Review

MOLECULAR METABOLISM

Emerging role of glial cells in the control of body weight

Cristina García-Cáceres [a,c], Esther Fuente-Martín [b,c], Jesús Argente [b,c,d], Julie A. Chowen [b,c,*]

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 over-expression 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

[a]Institute of Diabetes and Obesity, Helmholtz Center Munich, German Research Center for Environmental Health (GmbH), Munich, Germany [b]Hospital Infantil Universitario Niño Jesús, Department of Endocrinology, Instituto de Investigación La Princesa, Madrid, Spain [c]CIBER de Fisiopatología de Obesidad y Nutrición, Instituto de Salud Carlos III, Madrid, Spain [d]Department of Pediatrics, Universidad Autónoma de Madrid, Madrid, Spain

*Corresponding author at: Department of Endocrinology, Hospital Infantil Universitario Niño Jesús, Avenida Menéndez Pelayo 65, 28009 Madrid, Spain. Tel./fax: +34 91 503 5939. Email: julieann.chowen@salud.madrid.org (J.A. Chowen)

Received May 30, 2012 • Revision received July 9, 2012 • Accepted July 9, 2012 • Available online August 8, 2012

http://dx.doi.org/10.1016/j.molmet.2012.07.001

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 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

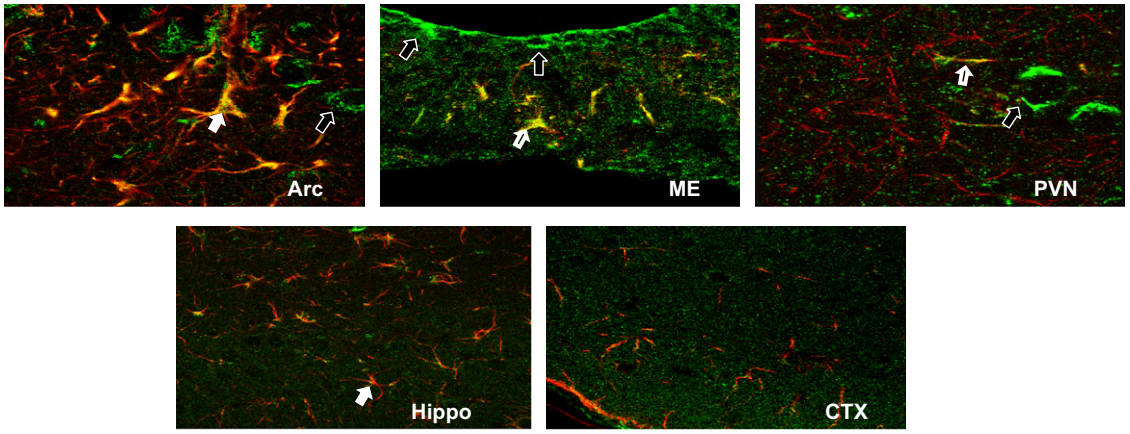

Fig. 1: Microphotographs of double immunofluorescence for glial fibrillary acidic protein (GFAP; red) and leptin receptor (LepR; green) in different areas of the adult male rat brain. Brain sections (40 μm) were incubated in flotation with the primary antibodies mouse anti-GFAP (1:1000, Sigma) and goat 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.

[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 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].

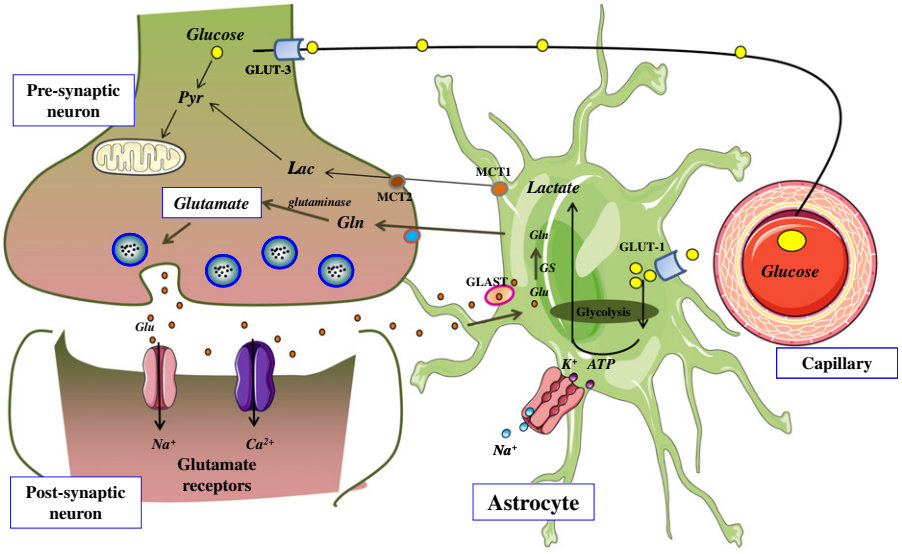

Fig. 2: Schematic representation of glucose and glutamate transport, metabolism and secretion by astrocytes and neurons. The glutamate/glutamine cycle is tightly coupled to glucose oxidation in astrocytes, which then release lactate to be taken up by neurons and be oxidized. Lac: lactate; Pyr: pyruvate;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

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 [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.

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.

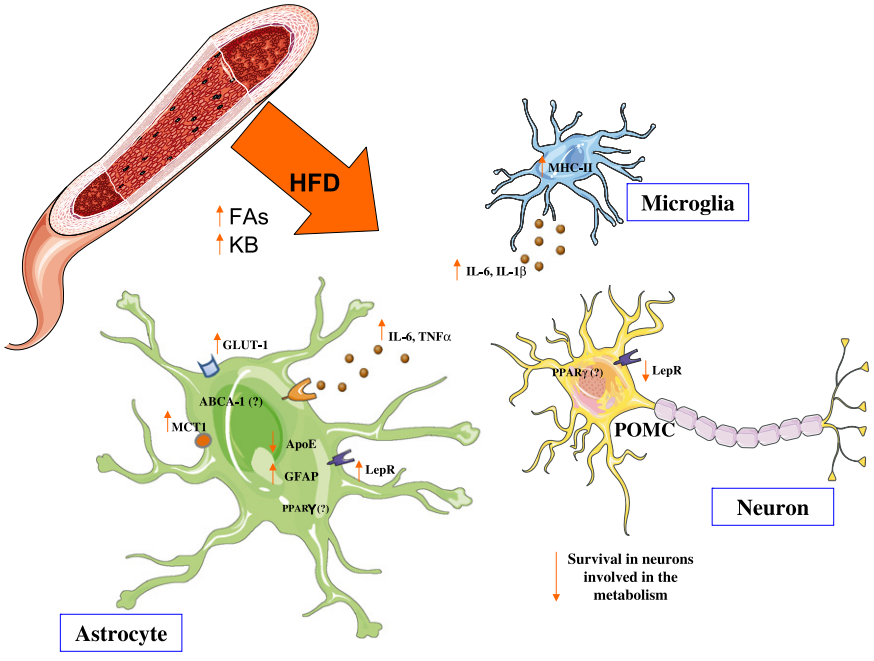

Fig. 3: Schematic representation of known changes in hypothalamic astrocytes, microglia and proopiomelanocortin (POMC) neurons in response to a high fat diet (HFD). ABCA: ATP-binding cassette transporters; ApoE: apolipoprotein E; FA: fatty acids; KB: ketone bodies; GFAP: glial fibrillary acidic protein;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

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 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 interest. None declared.

REFERENCES

[1] Barres, B.A., 1991. New roles for glia. Journal of Neuroscience 11 (12), 3685–3694.

[2] Barres, B.A., 1991. Glial ion channels. Current Opinion in Neurobiology 1 (3), 354–359.

[3] Araque, A., Carmignoto, G., and Haydon, P.G., 2001. Dynamic signaling between astrocytes and neurons. Annual Review of Physiology 63:795–813.

[4] Fields, R.D., and Stevens-Graham, B., 2002. New insights into neuron–glia communication. Science 298 (5593), 556–562.

[5] Perea, G., Navarrete, M., and Araque, A., 2009. Tripartite synapses: astrocytes process and control synaptic information. Trends in Neurosciences 32 (8), 421–431.

[6] Tasker, J.G., Oliet, S.H., Bains, J.S., Brown, C.H., and Stern, J.E., 2012. Glial regulation of neuronal function: from synapse to systems physiology. Journal of Neuroendocrinology 24 (4), 566–576.

[7] Skoff, R.P, and Knapp, P.E., 1995. The origins and lineages of macroglial cells. In: Kettenmann, H., Ransom, B.R. (Eds.), Neuroglia. Oxford University Press, New York, pp. 135–148.

[8] Theele, D.P., and Streit, W.J., 1993. A chronicle of microglial ontogeny. Glia 7 (1), 5–8.

[9] Altman, J., 1994. Microglia emerge from the fog. Trends in Neurosciences 17 (2), 47–49.

[10] Lewis, P.D., 1968. The fate of the subependymal cell in the adult rat brain, with a note on the origin of microglia. Brain 91 (4), 721–736.

[11] Kitamura, T., Miyake, T., and Fujita, S., 1984. Genesis of resting microglia in the gray matter of mouse hippocampus. Journal of Comparative Neurology 226 (3), 421–433.

[12] Neuhaus, J., and Fedoroff, S., 1994. Development of microglia in mouse neopallial cell cultures. Glia 11 (1), 11–17.

[13] Perry, V.H., and Gordon, S., 1988. Macrophages and microglia in the nervous system. Trends in Neurosciences 11 (6), 273–277.

[14] Ling, E.A., and Wong, W.C., 1993. The origin and nature of ramified and amoeboid microglia: a historical review and current concepts. Glia 7 (1), 9–18.

[15] Thaler, J.P., Yi, C.X., Schur, E.A., Guyenet, S.J., Hwang, B.H., Dietrich, M.O., et al., 2012. Obesity is associated with hypothalamic injury in rodents and humans. Journal of Clinical Investigation 122 (1), 153–162.

[16] Tapia-Gonzalez, S., Garcia-Segura, L.M., Tena-Sempere, M., Frago, L.M., Castellano, J.M., Fuente-Martin, E., et al., 2011. Activation of microglia in specific hypothalamic nuclei and the cerebellum of adult rats exposed to neonatal overnutrition. Journal of Neuroendocrinology 23 (4), 365–370.

[17] Freeman, M.R., 2010. Specification and morphogenesis of astrocytes. Science 330 (6005), 774–778.

[18] Bushong, E.A., Martone, M.E., and Ellisman, M.H., 2004. Maturation of astrocyte morphology and the establishment of astrocyte domains during postnatal hippocampal development. International Journal of Developmental Neuroscience 22 (2), 73–86.

[19] Halassa, M.M., Fellin, T., Takano, H., Dong, J.H., and Haydon, P.G., 2007. Synaptic islands defined by the territory of a single astrocyte. Journal of Neuroscience 27 (24), 6473–6477.

[20] Ogata, K., and Kosaka, T., 2002. Structural and quantitative analysis of astrocytes in the mouse hippocampus. Neuroscience 113 (1), 221–233.

[21] Oberheim, N.A., Wang, X., Goldman, S., and Nedergaard, M., 2006. Astrocytic complexity distinguishes the human brain. Trends in Neurosciences 29 (10), 547–553.

[22] Ridet, J.L., Malhotra, S.K., Privat, A., and Gage, F.H., 1997. Reactive astrocytes: cellular and molecular cues to biological function. Trends in Neurosciences 20 (12), 570–577.

[23] Kreutzberg, G.W., 1996. Microglia: a sensor for pathological events in the CNS. Trends in Neurosciences 19 (8), 312–318.

[24] Mattiace, L.A., Davies, P., and Dickson, D.W., 1990. Detection of HLA-DR on microglia in the human brain is a function of both clinical and technical factors. American Journal of Pathology 136 (5), 1101–1114.

[25] Banati, R.B., Gehrmann, J., Schubert, P., and Kreutzberg, G.W., 1993. Cytotoxicity of microglia. Glia 7 (1), 111–118.

[26] Lucius, R., and Sievers, J., 1996. Postnatal retinal ganglion cells in vitro: protection against reactive oxygen species (ROS)-induced axonal degeneration by cocultured astrocytes. Brain Research 743 (1–2), 56–62.

[27] Desagher, S., Glowinski, J., and Premont, J., 1996. Astrocytes protect neurons from hydrogen peroxide toxicity. Journal of Neuroscience 16 (8), 2553–2562.

[28] Knott, C., Stern, G., and Wilkin, G.P., 2000. Inflammatory regulators in Parkinson's disease: iNOS, lipocortin-1, and cyclooxygenases-1 and -2. Molecular and Cellular Neurosciences 16 (6), 724–739.

[29] Sheng, J.G., Ito, K., Skinner, R.D., Mrak, R.E., Rovnaghi, C.R., Van Eldik, L.J., et al., 1996. In vivo and in vitro evidence supporting a role for the inflammatory cytokine interleukin-1 as a driving force in Alzheimer pathogenesis. Neurobiology of Aging 17 (5), 761–766.

[30] Johnstone, M., Gearing, A.J., and Miller, K.M., 1999. A central role for astrocytes in the inflammatory response to beta-amyloid; chemokines, cytokines and reactive oxygen species are produced. Journal of Neuroimmunology 93 (1–2), 182–193.

[31] Yi, C.X., Habegger, K.M., Chowen, J.A., Stern, J., and Tschop, M.H., 2011. A role for astrocytes in the central control of metabolism. Neuroendocrinology 93 (3), 143–149.

[32] Horvath, T.L., Sarman, B., Garcia-Caceres, C., Enriori, P.J., Sotonyi, P., Shanabrough, M., et al., 2010. Synaptic input organization of the melanocortin system predicts diet-induced hypothalamic reactive gliosis and obesity. Proceedings of the National Academy of Sciences of the United States of America 107 (33), 14875–14880.

[33] Abizaid, A., and Horvath, T.L., 2008. Brain circuits regulating energy homeostasis. Regulatory Peptides 149 (1–3), 3–10.

[34] Streit, W.J., Mrak, R.E., and Griffin, W.S., 2004. Microglia and neuroinflammation: a pathological perspective. Journal of Neuroinflammation 1 (1), 14.

[35] Dong, Y., and Benveniste, E.N., 2001. Immune function of astrocytes. Glia 36 (2), 180–190.

[36] Cheunsuang, O., and Morris, R., 2005. Astrocytes in the arcuate nucleus and median eminence that take up a fluorescent dye from the circulation express leptin receptors and neuropeptide Y Y1 receptors. Glia 52 (3), 228–233.

[37] Clarke, D.W., Boyd, F.T., Jr., Kappy, M.S., and Raizada, M.K., 1984. Insulin binds to specific receptors and stimulates 2-deoxy-D-glucose uptake in

cultured glial cells from rat brain. Journal of Biological Chemistry 259 (19), 11672–11675.

[38] Dixit, V.D., Weeraratna, A.T., Yang, H., Bertak, D., Cooper-Jenkins, A., Riggins, G.J., et al., 2006. Ghrelin and the growth hormone secretagogue receptor constitute a novel autocrine pathway in astrocytoma motility. Journal of Biological Chemistry 281 (24), 16681–16690.

[39] Garcia-Segura, L.M., Duenas, M., Busiguina, S., Naftolin, F., and Chowen, J.A., 1995. Gonadal hormone regulation of neuronal–glial interactions in the developing neuroendocrine hypothalamus. Journal of Steroid Biochemistry and Molecular Biology 53 (1–6), 293–298.

[40] Cheung, C.C., Clifton, D.K., and Steiner, R.A., 1997. Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. Endocrinology 138 (10), 4489–4492.

[41] Kang, L., Routh, V.H., Kuzhikandathil, E.V., Gaspers, L.D., and Levin, B.E., 2004. Physiological and molecular characteristics of rat hypothalamic ventromedial nucleus glucosensing neurons. Diabetes 53 (3), 549–559.

[42] Leloup, C., Arluison, M., Lepetit, N., Cartier, N., Marfaing-Jallat, P., Ferre, P., et al., 1994. Glucose transporter 2 (GLUT 2): expression in specific brain nuclei. Brain Research 638 (1–2), 221–226.

[43] Clarke, D.D., and Sokoloff, L., 1994. Circulation and energy metabolism of the brain. In: Siegel, G.J., Agranoff, B.W., Albers, R.W., Molinoff, P.B. (Eds.), Basic Neurochemistry, pp. 645–680.

[44] Pellerin, L., Pellegri, G., Bittar, P.G., Charnay, Y., Bouras, C., Martin, J.L., et al., 1998. Evidence supporting the existence of an activity-dependent astrocyte-neuron lactate shuttle. Developmental Neuroscience 20 (4–5), 291–299.

[45] Anderson, G.J., and Connor, W.E., 1988. Uptake of fatty acids by the developing rat brain. Lipids 23 (4), 286–290.

[46] Nehlig, A., and Pereira de Vasconcelos, A., 1993. Glucose and ketone body utilization by the brain of neonatal rats. Progress in Neurobiology 40 (2), 163–221.

[47] Edmond, J., 1992. Energy metabolism in developing brain cells. Canadian Journal of Physiology and Pharmacology Suppl: S118-29:70.

[48] Guzman, M., and Blazquez, C., 2001. Is there an astrocyte-neuron ketone body shuttle? Trends in Endocrinology and Metabolism 12 (4), 169–173.

[49] Cook, R.P., 1958. Cholesterol: chemistry, biochemistry, and pathology. Academic, New York. (p. 1–542).

[50] Pfrieger, F.W., 2003. Outsourcing in the brain: do neurons depend on cholesterol delivery by astrocytes? Bioessays 25 (1), 72–78.

[51] Wong, J., Quinn, C.M., Guillemin, G., and Brown, A.J., 2007. Primary human astrocytes produce 24(S), 25-epoxycholesterol with implications for brain cholesterol homeostasis. Journal of Neurochemistry 103 (5), 1764–1773.

[52] Pitas, R.E., Boyles, J.K., Lee, S.H., Foss, D., and Mahley, R.W., 1987. Astrocytes synthesize apolipoprotein E and metabolize apolipoprotein E-containing lipoproteins. Biochimica et Biophysica Acta 917 (1), 148–161.

[53] Rapoport, S.I., 2001. In vivo fatty acid incorporation into brain phosholipids in relation to plasma availability, signal transduction and membrane remodeling. Journal of Molecular Neuroscience 16 (2–3), 243–261, discussion 79–84.

[54] Moore, S.A., 2001. Polyunsaturated fatty acid synthesis and release by brain-derived cells in vitro. Journal of Molecular Neuroscience 16 (2–3), 195–200, discussion 15–21.

[55] Lopez, M., Lelliott, C.J., and Vidal-Puig, A., 2007. Hypothalamic fatty acid metabolism: a housekeeping pathway that regulates food intake. Bioessays 29 (3), 248–261.

[56] Hayashi, H., Campenot, R.B., Vance, D.E., and Vance, J.E., 2004. Glial lipoproteins stimulate axon growth of central nervous system neurons in compartmented cultures. Journal of Biological Chemistry 279 (14), 14009–14015.

[57] Poirier, J., 1994. Apolipoprotein E in animal models of CNS injury and in Alzheimer's disease. Trends in Neurosciences 17 (12), 525–530.

[58] Sunny, N.E., Satapati, S., Fu, X., He, T., Mehdibeigi, R., Spring-Robinson, C., et al., 2010. Progressive adaptation of hepatic ketogenesis in mice fed a high-fat diet. American Journal of Physiology, Endocrinology and Metabolism 298 (6), E1226–E1235.

[59] Leino, R.L., Gerhart, D.Z., Duelli, R., Enerson, B.E., and Drewes, L.R., 2001. Diet-induced ketosis increases monocarboxylate transporter (MCT1) levels in rat brain. Neurochemistry International 38 (6), 519–527.

[60] Wang, H., Astarita, G., Taussig, M.D., Bharadwaj, K.G., DiPatrizio, N.V., Nave, K.A., et al., 2011. Deficiency of lipoprotein lipase in neurons modifies the regulation of energy balance and leads to obesity. Cell Metabolism 13 (1), 105–113.

[61] Shen, L., Tso, P., Wang, D.Q., Woods, S.C., Davidson, W.S., Sakai, R., et al., 2009. Up-regulation of apolipoprotein E by leptin in the hypothalamus of mice and rats. Physiology and Behavior 98 (1–2), 223–228.

[62] Pitas, R.E., Boyles, J.K., Lee, S.H., Hui, D., and Weisgraber, K.H., 1987. Lipoproteins and their receptors in the central nervous system. Characterization of the lipoproteins in cerebrospinal fluid and identification of apolipoprotein B,E(LDL) receptors in the brain. Journal of Biological Chemistry 262 (29), 14352–14360.

[63] Boyles, J.K., Pitas, R.E., Wilson, E., Mahley, R.W., and Taylor, J.M., 1985. Apolipoprotein E associated with astrocytic glia of the central nervous system and with nonmyelinating glia of the peripheral nervous system. Journal of Clinical Investigation 76 (4), 1501–1513.

[64] Shen, L., Wang, D.Q., Tso, P., Jandacek, R.J., Woods, S.C., and Liu, M., 2011. Apolipoprotein E reduces food intake via PI3K/Akt signaling pathway in the hypothalamus. Physiology and Behavior 105 (1), 124–128.

[65] Moreno, S., Farioli-Vecchioli, S., and Ceru, M.P., 2004. Immunolocalization of peroxisome proliferator-activated receptors and retinoid X receptors in the adult rat CNS. Neuroscience 123 (1), 131–145.

[66] Diano, S., Liu, Z.W., Jeong, J.K., Dietrich, M.O., Ruan, H.B., Kim, E., et al., 2011. Peroxisome proliferation-associated control of reactive oxygen species sets melanocortin tone and feeding in diet-induced obesity. Nature Medicine 17 (9), 1121–1127.

[67] Tarr, P.T., and Edwards, P.A., 2008. ABCG1 and ABCG4 are coexpressed in neurons and astrocytes of the CNS and regulate cholesterol homeostasis through SREBP-2. Journal of Lipid Research 49 (1), 169–182.

[68] Vance, J.E., and Hayashi, H., 2010. Formation and function of apolipoprotein E-containing lipoproteins in the nervous system. Biochimica et Biophysica Acta 1801 (8), 806–818.

[69] Hirsch-Reinshagen, V., Zhou, S., Burgess, B.L., Bernier, L., McIsaac, S.A., Chan, J.Y., et al., 2004. Deficiency of ABCA1 impairs apolipoprotein E metabolism in brain. Journal of Biological Chemistry 279 (39), 41197–41207.

[70] Robinson, A.M., and Williamson, D.H., 1980. Physiological roles of ketone bodies as substrates and signals in mammalian tissues. Physiological Reviews 60 (1), 143–187.

[71] Halestrap, A.P., and Price, N.T., 1999. The proton-linked monocarboxylate transporter (MCT) family: structure, function and regulation. Biochemical Journal 343 (Part 2), 281–299.

[72] Broer, S., Rahman, B., Pellegri, G., Pellerin, L., Martin, J.L., Verleysdonk, S., et al., 1997. Comparison of lactate transport in astroglial cells and monocarboxylate transporter 1 (MCT 1) expressing *Xenopus laevis* oocytes. Expression of two different monocarboxylate transporters in astroglial cells and neurons. Journal of Biological Chemistry 272 (48), 30096–30102.

[73] Zhang, F., Vannucci, S.J., Philp, N.J., and Simpson, I.A., 2005. Monocarboxylate transporter expression in the spontaneous hypertensive rat: effect of stroke. Journal of Neuroscience Research 79 (1–2), 139–145.

[74] Pierre, K., Pellerin, L., Debernardi, R., Riederer, B.M., and Magistretti, P.J., 2000. Cell-specific localization of monocarboxylate transporters, MCT1 and MCT2, in the adult mouse brain revealed by double immunohistochemical labeling and confocal microscopy. Neuroscience 100 (3), 617–627.

[75] Lin, T., Koustova, E., Chen, H., Rhee, P.M., Kirkpatrick, J., and Alam, H.B., 2005. Energy substrate-supplemented resuscitation affects brain monocarboxylate transporter levels and gliosis in a rat model of hemorrhagic shock. Journal of Trauma 59 (5), 1191–1202.

[76] Konig, B., Koch, A., Giggel, K., Dordschbal, B., Eder, K., and Stangl, G.I., 2008. Monocarboxylate transporter (MCT)-1 is up-regulated by PPARalpha. Biochimica et Biophysica Acta 1780 (6), 899–904.

[77] Park, S., Kim da, S., and Daily, J.W., 2011. Central infusion of ketone bodies modulates body weight and hepatic insulin sensitivity by modifying hypothalamic leptin and insulin signaling pathways in type 2 diabetic rats. Brain Research 1401:95–103.

[78] Diano, S., Kalra, S.P., and Horvath, T.L., 1998. Leptin receptor immunoreactivity is associated with the Golgi apparatus of hypothalamic neurons and glial cells. Journal of Neuroendocrinology 10 (9), 647–650.

[79] Havel, P.J., 2001. Peripheral signals conveying metabolic information to the brain: short-term and long-term regulation of food intake and energy homeostasis. Experimental Biology and Medicine (Maywood) 226 (11), 963–977.

[80] Canabal, D.D., Song, Z., Potian, J.G., Beuve, A., McArdle, J.J., and Routh, V.H., 2007. Glucose, insulin, and leptin signaling pathways modulate nitric oxide synthesis in glucose-inhibited neurons in the ventromedial hypothalamus. American Journal of Physiology Regulatory, Integrative and Comparative Physiology 292 (4), R1418–R1428.

[81] Pan W, Hsuchou H, Jayaram B, Khan RS, Huang EY, Wu X, et al. Leptin action on nonneuronal cells in the CNS: potential clinical applications. Annals of the New York Academy of Sciences, http://dx.doi.org/10.1111/j.1749-6632.2012.06472.x, in press.

[82] Friedman, J.M., and Halaas, J.L., 1998. Leptin and the regulation of body weight in mammals. Nature 395 (6704), 763–770.

[83] Considine, R.V., Sinha, M.K., Heiman, M.L., Kriauciunas, A., Stephens, T.W., Nyce, M.R., et al., 1996. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. New England Journal of Medicine 334 (5), 292–295.

[84] Banks, W.A., DiPalma, C.R., and Farrell, C.L., 1999. Impaired transport of leptin across the blood–brain barrier in obesity. Peptides 20 (11), 1341–1345.

[85] Myers, M.G., Cowley, M.A., and Munzberg, H., 2008. Mechanisms of leptin action and leptin resistance. Annual Review of Physiology 70:537–556.

[86] Mori, H., Hanada, R., Hanada, T., Aki, D., Mashima, R., Nishinakamura, H., et al., 2004. Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. Nature Medicine 10 (7), 739–743.

[87] El-Haschimi, K., Pierroz, D.D., Hileman, S.M., Bjorbaek, C., and Flier, J.S., 2000. Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity. Journal of Clinical Investigation 105 (12), 1827–1832.

[88] Hsuchou, H., He, Y., Kastin, A.J., Tu, H., Markadakis, E.N., Rogers, R.C., et al., 2009. Obesity induces functional astrocytic leptin receptors in hypothalamus. Brain 132 (Part 4), 889–902.

[89] Tang, C.H., Lu, D.Y., Yang, R.S., Tsai, H.Y., Kao, M.C., Fu, W.M., et al., 2007. Leptin-induced IL-6 production is mediated by leptin receptor, insulin receptor substrate-1, phosphatidylinositol 3-kinase, Akt, NF-kappaB, and p300 pathway in microglia. Journal of Immunology 179 (2), 1292–1302.

[90] Lafrance, V., Inoue, W., Kan, B., and Luheshi, G.N., 2010. Leptin modulates cell morphology and cytokine release in microglia. Brain, Behavior, and Immunity 24 (3), 358–365.

[91] Lund-Andersen, H., 1979. Transport of glucose from blood to brain. Physiological Reviews 59 (2), 305–352.

[92] Chiu, S.L., and Cline, H.T., 2010. Insulin receptor signaling in the development of neuronal structure and function. Neural Development 5:7.

[93] Flores, M.B., Fernandes, M.F., Ropelle, E.R., Faria, M.C., Ueno, M., Velloso, L.A., et al., 2006. Exercise improves insulin and leptin sensitivity in hypothalamus of Wistar rats. Diabetes 55 (9), 2554–2561.

[94] Heni, M., Hennige, A.M., Peter, A., Siegel-Axel, D., Ordelheide, A.M., Krebs, N., et al., 2011. Insulin promotes glycogen storage and cell proliferation in primary human astrocytes. PLoS One 6 (6), e21594.

[95] Ji, Y.F., Xu, S.M., Zhu, J., Wang, X.X., and Shen, Y., 2011. Insulin increases glutamate transporter GLT1 in cultured astrocytes. Biochemical and Biophysical Research Communications 405 (4), 691–696.

[96] Penicaud, L., Leloup, C., Lorsignol, A., Alquier, T., and Guillod, E., 2002. Brain glucose sensing mechanism and glucose homeostasis. Current Opinion in Clinical Nutrition and Metabolic Care 5 (5), 539–543.

[97] Rouach, N., Koulakoff, A., Abudara, V., Willecke, K., and Giaume, C., 2008. Astroglial metabolic networks sustain hippocampal synaptic transmission. Science 322 (5907), 1551–1555.

[98] Tsacopoulos, M., and Magistretti, P.J., 1996. Metabolic coupling between glia and neurons. Journal of Neuroscience 16 (3), 877–885.

[99] Levin, B.E., Routh, V.H., Kang, L., Sanders, N.M., and Dunn-Meynell, A.A., 2004. Neuronal glucosensing: what do we know after 50 years? Diabetes 53 (10), 2521–2528.

[100] Wang, R., Liu, X., Hentges, S.T., Dunn-Meynell, A.A., Levin, B.E., Wang, W., et al., 2004. The regulation of glucose-excited neurons in the hypothalamic arcuate nucleus by glucose and feeding-relevant peptides. Diabetes 53 (8), 1959–1965.

[101] Mayer, J., 1953. Glucostatic mechanism of regulation of food intake. New England Journal of Medicine 249 (1), 13–16.

[102] Oomura, Y., Kimura, K., Ooyama, H., Maeno, T., Iki, M., and Kuniyoshi, M., 1964. Reciprocal activities of the ventromedial and lateral hypothalamic areas of cats. Science 143 (3605), 484–485.

[103] Marty, N., Dallaporta, M., and Thorens, B., 2007. Brain glucose sensing, counterregulation, and energy homeostasis. Physiology (Bethesda) 22:241–251.

[104] Levin, B.E., Magnan, C., Dunn-Meynell, A., and Le Foll, C., 2011. Metabolic sensing and the brain: who, what, where, and how? Endocrinology 152 (7), 2552–2557.

[105] Pellerin, L., 2005. How astrocytes feed hungry neurons. Molecular Neurobiology 32 (1), 59–72.

[106] Lam, T.K., Gutierrez-Juarez, R., Pocai, A., and Rossetti, L., 2005. Regulation of blood glucose by hypothalamic pyruvate metabolism. Science 309 (5736), 943–947.

[107] Morgello, S., Uson, R.R., Schwartz, E.J., and Haber, R.S., 1995. The human blood–brain barrier glucose transporter (GLUT1) is a glucose transporter of gray matter astrocytes. Glia 14 (1), 43–54.

[108] Pellerin, L., Bouzier-Sore, A.K., Aubert, A., Serres, S., Merle, M., Costalat, R., et al., 2007. Activity-dependent regulation of energy metabolism by astrocytes: an update. Glia 55 (12), 1251–1262.

[109] Pellerin, L., and Magistretti, P.J., 1994. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proceedings of the National Academy of Sciences of the United States of America 91 (22), 10625–10629.

[110] Kacem, K., Lacombe, P., Seylaz, J., and Bonvento, G., 1998. Structural organization of the perivascular astrocyte endfeet and their relationship with the endothelial glucose transporter: a confocal microscopy study. Glia 23 (1), 1–10.

[111] Chari, M., Yang, C.S., Lam, C.K., Lee, K., Mighiu, P., Kokorovic, A., et al., 2011. Glucose transporter-1 in the hypothalamic glial cells mediates glucose sensing to regulate glucose production in vivo. Diabetes 60 (7), 1901–1906.

[112] Ngarmukos, C., Baur, E.L., and Kumagai, A.K., 2001. Co-localization of GLUT1 and GLUT4 in the blood–brain barrier of the rat ventromedial hypothalamus. Brain Research 900 (1), 1–8.

[113] Garcia, M.A., Millan, C., Balmaceda-Aguilera, C., Castro, T., Pastor, P., Montecinos, H., et al., 2003. Hypothalamic ependymal–glial cells express

the glucose transporter GLUT2, a protein involved in glucose sensing. Journal of Neurochemistry 86 (3), 709–724.

[114] Marty, N., Dallaporta, M., Foretz, M., Emery, M., Tarussio, D., Bady, I., et al., 2005. Regulation of glucagon secretion by glucose transporter type 2 (glut2) and astrocyte-dependent glucose sensors. Journal of Clinical Investigation 115 (12), 3545–3553.

[115] Young, J.K., and McKenzie, J.C., 2004. GLUT2 immunoreactivity in Gomori-positive astrocytes of the hypothalamus. Journal of Histochemistry and Cytochemistry 52 (11), 1519–1524.

[116] Stolarczyk, E., Guissard, C., Michau, A., Even, P.C., Grosfeld, A., Serradas, P., et al., 2010. Detection of extracellular glucose by GLUT2 contributes to hypothalamic control of food intake. American Journal of Physiology—Endocrinology and Metabolism 298 (5), E1078–E1087.

[117] Maher, F., Vannucci, S., Takeda, J., and Simpson, I.A., 1992. Expression of mouse-GLUT3 and human-GLUT3 glucose transporter proteins in brain. Biochemical and Biophysical Research Communications 182 (2), 703–711.

[118] Brant, A.M., Jess, T.J., Milligan, G., Brown, C.M., and Gould, G.W., 1993. Immunological analysis of glucose transporters expressed in different regions of the rat brain and central nervous system. Biochemical and Biophysical Research Communications 192 (3), 1297–1302.

[119] Nagamatsu, S., Sawa, H., Kamada, K., Nakamichi, Y., Yoshimoto, K., and Hoshino, T., 1993. Neuron-specific glucose transporter (NSGT): CNS distribution of GLUT3 rat glucose transporter (RGT3) in rat central neurons. FEBS Letters 334 (3), 289–295.

[120] McCall, A.L., Van Bueren, A.M., Moholt-Siebert, M., Cherry, N.J., and Woodward, W.R., 1994. Immunohistochemical localization of the neuron-specific glucose transporter (GLUT3) to neuropil in adult rat brain. Brain Research 659 (1–2), 292–297.

[121] Gerhart, D.Z., Leino, R.L., Borson, N.D., Taylor, W.E., Gronlund, K.M., McCall, A.L., et al., 1995. Localization of glucose transporter GLUT 3 in brain: comparison of rodent and dog using species-specific carboxyl-terminal antisera. Neuroscience 66 (1), 237–246.

[122] Leino, R.L., Gerhart, D.Z., and Drewes, L.R., 1999. Monocarboxylate transporter (MCT1) abundance in brains of suckling and adult rats: a quantitative electron microscopic immunogold study. Brain Research—Developmental brain Research 113 (1–2), 47–54.

[123] Pierre, K., Magistretti, P.J., and Pellerin, L., 2002. MCT2 is a major neuronal monocarboxylate transporter in the adult mouse brain. Journal of Cerebral Blood Flow and Metabolism 22 (5), 586–595.

[124] Rafiki, A., Boulland, J.L., Halestrap, A.P., Ottersen, O.P., and Bergersen, L., 2003. Highly differential expression of the monocarboxylate transporters MCT2 and MCT4 in the developing rat brain. Neuroscience 122 (3), 677–688.

[125] Bergersen, L.H., 2007. Is lactate food for neurons? Comparison of monocarboxylate transporter subtypes in brain and muscle. Neuroscience 145 (1), 11–19.

[126] Parsons, M.P., and Hirasawa, M., 2010. ATP-sensitive potassium channel-mediated lactate effect on orexin neurons: implications for brain energetics during arousal. Journal of Neuroscience 30 (24), 8061–8070.

[127] Yang, C.Z., Zhao, R., Dong, Y., Chen, X.Q., and Yu, A.C., 2008. Astrocyte and neuron intone through glutamate. Neurochemical Research 33 (12), 2480–2486.

[128] Schmitt, A., Asan, E., Puschel, B., and Kugler, P., 1997. Cellular and regional distribution of the glutamate transporter GLAST in the CNS of rats: nonradioactive in situ hybridization and comparative immunocytochemistry. Journal of Neuroscience 17 (1), 1–10.

[129] Yamada, K., Fukaya, M., Shibata, T., Kurihara, H., Tanaka, K., Inoue, Y., et al., 2000. Dynamic transformation of Bergmann glial fibers proceeds in correlation with dendritic outgrowth and synapse formation of cerebellar Purkinje cells. Journal of Comparative Neurology 418 (1), 106–120.

[130] Regan, M.R., Huang, Y.H., Kim, Y.S., Dykes-Hoberg, M.I., Jin, L., Watkins, A.M., et al., 2007. Variations in promoter activity reveal a differential expression and physiology of glutamate transporters by glia in the developing and mature CNS. Journal of Neuroscience 27 (25), 6607–6619.

[131] Cholet, N., Pellerin, L., Magistretti, P.J., and Hamel, E., 2002. Similar perisynaptic glial localization for the Na+,K+-ATPase alpha 2 subunit and the glutamate transporters GLAST and GLT-1 in the rat somatosensory cortex. Cerebral Cortex 12 (5), 515–525.

[132] Rose, E.M., Koo, J.C., Antflick, J.E., Ahmed, S.M., Angers, S., and Hampson, D.R., 2009. Glutamate transporter coupling to Na,K-ATPase. Journal of Neuroscience 29 (25), 8143–8155.

[133] Serres, S., Bouyer, J.J., Bezancon, E., Canioni, P., and Merle, M., 2003. Involvement of brain lactate in neuronal metabolism. NMR in Biomedicine 16 (6–7), 430–439.

[134] Serres, S., Bezancon, E., Franconi, J.M., and Merle, M., 2004. Ex vivo analysis of lactate and glucose metabolism in the rat brain under different states of depressed activity. Journal of Biological Chemistry 279 (46), 47881–47889.

[135] Lee, D.A., Bedont, J.L., Pak, T., Wang, H., Song, J., Miranda-Angulo, A., et al., 2012. Tanycytes of the hypothalamic median eminence form a diet-responsive neurogenic niche. Nature Neuroscience 15 (5), 700–702.

[136] Rodriguez, E.M., Blazquez, J.L., Pastor, F.E., Pelaez, B., Pena, P., Peruzzo, B., et al., 2005. Hypothalamic tanycytes: a key component of brain–endocrine interaction. International Review of Cytology 247:89–164.

[137] Garcia, M.A., Carrasco, M., Godoy, A., Reinicke, K., Montecinos, V.P., Aguayo, L.G., et al., 2001. Elevated expression of glucose transporter-1 in hypothalamic ependymal cells not involved in the formation of the brain–cerebrospinal fluid barrier. Journal of Cellular Biochemistry 80 (4), 491–503.

[138] Sanders, N.M., Dunn-Meynell, A.A., and Levin, B.E., 2004. Third ventricular alloxan reversibly impairs glucose counterregulatory responses. Diabetes 53 (5), 1230–1236.

[139] Frayling, C., Britton, R., and Dale, N., 2011. ATP-mediated glucosensing by hypothalamic tanycytes. Journal of Physiology 589 (Part 9), 2275–2286.

[140] Berger, U.V., and Hediger, M.A., 2001. Differential distribution of the glutamate transporters GLT-1 and GLAST in tanycytes of the third ventricle. Journal of Comparative Neurology 433 (1), 101–114.

[141] Diano, S., Naftolin, F., and Horvath, T.L., 1998. Kainate glutamate receptors (GluR5-7) in the rat arcuate nucleus: relationship to tanycytes, astrocytes, neurons and gonadal steroid receptors. Journal of Neuroendocrinology 10 (4), 239–247.

[142] Hokfelt, T., Foster, G., Schultzberg, M., Meister, B., Schalling, M., Goldstein, M., et al., 1988. DARPP-32 as a marker for D-1 dopaminoceptive cells in the rat brain: prenatal development and presence in glial elements (tanycytes) in the basal hypothalamus. Advances in Experimental Medicine and Biology 235:65–82.

[143] Prentice, A., and Jebb, S., 2004. Energy intake/physical activity interactions in the homeostasis of body weight regulation. Nutrition Reviews 62 (7, Part 2), S98–S104.

[144] Molteni, R., Barnard, R.J., Ying, Z., Roberts, C.K., and Gomez-Pinilla, F., 2002. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience 112 (4), 803–814.

[145] Moraes, J.C., Coope, A., Morari, J., Cintra, D.E., Roman, E.A., Pauli, J.R., et al., 2009. High-fat diet induces apoptosis of hypothalamic neurons. PLoS One 4 (4), e5045.

[146] Beltowski, J., Wojcicka, G., Gorny, D., and Marciniak, A., 2000. The effect of dietary-induced obesity on lipid peroxidation, antioxidant enzymes and total plasma antioxidant capacity. Journal of Physiology and Pharmacology 51 (4, Part 2), 883–896.

[147] Halliwell, B., 2001. Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. Drugs & Aging 18 (9), 685–716.

[148] Santin, K., da Rocha, R.F., Cechetti, F., Quincozes-Santos, A., de Souza, D.F., Nardin, P., et al., 2011. Moderate exercise training and chronic caloric restriction modulate redox status in rat hippocampus. Brain Research 1421:1–10.

[149] Carro, E., Trejo, J.L., Busiguina, S., and Torres-Aleman, I., 2001. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. Journal of Neuroscience 21 (15), 5678–5684.

[150] Lu, M., and Hu, G., 2012. Targeting metabolic inflammation in Parkinson's disease: implications for prospective therapeutic strategies. Clinical and Experimental Pharmacology & Physiology 39 (6), 577–585.

[151] Srivastava, S., and Haigis, M.C., 2011. Role of sirtuins and calorie restriction in neuroprotection: implications in Alzheimer's and Parkinson's diseases. Current Pharmaceutical Design 17 (31), 3418–3433.

[152] Qian, Y., Guan, T., Tang, X., Huang, L., Huang, M., Li, Y., et al., 2011. Astrocytic glutamate transporter-dependent neuroprotection against glutamate toxicity: an in vitro study of maslinic acid. European Journal of Pharmacology 651 (1–3), 59–65.

[153] Fernandez-Fernandez, S., Almeida, A., and Bolanos, J.P., 2012. Antioxidant and bioenergetic coupling between neurons and astrocytes. Biochemical Journal 443 (1), 3–11.

[154] Perera, T.D., Lu, D., Thirumangalakudi, L., Smith, E.L., Yaretskiy, A., Rosenblum, L.A., et al., 2011. Correlations between hippocampal neurogenesis and metabolic indices in adult nonhuman primates. Neural Plasticity 2011:1–6.

[155] Nichols, N.R., Finch, C.E., and Nelson, J.F., 1995. Food restriction delays the age-related increase in GFAP mRNA in rat hypothalamus. Neurobiology of Aging 16 (1), 105–110.

[156] Kushner, P.D., Stephenson, D.T., and Wright, S., 1991. Reactive astrogliosis is widespread in the subcortical white matter of amyotrophic lateral sclerosis brain. Journal of Neuropathology and Experimental Neurology 50 (3), 263–277.

[157] McGeer, P.L., Itagaki, S., Boyes, B.E., and McGeer, E.G., 1988. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 38 (8), 1285–1291.

[158] Ahima, R.S., Bjorbaek, C., Osei, S., and Flier, J.S., 1999. Regulation of neuronal and glial proteins by leptin: implications for brain development. Endocrinology 140 (6), 2755–2762.

[159] Montague, C.T., Farooqi, I.S., Whitehead, JP, Soos, MA, Rau, H., Wareham, N.J., et al., 1997. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 387 (6636), 903–908.

[160] Licinio, J., Caglayan, S., Ozata, M., Yildiz, B.O., de Miranda, P.B., O'Kirwan, F., et al., 2004. Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. Proceedings of the National Academy of Sciences of the United States of America 101 (13), 4531–4536.

[161] Chen, H., Charlat, O., Tartaglia, L.A., Woolf, E.A., Weng, X., Ellis, S.J., et al., 1996. Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in db/db mice. Cell 84 (3), 491–495.

[162] Pinto, S., Roseberry, A.G., Liu, H., Diano, S., Shanabrough, M., Cai, X., et al., 2004. Rapid rewiring of arcuate nucleus feeding circuits by leptin. Science 304 (5667), 110–115.

[163] Garcia-Caceres, C., Fuente-Martin, E., Burgos-Ramos, E., Granado, M., Frago, L.M., Barrios, V., et al., 2011. Differential acute and chronic effects of leptin on hypothalamic astrocyte morphology and synaptic protein levels. Endocrinology 152 (5), 1809–1818.

[164] Garcia-Segura, L.M., Luquin, S., Parducz, A., and Naftolin, F., 1994. Gonadal hormone regulation of glial fibrillary acidic protein immunoreactivity and glial ultrastructure in the rat neuroendocrine hypothalamus. Glia 10 (1), 59–69.

[165] Shimizu, H., Shargill, N.S., Bray, G.A., Yen, T.T., and Gesellchen, P.D., 1989. Effects of MSH on food intake, body weight and coat color of the yellow obese mouse. Life Sciences 45 (6), 543–552.

[166] Michaud, E.J., Bultman, S.J., Klebig, M.L., van Vugt, M.J., Stubbs, L.J., Russell, L.B., et al., 1994. A molecular model for the genetic and phenotypic characteristics of the mouse lethal yellow (Ay) mutation. Proceedings of the National Academy of Sciences of the United States of America 91 (7), 2562–2566.

[167] Pan, W., Hsuchou, H., Xu, C., Wu, X., Bouret, S.G., and Kastin, A.J., 2011. Astrocytes modulate distribution and neuronal signaling of leptin in the hypothalamus of obese A vy mice. Journal of Molecular Neuroscience 43 (3), 478–484.

[168] Pan, W., Hsuchou, H., He, Y., Sakharkar, A., Cain, C., Yu, C., et al., 2008. Astrocyte leptin receptor (ObR) and leptin transport in adult-onset obese mice. Endocrinology 149 (6), 2798–2806.

[169] Spiegelman, B.M., and Flier, J.S., 2001. Obesity and the regulation of energy balance. Cell 104 (4), 531–543.

[170] Lumeng, C.N., and Saltiel, A.R., 2011. Inflammatory links between obesity and metabolic disease. Journal of Clinical Investigation 121 (6), 2111–2117.

[171] Hotamisligil, G.S., Arner, P., Caro, J.F., Atkinson, R.L., and Spiegelman, B.M., 1995. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. Journal of Clinical Investigation 95 (5), 2409–2415.

[172] Thaler, J.P., and Schwartz, M.W., 2010. Minireview: inflammation and obesity pathogenesis: the hypothalamus heats up. Endocrinology 151 (9), 4109–4115.

[173] Velloso, L.A., Araujo, E.P., and de Souza, C.T., 2008. Diet-induced inflammation of the hypothalamus in obesity. Neuroimmunomodulation 15 (3), 189–193.

[174] Gautron, L., and Laye, S., 2009. Neurobiology of inflammation-associated anorexia. Frontiers in Neuroscience 3:59.

[175] Lee, E.B., and Ahima, R.S., 2012. Alteration of hypothalamic cellular dynamics in obesity. Journal of Clinical Investigation 122 (1), 22–25.

[176] McNay, D.E., Briancon, N., Kokoeva, M.V., Maratos-Flier, E., and Flier, J.S., 2012. Remodeling of the arcuate nucleus energy-balance circuit is inhibited in obese mice. Journal of Clinical Investigation 122 (1), 142–152.

[177] Hsuchou, H., Kastin, A.J., and Pan, W., 2012. Blood-borne metabolic factors in obesity exacerbate injury-induced gliosis. Journal of Molecular Neuroscience 47 (2), 267–277.

[178] Gupta, S., Knight, A.G., Gupta, S., Keller, J.N., and Bruce-Keller, A.J., 2012. Saturated long-chain fatty acids activate inflammatory signaling in astrocytes. Journal of Neurochemistry 120 (6), 1060–1071.

[179] Zeitler, P., Hirst, K., Pyle, L., Linder, B., Copeland, K., Arslanian, S., et al., 2012. A clinical trial to maintain glycemic control in youth with type 2 diabetes. New England Journal of Medicine 366 (24), 2247–2256.

[180] Bouret, S.G., 2010. Role of early hormonal and nutritional experiences in shaping feeding behavior and hypothalamic development. Journal of Nutrition 140 (3), 653–657.

[181] Morris, M.J., and Chen, H., 2009. Established maternal obesity in the rat reprograms hypothalamic appetite regulators and leptin signaling at birth. International Journal of Obesity (London) 33 (1), 115–122.

[182] Levin, B.E., and Govek, E., 1998. Gestational obesity accentuates obesity in obesity-prone progeny. American Journal of Physiology 275 (4, Part 2), R1374–R1379.

[183] Bouret, S.G., 2009. Early life origins of obesity: role of hypothalamic programming. Journal of Pediatric Gastroenterology and Nutrition 48 (Suppl. 1), S31–S38.

