MOLECULAR METABOLISM

Emerging role of glial cells in the control of body weight

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ABSTRACT

Glia are the most abundant cell type in the brain and are indispensible for the normal execution of neuronal actions. They protect neurons from noxious insults and modulate synaptic transmission through affectation of synaptic inputs, release of glial transmitters and uptake of neurotransmitters from the synaptic cleft. They also transport nutrients and other circulating factors into the brain thus controlling the energy sources and signals reaching neurons. Moreover, glia express receptors for metabolic hormones, such as leptin and insulin, and can be activated in response to increased weight gain and dietary challenges. However, chronic glial activation can be detrimental to neurons, with hypothalamic astrocyte activation or gliosis suggested to be involved in the perpetuation of obesity and the onset of secondary complications. It is now accepted that glia may be a very important participant in metabolic control and a possible therapeutical target. Here we briefly review this rapidly advancing field.

Keywords Astrocytes; Gliosis; Metabolic control; Hypothalamus; Obesity

1. INTRODUCTION

Glia were historically considered by many to be the cellular "glue" of the brain, providing only passive support for neurons. The contemporary view of glial cells is quite distinct as we now know that they are involved in all aspects of neuronal function, including regulation of neuronal metabolism, neuroprotection, synaptogenesis and neurotransmission, amongst numerous other functions [1–6]. Indeed, both neurons and glial cells are required for normal functioning of the brain during development and throughout adult life. Glia are the most abundant cell type in the brain and can be broadly classified as macroglia or microglia depending on their cellular origin. Macroglia are derived from the neuroectoderm and include both astrocytes and oligodendrocytes [7]. However, the origin of microglia remains under debate [8,9], with these cells believed to be derived from either the neuroepithelia [10–12] or from the hematopoietic cells (i.e., monocytes) [13,14]. As both astrocytes and microglia have been shown to be activated in response to metabolic signals [15,16], they will be the primary focus of this review.

Glial activation is a process by which astrocytes and microglia develop a hypertrophic or reactive phenotype that is also referred to as gliosis. Astrocytes are stellate cells with multiple fine processes that radiate from the cell body and terminate in end-feet on blood vessels, in direct contact with other astrocytes or as ensheathment of neuronal somas or synapses [17–21]. Most astrocytes contain an exclusive protein called glial fibrillary acidic protein (GFAP) that acts as an intermediate filament and is up-regulated in reactive astrocytes, as is another structural filament called vimentin [22]. Microglia are considered brain macrophages and like astrocytes can switch to an activated state undergoing structural and functional transformations [23], including the overexpression of major histocompatibility complex II and inducible nitric oxide [23–25]. Therefore, both astrocytes and microglia respond to injury or disease by developing a reactive phenotype that can lead to functional changes resulting in beneficial effects on neurons, such as the clearance of damaged or dead cells [23] or reducing oxidative stress [26,27]. However, the long-term activation of these glial cells can have detrimental results, such as increasing tissue damage through the release of inflammatory factors (e.g., reactive oxygen species, cytokines), as observed in various chronic central nervous system (CNS) diseases [28–30].

Although the role of glial cells has been extensively studied in neurodegenerative diseases, their function in the development of metabolic diseases such as obesity has only recently come to the forefront [15,31–33]. Indeed, hypothalamic inflammation is now thought to be an important process in both the development and perpetuation of obesity and glial cells are a fundamental player in these inflammatory processes [30,34,35]. However, there is still much to be discovered regarding the mechanisms involved.

2. GLIAL CELLS ACT AS METABOLIC SENSORS IN THE BRAIN

The brain is very sensitive to metabolic fluctuations with both neurons and glial cells expressing a wide array of metabolite receptors, transporters and regulators [36–42]. Blood-borne glucose is considered to be the major nutrient in the brain [43], but neurons also use lactate that can either be taken up from the circulation or synthesized by astrocytes [44], as well as fatty acids (FAs) and ketone bodies. Like glucose, these metabolites are transported into and within the CNS [45,46] mainly by astrocytes [47,48]. Energy requirements of the brain are linked to activity and these requirements are met depending on the type of nutrients available, with astrocytes cells playing a crucial role in

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this process. This also includes modulating the local environment of specialized nutrient sensing neurons in the hypothalamus.

2.1. Lipid transporters

The brain is the most cholesterol-rich region in the body [49] and lipid homeostasis, which is essential for normal functioning of neurons, is primarily controlled by astrocytes [50–52]. In the CNS, FAs are derived either from the diet [53] or de novo synthesis [54] and both glia and neurons require FAs to maintain their metabolic homeostasis [55]. Under normal conditions, astrocytes are the primary source of lipoproteins in order that synaptogenesis, synaptic remodeling and axonal growth can occur [56,57]. During periods of fasting or high fat diet (HFD) intake astrocytes transport higher concentrations of FAs and ketone bodies from the peripheral circulation to the brain [58,59] to be used as alternative fuels and long-term imbalances in brain lipid metabolism are associated with the development of obesity [60].

Apolipoprotein E (ApoE) is the most abundant lipid transporter in the CNS and it is produced mainly by astrocytes [61–63]. Not only does ApoE regulate the uptake of lipids into target cells, but in the hypothalamus it also acts as a satiety factor [64]. It is suggested that the inhibitory effects of leptin on feeding are partially mediated through ApoE, as central ApoE levels are reduced in both fasting and obesity and can be restored by leptin treatment [61]. Another critical sensor of lipid concentrations in the brain is peroxisome proliferator-activated receptor gamma (PPARγ), which is expressed both by astrocytes and neurons [65]. PPARγ is involved in central regulation of energy metabolism in states of leptin resistance [66]. Diano and colleagues have recently demonstrated that HFD intake induces the expression of PPARγ in the hypothalamus and this reduces ROS production in proopiomelanocortin (POMC) neurons thereby altering the ability to inhibit food intake in lean mice on a HFD [66]. ATP-binding cassette transporters (ABCA) also participate in cellular lipid processes in the brain [67]. These transporters are expressed by both astrocytes and neurons and mediate the release of ApoE-containing glial lipoproteins such as cholesterol [67–69]. Therefore, ABCA-1 expression determines cholesterol and ApoE concentrations in the brain, but its implication in metabolic diseases remains to be investigated.

Ketone bodies, which can be taken up from the bloodstream or produced through FA oxidation by astrocytes, are another important energy source for the brain [46,70]. The main transporter of ketone bodies into and out of cells in the CNS is monocarboxylate transporter (MCT)-1 [71]. This transporter is reported to be expressed by astrocytes, neurons and endothelial cells, although this expression may depend on age and anatomical location [44,72–74], as well as activational state as it is up-regulated in gliosis [75]. Brain MCT-1 levels can be enhanced by HFD intake [59,76] in response to the increased concentration of circulating ketone bodies. Although the effect of ketogenic diets on energy homeostasis remains under debate, ketone bodies have been shown to have direct effects on energy homeostasis and glucose metabolism through modulation of both leptin and insulin signaling in the hypothalamus [77]. How lactate transport by astrocytes is regulated remains to be determined, but one mechanism by which these glial cells could modify systemic metabolism is through control of central ketone body concentrations.

2.2. Hormone receptors

In the hypothalamus both neurons and glia respond to hormones to regulate neuroendocrine systems [39]. Indeed, glial cells express a vast array of receptors including those for hormones involved in controlling appetite and food intake [36–38,78]. Insulin and leptin inform the brain regarding energy availability and regulate food intake and lipid metabolism [79], having effects on both glia and neurons [37,80,81]. Leptin, the adipocyte secreted hormone, is well known for its role as a satiety factor [82] and astrocytes express various isoforms of its receptor [81]. However, diet-induced obesity is often associated with high concentrations of serum leptin suggesting that leptin resistance exists and that the central anorexic effects of this hormone are reduced [83]. Several mechanisms for leptin resistance have been proposed including impaired transport of leptin across the blood–brain barrier (BBB) [84] or the attenuation of leptin signaling due to the presence of suppressors of leptin signaling pathways [85–87]. Moreover, the observation that diet-induced obesity results in opposite changes of leptin receptor (LepR) in hypothalamic neurons and astrocytes, with an increase being found in these glial cells and a decrease in neurons [88], suggests that both cell types are involved in central leptin responsiveness and that their functions may be quite different. Moreover, LepR expression in astrocytes does not appear to be uniform throughout the brain, with apparently higher levels being found in some areas such as the arcuate nucleus (Fig. 1) indicating that leptin's effects on astrocytes may also be anatomically specific. Microglia also express

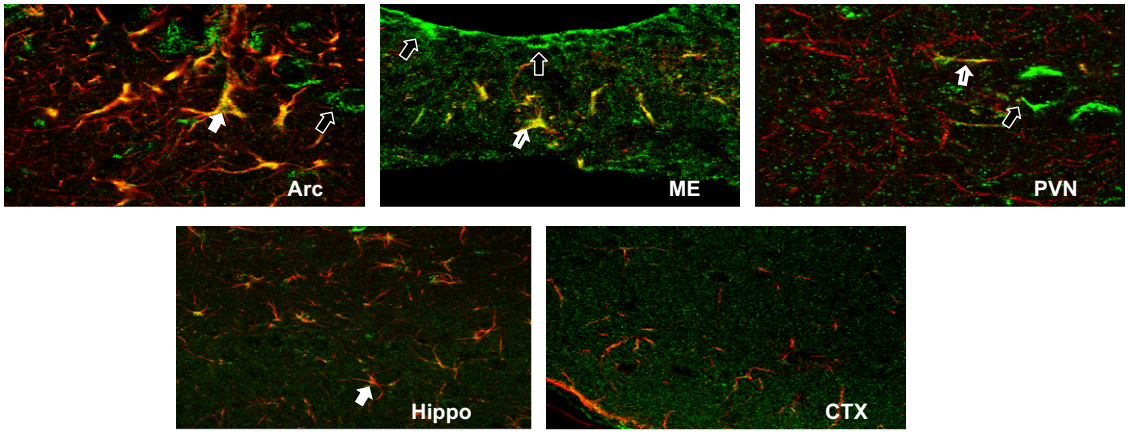

Fig. 1: Microphotographs of double immunofluorescence for glial fibrillary acidic protein (GFAP; red) and leptin receptor (LepR; green) in different areas of the adult male rat brain. Brain sections (40 μm) were incubated in flotation with the primary antibodies mouse anti-GFAP (1:1000, Sigma) and goat anti-LepR (1:250, Santa Cruz) for 48 h at 4 °C. Sections were then incubated with Alexa-633 anti-mouse and Alexa-488 anti-goat (both 1:1000, Molecular Probes) for 2.5 h. Images were captured with a confocal microscope. Solid arrows indicate cells that are GFAP and LepR positive and hollow arrows cells that are positive for LepR, but not GFAP. In the cerebral cortex (CTX) GFAP positive cells were not found to express the LepR. Arc: hypothalamic arcuate nucleus; ME: median eminence; PVN: hypothalamic paraventricular nucleus; Hippo: hippocampus; CTX: cortex.

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LepRs and this hormone can modify their activational state and production of cytokines [89,90].

Energy consumption by brain cells is considered to be insulin-independent as glucose uptake is not significantly stimulated by insulin [91]. However, insulin receptors are expressed by neurons and glia with both of these cell types contributing to the central actions of this hormone [37,92]. Insulin's effects in the hypothalamus clearly have important repercussions on systemic energy balance. For example, short-term HFD intake very rapidly induces hypothalamic insulin resistance [15] and can be reversed by exercise induced weight loss [93]. Insulin is not only important for astrocyte proliferation, but it promotes glycogen storage [94] and increases glutamate transporters [95] in these glial cells. However, the role of astrocytes in regulating insulin sensitivity in the hypothalamus remains to be clarified.

2.3. Glucose transporters

Central glucose concentrations play a critical role in the regulation of energy metabolism [96]. Glucose is the primary metabolite for the brain and is stored in astrocytes as glycogen to safeguard against hyperglycemia [97,98]. Electrophysiological studies have shown that some brain areas, including the hypothalamus, have a population of neurons possessing specialized mechanisms to act as glucosensors [99–102]. These neurons modify their firing rates with changing external glucose concentrations, with glucose-excited neurons increasing and glucose-inhibited neurons decreasing their activity as ambient glucose levels rise [101,102]. These glucose sensing systems are involved in the control of food intake and glucose homeostasis [103]; however, they do not function alone. Astrocytes also participate in glucose transport and metabolism [104,105], modulating peripheral and central glucose levels [106] and providing glucose to the extracellular space in the brain for uptake by neurons.

Communication between astrocytes and neurons is required for glucose to be used as a fuel source, with astrocytes, neurons and blood vessels working together as functional units [17] (Fig. 2). Blood vessels in the brain are almost completely surrounded by a network of astrocytes that highly express glucose transporters (GLUTs) [107], raising the possibility that regulation of glucosensing neurons by changes in glucose concentrations is, at least in part, indirectly controlled by astrocytes.

Astroglia are the main metabolizers of glucose in the brain and they respond to alterations in glucose levels by modifying their release of lactate, which is then provided to neurons as an energy substrate [108,109]. Astrocytes that surround capillaries express GLUT-1 and transport glucose into the brain [107,110]. Recent studies show that diabetes-related hyperglycemia reduces GLUT-1 expression in hypothalamic glial cells resulting in the inability of increased intra-hypothalamic glucose to reduce systemic glucose production, with this reduction in glucose-sensing capacity being restored with over-expression of GLUT-1 in GFAP-positive cells in the hypothalamus [111]. GLUT-2 is expressed in brain areas involved in controlling food intake, such as the hypothalamus [112,113]. In the hypothalamus this transporter is located in astrocytes, ependymal cells, tanycytes and glucose-sensitive neurons [41,42,113–115] and it is essential for central glucose sensing and regulation of food intake [116]. In the brain GLUT-3 is almost exclusively expressed in neurons, acting as their main glucose transporter [117–121].

Astrocytes, through GLUT-1 and GLUT-2, capture and store glucose as glycogen from which they produce lactate that is transferred to neurons as an energy substrate. Indeed, some authors suggest that lactate is the primary energy source for neurons. As mentioned above, lactate is transported through MCTs, including MCT-1 located in astrocytes, neurons and epithelial cells, MCT-2 in neurons and MCT-4 in astrocytes during all stages of development [71–74,122–124]. Lactate is transported out of the cell through MCT-4 [125], indicating that astrocytes regulate extracellular concentrations of lactate. Neuronal populations involved in metabolic control not only use lactate as an energy source, but the activity of orexin neurons is reported to be lactate sensitive with this lactate being derived from astrocytes [126].

2.4. Glutamate transporters

Glutamate transporters, or excitatory amino acid transporters (EAATs), are highly expressed in astrocytes and have an important role in the communication between these glial cells and neurons [127]. Glial glutamate transporter (GLT)-1 is found almost exclusively in astrocytes and glutamate aspartate transporter (GLAST) is expressed in astrocytes and other glial cells [128–130]. These transporters are ion pumps that transport L-glutamate, coupling it to Na^+ and K^+ symport/antiport

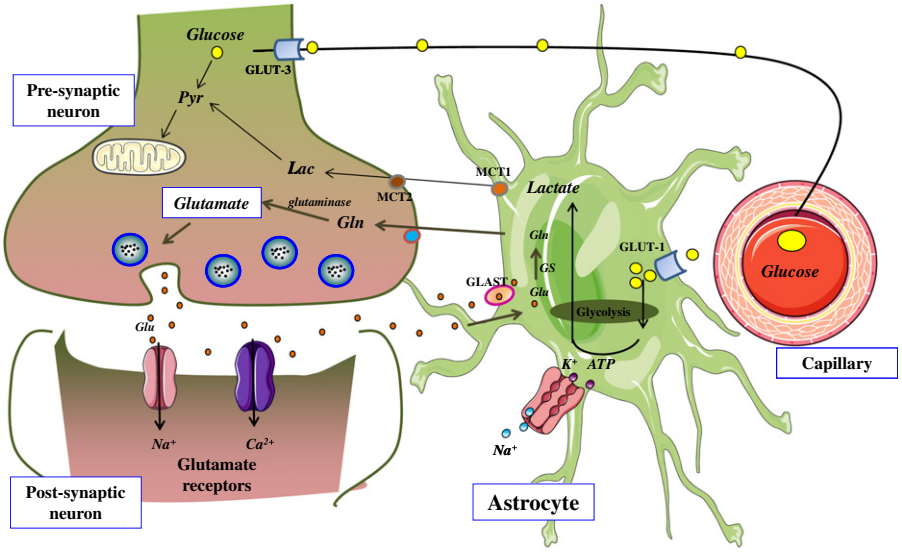

Fig. 2: Schematic representation of glucose and glutamate transport, metabolism and secretion by astrocytes and neurons. The glutamate/glutamine cycle is tightly coupled to glucose oxidation in astrocytes, which then release lactate to be taken up by neurons and be oxidized. Lac: lactate; Pyr: pyruvate; Glu: glutamate; MCT: monocarboxylate transporter; GLAST; glutamate/aspartate transporter; GLUT: glucose transporter; GS: glutamine synthetase; GLN: glutamine.

[131,132]. Glutamate uptake by astrocytes is fundamental for controlling extracellular concentrations of this excitatory amino acid, thus not only modulating synaptic transmission, but also impeding excitotoxicity. Moreover, glutamate transport into astrocytes activates intracellular glycolysis, increasing lactate production and its distribution to neurons [105,109,133,134], thus controlling their nutrient availability. Therefore, changes in the number, morphology or function of hypothalamic astrocytes could significantly modify neuronal responses and hence, metabolism.

2.5. Glucose and glutamate transport in tanycytes

Tanycytes, glial cells present in the lateral lower portion and the floor of the third ventricle, also appear to have a role in glucose metabolism. These cells are in close proximity to the ventromedial hypothalamic nucleus and arcuate nucleus and thus, to neurons responsible for regulation of energy balance [135]. Not only do they have a strategic location, contacting both the cerebrospinal fluid and blood circulation, but they also express genes involved in glucose sensing including GLUT-2, glucokinase and MCT-1 and -4 [113,136–138]. Indeed, recent studies have demonstrated that these specialized glial cells respond rapidly to changes in glucose concentrations [139].

Tanycytes express a broad array of receptors for different hormones, enzymes and growth factors and their location close to the hypothalamus suggests that they are involved in neuroendocrine control, including metabolism and nutrient sensing [137]. Tanycytes also express both GLAST and GLT-1 [140], glutamate receptors [141] and dopamine-responsive elements [142], indicating that they participate in glutamate uptake and can respond to changes in neurotransmitters. However, to date very little is known regarding the functions of this specialized glial cell in systemic metabolic control.

3. IMPLICATION OF GLIAL CELLS IN METABOLIC DISRUPTIONS

Throughout its lifetime the organism attempts to modulate its metabolic state in response to a continuously changing environment (e.g., diet, exercise, stress). However, homeostasis is not always achieved due to a mismatch between food intake and energy expenditure, with this resulting in modifications in circulating metabolic signals [143]. The degree to which a specific metabolic substrate is used by the brain depends on its concentration in the plasma and the brain's ability to capture and metabolize it, which as mentioned above depends largely on astrocytes, in addition to tanycytes. Moreover, the low or high availability of a specific substrate such as lipids or glucose can lead to undesirable effects on the target cells responsible for their uptake.

3.1. Physical activity and caloric restriction

Excessive intake of high fat foods increases oxidative rates in the organism and can cause detrimental effects on neurons [15,144–146]. Indeed, many neurological disorders are associated with increased oxidative stress and reduction of these stressors can improve their prognosis [147]. Exercise and dietary modifications have clear health benefits including not only improvement in systemic metabolism, but also protection or improvement of neurological function by diverse mechanisms including increasing important neurotrophic factors and antioxidants [148–151]. Antioxidant effects in the brain are highly coupled to astrocyte activity, with these glial cells being the main defence against excitotoxicity and other insults [152,153]. In addition to reducing body weight, dietary restriction also restores the rate of neurogenesis in obese mice [154] and attenuates the age-related astrogliosis in the hypothalamus [155]. This gliosis is often related to neuronal dysfunction in chronic neurodegenerative diseases [156,157], with astrocyte activation first being protective and if prolonged having damaging effects. Likewise, hypothalamic gliosis is most likely involved in neuroendocrine changes associated with aging or other processes. However, this possibility has been largely ignored. Indeed, overfeeding and weight gain increase astroglia and microglia activation [15] and neuronal apoptosis in the hypothalamus [145], but how this glial activation participates in neuronal dysfunction in obesity remains largely unknown.

3.2. Genetic obesity

3.2.1. Leptin signaling deficient models

The complete absence of leptin (ob/ob) causes severe obesity in mice [158] and humans [159] and exogenous leptin treatment leads to reduced body weight in these individuals [160]. Likewise, mice with a global mutation in the leptin receptor (db/db) develop an obese phenotype that is indistinguishable from that of ob/ob mice, but that is not reversible by leptin treatment [161]. Apart from the action of leptin in regulating energy balance, leptin plays a key role in brain development during early life [158] and the lack of leptin signaling in both ob/ob and db/db mice results in a reduction in brain weight and in hypothalamic glial proteins such as GFAP [158] and ApoE that, as stated above, acts as a mediator of the inhibitory effects of leptin on food intake [61]. In addition, Pinto and colleagues have shown that ob/ob mice differ from wild type mice by having more excitatory, compared to inhibitory, synapses on neuropeptide Y (NPY) and POMC neurons, which can be rapidly reversed by leptin treatment [61,162]. GFAP protein levels and astrocyte coverage of POMC neurons are inversely correlated with the number of synaptic inputs to these neurons in the hypothalamus of obese mice [32]. Our studies have demonstrated that leptin can modulate the morphology of astrocytes in the arcuate nucleus, increasing the length of their projections, which is associated with a decrease in synaptic protein concentrations [163]. In other neuroendocrine systems astrocyte coverage and the number of synaptic inputs to specific neurons in the hypothalamus have been shown to be inversely related and modulated by hormonal signals [164]. Therefore, these data suggest that astrocytes regulate synaptic inputs to hypothalamic neurons controlling metabolism and these morphological changes could occur in response to specific hormonal signals.

3.2.2. The agouti viable yellow mouse model (A^{vy})

The spontaneous mutation in A^{vy} mice provides a unique model to study the effects of melanocortin receptor signaling deficits [165]. A^{vy} mice exhibit two prominent phenotypical features, an agouti coat color and adult-onset-obesity [166]. Recently, Pan and colleagues demonstrated that the onset of obesity in adulthood in these mice is associated with region-specific up-regulation of astrocytic LepR expression [167]. In the hypothalamus, A^{y} mice show a reduction in the expression of LepR in neurons and a corresponding increase in astrocytes [168]. When astrocyte activity is inhibited in these mice by fluorocitrate administration, neuronal leptin signaling is enhanced in the hypothalamus [167]. However, the mechanism by which up-regulation of LepR expression in astrocytes affects neuronal leptin signaling is still unclear.

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3.3. Diet-induced obesity

In the last two decades, there has been a dramatic increase in obesity partly due to increased intake of energy-dense foods with a high fat content [169] and the study of hypothalamic dysfunction associated with the development of obesity is currently an important area of investigation in attempt to understand and curtail this phenomenon [15,31,145,170]. The multisystemic effects of obesity, including an increase in circulating cytokines [170,171] and a decrease in protective factors, confirm that the communication between inflammatory and metabolic cells is an important aspect of this process [170,172]. Obesity induces a chronic low-grade inflammation in diverse tissues, including the hypothalamus, resulting in alterations in insulin and leptin sensitivity [173], with the central inflammatory responses being promoted primarily by microglia and astrocytes. Interestingly, central inflammation in response to infection or infusion of proinflammatory cytokines to the hypothalamus can induce a state of negative energy balance [174]. Thus, comparing the mechanisms underlying these two inflammatory situations and determining cause and effect relationships may give insight into how the different metabolic outcomes are achieved.

During the past few years, several studies have reported that in addition to the well-known weight gain and peripheral inflammatory responses, long-term HFD intake increases the number and size of glial cells (gliosis) [15], reduces neurogenesis [15,145,175,176] and promotes astrocyte coverage of specific neuronal populations and blood vessels in the hypothalamus [32], possibly altering the passage of circulating factors to target receptors in the CNS. Moreover, mice exposed to only one day of HFD develop inflammation that is only detected in the hypothalamus, suggesting that hypothalamic inflammation is an event prior to substantial weight gain [15]. This can be explained by the fact that both astrocyte and microglia respond rapidly when faced with an injury or insult, resulting in inflammation and gliosis in attempt to prevent neuronal injury. However, chronic exposure to HFD could exceed their protective ability, with neuronal damage and loss no longer being avoidable [15]. Recently, in vitro studies have demonstrated that metabolic factors derived from HFD such as saturated FAs directly induce reactive gliosis and the release of pro-inflammatory cytokines in cultured primary astrocytes [177,178]. Likewise, diet-induced obese (DIO) mice exhibit a lipid imbalance in the hypothalamus, resulting in increased PPARγ [66] and decreased ApoE expression [61] that might participate in the development of central leptin resistance. These data further suggest that glial cells, the main regulators of inflammation and lipid metabolism in the brain, actively participate in the development of obesity and metabolic syndrome.

Another recent concern for Western countries is the growing rate of childhood obesity and type II diabetes [179]. This is particularly problematic given that both diseases progress more rapidly and are harder to treat in children than in adults [179]. During early stages of life, the brain is more susceptible to long-lasting effects of nutritional changes as there is a critical period during which neural circuits involved in regulating energy balance are developing [180]. In this critical period inadequate nutrition can have permanent outcomes in the brain [180,181] that result in a greater susceptibility to obesity [181,182], with some of these changes being the result of modifications in leptin concentrations [183]. Neonatal over-nutrition due to a reduction in litter size also increases body weight in adulthood and affects astrocytes [163], as well as the number of microglia in specific hypothalamic nuclei [16]. These glial changes are associated with modifications in synaptic protein and hypothalamic cytokine concentrations. Thus, nutritional signals from HFD are not the sole cause of glial affectation in states of positive energy balance. What signals underlie glial activation in non-HFD induced weight gain remain to be identified. Likewise, how early modifications in nutrition affect glial development and their functioning in adulthood remains to be determined.

4. CONCLUDING REMARKS

Rapidly accumulating evidence indicates that glial cells play a key role in the development of obesity, with some of their functions and hormonal responses summarized in Fig. 3. Neuronal output is closely

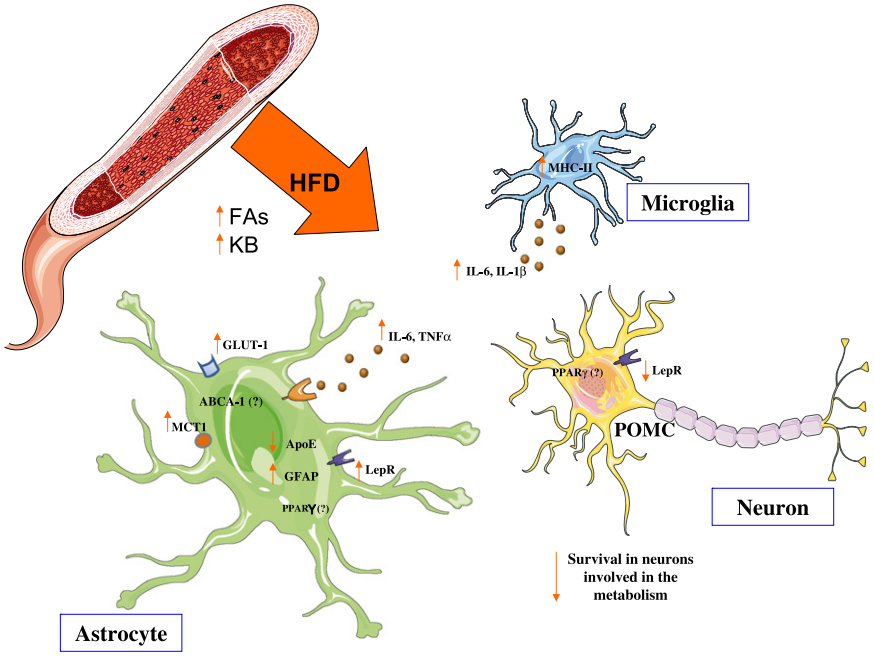

Fig. 3: Schematic representation of known changes in hypothalamic astrocytes, microglia and proopiomelanocortin (POMC) neurons in response to a high fat diet (HFD). ABCA: ATP-binding cassette transporters; ApoE: apolipoprotein E; FA: fatty acids; KB: ketone bodies; GFAP: glial fibrillary acidic protein; GLUT: glucose transporter; IL: interleukin; LepR: leptin receptor; MHC: major histocompatibility complex; MCT: monocarboxylate transporter; PPAR: peroxisome proliferator-activated receptor; TNF: tumor necrosis factor.

associated to astrocytic functions throughout the brain; however, astrocytes are not identical in all brain areas, nor are neuronal functions. The hypothalamic gliosis associated with obesity could be one of the main causes of altered nutritional sensing in the brain, resulting in further body weight gain and secondary metabolic complications. However, much more investigation is needed to understand this process, including the signals involved in its onset and perpetuation. Moreover, it would be of great interest to identify processes that are specific to glial cell participation in systemic metabolic control. This could open the door for possible new targets for drug therapy.

Conflict of interestNone declared.

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