Hypothalamic cellular changes in neuroendocrine disorders

Human postmortem studies

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Chapter 1

Introduction

The role of Glia in Eating disorders

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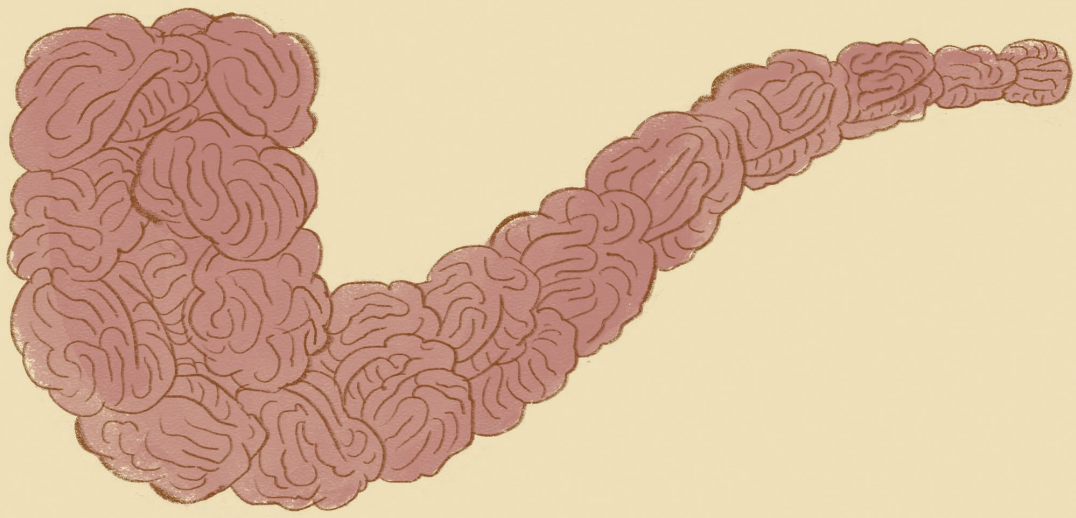

ABSTRACT

The hypothalamus is widely recognized as one of the key brain regions involved in the central regulation of energy homeostasis. Within the hypothalamus, peptidergic neurons play a crucial role in monitoring peripheral concentrations of metabolites and hormones, and they finely integrate the sensing of these factors, leading to the stimulation of either anorexigenic (appetite-suppressing) or orexigenic (appetite-stimulating) pathways. While cortical innervation of the hypothalamus does influence these processes, it is generally considered to be of secondary importance. A variety of disorders including diet-induced obesity and anorexia nervosa result from imbalances in energy intake and expenditure. The phenotypes of these disorders can be attributed to a large extent to dysfunctions in the hypothalamus (*i.e.* physiological and hedonic control of feeding behavior). Traditionally, it has been believed that hypothalamic dysfunction in these disorders primarily stems from defects in neural pathways. However, recent evidence challenges this perception by highlighting the active participation of glial cells in shaping both physiological and behavioral characteristics. This review aims to provide an overview of the latest insights into glial biology in two specific disorders: obesity and anorexia nervosa. In these disorders, neural dysfunction coincides with glial malfunction, suggesting that glia actively contribute to the physiopathology of these disorders. These findings underscore the importance and novel roles of glial cells and may open up potential new avenues for therapeutic interventions.

Keywords: Obesity, Anorexia nervosa, Microglia, Astrocytes, Tanycytes, Oligodendrocytes

INTRODUCTION

Maintenance of body homeostasis relies on genetic, physiological, and environmental components (Waterson and Horvath, 2015). Specialized neuronal networks that integrate feeding behavior with energy expenditure underpin body mass stability (Roh et al., 2016). These neural circuits sense and respond to central and peripheral born signals, leading to adaptive adjustments in feeding behavior and fuel flux in metabolically relevant organs (Roh et al., 2016). Adjustments in energy homeostasis combine a plethora of behaviors in response to contextual cues (*i.e.*, food seeking) with physiological adaptations (*i.e.*, fluctuations in insulin levels) (McLachlan et al., 2022; Oomura and Kita, 1981). Evidence from both animal models and humans demonstrates that the disruption of such neurocircuitry has direct consequences on body weight and glucose homeostasis (Farooqi et al., 2006). Over the last few decades, advances in understanding the role of the central nervous system in energy homeostasis have been made through the identification of the anatomical and molecular identity of neuronal populations engaged in energy homeostasis (Saucisse et al., 2021; Stachniak et al., 2014). Several mechanisms have been postulated to correlate the dysregulated metabolism with impaired neural networks. Thus, dysfunction of these neural pathways is a hallmark of eating disorders, such as anorexia nervosa and obesity.

Glial cells are the main support system for neurons and promote and maintain a healthy microenvironment for optimal neuronal function. Extensive research has demonstrated the role of glia in sensing and integrating a multitude of peripheral and central cues, particularly microglia and astrocytes (Jais and Bruning, 2017). Deviations in the function and structure of these cells may lead to neuronal malfunction, ultimately culminating in metabolic disorders (Bocarsly et al., 2015; Garcia-Caceres et al., 2016). This review focuses on the role of glial cells in the pathophysiology of eating disorders. First, we provide an overview of the control of feeding behavior, highlighting the role of the hypothalamus and other (sub-)cortical areas. Next, we provide an overview of the role of glial cells in eating disorders. Finally, we briefly discuss the similarities between these pathologies and the importance of glial cells in therapeutic approaches.

HOMEOSTATIC AND NON-HOMEOSTATIC CONTROL OF FEEDING BEHAVIOR

Energy homeostasis is tightly regulated and results from the monitoring of (micro) environmental cues and the activation of orexigenic and anorexigenic neural pathways (Waterson and Horvath, 2015). The hypothalamus is a highly heterogeneous central nervous system (CNS) structure that harbors neural populations responsible for a variety of neuroendocrine functions, including feeding behavior. In a simplified manner, neurons situated in the mediobasal hypothalamus coordinate food intake and energy expenditure by coupling periphery-born signals including fluctuations in key metabolites such as glucose, and central inputs (Meek et al., 2016). Neurons located in the infundibular nucleus (the arcuate nucleus in rodents) are the primary responders to these environmental cues, but metabolic signals propagate to a variety of distinct neuroendocrine populations throughout the hypothalamus (Campbell et al., 2017).

The neurons that are in control of energy homeostasis orchestrate metabolism by sensing dietary and endocrine mediators. The receptors for energy homeostasis-controlling hormones are broadly expressed in the central nervous system and are enriched in the hypothalamus (Koch et al., 2010). The hormonal control of metabolism is multilayered and depends on the temporal and tissue-dependent actions of a great variety of hormones. Considerable attention has been paid to insulin (of pancreatic origin), leptin (of adipose tissue origin), and ghrelin (of gastric origin) (Clement et al., 1998; Kalsbeek et al., 2020; Abdelhak et al., 2022; Marzullo et al., 2004). All of these interfere with the production and release of hypothalamic neuropeptides that affect food intake and energy expenditure and facilitate the synchronization of behavior with the peripheral metabolic status. Notably, glial cells also express functional receptors for these hormones, indicating that their action extrapolates to neural modulation (Milanova et al., 2022; Duquenne et al., 2021; Gao et al., 2018; Garcia-Caceres et al., 2016).

In addition to this homeostatic regulation food intake is also influenced by non-homeostatic components, including the hedonic and other cognitive aspects of feeding. A great diversity of neurocircuitries are engaged with these non-homeostatic features of feeding and are composed of cortical structures and mesolimbic dopaminergic systems (Gaykema et al., 2014; Petrovich et al., 2007). The mechanisms by which these neurons modulate feeding include sensory-specific satiety, motivational cues, reward systems, and behavioral adjustments to food availability or nutritional composition

(Clarke et al., 2018). All these systems are of great complexity and can be influenced by other biological variables, such as gender and age (Haase et al., 2011). Of importance, there is reciprocal and constant communication between the hypothalamic and non-homeostatic circuitries.

Hypothalamic neurons are embedded within glial cells, and dynamic neuron-glia interactions enable proper information processing, and consequently, behavior (Yi et al., 2017). Recent evidence has demonstrated the role of glia in metabolic integration, with special attention to microglia, astrocytes, and tanycytes. Ultimately, exposure to metabolic challenges leads to the impairment of glial function and contributes to abnormal eating behavior and impaired glucose homeostasis, among other metabolic disruptions. Such challenges include, but are not limited to, hypercaloric diets, dysregulation of circadian rhythms and abrupt body weight fluctuations (Lechuga-Sancho et al., 2006; Milanova et al., 2019). Like neurons, microglia, astrocytes, and tanycytes specialize in nutrient sensing and adapt to stimuli from the CNS. Furthermore, emerging evidence have demonstrated a role for oligodendrocytes in metabolic disorders as well (Djogo et al., 2016; Yoo et al., 2020).

OBESITY

Obesity is defined as abnormal or excessive body fat. Obesity is an important health challenge, as it significantly increases the risk of life-threatening comorbidities, such as atherosclerosis, myocardial infarction, and type 2 diabetes mellitus (T2DM) (Must et al., 1999). T2DM is one of the most common comorbidities of obesity and it is characterized by insulin resistance and consequent poor glycemic control.

The progression and development of the obese phenotype are rooted in both genetic and environmental factors, which are intertwined with feeding regulation (Farooqi et al., 2006; Xie et al., 2022). Hypothalamic feeding centers suffer from neuro-circuitry disorganization upon obesogenic cues, with numeric and functional loss of anorexigenic neuronal populations (in special proopiomelanocortin- and oxytocin-expressing neurons) (Challis et al., 2004; Lawson, 2017). These findings have been extensively recapitulated in diverse animal models and these losses are associated with sustained microglial activity and gliosis (Kalin et al., 2015). To date, few studies have explored hypothalamic anomalies in obese humans owing to technical (resolution of *in*

vivo imaging techniques) and availability (postmortem specimens) challenges. Limited current knowledge points to a great overlap between obesity-associated hypothalamic dysfunction in rodents and humans with a strong glial activation signature (Kalin et al., 2015). Neuroimaging studies have identified reactive gliosis and hypothalamic tissue damage associated with increased inflammatory markers in obese patients (Thaler et al., 2012). Furthermore, systemic low-grade inflammation found in obesity has been linked to reduced integrity of cortical areas in the control of the hedonic aspects of feeding in humans (O'Brien et al., 2017). Here, we summarize the cellular and temporal bases of glial biology under obesogenic conditions.

Tanycytes. The infundibular (arcuate) nucleus is positioned in an anatomically privileged site, with a higher permeability of the blood-brain barrier. This is an essential feature of food intake regulation, allowing neurons to be exposed to fluctuations in peripheral concentrations of nutrients, metabolites, and hormones (Lhomme et al., 2021). Tanycytes are specialized radial cells that are key components of this neurovascular structure. Typically, their cell bodies are lined in the ventricular wall associated with circumventricular organs (third ventricle for the mediobasal hypothalamus), but their processes extend to the gray matter (Langlet, 2014). Thus, tanycytic morphological features underpin their role as hypothalamic gatekeepers by conveying peripheral metabolic cues to the neural populations. Signal transduction is based on the transport of selective blood-borne molecules (Balland et al., 2014). A large range of metabolites are sensed by tanycytes, and interestingly, they are capable of fatty acid storage in lipid-rich organelles called lipid droplets, especially in the dorsal part of the third ventricle wall (Maya-Monteiro et al., 2021). Tanycytic lipid droplets accumulate in the hypothalamus of diet-induced obese mice, suggesting a role for these cells in buffering excessive lipid flux and the associated lipotoxicity (Maya-Monteiro et al., 2021). It is noteworthy that high-fat feeding leads to the loss of morphological integrity of tanycytes in the median eminence, a process that appears to be transient (Ramalho et al., 2018). Whether lipid droplets also accumulate in the human obese hypothalamus is still unknown; however, in diabetic patients, their hypothalamic content is reduced (Maya-Monteiro et al., 2021). These findings suggest that metabolic sensing performed by tanycytes is dynamic and is subject to the global metabolic status of the individual. Moreover, special attention has been given to the role of tanycytes in leptin transport and sensitivity and many observations point to a potential therapeutic value in manipulating tanycytic leptin

transport in obesity. Moreover, hypothalamic tanycytes control the output of the hypothalamus-pituitary-thyroid axis, and therefore are essential for homeostatic levels of thyroid hormone (Muller-Fielitz et al., 2017). The extent to which it is possible to apply these findings to human biology is yet to be determined.

Microglia. Microglia are the resident immune cells of the central nervous system and serve critical homeostatic functions such as synaptic pruning, circuit remodeling, and tissue clearance. These cells have a characteristic morphology, with long processes that constantly contract and expand, allowing them to scan their microenvironment (Nimmerjahn, 2012). Upon neuronal injury, microglia no longer display a homeostatic signature and respond through the production of cytokines and other neurotoxic intermediates. Obesity is associated with a chronic low-grade inflammatory state that affects both the peripheral and central nervous systems. Research in animal models has shown concomitant hypothalamic neuronal loss with microglial activation, indicating that inflammatory mediators are a major mechanistic node in neural impairment in obesity (Yi et al., 2017). Interestingly, inhibition of hypothalamic neuroinflammation prevents local neuronal loss and is associated with the attenuation of inflammatory markers and improvement of peripheral insulin sensitivity (Andre et al., 2017).

Of multifactorial etiology, an increase in the hypothalamic inflammatory state is mainly triggered by dietary components and endocrine imbalance. This is linked to metabolic disturbances, including, but not restricted to, body weight gain, ectopic fat accumulation, insulin resistance, and dyslipidemia (Lehrke and Lazar, 2004). Hypothalamic inflammation has been linked to the development and progression of obesity and dysregulation of glucose homeostasis (Posey et al., 2009). Moreover, hypothalamic inflammation is observed in rodents within 24 h of introduction of an obesogenic diet, in contrast to peripheral inflammation, which appears to be a consequence of obesity. It is noteworthy that this initial inflammatory response is transient, with normalization of the expression levels of pro-inflammatory cytokines within the days following the introduction of an obesogenic diet. Persistent hypothalamic microglial activation in rodents is observed at least, four weeks after the introduction of an obesogenic diet (Thaler et al., 2012). To date, it has been impossible to pinpoint chronic hypothalamic microglial activation as a cause or consequence of metabolic disruptions. Nevertheless, growing evidence has shown that microglia are key components of neuronal health, and continuous microglial malfunction is undoubtedly associated with the pathophysiology of obesity. Therapeutic

approaches to obesity and its comorbidities with anti-inflammatory properties have been shown to ameliorate dysregulated glycaemia and, to some extent, excess body weight (Jing et al., 2018).

Microglia-associated changes are not restricted to the hypothalamic nuclei, although disturbances in these neurons are directly related to the dysregulation of feeding behavior and energy expenditure. In chronically obese rodents, increased microglial activation is also observed in the cortical areas and is correlated with obesity comorbidities, such as cognitive decline in humans (Bocarsly et al., 2015). Finally, translational research has confirmed obesity-associated low-grade inflammation at the peripheral and CNS levels.

Hypothalamic inflammation precedes body weight gain, and microglial activation in obese rodents is primed by dietary components (1) and gut- and adipose tissue-derived hormones (2), rather than adiposity *per se*.

(1) The role of dietary components in microglia activation in obesity

Excessive intake of dietary components (*i.e.*, sugars and fatty acids) promotes obesity, which is associated with drastic changes in metabolically relevant organs including the brain (Koopman et al., 2013). The use of dietary interventions in combination with other behavioral approaches has been proven to reverse or ameliorate the pathological features of obesity and its comorbidities (Ruddick-Collins et al., 2022). Two major classes of macronutrients have been implicated in the establishment and progression of inflammatory changes associated with obesity.

Plasma free fatty acid levels are elevated in obesity, and the lipotoxic effects of saturated fatty acids have emerged as a major mechanistic link between excessive body weight and development of metabolic syndrome (Golay and Bobbioni, 1997). The first description of the induction of the inflammatory profile in the hypothalamus of rodents upon exposure to a hyperlipidic diet was dated in 2005 (De Souza et al., 2005). A microarray analysis of the hypothalamus of normal and hyperlipidic diet-fed animals was performed, and a significant increase in pro-inflammatory cytokines was observed. Neuroinflammation-related transcripts include cytokines and interleukins (*i.e.,* tumor necrosis factor alpha and interleukin 6), and their expression is orchestrated by the Nuclear Factor-κB (NFκB) signaling pathway (De Souza et al., 2005). Since then, numerous independent research groups have reached similar conclusions, and the concept that fatty acids are inducers of the inflammatory response has emerged. Accumulating evidence has indicated a microglia-derived neurotoxic environment with

an apparent predilection that affects anorexigenic neurons (Valdearcos et al., 2014). Importantly, palmitate (a saturated fatty acid) accumulates in the cerebrospinal fluid of patients with obesity (Melo et al., 2020). The mechanistic hypothesis in this scenario is that saturated fatty acids are able to bind Toll-like receptor 4 (TLR4) proteins in myeloid cells, both in the peripheral and central nervous systems (Milanski et al., 2009). TLR4 is an innate immune receptor that is highly conserved throughout evolution and specializes in recognizing lipopolysaccharides (LPS), a microbial component. Because of their similar molecular structures, saturated fatty acids were deemed to act as TLR4 non-microbial agonists and, therefore, to induce classical pro-inflammatory immunity (Rocha et al., 2016). In the periphery, the exclusive presence of TLR4 in myeloid cells is sufficient to cause diet-induced insulin resistance and liver dysfunction (Razolli et al., 2015). These results support the notion that dietary fats are key orchestrators of microglial inflammation in a TLR4-dependent manner. However, recent studies have indicated that lipid-induced inflammation in myeloid cells is not through their action as a direct agonist of TLR4; rather, saturated fatty acids promote molecular and metabolic remodeling of myeloid cells and prime TLR4-dependent responses (Lancaster et al., 2018). These results do not exclude the role of microglial lipid-induced inflammation but challenge the prevailing view of participation and the importance of TLR4. These data indicate that the sustained inflammatory response observed in obese animals requires continuous exposure to dietary fat.

Notably, dietary carbohydrates are also necessary for the neuroinflammatory response prompted by microglia. Epidemiological studies have extensively linked dietary sugar intake to obesity, and it is intimately associated with the development of T2DM (Veit et al., 2022). The combination of a high-sugar, high-fat diet is more representative of the human obesogenic diet profile, and further research is needed to gain detailed mechanistic insights into the role of dietary sugars in hypothalamic cellular reorganization in obesity (Koekkoek et al., 2021). Interestingly, the combined overconsumption of fat and sugar leads to increased hypothalamic neuronal glycation end-products, which trigger microgliosis and an inflammatory response (Gao et al., 2017a). The introduction of a diet with low carbohydrate and high fat content fails to induce glycation end-product accumulation in hypothalamic neurons and microgliosis (Gao et al., 2017a). These results indicate that fat consumption is not the sole deterministic factor in diet-induced microglial malfunction.

(2) Metabolically relevant hormones and microglial immunity

Leptin is an adipokine that promotes an anorexigenic state. In humans, leptin deficiency owing to genetic defects leads to early onset obesity and infertility (Clement et al., 1998). Rodents with non-functional leptin or its receptor also display severe metabolic disturbances, including obesity and glycemic imbalance (Zhang et al., 1994). Leptin is a known immunomodulator, and its signaling leads to the production of pro-inflammatory cytokines in a diverse range of immune cells (Lafrance et al., 2010; Lord, 2006). Leptin-deficient mice fed on a standard chow diet had a lower number of microglia in the arcuate nucleus of the hypothalamus than wild-type control mice. Moreover, the microglial processes in mutant mice were less branched, indicating impaired immunosurveillance capacity. When fed a high-fat diet, these mice display increased microglial numbers, comparable to diet-induced obese mice (Gao et al., 2014a). Interestingly, the mouse strain with a global deficiency of the leptin receptor had comparable microglial numbers in a standard chow diet, but with significantly decreased phagocytic capacity. Likewise, depletion of the leptin receptor, specifically in myeloid cells, downregulates hypothalamic microglial phagocytic capacity and defective hypothalamic neurocircuitry (Gao et al., 2018). It is well known that obese subjects are hyperleptinemic due to adipose tissue hyperplasia but concomitantly present molecular resistance to its signal in neurons (Knight et al., 2010), which hampers the use of leptin as an anti-obesity therapy.

Insulin is a hormone produced in the pancreatic islets, with glycemic control as its main function. Virtually every tissue is sensitive to insulin, but its impact on global metabolism is coordinated by its actions on adipose tissue, liver, skeletal muscle, and the brain (Jensen et al., 1989). Obese humans have hyperinsulinemia, but like leptin, its receptor also displays molecular resistance to its signals (Ferrannini et al., 2005). Insulin is a potent anorexigenic factor, and growing evidence points to its immunoregulatory role. Interestingly, under metabolic stress, peripheral macrophages lacking insulin signaling acquire an anti-inflammatory phenotype (Kubota et al., 2018). Further research is needed to elucidate the role of insulin in immunity, as *in vitro* studies have pointed to an anti-inflammatory role for insulin. This is also recapitulated in microglia in culture, in which insulin-treated microglia suppress proinflammatory cytokine production (Brabazon et al., 2018). The apparent paradoxical findings indicate that the immunomodulatory roles of insulin might be time-dependent or concentration-dependent; hence, plasma and central concentrations might differ significantly. To date, only one study in mice has depleted insulin receptors specifically in microglia. This study showed that a lack of

microglial insulin receptor signaling promotes disruption of microglial morphology, irrespective of diet (Milanova et al., 2022). The consequences on global metabolism and other cells in the hypothalamus seem to be sex-dependent, but overall, the impact is mild. Further research is necessary to elucidate the role of insulin in regulating microglial immunity in obesity.

Ghrelin is the only circulating orexigenic hormone produced by the stomach and gastrointestinal tract (Kojima et al., 1999). It promotes feeding behavior by activating appetite-modifying neurons in the arcuate nucleus of the hypothalamus, and its actions are mediated by the G protein-coupled growth hormone secretagogue receptor 1a (GSH-R1a) (Gnanapavan et al., 2002). Notably, recent evidence has demonstrated that ghrelin is rapidly sensed by appetite-curbing neurons (Schaeffer et al., 2013). Furthermore, the local blood flow velocity in the median eminence of the hypothalamus directly affects ghrelin-stimulated food intake (Romano et al., 2023). Therefore, changes in vascular permeability in the hypothalamus that are associated with obesity (discussed below) have a direct impact on ghrelin-associated changes in the feeding circuitry. Pharmacological ghrelin treatment in rodents leads to fat mass gain, partially due to elevated food consumption (Tschop et al., 2000), and ghrelin-deficient mouse models show improved peripheral insulin sensitivity (Zigman et al., 2005). Moreover, crescent evidence has shown that ghrelin acts on immune cells to suppress inflammation and induce an anti-inflammatory profile (Correa da Silva et al., 2019). Ghrelin-treated microglia display an anti-inflammatory and pro-resolution immune response, supporting the notion that hypothalamic microglia may display an anti-inflammatory phenotype upon ghrelin exposure (Liu et al., 2019a). Interestingly, the plasma levels of ghrelin in obese subjects were lower than those in lean-matched controls (Tschop et al., 2001). Furthermore, an inverse relationship has been established between plasma ghrelin levels, insulin resistance, and T2DM. Altogether, these data indicate that there is a reasonable potential to target ghrelin-GHS-R systems to treat obesity and T2DM in humans, and ameliorated microglial activation may be an important mechanistic node in this process.

Astrocytes. Hypothalamic astrocytes play a major role in nutrient and endocrine sensing, neurovascular coupling, and synaptic modulation. Astrocytic proliferation and hypertrophy are well-recognized features of central nervous system pathologies , such as multiple sclerosis and Alzheimer's Disease (Escartin et al., 2021). Moreover, reactive

astrocytes exhibit marked upregulation of structural proteins such as glial fibrillary acid protein (GFAP) and vimentin (Galou et al., 1996). In contrast, there is a reduction in the number of astrocytes in the hypothalamus of the poorly controlled diabetic rats. Growing evidence also indicates that impairment of astrocytic function leads to exaggerated body weight gain in rodents fed an obesogenic diet. Among the key nodes in astrocyte function, is its responsiveness to metabolism-regulating hormones (*i.e.*, insulin and leptin) and key components of cellular metabolism (Garcia-Caceres et al., 2016; Kim et al., 2014). Altogether, this evidence suggests that endocrine mediators and adiposity are major regulators of hypothalamic function. Notably, reactive astrogliosis in obesity, which is deemed to be reversible after weight loss in mice (Berkseth et al., 2014). Importantly, reactive gliosis was also observed in the hypothalamus of obese subjects, indicating that these observations in murine models are recapitulated in humans (Thaler et al., 2012).

Obesity-induced astrocytic dysfunction can be summarized into three categories: (1) perturbations in tissue microarchitecture, (2) functional impairment of hypothalamic neurons, and (3) production of neurotoxic/inflammatory mediators.

(1) Reactive astrocytes promote hypothalamic tissue remodeling in obesity

The distinct morphological features of astrocytes allow them to have close contact with neurons, providing them with trophic support. Moreover, astrocytes surround endothelial cells that compose the blood-brain barrier (BBB) and, therefore, have privileged access to periphery-derived metabolites and hormones (Obermeier et al., 2013).

Chronic high-fat diet promotes increased permeability of the BBB, and this intense vascular remodeling is dependent on angiogenic factors released by astrocytes. Vascular endothelial growth factor (VEGF) appears to be one of the major players in this process, alongside hyperleptinemia (Gruber et al., 2021). Interestingly, a shift in the cytoarchitecture of the BBB impairs the access of hypothalamic arcuate nucleus neurons to blood vessels in mice (Horvath et al., 2010). These findings indicate that gliovascular remodeling after exposure to an obesogenic diet makes the central nervous system more permissive to the entry of neurotoxic- and metabolic-derived factors from the periphery. Moreover, key neuronal populations controlling metabolism are deprived of proper nutritional and oxygen support under chronic obesogenic diet conditions.

Dysregulated cellular metabolism and continuous hypoxia lead to the functional and numeric loss of these neural populations.

(2) Astroglia modulate neuronal activity and feeding behavior

Astrocytes are homeostatic keepers of the neural microenvironment that provide optimal metabolic and trophic support for neuronal functions. This translates into the transfer of metabolites from the blood stream, production and release of growth and neuroprotective factors, and influences the formation, function, and plasticity of synapses (Ventura and Harris, 1999). Increased markers of neuronal injury and synaptic disorganization have been reported in the hypothalamus of obese rodents, in parallel with reactive gliosis (Horvath et al., 2010; Thaler et al., 2012). It is noteworthy that these perturbations are not solely due to astrocytic dysfunction; the reactive phenotype limits the functional and structural support that astrocytes would provide to neurons. Furthermore, reactive astrocytes release neurotransmitters and modulate neural functions (Lee et al., 2010). This is particularly observed in the lateral hypothalamic area (LHA), which harbors a variety of neuronal populations that control energy homeostasis through control of feeding behavior and innervation of peripheral metabolically relevant organs, such as adipose tissue. In diet-induced obesity, astrocytes from the LHA have been reported to release gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, inhibiting the function of surrounding neurons responsive to this signal (Sa et al., 2022). Both genetic and pharmacological manipulation of astrocytic GABA synthesis reduce astrogliosis in the LHA, accompanied by a reduction in body weight in high-fat diet-fed rodents (Sa et al., 2022). Furthermore, a recent report demonstrated that astrocytic control of extracellular glutamate in the hypothalamus is impaired in obesity (Herrera Moro Chao et al., 2022). This directly affects neuronal function, with direct implications on energy homeostasis and dysregulated glucose metabolism. Similarly, astrocytes in the orbitofrontal cortex have impaired glutamate transport, which eventually leads to synaptic disorganization of neurons in the control of the hedonic components of feeding (Lau et al., 2021).

(3) Astrocytic-derived inflammatory mediators in overnutrition

Resident immune cells of the central nervous system produce neurotoxic/inflammatory mediators following neuronal injury. The main cellular subset implicated in the production and release of proinflammatory cytokines and neurotoxic molecules is microglia. Hypothalamic neuroinflammation is maintained by microglial features, as

well as through the inflammatory activation of an astrocytic subset (Buckman et al., 2015). Astroglia also produce and release inflammatory mediators during overnutrition, although to a lesser extent than microglia. Inflammatory astrocytes lose the ability to promote synapse formation and exert neurotoxic effects. The astrocytic inflammatory response is orchestrated by the NF-κB pathway, and animals with selective genetic ablation of NF-κB components in astrocytes do not display an astrocytic reactive phenotype or characteristic hyperphagia and weight gain in obesity (Douglass et al., 2017; Jin et al., 2020; Zhang et al., 2008).

Oligodendrocytes. In metabolic diseases, the role of myelinating-oligodendrocytes and oligodendrocyte progenitor cells (OPCs) is the most underexplored. Most reports linking obesity with these cells establish impairment of myelinating capacity associated with the obese phenotype, both in the hypothalamic and extra-hypothalamic areas (Bouhrara et al., 2021; Huang et al., 2019; Sena et al., 1985). However, little is known about the effect of oligodendrocytes on global metabolic regulation. Notably, oligodendrocytes respond to leptin, and hypothalamic OPCs are key components for proper hypothalamic leptin signaling (Djogo et al., 2016; Udagawa et al., 2006). Genetic and pharmacological ablation of OPCs in the hypothalamic median eminence leads to weight gain, suggesting a fundamental role for these cells in body weight regulation. However, oligodendrocytes also support neuronal functions in addition to myelin production. In particular, nutritional support for neurons from oligodendrocytes has been documented and proposed to be disrupted in the obese hypothalamus (Ou et al., 2019). Further mechanistic insights are needed, but initial evidence in mice seems to corroborate the impact of hypothalamic oligodendrocytes as coordinators of neuronal health and function (Trevisiol and Nave, 2015). Thus, dysregulation of oligodendrocyte biology is implicated in the malfunctioning of hypothalamic neuropeptidergic systems. Importantly, these findings have yet to be confirmed in humans.

ANOREXIA NERVOSA

Anorexia nervosa (AN) is an eating disorder characterized by restrictive nutritional intake relative to energy requirements, which leads to excessive weight loss. AN patients fear body weight gain and present a distorted self-image that limits their perception

of the seriousness of the disease (Treasure et al., 2015). AN is strongly linked to mood and anxiety disorders, and it has multisystemic complications that include, but are not limited to, bone, cardiac, endocrine, and gastrointestinal changes (Treasure et al., 2015). Complications worsen with disease progression and are associated with a lower body mass index (Mehler et al., 2018).

Experimental animal models of AN can be achieved by either activity-based anorexia (this model combines maximum ad libitum food intake of 3 h daily combined with free access to a running wheel) or dehydration (animals are offered a 2.5% NaCl solution leading to reduced body weight due to dehydration) (Klenotich and Dulawa, 2012; Reyes-Ortega et al., 2022). Both have limitations but are considered to recapitulate the major features of human pathology and trigger brain alterations through the promotion of a negative energy balance. It has been widely recognized that there is evidence of brain atrophy in the acute underweight stage of AN. Neuroimaging studies have shown cortical thinning and a reduction in both gray and white matter volumes (King et al., 2018; Seitz et al., 2018). These changes are attributed to changes in neurons (*i.e.*, reduced synapses, smaller neurons, and accumulation of neurotoxic particles in neuronal cell bodies), but these changes are uncoupled from differences in oligodendrocyte density in a rat AN model (Frintrop et al., 2018). These neurological changes are restored upon body weight gain, suggesting dynamic remodeling of circuitries and cells related to the AN phenotype.

Microglia. A considerable amount of evidence indicates preservation of immune function in AN, in contrast to the pattern observed in malnutrition (Slotwinska and Slotwinski, 2017). Interestingly, proinflammatory cytokines are known anorectic mediators, and increased serum levels of cytokines have been reported in patients with AN compared to healthy controls (Fantino and Wieteska, 1993; Kahl et al., 2004; Kapas and Krueger, 1992). Limited information regarding microglial cells in AN pathophysiology is available, especially for those derived from human material.

Experimental models of anorexia display increased microglial presence in different cortical areas, such as hippocampus and prefrontal cortex (Ragu-Varman et al., 2019; Reyes-Ortega et al., 2020). These microglia are less ramified and are associated with augmented expression of proinflammatory cytokines, which is consistent with a classic activation profile in microglia (Ragu-Varman et al., 2019; Reyes-Ortega et al., 2020). This activation state has implications for neuronal health and affects astrocytic functions.

Such microglial activation is aligned with the behavioral features of anorexia animal models, such as memory performance and cognitive impairment (Paulukat et al., 2016).

Astrocytes. There is a significant reduction in GFAP-expressing astrocytes in the corpus callosum and cerebral cortex of experimental anorectic rats compared with matched controls (Reyes-Haro et al., 2016; Reyes-Ortega et al., 2020). These changes in cortical astrocytes are reversible upon normalization of feeding, but not in the corpus callosum, possibly due to differences in cellular turnover in the gray and white matter (Reyes-Haro et al., 2015). Interestingly, (partial) body weight restoration normalizes astrocytic count (Frintrop et al., 2019). When rodents are separated into resistant or prone to anorexia, it is possible to detect increased astrocytic density in the prefrontal cortex of AN-prone animals compared to resistant or control animals (Hurley et al., 2022; Reyes-Ortega et al., 2020). The prefrontal cortex integrates information on food perception and therefore contributes to food-seeking behavior (Petrovich et al., 2007).

One possible explanation for the diminished astrocytic density in experimental models of anorexia relies on the metabolic support these cells provide to the neurons. To enable optimal neuronal function, astrocytes perform metabolic shuttle reactions with neurons, typically known as the glutamate/GABA-glutamine cycle (Hertz, 2013). Here, astrocytes remove neurotransmitters from the synaptic site and convert them into glutamine, which is then incorporated into neurons. This serves the purpose of preventing toxicity due to excessive neurotransmitter content and provides metabolic support to neurons once glutamine is easily metabolized in mitochondrial respiration (Hertz, 2013). Anorexia reduces the expression of astrocytic enzymes associated with the glutamate-glutamine cycle in the prefrontal cortex, possibly to promote glutamine catabolism and therefore cope with the negative energy balance (Reyes-Ortega et al., 2022).

Finally, emerging evidence supports astrocytic dysfunction in patients with AN. Functional imaging studies have also reported reduced brain volume in AN subjects compared to controls (King et al., 2018), and it is reasonable to speculate that the lessening of astrocytes contributes to this. It is noteworthy that this is not the only possible explanation to diminished brain volume in AN. Notably, the use of serum GFAP as a biomarker for different neuropathological conditions has been proposed and validated (Abdelhak et al., 2022). A recent report showed increased serum GFAP levels in AN subjects compared to controls, and partial weight restoration decreased it

(Hellerhoff et al., 2021). These findings need to be further validated in different cohorts, and whether they reflect central astrocytic profiles also needs to be determined. In contrast, a case report indicated prominent gliosis in the periventricular regions related to dopaminergic mesolimbic pathways (Umeda et al., 2021). These regions are linked to emotion and cognition and might indicate dysfunction of the hedonic component of feeding.

Taken together, these findings point to an emerging role for microglia and astrocytes in AN pathology. Glial changes appear to be reversible after body weight restoration, and the main mechanism underlying glial dysfunction is starvation (Frintrop et al., 2019). Curiously, hypothalamic nuclei have not been the focus of research in the field of AN, despite their central role in feeding coordination.

CONCLUSION

The regulation of energy homeostasis involves a complex and multilayered interplay between neurons and glial cells. The major regulatory system in the central nervous system that controls metabolism is the hypothalamus, which harbors numerous neuronal populations engaged in feeding behavior, glycemic control, and energy expenditure. This review focused on eating-related disorders involving long-term positive or negative homeostasis, *i.e.*, obesity and anorexia nervosa. Although they do not necessarily have a hypothalamic etiology, hypothalamic dysfunction is a central node in their development and progression. In brief, appetite-curbing neurons are severely affected, which consequently disrupts the normal feeding and energy expenditure patterns. These eating disorders considerably impair physical health and can evolve into disabling and deadly conditions.

Glial cells are classically considered to be only a support system for neurons; however, emerging evidence demonstrates the active role of these cells in virtually all homeostatic systems. Thus, glial malfunction has been implicated in physiological and behavioral impairments. A considerable portion of the research discussed here is based on experimental animals, which cannot fully mimic human conditions. Nonetheless, current results from translational research demonstrate a considerable overlap in glia-related cellular and molecular alterations. In general, the roles of oligodendrocytes and tanycytes in the pathology of metabolic disorders are underexplored. In contrast, many

studies have evaluated the roles of astrocytes and microglia. Both cell types provide trophic and structural support to neurons, and their malfunctioning is a key mechanism of neural dysfunction.

All in all, the findings discussed here indicate that glial biology needs to be considered in therapeutic approaches for feeding-related disorders. The apparent reversibility of the glial changes, in contrast to those observed in neurons that appear to be permanently lost, reinforces the need to equate glia in future therapies. This is especially evident in positive energy balance disorders, but it also seems plausible in AN, based on empirical evidence obtained from other mood disorders. Collectively, this review covers the latest data on the proposed eating-related disorders involving glial cells, which possess several mechanistic targets for future therapies.

Abbreviations: AN = anorexia nervosa; CNS = central nervous system; OPC = oligodendrocyte progenitor cell; T2DM = type 2 diabetes mellitus.

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