The Astrocyte: Metabolic Hub of the Brain

L. Felipe Barros,[1,2] Stefanie Schirmeier,[3] and Bruno Weber[4]

[1]Centro de Estudios Científicos, Valdivia 5110465, Chile

[2]Universidad San Sebastián, Facultad de Medicina y Ciencia, Valdivia 5110693, Chile

[3]Technische Universität Dresden, Department of Biology, 01217 Dresden, Germany

[4]University of Zurich, Institute of Pharmacology and Toxicology, 8057 Zurich, Switzerland

Correspondence: bweber@pharma.uzh.ch

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Astrocytic metabolism has taken center stage. Interposed between the neuron and the vasculature, astrocytes exert control over the fluxes of energy and building blocks required for neuronal activity and plasticity. They are also key to local detoxification and waste recycling. Whereas neurons are metabolically rigid, astrocytes can switch between different metabolic profiles according to local demand and the nutritional state of the organism. Their metabolic state even seems to be instructive for peripheral nutrient mobilization and has been implicated in information processing and behavior. Here, we summarize recent progress in our understanding of astrocytic metabolism and its effects on metabolic homeostasis and cognition.

In the first edition of *Glia*, we discussed how excitatory synaptic activity is an avid consumer of metabolic energy, generated by the oxidation of blood-borne glucose.[5] Astrocytes are central players in brain metabolism (Fig. 1), supplying neurons with energy substrates and precursors for biosynthesis, while recycling neurotransmitters, oxidized scavengers, and other waste products (Weber and Barros 2015). Here, we review the energy metabolism of mammalian astrocytes and glial cells, which play similar roles in invertebrates, illuminated by emerging techniques, such as genetically encoded sensors. In a nutshell, astrocytes take the brunt of the metabolic load, subsidizing neurons so these can allocate more resources to information processing.

MORPHOLOGY OF ASTROCYTES AND THEIR ROLE AS INTERFACE CELLS

Neurons, glial cells, and the cerebral vasculature form a tightly coupled ensemble, adeptly described by the recently coined term "neuro-glia-vascular unit" (Kugler et al. 2021). This anatomical and functional unit is fundamental to our understanding of brain metabolism and astrocytes are responsible for its cohesion. Astrocytes are complex spongiform cells (Aten et al. 2022) with a central cell body and a dense radial arrangement of processes that follow a branch-branchlet-leaflet scheme, parceling the neuropil into largely non-overlapping domains. Terminal processes originate from every part of the astrocyte and can also form loop-like structures (Arizono et al.

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Figure 1. The astrocyte is the metabolic hub of the brain. The backbone of metabolism is the glycolytic pathway plus the Krebs cycle, where fuel and building blocks are generated for neural activity, growth, plasticity, and repair. Astrocytic glycogen is the main energy and carbon store of brain tissue. (*Left* panel) Wedged between blood and the rest of the parenchyma, the astrocyte inputs and integrates substrates, waste products, and regulatory signals, both local and systemic. (*Right* panel) The astrocyte controls the internal milieu of the brain and sustains the function of neurons and other parenchymal cells through the controlled output of energy-rich lactate and other metabolic precursors and signals. Acting locally, the metabolism of astrocytes and equivalent glial cells in invertebrates affects multiple functions of the brain and distant organs. The coupling between astrocytes and neurons has received a great deal of attention and has been studied in various model systems, but less is known regarding the metabolic interaction between astrocytes and oligodendrocytes, microglia, smooth muscle, pericytes, and endothelial cells. (DHA) Dehydroascorbate.

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2020; Aten et al. 2022). Each astrocyte is estimated to enwrap about four neuronal somata and 10^5 synapses (Bushong et al. 2002; Halassa et al. 2007; Oberheim et al. 2008). Astrocytes cover virtually the entire basal lamina of the cerebral vasculature (Mathiisen et al. 2010) with delicate processes termed "perivascular astrocytic endfeet" (Reichenbach 1989). Recent data show that every astrocyte has contact with at least one but up to four capillaries (Hösli et al. 2022). Astrocytes also extend peripheral processes (Derouiche and Frotscher 2001) that make close contact with neurons at somata, dendrites, and axons (Aten et al. 2022). The term "tripartite synapse" (Araque et al. 1999) comes from the fact that most of the synapses, pre- and postsynapse, are touched by astrocytic processes (Ventura and Harris 1999). The synapse–astrocyte interface has attracted much attention in relation to neurotransmission (Halassa and Haydon 2010), but it is also of paramount importance for metabolism. The astrocyte removes the neurotransmitter glutamate from the synapse through high-affinity surface transporters, triggering intracellular metabolic events that are described elsewhere in this paper. The spatial relationship between astrocytes and synapses is complex (Bernardinelli et al. 2014a). Coverage of individual synapses by astrocytic processes varies across brain regions, reaching almost 100% in cerebellum (Grosche et al. 1999), 86% in hippocampus (Aten et al. 2022), and only 68% in neocortex (Kikuchi et al. 2020). The degree of coverage is dynamic and dependent on synaptic activity (Bernardinelli et al. 2014b); it modulates local levels of glutamate (Oliet et al. 2001) as well as its cotransmitter D-serine (Panatier et al. 2006). Conceivably, coverage may also modulate the metabolic exchange between astrocytes and neurons.

ANATOMY OF METABOLISM AND METABOLITE TRANSPORT

The presence of the blood–brain barrier (BBB) means that brain tissue is relatively isolated metabolically. The BBB prevents free diffusion of circulating molecules, protecting neural cells from harmful substances while permitting precise regulation of the brain extracellular milieu, which is essential for signaling. But the BBB also taxes endothelial cells with the transport of metabolic substrates and waste (for review, see Weiler et al. 2017). Metabolite flux across the BBB is tightly controlled. Only small gases like O_2 and CO_2 and lipophilic molecules under 450 Da and with a polar surface area of lower than 90 $Å^2$ can diffuse freely in and out of the nervous system (van de Waterbeemd et al. 1998). Through regulation of metabolite transport, the BBB protects the nervous system from changes in circulating metabolite concentrations, occurring as, for example, the effects of malnutrition (Kumagai et al. 1995; Simpson et al. 1999; Hertenstein et al. 2021).

The main energy source for the brain is glucose (Siesjö 1978). Glucose is transported across the BBB via the endothelial isoform of GLUT1 (55 kDa) (Dick et al. 1984; Gerhart et al. 1989; Sivitz et al. 1989; Harik et al. 1990; Farrell and Pardridge 1991; Maher et al. 1991; Simpson et al. 2001). Endothelial GLUT1 expression is up-regulated during hypoglycemia (Kumagai et al. 1995; Simpson et al. 1999). Furthermore, expression of the sodium-dependent glucose transporters, SGLT1 and SGLT2, is induced in endothelial cells by ischemia (Nishizaki et al. 1995; Nishizaki and Matsuoka 1998; Enerson and Drewes 2006; Vemula et al. 2009). Plus, the transport of other metabolites, like ketone bodies or fatty acids, can be adapted to the nutritional status of the organism (Pifferi et al. 2021; Düking et al. 2022). Such adaptations are likely protecting the brain from metabolic stress and seem to be a conserved mechanism that is also present in insects (Hertenstein et al. 2021).

Glucose is then further transported into astrocytic endfeet that enwrap microvessels and express the astrocytic form of GLUT1 (45 kDa) (Maher et al. 1991, 1994; Mathiisen et al. 2010). Astrocytes maintain a substantial pool of glucose, unlike other cell types (Bittner et al. 2010, 2011; Prebil et al. 2011; Ruminot et al. 2011). Since GLUT1 is a rather low affinity transporter, it can facilitate both the influx and efflux of glucose. The neuronal transporter GLUT3, however, has a higher affinity and is therefore best suited for glucose uptake (Barros and Deitmer 2010). Intuitively, we would expect neurons to consume more glucose than astrocytes in the nervous system. However, it is, in fact, astrocytes that con-

sume most, at least as primary cells and in tissue slices (Bouzier-Sore et al. 2003, 2006; Barros et al. 2009; Jakoby et al. 2014).

Notably, there seems to be a discrepancy between the rate of glycolysis and the rate of mitochondrial oxidative phosphorylation in astrocytes (Hyder et al. 2006), resulting from differential transcriptional and posttranslational regulation of key enzymes (Lovatt et al. 2007; Cahoy et al. 2008; Herrero-Mendez et al. 2009; Halim et al. 2010). A glycolytic rate that outruns the rate of oxidative phosphorylation leads to a net production of pyruvate in astrocytes, which is exported as lactate and used as an efficient fuel for the neuronal tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) (Schurr et al. 1988; Bouzier-Sore et al. 2006; Wyss et al. 2011; Mächler et al. 2016). Their low dependence on OXPHOS as a source of ATP and their greater metabolic flexibility renders astrocytes rather insensitive to OXPHOS inhibition in vitro and in vivo (Bolaños et al. 1994; Almeida et al. 2001; San Martín et al. 2017; Supplie et al. 2017; Fiebig et al. 2019). Inhibition of OXPHOS in astrocytes leads to a compensatory up-regulation of glycolysis (Almeida et al. 2004). Neurons in contrast, are very sensitive to a lack of OXPHOS, as they are unable to upregulate glycolysis as efficiently (Bolaños et al. 2010). In neurons, the glycolytic rate needs to be kept low, because a significant amount of glucose must be metabolized in the pentose–phosphate pathway (PPP) to produce building blocks and NADPH, an essential cofactor in antioxidant protection of neurons (see Bonvento and Bolaños 2021 for a comprehensive review). Astrocytes and neurons have very different metabolic machinery and thus very different metabolic needs. While the flux of glucose through glycolysis must be kept low in neurons to allow for a sufficient level of antioxidants, high levels of glycolysis are essential for astrocytes, forcing neurons and astrocytes to cooperate metabolically to maintain nervous system function.

This metabolic coupling involves the transfer of lactate from the astrocyte to the neuron; a phenomenon termed the astrocyte neuron lactate shuttle (ANLS) (Pellerin and Magistretti 1994). The vectorial flux of lactate is fostered by differential expression of transporters and enzymes. Astrocytes express the monocarboxylate transporter 4 (MCT4) lactate-permeable ion channels and lactate dehydrogenase 5 (LDH5) all of which promote lactate export (Pierre and Pellerin 2005; Sotelo-Hitschfeld et al. 2015; Karagiannis et al. 2016; Contreras-Baeza et al. 2019), whereas neurons express MCT2 and LDH1, which promote lactate import (Aubert et al. 2005; Barros and Deitmer 2010). MCT2 expression maps local glucose consumption and the expression of genes involved in local K^+ dynamics across the brain (Medel et al. 2022) and its inhibition disrupts neurovascular coupling (Roumes et al. 2021). As discussed below, glucose uptake, glycolytic rate, and lactate production by astrocytes are all sensitive to neuronal activity and thus the rate of neuronal ATP consumption.

In contrast to synapses, long axons are not in ample contact with astrocytes, and they are often myelinated. On the one hand, myelination permits efficient signal transduction, but on the other hand, it blocks axonal access to the interstitial space and thus to circulation-derived metabolites. Axons and oligodendrocytes have been shown to have a similar metabolic relationship as synapses and astrocytes (Fünfschilling et al. 2012; Lee et al. 2012; Saab et al. 2016).

The metabolic division between glial cells and neurons has long been thought to be an adaptation to the highly complex mammalian nervous system. In recent years, however, increasing evidence suggests that metabolic specialization of glial cells and neurons is a basic mechanism of nervous system function, since it is conserved from insects to man (Volkenhoff et al. 2015; Delgado et al. 2018; González-Gutiérrez et al. 2020; reviewed in Rittschof and Schirmeier 2018). In insects, glial cells are glycolytic and produce lactate and alanine that are shuttled to neurons (Rittschof and Schirmeier 2017; Rabah et al. 2023). Lactate supply is essential for neuronal function as lack of glial glycolysis induces severe neurodegeneration and premature death (Volkenhoff et al. 2015). Remarkably, glycolysis in insect neurons is largely dispensable, even though neurons take up glucose and can likely metabolize it via glycolysis and the phosphogluconate pathway (PPP) (Volkenhoff et al. 2015, 2018).

COMPARTMENTALIZATION AND ENERGY RESERVOIRS

The BBB provides protection against circulating toxins (Obermeier et al. 2013), behavioral stability in the face of starvation and disease, and the possibility of metabolic specialization, for example, co-option of the amino acid glutamate for the purposes of neurotransmission. A necessary trade-off is that complex and energetically expensive chemical reactions need to be carried out "in-house." Neurons are deficient in several metabolic pathways, which are correspondingly stronger in astrocytes, including the production of building blocks for biosynthesis (Yu et al. 1983; Herrero-Mendez et al. 2009) antioxidation (Schmidt and Dringen 2012), and waste disposal (Bak et al. 2006; Bélanger et al. 2011). The metabolic reactions in astrocytes are also present in other cell types of the body. The uniqueness of astrocytic metabolism stems from its intimate and heavily biased relationship with the super-specialized neuron, in a context of relative insulation from circulation.

Metabolic processes occurring within neurons and astrocytes are distributed between membrane compartments and are undertaken by enzymes and transporters. Enzymes transform molecules while transporters move them between compartments. As the control of flux is distributed throughout multiple nodes of the metabolic network, specific enzymes or transporters are no longer considered to be rate limiting. Mitochondria, the endoplasmic reticulum, and other membrane-bound organelles host specific reactions, integrated with the rest of the metabolic network through exchange with the cytosol. The nucleus is well connected to the cytosol, behaving as a metabolic buffer.

METABOLISM DEPENDENT ON NEURONAL ACTIVITY

Glucose enters the brain parenchyma via endothelial GLUT1, a facilitative transporter whose commanding role is underscored by the neurological manifestations of GLUT1 haploinsufficiency (Wang et al. 2015). What happens to the sugar beyond the endothelium is still unclear. Electron microscopy of chemically fixed tissue showed that capillaries are fully enwrapped by astrocytic endfeet (Mathiisen et al. 2010), suggesting astrocytes would control the flux of glucose to neurons. Alternatively, cryofixating brain tissue, considered a less invasive method, showed only partial coverage (Korogod et al. 2015), suggesting the brain interstice is a single well-mixed compartment that feeds all parenchymal cells on equal terms.

According to biophysical considerations, neural activity imposes comparable metabolic demands on both astrocytes and neurons, in line with their similar mitochondrial endowment and TCA cycle fluxes (Attwell and Laughlin 2001; Harris et al. 2012; Barros 2022). The unexpected discovery of energy-inefficient lactate production despite oxygen availability (i.e., aerobic glycolysis) showed that activated brain metabolism is not only greater but is different (Fox et al. 1988; Prichard et al. 1991; Hu and Wilson 1997). Astrocytes have been found to play a central role in aerobic glycolysis. Extracellular K^+ is a major mediator between excitatory neuronal activity and astrocytic energy metabolism. This cation is released by postsynaptic neurons, amplifying the presynaptic release of glutamate by a factor of 100. Upon reaching astrocytic processes (Rasmussen et al. 2019; Armbruster et al. 2022), K^+ stimulates their glucose transport and consumption (Bittner et al. 2011; Fernández-Moncada et al. 2021), the latter comediated by the Na^+-bicarbonate transporter NBCe1 and the $\alpha2\beta2$ Na^+/K^+ ATPase (Ruminot et al. 2011, 2019; Köhler et al. 2018). Activation of glycolysis produces an ATP surplus and acute inhibition of astrocytic oxygen consumption, the so-called crabtree effect (Fernández-Moncada et al. 2018). At the same time, astrocytes release lactate through a voltage-sensitive anion channel (Sotelo-Hitschfeld et al. 2015; Zuend et al. 2020), diminishing its tonic hold of glycolysis (Sotelo-Hitschfeld et al. 2012). Glutamate, NH_4^+ and nitric oxide are also capable of modulating astrocytic metabolism in an acute manner. Glutamate activates GLUT1 and has a delayed stimulatory effect on glycolysis that evolves over minutes (Pellerin and Magistretti 1994; Loaiza et al. 2003; Bittner et al. 2011), the occurrence that gave birth to the astrocyte-to-neu-

ron lactate shuttle hypothesis (Pellerin and Magistretti 1994; Pellerin et al. 2007; Magistretti and Allaman 2018). NH_4^+ and nitric oxide veer glycolytic pyruvate away from mitochondria into lactate (Lerchundi et al. 2015; San Martín et al. 2017). The net result of these quick events is that more oxygen and lactate are made available to the active brain area (Zuend et al. 2020; Hosford et al. 2022; Barros et al. 2023). Aerobic glycolysis in astrocytes also promotes the production of D-serine, an NMDA receptor co-agonist that is defective in mice with Alzheimer's disease (Le Douce et al. 2020).

Astrocytes can store glucose in the form of glycogen, which is converted into lactate during memory processing, exercise, hypoglycemia, and ischemia (Dringen et al. 1993; Gibbs et al. 2006; Newman et al. 2011; Suzuki et al. 2011; Oe et al. 2016; Matsui et al. 2017; Waitt et al. 2017). Several neuronal signals might mobilize glycogen, including noradrenaline, adenosine, and vasoactive intestinal peptide (VIP). Extracellular K^+ has been proposed to mobilize glycogen via the soluble adenylyl cyclase (sAC) (Choi et al. 2012), a mechanism that awaits confirmation (Theparambil et al. 2016; Horvat et al. 2021; Jakobsen et al. 2021). A fraction of the glucose captured by astrocytes may go through glycogen before becoming pyruvate and lactate, a phenomenon termed the "glycogen shunt" (Shulman et al. 2001; Walls et al. 2009).

Meanwhile, active neurons increase their energy consumption, chiefly at the α3β1 Na^+/K^+ ATPase (Harris et al. 2012; Baeza-Lehnert et al. 2019). The identity of the substrate that fuels active neurons (i.e., glucose versus astrocytic lactate) is an ongoing debate (Bak and Walls 2018; Barros and Weber 2018; Magistretti and Allaman 2018; Dienel 2019), informed by multiple technical approaches, including an expanding armamentarium of genetically encoded sensors (Barros et al. 2018; Koveal et al. 2022; San Martín et al. 2022). Genetically encoded indicators have become the gold standard to measure calcium transients (e.g., using GCaMPs). Measuring intracellular metabolite concentrations is far more challenging, because small and slow changes imposed on high baseline levels need to be detected. Whenever possible, intensiometric or fluorescent lifetime signals should be converted into molar metabolite concentrations. Two recent in vitro studies were based on genetically encoded metabolite sensors. The first, explored the initial few seconds after neurotransmission in hippocampal granule cells in acute slices and showed a transient increase in cytosolic NADH/NAD^+, pointing to a transient mismatch between glycolysis and mitochondrial metabolism. Still, these cells did not appear to release lactate (Díaz-García et al. 2017). In the second study, pyramidal cells electrically stimulated in culture showed similar degrees of activation of glucose consumption and mitochondrial pyruvate consumption, without apparent changes in the intracellular levels of lactate or pyruvate (Baeza-Lehnert et al. 2019). Whether or not neurons produce lactate and hence contribute to aerobic glycolysis under physiological conditions remains to be clarified. Also unclear is the extent to which neurons are energized by glucose versus lactate, how much of the glucose is diverted through the PPP (Herrero-Mendez et al. 2009), and whether there are different fueling strategies for neuronal subtypes and across brain regions. In this respect, juvenile neurons subjected to memory tasks were found to rely more on glucose than adult neurons, an observation that helps to reconcile ostensibly conflicting observations (Cruz et al. 2022). Comprehensive reviews of the energetics of neurotransmission are available (Magistretti and Allaman 2018; Yellen 2018; Dienel 2019; Bonvento and Bolaños 2021; Barros et al. 2023).

SUPPLY OF BUILDING BLOCKS

The brain responds to developmental and environmental cues with structural changes that underlie performance, ranging from synaptic growth to cell proliferation. The new structures are made of amino acids, sugars, lipids, nucleotides, and cofactors, most of which are generated locally de novo, either from glycolytic intermediates or from TCA cycle intermediates. While acute aerobic glycolysis caters for the urgent energy demands of neurotransmission (see above), persistent aerobic glycolysis defines the conditions for the generation of building blocks for tissue plasticity, akin to the Warburg effect occurring in tumors, inflammation, wound repair, and other proliferative condi-

tions (Warburg 1925; Vander Heiden et al. 2009; Goyal et al. 2014; Russell et al. 2019). Standing brain tissue aerobic glycolysis peaks during early childhood, declines with aging (Goyal et al. 2017), and might be protective against Alzheimer's disease (Goyal et al. 2023). As well as its involvement in D-serine generation for glutamatergic signaling (Le Douce et al. 2020), the phosphorylated pathway that branches off astrocytic glycolysis is required to generate glycine, cysteine, phosphoglycerides, sphingolipids, phosphatidylserine, and methylenetetrahydrofolate for neurons, precursors that may be in short supply when aerobic glycolysis is defective. Building block synthesis requires continuous replenishment of TCA cycle intermediates (i.e., anaplerosis), a process occurring mostly in astrocytes through the carboxylation of pyruvate (Yu et al. 1983) and only to a lesser extent in neurons, either from astrocytic glutamine or directly from extracellular glutamate (Divakaruni et al. 2017). Cholesterol is another component of neurons that is synthetized in astrocytes (Pfrieger and Ungerer 2011; Ferris et al. 2017). A striking example of the importance of glial cell metabolism for neurons is that a single amino acid substitution in the PPP enzyme transketolase, involved in glial lipid synthesis, is the main reason why the frontal neocortex of the modern human brain has more neurons than that of Neanderthals (Pinson et al. 2022).

WASTE RECYCLING

Neuronal function produces waste products that must be recycled to avoid toxicity and/or replenish precursor pools. Mitochondrial respiration generates CO_2 and reactive oxygen species (ROS). Since CO_2 is a small gas, it can diffuse freely into the blood, to be excreted by the lungs. ROS are highly reactive compounds that need to be detoxified fast. Glutathione (GSH) and ascorbate are the most important scavengers of ROS in neurons (Harrison and May 2009; Schmidt and Dringen 2012). Glutathione is oxidized in the detoxification process of ROS, xenobiotics, and endogenous toxins. Most oxidized glutathione is reduced in situ to replenish the GSH pool, but a fraction of this is lost via multidrug resistance transporters and has to be replenished by de novo synthesis. Neuronal GSH synthesis requires cysteine supplied by astrocytes (Schmidt and Dringen 2012). Dehydroascorbic acid (DHA), the oxidized form of ascorbate is reduced locally by reactions consuming NAD(P)H. However, some DHA, which is toxic, is transported into astrocytes via glucose transporters and recycled to ascorbate through GSH or enzymatic reactions (Nualart et al. 2003). Ascorbate is then shuttled back to neurons in an activity-dependent manner (Siushansian et al. 1996; Harrison and May 2009).

The activity-dependent production of ROS in neurons leads to the formation of peroxidated lipids. These lipids are transported into astrocytes in an ApoE- or ApoD- (in insects) dependent manner and stored within lipid droplets (LDs) to prevent cytotoxicity (Liu et al. 2015, 2017; Ioannou et al. 2019; Smolič et al. 2021; Yin et al. 2021). Astrocytes can then use for energy production via β-oxidation. In a very similar manner, excess lactate derived from glial cells is recycled and used in neurons to produce acetyl-CoA, which in turn allows for production of free fatty acids that are shuttled back to the glial cells, where they can likewise be stored in LDs for use in energy production (Liu et al. 2017). Such toxic fatty acids are mainly produced in hyperactive neurons, in which ROS production is also elevated. Thus fatty acid/lipid transfer from neurons to glial cells is a mechanism that allows neurons to deal with the cytotoxic effects of lipid peroxidation and fatty acid production that occur when neurons are highly activity (Ioannou et al. 2019; Smolič et al. 2021; Yin et al. 2021). It is worth highlighting that several risk genes for Alzheimer's disease have been linked to neuron–glia lipid shuttling and glial lipid metabolism (Moulton et al. 2021). Thus, carefully regulated neural lipid homeostasis seems to play an essential role in preventing neurodegenerative phenotypes and its deregulation contributes to Alzheimer's disease progression and likely the advance of other neurodegenerative diseases (Di Paolo and Kim 2011; Reed 2011; Kunkle et al. 2019; Lin et al. 2019; Chung et al. 2020; Yang et al. 2022).

Other waste products of neuronal activity are ammonia and K^+, which are both recycled via astrocytes. Ammonia (NH_3) is formed during

the glutamate and GABA cycles and when glutamine is used for anaplerosis. NH_3 captures a proton in the neuronal cytosol forming ammonium (NH_4^+). As neurons lack glutamine synthase, they cannot process this nitrogen excess, which is shuttled to astrocytes as NH_4^+, NH_3, or amino acids (Bak et al. 2006; Cooper 2012; Rothman et al. 2012). The NH_4^+ that enters astrocytes via K^+ channels and transporters is recycled to glutamine, which is ferried back to neurons (Nagaraja and Brookes 1998; Kelly and Rose 2010). Metabolism also generates other toxins, such as methylglyoxal, a by-product of glycolysis that promotes the formation of advanced glycation end products that leads to slowly progressing cell degeneration. Due to their high glycolytic rates, astrocyte produce rather high amounts of methylglyoxal and thus express a robust glyoxalase system that protects both themselves and neurons against methylglyoxal toxicity (Bélanger et al. 2011).

ASTROCYTES AS METABOLIC SENSORS AND KEY REGULATORS OF SYSTEMIC METABOLISM

As summarized above, astrocytes play multiple roles in provision of metabolites to neurons and in maintaining metabolic homeostasis in the nervous system. In has recently become apparent that astrocytes participate in nutrient sensing, regulating systemic metabolism and behavior (see below). By expressing diverse metabolic and neurotransmitter receptors/transporters, astrocytes are capable of sensing and responding to metabolic and synaptic cues (Perea et al. 2009; García-Cáceres et al. 2019). The role of astrocytic Ca^{2+} responses and gliotransmission in regulating local metabolism and synapse physiology is well known (Araque et al. 2014; Verkhratsky and Nedergaard 2018; Schaeffer and Iadecola 2021). But exploration of astrocyte impact on systemic metabolism is only just beginning.

Astrocytes closely monitor glucose concentrations in the nervous system. By expressing glucose transporters of different affinities, astrocytes are able to monitor a wide range of glucose concentrations (Simpson et al. 2007; Thorens 2015; Koepsell 2020). In the hypothalamus and the hindbrain, the two main areas of central glucose sensing in the brain, astrocytes have been directly implicated in regulating systemic homeostasis (Donovan and Watts 2014). In the hypothalamus, astrocytic insulin signaling seems to be essential for regulation of systemic glucose handling and transport of glucose into the brain (Guillod-Maximin et al. 2004; García-Cáceres et al. 2016). Elevated glucose levels also induce reduced astrocytic coverage of pro-opiomelanocortin (POMC) neurons that are implicated in feeding behavior. This leads to increased excitatory input onto those neurons (Nuzzaci et al. 2020). In the hindbrain, glucose deprivation has been shown to trigger astrocytic Ca^{2+} responses that precede neuronal Ca^{2+} responses (McDougal et al. 2013; Rogers et al. 2020). Further, purinergic signaling in hindbrain astrocytes has been implicated in regulating the rise in blood glucose levels following hypoglycemia in rats (Rogers et al. 2016, 2018).

In addition to closely monitoring glucose levels and instructing the adaptation of blood glucose levels, glial lipid metabolism acts as a sensor for the body metabolic status, while glial cells seem to influence systemic lipid and carbohydrate mobilization in response to changes in glial lipid metabolism (Varela et al. 2021; McMullen et al. 2023). Astrocytes might be involved in the neuroprotective effects of short-chain fatty acids produced by gut bacteria from dietary fibers (Cuervo-Zanatta et al. 2023).

BRAIN METABOLISM GOVERNING BEHAVIOR

Neural activity and cognition are quickly compromised by hypoxia, hypoglycemia and ischemia. In want of energy, neurotransmission and action potentials cease and the tissue is brought to an electric standstill that helps preserve cell viability. Chronic energy deprivation may also lead to a compensatory deficit in function, as demonstrated by the inhibitory effect of food scarcity on AMPA currents of cortical neurons, which saves ATP at the cost of coding precision in the visual cortex (Padamsey et al. 2022). Less intuitively, causality also works in the opposite direction. Cellular-resolution imaging of energy metabolism revealed that up-regulation of mushroom body energy flux is both necessary and sufficient to

drive long-term memory formation in *Drosophila*, with lactate and alanine shuttling between glial cells and neurons mediating different types of memory (Plaçais et al. 2017; Barros 2023; Rabah et al. 2023), whereas inhibition of OXPHOS mediates the aggressive response of honey bees exposed to pheromones and induces aggression in flies (Li-Byarlay et al. 2014). Also, as mentioned above, the anaplerotic function of a metabolic enzyme has been singled out as a major factor in the evolution of our thick frontal neocortex, which is involved in social behavior (Pinson et al. 2022). These experimental findings support the concept that energy metabolism not only has a permissive role but may determine network behavior and cognition under physiological conditions (Vergara et al. 2019).

CONCLUDING REMARKS

The astrocyte structures the microscopic anatomy of the brain and, by expressing highly regulated metabolic enzymes and transporters, it plays central roles in the supply of building blocks for tissue growth and remodeling, waste recycling, and activity-dependent energy homeostasis. There has been substantial progress over the last decade on the mechanistic understanding of astrocytic metabolism and its regulation, aided by insights from studying invertebrates. The emerging picture is that of a highly plastic cell, which adapts quickly to the demands of neurotransmission, but that also uses metabolic signals to control neuronal output. Challenges ahead are to figure out the additional ways in which metabolism is linked to activity, and whether it is used to regulate neural circuit function, as well as to determine the relative contribution of these mechanisms over various spatiotemporal scales, and their response to disease. Across the brain, astrocytes differ in terms of morphology and gene expression (Zeisel et al. 2018; Batiuk et al. 2020), setting the stage for metabolic diversity. Thus, current general conclusions might be less valid for certain brain regions. The development of methods that allow targeting of specific astrocytic subtypes seems imperative.

Brain metabolism has been assumed to be rather rigid. Recent data, however, suggest that glial metabolism adapts to support neuronal function under adverse conditions (Lavrentyev et al. 2004; Schulz et al. 2015; Ioannou et al. 2019; Weightman Potter et al. 2019; White et al. 2020; Hertenstein et al. 2021; Asadollahi et al. 2022; Silva et al. 2022). Changes in brain metabolism observed during disease are usually perceived as pathological. But are they part of the problem or part of the adaptation? A more thorough understanding of this metabolic flexibility would seem essential to further probe the complexities of brain disease.

Energy metabolism continues to be the main area of metabolic research, but metabolism is a far wider-reaching field. Making inroads into neglected metabolic pathways appears increasingly feasible thanks to progress made with single-cell omics technology, targeted gene manipulation, and high-resolution metabolic imaging. Studies using these techniques will likely reveal important insights into metabolic interactions in the future.

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