MECHANISMS IN ENDOCRINOLOGY

Hypothalamic inflammation and nutrition

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Abstract

Selected subpopulations of hypothalamic neurons play important roles in the regulation of whole body energy homeostasis. Studies have shown that the saturated fats present in large amounts in western diets can activate an inflammatory response in the hypothalamus, affecting the capacity of such neurons to respond appropriately to satiety and adipostatic signals. In the first part of this review, we will explore the mechanisms behind saturated fatty acid-induced hypothalamic dysfunction. Next, we will present and discuss recent studies that have identified the mechanisms that mediate some of the anti-inflammatory actions of unsaturated fatty acids in the hypothalamus and the potential for exploring these mechanisms to prevent or treat obesity.

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Introduction

Food intake and energy expenditure are controlled by specialized neurons of the hypothalamus that respond to adipostatic and satiety factors present in the circulation (1, 2, 3). Leptin provides the most robust adipostatic signals, whereas insulin, cholecystokinin, ghrelin, glucagon-like peptide-1 (GLP1), and a number of nutrients act as modulators of the activity of such neurons (4, 5, 6, 7).

The balanced activity of hypothalamic neurons is important for maintaining body mass stability over time (2, 3). However, studies have shown that the increased dietary consumption of saturated fats can disturb this system, leading to a progressive increase in anabolism, which results in obesity (8, 9, 10).

Long-chain saturated fats are commonly found in occidental diets and their negative impact on cardiovascular diseases has been extensively reported (11, 12). More

recently, studies have shown that saturated fats can induce an inflammatory response in the hypothalamus, leading to progressive damage of the neurons that control food intake and energy expenditure (13, 14, 15, 16, 17). Here, we review the data that place dietary fats as important inducers of hypothalamic inflammation and dysfunction in obesity. In addition, we present studies that support a potential beneficial role of polyunsaturated fatty acids (PUFAs) as anti-inflammatory agents that protect the hypothalamus from diet-induced inflammation.

Hypothalamic leptin resistance is an important feature of obesity

The identification of leptin in 1994 (18) created great expectations regarding the potential use of recombinant

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leptin as a pharmacological approach to treating obesity. However, most humans with obesity are hyperleptinemic, and exogenous leptin promotes only minor changes in body mass (19, 20). Taken together, experimental and clinical studies revealed that most obese subjects and animal models of diet-induced obesity are resistant to the adipostatic actions of leptin (21, 22, 23). However, defining leptin resistance and identifying the mechanisms behind its development have been a matter of intense investigation and discussion (24, 25). First, defining leptin resistance simply as a biological phenomenon characterized by the reduced capacity of leptin to inhibit food intake and promote body mass loss may lead to a conceptual misunderstanding. For example, the rather common genetic defects of *MCR4* do not produce an impairment of leptin signal transduction but results in the impaired feeding response to leptin (26). A similar concept can be employed for all causes of obesity that arise from defects that are downstream to the early elements of the leptin pathway or affect signaling pathways other than the leptin signaling system (25). Nevertheless, it is currently accepted that in most cases of obesity, leptin resistance plays an important mechanistic role (24). Early attempts to characterize the mechanisms behind leptin resistance identified SOCS3 (suppressor of cytokine signaling-3) as a negative modulator of the leptin signal that is induced in hypothalamic neurons in response to leptin stimulation (27). Leptin-induced SOCS3 binds to JAK2 (Janus kinase-2) and inhibits downstream leptin signal transduction without affecting the expression of the leptin receptor, OBRB (27). Moreover, SOCS3 deficiency in the brain increases leptin sensitivity and protects mice from diet-induced obesity (28, 29). Therefore, SOCS3 is an important mechanism involved in the development of leptin resistance in hyperleptinemic states (30). However, in most cases of obesity, hyperleptinemia develops in parallel with body mass gain and is expected to become a relevant phenomenon at later stages of obesity.

To explore the early mechanisms involved in the development of hypothalamic leptin resistance, studies have evaluated the effects of high-fat diets in the hypothalamus. Great advance in the field has been provided by the demonstration that dietary fats can induce the expression of inflammatory proteins, particularly tumor necrosis factor- α (TNF α) and interleukin-1 β (IL1 β), in the hypothalamus (13). Long-chain saturated fatty acids trigger hypothalamic inflammation by inducing the activation of toll-like receptor-4 (TLR4) signaling in microglia (15). Inflammatory cytokines released by

microglia in the hypothalamic microenvironment induce the expression of CX3CL1 (fractalkine) by neurons (31). Fractalkine produced in this context recruits peripheral monocytes to potentiate and perpetuate hypothalamic inflammation (31). An important aspect of diet-induced hypothalamic inflammation is that intracellular serine/threonine kinases activated in response to inflammatory signals can target and inhibit key proteins of the leptin and insulin signaling systems, therefore establishing a mechanistic link between hypothalamic inflammation and the resistance to adipostatic signals (25).

Defining hypothalamic inflammation in obesity

Obesity-associated hypothalamic inflammation occurs in two phases, as in most inflammatory processes in the body (17, 32, 33). As classically defined, the first phase occurs early after exposure to the antigen and involves recruitment of inflammatory cells and local production of chemokines and cytokines; upon elimination of the threatening antigen, the second phase, or resolution phase, provides an appropriate environment to gradually return to homeostasis (17, 32, 33). When the antigenic stimulus persists, the transition from first to second phase can be disturbed leading to chronicity and eventually to functional loss (17, 32, 33). In the case of obesity-associated hypothalamic inflammation, the first wave of inflammatory activity is detected as early as 1 day after the introduction of large amount of dietary fats (17). The intensity of inflammation is greatly reduced during week 2 and 3, and only to return after 3–4 weeks with much higher intensity (17). Upon persistence of feeding on a high-fat diet (HFD), hypothalamic inflammation is enhanced (thus, characterizing a disturbance in resolution phase) by the activation of additional mechanisms, such as endoplasmic reticulum stress (ERS) and protein kinase-C- θ (PKC θ) (14, 16, 34), which in the long run will play important roles in the inflammatory-associated damage of the hypothalamus.

In experimental diet-induced obesity, the fat composition of the diets is complex, and identifying the types of fatty acids with the highest pro-inflammatory activity in the hypothalamus could help to design the most appropriate dietary approaches to preventing and treating obesity. The screening for pro- and anti-inflammatory effects of fatty acids injected directly into the hypothalamus revealed that stearate (C18:0), arachidate (C20:0), and behenic acid (C22:0) were

the ones with the most potent inflammatory activity, inducing the increased hypothalamic expression of TNF α and IL1 β (15). Conversely, oleic acid (C18:1) and linolenic acid (C18:3) exerted the most potent anti-inflammatory activity, inducing the expression of interleukin-10 (IL10) and interleukin-6 (IL6) in the hypothalamus (15). Both genetic and pharmacological inhibition of TLR4 is capable of reducing the inflammatory activity of saturated fats in the hypothalamus (15, 35). Moreover, the inhibition of TLR4 can also attenuate diet-induced ERS, suggesting that TLR4 is upstream of ERS in obesity-associated hypothalamic inflammation (15). However, studies have demonstrated that ERS is also an important component of the inflammatory activity of the hypothalamus in obese animals and the inhibition of ERS with chemical chaperones is capable of reducing the impact of dietary fats in the anomalous regulation of hypothalamic neurons involved in energy homeostasis (16, 36). Figure 1 shows a current view of the mechanism and cells involved in diet-induced hypothalamic inflammation.

It is noteworthy that not only fatty acids present in the diet can trigger hypothalamic inflammation. Studies have shown that diets rich in carbohydrates can also, under certain experimental conditions, activate hypothalamic inflammation. For example, a sucrose-rich diet can induce hypothalamic inflammation without astrogliosis, but the extent of inflammation and its association with obesity depends on the period of life when diet is introduced (37). Another study has shown that a fructose-rich diet can induce the activation of inflammatory markers, particularly fractalkine and its receptor in the hypothalamus of rodents, a response that involves microglia and astrocytes (38). In the future, it will be important to define if the effects of dietary carbohydrates to induce hypothalamic inflammation are direct or involve intermediates such as the increased peripheral synthesis of fatty acids.

Chronic diet-induced hypothalamic inflammation disrupts neuronal circuitries involved in whole-body energy homeostasis

Most obese humans seeking medical and nutritional attention to control adiposity fail to maintain body mass reduction for prolonged periods (39, 40, 41). Even patients submitted to bariatric surgery present some body mass regain years after surgery (42). Thus, it seems that long-term obesity results in a resetting of the hypothalamic adipostat, as proposed previously (1, 43). Experimental studies have shown that upon prolonged feeding on an HFD, hypothalamic neurons may undergo severe damage that may result in apoptosis (17, 44). Interestingly, at least three distinct studies have identified POMC (proopiomelanocortin) neurons as the main targets of inflammation-associated apoptosis (17, 44, 45). Progressive reduction in hypothalamic POMC neuron population results in an imbalance in POMC/NPY (neuropeptide Y) neurons, which may provide a cellular basis for explaining the resetting of the hypothalamic adipostat.

Several studies have explored the effects of long-term diet-induced obesity on hypothalamic function (13, 14, 15, 16, 17, 44, 46, 47). Dysfunctions of different aspects of the protein homeostasis (proteostasis) machinery have emerged as important mechanisms contributing to hypothalamic neuronal damage. Proteostasis is a process through which cells maintain proteins in an adequate functional state (48). Because of the multiplicity of mechanisms involved in the synthesis, sorting, folding, and degradation of proteins, proteostasis is a complex function for any cell to perform (49). Despite the fact that the amino acid sequence is important to the function of a protein, only when proteins are appropriately folded, they do become fully functional (50). In eukaryotic cells, some subcellular compartments have evolved to

Figure 1

Dietary fats induce hypothalamic inflammation. Long-chain saturated fats present in the diet act through toll-like receptor 4 (TLR4), endoplasmic reticulum stress (ERS), and protein kinase C α (PKC α) in the hypothalamus to promote the dysfunction of key neurons involved in the response to satiety and adipostatic factors and, thus, predisposing to obesity.

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create proper environments that are conducive to correct protein folding (50). As a whole, this system is known as the proteostasis network (51).

Both the consumption of large amounts of dietary fats and the process of aging can induce the expression of transforming growth factor-beta (TGF β) by hypothalamic astrocytes (52). Upon its release from the astrocytes, TGF β activates TGF β R2 in POMC neurons, inducing the formation of RNA stress granules that affect proteostasis by modifying the rate of translation of certain proteins (52). In the case of obesity and aging, stress granules in POMC neurons induce the activation of nuclear factor kappa B (NF κ B) signaling, leading to the dysfunction of POMC neuron activity. An important outcome of this process is that the hypothalamus can no longer exert appropriate control on hepatic gluconeogenesis (52). Thus, an early defect in a mechanism tightly connected to neuronal proteostasis can contribute to glucose intolerance through a connection between the hypothalamus and the liver (52, 53).

Dietary fats can also affect proteostasis by inducing ERS in hypothalamic neurons (14, 15, 16). The ER is the organelle responsible for translating and folding up to 30% of membrane and secretory proteins (54). Dietary fats can act either directly or indirectly to induce ERS (55). Early studies have shown that an overload of nutrients, including lipids, can be sensed by the ER, leading to the activation of the unfolded protein response (56, 57). This process was initially identified in peripheral tissues that are targets for insulin action (56, 57). Later, it was shown that it also occurs in the hypothalamus, contributing to the development of leptin resistance (14, 15, 16). In addition, TLR4 activated in response to dietary fat overload provides additional signals that potentiate ERS in distinct tissues, including the hypothalamus (15, 58). During early induction of ERS, there are stimuli to increase the expression of chaperones that aim to re-establish ER homeostasis (55, 59). However, the persistence of the exposure to dietary fats accentuates ERS, leading to the activation of inflammatory signaling and eventually to apoptosis (55, 59).

If, on one hand, transcription and folding are important steps involved in proteostasis because they load the cell's proteome, on the other hand, there are mechanisms involved in the removal and recycling of old and misfolded proteins in order to avoid the accumulation of cargo that could damage the integrity of the cell (48). At least two of these mechanisms have been evaluated in the hypothalamus for experimental models of obesity: the ubiquitin/proteasome system and autophagy.

A recent study has employed a real-time PCR array to evaluate the impact of dietary fat consumption on the expression of transcripts encoding hypothalamic proteins involved in the ubiquitin/proteasome system (UPS) (46). As a whole, the UPS is responsible for the degradation of up to 80% of short-lived proteins in any cell of the body (60). The targeting of proteins for degradation depends on the action of a complex enzymatic system that activates ubiquitin molecules to be bonded to certain lysine residues in the target protein (61). Once ubiquitinated, proteins are sorted for degradation by the proteasome (61). In the hypothalamus of obese rodents, up to 15% of the proteins involved in the UPS are somehow modulated (46). This results in drastic changes in the amount of ubiquitinated proteins and proteasome in hypothalamic neurons (46). The longer the exposure to dietary fats, the more the UPS is affected, suggesting that the consumption of large amounts of dietary fats exerts a time-dependent effect that damages the UPS in key hypothalamic neurons, which impacts whole-body energy homeostasis (46).

The UPS is capable of degrading most peptides and noncomplex proteins (60); however, large protein complexes and anomalous protein aggregates frequently escape from the UPS and end up being degraded by autophagy (62). Lean mice present constitutive autophagy in hypothalamic neurons (46, 47). However, upon high-fat feeding, the autophagic activity in the medium-basal hypothalamus is severely impaired (46, 47, 63). The inhibition of hypothalamic autophagy in lean mice is capable of inducing increased caloric intake and obesity, which is accompanied by the activation of hypothalamic inflammation through the NF κ B signaling pathway (47). Interestingly, manipulation of autophagy in different subsets of neurons of the medium-basal hypothalamus produces different phenotypic outcomes. When autophagy is inhibited in AgRP neurons, mice eat less and are lean (64), whereas when autophagy is inhibited in POMC neurons, mice eat more and are obese (65, 66). Thus, it seems that the regulation of autophagy in response to dietary stimuli is an important mechanism involved in the control of whole-body energy homeostasis. In fact, it has been proposed that autophagy functions in parallel with malonyl-CoA and PKC α as lipid sensors in the hypothalamus (67).

Polyunsaturated fatty acids and the repair of diet-induced hypothalamic damage

Epidemiological studies have provided undisputed evidence for the beneficial role of dietary PUFAs in

cardiovascular diseases (68, 69). Most of the beneficial effects of PUFAs have been attributed to their anti-inflammatory properties (70), and studies carried out over the last 40 years have identified distinct mechanisms by which PUFAs can attenuate inflammation (70, 71, 72, 73, 74). Among the many systemic effects of PUFAs, the attenuation of insulin resistance has emerged as an important factor that could explain the long-term metabolic benefits of this class of dietary lipids (75, 76). However, it was only in 2010 that a great advancement was made in this field with the identification of an atypical mechanism by which PUFAs reduce metabolic inflammation and attenuate insulin resistance (73).

Upon binding to GPR120, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) can activate an atypical signaling pathway that impairs $\text{TNF}\alpha$ - and TLR4-dependent activation of c-Jun N terminal kinase (JNK) and $\text{NF}\kappa\text{B}$ (73). GPR120 belongs to a large family of G-protein-coupled receptors (73); upon ligand binding, GPR120 recruits and binds to β -arrestin-2, which is essential for the anti-inflammatory actions of the receptor. When β -arrestin-2 is bound to GPR120, it sequesters TAB1 preventing its interaction with TAK, an important intermediary in the pro-inflammatory actions triggered by the activation of the $\text{TNF}\alpha$ receptor and TLR4 (73). In systemic insulin resistance, both PUFAs, which act as natural ligands for GPR120, and a pharmacological compound with high affinity for the receptor were capable of reducing metabolic inflammation and attenuating glucose intolerance (73). The recent development of a small molecule capable of activating GPR120 and reducing glucose intolerance in an animal model of diabetes placed this receptor in a strategic position as a potential target for the treatment of metabolic diseases (77).

PUFAs can also attenuate hypothalamic inflammation in animal models of obesity (78). In diet-induced obesity, the dietary substitution of lard with either flaxseed or olive oil resulted in reduced caloric intake and reduced body mass gain (78). These effects were accompanied by the reduced expression of inflammatory cytokines in the hypothalamus and improved whole body glucose tolerance (78). To test the hypothesis that the beneficial effects of PUFAs were due to direct action in the hypothalamus, obese mice were treated by injections of pure preparations of either oleic or linolenic acids in the hypothalamus and a number of inflammatory and metabolic parameters were evaluated. Both unsaturated fatty acids injected in the hypothalamus were capable of reducing food intake and reducing body mass gain. This was accompanied by the reduction of hypothalamic inflammation and

a reduced expression of pro-apoptotic markers (78). As expected, the reduction of hypothalamic inflammation was accompanied by the attenuation of leptin resistance and by the increased expression of POMC (78). Similar to the effects of PUFAs on adipose tissue and the liver, oleic and linolenic acids were capable of activating GPR120 and inhibiting the inflammatory recruitment of TAB1 in the hypothalamus (78).

The capacity of PUFAs to induce hypothalamic neurogenesis has recently been emerged as another important aspect of their beneficial actions in the hypothalamus (79). The dietary substitution of saturated fats with unsaturated fats was capable of increasing neurogenesis in the hypothalamus of obese mice (79). Even in lean mice, increased dietary consumption of

Figure 2

Unsaturated fats trigger anti-inflammatory and neurogenic signals in the hypothalamus. Saturated fats trigger inflammatory signaling in the hypothalamus, which on the long run can induce apoptosis of neurons involved in the response to satiety and adipostatic signals. Dietary polyunsaturated fatty acids (PUFAs) can act through GPR120 to inhibit diet-induced hypothalamic inflammation and through GPR40 to induce the neurogenesis of key hypothalamic neurons involved in the control of food intake and energy expenditure. These hypothalamic actions of PUFAs are expected to result in beneficial effects in the control of obesity and metabolic disorders.

Figure 3

An integrated view of the pro- and anti-inflammatory effects of dietary fats in the hypothalamus. Dietary fats reach the hypothalamus through the bloodstream. The saturated fats (A) can induce inflammation by triggering toll-like receptors (endoplasmic reticulum stress and atypical protein kinase C are also involved but are not shown in this figure). Upon activation of the inflammatory response, intracellular serine-threonine kinases, such as JNK and NFκB, are activated and induce the expression of additional inflammatory molecules. The induction of SOCS3 is one of the mechanisms inducing leptin resistance. Persistent inflammation can eventually lead to neuronal apoptosis. Conversely, unsaturated fats (B) can act through GPR40 and GPR120 to attenuate inflammation by inhibiting TAK1-dependent activation of JNK and NFκB. This, in turn, alleviates saturated fatty acid-induced neuronal damage.

PUFAs resulted in a trend of increasing hypothalamic neurogenesis. When injected directly in the hypothalamus, DHA induced neurogenesis at levels superior to brain-

derived neurotrophic factor (BDNF), a well-known stimulator of neurogenesis (79, 80).

The characterization of the mechanisms involved in DHA-induced hypothalamic neurogenesis revealed GPR40 as the receptor mediating at least part of the effects of PUFAs (79). GPR40 expression in the hypothalamus is induced by PUFAs, leading to an increase in hypothalamic BDNF expression and the stimulation of neurogenesis. The pharmacological inhibition of GPR40 reduces hypothalamic BDNF expression and impairs DHA-induced hypothalamic neurogenesis. Interestingly, most of the newborn neurons stimulated by DHA express the anorexigenic neurotransmitter POMC (79). Nevertheless, it is important to mention that because obesity increases with aging, physiological, age-dependent impairment of neurogenesis can impact negatively on mechanisms that promote neurogenesis at younger ages. In concert, a recent study has shown that aging, even independently of obesity, can induce an inflammatory response in the hypothalamus that affects the hypothalamic neurogenic niche (81). In the future, it will be important to evaluate if nutritional factors can attenuate or even revert the antineurogenic effects of aging. Figure 2 provides a current view of the mechanisms involved in the beneficial effects of PUFA in the hypothalamus.

Concluding remarks

Dietary fats are important determinants of the activity of hypothalamic neurons involved in the control of food intake and energy expenditure. Early studies showed that the regulatory actions of dietary fats depend on their metabolism in selected hypothalamic neuronal subpopulations (7, 82). However, it is currently known that dietary saturated fats can exert a direct effect on the function of hypothalamic neurons by inducing an inflammatory response through the activation of TLR4 and ERS (15, 16). Intracellular kinases activated in response to dietary fats can impair the responsiveness of hypothalamic neurons to satiety and adipostatic factors, causing a predisposition to obesity. Moreover, dietary fats can chronically induce apoptosis of key hypothalamic neurons, which may contribute to the common recurrence of obesity.

Aside from the damaging effects that saturated fats exert on hypothalamic neurons, studies have shown that PUFAs can reduce diet-induced hypothalamic inflammation and also promote the recovery of key neuronal subpopulations by inducing neurogenesis.

Therefore, hypothalamic signaling pathways responsive to PUFAs emerge as attractive targets for both nutritional and pharmacological approaches aimed at treating obesity. Figure 3 shows an integrated view summarizing our current understanding of the pro-, and anti-inflammatory actions of dietary fats in the hypothalamus.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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