during fasting (94), demonstrates a mechanism by which excessive consumption of dietary fats may lead to ROS generation and fuel oxidative stress in hypothalamic neurons. Indeed, intraperitoneal injection of triacylglycerols (Intralipid®) increased mitochondrial respiration and ROS production in the hypothalami of rats (95).

Examining the physiological impact of oxidative stress on hypothalamic function has revealed that increased ROS generation is associated with abnormal hypothalamic glucose sensing in Zucker fatty rats (94) and other rodent models (95). Increased ROS generation has also been linked to abnormal lipid sensing in rodents (96). Future research is needed to determine (*a*) the relationship between oxidative stress and the induction of hypothalamic metabolic inflammation and (*b*) the potential benefits of targeting hypothalamic ROS generation to prevent diet-induced metabolic dysfunction.

### Autophagy

Autophagy is a cellular process that eliminates damaged cytoplasmic elements and organelles to maintain internal homeostasis and structural integrity. Autophagy also plays a key role in the response of cells to metabolic stress (97). In the setting of overnutrition, autophagic pathways are induced by both ER stress and oxidative stress (98, 99). Recently, the importance of autophagy in the MBH was revealed after virally mediated knockdown of the gene encoding ATG7, a key mediator of autophagy in mice (100). Partially abrogating the levels of ATG7 in the MBH in this way resulted in mice that ate more, gained more weight, and had increased hypothalamic activation of IKKβ/NF-κB. Interestingly, in this same mouse model, inhibiting IKKβ relieved the metabolic dysfunction, thus providing evidence that defective autophagy is tightly linked to hypothalamic inflammation. These findings mirror the close association between autophagy and inflammatory signaling in other tissues. For example, defective autophagy resulted in enhanced lipopolysaccharide (LPS)-induced IKKβ/NF-κB activation in the intestinal epithelia of mice (101). Given that there are emerging pharmacological tools to modulate autophagic processes, the finding that autophagy is involved in diet-induced hypothalamic inflammation and its consequences is intriguing.

## CONTRIBUTION OF SPECIFIC CELL TYPES TO HYPOTHALAMIC METABOLIC INFLAMMATION

### Neurons

The hypothalamus contains circumventricular organs that are proximal to the BBB and that have evolved to sense signals emanating from the peripheral circulation. Given that the MBH also lies close to the BBB, neurons and other cells in the MBH are anatomically well positioned to sense and integrate information conveyed by circulating diffusible factors, for example, nutrients, to mount coordinated neurophysiological responses.

However, this privileged position also makes the MBH vulnerable to the stress-promoting and potentially toxic effects of circulating factors from the environment, including those associated with chronic overnutrition (**Figure 2**). Research has shown that hypothalamic neurons are particularly susceptible to nutrient-induced oxidative stress and mitochondrial dysfunction (102). Studies indicate that first-order POMC and AgRP neurons are among the first to feel the

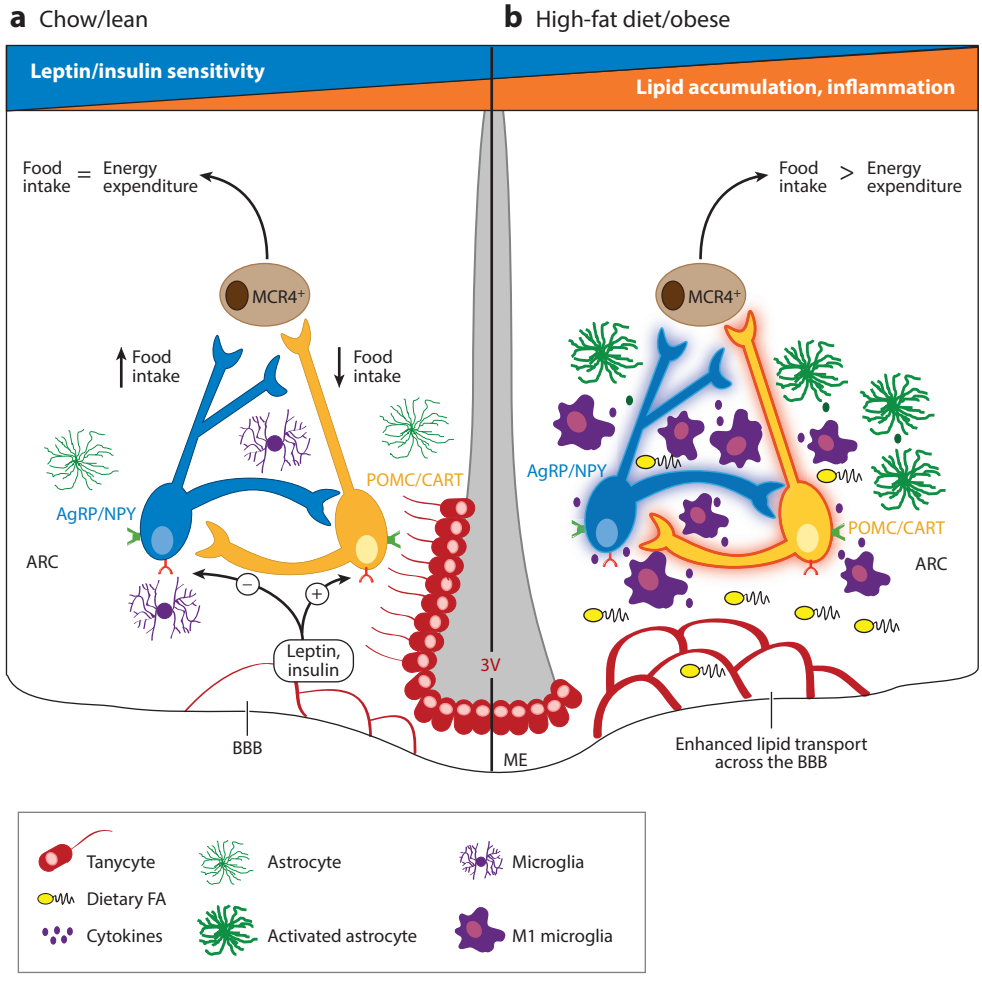



**Figure 2**

Contributors to hypothalamic metabolic inflammation. (*a*) Normal hypothalamic function involves a reciprocal interaction between AgRP/NPY and POMC/CART neurons in the ARC. Such neurons respond to signals from leptin and insulin and regulate both food intake and energy expenditure pathways. (*b*) In the setting of chronic dietary excess, this finely tuned regulation is disrupted by the accumulation of nutrients, including dietary FAs, microglia and astrocytes (both of which undergo a specific form of morphological and functional alteration), and inflammatory cytokines that exert multiple effects on a variety of cell types. In this inflammatory context, the normal activity of AgRP/NPY and POMC/CART neurons gives way to dysfunction, with potentially deleterious effects on energy, lipid, and glucose homeostasis. Tanycytes lining the ventricular walls, which both assist in transport across the BBB and potentially give rise to new neurons and glia, are not shown in the figure to depict the impact of hypothalamic inflammation on neogenic capacity. Also, the BBB is highlighted to indicate its important role in the transport of nutrients, including FAs and hormones, and its close association with glial cells and neurons in the ME that may be able to sample the levels of factors present in the systemic circulation. Abbreviations: 3V, third ventricle; AgRP, agouti-related peptide; ARC, arcuate nucleus of the hypothalamus; BBB, blood-brain barrier; CART, cocaine- and amphetamine-regulated transcript; FA, fatty acid; ME, median eminence of the hypothalamus; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

effects of hypothalamic inflammation, which produces a detrimental effect on neuronal signaling in response to leptin and insulin and compromises the secretion of anorexigenic POMC-derived α-MSH and CART (cocaine- and amphetamine-regulated transcript), corresponding to increased appetite and a positive energy balance (18).

**PAMP:** pathogen-associated molecular pattern

By contrast with the in vivo effects of a HFD on hypothalamic inflammation, treating cultured primary hypothalamic neurons with SFAs, for example, does not directly promote inflammatory pathways or impair insulin action (103). These data suggest that, rather than having a direct effect on neurons, SFAs alter hypothalamic neuronal function in vivo by modulating the function of nonneuronal cells, most likely microglia. However, prolonged exposure of cultured neurons to SFAs does induce ER stress and apoptosis, as is common among many mammalian cell types, although the mechanism for these in vitro responses is unknown (103, 104).

Whereas IKKβ/NF-κB signaling plays a critical role in the pathogenesis of insulin resistance in peripheral tissues (7, 105), the metabolic impact of IKKβ/NF-κB activation in the CNS is still a matter of debate. Injecting TNF-α into the third ventricles of mice markedly induced IKKβ phosphorylation and IκBα degradation in the ARC, particularly in POMC neurons, and less so in NPY/AgRP neurons (106). Preferential activation of POMC and not NPY/AgRP neurons by TNF-α might be expected to disrupt the reciprocal inputs controlling MBH neurocircuitry and to tip energy balance toward increased food intake and obesity. However, such effects have not been observed in mouse models that conditionally delete IKKβ in POMC neurons. Instead, these mice exhibit reduced cachexia when induced by classical inflammatory activators such as LPS (107). In contrast, mice lacking IKKβ specifically in AgRP neurons are partially protected from hyperphagia and weight gain when fed a HFD. Therefore, NF-κB signaling in hypothalamic POMC and AgRP neurons may have differential metabolic effects in severe or acute forms of inflammation, as opposed to milder, more chronic forms of inflammation such as that induced by dietary excess (18).

Investigators have also manipulated neuron-specific inflammatory signaling through TLRs, which respond to a variety of proinflammatory PAMPs. For example, conditionally deleting MyD88, an adaptor protein needed for TLRs and IL-1 signaling, in nestin-expressing cells protected mice from the effects of HFD (41).

Finally, there is increasing evidence that, in addition to innate immune cell types, neurons also possess functionally important NLRP complexes that form inflammasomes capable of coupling signal recognition to caspase-1-dependent cleavage of pro-IL-1β to form mature IL-1β (108–111). For example, spinal cord neurons, which are not classically known to serve an immune or inflammatory function, express NLRP1 inflammasome proteins (112). Moreover, the expression and cellular localization of neuronal NLRP1 are changed after cervical injury, suggesting that the NLRP1 inflammasome may play a role in the neuronal response to injury (112). Future work should focus on determining the relative importance of neuronal NLRP inflammasomes in nutrient- and/or obesity-induced hypothalamic inflammation.

## Microglia

Over the last decade, it has become evident that microglia are the patrolling sentinels of innate immunity in the brain and act analogously to resident macrophages in peripheral tissues, as they are capable of phagocytizing bacteria, debris, and damaged cells. They also help to mount defensive responses against infectious agents and to physical damage and DAMPs (113). However, microglia, which are yolk sac derived and populate the brain early in embryogenesis, are also critical players in maintaining the functional and architectural homeostasis of the brain and its neurocircuitry (114). As such, they play key roles in the remodeling of neurological circuits (115),

in synaptic pruning (116), and in neurogenesis (117). Indeed, microglia are activated in the context of several neurodegenerative disease processes. However, it remains unknown whether the sole role of microglia in this context is to restore homeostasis and normal function, whether microglial activation is harmful and hastens disease progression, or whether microglia exert both beneficial and destructive properties in a context-dependent manner (118).

In pursuing this question, recent exciting work shows that hypothalamic microglia respond to SFAs. Indeed, microglia, like peripheral macrophages, express TLRs and are highly responsive to LPS stimulation (119). Moreover, primary cultures of microglia mount an inflammatory response that is highly reminiscent of that of macrophages when treated with long-chain SFAs such as palmitic acid. This nutrient responsiveness is potentially unique to microglia, as primary astrocytes do not respond to SFA treatment in this way (66).

As observed for macrophages within white adipose tissue and peripheral metabolic tissues, microglia that have morphological features of inflammatory activation and that are positive for inflammatory cytokines accumulate within the ARC and ME of rodents fed HFD and obese humans (16, 39, 66). These activated microglia are associated with the hypothalamic buildup of dietary lipids (43, 67), including FA species, which mirror dietary composition (66). Indeed, feeding mice specific FA species in an isocaloric manner by enteric gavage showed that the excess consumption of long-chain SFAs specifically induces microglial activation within the MBH, strongly suggesting that hypothalamic microglia can sense and respond to rising levels of SFAs to initiate metabolic inflammation (66).

Activated hypothalamic microglia also engage proinflammatory signaling cascades and secrete high levels of proinflammatory cytokines that may in turn alter local neuronal circuits involved in metabolic control. Experimental evidence supports the notion that cross talk between activated microglia and local neurons in the hypothalamus is important in controlling energy balance. For example, α-MSH and NPY produced in the ARC modulate nitric oxide production and cytokine secretion by microglia (120–122). In turn, microglia are also implicated in modulating hypothalamic function. For instance, ICV administration of IL-4 into rats skews microglia toward an alternative, anti-inflammatory, M2-like state reminiscent of the peripheral macrophage responses to IL-4. This IL-4-induced, M2-like activation of microglia promoted weight gain in mice, and these effects were abolished by central administration of an IKKβ inhibitor (123), illustrating that microglia and their polarization state may exert profound effects on hypothalamic pathways relevant to energy homeostasis.

Building on this concept, we recently showed that increasing the basal number of microglia in the MBH potentiates the intensity of hypothalamic inflammation triggered by excess consumption of dietary SFAs. In contrast, specifically depleting microglia from the MBH abrogates SFA-induced hypothalamic inflammation (66). Therefore, microglial content in the MBH may be critical in orchestrating hypothalamic metabolic inflammation. Moreover, we found that microglia mediate the cellular stress response in MBH neurons, as marked by HSP72, to excess dietary SFA consumption. Indeed, depleting microglia from mice consuming excess dietary SFAs was associated with enhanced hypothalamic signaling in response to peripherally injected leptin (66). The task now is to determine how microglia orchestrate the operation of hypothalamic circuits, which control peripheral metabolic functions and go awry in DIO.

What fuels hypothalamic activation of microglia or microgliosis in response to dietary excess? Is such activation (*a*) a consequence of local proliferation, migration, and differentiation of CNS-resident progenitor cells; (*b*) a consequence of infiltration of bone marrow–derived cells; or (*c*) due to a combination of these phenomena? Researchers recently reported that HFD-induced macrophage accumulation in the white adipose tissue is largely due to the proliferation of resident

## THE IMPORTANCE OF MICROGLIAL SELF-RENEWAL

How do microglia accumulate within the MBH in the context of dietary excess and obesity? There is emerging interest in determining what contextual cues drive this process and what mechanisms are responsible for rapidly increasing microglial number in response to noninfectious stimuli. One possibility is that microglia accumulate in the MBH by migrating from other brain areas along gradients established by inflammatory chemokines or possibly lipids. Another possibility is that bone marrow–derived mononuclear cells from the systemic circulation cross the fenestrated blood-brain barrier lining the MBH and alter their morphology, and potentially their function, to resemble that of microglia once they arrive. Some compelling data from murine models support this concept. Perhaps the most intriguing possibility, however, stems from recent work pointing to the existence of CNS-resident, nestin-positive progenitor cells that proliferate and specifically give rise to microglia under conditions in which microglial content needs to expand. Understanding how these possibilities account for the remarkable plasticity of microglia has the potential to produce breakthroughs in our understanding of neuroinflammation and neurodegeneration.

macrophages (124), as detailed in the sidebar entitled The Importance of Microglial Self-Renewal, although infiltration by circulating monocytes may also contribute to their accumulation in this tissue (125). Approaches that experimentally deplete microglia from the brains of mice have shown that microglia are able to proliferate to repopulate CNS tissues (66, 126). Recently, investigators showed that a nestin-positive precursor cell type gives rise to mature microglia and that the proliferation and differentiation potential of these precursor cells depends on stimulation of the CSF1 receptor (CSF1R) (127). Emerging work is applying pharmacological approaches that block CSF1R in the brain to control microglial self-renewal for therapeutic purposes. Such a strategy may have applications in the setting of overnutrition.

Metabolic signals may also play a role in regulating the activation state and number of microglia in the hypothalamus. For example, treating mice with leptin directly stimulates microglia to secrete inflammatory cytokines and to assume an activated morphology (128, 129). By contrast, microglial activation in HFD-fed mice is shifted by exercise toward an anti-inflammatory polarization state that is also associated with improved glucose tolerance (130).

What cellular signaling pathways mediate microglial activation within the hypothalamus? Chronic overnutrition in adult mice leads to IKKβ/NF-κB hyperactivation in hypothalamic NSCs and signs of neurodegeneration, consistent with accelerated aging (56). Obesity-associated neurodegeneration in this model was attributed to excessive TNF-α and IL-1β production by microglia, which were maintained in an M1-like state, although how this polarization is maintained is unclear. Microglia-specific IKKβ ablation appeared to break the inflammatory cross talk between microglia and NSCs and promoted hypothalamic NSC survival and neurogenesis (56). Not surprisingly, murine microglia express components of the NLRP3 and NLRP4 inflammasomes, which are activated by relevant stimuli, including SFAs and cholesterol crystals (131, 132). However, it is not known whether a distinct subpopulation of microglia express and activate different inflammasomes according to their anatomical location in the CNS. For example, deleting *Nlrp3* in the CNS of mice reduced the age-related activation and inflammatory responses of hippocampal microglia (133), but not those of hypothalamic microglia (133). The idea that different subsets of microglia exist within the CNS is a new topic in brain research, and exploring microglial diversity in the context of metabolic inflammation therefore represents a new frontier.

Additionally, the relative contributions of TLR-dependent signaling, NF-κB-dependent signaling, and inflammasome-dependent signaling to microglial polarity within the hypothalamus are not known. Dissecting these inputs, particularly in the context of nutrient excess, is an important area for future research.

## Astrocytes

Astrocytes participate in several functions within the brain, including the supply of neurons with nutrients; synaptic plasticity; and the release of neuromodulators, such as glutamate, ATP, and GABA (134). Astrocytes are heterogeneous, exhibiting different morphologies and expressing different receptors according to their anatomical location (135). Although their specific function in the hypothalamus is poorly understood, there are clues that they may respond to signaling events that target the hypothalamus. For example, hypothalamic astrocytes express various isoforms of the leptin receptor (135, 136), suggesting that leptin may exert direct effects on them. Indeed, experimentally manipulating leptin levels can modify the morphology and function of astrocytes both in vivo and in vitro (137, 138). Given that specific mechanisms may exist to transport leptin into the hypothalamus, and given that leptin exerts major effects in this part of the brain, it is intriguing that astrocytes respond to leptin.

Astrocytes may also exert control over neurons involved in metabolic control (139). A recent report showed that deleting leptin receptors on GFAP (glial fibrillary acidic protein)-expressing astrocytes altered synaptic connections in hypothalamic circuits controlling feeding behavior and led to increased food intake after fasting or ghrelin administration (136). Astrocytes also control the uptake and metabolism of glucose (140) as well as lipids (141) by local neurons. In the case of lipids, astrocytes produce significant levels of apolipoprotein E, the most abundant lipid transporter in the CNS. Leptin is proposed to stimulate the secretion of apolipoprotein E by astrocytes in the hypothalamus, which in turn may facilitate the stimulation of POMC neurons to reduce food intake and body weight (141). Astrocytes also oxidize FAs to produce ketone bodies, which can be used as an energy source for neurons (142).

HFDs are associated with the accumulation of not only microglia (microgliosis) but also astrocytes (astrogliosis) within the hypothalamus, and such accumulation may be involved in the development of hypothalamic leptin and insulin resistance (16, 143). In exploring what triggers astrogliosis in the setting of overnutrition, early studies reported that cultured primary astrocytes mount an inflammatory response after treatment with long-chain SFAs (144). However, primary astrocytes are difficult to culture without contamination from other cell types (145). We recently used two separate approaches to culture highly pure populations of astrocytes while eliminating any contaminating microglia and neurons and found that murine astrocytes failed to secrete inflammatory cytokines following SFA treatment. These data have led us to hypothesize that nutritional stimuli trigger inflammatory responses by microglia within the MBH, whereas astrogliosis may be secondary to this microglial response. Still, astrocytes continue to be implicated as key cell types in diet-induced hypothalamic inflammation (43), suggesting that more research into what triggers their activation is needed.

In contrast, astrocytes in retinal-pigmented epithelial cells and the NLRP2 inflammasome (146, 147) contribute to CNS neuroinflammation. Moreover, diet- and aging-induced hippocampal astrogliosis was reduced in *Nlrp3*-deficient mice, and whether this reduction is due to a primary loss of inflammasome activity in astrocytes remains unclear (133). Future research must therefore continue to explore the potentially important role of astrocytes in coordinating metabolic inflammation and its impact in the brain.

## Tanycytes

Tanycytes are specialized glial cells that extend from ventricular ependymal surfaces to connect with vascular plexuses at the pial surface of the brain. Within the hypothalamus, tanycytes are located in the ME and extend from the ependymal surface of the third ventricle to a vascular plexus that is particularly fenestrated and permeable to circulating factors. These hypothalamic tanycytes are emerging as a key component of the leptin-responsive network that controls body weight and energy balance (148, 149). Recent evidence suggests that tanycytes respond to glucose and several transmitters, such as ATP, histamine, and acetylcholine, with rapid and robust $Ca^{2+}$ signaling (150, 151). Specifically, tanycytes are proposed to control the transport of leptin across the BBB and to act as checkpoints before leptin reaches neurons in the MBH (152). Tanycytes may also represent neuronal progenitors, as they are called into action under specific physiological conditions.

In this context, starting a HFD in mice acutely stimulates tanycytes to proliferate and to potentially differentiate into functional neurons, as revealed by lineage tracing using a nestin-Cre strategy (148). However, chronic DIO may lead to a depletion of proliferating progenitor-like cells in the hypothalamus (58), including tanycytes.

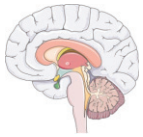
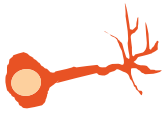
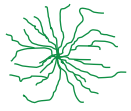
Tanycytes may also participate in hypothalamic inflammation. Endotoxin administration in rats induced tanycytes to increase their expression of TNFR1 (153) and macrophage migration inhibitory factor (154). Additionally, TNFR1 expression in the hypothalami of mice is found mostly in nonneuronal cells, including notably tanycytes located in the ME and along the third ventricular wall (106). Thus, tanycytes may respond to inflammatory signals and relay information to other hypothalamic cell types and to general neuroendocrine circuits. Further studies are necessary to define how tanycytes function and sample nutritional, hormonal, or inflammatory signals across the BBB.

# TARGETING HYPOTHALAMIC INFLAMMATION TO RESTORE METABOLIC HOMEOSTASIS

Building on data from genetically modified mice (**Table 1**), evidence from both rodent models and clinical studies supports the concept that targeting metabolic inflammation may hold promise as a means to treat and/or prevent insulin resistance, type 2 diabetes, and cardiovascular disease. For example, salicylates, which block inflammatory signaling by inhibiting NF-κB activity, improve insulin sensitivity and glucose metabolism in obese mice (155) and enhance insulin sensitivity in diabetic patients (12).

Additionally, many reports have described the role of proinflammatory cytokines in promoting insulin resistance (13). For example, blocking the actions of TNF-α improves insulin resistance in rodents (14), and neutralizing antibodies against TNF-α show only modest effects on lowering fasting glucose levels in obese patients (156). In contrast, a recent study found that TNF-α inhibitors improve type 2 diabetes in patients who take them for systemic inflammatory conditions such as rheumatoid arthritis and psoriasis; other disease-modifying antirheumatic drugs do not have this effect (157). Similarly, inhibiting IL-1β, another proinflammatory cytokine, also produces a modest improvement in glycemic control and an enhancement of β cell function in rodents (158, 159) and humans (160). These collective findings suggest that inflammation directly contributes to the development of diet-induced metabolic disease and that translating strategies to specifically reduce antecedent metabolic inflammation may be optimized to produce a strategy to prevent and/or treat these diseases. With this in mind, determining exactly what pathways, cell types, and tissue contexts are most important in driving metabolic inflammation is at the forefront of obesity and metabolic research.

**Table 1 Strategies using murine models to demonstrate the role of inflammatory pathways and individual cell types in key aspects of hypothalamic control**

| Cell type or tissue | Approach | Phenotype or outcome | Reference |
|---|---|---|---|
| Brain  | JNK1 knockout (nestin-Cre) | Protected from HFD-induced obesity | 123 |
| | MyD88 knockout (nestin-Cre) | Protected from central obesity and leptin/insulin resistance | 45 |
| | IKKβ knockout (nestin-Cre; MBH-Cre with adenovirus) | Protected from HFD-induced obesity | 24 |
| Neurons  | IKKβ knockout in AgRP neurons | Protected from HFD-induced hyperphagia and obesity | 24 |
| | IKKβ knockout in POMC neurons | Protected from LPS-induced cachexia | 67 |
| Microglia  | Iba1 staining in brains of HFD-fed mice | Resulted in microgliosis and M1-like activation in the MBH | 62 |
| | IKKβ knockout (CD11b-Cre with lentivirus) | Protected from impact of aging | 22 |
| | Depletion of hypothalamic content | Reduced SFA-induced inflammation | 116 |
| Astrocytes  | GFAP staining in brains of HFD-fed mice | Resulted in astrogliosis in the MBH | 22 |
| | Leptin receptor knockout (GFAP-Cre) | Increased food intake after fasting | 120 |
| Tanycytes  | TNFR1 staining | Resulted in TNFR1 expression | 107 |
| | Primary cell culture | Resulted in LPS-induced inflammation | 68 |

Abbreviations: AgRP, agouti-related peptide; GFAP, glial fibrillary acidic protein; HFD, high-fat diet; JNK1, c-Jun N-terminal kinase 1; LPS, lipopolysaccharide; MBH, mediobasal hypothalamus; MyD88, myeloid differentiation primary response gene 88; POMC, pro-opiomelanocortin; SFA, saturated fatty acid; TNFR1, TNF-α type 1 receptor.

In addition to highlighting the role of molecules downstream of leptin and insulin signaling [e.g., suppressor of cytokine signaling 3 (SOCS3) (161, 162) and protein tyrosine phosphatase 1B (PTP1B) (163)] in mediating obesity and peripheral insulin resistance, research focused on brain pathways driving these disease processes has uncovered molecules involved in controlling IKKβ/NF-κB signaling [e.g., MyD88 (41) and c-Jun N-terminal kinase 1 (JNK1) (164–166)]. Indeed, brain-specific ablation of IKKβ (18) and MyD88 (41) improves leptin sensitivity and alleviates diet-induced weight gain and obesity, respectively. Similarly, JNK1 deletion in the brain, but not in other tissues, protects against obesity in mice. Consistent with these findings, brain-specific SOCS3 knockout mice have enhanced leptin sensitivity and are protected against obesity when fed a HFD (167).

Neurons have historically been the primary focus of research on the regulation of energy balance. However, recent studies point to an emerging role for glial cells in the neuroendocrine control of systemic metabolism and obesity. On the basis of the studies mentioned above,

hypothalamic metabolic inflammation may result from the combined, and potentially integrated, contribution of both neuronal and nonneuronal cell types. Therefore, translating the promising results of animal models into effective therapeutic strategies that target hypothalamic inflammation to mitigate metabolic disease in humans may require separate approaches focused on both neurons and glia. To this end, some recent studies are worth mentioning.

Pharmacological or genetic disruption of hypothalamic inflammation reduces food intake and lowers body weight in mice fed a HFD, but not in mice fed a control (low-fat) diet (18). Diet-induced metabolic inflammation in peripheral tissues such as the skeletal muscle, white adipose tissue, and the liver is implicated in inducing tissue-specific insulin resistance. For example, blocking inflammatory pathways in hepatocytes improves hepatic insulin sensitivity (105). Mirroring what occurs in these tissues, the induction of hypothalamic inflammation and associated weight gain is strongly linked to the induction of hypothalamic resistance to hormones such as leptin and insulin (15, 42). However, hypothalamic metabolic inflammation may impact a wider array of functional processes than does inflammation in peripheral tissues. For example, inhibiting hypothalamic inflammation in the setting of DIO improves hepatic insulin action in mice and reduces both hepatic steatosis and glucose production (168). Indeed, vagotomy or pharmacological blockade of muscarinic acetylcholine receptors reversed the beneficial effects of inhibiting hypothalamic inflammation on hepatic insulin sensitivity (168).

Microglia are very attractive therapeutic targets in attempting to limit metabolic inflammation in the hypothalamus. Given that microglia engage in rapid chemotaxis and are highly efficient phagocytes, delivery of traditional pharmacological agents and cell type–specific RNAi to microglia is feasible. For example, it was recently shown that quantum dots (QDs) are avidly taken up by microglia and can effectively deliver biologically active molecules selectively to microglia both in vitro and in vivo (169). Viral vectors with specific promoters (CD11b, CSF1R, CX3CR1) (170, 171) are now widely used in vivo to selectively modulate gene expression in microglia and not in peripheral myeloid cell populations (172, 173). Although these viral strategies are useful in experimental models, their utility in clinical translation is limited by the fact that even modified viruses, when delivered to brain regions, can nonspecifically induce inflammation as well as toxicity. Moreover, whereas viral vectors cannot deliver chemical compounds, QDs and other nanoparticles could effectively deliver therapeutic agents to microglia that are applicable to a wide range of neurological and metabolic diseases.

A recently developed nanoparticle encapsulation system that exploits yeast-derived glucan shells to entrap siRNA has been used to specifically target siRNAs to phagocytes in vivo. Glucan nanoparticles containing fluorescently labeled siRNA are readily internalized by phagocytes, but not by other cell types, and can knock down gene expression in a cell type–specific manner (174). Intraperitoneal administration of such glucan shells was used to selectively silence genes in macrophages located in the epididymal white adipose tissue of obese mice without affecting gene expression in other macrophage populations (175). Although highly promising, this approach has yet to be tested for effectiveness in the hypothalamus.

One caveat to selectively targeting microglia is that, under conditions of acute inflammation and/or loss of BBB integrity, peripheral monocytes and other hematopoietic cell types migrate into the brain and can differentiate into cells that have morphological and functional features akin to those of microglia. This development has been well documented, for example, following brain irradiation (176–178). Recent findings suggest that peripheral immune cells may be recruited to the CNS in response to chronic obesity and may contribute to the inflammatory response (179). The idea that bone marrow–derived cells are involved in maintaining microglial numbers in adult mice under normal physiological conditions is controversial (180), but there is increasing interest in exploring this possibility as a means to prevent neurodegenerative and neuropsychiatric diseases.

If peripheral monocytes and/or progenitor cells are capable of gaining microglia-like functionality once in the CNS, they may be engineered as therapeutic tools and administered into the CNS with astounding therapeutic possibilities.

For example, Rett syndrome is a neurodegenerative disorder caused in most cases by mutations in the *Mecp2* gene located on the X chromosome, which encodes a methyl-CpG-binding protein (181, 182). Glia were recently recognized to play a role in the development of Rett syndrome (183). Transplanting wild-type bone marrow into irradiated *Mecp2*-deficient mice resulted in the stable engraftment of bone marrow–derived myeloid cells into the brain parenchyma of recipient mice, and importantly, these transplanted cells displayed several features of microglia. Remarkably, this engraftment arrested disease development. However, when the heads of the recipient mice were protected by lead shielding during irradiation to protect the BBB from breakdown, brain engraftment by donor myeloid cells was prevented, and disease progression was no longer arrested (184). These findings combine to define monocyte-derived cells, in addition to resident microglia, as potential targets to prevent chronic, diet-induced hypothalamic inflammation.

## ADAPTIVE SIGNIFICANCE OF NUTRIENT-INDUCED HYPOTHALAMIC INFLAMMATION

Given that obesity is a relatively new advent on the evolutionary timescale, it is hard to invoke hypothalamic or peripheral tissue inflammation simply as a component of the process leading to insulin resistance or other metabolic disturbances. Rather, the hypothalamus may sense elevated levels of nutrients, for example, FAs, as a way to signal acute changes in nutrient availability, environmental conditions, or other physiological states. Neurons, microglia, and other hypothalamic cell types must be responsive to these signals to effectively adapt to physiological extremes. For example, whereas herbivorous grazing mammals consume relatively small amounts of food on a frequent and consistent basis, carnivorous mammals may go for prolonged periods of time prior to each meal, expending precious energy stores in the process of finding prey. Once carnivores finally succeed and consume their meal, selective pressure may mount to consume as much food and calories as possible. Indeed, carnivores can consume a large percentage of their preexisting body weight in a given meal, gaining significant amounts of weight in the process. Interestingly, circulating SFA levels go up dramatically after the consumption of a large meal consisting of meat. We showed that SFA levels rise preferentially in the hypothalamus following an acute challenge with dietary saturated fat. Perhaps the capacity to sense hypothalamic FAs and to initiate an inflammatory response in the hypothalamus reprograms the neurocircuitry to eliminate preexisting brakes on food intake and facilitate maximal food consumption.

If the abrupt elevations in hypothalamic FA levels are indeed able to remodel circuits related to hunger and satiety, for example, then what we term hypothalamic inflammation may very well represent a conserved mechanism that allows for adaptive responses during refeeding after a prolonged fast. In this paradigm, one of the problems with the modern world is that food consumption is not tempered by periods of prolonged fasting. Indeed, common forms of human obesity are associated with the chronic, consistent consumption of foods rich in saturated fat, calories, and sugar. Therefore, whereas acute elevations in hypothalamic SFAs may have an adaptive role, chronic elevations may promote a more severe, sustained form of inflammation that predisposes individuals to metabolic disease. In this way, chronic, diet-induced hypothalamic metabolic inflammation represents the hijacking of an otherwise evolutionary beneficial mechanism. Experimentally determining the physiological significance of SFA responsiveness among hypothalamic cell types

will be crucial to informing our understanding of exactly what goes awry in the context of the modern obesity epidemic.

## SUMMARY POINTS

1. Given that controlling diet-induced inflammation in peripheral tissues has emerged as a potential strategy to mitigate the metabolic consequences of obesity, there is growing interest in exploring diet-induced hypothalamic inflammation, which bears a resemblance to inflammation that occurs in peripheral tissues.
2. The mediobasal hypothalamus controls a diverse array of metabolic functions, including hunger and satiety, energy metabolism, peripheral lipid metabolism, glucose homeostasis, and thermogenic capacity.
3. These controls go awry in the setting of diet-induced obesity, along with the accumulation of microglia, astrocytes, dietary lipids, and inflammatory cytokines, and there is evidence of cellular stress among neurons engaged in metabolic control.
4. Microglia directly respond to saturated fats that can accumulate in the hypothalamus when consumed in excess, and as a result, they rapidly take on a proinflammatory polarity that is highly reminiscent of M1-like macrophages that accumulate in the white adipose tissue in response to obesity.
5. Inflammatory pathways in microglia, astrocytes, neurons, and supporting cell types such as tanycytes may be engaged in the setting of dietary excess and may play a role in promoting altered hypothalamic control over metabolic function.
6. New approaches to target individual cell types within the brain may allow for the manipulation of hypothalamic inflammation for therapeutic purposes.
7. As opposed to their potentially harmful roles in the setting of chronic obesity, inflammatory pathways in the hypothalamus may have evolutionarily conserved adaptive functions when acutely activated for short periods by nutrient-level fluctuations that may be seen, for example, in response to prolonged periods of fasting followed by refeeding.

## FUTURE ISSUES

1. It will be important to determine whether acutely stimulating inflammatory pathways in hypothalamic cell types for short periods of time has an adaptive significance to normal physiology and whether these pathways are hijacked to produce deleterious consequences in the setting of diet-induced obesity.
2. Determining how hypothalamic cell types (microglia, astrocytes, and neurons) take up, metabolize, and store dietary lipids will provide insight into how dietary lipids modulate hypothalamic function under normal conditions and into how excessive hypothalamic lipid accumulation leads to inflammation and the dysfunction of metabolic control.
3. Identifying the mechanistic links between hypothalamic inflammation and altered CNS control over peripheral metabolic processes—including energy balance, thermogenesis, hepatic glucose production and lipid storage, and insulin sensitivity—will be crucial to determining the translational potential of anti-inflammatory strategies aimed at the brain.

4. It will be important to dissect the mechanisms that facilitate cachexia and negative energy balance in response to some forms of CNS inflammation from those mechanisms associated with positive energy balance and weight gain in the setting of diet-induced hypothalamic inflammation.
5. There is an urgent need to identify resident neural stem cells and progenitor cells that give rise to other cell types (microglia, astrocytes) within the brain so as to devise regenerative strategies to alleviate neurodegeneration, which may be hastened in the hypothalamus by advancing age and potentially by chronic obesity.
6. It is important to understand the relative importance of NF-κB-driven inflammatory pathways, oxidative stress, ER stress, NLRP3 inflammasome activation, and autophagy across individual cell types in the development and maintenance of diet-induced hypothalamic inflammation and its specific metabolic consequences.
7. There is emerging interest in using nanotechnology to specifically target microglia for therapeutic purposes.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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## LITERATURE CITED

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. 2012. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA* 307:491–97
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. 2012. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *JAMA* 307:483–90
3. Hotamisligil GS. 2006. Inflammation and metabolic disorders. *Nature* 444:860–67
4. Odegaard JI, Chawla A. 2013. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. *Science* 339:172–77
5. Xu H, Barnes GT, Yang Q, Tan G, Yang D, et al. 2003. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Investig.* 112:1821–30
6. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. 2003. Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Investig.* 112:1796–808
7. Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, et al. 2005. Local and systemic insulin resistance resulting from hepatic activation of IKK-β and NF-κB. *Nat. Med.* 11:183–90
8. Itani SI, Ruderman NB, Schmieder F, Boden G. 2002. Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IκB-α. *Diabetes* 51:2005–11
9. Bandyopadhyay GK, Yu JG, Ofrecio J, Olefsky JM. 2005. Increased p85/55/50 expression and decreased phosphotidylinositol 3-kinase activity in insulin-resistant human skeletal muscle. *Diabetes* 54:2351–59
10. Ehses JA, Boni-Schnetzler M, Faulenbach M, Donath MY. 2008. Macrophages, cytokines and β-cell death in Type 2 diabetes. *Biochem. Soc. Trans.* 36:340–42

11. Donath MY, Boni-Schnetzler M, Ellingsgaard H, Halban PA, Ehses JA. 2010. Cytokine production by islets in health and diabetes: cellular origin, regulation and function. *Trends Endocrinol. Metab.* 21:261–67
12. Hundal RS, Petersen KF, Mayerson AB, Randhawa PS, Inzucchi S, et al. 2002. Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. *J. Clin. Investig.* 109:1321–26
13. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. 1997. Protection from obesity-induced insulin resistance in mice lacking TNF-α function. *Nature* 389:610–14
14. Hotamisligil GS, Shargill NS, Spiegelman BM. 1993. Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance. *Science* 259:87–91
15. **De Souza CT, Araujo EP, Bordin S, Ashimine R, Zollner RL, et al. 2005. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. *Endocrinology* 146:4192–99**
16. **Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, et al. 2012. Obesity is associated with hypothalamic injury in rodents and humans. *J. Clin. Investig.* 122:153–62**
17. Holland WL, Bikman BT, Wang LP, Yuguang G, Sargent KM, et al. 2011. Lipid-induced insulin resistance mediated by the proinflammatory receptor TLR4 requires saturated fatty acid–induced ceramide biosynthesis in mice. *J. Clin. Investig.* 121:1858–70
18. **Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. 2008. Hypothalamic IKKβ/NF-κB and ER stress link overnutrition to energy imbalance and obesity. *Cell* 135:61–73**
19. Mraz M, Haluzik M. 2014. The role of adipose tissue immune cells in obesity and low-grade inflammation. *J. Endocrinol.* 222:R113–27
20. Mori MA, Liu M, Bezy O, Almind K, Shapiro H, et al. 2010. A systems biology approach identifies inflammatory abnormalities between mouse strains prior to development of metabolic disease. *Diabetes* 59:2960–71
21. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. 2006. Central nervous system control of food intake and body weight. *Nature* 443:289–95
22. Coll AP, Farooqi IS, O'Rahilly S. 2007. The hormonal control of food intake. *Cell* 129:251–62
23. Sandoval D, Cota D, Seeley RJ. 2008. The integrative role of CNS fuel-sensing mechanisms in energy balance and glucose regulation. *Annu. Rev. Physiol.* 70:513–35
24. Clark JT, Kalra PS, Crowley WR, Kalra SP. 1984. Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. *Endocrinology* 115:427–29
25. Ollmann MM, Wilson BD, Yang YK, Kerns JA, Chen Y, et al. 1997. Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein. *Science* 278:135–38
26. Dietrich MO, Horvath TL. 2013. Hypothalamic control of energy balance: insights into the role of synaptic plasticity. *Trends Neurosci.* 36:65–73
27. Saper CB, Chou TC, Elmquist JK. 2002. The need to feed: homeostatic and hedonic control of eating. *Neuron* 36:199–211
28. Ibrahim N, Bosch MA, Smart JL, Qiu J, Rubinstein M, et al. 2003. Hypothalamic proopiomelanocortin neurons are glucose responsive and express $K_{ATP}$ channels. *Endocrinology* 144:1331–40
29. Fioramonti X, Contie S, Song Z, Routh VH, Lorsignol A, Penicaud L. 2007. Characterization of glucosensing neuron subpopulations in the arcuate nucleus: integration in neuropeptide Y and pro-opio melanocortin networks? *Diabetes* 56:1219–27
30. Levin BE, Sullivan AC. 1987. Glucose, insulin and sympathoadrenal activation. *J. Auton. Nerv. Syst.* 20:233–42
31. Acheson KJ, Ravussin E, Wahren J, Jequier E. 1984. Thermic effect of glucose in man. Obligatory and facultative thermogenesis. *J. Clin. Investig.* 74:1572–80
32. Sakaguchi T, Bray GA. 1987. The effect of intrahypothalamic injections of glucose on sympathetic efferent firing rate. *Brain Res. Bull.* 18:591–95
33. Pocai A, Lam TK, Gutierrez-Juarez R, Obici S, Schwartz GJ, et al. 2005. Hypothalamic $K_{ATP}$ channels control hepatic glucose production. *Nature* 434:1026–31
34. Lam TK, Gutierrez-Juarez R, Pocai A, Bhanot S, Tso P, et al. 2007. Brain glucose metabolism controls the hepatic secretion of triglyceride-rich lipoproteins. *Nat. Med.* 13:171–80
35. Obici S, Feng Z, Morgan K, Stein D, Karkanias G, Rossetti L. 2002. Central administration of oleic acid inhibits glucose production and food intake. *Diabetes* 51:271–75

**15. Using microarrays in rats, this paper is the first to document the induction of inflammatory genes in the hypothalamus after 16 weeks of high-fat feeding.**

**16. Shows that the expression of inflammatory genes in the hypothalamus can be induced rapidly, within 24 h of initiating a high-fat diet in rodents. Also shows glial cell accumulation in the hypothalami of obese humans.**

**18. Shows that both pharmacologically and genetically disrupting hypothalamic inflammation reduces food intake and lowers body weight in mice fed a high-fat diet, but not in mice fed a low-fat control diet.**

36. Morgan K, Obici S, Rossetti L. 2004. Hypothalamic responses to long-chain fatty acids are nutritionally regulated. *J. Biol. Chem.* 279:31139–48
37. Mead JR, Irvine SA, Ramji DP. 2002. Lipoprotein lipase: structure, function, regulation, and role in disease. *J. Mol. Med.* 80:753–69
**38. Wang H, Astarita G, Taussig MD, Bharadwaj KG, DiPatrizio NV, et al. 2011. Deficiency of lipoprotein lipase in neurons modifies the regulation of energy balance and leads to obesity. *Cell Metab.* 13:105–13**
39. Milanski M, Degasperi G, Coope A, Morari J, Denis R, et al. 2009. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. *J. Neurosci.* 29:359–70
40. Wang X, Ge A, Cheng M, Guo F, Zhao M, et al. 2012. Increased hypothalamic inflammation associated with the susceptibility to obesity in rats exposed to high-fat diet. *Exp. Diabetes Res.* 2012:847246
41. Kleinridders A, Schenten D, Konner AC, Belgardt BF, Mauer J, et al. 2009. MyD88 signaling in the CNS is required for development of fatty acid–induced leptin resistance and diet-induced obesity. *Cell Metab.* 10:249–59
42. Enriori PJ, Evans AE, Sinnayah P, Jobst EE, Tonelli-Lemos L, et al. 2007. Diet-induced obesity causes severe but reversible leptin resistance in arcuate melanocortin neurons. *Cell Metab.* 5:181–94
43. Morselli E, Fuente-Martin E, Finan B, Kim M, Frank A, et al. 2014. Hypothalamic PGC-1α protects against high-fat diet exposure by regulating ERα. *Cell Rep.* 9:633–45
44. Kang YM, Ma Y, Zheng JP, Elks C, Sriramula S, et al. 2009. Brain nuclear factor-κB activation contributes to neurohumoral excitation in angiotensin II–induced hypertension. *Cardiovasc. Res.* 82:503–12
45. Calegari VC, Torsoni AS, Vanzela EC, Araújo EP, Morari J, et al. 2011. Inflammation of the hypothalamus leads to defective pancreatic islet function. *J. Biol. Chem.* 286:12870–80
46. Purkayastha S, Zhang H, Zhang G, Ahmed Z, Wang Y, Cai D. 2011. Neural dysregulation of peripheral insulin action and blood pressure by brain endoplasmic reticulum stress. *PNAS* 108:2939–44
47. Sharp FR, Massa SM, Swanson RA. 1999. Heat-shock protein protection. *Trends Neurosci.* 22:97–99
48. Choi C, Kutsch O, Park J, Zhou T, Seol DW, Benveniste EN. 2002. Tumor necrosis factor–related apoptosis-inducing ligand induces caspase-dependent interleukin-8 expression and apoptosis in human astroglioma cells. *Mol. Cell. Biol.* 22:724–36
49. Degasperi GR, Romanatto T, Denis RG, Araújo EP, Moraes JC, et al. 2008. UCP2 protects hypothalamic cells from TNF-α-induced damage. *FEBS Lett.* 582:3103–10
50. Arruda AP, Milanski M, Coope A, Torsoni AS, Ropelle E, et al. 2011. Low-grade hypothalamic inflammation leads to defective thermogenesis, insulin resistance, and impaired insulin secretion. *Endocrinology* 152:1314–26
51. Arruda AP, Milanski M, Romanatto T, Solon C, Coope A, et al. 2010. Hypothalamic actions of tumor necrosis factor α provide the thermogenic core for the wastage syndrome in cachexia. *Endocrinology* 151:683–94
52. Romanatto T, Roman EA, Arruda AP, Denis RG, Solon C, et al. 2009. Deletion of tumor necrosis factor-α receptor 1 (TNFR1) protects against diet-induced obesity by means of increased thermogenesis. *J. Biol. Chem.* 284:36213–22
53. Withers DJ, Gutierrez JS, Towery H, Burks DJ, Ren JM, et al. 1998. Disruption of IRS-2 causes type 2 diabetes in mice. *Nature* 391:900–4
54. Burgos-Ramos E, Gonzalez-Rodriguez A, Canelles S, Baquedano E, Frago LM, et al. 2012. Differential insulin receptor substrate-1 (IRS1)-related modulation of neuropeptide Y and proopiomelanocortin expression in nondiabetic and diabetic IRS2$^{-/-}$ mice. *Endocrinology* 153:1129–40
55. Thaler JP, Choi SJ, Schwartz MW, Wisse BE. 2010. Hypothalamic inflammation and energy homeostasis: resolving the paradox. *Front. Neuroendocrinol.* 31:79–84
**56. Li J, Tang Y, Cai D. 2012. IKKβ/NF-κB disrupts adult hypothalamic neural stem cells to mediate a neurodegenerative mechanism of dietary obesity and pre-diabetes. *Nat. Cell Biol.* 14:999–1012**
57. Sousa-Ferreira L, de Almeida LP, Cavadas C. 2014. Role of hypothalamic neurogenesis in feeding regulation. *Trends Endocrinol. Metab.* 25:80–88
58. McNay DE, Briancon N, Kokoeva MV, Maratos-Flier E, Flier JS. 2012. Remodeling of the arcuate nucleus energy-balance circuit is inhibited in obese mice. *J. Clin. Investig.* 122:142–52

**38. By targeting lipoprotein lipase, this paper highlights the potential role of circulating lipoprotein-encapsulated lipids in neuronal function in the hypothalamic regulation of energy balance.**

**56. Shows that microglia-specific IKKβ deletion breaks the proinflammatory cross talk between microglia and neural stem cells and promotes hypothalamic neural stem cell survival and neurogenesis.**

59. Rolls A, Shechter R, London A, Ziv Y, Ronen A, et al. 2007. Toll-like receptors modulate adult hippocampal neurogenesis. *Nat. Cell Biol.* 9:1081–88
60. Boden G. 2008. Obesity and free fatty acids. *Endocrinol. Metab. Clin. N. Am.* 37:635–46, viii–ix
61. Lee JY, Ye J, Gao Z, Youn HS, Lee WH, et al. 2003. Reciprocal modulation of Toll-like receptor-4 signaling pathways involving MyD88 and phosphatidylinositol 3-kinase/AKT by saturated and polyunsaturated fatty acids. *J. Biol. Chem.* 278:37041–51
62. Lee JY, Plakidas A, Lee WH, Heikkinen A, Chanmugam P, et al. 2003. Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. *J. Lipid Res.* 44:479–86
63. Posey KA, Clegg DJ, Printz RL, Byun J, Morton GJ, et al. 2009. Hypothalamic proinflammatory lipid accumulation, inflammation, and insulin resistance in rats fed a high-fat diet. *Am. J. Physiol. Endocrinol. Metab.* 296:E1003–12
64. DeLany JP, Windhauser MM, Champagne CM, Bray GA. 2000. Differential oxidation of individual dietary fatty acids in humans. *Am. J. Clin. Nutr.* 72:905–11
65. Cintra DE, Ropelle ER, Moraes JC, Pauli JR, Morari J, et al. 2012. Unsaturated fatty acids revert diet-induced hypothalamic inflammation in obesity. *PLOS ONE* 7:e30571
**66. Valdearcos M, Robblee MM, Benjamin DI, Nomura DK, Xu AW, Koliwad SK. 2014. Microglia dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal function. *Cell Rep*. 9:1–15**
67. Martinez de Morentin PB, Varela L, Ferno J, Nogueiras R, Dieguez C, Lopez M. 2010. Hypothalamic lipotoxicity and the metabolic syndrome. *Biochim. Biophys. Acta* 1801:350–61
68. Benoit SC, Kemp CJ, Elias CF, Abplanalp W, Herman JP, et al. 2009. Palmitic acid mediates hypothalamic insulin resistance by altering PKC-$\theta$ subcellular localization in rodents. *J. Clin. Investig.* 119:2577–89
69. Borg ML, Omran SF, Weir J, Meikle PJ, Watt MJ. 2012. Consumption of a high-fat diet, but not regular endurance exercise training, regulates hypothalamic lipid accumulation in mice. *J. Physiol.* 590:4377–89
70. Romanatto T, Cesquini M, Amaral ME, Roman EA, Moraes JC, et al. 2007. TNF-$\alpha$ acts in the hypothalamus inhibiting food intake and increasing the respiratory quotient—effects on leptin and insulin signaling pathways. *Peptides* 28:1050–58
71. Ventre J, Doebber T, Wu M, MacNaul K, Stevens K, et al. 1997. Targeted disruption of the tumor necrosis factor-$\alpha$ gene: metabolic consequences in obese and nonobese mice. *Diabetes* 46:1526–31
72. Stienstra R, van Diepen JA, Tack CJ, Zaki MH, van de Veerdonk FL, et al. 2011. Inflammasome is a central player in the induction of obesity and insulin resistance. *PNAS* 108:15324–29
73. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, et al. 2011. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nat. Med.* 17:179–88
74. Wen H, Gris D, Lei Y, Jha S, Zhang L, et al. 2011. Fatty acid–induced NLRP3-ASC inflammasome activation interferes with insulin signaling. *Nat. Immunol.* 12:408–15
75. Schroder K, Zhou R, Tschopp J. 2010. The NLRP3 inflammasome: a sensor for metabolic danger? *Science* 327:296–300
76. Lamkanfi M, Kanneganti TD. 2012. The inflammasome: a remote control for metabolic syndrome. *Cell Res.* 22:1095–98
77. Ropelle ER, Flores MB, Cintra DE, Rocha GZ, Pauli JR, et al. 2010. IL-6 and IL-10 anti-inflammatory activity links exercise to hypothalamic insulin and leptin sensitivity through IKK$\beta$ and ER stress inhibition. *PLOS Biol.* 8:e1000465
78. Gotoh K, Inoue M, Masaki T, Chiba S, Shimasaki T, et al. 2012. A novel anti-inflammatory role for spleen-derived interleukin-10 in obesity-induced inflammation in white adipose tissue and liver. *Diabetes* 61:1994–2003
79. Butti E, Bergami A, Recchia A, Brambilla E, Del Carro U, et al. 2008. IL4 gene delivery to the CNS recruits regulatory T cells and induces clinical recovery in mouse models of multiple sclerosis. *Gene Ther.* 15:504–15
80. Combs CK, Johnson DE, Cannady SB, Lehman TM, Landreth GE. 1999. Identification of microglial signal transduction pathways mediating a neurotoxic response to amyloidogenic fragments of $\beta$-amyloid and prion proteins. *J. Neurosci.* 19:928–39

**66. Contains the first data showing the primary role of microglia in initiating diet-induced hypothalamic inflammation and controlling its intensity and demonstrates the direct proinflammatory effects of enteric saturated fats on hypothalamic microglia in vivo.**

81. Oh-I S, Thaler JP, Ogimoto K, Wisse BE, Morton GJ, et al. 2010. Central administration of interleukin-4 exacerbates hypothalamic inflammation and weight gain during high-fat feeding. *Am. J. Physiol. Endocrinol. Metab.* 299(1):E47–53
82. Hotamisligil GS. 2010. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 140:900–17
83. Deng J, Lu PD, Zhang Y, Scheuner D, Kaufman RJ, et al. 2004. Translational repression mediates activation of nuclear factor κB by phosphorylated translation initiation factor 2. *Mol. Cell. Biol.* 24:10161–68
84. Hu P, Han Z, Couvillon AD, Kaufman RJ, Exton JH. 2006. Autocrine tumor necrosis factor α links endoplasmic reticulum stress to the membrane death receptor pathway through IRE1α-mediated NF-κB activation and down-regulation of TRAF2 expression. *Mol. Cell. Biol.* 26:3071–84
85. Yamazaki H, Hiramatsu N, Hayakawa K, Tagawa Y, Okamura M, et al. 2009. Activation of the Akt–NF-κB pathway by subtilase cytotoxin through the ATF6 branch of the unfolded protein response. *J. Immunol.* 183:1480–87
86. Ozcan L, Ergin AS, Lu A, Chung J, Sarkar S, et al. 2009. Endoplasmic reticulum stress plays a central role in development of leptin resistance. *Cell Metab.* 9:35–51
87. Matsuzawa-Nagata N, Takamura T, Ando H, Nakamura S, Kurita S, et al. 2008. Increased oxidative stress precedes the onset of high-fat diet–induced insulin resistance and obesity. *Metabolism* 57:1071–77
88. Saitoh T, Fujita N, Jang MH, Uematsu S, Yang BG, et al. 2008. Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1β production. *Nature* 456:264–68
89. Zhou L, Aon MA, Almas T, Cortassa S, Winslow RL, O'Rourke B. 2010. A reaction-diffusion model of ROS-induced ROS release in a mitochondrial network. *PLOS Comput. Biol.* 6:e1000657
90. Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, et al. 2011. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nat. Immunol.* 12:222–30
91. Zhou R, Yazdi AS, Menu P, Tschopp J. 2011. A role for mitochondria in NLRP3 inflammasome activation. *Nature* 469:221–25
92. Raichle ME, Gusnard DA. 2002. Appraising the brain's energy budget. *PNAS* 99:10237–39
93. Melov S. 2004. Modeling mitochondrial function in aging neurons. *Trends Neurosci.* 27:601–6
94. Kaushik S, Rodriguez-Navarro JA, Arias E, Kiffin R, Sahu S, et al. 2011. Autophagy in hypothalamic AgRP neurons regulates food intake and energy balance. *Cell Metab.* 14:173–83
95. Benani A, Troy S, Carmona MC, Fioramonti X, Lorsignol A, et al. 2007. Role for mitochondrial reactive oxygen species in brain lipid sensing: redox regulation of food intake. *Diabetes* 56:152–60
96. Leloup C, Magnan C, Benani A, Bonnet E, Alquier T, et al. 2006. Mitochondrial reactive oxygen species are required for hypothalamic glucose sensing. *Diabetes* 55:2084–90
97. Yorimitsu T, Klionsky DJ. 2005. Autophagy: molecular machinery for self-eating. *Cell Death Differ.* 12(Suppl. 2):1542–52
98. Butler D, Bahr BA. 2006. Oxidative stress and lysosomes: CNS-related consequences and implications for lysosomal enhancement strategies and induction of autophagy. *Antioxid. Redox Signal.* 8:185–96
99. Yorimitsu T, Nair U, Yang Z, Klionsky DJ. 2006. Endoplasmic reticulum stress triggers autophagy. *J. Biol. Chem.* 281:30299–304
100. Meng Q, Cai D. 2011. Defective hypothalamic autophagy directs the central pathogenesis of obesity via the IκB kinase β (IKKβ)/NF-κB pathway. *J. Biol. Chem.* 286:32324–32
101. Fujishima Y, Nishiumi S, Masuda A, Inoue J, Nguyen NM, et al. 2011. Autophagy in the intestinal epithelium reduces endotoxin-induced inflammatory responses by inhibiting NF-κB activation. *Arch. Biochem. Biophys.* 506:223–35
102. Singh RB, Gupta S, Dherange P, De Meester F, Wilczynska A, et al. 2012. Metabolic syndrome: a brain disease. *Can. J. Physiol. Pharmacol.* 90:1171–83
103. Choi SJ, Kim F, Schwartz MW, Wisse BE. 2010. Cultured hypothalamic neurons are resistant to inflammation and insulin resistance induced by saturated fatty acids. *Am. J. Physiol. Endocrinol. Metab.* 298:E1122–30

104. Mayer CM, Belsham DD. 2010. Palmitate attenuates insulin signaling and induces endoplasmic reticulum stress and apoptosis in hypothalamic neurons: rescue of resistance and apoptosis through adenosine 5′ monophosphate–activated protein kinase activation. *Endocrinology* 151:576–85
105. Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, et al. 2005. IKK-β links inflammation to obesity-induced insulin resistance. *Nat. Med.* 11:191–98
106. Purkayastha S, Zhang G, Cai D. 2011. Uncoupling the mechanisms of obesity and hypertension by targeting hypothalamic IKK-β and NF-κB. *Nat. Med.* 17:883–87
107. Jang PG, Namkoong C, Kang GM, Hur MW, Kim SW, et al. 2010. NF-κB activation in hypothalamic pro-opiomelanocortin neurons is essential in illness- and leptin-induced anorexia. *J. Biol. Chem.* 285:9706–15
108. Karatas H, Erdener SE, Gursoy-Ozdemir Y, Lule S, Eren-Kocak E, et al. 2013. Spreading depression triggers headache by activating neuronal Panx1 channels. *Science* 339:1092–95
109. Compan V, Baroja-Mazo A, Lopez-Castejon G, Gomez AI, Martinez CM, et al. 2012. Cell volume regulation modulates NLRP3 inflammasome activation. *Immunity* 37:487–500
110. Ramos HJ, Lanteri MC, Blahnik G, Negash A, Suthar MS, et al. 2012. IL-1β signaling promotes CNS-intrinsic immune control of West Nile virus infection. *PLOS Pathog.* 8:e1003039
111. Kummer JA, Broekhuizen R, Everett H, Agostini L, Kuijk L, et al. 2007. Inflammasome components NALP 1 and 3 show distinct but separate expression profiles in human tissues suggesting a site-specific role in the inflammatory response. *J. Histochem. Cytochem.* 55:443–52
112. de Rivero Vaccari JP, Lotocki G, Marcillo AE, Dietrich WD, Keane RW. 2008. A molecular platform in neurons regulates inflammation after spinal cord injury. *J. Neurosci.* 28:3404–14
113. Ransohoff RM, Brown MA. 2012. Innate immunity in the central nervous system. *J. Clin. Investig.* 122:1164–71
114. Wake H, Moorhouse AJ, Miyamoto A, Nabekura J. 2013. Microglia: actively surveying and shaping neuronal circuit structure and function. *Trends Neurosci.* 36:209–17
115. Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, et al. 2012. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* 74:691–705
116. Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, et al. 2011. Synaptic pruning by microglia is necessary for normal brain development. *Science* 333:1456–58
117. Gemma C, Bachstetter AD. 2013. The role of microglia in adult hippocampal neurogenesis. *Front. Cell. Neurosci.* 7:229
118. Sierra A, Abiega O, Shahraz A, Neumann H. 2013. Janus-faced microglia: beneficial and detrimental consequences of microglial phagocytosis. *Front. Cell. Neurosci.* 7:6
119. Lehnardt S, Massillon L, Follett P, Jensen FE, Ratan R, et al. 2003. Activation of innate immunity in the CNS triggers neurodegeneration through a Toll-like receptor 4–dependent pathway. *PNAS* 100:8514–19
120. Delgado R, Carlin A, Airaghi L, Demitri MT, Meda L, et al. 1998. Melanocortin peptides inhibit production of proinflammatory cytokines and nitric oxide by activated microglia. *J. Leukoc. Biol.* 63:740–45
121. Goncalves J, Ribeiro CF, Malva JO, Silva AP. 2012. Protective role of neuropeptide Y $Y_2$ receptors in cell death and microglial response following methamphetamine injury. *Eur. J. Neurosci.* 36:3173–83
122. Ferreira R, Santos T, Viegas M, Cortes L, Bernardino L, et al. 2011. Neuropeptide Y inhibits interleukin-1β-induced phagocytosis by microglial cells. *J. Neuroinflamm.* 8:169
123. Oh IS, Thaler JP, Ogimoto K, Wisse BE, Morton GJ, Schwartz MW. 2010. Central administration of interleukin-4 exacerbates hypothalamic inflammation and weight gain during high-fat feeding. *Am. J. Physiol. Endocrinol. Metab.* 299:E47–53
124. Amano SU, Cohen JL, Vangala P, Tencerova M, Nicoloro SM, et al. 2014. Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation. *Cell Metab.* 19:162–71
125. Ito A, Suganami T, Yamauchi A, Degawa-Yamauchi M, Tanaka M, et al. 2008. Role of CC chemokine receptor 2 in bone marrow cells in the recruitment of macrophages into obese adipose tissue. *J. Biol. Chem.* 283:35715–23
126. Varvel NH, Grathwohl SA, Baumann F, Liebig C, Bosch A, et al. 2012. Microglial repopulation model reveals a robust homeostatic process for replacing CNS myeloid cells. *PNAS* 109:18150–55

**127. Elmore MR, Najafi AR, Koike MA, Dagher NN, Spangenberg EE, et al. 2014. Colony-stimulating factor 1 receptor signaling is necessary for microglia viability, unmasking a microglia progenitor cell in the adult brain. *Neuron* 82:380–97**

**127. This landmark study determines that microglia require CSF1 receptor signaling to maintain their viability and their numbers within the brain, identifying a promising strategy to manipulate microglial content in specific brain areas for therapeutic purposes.**

128. Lafrance V, Inoue W, Kan B, Luheshi GN. 2010. Leptin modulates cell morphology and cytokine release in microglia. *Brain Behav. Immun.* 24:358–65
129. Tang CH, Lu DY, Yang RS, Tsai HY, Kao MC, et al. 2007. Leptin-induced IL-6 production is mediated by leptin receptor, insulin receptor substrate-1, phosphatidylinositol 3-kinase, Akt, NF-κB, and p300 pathway in microglia. *J. Immunol.* 179:1292–302
130. Yi CX, Al-Massadi O, Donelan E, Lehti M, Weber J, et al. 2012. Exercise protects against high-fat diet–induced hypothalamic inflammation. *Physiol. Behav.* 106:485–90
131. Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, et al. 2008. The NALP3 inflammasome is involved in the innate immune response to amyloid-β. *Nat. Immunol.* 9:857–65
132. Hanamsagar R, Torres V, Kielian T. 2011. Inflammasome activation and IL-1β/IL-18 processing are influenced by distinct pathways in microglia. *J. Neurochem.* 119:736–48
133. Youm YH, Grant RW, McCabe LR, Albarado DC, Nguyen KY, et al. 2013. Canonical Nlrp3 inflammasome links systemic low-grade inflammation to functional decline in aging. *Cell Metab.* 18:519–32
134. Sofroniew MV, Vinters HV. 2010. Astrocytes: biology and pathology. *Acta Neuropathol.* 119:7–35
135. Oberheim NA, Wang X, Goldman S, Nedergaard M. 2006. Astrocytic complexity distinguishes the human brain. *Trends Neurosci.* 29:547–53
136. Kim JG, Suyama S, Koch M, Jin S, Argente-Arizon P, et al. 2014. Leptin signaling in astrocytes regulates hypothalamic neuronal circuits and feeding. *Nat. Neurosci.* 17:908–10
137. Fuente-Martin E, Garcia-Caceres C, Granado M, de Ceballos ML, Sanchez-Garrido MA, et al. 2012. Leptin regulates glutamate and glucose transporters in hypothalamic astrocytes. *J. Clin. Investig.* 122:3900–13
138. Garcia-Caceres C, Fuente-Martin E, Burgos-Ramos E, Granado M, Frago LM, et al. 2011. Differential acute and chronic effects of leptin on hypothalamic astrocyte morphology and synaptic protein levels. *Endocrinology* 152:1809–18
139. Garcia-Caceres C, Yi CX, Tschop MH. 2013. Hypothalamic astrocytes in obesity. *Endocrinol. Metab. Clin. N. Am.* 42:57–66
140. Levin BE, Magnan C, Dunn-Meynell A, Le Foll C. 2011. Metabolic sensing and the brain: who, what, where, and how? *Endocrinology* 152:2552–57
141. Shen L, Tso P, Wang DQ, Woods SC, Davidson WS, et al. 2009. Up-regulation of apolipoprotein E by leptin in the hypothalamus of mice and rats. *Physiol. Behav.* 98:223–28
142. Blazquez C, Sanchez C, Velasco G, Guzman M. 1998. Role of carnitine palmitoyltransferase I in the control of ketogenesis in primary cultures of rat astrocytes. *J. Neurochem.* 71:1597–606
143. Marino JS, Xu Y, Hill JW. 2011. Central insulin and leptin-mediated autonomic control of glucose homeostasis. *Trends Endocrinol. Metab.* 22:275–85
144. Gupta S, Knight AG, Gupta S, Keller JN, Bruce-Keller AJ. 2012. Saturated long-chain fatty acids activate inflammatory signaling in astrocytes. *J. Neurochem.* 120:1060–71
145. Saura J. 2007. Microglial cells in astroglial cultures: a cautionary note. *J. Neuroinflamm.* 4:26
146. Minkiewicz J, de Rivero Vaccari JP, Keane RW. 2013. Human astrocytes express a novel NLRP2 inflammasome. *Glia* 61:1113–21
147. Tarallo V, Hirano Y, Gelfand BD, Dridi S, Kerur N, et al. 2012. DICER1 loss and Alu RNA induce age-related macular degeneration via the NLRP3 inflammasome and MyD88. *Cell* 149:847–59

**148. Highlights the emerging role of nonneuronal cells in the neuroendocrine control of systemic metabolism and obesity.**

**148. Lee DA, Bedont JL, Pak T, Wang H, Song J, et al. 2012. Tanycytes of the hypothalamic median eminence form a diet-responsive neurogenic niche. *Nat. Neurosci.* 15:700–2**

149. Bolborea M, Dale N. 2013. Hypothalamic tanycytes: potential roles in the control of feeding and energy balance. *Trends Neurosci.* 36:91–100
150. Frayling C, Britton R, Dale N. 2011. ATP-mediated glucosensing by hypothalamic tanycytes. *J. Physiol.* 589:2275–86
151. Dale N. 2011. Purinergic signaling in hypothalamic tanycytes: potential roles in chemosensing. *Semin. Cell Dev. Biol.* 22:237–44

152. Balland E, Dam J, Langlet F, Caron E, Steculorum S, et al. 2014. Hypothalamic tanycytes are an ERK-gated conduit for leptin into the brain. *Cell Metab.* 19:293–301
153. Nadeau S, Rivest S. 1999. Effects of circulating tumor necrosis factor on the neuronal activity and expression of the genes encoding the tumor necrosis factor receptors (p55 and p75) in the rat brain: a view from the blood-brain barrier. *Neuroscience* 93:1449–64
154. Nishibori M, Nakaya N, Mori S, Saeki K. 1997. Immunohistochemical localization of macrophage migration inhibitory factor (MIF) in tanycytes, subcommissural organ and choroid plexus in the rat brain. *Brain Res.* 758:259–62
155. Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, et al. 2001. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of *Ikkβ*. *Science* 293:1673–77
156. Stanley TL, Zanni MV, Johnsen S, Rasheed S, Makimura H, et al. 2011. TNF-α antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. *J. Clin. Endocrinol. Metab.* 96:E146–50
157. Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. 2011. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. *JAMA* 305:2525–31
158. Sauter NS, Schulthess FT, Galasso R, Castellani LW, Maedler K. 2008. The antiinflammatory cytokine interleukin-1 receptor antagonist protects from high-fat diet–induced hyperglycemia. *Endocrinology* 149:2208–18
159. Osborn O, Brownell SE, Sanchez-Alavez M, Salomon D, Gram H, Bartfai T. 2008. Treatment with an Interleukin 1 beta antibody improves glycemic control in diet-induced obesity. *Cytokine* 44:141–48
160. Larsen CM, Faulenbach M, Vaag A, Volund A, Ehses JA, et al. 2007. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. *N. Engl. J. Med.* 356:1517–26
161. Howard JK, Cave BJ, Oksanen LJ, Tzameli I, Bjorbaek C, Flier JS. 2004. Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of Socs3. *Nat. Med.* 10:734–38
162. Howard JK, Flier JS. 2006. Attenuation of leptin and insulin signaling by SOCS proteins. *Trends Endocrinol. Metab.* 17:365–71
163. Zabolotny JM, Kim YB, Welsh LA, Kershaw EE, Neel BG, Kahn BB. 2008. Protein-tyrosine phosphatase 1B expression is induced by inflammation in vivo. *J. Biol. Chem.* 283:14230–41
164. Sabio G, Cavanagh-Kyros J, Barrett T, Jung DY, Ko HJ, et al. 2010. Role of the hypothalamic-pituitary-thyroid axis in metabolic regulation by JNK1. *Genes Dev.* 24:256–64
165. Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, et al. 2002. A central role for JNK in obesity and insulin resistance. *Nature* 420:333–36
166. Solinas G, Vilcu C, Neels JG, Bandyopadhyay GK, Luo JL, et al. 2007. JNK1 in hematopoietically derived cells contributes to diet-induced inflammation and insulin resistance without affecting obesity. *Cell Metab.* 6:386–97
167. Mori H, Hanada R, Hanada T, Aki D, Mashima R, et al. 2004. Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. *Nat. Med.* 10:739–43
**168. Milanski M, Arruda AP, Coope A, Ignacio-Souza LM, Nunez CE, et al. 2012. Inhibition of hypothalamic inflammation reverses diet-induced insulin resistance in the liver. *Diabetes* 61:1455–62**
169. Minami SS, Sun B, Popat K, Kauppinen T, Pleiss M, et al. 2012. Selective targeting of microglia by quantum dots. *J. Neuroinflamm.* 9:22
170. Zhang G, Li J, Purkayastha S, Tang Y, Zhang H, et al. 2013. Hypothalamic programming of systemic ageing involving IKK-β, NF-κB and GnRH. *Nature* 497:211–16
171. Frakes AE, Ferraiuolo L, Haidet-Phillips AM, Schmelzer L, Braun L, et al. 2014. Microglia induce motor neuron death via the classical NF-κB pathway in amyotrophic lateral sclerosis. *Neuron* 81:1009–23
172. Parkhurst CN, Yang G, Ninan I, Savas JN, Yates JR 3rd, et al. 2013. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell* 155:1596–609
**173. Goldmann T, Wieghofer P, Muller PF, Wolf Y, Varol D, et al. 2013. A new type of microglia gene targeting shows TAK1 to be pivotal in CNS autoimmune inflammation. *Nat. Neurosci.* 16:1618–26**

**168. Shows that chemically blocking hypothalamic, TNF-α-driven inflammation within the hypothalamus in the setting of diet-induced obesity improves hepatic insulin action in mice and reduces both hepatic steatosis and glucose production.**

**173. The first published work describing the utility of Cx3CR1-Cre ER mice in permitting genetic targeting solely in microglia without impacting gene expression in peripheral myeloid cell types.**

174. Tesz GJ, Aouadi M, Prot M, Nicoloro SM, Boutet E, et al. 2011. Glucan particles for selective delivery of siRNA to phagocytic cells in mice. *Biochem. J.* 436:351–62
175. Aouadi M, Tencerova M, Vangala P, Yawe JC, Nicoloro SM, et al. 2013. Gene silencing in adipose tissue macrophages regulates whole-body metabolism in obese mice. *PNAS* 110:8278–83
176. Ladeby R, Wirenfeldt M, Garcia-Ovejero D, Fenger C, Dissing-Olesen L, et al. 2005. Microglial cell population dynamics in the injured adult central nervous system. *Brain Res. Brain Res. Rev.* 48:196–206
177. Flugel A, Berkowicz T, Ritter T, Labeur M, Jenne DE, et al. 2001. Migratory activity and functional changes of green fluorescent effector cells before and during experimental autoimmune encephalomyelitis. *Immunity* 14:547–60
178. Hanisch UK, Kettenmann H. 2007. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat. Neurosci.* 10:1387–94
179. Buckman LB, Hasty AH, Flaherty DK, Buckman CT, Thompson MM, et al. 2014. Obesity induced by a high-fat diet is associated with increased immune cell entry into the central nervous system. *Brain Behav. Immun.* 35:33–42
180. Ajami B, Bennett JL, Krieger C, Tetzlaff W, Rossi FM. 2007. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. *Nat. Neurosci.* 10:1538–43
181. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. 1999. Rett syndrome is caused by mutations in X-linked *MECP2*, encoding methyl-CpG-binding protein 2. *Nat. Genet.* 23:185–88
182. Van den Veyver IB, Zoghbi HY. 2001. Mutations in the gene encoding methyl-CpG-binding protein 2 cause Rett syndrome. *Brain Dev.* 23(Suppl. 1):147–51
183. Lioy DT, Garg SK, Monaghan CE, Raber J, Foust KD, et al. 2011. A role for glia in the progression of Rett's syndrome. *Nature* 475:497–500
184. Derecki NC, Cronk JC, Lu Z, Xu E, Abbott SB, et al. 2012. Wild-type microglia arrest pathology in a mouse model of Rett syndrome. *Nature* 484:105–9