Neurochemical Research (2021) 46:23–33
https://doi.org/10.1007/s11064-020-02965-9

ORIGINAL PAPER

Intertwined ROS and Metabolic Signaling at the Neuron-Astrocyte Interface

Carlos Vicente-Gutiérrez[1,2] · Daniel Jiménez-Blasco[1,2,3] · Rubén Quintana-Cabrera[1,2,4]

Received: 4 September 2019 / Revised: 3 January 2020 / Accepted: 16 January 2020 / Published online: 27 January 2020

Abstract

Metabolism and redox signalling share critical nodes in the nervous system. In the last years, a series of major findings have challenged the current vision on how neural reactive oxygen species (ROS) are produced and handled in the nervous system. Once regarded as deleterious by-products, ROS are now shown to be essential for a metabolic and redox crosstalk. In turn, this coupling defines neural viability and function to control behaviour or leading to neurodegeneration when compromised. Findings like a different assembly of mitochondrial respiratory supercomplexes in neurons and astrocytes stands behind a divergent production of ROS in either cell type, more prominent in astrocytes. ROS levels are however tightly controlled by an antioxidant machinery in astrocytes, assumed as more efficient than that of neurons, to regulate redox signalling. By exerting this control in ROS abundance, metabolic functions are finely tuned in both neural cells. Further, a higher engagement of mitochondrial respiration and oxidative function in neurons, underpinned by redox equivalents supplied from the pentose phosphate pathway and from glia, differs from the otherwise strong glycolytic capacity of astrocytes. Here, we recapitulate major findings on how ROS and metabolism differ between neural cells but merge to define reciprocal signalling pathways, ultimately defining neural function and fate.

Keywords Neuron · Astrocyte · Metabolism · Oxidative stress · Mitochondria · Neurodegeneration

Introduction

Studies from one of the founders of modern neuroscience, Santiago Ramón y Cajal, on the characterization of the nervous system, have made part of every textbook the notion that neurons are indivisible cells not replaced by new ones. This view has long remained as a cornerstone in our understanding and search for strategies to overcome neurodegeneration, even if challenged -not without discussion [1]—over the last years by the finding and characterization of neurogenic niches [2–4]. Indeed, uncovering the mechanisms that lead to neuronal death in diseases such as Alzheimer, Parkinson or Huntington is still a matter of intense research in neurosciences.

As for neurogenesis, challenges to other fields of neurosciences have been profound, and our vision on oxidative stress and metabolic processes has not been an exemption, thus contributing to update key concepts critical to understand neural physiology. As a main driver for such discoveries, the search for neuroprotective strategies have misleadingly considered the production of reactive oxygen species (ROS) as an obligated deleterious process in neurodegeneration, concomitant with an aberrant mitochondrial function, metabolism and antioxidant homeostasis triggering neural loss. Here, we follow key findings and rationale behind current progress in the neuroenergetic and neurometabolic fields. Departing from the first studies on neural metabolism and antioxidant pathways, we show how the integration of

Special Issue: In Honor of Professor Juan Bolanos.

✉ Rubén Quintana-Cabrera
ruben310@usal.es

1 Institute of Functional Biology and Genomics (IBFG), University of Salamanca, CSIC, Salamanca, Spain

2 Institute of Biomedical Research of Salamanca (IBSAL), University Hospital of Salamanca, University of Salamanca, CSIC, Salamanca, Spain

3 Centro de Investigación Biomédica en Red sobre Fragilidad y Envejecimiento Saludable (CIBERFES), Instituto de Salud Carlos III, Madrid, Spain

4 Department of Biochemistry and Molecular Biology, University of Salamanca, Salamanca, Spain

both captures the way ROS and metabolic signalling intertwin to define neural function and survival.

ROS and Neurodegeneration

Neurotransmission does not simply start or end with the release and capture of neurotransmitters from synapses. A major event paralleling this process is the production of reactive oxygen species (ROS) derived from different sources, usually involving Ca^{2+} influx and glutamatergic stimulation [5], but also the handling of neurotransmitters such as dopamine [6, 7]. Indeed, dopamine catabolism and monoamine oxidase activity generate hydrogen peroxide (H_2O_2), further implemented by superoxide anion ($O_2^{\cdot-}$) and reactive products such as semiquinones that harbour oxidative capacity [6, 7]. Along with high mitochondrial respiration rates and metabolic activity during neurotransmission, these features stand behind an elevated ROS generation in neurons that has to be faced by antioxidant systems.

Among the many ROS species produced during neural activity, it is worth underlying that $O_2^{\cdot-}$ represents the first molecule originated from the acceptance of, at least, one electron by oxygen. $O_2^{\cdot-}$ further evolves to hydrogen peroxide (H_2O_2) and hydroxyl radical (·OH) through reactions respectively catalyzed by superoxide dismutase (SOD) or chemical reactions with metallic ions. Peroxiredoxins (Prxs), glutathione peroxidases (GPxs) and catalase, the latter exclusively cytosolic, [8, 9] convert H_2O_2 to H_2O, thus avoiding cellular damage when their levels are under a certain threshold [8]. Notably, GPxs and thioredoxins (Trxs) rely on NADPH as a reducing agent, which mainly derives from the pentose phosphate pathway (PPP) [10], thus linking glucose metabolism and redox homeostasis, as discussed below. The use of NADPH likely makes the antioxidant glutathione (GSH) its main consumer in the adult brain, particularly in neurons. In these cells, the recycling version of the PPP can derive glucose-6-phosphate to produce NADPH that is required for efficient GSH reduction, thus deriving lower amounts of glucose to glycolysis than astrocytes [11]; this is also in line with the synthesis of ribose-5-phosphate not acting as a central function of PPP in neurons [12]. The reduction of oxidized GSH is critical for neuronal viability, since among the varied ROS detoxification paths within the nervous system, GSH is considered the most abundant antioxidant in the brain. GSH is mainly synthetized in astrocytes in two steps catalyzed by glutamate-cysteine ligase (GCL) and glutathione synthetase (GSS) [8]. Although present at a lower abundance, neurons also use this biosynthetic machinery to resynthesize GSH after capturing its aminoacidic precursors, which result from GSH breakdown in astrocytes before donation to neurons [8, 13, 14]. The lack of a proper antioxidant capacity has been linked to neuronal death, as suggested by the loss of GSH and the subsequent loss of neurons and cognitive decline occurring in neurodegeneration [15, 16]. Full GSH depletion results in embryonic lethality [17], while specific tissue-driven disruption of GCL, the rate-limiting enzyme for GSH synthesis, is enough to drive neuronal death [18]. The resultant neuronal loss is concomitant with extended redox stress and loss of dendrites in the hippocampus, as well as cognitive dysfunction even when GCL is mildly ablated in neurons [15]. In this context, protein glutathionylation and carbonylation are increased in the hippocampus, correlated with further protein modifications under low levels of GSH [15, 19, 20]. Notably, the proteins detected as modified by low GSH levels are related to axonal growth and guidance, energy metabolism or lysosomal trafficking [15], key for neural survival. Accordingly, dendritic spines get loss in the hippocampal regions, particularly CA1, which are highly vulnerable to metabolic stress [21], upon GCL ablation. These features result in a mild spatial and short time memory impairment, recapitulating some of the neurological features associated with partial GSH loss, that does not require the abrupt neuronal death that instead occurs under full GCL disruption [18].

In view of the need of GSH to preserve neuronal function, increasing GSH levels shows a robust strategy to provide neuroprotection [22]. This occurs even if full conversion to GSH is not reached and its immediate precursor, γ-glutamylcysteine, can still be used by glutathione peroxidase 1 (GPx1) to dispose H_2O_2 and confer protection against neuronal loss and motor impairment [23].

Mitochondria, Key to Understand Neural ROS Production

Neurons mainly rely on mitochondrial oxidative phosphorylation (OXPHOS) for energy production and viability; however, a high amount of ROS are generated in consequence, making mitochondria the major producer of endogenous ROS within a cell [24, 25]. Along with other enzymatic sources within mitochondria [26], the main ROS source in these organelles derives from the transfer of electrons across mitochondrial complexes during OXPHOS [24]. Mitochondrial ROS production is highly dependent on the NADH/NAD^+ isopotential group and, more strikingly, on the QH_2/Q isopotential groups in complex I (CI) and III (CIII) [27], with reverse electron transport acting to generate ROS when the NADH/NAD^+ ratio is high [24].

Mitochondrial respiration can be stressed during neurotransmission, as evidenced by the inhibition of the ETC in neural cells by endogenous nitric oxide, its by-products or other agents [28, 29]. Respiration is also compromised under glutamatergic overstimulation, that results in higher glucose uptake [30] and glycolysis [31] in astrocytes.

Primed by the hypoxia responsive element Hif1 and the subsequent upregulation of GLUT1 and GLUT3 transporters, glucose is vastly consumed in astrocytes to activate the reversal activity of ATPase and sustain the mitochondrial membrane potential [29, 32]. Moreover, glycolytic-derived lactate can be released from astrocytes to improve survival [33]. Conversely, neurons are less efficient at upregulating glycolysis to compensate for energy production and restore mitochondrial respiration, thus being more vulnerable to mitochondrial dysfunction [30, 31, 34, 35]. This represents a differential feature between neurons and astrocytes, where the latter do not exclusively rely on OXPHOS and instead capitalize on glycolysis as an essential mechanism to cover bioenergetic demands during neurotransmission and cell survival [33, 35, 36].

The different activity and reliance on mitochondria in neurons and astrocytes may account for their differential ROS production. Now we know that a key feature merging the divergent features between neurons and astrocytes on mitochondrial respiration, bioenergetics and ROS generation is a different configuration of the electron transport chain (ETC) (Fig. 1). To account for an efficient ETC function and ATP production from respiration, mitochondrial respiratory complexes assemble into quaternary structures termed respiratory supercomplexes (RSC) [37, 38]. Unexpectedly, astrocytes scarcely embed complex I (CI) along with CIII and CIV to form RSC; conversely, neurons have their ETC complexes mostly embedded into RSC harboring CI, CIII and CIV [25, 38]. An interspecies analysis further revealed that ETC activities and assemblies vary depending on the rodent species and

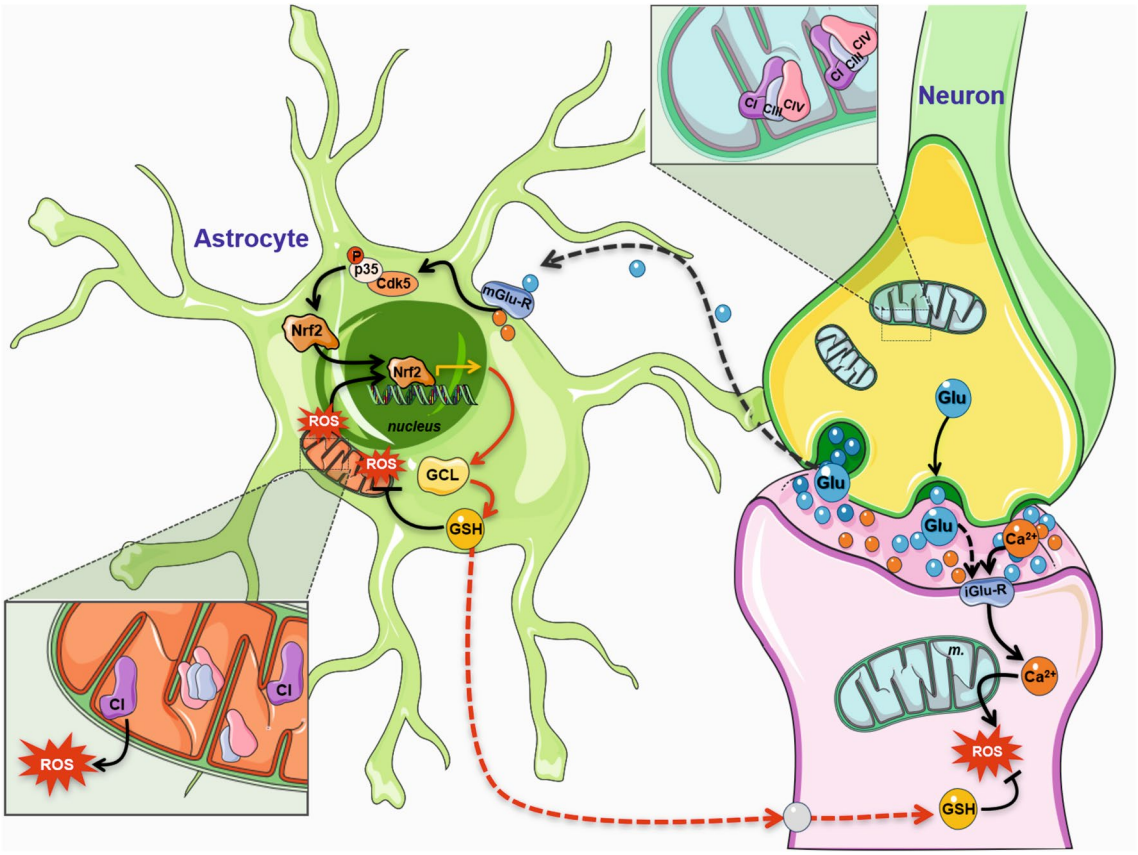

Fig. 1 Neuron-astrocyte redox coupling. Astrocytes comprise a strong antioxidant capacity to fulfill redox equivalents for ROS disposal, both at neurons and astrocytes. The antioxidant program is mastered by the transcription factor Nrf2 (Nuclear erythroid-related factor 2) upon cysteine oxidation by ROS. Among other sources, ROS are abundantly produced by astrocytic mitochondria (*bottom inset*), as a result from destabilized respiratory complex I (CI). In astrocytes, CI does not efficiently assemble into respiratory supercomplexes, as occurs in neurons (*upper inset*). Nrf2 activation may also occur upon stimulation of metabotropic glutamatergic receptors (mGlu-R), subsequent Ca^{2+} entry and activation of Cdk5 by phosphorylated p35. Nuclear translocated Nrf2 transcriptionally upregulates the gene expression of antioxidant enzymes such as glutamate-cysteine ligase (GCL), rate limiting for glutathione (GSH) biosynthesis. GSH released to the extracellular medium is cleaved to provide precursors for de novo synthesis of GSH within neurons. Neuronal GSH dispose ROS derived from an excessive stimulation of postsynaptic glutamatergic receptors (i.e., NMDAR; N-methyl-D-aspartate receptor) and Ca^{2+} entry and overload. Red lines track the synthesis of antioxidants (GSH) from astrocytes and its use by neurons to reduce excessive ROS

strains tested. Astrocytic CI activity in rats, either Wistar or Sprague–Dawley, is higher than that found in C57BL/6 mice, and particularly in Wistar rats astrocytic CI activity is around six times higher than that of their own neurons. Assembly into CI–III–IV RSC increase CI activity in astrocytes compared to neurons, remaining similar in both cell types in strains not assembling such supercomplexes [39].

As a result of compromised assembly, the free, less active CI found in C57BL/6 astrocytes accounts for a less efficient respiration and bioenergetics, along with an increased ROS generation that is rescued by the RSC assembly factor NDUFS1 [25]. In free CI, the flavin mononucleotide-containing subunit NDUFV1 is more available to interact with O_2 [38]. In this scenario, $O_2^{\cdot-}$ generation is allowed given that the ETC is maintained on its oxidized status [40], with a low efficiency to consume O_2 from NADH substrates in astrocytes, as compared to neurons. Mitochondrial ROS originated from a less efficient ETC transfer cause a subsequent lipid oxidation and oxidative damage, specially to CI, that contributes to a vicious cycle further increasing ROS production [40]. In this cycle, reducing ROS levels results in partially prevented CI release and recovery of RCS [25, 40], indicative of a mutual relationship between ROS production and RSC stability. These evidences are in line with the notion that during aging, RSC are less abundant despite the activity of individual ETC complexes may be conserved, thus contributing to explain the link between higher ROS and mitochondrial dysfunction during aging as a probable cause for neuronal loss [41].

Not only the assembly of RCS defines the production of ROS in neural cells. Dysfunctional mitochondria, through an aberrant respiration and signaling, may contribute to generate ROS and aggravate the inherent consequences of mitochondrial loss of function. To prevent this, mitophagy constitutes a specific and multifaced path that controls the degradation of damaged mitochondria. Inefficient mitophagy results in neurodegeneration, as characterized from Parkinson's disease (PD) mutations in genes encoding for the PINK1-Parkin axis, master regulators of mitophagy [42]. Fostered by an impaired respiration and signaling, the loss of PINK1 activity results in mitochondrial ROS generation, that is probably fostered by cytosolic ROS to stabilize Hif1α even when its mRNA levels are low; as a result, Hif1α primes the upregulation of glucose metabolism [43]. While higher glycolysis rates promote cellular growth and may stand behind the higher astroglial proliferation in PD patients [44], an increased glycolytic flux in neurons would instead result in a compromised PPP activity and antioxidant capacity [36]. As a result, this metabolic switch may account for neuronal loss in PD and other neurodegenerative diseases coursing with aberrant mitophagy. Altogether, a proper control of mitochondrial function, along with a correct assembly of RSC and disposal of damaged organelles, shows crucial for neuronal function and survival.

Neurons are Not Alone at Disposing ROS

A high dependency of neurons on oxidative phosphorylation [45, 46] and exposure to ROS [25] throughout the large living cycle of such postmitotic cells, may explain why ROS could lead to neurodegeneration and neurological diseases associated with aging [9, 47–49]. Despite the presence of intrinsic antioxidant defences [50–52], neurons still have a weak antioxidant potential when compared to astrocytes; thus, neurons are particularly sensitive to oxidative challenges that can make them succumb to excess ROS [45, 53, 54]. The higher susceptibility of neurons to ROS is extensively due to the continuous destabilization and degradation of the master antioxidant transcriptional activator nuclear erythroid-related factor 2 (Nrf2) by Cullin 3/Kelch-like ECH-associated protein 1 [55, 56]. Nrf2 masters the transcription of a wide spectrum of antioxidant enzymes. It is required not only for the GSH pathway, by inducing GCL, GPx or GST expression, but also to induce other antioxidant genes such as hemooxygenase-1 (HO-1), thioredoxin (Txn) or NAD(P)H dehydrogenase quinone (Nqo-1), as well as genes involved in NADPH regeneration (G6pd, Idh1, Pgd) [55-57]. In basal conditions, NRF2 binds to the redox sensor KEAP1 (Kech-like ECH-associated protein 1), which in absence of ROS allows the interaction of NRF2 with CUL3 (Cullin 3) for the polyubiquitination and proteasomal degradation of the former. Upon ROS accumulation, the oxidation of key cysteines in KEAP1 allows NRF2 nuclear translocation and transcriptional activity [57, 58], in a similar fashion as also occurs for HIF1α stabilization and subsequent metabolic reprogramming, that fosters cell survival [59]. Whereas NRF2 degradation is continuous in neurons and render these cells particularly vulnerable to ROS, NRF2 is more stabilized in astrocytes, making them master the disposal of ROS in the nervous system, since antioxidants are not only kept within astrocytes but are also furnished to neurons [56, 60]. For instance, NRF2 induction of GCL increases GSH synthesis in astrocytes, which as mentioned above can subsequently be exported to the extracellular medium and processed into precursors for GSH synthesis in neurons both in vitro and in vivo [56, 61, 62]. Therefore, astrocytes are key to provide antioxidant capacity to neurons [46, 63, 64].

In astrocytes, activation of glutamatergic receptors (GluR) triggers a phospholipase C-mediated release of Ca^{2+} from the endoplasmic reticulum and the subsequent activation of protein kinase Cδ (PKCδ) to phosphorylate and stabilize p35, a cofactor of the cyclin-dependent kinase-5 (CDK5) [65]. Nrf2 phosphorylation by Cdk5/p35 or other

pathways provides an antioxidant pool that neurons use to detoxify ROS generated by Ca^{2+} entry and overload, that normally occurs upon overstimulation of neuronal glutamate receptors, particularly N-methyl-D-aspartate (NMDA) [56]. The rise of intracellular Ca^{2+} following excessive activation of NMDA receptors by glutamate in neurons accounts for a so-called excitotoxic response, that leads to neuronal death when unresolved [66]. Altogether, neuronal activity engages a response from astrocytes that engages, among other antioxidant mechanisms, de novo biosynthesis and release of GSH through the astrocyte-neuronal glutathione shuttle (ANGS). This path hence couples neurotransmission mediated by NMDA receptors with neuronal survival, as demonstrated during ischemic preconditioning [67].

As noted, the endogenous levels of astrocytic mitochondrial ROS are about one order of magnitude higher than neurons [25]. Despite a higher abundance of ROS, this is in line with the concept of hormesis, defined as a short-lived or persistent, but not lethal, stressor that primes a resistance to such stress [68–70], probably due to a higher antioxidant capacity. This would explain how astrocytes are prepared to efficiently handle oxidative stress, and how the redox homeostasis could be a new compartmentalization example of brain cells, closely related to brain metabolism [71] as described below.

Metabolic Coupling Between Neurons and Astrocytes

The high-energy supply required for neuronal activity has been classically linked to the use of glucose as key energetic substrate in the brain [59, 72], along with the consumption of nearly 20% of inhaled O_2 [73]. These energetic costs extensively rely on the metabolic coupling with astrocytes to control energy and redox homeostasis [29], given their role as essential partners for neurotransmission and behaviour [74, 75]. To this end, astrocytes form a syncytium through the establishment of cellular processes to contact capillaries, neuronal perikaryal or synapses. Along with abundant gap junctions, such processes account for an intense exchange of intermediates that cover the metabolic and energetic demands in the nervous system [59].

The astrocytic-neuronal metabolic coupling is further illustrated by the restoration of neuronal glutamate levels upon Ca^{2+} influx and membrane depolarization during neurotransmission, a mechanism that requires from astrocytes and an active Na^+-dependent transport to take up glutamate from the synaptic space [76]. This occurs at the expense of ATP, used to restore the Na^+ gradient through the Na^+/K^+ ATPase [29]. In astrocytes, glutamate can be converted in glutamine by glutamine synthetase, which is absent in neurons. However, neurons use glutaminase to recover glutamate from the synaptically inactive glutamine that is released from astrocytes. The fate of glutamate in astrocytes may also pass through its conversion into α-ketoglutarate for oxidation by the tricarboxylic acid (TCA) cycle in mitochondria, which provides ATP [77]. Importantly, activation of the Na^+/K^+ ATPase for glutamate processing is paralleled by an enhanced glucose uptake from capillaries [78, 79] and hence coupling with a higher glycolytic flux, either in a persistent or in a rapid, reversible manner in astrocytes [80].

Glycolysis is also fostered in astrocytes by the fact that APC/C-Cdh1 has low negative input at degrading PFKFB3, which would impair the production of fructose-2,6 bisphosphate ($F2,6P_2$), the most potent activator of 6-phosphofructo-1-kinase (PFK1) [81]; therefore, glycolytic activity will not be reduced in astrocytes by this pathway, as occurs in neurons [36] (Fig. 2). Astrocytes can also store glycogen [82], which upon glycogenolysis serves to supply lactate -the major product of glycolysis-, that enters the TCA cycle and supports neuronal activity, especially during hypoglycemia [83, 84]. Thus, astrocyte-derived glycolytic lactate represents a key energetic supply to neurons, which mainly rely on the TCA cycle to sustain bioenergetics and metabolism; conversely, the oxidation of lactate is comparatively less efficient in astrocytes [85]. In astrocytes, the conversion of pyruvate into lactate is facilitated by the absence of a mitochondrial aspartate/glutamate carrier, reducing the capacity of the malate/aspartate shuttle to transfer reducing equivalent as nicotinamide adenine dinucleotide (NADH) to mitochondria to recover NAD^+. To keep active the glycolytic flux, NADH is rather converted to NAD^+ through the lactate dehydrogenase isoform LDH5 in the cytosol [82].

Altogether, the metabolic differences between astrocytes and neurons explain how these cells have adapted to couple their metabolism, transferring lactate from the glial to the neuronal compartment [82], hence coordinating the energetic supply through the astrocyte-neuronal lactate shuttle (ANLS) [86, 87]. This phenomenon consists in the astrocytic activity-dependent uptake of glucose and release of L-lactate, subsequently imported by neurons through monocarboxylate transporters (MCTs), which are also able to transport pyruvate and ketone bodies. Lactate is released from astrocytes by the monocarboxylate transporters MCT1 and MCT4, the former also found in endothelial cells from blood vessels, whereas the high-affinity transporter MCT2 is mainly expressed in neurons and contributes to long-term adaptation of energy supply [82]. Lactate uptake may be enhanced in neurons by ascorbic acid, with a concomitant reduction in glucose uptake, while LDH1 facilitates the conversion of lactate to pyruvate [59]. The occurrence of the ANLS has been probed in vivo [88] and constitutes a conserved mechanism in the evolution of neuronal survival [89]. Importantly, altered ANLS that occurs with dysfunctional MCT2, MCT4 and lactate content in the brain has been

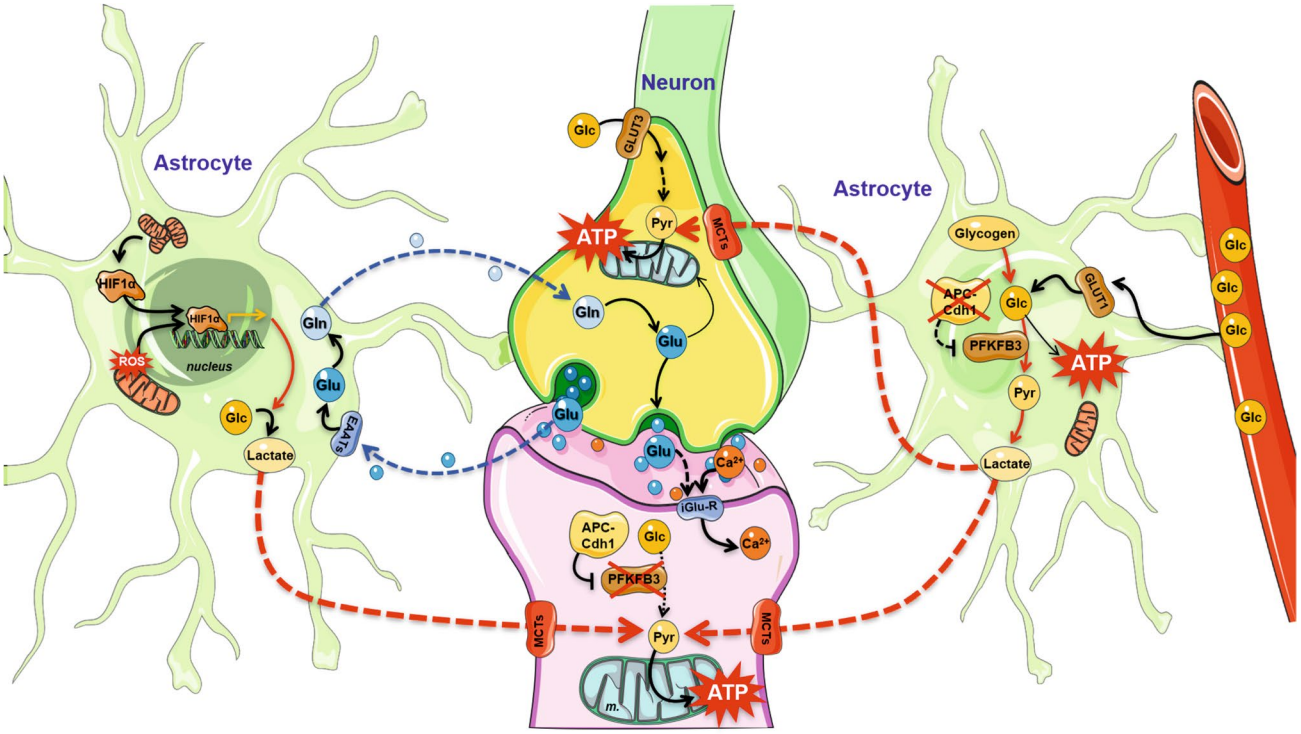

Fig. 2 Neuron-astrocyte metabolic and bioenergetic coupling**.** Glucose (Glc) constitutes a major metabolic substrate to the nervous system, where astrocytes take it from capillaries through the GLUT1 transporters (*right astrocyte*). Along with the processing of glycogen stores (glycogenolysis), astrocytic glycolysis produces lactate as a final product, later released and imported by neurons through monocarboxylate transporters (MCTs; e.g. MCT2 in neurons; in astrocytes, MCT1 and MCT4 contribute to lactate release). Glycolysis can be also stimulated in astrocytes by impaired degradation of mitochondria by mitophagy, which along with mitochondrial ROS generation triggers HIF1α-dependent glycolysis (*left astrocyte*). Upon neuronal importation, lactate is converted to pyruvate (Pyr) and enters the tricarboxylic acid cycle to foster mitochondrial ATP production (*bottom neuron*). Glycolysis is constitutively interrupted in neurons by the continuous degradation of the glycolytic enzyme PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase) via anaphase-promoting complex/cyclosome (APC-Cdh1), which inhibitory effect in glycolysis is instead blunted in astrocytes. Glutamate further stimulates mitochondrial respiration in neurons (*upper neuron*). Glutamate from the synaptic space enters astrocytes (left astrocyte) through EAAT (excitatory amino acid transporters) and is converted by glutamine synthetase to the synaptically inactive glutamine. After release, glutamine can be imported into neurons and re-converted to glutamate by glutaminase. Along with Ca^{2+} entry following stimulation of ionotropic glutamatergic receptors (iGlu-R; i.e. NMDAR), glutamate fosters mitochondrial ATP production for neurotransmission in neurons. Red and blue dotted lines respectively track the fate of glycolytic products and glutamate in the metabolic coupling between astrocytes and neurons

described in Alzheimer's disease [59, 90, 91], and deletion of MCT1 results in neurodegeneration, its expression being affected by mutant SOD1 in familial amyotrophic lateral sclerosis (ALS) [92]. These features highlight the relevance of MCTs for neuronal survival in coordination with oxidative stress regulation.

As indicated, lactate can take over the energetic supply to sustain neuronal function during glucose deprivation. This may be implemented by ketone bodies to fulfil energetic demands occurring during fasting, in breast-fed new-born babies and in diabetes, or by acetate during hypoglycemia or chronic alcohol abuse [59]. Several studies have discussed this hypothesis, arguing a higher affinity of neuronal glucose transporter GLUT3 over astrocytic GLUT1 for glucose uptake, or the ability of neurons to upregulate glycolysis and release lactate, rather than importing it from astrocytes (reviewed by [59]). Conversely, recent studies have demonstrated that glucose is preferentially consumed by glial cells in the nervous system and that derived metabolites such as lactate are mainly exported by glial cells [59, 92–95] and, to a lesser extent, by neurons [96]. In this scenario, glial GLUT1 would be key for the neurovascular coupling that is required for a continuous glucose uptake from the blood [97], hence indicating a rate-limiting role for GLUT1, even if its glucose affinity is lower than neuronal GLUT3 (Fig. 2). Moreover, astrocytes are more efficient at exerting glycolysis and lactate production than neurons [98], mainly by LDH5, whilst LDH1 converts lactate to pyruvate in neurons. Of note, astrocytes can store glucose as glycogen and export glycogen-derived lactate, although at lower rates than glucose-derived lactate [99]. In sum, the classic vision on glucose as key for energetic supply to neurons has been

challenged by studies on the cellular compartmentalization in the use of substrates, along with the demonstration that lactate is central for axonal myelination and regeneration, and thus crucial for excitability, plasticity and memory consolidation [86]. These features make lactate to be considered a preferred energetic supplier in the nervous system when glucose or oxygen supply are limiting, or during high neuronal activity [59]. Indeed, neurotransmission primed by glutamate coincides with a blunted GLUT3 activity and glucose import that fosters lactate uptake in neurons [100]. This is in line with the current assumption that neurons are preferentially oxidative, whereas astrocytes and oligodendrocytes display a highly active glycolysis to supply glucose derivatives as lactate [86].

Despite the many evidences for the occurrence of ANLS, some aspects still rise concerns [72, 101–103]. A critical aspect is that ANLS was originally formulated from observations made under conditions of glutamatergic stimulation [87] and therefore may underestimate other metabolic states of astrocyte bioenergetics [72]. Another criticism on the ANLS theory is that somehow may also underestimate that TCA and mitochondrial metabolism in astrocytes, or the glycolytic pathway in neurons, that may still work as key energetic sources [101]. Furthermore, mitochondrial astrocytic metabolism may be also relevant in other aspects such as fatty acid oxidation, which coexists with astrocyte glycolysis and is inhibited by glutamate [104]. Trying to reconcile such facts, it has been proposed a loosening of the coupling between both processes, where astrocytic glycolysis would be followed by oxidative metabolism in neurons [105]. Despite the demonstration of the occurrence of the ANLS in vivo as key to support the existence of ANLS in the brain [88], further studies are guaranteed solve discrepancies on some aspects of ANLS (see [103] for further discussion).

ROS Signaling and Metabolic Coupling

ROS and metabolism in the nervous system are intrinsically linked. In neural cells, endogenous or exogenous ROS can activate AMPK to modulate glucose intake [106]. ROS can also inhibit glycolytic enzymes such as glyceraldehyde 3-phosphate dehydrogenase (GAPDH) or pyruvate kinase M2 (PFKM2) through modification of cysteine residues [107]. In the last years, the work done by Prof. J. P. Bolaños and cols. has extensively contributed to our current understanding on how neurons and astrocytes differentially capitalize on glycolysis and PPP to intertwin metabolism and ROS signaling [54]. To accomplish with redox signaling in neurons and astrocytes, glucose is not merely used as a bioenergetic substrate for glycolysis. Instead, the pentose phosphate pathway (PPP) derives the use of glucose towards the production of NADPH in neurons, required as a reductive cofactor for the regeneration of GSH and ROS disposal [36]. As a result of the continuous degradation of PFKFB3 by Cdh1, the glycolytic flux is blunted while PPP is constitutively active in neurons. This becomes especially relevant under glutamate excitotoxicity, where bursts of Ca^{2+} activate calpain and the Cdk5-dependent phosphorylation of Cdh1, finally resulting in PFKFB3 stabilization, aberrant induction of glycolysis and consequent oxidative stress during neuronal cell death [36, 65, 108] and altered PPP underlying neurodegeneration [109, 110] (Fig. 2).

Further work has explored also the opposite; i.e., the possibility that ROS levels, particularly arising from mitochondria as the main source of ROS in the cell, could alter metabolism. This hypothesis departs from the finding that astrocytes have a stronger antioxidant machinery, probably to cope with their higher generation of ROS due to a less assembled mitochondrial complex I [25]. Capitalizing on a model of specific targeted expression of the cytosolic antioxidant enzyme catalase to mitochondria, Vicente-Gutierrez et al. [71] have recently explored the possibility that ROS generation in astrocytes could sustain a continuous engagement of an antioxidant response that may also impact metabolism. Using this model, they show that astrocytes control redox homeostasis through the modulation of NADPH-oxidases (NOX) and GSH synthesis, mastered by the transcriptional activity of Nrf2 in response to ROS. Strikingly, astrocytes expressing mitochondrial catalase to blunt ROS production in mitochondria, turned off the endogenous synthesis of antioxidants, thus resulting in a compromised supply of GSH and neuronal viability (Fig. 1). In this context, a higher abundance of ROS shows to be essential in the maintenance of neural metabolism, with aberrant consequences in behaviour [71]. In astrocytes, mitochondrial ROS are needed to physiologically regulate glucose metabolism by promoting glycolysis and repressing the pentose phosphate pathway (PPP). The mitochondrial response in astrocytes controls neuronal survival by regulating bioenergetics and redox metabolism [71]. Mechanistically, astrocytic ROS engage at least two paths to exert these functions. On the one hand, ROS keep the histone HDAC4 oxidized, allowing miR-206 expression and consequent G6PD repression. On the other hand, mitochondrial ROS in astrocytes conserve Nrf2 transcriptionally active to repress the extracellular release of ROS mediated by NOX-1 and NOX2. Moreover, Nrf2 serves also to synthetize GSH in astrocytes, afterwards used to replenish neuronal GSH through the astrocyte-neuron shuttle. In brain, astrocytic mitochondrial ROS modulate their genetic program, but do not deeply alter the expression of neuronal genes; however, signs of altered neuronal structure are shown and are compatible with cognitive defects in novel object recognition and open field tests, suggestive of altered cognition and social behaviour [71]. Altogether, astrocytic ROS emerge as determinants of metabolism and

vice versa, requiring from a reciprocal balance to sustain neuronal function and prevent neurodegeneration and cognitive defects. Importantly, the need of astrocytic ROS to keep active the antioxidant machinery and metabolism, may lead behind the failed ability of antioxidant therapies to provide neuroprotection [111–113].

Conclusions

The highly energetically demanding activity of neurons coordinates with surrounding neural cells to engage a metabolic and redox crosstalk, that is required for normal brain function. Regarding metabolism, astrocytes are no longer referred to as mere supportive cells, proven their essential role to cover the metabolic needs of neurons for neurotransmission and survival. In the last years, several works have made huge advances in understanding molecular and cellular aspects of this astrocytic-neuronal coupling, capitalizing on cutting-edge approaches and novel animal models.

Many attempts have pursued the use of antioxidant therapies as a tool to slow down the progression of these disorders [111, 112]. Unfortunately, almost all therapies tested in clinical trials have failed to provide neuroprotection, calling for a reassessment and a better understanding of neural redox biology. A starting point is to consider ROS as not mere by-products or harming agents. Challenging the established but still broadly simplistic view of ROS as harmful molecules, can be regarded as a main message from the evolution of the redox and metabolic fields in the nervous system over the last years. Although a deleterious role for ROS holds true over certain threshold levels, ROS should be physiologically regarded as key signaling molecules coupling metabolism in astrocytes and neurons, with broad pathophysiological implications when dysregulated. In the CNS, several evidences have now showed that ROS regulation and metabolism are differentially regulated in either neurons, with a more prominent reliance on oxidative phosphorylation and PPP, and astrocytes, which count on a strong antioxidant capacity and glycolytic handling to provide metabolic and redox precursors in their cross-talk with neurons. Hence, although classically assumed as secondary actors, astrocytes are currently considered as critical in regulating metabolism and redox signaling in the nervous system [8, 59, 71, 86]. As a key phenotypical consequence, astrocytes contribute to define behaviour through the modulation of neuronal plasticity and memory [114, 115]. In sum, a coordinated neural metabolism and redox status defines neuronal viability and functionality, thus accounting for behavioural phenotypes and, ultimately, neurological and neurodegenerative diseases. Future work will be needed to explore other expected metabolic pathways that may participate in neuronal and brain homeostasis, influenced by the astrocytic redox and metabolic status, with cellular specificity. Such studies should also elucidate whether and how other aspects of redox regulation, such as post-translational modifications or transcriptional regulation, impact the reciprocal modulation of metabolism and redox homeostasis underlying (dys) function in the nervous system.

Acknowledgements We are grateful to Prof. Juan P. Bolaños for his continuous support, mentoring and insightful scientific input. This publication is supported by funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie Grant Agreement No. 793987. Figures were modified from templates provided by Servier Medical Art.

References

1. Arellano JI, Rakic P (2011) Gone with the wean. Nature 478:333–334. https://doi.org/10.1038/478333a
2. Moreno-Jiménez EP, Flor-García M, Terreros-Roncal J et al (2019) Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat Med 25:554–560. https://doi.org/10.1038/s41591-019-0375-9
3. Eriksson PS, Perfilieva E, Björk-Eriksson T et al (1998) Neurogenesis in the adult human hippocampus. Nat Med 4:1313–1317. https://doi.org/10.1038/3305
4. Spalding KL, Bergmann O, Alkass K et al (2013) Dynamics of hippocampal neurogenesis in adult humans. Cell 153:1219–1227. https://doi.org/10.1016/j.cell.2013.05.002
5. Mattson MP, Liu D (2002) Energetics and oxidative stress in synaptic plasticity and neurodegenerative disorders. NeuroMolecular Med 2:215–232. https://doi.org/10.1385/NMM:2:2:215
6. McLaughlin BA, Nelson D, Erecińska M, Chesselet M-F (2002) Toxicity of dopamine to striatal neurons in vitro and potentiation of cell death by a mitochondrial inhibitor. J Neurochem 70:2406–2415. https://doi.org/10.1046/j.1471-4159.1998.70062406.x
7. Meiser J, Weindl D, Hiller K (2013) Complexity of dopamine metabolism. Cell Commun Signal 11:34. https://doi.org/10.1186/1478-811X-11-34
8. Quintana-Cabrera R, Bolaños JP (2013) Glutathione and γ-glutamylcysteine in hydrogen peroxide detoxification. Methods Enzymol 527:129–144. https://doi.org/10.1016/B978-0-12-405882-8.00007-6
9. Temple MD, Perrone GG, Dawes IW (2005) Complex cellular responses to reactive oxygen species. Trends Cell Biol 15:319–326. https://doi.org/10.1016/j.tcb.2005.04.003
10. Wamelink MMC, Struys EA, Jakobs C (2008) The biochemistry, metabolism and inherited defects of the pentose phosphate pathway: a review. J Inherit Metab Dis 31:703–717. https://doi.org/10.1007/s10545-008-1015-6
11. Bouzier-Sore AK, Bolaños JP, Bolaños JP (2015) Uncertainties in pentose-phosphate pathway flux assessment underestimate its contribution to neuronal glucose consumption: relevance for neurodegeneration and aging. Front Aging Neurosci 7:1–5. https://doi.org/10.3389/fnagi.2015.00089
12. Dringen R, Hoepken HH, Minich T, Ruedig C (2007) 1.3 pentose phosphate pathway and NADPH metabolism. In: Handbook of neurochemistry and molecular neurobiology. Springer US, Boston, MA, pp 41–62. https://doi.org/10.1007/978-0-387-30411-3_3
13. Bolaños JP, Heales SJR, Land JM, Clark JB (2002) Effect of peroxynitrite on the mitochondrial respiratory chain:

differential susceptibility of neurones and astrocytes in primary culture. J Neurochem 64:1965–1972. https://doi.org/10.1046/j.1471-4159.1995.64051965.x
14. Dringen R, Pfeiffer B, Hamprecht B (1999) Synthesis of the antioxidant glutathione in neurons: supply by astrocytes of CysGly as precursor for neuronal glutathione. J Neurosci 19:562–569
15. Fernandez-Fernandez S, Bobo-Jimenez V, Requejo-Aguilar R et al (2018) Hippocampal neurons require a large pool of glutathione to sustain dendrite integrity and cognitive function. Redox Biol 19:52–61. https://doi.org/10.1016/J.REDOX.2018.08.003
16. Henchcliffe C, Beal MF (2008) Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. Nat Clin Pract Neurol 4:600–609. https://doi.org/10.1038/ncpneuro0924
17. Dalton TP, Dieter MZ, Yang Y et al (2000) Knockout of the mouse glutamate cysteine ligase catalytic subunit (Gclc) gene: embryonic lethal when homozygous, and proposed model for moderate glutathione deficiency when heterozygous. Biochem Biophys Res Commun 279:324–329. https://doi.org/10.1006/bbrc.2000.3930
18. Feng W, Rosca M, Fan Y et al (2017) Gclc deficiency in mouse CNS causes mitochondrial damage and neurodegeneration. Hum Mol Genet 26:1376–1390. https://doi.org/10.1093/hmg/ddx040
19. Butterfield DA, Gu L, Di DF, Robinson RAS (2014) Mass spectrometry and redox proteomics: applications in disease. Mass Spectrom Rev 33:277–301. https://doi.org/10.1002/mas.21374
20. Franco R, Cidlowski JA (2009) Apoptosis and glutathione: beyond an antioxidant. Cell Death Differ 16:1303–1314. https://doi.org/10.1038/cdd.2009.107
21. Davey GP, Canevari L, Clark JB (2002) Threshold effects in synaptosomal and nonsynaptic mitochondria from hippocampal CA1 and paramedian neocortex brain regions. J Neurochem 69:2564–2570. https://doi.org/10.1046/j.1471-4159.1997.69062564.x
22. Diaz-Hernandez JI, Almeida A, Delgado-Esteban M et al (2005) Knockdown of glutamate-cysteine by ligase by small hairpin RNA reveals that both catalytic and modulatory subunits are essential for the survival of primary neurons. J Biol Chem. https://doi.org/10.1074/jbc.M507065200
23. Quintana-Cabrera R, Fernandez-Fernandez S, Bobo-Jimenez V et al (2012) γ-Glutamylcysteine detoxifies reactive oxygen species by acting as glutathione peroxidase-1 cofactor. Nat Commun 3:718. https://doi.org/10.1038/ncomms1722
24. Murphy MP (2009) How mitochondria produce reactive oxygen species. Biochem J 417:1–13. https://doi.org/10.1042/BJ20081386
25. Lopez-Fabuel I, Le Douce J, Logan A et al (2016) Complex I assembly into supercomplexes determines differential mitochondrial ROS production in neurons and astrocytes. Proc Natl Acad Sci USA 113:13063–13068. https://doi.org/10.1073/pnas.1613701113
26. Brand MD (2010) The sites and topology of mitochondrial superoxide production. Exp Gerontol 45:466–472. https://doi.org/10.1016/J.EXGER.2010.01.003
27. Brand MD (2016) Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling. Free Radic Biol Med 100:14–31. https://doi.org/10.1016/j.freeradbiomed.2016.04.001
28. Bolaños JP, Heales SJR, Land JM, Clark JB (1995) Effect of peroxynitrite on the mitochondrial respiratory chain: differential susceptibility of neurones and astrocytes in primary culture. J Neurochem 64:1965–1972. https://doi.org/10.1046/j.1471-4159.1995.64051965.x
29. Almeida A, Bolaños JP (2001) A transient inhibition of mitochondrial ATP synthesis by nitric oxide synthase activation triggered apoptosis in primary cortical neurons. J Neurochem 77:676–690. https://doi.org/10.1046/j.1471-4159.2001.00276.x
30. Porras OH, Loaiza A, Barros LF (2004) Glutamate mediates acute glucose transport inhibition in hippocampal neurons. J Neurosci 24:9669–9673. https://doi.org/10.1523/JNEUROSCI.1882-04.2004
31. Delgado-Esteban M, Almeida A, Bolaños JP (2002) D-Glucose prevents glutathione oxidation and mitochondrial damage after glutamate receptor stimulation in rat cortical primary neurons. J Neurochem 75:1618–1624. https://doi.org/10.1046/j.1471-4159.2000.0751618.x
32. Beltran B, Mathur A, Duchen MR et al (2000) The effect of nitric oxide on cell respiration: a key to understanding its role in cell survival or death. Proc Natl Acad Sci 97:14602–14607. https://doi.org/10.1073/pnas.97.26.14602
33. Bolaños JP, Almeida A, Moncada S (2010) Glycolysis: a bioenergetic or a survival pathway? Trends Biochem Sci 35:145–149. https://doi.org/10.1016/j.tibs.2009.10.006
34. Almeida A, Almeida J, Bolaños JP, Moncada S (2001) Different responses of astrocytes and neurons to nitric oxide: the role of glycolytically generated ATP in astrocyte protection. Proc Natl Acad Sci USA 98:15294–15299. https://doi.org/10.1073/pnas.261560998
35. Bolaños JP (2016) Bioenergetics and redox adaptations of astrocytes to neuronal activity. J Neurochem 139:115–125. https://doi.org/10.1111/jnc.13486
36. Herrero-Mendez A, Almeida A, Fernández E et al (2009) The bioenergetic and antioxidant status of neurons is controlled by continuous degradation of a key glycolytic enzyme by APC/C-Cdh1. Nat Cell Biol 11:747–752. https://doi.org/10.1038/ncb1881
37. Chaban Y, Boekema EJ, Dudkina NV (2014) Structures of mitochondrial oxidative phosphorylation supercomplexes and mechanisms for their stabilisation. Biochim Biophys Acta 1837:418–426. https://doi.org/10.1016/j.bbabio.2013.10.004
38. Enríquez JA (2016) Supramolecular organization of respiratory complexes. Annu Rev Physiol 78:533–561. https://doi.org/10.1146/annurev-physiol-021115-105031
39. Lopez-Fabuel I, Martin-Martin L, Resch-Beusher M et al (2017) Mitochondrial respiratory chain disorganization in Parkinson's disease-relevant PINK1 and DJ1 mutants. Neurochem Int 109:101–105
40. Genova ML, Lenaz G (2015) The interplay between respiratory supercomplexes and ROS in aging. Antioxid Redox Signal 23:208–238. https://doi.org/10.1089/ars.2014.6214
41. Gómez LA, Monette JS, Chavez JD et al (2009) Supercomplexes of the mitochondrial electron transport chain decline in the aging rat heart. Arch Biochem Biophys 490:30–35. https://doi.org/10.1016/j.abb.2009.08.002
42. Whitworth AJ, Pallanck LJ (2017) PINK1/Parkin mitophagy and neurodegeneration-what do we really know in vivo? Curr Opin Genet Dev 44:47–53. https://doi.org/10.1016/j.gde.2017.01.016
43. Requejo-Aguilar R, Lopez-Fabuel I, Fernandez E et al (2014) PINK1 deficiency sustains cell proliferation by reprogramming glucose metabolism through HIF1. Nat Commun 5:4514. https://doi.org/10.1038/ncomms5514
44. Prestel J, Gempel K, Hauser TK et al (2008) Clinical and molecular characterisation of a Parkinson family with a novel PINK1 mutation. J Neurol 255:643–648. https://doi.org/10.1007/s00415-008-0763-4
45. Fernandez-Fernandez S, Almeida A, Bolaños JP et al (2012) Antioxidant and bioenergetic coupling between neurons and astrocytes. Biochem J 443:3–11. https://doi.org/10.1042/BJ20111943

46. Bolaños JP, Duchen MR, Hampton MB et al (2016) Introduction to special issue on mitochondrial redox signaling in health and disease. Free Radic Biol Med 100:1–4
47. Barja G (2004) Free radicals and aging. Trends Neurosci 27:595–600. https://doi.org/10.1016/j.tins.2004.07.005
48. Halliwell B (2011) Free radicals and antioxidants—quo vadis? Trends Pharmacol Sci 32:125–130. https://doi.org/10.1016/j.tips.2010.12.002
49. Bolaños JP, Moro MA, Lizasoain I, Almeida A (2009) Mitochondria and reactive oxygen and nitrogen species in neurological disorders and stroke: therapeutic implications. Adv Drug Deliv Rev 61:1299–1315. https://doi.org/10.1016/j.addr.2009.05.009
50. Papadia S, Soriano FX, Léveillé F et al (2008) Synaptic NMDA receptor activity boosts intrinsic antioxidant defenses. Nat Neurosci 11:476–487. https://doi.org/10.1038/nn2071
51. Baxter PS, Bell KFS, Hasel P et al (2015) Synaptic NMDA receptor activity is coupled to the transcriptional control of the glutathione system. Nat Commun 6:6761. https://doi.org/10.1038/ncomms7761
52. Deighton RF, Markus NM, Al-Mubarak B et al (2014) Nrf2 target genes can be controlled by neuronal activity in the absence of Nrf2 and astrocytes. Proc Natl Acad Sci 111:E1818–E1820. https://doi.org/10.1073/pnas.1402097111
53. Cobley JN, Fiorello ML, Bailey DM (2018) 13 reasons why the brain is susceptible to oxidative stress. Redox Biol 15:490–503
54. Bolaños JP, Bolanos JP, Bolaños JP (2016) Bioenergetics and redox adaptations of astrocytes to neuronal activity. J Neurochem 139:115–125. https://doi.org/10.1111/jnc.13486
55. Bell KFS, Al-Mubarak B, Martel M-A et al (2015) Neuronal development is promoted by weakened intrinsic antioxidant defences due to epigenetic repression of Nrf2. Nat Commun 6:7066. https://doi.org/10.1038/ncomms8066
56. Jimenez-Blasco D, Santofimia-Castaño P, Gonzalez A et al (2015) Astrocyte NMDA receptors' activity sustains neuronal survival through a Cdk5–Nrf2 pathway. Cell Death Differ. https://doi.org/10.1038/cdd.2015.49
57. Tonelli C, Chio IIC, Tuveson DA (2018) Transcriptional Regulation by Nrf2. Antioxid Redox Signal 29:1727–1745. https://doi.org/10.1089/ars.2017.7342
58. Kobayashi A, Kang M-I, Watai Y et al (2006) Oxidative and electrophilic stresses activate Nrf2 through inhibition of ubiquitination activity of Keap1. Mol Cell Biol 26:221–229. https://doi.org/10.1128/MCB.26.1.221-229.2006
59. Jha MK, Morrison BM (2018) Glia-neuron energy metabolism in health and diseases: new insights into the role of nervous system metabolic transporters. Exp Neurol 309:23–31. https://doi.org/10.1016/J.EXPNEUROL.2018.07.009
60. Habas A, Hahn J, Wang X, Margeta M (2013) Neuronal activity regulates astrocytic Nrf2 signaling. Proc Natl Acad Sci 110:18291–18296. https://doi.org/10.1073/pnas.1208764110
61. Dringen R, Brandmann M, Hohnholt MC, Blumrich E-M (2015) Glutathione-dependent detoxification processes in astrocytes. Neurochem Res 40:2570–2582. https://doi.org/10.1007/s11064-014-1481-1
62. Hilgier W, Węgrzynowicz M, Ruszkiewicz J et al (2010) Direct exposure to ammonia and hyperammonemia increase the extracellular accumulation and degradation of astroglia-derived glutathione in the Rat Prefrontal Cortex. Toxicol Sci 117:163–168. https://doi.org/10.1093/toxsci/kfq171
63. Bota DA, Davies KJA (2016) Mitochondrial Lon protease in human disease and aging: including an etiologic classification of Lon-related diseases and disorders. Free Radic Biol Med 100:188–198. https://doi.org/10.1016/j.freeradbiomed.2016.06.031
64. Baxter PS, Hardingham GE (2016) Adaptive regulation of the brain's antioxidant defences by neurons and astrocytes. Free Radic Biol Med 100:147–152. https://doi.org/10.1016/j.freeradbiomed.2016.06.027
65. Maestre C, Delgado-Esteban M, Gomez-Sanchez JC et al (2008) Cdk5 phosphorylates Cdh1 and modulates cyclin B1 stability in excitotoxicity. EMBO J 27:2736–2745. https://doi.org/10.1038/emboj.2008.195
66. Rodriguez-Rodriguez P, Almeida A, Bolaños JP (2013) Brain energy metabolism in glutamate-receptor activation and excitotoxicity: Role for APC/C-Cdh1 in the balance glycolysis/pentose phosphate pathway. Neurochem Int 62:750–756. https://doi.org/10.1016/j.neuint.2013.02.005
67. Bell KF, Al-Mubarak B, Fowler JH et al (2011) Mild oxidative stress activates Nrf2 in astrocytes, which contributes to neuroprotective ischemic preconditioning. Proc Natl Acad Sci 108:E1–E2. https://doi.org/10.1073/pnas.1015229108
68. Schieber M, Chandel NS (2014) ROS function in redox signaling and oxidative stress. Curr, Biol, p 24
69. Schulz TJ, Zarse K, Voigt A et al (2007) Glucose restriction extends *Caenorhabditis elegans* life span by inducing mitochondrial respiration and increasing oxidative stress. Cell Metab 6:280–293. https://doi.org/10.1016/j.cmet.2007.08.011
70. López-otín C, Blasco MA, Partridge L, Serrano M (2013) Europe PMC Funders Group the hallmarks of aging. Cell 153:1194–1217. https://doi.org/10.1016/j.cell.2013.05.039.The
71. Vicente-Gutierrez C, Bonora N, Bobo-Jimenez V et al (2019) Astrocytic mitochondrial ROS modulate brain metabolism and mouse behaviour. Nat Metab 1:201. https://doi.org/10.1038/s42255-018-0031-6
72. Hertz L, Peng L, Dienel GA (2007) Energy metabolism in astrocytes: high rate of oxidative metabolism and spatiotemporal dependence on glycolysis/glycogenolysis. J Cereb Blood Flow Metab 27:219–249. https://doi.org/10.1038/sj.jcbfm.9600343
73. Magistretti PJ, Allaman I (2015) A cellular perspective on brain energy metabolism and functional imaging. Neuron 86:883–901. https://doi.org/10.1016/J.NEURON.2015.03.035
74. Perea G, Sur M, Araque A (2014) Neuron-glia networks: integral gear of brain function. Front Cell Neurosci 8:378. https://doi.org/10.3389/fncel.2014.00378
75. Oliveira JF, Sardinha VM, Guerra-Gomes S et al (2015) Do stars govern our actions? Astrocyte involvement in rodent behavior. Trends Neurosci 38:535–549. https://doi.org/10.1016/j.tins.2015.07.006
76. Allen NJ, Barres BA (2009) Glia—more than just brain glue. Nature 457:675–677. https://doi.org/10.1038/457675a
77. Magistretti PJ (2009) Role of glutamate in neuron-glia metabolic coupling. Am J Clin Nutr 90:875S–880S. https://doi.org/10.3945/ajcn.2009.27462CC
78. Porras OH, Ruminot I, Loaiza A, Barros LF (2008) Na^{+}–Ca^{2+} cosignaling in the stimulation of the glucose transporter GLUT1 in cultured astrocytes. Glia 56:59–68. https://doi.org/10.1002/glia.20589
79. Loaiza A, Porras OH, Barros LF (2003) Glutamate triggers rapid glucose transport stimulation in astrocytes as evidenced by real-time confocal microscopy. J Neurosci 23:7337–7342
80. Bittner CX, Valdebenito R, Ruminot I et al (2011) Fast and reversible stimulation of astrocytic glycolysis by K+ and a delayed and persistent effect of glutamate. J Neurosci 31:4709–4713. https://doi.org/10.1523/JNEUROSCI.5311-10.2011
81. Van Schaftingen E, Lederer B, Bartrons R, Hers H-G (1982) A kinetic study of pyrophosphate: fructose-6-phosphate phosphotransferase from potato tubers: application to a microassay of fructose 2,6-bisphosphate. Eur J Biochem 129:191–195. https://doi.org/10.1111/j.1432-1033.1982.tb07039.x
82. Pellerin L, Magistretti PJ (2012) Sweet sixteen for ANLS. J Cereb Blood Flow Metab 32:1152–1166. https://doi.org/10.1038/jcbfm.2011.149

83. Brown AM, Ransom BR (2007) Astrocyte glycogen and brain energy metabolism. Glia 55:1263–1271. https://doi.org/10.1002/glia.20557
84. Suh SW, Bergher JP, Anderson CM et al (2007) Astrocyte glycogen sustains neuronal activity during hypoglycemia: studies with the glycogen phosphorylase inhibitor CP-316,819 ([*R* − *R* *, *S* *]-5-chloro-*N*-[2-hydroxy-3-(methoxymethylamino)-3-oxo-1-(phenylmethyl)propyl]-1 %3ci%3e. J Pharmacol Exp Ther 321:45–50. https://doi.org/10.1124/jpet.106.115550
85. Bouzier-Sore A-K, Voisin P, Bouchaud V et al (2006) Competition between glucose and lactate as oxidative energy substrates in both neurons and astrocytes: a comparative NMR study. Eur J Neurosci 24:1687–1694. https://doi.org/10.1111/j.1460-9568.2006.05056.x
86. Magistretti PJ, Allaman I (2018) Lactate in the brain: from metabolic end-product to signalling molecule. Nat Rev Neurosci 19:235–249. https://doi.org/10.1038/nrn.2018.19
87. Pellerin L, Magistretti PJ (1994) Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc Natl Acad Sci USA 91:10625. https://doi.org/10.1073/PNAS.91.22.10625
88. Mächler P, Wyss MT, Elsayed M et al (2016) In vivo evidence for a lactate gradient from astrocytes to neurons. Cell Metab 23:94–102. https://doi.org/10.1016/j.cmet.2015.10.010
89. Volkenhoff A, Weiler A, Letzel M et al (2015) Glial glycolysis is essential for neuronal survival in drosophila. Cell Metab 22:437–447. https://doi.org/10.1016/j.cmet.2015.07.006
90. Lu W, Huang J, Sun S et al (2015) Changes in lactate content and monocarboxylate transporter 2 expression in Aβ25-35-treated rat model of Alzheimer's disease. Neurol Sci 36:871–876. https://doi.org/10.1007/s10072-015-2087-3
91. Perkins M, Wolf AB, Chavira B et al (2016) Altered energy metabolism pathways in the posterior cingulate in young adult apolipoprotein E ε4 carriers. J Alzheimer's Dis 53:95–106. https://doi.org/10.3233/JAD-151205
92. Lee Y, Morrison BM, Li Y et al (2012) Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature 487:443–448. https://doi.org/10.1038/nature11314
93. Fünfschilling U, Supplie LM, Mahad D et al (2012) Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Nature 485:517–521. https://doi.org/10.1038/nature11007
94. Amaral AI, Hadera MG, Tavares JM et al (2016) Characterization of glucose-related metabolic pathways in differentiated rat oligodendrocyte lineage cells. Glia 64:21–34. https://doi.org/10.1002/glia.22900
95. Saab AS, Tzvetavona ID, Trevisiol A et al (2016) Oligodendroglial NMDA receptors regulate glucose import and axonal energy metabolism. Neuron 91:119–132. https://doi.org/10.1016/J.NEURON.2016.05.016
96. Baltan S (2015) Can lactate serve as an energy substrate for axons in good times and in bad, in sickness and in health? Metab Brain Dis 30:25–30. https://doi.org/10.1007/s11011-014-9595-3
97. Mergenthaler P, Lindauer U, Dienel GA, Meisel A (2013) Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends Neurosci 36:587–597. https://doi.org/10.1016/J.TINS.2013.07.001
98. Bélanger M, Allaman I, Magistretti PJ (2011) Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab 14:724–738. https://doi.org/10.1016/J.CMET.2011.08.016
99. Sickmann HM, Schousboe A, Fosgerau K, Waagepetersen HS (2005) Compartmentation of lactate originating from glycogen and glucose in cultured astrocytes. Neurochem Res 30:1295–1304. https://doi.org/10.1007/s11064-005-8801-4
100. Barros LF (2010) Glucose and lactate supply to the synapse. Brain Res Rev 63:149–159. https://doi.org/10.1016/J.BRAINRESREV.2009.10.002
101. Allaman I, Bélanger M, Magistretti PJ (2011) Astrocyte-neuron metabolic relationships: for better and for worse. Trends Neurosci 34:76–87. https://doi.org/10.1016/j.tins.2010.12.001
102. Kasischke KA (2015) 2014 update of the original article: Kasischke KA (2009) Activity-dependent Metabolism in Glia and Neurons. In: Squire LR (ed) New encyclopediaof neuroscience, vol 1. Elsevier Ltd., Oxford, UK, pp 53–60. https://doi.org/10.1016/B978-0-12-801238-3.04487-1
103. Mason S (2017) Lactate shuttles in neuroenergetics-homeostasis, allostasis and beyond. Front Neurosci 11:43
104. Eraso-Pichot A, Brasó-Vives M, Golbano A et al (2018) GSEA of mouse and human mitochondriomes reveals fatty acid oxidation in astrocytes. Glia 66:1724–1735. https://doi.org/10.1002/glia.23330
105. Pellerin L, Magistretti PJ (2004) Let there be (NADH) light. Science 305:50–52
106. Liemburg-Apers DC, Willems PHGM, Koopman WJH, Grefte S (2015) Interactions between mitochondrial reactive oxygen species and cellular glucose metabolism. Arch Toxicol 89:1209–1226. https://doi.org/10.1007/s00204-015-1520-y
107. Mullarky E, Cantley LC (2015) Diverting glycolysis to combat oxidative stress. Springer, Berlin
108. Rodriguez-Rodriguez P, Fernandez E, Almeida A, Bolaños JP (2012) Excitotoxic stimulus stabilizes PFKFB3 causing pentose-phosphate pathway to glycolysis switch and neurodegeneration. Cell Death Differ 19:1582–1589. https://doi.org/10.1038/cdd.2012.33
109. Ferreira IL, Cunha-Oliveira T, Nascimento MV et al (2011) Bioenergetic dysfunction in Huntington's disease human cybrids. Exp Neurol 231:127–134. https://doi.org/10.1016/j.expneurol.2011.05.024
110. Soucek T, Cumming R, Dargusch R et al (2003) The regulation of glucose metabolism by HIF-1 mediates a neuroprotective response to amyloid beta peptide. Neuron 39:43–56. https://doi.org/10.1016/s0896-6273(03)00367-2
111. Neves Carvalho A, Firuzi O, Joao Gama M et al (2017) Oxidative stress and antioxidants in neurological diseases: is there still hope? Curr Drug Targets. https://doi.org/10.2174/1389450117666160401120514
112. Juránek I, Nikitovic D, Kouretas D et al (2013) Biological importance of reactive oxygen species in relation to difficulties of treating pathologies involving oxidative stress by exogenous antioxidants. Food Chem Toxicol 61:240–247. https://doi.org/10.1016/j.fct.2013.08.074
113. Kamat CD, Gadal S, Mhatre M et al (2008) Antioxidants in central nervous system diseases: preclinical promise and translational challenges. J Alzheimer's Dis 15:473–493. https://doi.org/10.3233/JAD-2008-15314
114. De Pittà M, Brunel N, Volterra A (2016) Astrocytes: orchestrating synaptic plasticity? Neuroscience 323:43–61. https://doi.org/10.1016/J.NEUROSCIENCE.2015.04.001
115. Adamsky A, Goshen I (2018) Astrocytes in memory function: pioneering findings and future directions. Neuroscience 370:14–26. https://doi.org/10.1016/j.neuroscience.2017.05.033