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The neuron–astrocyte metabolic unit as a cornerstone of brain energy metabolism in health and disease

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Over the past years, substantial advances have deepened our understanding of the cellular and molecular drivers of brain energy metabolism. Enabled by transformative technologies offering cellular-level resolution, these insights have revealed a highly regulated and dynamic metabolic interplay among brain cell types, particularly between neurons and astrocytes. In this Review, we shed light on the intricate ways in which neurons and astrocytes operate as a metabolically coupled unit, optimized to sustain the energetic demands of neurotransmission while ensuring neuroprotection. We highlight intercellular cooperation as a key determinant of brain function and provide examples of how disruption of the neuron–astrocyte metabolic unit contributes to numerous diseases of the nervous system, underscoring the critical importance of continued fundamental research to dissect the regulatory principles and vulnerabilities of this intercellular metabolic axis and identify potential therapeutic targets.

Seminal positron emission tomography (PET) functional imaging studies in humans by Fox and Raichle revealed that, during sensory activation, glucose utilization and oxygen consumption are uncoupled, suggesting the presence of aerobic glycolysis, that is, a transient non-oxidative consumption of glucose despite the presence of sufficient oxygen[1,2]. This phenomenon challenged the prevailing view, rooted in classical arteriovenous measurements and autoradiographic studies, that glucose in the brain is almost entirely oxidized under physiological conditions[3]. The resulting discrepancy raised fundamental questions regarding the cellular basis of this metabolic uncoupling.

Even before these imaging findings, several lines of evidence had begun to redefine the metabolic architecture of the brain. By the late 1970s and early 1980s, a number of studies had already demonstrated that astrocytes possess a high glycolytic capacity and preferentially metabolize glucose to lactate. Studies had shown that astrocytes, unlike neurons, readily engage in glycolysis and store glycogen, which can be mobilized during periods of increased neural activity[4,5] by selected neurotransmitters such as vasoactive intestinal peptide and noradrenaline that promote glycogenolysis in the cerebral cortex[6]. Enzymatic studies further supported these functional differences: key glycolytic enzymes such as hexokinase and phosphofructokinase showed higher activity in glial cells than in neurons[7]. Additionally, metabolic mapping efforts revealed that the bulk of glucose consumption during functional activation occurred in regions rich in neuropil: areas dominated by synaptic terminals and astrocytic processes rather than neuronal somata[8].

These foundational observations set the stage for a conceptual leap. The answer to the PET-based paradox came from studies in purified cellular preparations that brought into focus the critical role of astrocytes in brain glucose metabolism. Pellerin and Magistretti demonstrated that astrocytes respond to glutamate, the principal excitatory neurotransmitter in the brain, released at more than 80% of synapses, by increasing glucose uptake and releasing lactate, thereby engaging in aerobic glycolysis[9]. The sensing of glutamate by astrocytes was mediated by sodium-dependent uptake, a function already well characterized in astrocytic physiology at the time. This discovery

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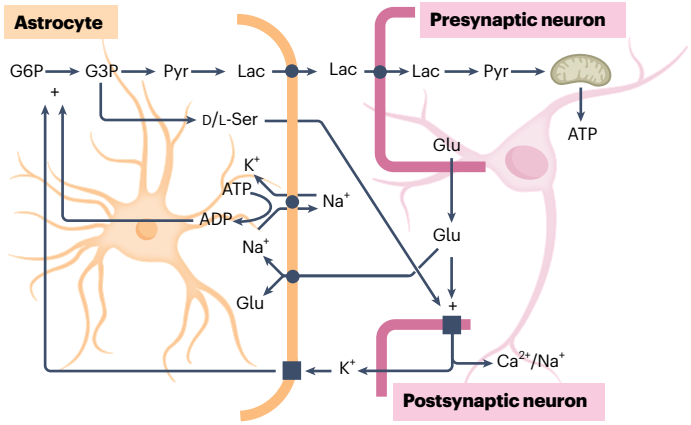

Fig. 1 | Glutamatergic neurotransmission is coupled to glycolytic activation in astrocytes. The mechanism involves K^+ and ADP signalling. Astrocytic glycolysis releases lactate, which is taken up by neurons where, after conversion into pyruvate, it is used for mitochondrial energy production. Glycolysis in astrocytes also contributes to L-serine formation, which, after transformation into D-serine, positively regulates glutamate receptors to facilitate neurotransmission. Abbreviations: D/L-Ser, D-serine and L-serine; G6P, glucose 6-phosphate; G3P, glycerol 3-phosphate; Glu, glutamate; Lac, lactate; Pyr, pyruvate. For simplicity, we have made no attempt to show the stoichiometry of the biochemical reactions.

provided the mechanistic basis for understanding how excitatory synaptic activity could drive a shift in astrocytic glucose metabolism and thereby support neuronal energy demands.

The astrocyte–neuron metabolic unit

Astrocytic glycolysis and neuronal energy support. While initially provoking, the notion that neurons could use lactate as an energy substrate under normoxic conditions was well established experimentally already in the 1950s by Henry McIlwain[10] and later by others[11]. Additional in vivo results showed that impairing glutamate uptake selectively in astrocytes resulted in a massive decrease in glucose uptake into the brain[12,13]. Mirror experiments demonstrated that increasing glutamate uptake into astrocytes sustains brain glucose utilization as monitored in vivo by PET with fluorodeoxyglucose[14]. Furthermore, during glutamatergic neurotransmission, along with glutamate, neurons release K^+, which is also sensed by astrocytes, accounting for fast activation of astrocytic glycolysis[15–17] (Fig. 1). Thus, transient aerobic glycolysis occurs in astrocytes during activation in which glucose uptake mostly results in lactate release for use by neurons, which can then oxidize it after conversion to pyruvate. The question that remained open was to what degree glucose could be used directly by neurons.

Neuronal glycolysis is suppressed in favour of antioxidant metabolism. Thanks to the use of genetic approaches combined with cell type-resolved analysis and imaging, it has been possible to clarify this issue. Indeed, glucose is the main energy metabolic precursor to sustain brain function and neurotransmission[18]. However, in an apparent paradox, glucose is scarcely used by neurons via glycolysis[19,20], that is, one of the most conserved metabolic pathways in nature. This is accounted for by the constant degradation of a key proglycolytic enzyme, namely, 6-phosphofructo-2-kinase–fructose-2,6-bisphosphatase 3 (PFKFB3), which by contrast is highly stable in astrocytes[19,20] (Fig. 2). Mice with neurons genetically manipulated to become glycolytic cells, like their neighbour astrocytes, develop mitophagy impairment, leading to accumulation of damaged mitochondria and lipid droplets[21]. More importantly, they slowed down the use of glucose via the pentose phosphate pathway (PPP), a central metabolic route in antioxidant protection, thereby causing redox stress[21]. Thus, glucose is used by neurons to feed the PPP and produce reducing equivalents that are important for reactive oxygen species (ROS) scavenging[20]. Interestingly, this mechanism ensures higher-order organismal welfare, including memory performance and metabolic fitness[21]; in fact, failure to efficiently degrade PFKFB3 in neurons leads to neuronal death in models of both neuronal ceroid lipofuscinosis[22] and multiple sclerosis[23], underscoring PFKFB3 as a promising therapeutic target for combating neurodegenerative diseases.

Astrocytic detoxification of glycolytic by-products. Another reason why neurons cannot sustain a high glycolytic rate is the fact that methylglyoxal, a toxic compound, is a by-product of glycolysis. This metabolite is endogenously formed from the glycolytic intermediate glyceraldehyde 3-phosphate[24]. Its detoxification begins with conjugation to glutathione, followed by enzymatic processing by glyoxalase (GLO)1, that is, the rate-limiting step in methylglyoxal catabolism. Astrocytes possess a very active glyoxylase system, GLO1 and GLO2, which eventually leads to the formation of D-lactate[24]. Interestingly, in proliferating cells, D-lactate stimulates the mitochondrial electron transport chain, promoting in this way ATP production through oxidative phosphorylation and reducing glycolysis[25]. Whether this metabolic regulation, which is independent of lactate metabolism, operates in astrocytes and neurons is an interesting possibility deserving elucidation. Neurons are not equipped to detoxify methylglyoxal; they depend on astrocytes for the de novo synthesis of glutathione and have very weak GLO1 and GLO2 activity, which renders them very vulnerable to methylglyoxal[24]. These data are yet another example of the subtle metabolic complementarity that exists between astrocytes and neurons.

The astrocyte–neuron lactate shuttle

Core concept of the astrocyte–neuron lactate shuttle. Functional and gene expression data have revealed that, while neurons mainly perform oxidative phosphorylation, astrocytes avidly consume glucose via glycolysis and release lactate[26–28]. The astrocyte–neuron lactate shuttle (ANLS)[9] hypothesis posits that lactate is taken up by neurons to feed oxidative phosphorylation and hence fuel the energy needed to sustain neurotransmission. Therefore, astrocytes sustain energy

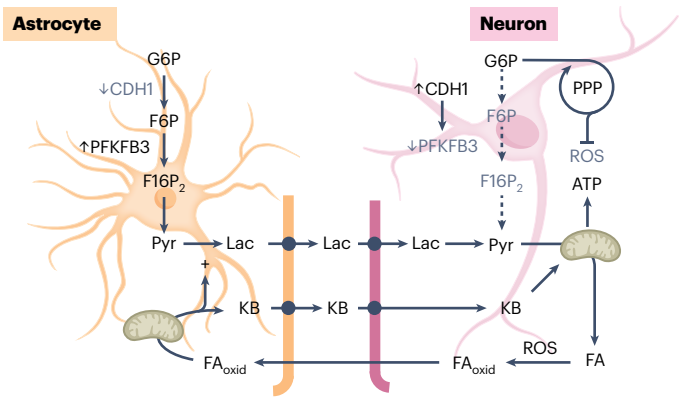

Fig. 2 | Different abundances of PFKFB3 explain high glycolysis in astrocytes and low glycolysis in neurons. The abundance of the proglycolytic enzyme PFKFB3 is determined by distinct activities of a ubiquitin ligase cofactor, CDH1. By keeping glycolysis low, glucose 6-phosphate is allowed to be metabolized via the PPP to exert antioxidant protection in neurons. Lipids in neurons may be formed from lactate and pyruvate; when these lipids become oxidized by ROS, they are transferred to astrocytes, where they are catabolized via β-oxidation, leading to ketone body production (ketogenesis), a process that stimulates pyruvate-to-lactate conversion, hence replenishing neuronal lactate. Ketone bodies are also transferred from astrocytes to neurons, where they can be used by mitochondria as an energy source by ketolysis. Abbreviations: FA, fatty acids; FA_{oxid}; oxidized fatty acids; $F16P_2$, fructose 1,6-bisphosphate; F6P, fructose 6-phosphate; KB, ketone bodies. For simplicity, we have made no attempt to show the stoichiometry of the biochemical reactions.

demands of neurons by providing them with glycolytically released lactate, whereas neurons preserve glucose for antioxidant purposes (Figs. 1 and 2). This necessary intercellular cooperation sets up the basis of a functional metabolic unit between neurons and astrocytes.

Currently available evidence from several independent laboratories has demonstrated the need for astrocyte-released lactate for neuronal function in vivo[14,29–32]. The ANLS has provided over the past decade a strong impetus to explore and demonstrate its implication in a variety of physiological and pathological conditions related to higher brain functions such as memory[33,34], neuroprotection[35,36], sleep[37] and mood disorders[38]. Furthermore, the conservation of a neuron–astrocyte metabolic unit across species has been shown in vivo in *Drosophila* in which glial-derived alanine (alanine being the equivalent of lactate produced from pyruvate in invertebrates) or lactate in the mushroom body is an essential mechanism that sustains memory consolidation[39–41].

Neuronal glycolysis in context: refining the ANLS framework. The weak contribution of glucose for neuronal energy requirements has been further confirmed by genetically ablating key steps of glucose uptake and metabolism[42]. Thus, mice with neurons lacking the ability to use glucose do not show functional disturbances except during ageing[42], when the metabolic support of neighbouring astrocytes is functionally impaired[43,44].

While the ANLS model remains the prevailing scheme for fundamental neuronal energy supply, emerging data suggest that neurons can use glycolysis in specific compartments or states. Thus, analysis in slices of dentate granule neurons (a highly specific type of neurogenic neuron of the dentate gyrus that represents approximately 1.4% of the total brain neuronal population and that lacks surrounding astrocytes[45]) must rely on their own glycolysis for neurotransmission[46]. Moreover, consistent with the typical robust glucose-based energy metabolism nature of neurogenic cells[47,48], dentate granule neurons easily upregulate glycolysis during neurotransmission in the absence of neighbouring astrocytes[46], thus representing a process rather specific and limited to a very restricted subpopulation of neurons.

Another in vitro condition in which neuronal activation has been studied in the absence of astrocytes[49] shows a commensurate increase in glucose consumption and mitochondrial pyruvate consumption, while cytosolic pyruvate and lactate levels remain constant. In other words, when measured in the absence of astrocytic lactate, neuronal glucose consumption is able to match its own oxidative phosphorylation. The same study showed that mimicking the contribution of astrocytes by augmenting extracellular lactate caused a substantial inhibition of neuronal glucose consumption, an observation that further supports the ANLS hypothesis.

A few studies illustrate this compartment-specific perspective. In hippocampal dentate neurons, stimulation with a cannabinoid receptor 1 agonist activated growth cone collapse and axonal retraction, which triggered rapid cytosolic nicotinamide adenine dinucleotide (NADH) increases driven by direct glucose metabolism[50], a transient burst of neuronal glycolysis that outpaces mitochondrial oxidation at least briefly yet does not indicate a basal reliance on glycolysis over oxidative phosphorylation. In axons, glycolytic enzymes anchored to vesicles fuel fast transport mechanisms, supporting extension and maintenance of growth cones as demonstrated in sensory neurons[51], while actomyosin-driven axonal retraction similarly depends on locally generated glycolytic ATP[50]. In neuronal cell bodies, somatic pyruvate kinase M2-driven aerobic glycolysis provides antioxidant defence: namely, loss of pyruvate kinase M2 shifts metabolism towards oxidative phosphorylation, elevates oxidative damage and leads to neurodegeneration, further illustrating that glycolysis is tuned to protective rather than bulk energetic roles[52]. Importantly, these glucose-driven enhancements are transient, context specific and constrained to restricted neuronal populations and subcellular domains; they still remain far below the sustained, high-level glycolytic capacity characteristic of astrocytes.

In sum, a refined framework of neuronal energy metabolism has emerged. Although astrocyte-derived lactate remains the primary fuel for neuronal mitochondria via the ANLS, under very specific circumstances, neurons do retain a refined ability to engage glycolysis. Rather than constituting an alternative energy pathway that is leveraged over extended periods of time, neuronal glycolysis serves as a finely regulated, compartmentalized adjunct, carefully tailored to complement, not compete with, the core lactate-driven metabolic architecture.

Expanding the neurometabolic map

Fatty acid oxidation in astrocytes

Machinery and kinetics of astrocytic fatty acid oxidation. Is glucose the only available metabolic energy precursor for brain function? Astrocytes are equipped with the necessary enzymatic machinery to metabolize fatty acids via β-oxidation, which transforms long- and medium-chain fatty acids into acetyl coenzyme A (CoA) within mitochondria, thereby providing an alternative and flexible metabolic route under fluctuating nutrient conditions. Transcriptomic and proteomic studies have confirmed a prominent expression of genes and proteins related to fatty acid oxidation (FAO) in astrocytes, including carnitine palmitoyltransferase I, acyl-CoA dehydrogenases and electron transfer flavoproteins, across several mammalian species[53–55].

Bioenergetic efficiency of astrocytic FAO. Interestingly, metabolic flux analyses reveal that, in astrocytes, β-oxidation of fatty acids may generate important, underappreciated energy precursors in glial metabolism[56]. However, the energy yield from fatty acid oxidative phosphorylation is not as high as that from the oxidation of glucose-derived pyruvate; a considerable portion of electrons entering the electron transport chain from FAO are shuttled via electron transfer flavoprotein, which reduces ubiquinone and bypasses mitochondrial complex I. This shortcut limits the proton gradient generated across the inner mitochondrial membrane and therefore the ATP yield per oxygen molecule consumed[56].

Functional advantages of FAO. Nonetheless, β-oxidation in astrocytes provides at least three crucial advantages. First, it maintains complex I in a partially disassembled conformation relative to complex III, promoting enhanced mitochondrial production of ROS, which, in turn, act as signalling molecules regulating gene expression, metabolic plasticity and organismal functions[57–59]. Second, FAO-derived acetyl-CoA is preferentially converted into ketone bodies (such as β-hydroxybutyrate and acetoacetate) within astrocytic mitochondria[60]; these ketone bodies are subsequently released and taken up by neurons to fuel mitochondrial oxidative phosphorylation, particularly during fasting or glucose-limiting conditions[61]. Interestingly, these processes are conserved in *Drosophila*[62,63]. And third, a higher reliance on fatty acids spares pyruvate from oxidation, allowing it to be converted to lactate, thereby sustaining the metabolic link between astrocytic glycolysis and neuronal support via the lactate shuttle[56].

Lipid metabolism and the neuron–astrocyte lipid shuttle

Beyond serving as substrates for oxidation or ketogenesis, fatty acids and their derivatives participate in a dynamic metabolic exchange between neurons and astrocytes. Lipid accumulation as cytosolic lipid droplets has been observed in astrocytes in vivo in response to neuronal oxidative stress, particularly under conditions of mitochondrial dysfunction[64].

This process is probably driven by enhanced neuronal lipid synthesis, a compensatory mechanism for ROS detoxification, which results in the export of oxidized lipid species to surrounding astrocytes[56]. These oxidized lipids are subsequently catabolized in astrocytes via

β-oxidation and converted into ketone bodies, contributing to redox buffering and sustaining lactate production. Interestingly, the carbon necessary for lipid synthesis in oxidatively stressed neurons is provided by astrocyte-derived lactate[65]. This bidirectional trafficking of lipid-derived metabolites between neurons and astrocytes may represent a neuroprotective mechanism against oxidative stress and can be conceptualized as the neuron–astrocyte lipid shuttle.

Metabolic flexibility of neurons under stress conditions

Traditionally, neurons have been considered poorly equipped for FAO, largely depending on glucose or astrocyte-derived lactate. However, recent transcriptomic and metabolic studies challenge this view, suggesting that, under specific conditions, particularly glucose deprivation, neurons may upregulate FAO-related pathways. Nerve terminals are enriched with the neuron-specific triglyceride lipase DDHD2 (refs. 66,67), and blocking its activity leads to presynaptic accumulation of lipid droplets. Furthermore, fatty acids derived from axonal lipid droplets drive local mitochondrial ATP production, allowing nerve terminals to sustain function in the complete absence of glucose. Remarkably, sortilin 1, a lipoprotein receptor associated with hypercholesterolaemia and Alzheimer's disease (AD), mediates neuronal uptake of polyunsaturated fatty acids carried by APOE[68], pointing to sortilin in metabolic fuel choice in neurons when glucose supply is limited.

Although the higher-order functional relevance of neuronal FAO remains to be fully elucidated, these findings[66–68] hint at an unexpected metabolic plasticity, potentially contributing to neuronal survival under energy stress conditions.

Serine metabolism: a signalling arm of astrocytic support

Serine metabolism emerges as another crucial arm of the neurometabolic network, predominantly governed by astrocytes. The de novo synthesis of L-serine from 3-phosphoglycerate via the phosphorylated pathway, which includes three glycolytically derived enzymatic activities (3-phosphoglycerate dehydrogenase, phosphoserine aminotransferase 1 and phosphoserine phosphatase), occurs almost exclusively in astrocytes and provides the precursor for several key metabolites. Among them, D-serine has a particularly important role as a co-agonist of *N*-methyl-D-aspartate (NMDA) receptors, modulating synaptic plasticity, learning and memory[69,70]. Impairment of 3-phosphoglycerate dehydrogenase in astrocytes leads to reduced levels of L-serine and D-serine in the brain, with direct consequences for hippocampal long-term potentiation and cognitive performance[71].

Additionally, L-serine contributes one-carbon units for folate metabolism and glutathione synthesis, linking astrocyte-derived serine to antioxidant defence and epigenetic regulation[18]. Together, these findings highlight astrocytes as central hubs not only for energetic support but also for metabolic control of neurotransmission and redox balance.

Physiological implications: cognition and plasticity

Lactate as a signalling molecule

Role in memory and plasticity. An interesting dimension of the neuron–astrocyte metabolic unit that has recently come to light is the fact that certain metabolites produced by astrocytes are not only energy substrates but also signalling molecules[72]. Thus, the transfer of lactate from astrocytes to neurons is necessary for memory consolidation and in vivo maintenance of the cellular mechanism of plasticity and long-term potentiation[33,73,74]. Of note is also the fact that, for low synaptic and cognitive workloads, neuronal glucose is sufficient, whereas, for higher synaptic and cognitive workloads in particular related to plasticity and memory, lactate becomes necessary[29], further supporting the importance of the neuron–astrocyte metabolic unit for higher brain functions.

Redox-mediated NMDA potentiation. These effects of lactate are not only dependent on its ability to provide energy to neurons but also to induce the expression of genes that are key for synaptic plasticity such as activity-regulated cytoskeletal protein, cAMP response element-binding protein and cofilin[33]. To express this memory-related signalling action, lactate potentiates NMDA receptor (NMDAR) signalling by increasing the $NADH(H^+)/NAD^+$ ratio subsequent to the transformation of lactate into pyruvate. Signalling by NMDAR potentiated by changes in the neuronal redox state result in larger NMDA-evoked calcium currents[69]. Recent observations at the molecular level indicate that lactate-induced changes in the redox environment in neurons promote the reduction of two cysteines in the intracellular loop of the N2B subunit of the NMDAR[75]. This process facilitates the interaction between NMDAR and calcium–calmodulin kinase II, resulting in increased NMDAR-mediated signalling[75]. These recent findings reveal a novel pathway by which lactate enhances NMDAR function through metabolic conversion and redox-sensitive interactions requiring calcium–calmodulin kinase II, linking astrocyte energy metabolism to synaptic modulation.

D-serine and NMDAR modulation

Another glycolysis-derived molecule, D-serine, modulates NMDAR activity[71,76,77]. The phosphorylation pathway converts the glycolytic intermediate 3-phosphoglycerate into L-serine, which is transformed into its racemic derivative D-serine and released from astrocytes to act on the neuronal NMDAR[18]. This is yet another example in which astrocytic glycolysis sustains metabolites needed for neurotransmission (Fig. 1). These observations further substantiate the concept that the neuron–astrocyte cell pair works as a unique metabolic unit needed for brain function.

Pathological implications: from dysfunction to disease

A large body of literature has documented over the years alterations in brain energy metabolism in neurodegenerative diseases and in particular the contribution of astrocytes to these conditions (for a Review, see ref. 78). For instance, ageing is one of the main risk factors for the expression of neurodegenerative disorders[79]. Decrease in glucose utilization as, for example, determined by PET with fluorodeoxyglucose is a hallmark of ageing particularly in brain regions such the anterior cingulate cortex, several parts of the orbital and frontal gyrus and in the thalamus. Impaired aerobic glycolysis is in fact the major contributor to this glucose hypometabolism[80–82]. Studies in animal models showed that ageing is characterized by decreased aerobic glycolysis in astrocytes and mitochondrial oxidative phosphorylation in neurons[83,84], thus providing additional evidence of the metabolic complementarity that exists between astrocytes (mainly glycolytic) and neurons (mainly oxidative). Here, we will focus on selected examples of neurodegenerative diseases that are particularly illustrative of impairments of the neuron–astrocyte metabolic unit.

Neurodegenerative disorders

Amyotrophic lateral sclerosis. Widespread alterations in glucose utilization are present throughout the brain and spinal cord of patients with sporadic amyotrophic lateral sclerosis (ALS)[85]. In the brain and spinal cord of animal models of ALS (SOD1-G93A and TDP-43-A315T mice), glucose utilization levels are markedly decreased in several brain areas[86,87]. Interestingly, in the SOD1-G93A mouse, this decrease occurs even before symptom onset[88]. Furthermore, in the same *Sod1* mutant, expression of the glucose transporter GLUT1 is lower in capillary endothelial cells in the brain and spinal cord[85]; interestingly, the monocarboxylate transporter 1, which is the predominant form expressed in astrocytes and oligodendrocytes (OLs), also has decreased expression[89]. This setup is consistent with a decreased entry of glucose into the brain through GLUT1 and a decreased ability to release lactate from glial cells.

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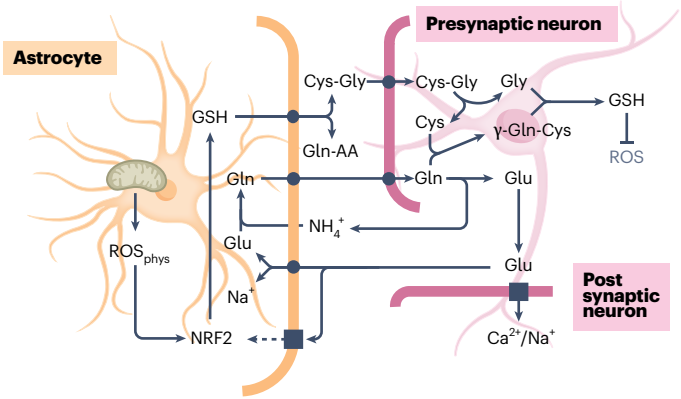

Fig. 3 | Glutamatergic neurotransmission is coupled to neuronal antioxidant protection. Activation of glutamate receptors in astrocytes leads to nuclear factor erythroid 2-related factor 2 (NRF2) activation. Physiological astrocytic ROS contribute to keep NRF2 active. NRF2 promotes transcriptional activation of antioxidant enzymes, leading to the biosynthesis of glutathione (GSH), which is cleaved into cysteinylglycine (Cys-Gly) by γ-glutamyltransferase and thus transported to neurons as Cys and Gly, which, together with Gln, are used to synthesize de novo glutathione to combat redox stress. Abbreviations: Gln-AA, γ-glutamyl-amino acid; NH_4^+, ammonium; ROS_{phys}, physiological ROS. For simplicity, we have made no attempt to show the stoichiometry of the biochemical reactions.

Parkinson's disease. In Parkinson's disease, dysregulation of astrocyte energy metabolism is observed[90], in particular in astrocyte-dependent redox balance mediated by glutathione around dopaminergic neurons in the substantia nigra[91]. For example, glutathione peroxidase-expressing astrocytes are more numerous around surviving dopaminergic neurons than degenerating ones[92]. As mentioned earlier, glutathione peroxidase is part of the ROS-scavenging, hence neuroprotective, machinery. Consistently, decreased levels of glutathione are present in the brain of patients with Parkinson's disease and animal models[93]. Transplantation of healthy astrocytes into the brain of a Parkinson's disease rat model rescued populations of dopaminergic neurons[94].

AD and *APOE* genotype. Hypometabolism and oxidative stress are consistent findings in patients with AD[95,96] but also in individuals with mild cognitive impairment, many of who will later develop AD. Restoring hippocampal glucose metabolism rescues cognition in AD models via an ANLS mechanism[97]. In individuals carrying the *APOE4* genotype, which confers a five times greater probability of developing AD, marked decreases in glucose utilization are detected well before the appearance of cognitive impairment symptoms or structural imaging evidence of loss of grey matter[98]. These observations point to a key role of dysfunctions in energy metabolism and potentially have a causative role in the pathophysiology of AD. By contrast, individuals carrying the *APOE2* gene have a lower risk of developing AD. Interestingly, astrocytes expressing the human *APOE2* or *APOE4* gene variant mirror this metabolic behaviour: glucose uptake is impaired in *APOE4*-expressing astrocytes, whereas *APOE2*-expressing astrocytes take up glucose more rapidly[98].

Glucose transporter deficiency syndrome. Possibly the most paradigmatic disease in terms of implication of the neuro–astrocyte metabolic unit is De Vivo disease or GLUT1 deficiency syndrome (GLUT1DS)[99,100]. This disease is caused by mutations in GLUT1, which is present in the brain in capillary endothelial cells and astrocytes (whereas neurons express primarily GLUT3). Characterized by a chronic energy crisis in the brain, GLUT1DS results in absence seizures in infants, which abate during adolescence but cause developmental delay and motor coordination dysfunctions later in life. A key diagnostic criterion of GLUT1DS is a marked decrease in both glucose and lactate levels in the cerebrospinal fluid. The only current treatment that reduces the otherwise pharmacoresistant absence seizures is strict adherence to a ketogenic diet.

BOX 1

Metabolism meets redox protection in neurotransmission

It is well known that neurons constitutively express a weak ROS-scavenging machinery[106–108], making these cells dependent on astrocytes for antioxidant defence[109]. In addition, as mentioned above, the metabolism of glucose via the PPP in neurons is essential for survival[21] (Fig. 2). However, in the context of antioxidant defence, the PPP mainly serves as a metabolic route that regenerates NADPH(H^+), an essential cofactor that is needed to reduce oxidized glutathione (GSSG) back into glutathione after the oxidizing effects of ROS produced by their active oxidative phosphorylation. However, aside from the regeneration of reduced glutathione, neurons need to keep high levels of the glutathione pool, a process for which they are entirely dependent on astrocytes[109]. A key protein in cellular antioxidant defence is NRF2, a transcription factor that governs the gene expression of a battery of antioxidant enzymes including γ-glutamyl-cysteinyl synthetase, which is responsible for the rate-limiting step in glutathione biosynthesis. The protein levels and transcriptional activity of NRF2 in neurons are known to be very low, which largely explains the inability of these cells to robustly synthesize glutathione and other antioxidants[109,110]. By contrast, NRF2 in astrocytes is very stable and provides them with a robust antioxidant system[109]. NRF2 is regulated, among other ways, by ROS-mediated inhibition of NRF2 cytosol sequestration; thus, cells with naturally high ROS levels like astrocytes keep NRF2 more stable than cells with low ROS levels[58] (Fig. 3). Accordingly, astrocytes are cells that physiologically produce ROS at a high rate from complex I, as mentioned[57], a phenomenon that is necessary to maintain NRF2 stability and nuclear location[58] to promote the expression of antioxidant enzymes[109]. Furthermore, astrocytes release glutathione to the extracellular space via the action of γ-glutamyltransferase, which converts glutathione into glutamine and the dipeptide Cys-Gly. It is known that, via this mechanism, astrocytes provide neurons with the Cys-Gly dipeptide, which neurons cleave into single amino acids, and add glutamine from the recycling reamination of glutamate[111] (Fig. 3). In this way, neurons can replenish the pool of intracellular glutathione, which can then be reduced by NADPH produced by the PPP to regenerate reduced glutathione needed to complement antioxidant defence[111]. In other words, neurons live a dangerous life! They are highly vulnerable to excess ROS but depend on astrocytes for their defence.

Conclusions and future perspectives

Metabolic cooperation as a homeostatic loop

The metabolism of adjacent neurons and astrocytes is mutually dependent, functioning as a dynamic unit committed to sustaining neurotransmission and maintaining redox (Fig. 3 and Box 1) and metabolic homeostasis. This neuron–astrocyte metabolic unit reflects an evolutionarily[101] optimized solution to a paradox: the brain's extraordinarily high energy demands coexisting with its almost nonexistent energetic reserves. Neurons rely heavily on oxidative phosphorylation,

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BOX 2

Metabolic support by OLs: an essential but underappreciated glial function

OLs have long been considered as passive insulators of axons, with their role largely reduced to the structural generation of myelin. However, compelling evidence over the past decade has dramatically shifted this view, revealing that OLs also have a vital metabolic role in maintaining long-term axonal function and integrity. The concept of metabolic cooperation between OLs and axons gained strong support after the demonstration that OLs rely heavily on glycolysis rather than on oxidative phosphorylation[112]. This metabolic configuration enables them to produce lactate that can be exported to the periaxonal space, where it is taken up by axons to sustain ATP production via mitochondrial respiration. The critical nature of this lactate shuttle was further supported[89] by the findings that genetic disruption of monocarboxylate transporter 1 in OLs leads to progressive axonal degeneration, even in the presence of intact myelin, firmly establishing that trophic metabolic support is separable from myelination per se. More recently, work revealed that this metabolic support is activity dependent and dynamically regulated[113]. Thus, during neuronal firing, levels of extracellular potassium increase and activate Kir4.1 channels on OLs, triggering increases in intracellular calcium levels that enhance glycolytic activity and lactate export. This coupling between axonal activity and OL metabolism suggests that white matter is not a static, energy-passive structure but a metabolically responsive network synchronized with neuronal demand.

Adding another dimension, it appears that the cellular distribution of lactate dehydrogenase A in white matter tracts facilitates rapid and efficient transport of glycolysis products among glial and axonal compartments[114]. Furthermore, it was recently highlighted that OLs possess the capacity to oxidize fatty acids under energy stress conditions[115], a feature that may explain myelin exhaustion in marathon runners[116]. This β-oxidation-based metabolism not only provides ATP for the OLs themselves but may also generate metabolic intermediates that can be shared with axons, particularly under conditions of glucose restriction or mitochondrial dysfunction. Together, these findings expand the metabolic toolkit of OLs well beyond glycolysis and suggest a degree of metabolic plasticity comparable to that of astrocytes.

but their low glycolytic capacity and sensitivity to ROS necessitate tight metabolic cooperation with astrocytes, which are better equipped for glycolysis, FAO and ROS handling.

Crucially, this crosstalk extends beyond energy delivery. Metabolites such as lactate and serine operate as neuromodulatory agents (modulating NMDAR function and redox state), underscoring that metabolism and neurotransmission are not separate domains but intimately entangled processes. This dual role of metabolites, as fuel and as signalling molecules, challenges the field to reframe our conceptual models of brain energy metabolism and function. It also raises the provocative question of whether these molecules should be classified primarily by their bioenergetic role or whether they should be seen as signalling currencies with functional equivalence to classical neurotransmitters. In the latter case, they might be dubbed as gliotransmitters. This complexity is especially salient for glutamatergic transmission. Glutamate signalling disrupts ionic gradients and redox balance in neurons, posing a potential threat to neuronal integrity. Astrocytes act as a buffer against this danger via spatiotemporally precise metabolic responses, reuptake of glutamate, production of redox capacity and the release of lactate and serine for energy and signalling purposes. These dynamics constitute a homeostatic feedback loop that protects neurons from an energetic crisis, excitotoxicity and oxidative stress: a loop for which disruption is increasingly implicated in neurodegenerative and psychiatric diseases.

Open questions and technological gaps

Need for high-resolution metabolic mapping. Future research must address several major conceptual and technical challenges. First, our understanding of metabolic compartmentalization remains rudimentary. How finely tuned is the intracellular localization of key enzymes or transporters? Emerging tools such as genetically encoded sensors for glucose, lactate or NADH, along with high-resolution imaging, now allow single-cell, even subcellular, readouts of metabolic fluxes. But these methods must be widely adopted and standardized to compare findings across models and laboratories and to enhance the reproducibility of quantitative data reporting.

Second, the field lacks a comprehensive atlas of cell type-specific metabolic states across brain regions, developmental stages and disease conditions. This knowledge is crucial, as metabolic diversity, not only between astrocytes and neurons but also among astrocyte subpopulations or neuron subtypes, might explain the region-specific vulnerability observed in conditions such as AD, ALS or schizophrenia.

Third, technical limitations continue to hamper our ability to capture the temporal dynamics of metabolic crosstalk during real-time brain activity. Most existing data are derived from static measurements or in vitro systems that fail to replicate the fast, fluctuating nature of neurotransmission-driven metabolism in living organisms. In vivo biosensors, two-photon microscopy and metabolomics with high spatiotemporal resolution will be essential to remove this bottleneck.

Beyond methodological advances, the field must wrestle with fundamental conceptual ambiguities. For instance, what defines a 'metabolic shuttle' versus a 'diffusive exchange' (ref. 102); whether every metabolite transfer implies a regulatory mechanism, or whether some by-products are passively removed; and the threshold at which a supportive metabolic pathway becomes indispensable for neuronal viability. A related emerging area of interest is the transfer of mitochondria between astrocytes and neurons, observed in injury models such as stroke and trauma, in which astrocytes donate mitochondria to support neuronal survival[103,104]. Although promising, this process remains poorly understood and may carry risks, such as triggering inflammatory responses through mitochondrial damage-associated molecular patterns[105], highlighting the need for mechanistic clarity and careful therapeutic exploration.

Towards mechanistic and therapeutic models

Potential therapeutic strategies. Neurodegenerative diseases frequently exhibit early signs of metabolic dysregulation, including reduced glucose uptake, oxidative stress and impaired glial support. Rather than being downstream consequences, these dysfunctions may constitute primary events in disease initiation. Therapeutic strategies that restore glial metabolism, whether by enhancing glycolysis, promoting lactate production or modulating redox tone, could re-establish neuroprotective homeostasis. For example, selectively

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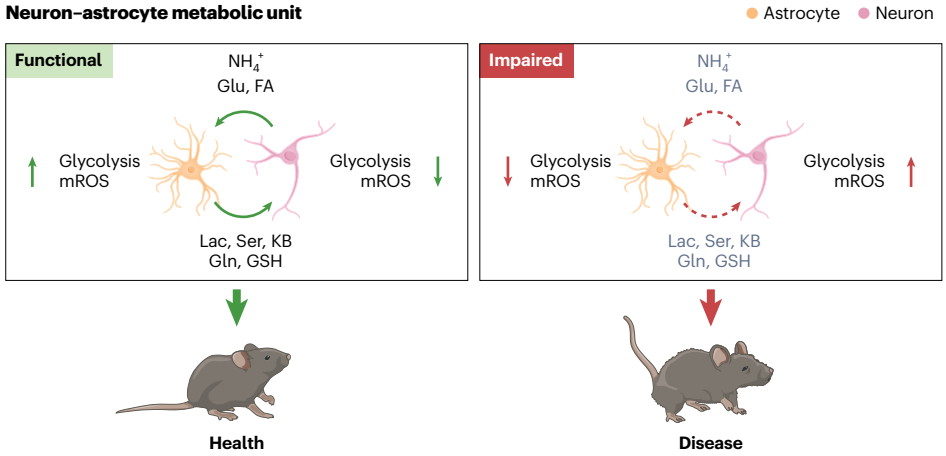

Fig. 4 | Functional and dysfunctional neuron–astrocyte metabolic unit. Bidirectional metabolic interactions between astrocytes and neurons constitute a critical component of brain energy homeostasis. Under healthy conditions (left), astrocytes take up neuronal by-products such as NH_4^+, glutamate and fatty acids, while providing essential metabolic support through the release of lactate, serine, ketone bodies, glutamine and glutathione. This tightly coordinated exchange is sustained by the control of glycolytic rate and mitochondrial ROS (mROS; high in astrocytes, weak in neurons), thus supporting neuronal function and systemic health. By contrast, during pathological conditions (right), this metabolic coupling is impaired, leading to disrupted metabolite exchange and contributing to neuronal dysfunction and disease phenotypes.

inhibiting PFKFB3 in neurons to prevent aberrantly sustained glycolytic activation during neurodegeneration represents a compelling therapeutic strategy. This approach may hold promise in conditions in which synaptic dysfunction precedes cell death. Understanding how the neuron–astrocyte and OL–axon (Box 2) metabolic modules integrate, or fail to integrate, under pathological conditions is an urgent priority.

The neuron–astrocyte metabolic unit model proposed here represents far more than a division of labour: it is a tightly regulated, adaptive network of interactions with implications for cognition, behaviour and disease (Fig. 4). To fully exploit its therapeutic potential, the field must shift from descriptive to mechanistic models, incorporate systems-level perspectives and embrace technological advances capable of revealing its astonishing dynamism in vivo.

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Author contributions

J.P.B. and P.J.M. conceived the idea and wrote, edited and approved the manuscript.

Competing interests

P.J.M. is the scientific founder of GliaPharm. J.P.B declares no competing interests.

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