Glial cells and energy balance

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Abstract

The search for new strategies and drugs to abate the current obesity epidemic has led to the intensification of research aimed at understanding the neuroendocrine control of appetite and energy expenditure. This intensified investigation of metabolic control has also included the study of how glial cells participate in this process. Glia, the most abundant cell type in the central nervous system, perform a wide spectrum of functions and are vital for the correct functioning of neurons and neuronal circuits. Current evidence indicates that hypothalamic glia, in particular astrocytes, tanycytes and microglia, are involved in both physiological and pathophysiological mechanisms of appetite and metabolic control, at least in part by regulating the signals reaching metabolic neuronal circuits. Glia transport nutrients, hormones and neurotransmitters; they secrete growth factors, hormones, cytokines and gliotransmitters and are a source of neuroprogenitor cells. These functions are regulated, as glia also respond to numerous hormones and nutrients, with the lack of specific hormonal signaling in hypothalamic astrocytes disrupting metabolic homeostasis. Here, we review some of the more recent advances in the role of glial cells in metabolic control, with a special emphasis on the differences between glial cell responses in males and females.

Key Words
- hypothalamic inflammation
- gliosis
- high-fat diet
- sexual dimorphism

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Introduction

Glial cells play an active role in numerous physiological processes including neurogenesis, synaptogenesis and synaptic plasticity; they transport nutrients and metabolic factors essential for neuronal survival and function from the periphery into the brain and participate in synaptic transmission (Tsacopoulos & Magistretti 1996, Kacem *et al*. 1998, Vesce *et al*. 1999). Glial cells are also the first line of defense in the central nervous system (CNS) highlighting the role of microglial cells in processes such as neuroinflammation and brain injury (Loane & Kumar 2016) and contribute to the maintenance of the blood–brain barrier (BBB) (Nakagawa *et al*. 2009, Abbott *et al*. 2010). Although glial cells throughout the CNS share many common functions, some of their responses/outputs vary, both between and within anatomical regions of the brain (Oberheim *et al*. 2012). These functional differences are most likely due to innate differences in glial populations, although we currently do not have sufficient information regarding this aspect, and due to their neuronal environment. That is, the physiological functions affected by glial cell activity are invariably linked to the output of the neurons in their local network.

Studies indicating that the activation of hypothalamic glial cells in response to high-fat diet (HFD) intake is involved in central inflammation and insulin resistance have drawn increasing attention to the role that these cells play in metabolic control (Thaler *et al*. 2012, Buckman *et al*. 2013, Valdearcos *et al*. 2014).

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This HFD-induced inflammatory reaction specifically involves the hypothalamus (De Souza *et al*. 2005, Thaler *et al*. 2012, Wang *et al*. 2012, Berkseth *et al*. 2014), the key site for the regulation of energy balance. Indeed, numerous studies in animals have shown evidence of inflammation/gliosis in response to HFD (Thaler *et al*. 2012, Buckman *et al*. 2014, Valdearcos *et al*. 2014), whereas this has also been reported to occur in humans with an elevated body mass index (BMI) (Thaler *et al*. 2012). However, hypothalamic glial cells not only participate in pathological events, such as the inflammatory response that occurs as a consequence of HFD consumption (Milanski *et al*. 2009, Thaler *et al*. 2012, Buckman *et al*. 2014, Valdearcos *et al*. 2014, Yan *et al*. 2014), but they are also intricately involve in the physiological control of the surrounding neurons, including those dictating energy balance. The importance of this relationship is even further emphasized by the fact that these glial cells express receptors and systems of transport for numerous metabolic hormones and factors (Boyles *et al*. 1985, Vielkind *et al*. 1990, Zhu *et al*. 1990, Vannucci *et al*. 1997, Marty *et al*. 2005, Pan *et al*. 2008, Hsuchou *et al*. 2009, Baquedano *et al*. 2013), suggesting that at least part of the central effects of these metabolic signals are mediated through these non-neuronal cells. Thus, a deeper understanding of glial cell function will allow both a better understanding of their role in normal brain physiology, as well as their participation in pathological processes, and hopefully lead to the identification of new therapeutic targets for obesity treatment.

It is important to remember that the responses of males and females to obesity and its secondary complications are different (Palmer & Clegg 2015). This is at least partially due to the influence of sex steroids, as the decline in estrogen levels that occurs in postmenopausal women is associated with an increased propensity to accumulate fat mass and the development of obesity-associated diseases compared to premenopausal women (Gambacciani *et al*. 1997). Unfortunately, most studies analyzing the glial response to obesity and HFD have been performed exclusively in males; thus, little is known as to whether sex differences in the hypothalamic glial response to metabolic cues are involved in the different propensities of males and females to develop obesity and its comorbidities. This possibility is suggested by the fact that glial cells present sexually dimorphic characteristics and responses, with these differences being at least partially due to the influence of sex steroids (Chowen *et al*. 1995, Melcangi *et al*. 2001, Acaz-Fonseca *et al*. 2016). Indeed, astrocytes express receptors for estrogens, androgens and progesterone (Pfaff & Keiner 1973, Garcia-Segura *et al*. 1996*b*, Melcangi *et al*. 2001, Garcia-Ovejero *et al*. 2005) and sex steroids are reported to modulate the glial response to HFD (Louwe *et al*. 2012, Morselli *et al*. 2014). Sex steroids exert neuroprotective effects in various brain regions, with glial cells participating in this phenomenon (Azcoitia *et al*. 2003, Garcia-Ovejero *et al*. 2005, Barreto *et al*. 2009, Ghorbanpoor *et al*. 2014); thus, it is possible that sex hormones could protect against the deleterious effects of HFD-induced obesity on hypothalamic metabolic neuronal circuits by actions on the neighboring glia.

Here, we will review some of the current areas of interest regarding glial cell involvement in metabolic control. In addition, special emphasis will be placed on what is known regarding the differential responses of glial cells from males and females to metabolic signals.

Glial cells in metabolic control

Glia are the most abundant cell type in the CNS and are classified as microglia or macroglia, with the latter including astrocytes, tanycytes, oligodendrocytes and ependymal cells. Among these, microglia, astrocytes and tanycytes have been most clearly implicated in metabolic control, with some of their functions being summarized in Fig. 1.

Astrocytes in metabolic control

Astrocytes, the most bountiful cells within the brain, are clearly implicated in the physiological and pathophysiological control of metabolism, although the mechanisms by which they do so remain to be fully elucidated. Neuronal protection, maintenance and metabolism, anatomical support, synaptogenesis, synaptic connectivity and transmission, electrolyte and glucose homeostasis and cytokine production are all known functions performed by these 'star-shaped' cells (Nedergaard *et al*. 2003, Clarke & Barres 2013). Together with blood vessels and neurons, astrocytes form a sensing unit that mediates the metabolic communication between the periphery and the CNS. Astrocytes participate, therefore, in the regulation of nutrient entry into the brain, serving as metabolic sensors and promoting neuronal survival and the maintenance of CNS homeostasis (Tsacopoulos & Magistretti 1996, Abbott *et al*. 2010, Wang *et al*. 2014).

In addition to aiding in glucose and lipid sensing (Leloup *et al*. 2016), astrocytes express receptors for and respond to hormones implicated in the control of food

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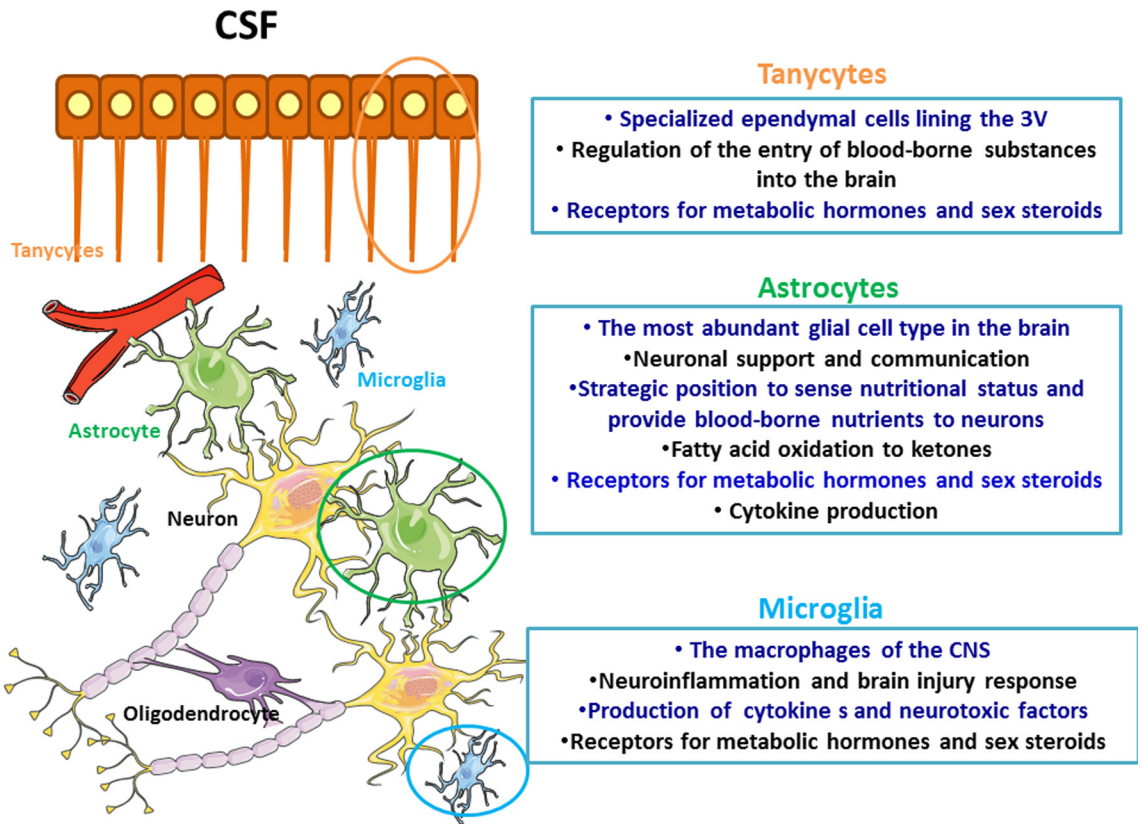

Figure 1
Summary of some of the most relevant functions performed by glial cells in metabolic control. Graphic illustration of the various cell types found in the central nervous system (CNS). Glial cells are the most abundant cell type in the CNS and are involved in both physiology and pathophysiology of energy homeostasis. Amongst glial cells, microglia, astrocytes and tanycytes have been most clearly implicated in metabolic control. 3V, third ventricle; CNS, central nervous system; CSF, cerebrospinal fluid.

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intake, such as leptin, ghrelin and insulin (Diano *et al*. 1998*a*, Hsuchou *et al*. 2009, Baquedano *et al*. 2013, Kim *et al*. 2014). They are the only cells within the CNS able to beta-oxidize fatty acids (FAs) for the production of ketone bodies, which signals to the surrounding neurons. Many of these hormonal and metabolic factors have been shown to modify astrocytic morphology and functions, including their production of cytokines and/or other factors and their transport of nutrients and neurotransmitters (Garcia-Caceres *et al*. 2011, 2016, Gupta *et al*. 2012, Fuente-Martin *et al*. 2013). For example leptin, an important anorexic signal, modifies astrocyte morphology within the hypothalamus by changing the length and number of their primary projections (Garcia-Caceres *et al*. 2011, Kim *et al*. 2014). This is associated with changes in the extension of glial coverage and the number and balance of synaptic inputs on the local metabolic neurons, which in turn affects their functioning and output (Horvath *et al*. 2010, Kim *et al*. 2014). These modifications in astrocyte morphology could participate in the adaptation of hypothalamic neuronal circuits to new metabolic conditions, as seen in the acute stages of HFD consumption (Thaler *et al*. 2012, Buckman *et al*. 2014). However, if an adverse situation extends over time, such as extended HFD intake or long-term obesity, astrocytic modifications could possibly lead to, or be involved in, pathological situations. For example, astroctyes respond to both leptin and ghrelin, but the effects of these hormones on their synthesis and release of cytokines and on glutamate and glucose transport are both time dependent, with short- and long-term exposure often inducing completely opposite effects (Garcia-Caceres *et al*. 2011, Fuente-Martin *et al*. 2012*a*). It should also be kept in mind that cytokine release by astrocytes can have either beneficial or detrimental effects depending on the type, intensity and duration of the stimulus (Choi *et al*. 2014).

The physiological importance of metabolic hormone signaling in astrocytes has been clearly demonstrated by the study of genetically engineered animal models. Ablation of the leptin receptor (Ob-R) specifically in astrocytes modifies the synaptic organization of

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the melanocortin system (Kim *et al*. 2014). Kim and coworkers demonstrated that the number and length of astrocytic primary projections are reduced in the absence of Ob-R, and this is associated with decreased astrocytic coverage of POMC neurons and modifications in the electrical activity of POMC and AgRP neurons (Kim *et al*. 2014). These anatomical and functional changes are associated with the attenuation of the anorexigenic response to leptin and augmentation of the ghrelin-induced response to fasting. Moreover, when mice that specifically lack Ob-R in astrocytes are subjected to HFD, they appear to be resistant to the hyperleptinemia and leptin resistance provoked by diet-induced obesity (Jayaram *et al*. 2013).

More recently, the generation and study of animals lacking the insulin receptor in astrocytes, either throughout the brain or specifically in the mediobasal hypothalamus, indicate that insulin's action on hypothalamic astrocytes is directly involved in systemic glucose sensing (Garcia-Caceres *et al*. 2016). The expression of insulin receptors in astrocytes was shown to be important for the uptake of insulin and glucose into the brain, and in the hypothalamus, the lack of insulin signaling in astrocytes impairs the normal response to changes in glycemia (Garcia-Caceres *et al*. 2016).

Astrocyte activation has also been shown to attenuate ghrelin-induced food intake and to facilitate the satiety effects of leptin (Yang *et al*. 2015). Yang and coworkers suggest that glial cells alter feeding by modulating extracellular levels of adenosine, which affects the firing rate of AgRP neurons (Yang *et al*. 2015). Ghrelin can also act directly on hypothalamic astrocytes, as not only do they express receptors for this orexigenic hormone (Baquedano *et al*. 2013, Fuente-Martin *et al*. 2016), but *in vitro* studies show that ghrelin modifies the ability of astrocytes to transport glutamate and glucose, as well as their expression of glutamine synthetase, lactate dehydrogenase, glycogen phosphorylase and lactate transporters (Fuente-Martin *et al*. 2016). These observations suggest a possible direct effect of ghrelin on glutamate and carbohydrate metabolism by astrocytes.

Evidence also indicates that nutrients, such as carbohydrates and FAs, can directly affect astrocytes. Fructose induces hypothalamic astrogliosis both *in vivo* and *in vitro* (Li *et al*. 2014). On the contrary, although high sucrose intake induces hypothalamic inflammation, this was not found to be associated with astrogliosis (Fuente-Martin *et al*. 2013). Thus, the astroglial response may depend on what type of carbohydrate is ingested in excess, although further studies are necessary to determine the mechanisms underlying these differential responses and if they are involved in the final metabolic outcome.

Circulating FAs are elevated in obese individuals, and this is associated with adipocyte dysfunction and the development of insulin resistance (Boden & Shulman 2002, Guilherme *et al*. 2008). This elevation also results in increased FA transport into the brain, with the type and degree of FA saturation being of great importance. Saturated FAs, such as palmitic acid, cause an inflammatory response in different cell types (Boden & Shulman 2002, Iyer *et al*. 2010) in addition to endoplasmic reticulum (ER) stress (Gregor & Hotamisligil 2007). The effects of long-chain saturated FAs are seen in both astrocytes and microglia, where they induce the release of inflammatory molecules. In contrast, this inflammation does not occur in response to non-saturated FAs (Milanski *et al*. 2009, Gupta *et al*. 2012, Morselli *et al*. 2014, Valdearcos *et al*. 2014). Thus, the astrocytic signals released to the surrounding neurons depend on the specific type of nutrient perceived by these cells and this in turn most likely affects neuronal metabolic sensing.

Some foods, such as those containing antioxidants, can exert protective effects in the CNS. Some of these effects appear to be mediated through astrocytes, although how these compounds exert their protection is only now beginning to be elucidated. One widely studied example is resveratrol, a polyphenol found in grapes, wine and blueberries. This antioxidant wields glioprotective actions by preventing mitochondrial damage in these cells, thus maintaining mitochondrial function and redox homeostasis (Bellaver *et al*. 2016). How these compounds could help to attenuate the effects of fat-rich diets through their protective actions on astrocytes deserves further investigation.

Differences between males and females in the astrocytic response

Role of estrogens As stated previously, astrocytes express receptors for estrogens, androgens and progesterone (Garcia-Segura *et al*. 1996*a*, Melcangi *et al*. 2001, Garcia-Ovejero *et al*. 2005, Acaz-Fonseca *et al*. 2016), with sex steroids possibly participating in the different astroglial responses observed in males and females as a consequence of weight gain and/or obesity. Estrogens are protective against weight gain, adiposity and obesity-associated complications (Stubbins *et al*. 2012, Dakin *et al*. 2015). These effects are mediated through estrogen receptor alpha (ERα), as activation of this receptor regulates food intake, glucose homeostasis and energy

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expenditure (Musatov *et al*. 2007, Xu *et al*. 2011), with activation of ERs in the hypothalamic ventromedial nucleus specifically augmenting energy expenditure (Gambacciani *et al*. 1997, Musatov *et al*. 2007, Xu *et al*. 2011). Estrogens increase the activity of anorexigenic signals such as leptin and decrease orexigenic signals such as ghrelin (Tarttelin & Gorski 1971, Clegg *et al*. 2006, 2007, Shen *et al*. 2010, Zhu *et al*. 2013). In this line, women undergo fluctuations in food intake depending on the phase of their menstrual cycle, for example, eating less during the periovulatory days, when estradiol concentrations are highest (Barr *et al*. 1995, Buffenstein *et al*. 1995, Davidsen *et al*. 2007). This phenomenon has also been demonstrated in female rodents (Tarttelin & Gorski 1971, Asarian & Geary 2013), sustaining the association between estradiol concentrations and food intake. Moreover, in response to HFD consumption, female rats gain less weight than males, but this differential response is no longer observed after ovariectomy (Stubbins *et al*. 2012), which is similar to the tendency for postmenopausal women to increase their body weight as their estrogen levels decrease (Brown *et al*. 2010, Hamilton *et al*. 2016). In fact, females are reported to be more resistant to obesity than males in part due to the higher expression of ERα in astrocytes (Morselli *et al*. 2015).

Astrocyte morphology changes throughout the estrous cycle in association with the fluctuations in sex steroid levels, with the opposition of astroglial cells to GnRH neurons decreasing when estradiol concentrations are high (Garcia-Segura & McCarthy 2004). In contrast, astrocyte surface contact with non-GnRH neurons in the hypothalamic arcuate nucleus is increased when estradiol concentrations are elevated (Garcia-Segura & McCarthy 2004, Gao *et al*. 2007). As mentioned previously, these differential responses may be due to innate differences in astrocytes and/or to their local environment and possible interaction with surrounding cells. The effects of estrogens and sex hormones on astrocytes and how astrocytes differ between males and females, as well as the molecular mechanisms involved, are not well understood and an important area to be explored.

Astrocytes in pathophysiological response to high-fat diets and obesity

Consumption of HFD can lead to overweight and obesity, and in consequence, disruption of metabolic status and comorbidities. Obesity is characterized by a low-grade inflammatory state, not only involving the periphery but, as mentioned previously, also the hypothalamus, with this possibly involving hypothalamic astrogliosis (De Souza *et al*. 2005, Milanski *et al*. 2009, Thaler *et al*. 2012). Astrogliosis can be defined as a change in astrocyte number and/or morphology, which can lead to modifications in their contacts with neurons, including their ensheathment of neuronal somas, and the number of synaptic inputs to these neurons. Indeed, an increase or a decrease in the number of primary astrocytic projections can lead to changes in cell-to-cell communication, contact with blood vessels and changes in synaptic inputs in metabolic circuits (Horvath *et al*. 2010). For example, there is a reduction in the number of synapses on POMC perikarya as a consequence of synaptic reorganization due to HFD intake (Horvath *et al*. 2010). Modifications in astrocyte number or morphology can also be accompanied by the release of inflammatory cytokines and neurotoxic factors associated with oxidative stress. In overweight or obesity, the excess adiposity is associated with an increase in the circulating concentrations of leptin, as well as in FAs, that can directly activate astrocytes (Garcia-Caceres *et al*. 2011, Gupta *et al*. 2012), thus suggesting that hypothalamic inflammation and gliosis are a result of dietary factors and hormonal changes associated with increased adiposity.

Activation of astrocytes is reported to occur as early as 24 h after HFD consumption (Thaler *et al*. 2012, Buckman *et al*. 2014). This rapid activation could function initially as a neuroprotective response and an attempt to maintain energy homeostasis. The downside of this 'activation' occurs when it is sustained over time; inflammatory and neurotoxic factors released by astrocytes can cause neuronal damage (Pekny & Pekna 2014), and it is possible that the plasticity of the system, including changes in glial–neuronal interactions and synaptic inputs, could also be affected. This astrogliosis can be prolonged as a consequence of long-term HFD consumption, where peripheral FA concentrations rise and thus the amount of FAs reaching the brain where they can directly activate glial cells (Gupta *et al*. 2012). As mentioned previously, saturated FAs induce the release of cytokines in the hypothalamus, whereas this is not observed in response to unsaturated FAs (Milanski *et al*. 2009). One possible outcome of prolonged hypothalamic inflammation/astrocytosis is the development of leptin and insulin resistance, further provoking the disruption of energy homeostasis and perpetuating the complications associated with overweight and obesity (Carvalheira *et al*. 2003, De Souza *et al*. 2005).

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Sex differences in the astroglial response to FAs

The activation of astrocytes by FAs is different between the sexes and can be modulated by sex steroids. Moreover, females may be more resistant than males to obesity-associated secondary effects due, at least in part, to the higher expression of ERα in astrocytes (Morselli *et al*. 2014). Thus, the sex differences observed in these cells could possibly participate in the sexually dimorphic inflammatory response to HFDs (Louwe *et al*. 2012, Morselli *et al*. 2014).

Most studies of experimental obesity have used HFDs to induce weight gain; however, increased adipose tissue accrual can also occur under other circumstances, and astrocytic changes are also observed in some of these animal models (Garcia-Caceres *et al*. 2011, Fuente-Martin *et al*. 2012*a*, Gao *et al*. 2014). This indicates that astroglial responses are not due to dietary signals, such as FAs, alone. Indeed, systemic changes that result from increased weight gain, such as increased circulating leptin levels, most likely participate in this process. The metabolic response to some of these other paradigms of overweight/obesity induction, such as high sucrose intake and the long-term effects of neonatal overnutrition also differs between male and female rodents (Fuente-Martin *et al*. 2012*b*), and the response of hypothalamic astrocytes appear to differ between the sexes in these experimental models also (P Argente-Arizón, J Argente & JA Chowen, unpublished observations).

Tanycytes in metabolic control

Our understanding of how tanycytes participate in the control of feeding has increased dramatically in recent years. Tanycytes are specialized ependymal cells occupying the floor and the ventro-lateral walls of the third ventricle (3V) of the hypothalamus. There are two major subtypes of tanycytes that are classified as either α or β, with their differences residing in both their localization and biological functions (Rodriguez *et al*. 2005, Goodman & Hajihosseini 2015). Along with capillary endothelia, these glial cells regulate BBB permeability and therefore the entry of blood-borne substances into the brain. The privileged localization of tanycytes grants them a key role in determining whether molecules will be allowed into the CNS, resulting in these cells being referred to as 'gatekeepers'. This process also involves the regulation of nutrients and hormones into the hypothalamus, which in turn determines the signals reaching metabolic neuronal circuits and their subsequent responses; this ultimately affects appetite, metabolism and body weight.

Tanycytes connect the cerebrospinal fluid (CSF) with metabolic neuronal circuits in the arcuate and ventromedial nuclei of the hypothalamus through long processes, with this communication being modified by an individual's nutritional and hormonal status. The expression of glucose transporter 2 (GLUT2) in tanycytes is fundamental for their glucose-sensing properties (García *et al*. 2003, Salgado *et al*. 2014), a process that is essential for the appropriate response to hypoglycemia (Sanders *et al*. 2004). Indeed, these specialized glial cells reorganize themselves under fasting conditions to evoke adequate responses to control glucose homeostasis (Langlet *et al*. 2013). Their adaptive responses to their environment involve the regulation of BBB permeability by releasing vascular endothelial growth factor A (VEGF-A) (Langlet *et al*. 2013), which facilitates increased communication between circulating metabolites and metabolic neurons.

Tanycyte-regulated passage of specific metabolic signals, such as leptin, across the BBB and into the hypothalamus requires the activation of the ERK signaling pathway (Balland *et al*. 2014). This mechanism for leptin transport into the brain is compromised in situations of chronic HFD intake (Balland *et al*. 2014) and may contribute to the development of decreased central leptin signaling. Obesity during gestation has also been shown to alter BBB permeability by, among other things, reducing tanycyte processes at the level of the arcuate nucleus (Kim *et al*. 2016).

The participation of tanycytes in thyroid hormone (TH) metabolism was first suggested when they were shown to express deiodinase enzyme II (Dio2) (Diano *et al*. 1998*b*), the molecule responsible for the conversion of the prohormone T_4 into the active form, T_3. These glial cells capture T_4 from the peripheral circulation and then liberate T_3 into the hypothalamus (Barrett *et al*. 2007) where it regulates, for example, the response of the orexigenic NPY/AgRP neurons (Coppola *et al*. 2007). The expression of Dio2 is increased in these glial cells in conditions of starvation or inflammation and follows a photoperiodic pattern in seasonal mammals (Bolborea *et al*. 2015). In rats, the intracerebroventricular administration of TSH for 2 weeks increases Dio2 levels in the ependymal layer (Helfer *et al*. 2013) and TSH also stimulates Dio2 synthesis *in vitro* in primary tanycyte cultures (Bolborea *et al*. 2015), indicating a direct effect on these cells. Indeed, they express the TSH receptor (TSHR), with TSHR expression being very high in the ventral region of the ependyma lining the third ventricle (Bolborea *et al*. 2015), an area with a high density of tanycytes. The response of

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tanycytes to TSH elicits both an increase in cAMP levels and ERK1/2 activation (Bolborea *et al*. 2015), but it is still unclear if this signaling is common to all tanycytes or if it is region specific (Bolborea *et al*. 2015). In summary, tanycytes determine the T_3 levels in the hypothalamus through Dio2 activity, which is modulated by TSH levels in the third ventricle.

Tanycytes can serve as progenitor cells in both the postnatal and adult brains, differentiating into both neurons and astrocytes (Oyarce & Nualart 2014), with tanycytes in the median eminence exhibiting high neurogenic potential (Lee *et al*. 2014). In adulthood, neurogenesis in the hypothalamus is regulated by specific hormones, including estradiol levels, growth factors such as IGF1, and the nutritional status and the type of diet ingested (Perez-Martin *et al*. 2003, Migaud *et al*. 2010, Lee *et al*. 2012, 2014, Bless *et al*. 2014). IGF-1, a growth factor known to be involved in metabolism (Brown-Borg & Bartke 2012, Sadagurski & White 2013), is also reported to stimulate the proliferation of tanycytes (Mirzadeh *et al*. 2008, Rojczyk-Golebiewska *et al*. 2014). In the brain, the common signaling pathway between IGF-1 and insulin acting through IRS2 constitutes a link between complex events such as metabolic modulation, life span and, at least in mammals, cognition (White 2014).

In the hypothalamus, HFD intake has an anatomically specific effect on neurogenesis, inhibiting it in the mediobasal hypothalamic parenchyma and enhancing it in the median eminence in female mice, with this response being sexually dimorphic (Lee *et al*. 2014). The enhancement of neurogenesis in the median eminence appears to be associated to its anatomical location as it is in contact with the third ventricle, and exposed to hormones, molecules and factors from the cerebrospinal fluid and blood and is purported to restore the neurons that die as a result of the toxic effect of HFD (Lee *et al*. 2014). However, the mechanism that underlies the sexually dimorphic responses to HFD in the hypothalamus remains to be elucidated.

Dietary intake not only affects neurogenesis in the hypothalamus but also other brain structures, such as the hippocampus, which is known to maintain neurogenesis even in adulthood (Park *et al*. 2010). In the hippocampus, HFD reduces neurogenesis in the dentate gyrus (Lindqvist *et al*. 2006) and triggers oxidative stress and lipid peroxidation (Park *et al*. 2010), with the lipotoxicity caused by palmitic acid affecting the neural progenitor cells (NPCs) (Park *et al*. 2011), which is associated with a reduction in hippocampal brain-derived neurotrophic factor (BDNF) levels (Park *et al*. 2010). Lindqvist and coworkers reported that an increase in corticosterone levels is also involved in HFD-induced decrease in hippocampal neurogenesis, with males being more affected than females (Lindqvist *et al*. 2006). In contrast, dietary restriction results in higher levels of BDNF and neurotrophin-3 (NT-3), with an increase in neurogenesis (Lee *et al*. 2002). In accordance with this, moderate aerobic exercise is reported to stimulate adult hippocampal neurogenesis in rodents (Nokia *et al*. 2016), taking part in hippocampal-dependent memory, such as that needed in place conditioning (Shors *et al*. 2001) and reinforcing synaptic connections in pre-existing neurons by changes in neural plasticity (Trejo *et al*. 2008, Llorens-Martin *et al*. 2010). These dietary effects on hippocampal neurogenesis could possibly be involved in feeding behavior and other conductual phenomena (Stangl & Thuret 2009).

Tanycytes are also influenced by sex steroids and participate in the neuroendocrine regulation of puberty by liberating growth factors such as transforming growth factor beta (TGFβ) that stimulates the synthesis and release of GnRH (Ojeda *et al*. 2010) and thus participating in the onset of puberty. Moreover, akin to astrocytes, estrogens modulate tanycyte plasticity similarly to what happens in fasting conditions. For example, tanycyte processes retract in response to the preovulatory surge of gonadotropins, facilitating an increase in the contact of GnRH neurons with blood vessels and the following secretion to the circulation (Prevot 2002). This retraction of tanycytic processes, and thus GnRH release, seems to be essential for the correct regulation of the female reproductive cycle (Ojeda *et al*. 1975). However, how estrogen regulation of tanycytes might affect metabolism requires further investigation.

The participation of tanycytes in metabolic and neuroendocrine control seems to be of undeniable importance; nonetheless, the effect of different metabolites and nutrients, such as the various types of FAs, on these glial cells and the specific outcomes are areas of research yet to be fully explored. Likewise, whether the tanycytic response to metabolic signals differs between males and females is yet to be determined.

Microglia in metabolic control

Microglial cells are considered to be the macrophages of the CNS (Rivest 2009), as they are constantly removing damaged cells and debris and are the first barrier against infections and pathogens, with their main role being to maintain a healthy brain (Aloisi 2001, Nimmerjahn *et al*. 2005). These glial cells can adopt different states depending on the surrounding environment. On the one hand,

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under physiological conditions, they appear as 'resting or ramified microglia' performing a variety of functions including modulation of synapses (Batchelor *et al*. 1999, Zhong *et al*. 2010) and production of certain substances such as cytokines when necessary. On the other hand, when environmental conditions are adverse, for example, when there is an overload of nutrients due to overnutrition or HFD consumption, they become reactive, undergoing morphological changes and releasing diverse factors. HFD intake (Thaler *et al*. 2012) and specifically saturated FAs (Milanski *et al*. 2009) activate microglia within the hypothalamus with this activation entailing the release of inflammatory cytokines and other factors such as nitric oxide (NO) or reactive oxygen species (ROS) by these cells. If the release of these inflammatory and oxidative stress factors becomes chronic, microglia reactivity worsens, causing toxicity in the surrounding area and possibly affecting neighboring neurons. Hypothalamic POMC neurons have been shown to be particularly vulnerable to this reaction (Block & Hong 2007). Microglia are responsive to metabolic neuropeptides, with NPY and αMSH modulating their secretion of cytokines and NO (Delgado *et al*. 1998, Ferreira *et al*. 2011). Therefore, there appears to be cross-talk between metabolic neurons and microglial cells, which possibly participates in the inflammatory process in obesity.

In addition to the direct effect of FAs on microglia (Milanski *et al*. 2009, Valdearcos *et al*. 2014), these glial cells can also be activated by hormonal signals such as the anorexigenic peptide leptin (Tang *et al*. 2007, Lafrance *et al*. 2010, Gao *et al*. 2014), with this hormone most likely participating in microglial activation in obese individuals. Indeed, Gao and coworkers (Gao *et al*. 2014) reported that transgenic ob/ob mice, which are obese due to the lack of leptin, actually present lower levels of microglial activation in the hypothalamus than control mice. Although HFD intake increased the activation of microglia in the hypothalami of ob/ob mice, it did not reach that seen in control levels. Thus, both nutrient and hormonal signals are involved in microglial activation in response to HFD. Moreover, leptin administration was sufficient to trigger microglial activation, independently of body weight (Gao *et al*. 2014).

Liberation of proinflammatory cytokines and potential neurotoxic factors by microglial cells may also take part in the development of insulin and/or leptin resistance that can occur in conjunction with central inflammation (De Souza *et al*. 2005, Shoelson *et al*. 2006). In contrast, physical activity counteracts the microglial activation induced by HFD, in addition to improving glucose tolerance (Yi *et al*. 2012).

The development and maturation of these immune cells are modulated by the early nutritional environment, with poor nutrition possibly affecting the response of these cells to future challenges (Bilbo *et al*. 2010, Clarke *et al*. 2012). For example, in nonhuman primate mothers fed a HFD during gestation, development of the melanocortin circuit in the offspring was affected by proinflammatory cytokines released by microglia (Grayson *et al*. 2010). Likewise, rodents born to mothers ingesting a HFD during gestation have increased microglial activation in the hippocampus at birth, as well as increased hippocampal microglial density in adulthood (Bilbo & Tsang 2010). Overnutrition during lactation results in microglial activation in the hypothalamus and other brain areas when these animals reach adulthood, in addition to having increased expression of inflammatory cytokines in the hypothalamus (Tapia-González *et al*. 2011, Tu *et al*. 2011, Ziko *et al*. 2014).

The responses of microglia may differ between the sexes, as these cells express receptors for estrogens and progesterone. The number and morphology of microglia in some brain areas are reported to be different between the sexes (Schwarz *et al*. 2012). Although there is little information regarding whether these cells respond differently to metabolic challenges in males and females, estradiol is known to reduce microglia reactivity (Baker *et al*. 2004, Tapia-Gonzalez *et al*. 2008) and decrease the secretion of inflammatory cytokines in astrocytes (Cerciat *et al*. 2010, Rubio *et al*. 2011). Moreover, estrogens and progesterone can block inflammatory cytokine secretion by microglial cells, promoting an anti-inflammatory state (Habib *et al*. 2013, Lei *et al*. 2014). However, further research is needed to investigate the effects of sex steroids in the response of microglia to metabolic signals.

Concluding remarks

Evidence has accumulated in the past decade to support a role for glial cells in the neuroendocrine control of metabolism. However, the mechanisms involved in the regulation of energy balance by these cells are far from being understood. Not only do the changes in peripheral hormones produced as a consequence of overweight and/or obesity affect these cells but also the diet. Moreover, it is not just the amount of energy ingested, but the type of nutrients ingested. Indeed, different effects are observed

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depending on the type and the degree of saturation of FAs and an equilibrium between antioxidants and the production of ROS is important to maintain the correct functioning of these cells. Thus, future studies of how glial cells respond to specific nutrients and hormonal changes are of great importance, as their responses will ultimately determine the signals reaching neuronal circuits.

Studies have also started to highlight the fact that males and females respond differently to metabolic challenges, and that it is possible that glial cells are involved in this phenomenon, although more studies are required to directly compare the responses of these cells to hormonal and nutritional challenges in males and females. This will allow the scientific community to not only further understand how glial cells participate in the physiological and pathophysiological control of metabolism but also the mechanisms involved in the differential metabolic responses of males and females, and thus hopefully the design of more refined treatments for metabolic disorders according to each sex.

Declaration of interest

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

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