The brain consumes about 20% of inhaled O$_2$ suggesting a high-energy-demanding tissue. Most of the neural energy expenditure is accounted for by the electrical impulses, which require continuous re-settling of ion (Na$^+$, K$^+$, and Ca$^{2+}$) gradients across the plasma membrane of dendrites and axons through primary active transporters, including Na$^+$/K$^+$- and Ca$^{2+}$-ATPase pumps (Cai and Sheng 2009). Accordingly, it is not unexpected that stimulation of glutamate-dereived glycolytic lactate thus sustains the energy needs of neurons, which in contrast to astrocytes mainly rely on oxidative phosphorylation. Neuronal activity unavoidably triggers reactive oxygen species, but the antioxidant defense of neurons is weak; hence, they use glucose for oxidation through the pentose-phosphate pathway to preserve the redox status. Furthermore, neuronal activity is coupled with erythroid-derived erythroid-activated 2-like 2 (Nrf2) mediated transcriptional activation of antioxidant genes in astrocytes, which boost the de novo glutathione biosynthesis in neighbor neurons. Thus, the bioenergetics and redox programs of astrocytes are adapted to sustain neuronal activity and survival. Developing therapeutic strategies to interfere with these pathways may be useful to combat neurological diseases.

Keywords: AMPK, Cdh1, Glycolysis, GSH, Nrf2, PFKFB3.

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receptors in cortical neurons causes rapid ATP consumption (Almeida and Bolaños 2001), which is immediately followed by a rise in mitochondrial O2 consumption (Thompson et al. 2003; Jekabsons and Nicholls 2004; Garcia et al. 2005). This suggests that the energy requirements of neurons during activity are met by mitochondrial oxidative phosphorylation (OXPHOS) (Nicholls 2008). Interestingly, prior to the rise in activity are met by mitochondrial oxidative phosphorylation (Nicholls et al. 2007). Furthermore, mitochondrial influx of Ca2+ alters mitochondrial OXPHOS efficiency; hence, the production of reactive oxygen species (ROS) by this organelle is an inherent phenomenon of neurotransmission (Perea et al. 2014; Oliveira et al. 2011). However, the nature of the lag between activation of cerebral blood flow and O2 consumption following neural activity (Fox and Raichle 1986) challenges this notion and lays the foundation for a long-lasting debate (Hertz et al. 2007; Pellerin et al. 2007; Ivanov et al. 2014). The aim of this review was to revisit our current knowledge on the brain’s management of the bioenergetics and redox needs that result from neural activity, as well as to identify potential gaps requiring future research.

Energy management of astrocytes during neural activity

Astrocytes are crucial to the metabolic and structural support of the brain (Parpura et al. 1994; Allen and Barres 2009), as they are essential partners in neurotransmission and behavior (Perea et al. 2014; Oliveira et al. 2015). During glutamatergic neurotransmission, astrocytes efficiently take up neuronal-derived glutamate from the synaptic space through secondary, Na+-dependent active transporters. Thus, glutamate uptake is energy-costly for astrocytes, as re-setting the Na+ gradient across the plasma membrane to the resting levels requires Na+ pumping by the Na+/K+-ATPase. The mechanism used by astrocytes to couple glutamate uptake with its energy requirement is currently controversial. Intracellular glutamate may follow at least two metabolic fates, namely conversion into α-ketoglutarate for oxidation within mitochondria via the tricarboxylic acid (TCA) cycle, or conversion into glutamine to be released and taken up by neighbor neurons, which convert it back into glutamate (Fig. 1). Estimations, made on the bases of the energetic efficiencies of substrates, initially concluded that the energy required for glutamate uptake exceeds that provided by the mitochondrial oxidation of glutamate alone (Hertz et al. 2007). Considering this, the increase in the rate of glucose uptake (Loaiza et al. 2003; Porras et al. 2008) coupled to glutamate influx by astrocytes, suggests that invoked glycolysis likely supplements the energy needs of the process, which is part of the so-called astrocyte-neuronal lactate shuttle (Pellerin and Magistretti 1994; Magistretti and Allaman 2015) that will be discussed below. Nonetheless, this issue has been the matter of debate. Comparing the use of glucose or lactate in cortical neurons and astrocytes under resting conditions by 13C-nuclear magnetic resonance (13C-NMR), it was concluded that lactate was a preferential TCA cycle substrate over glucose in neurons, whereas astrocytes oxidized less lactate indicating a less active oxidative metabolism than neurons (Bouzier-Sore et al. 2006). This notion has been confirmed in resting cerebellar neurons (Bak et al. 2006), albeit glucose – not lactate – utilization via TCA cycle oxidation increases upon glutamatergic activity in these cells (Bak et al. 2006, 2009, 2012). Therefore, it seems likely that cerebellar and cortical neurons have different intrinsic responses against depolarization. Interestingly, extracellular lactate inhibits glucose usage by astrocytes, an effect that is stronger in resting than in K+-stimulated conditions (Sotelo-Hitschfeld et al. 2012). This suggests the occurrence of a negative feedback regulatory mechanism of glucose consumption in astrocytes by lactate that diverts glucose utilization from resting to active zones. Moreover, astrocytes store glycogen particularly in areas of high synaptic activity (Pellerin and Magistretti 2012), and glycogen-derived lactate (Pellerin et al. 2007) can sustain neuronal activity specially during hypoglycemia (Brown and Ransom 2007; Suh et al. 2007) (Fig. 1). Neurons also synthesize glycogen that is continuously degraded (Vilchez et al. 2007), the physiological function of which is a matter of investigation (Duran and Guinovart 2015).

Therefore, it seems likely that cerebellar and cortical neurons have different intrinsic responses against depolarization. (Bittner et al. 2011). However, the nature of the functional coupling between glycolysis and Na+/K+-ATPase may not be energetic (Fernandez-Moncada and Barros 2014). The effect of glutamate on glycolysis is delayed and persistent, in contrast to the effect that is observed using K+ at concentrations compatible with those during glutamatergic neurotransmission, which stimulates glycolysis rapidly and reversibly (Bittner et al. 2011). Ammonium (NH4+), which is produced stoichiometrically with glutamate, can rapidly activate lactate release from astrocytes, as can glutamate (Lerchundi et al. 2015); however, this effect is not coupled with glycolysis but with inhibition of mitochondrial uptake of pyruvate. Thus, the long-lasting effect of glutamate (Bittner et al. 2011) suggests the action of adaptive metabolic mechanisms of astrocytes to neurotransmission, which will be discussed below. The mechanisms responsible for the short-term effects on glycolysis and lactate release triggered by K+ and NH4+ deserve further investigation.
Is OXPHOS dispensable for energy generation in astrocytes?

Nitric oxide (NO) is a neural messenger (Garthwaite et al. 1988) that is formed by neurons following glutamatergic neurotransmission. Experiments performed in astrocytes revealed the inhibition of the mitochondrial respiratory chain (MRC) by a NO synthase-mediated mechanism (Bolaños et al. 1994). The most susceptible component of the MRC was found to be cytochrome c oxidase (complex IV) (Bolaños et al. 1994). Subsequent studies confirmed this effect and revealed such inhibition to be reversible (Brown and Cooper 1994; Cleeter et al. 1994; Schweizer and Richter 1994), occurring by competition with O2 (Brown and Cooper 1994). During endogenous NO production inhibiting the MRC at cytochrome c oxidase in astrocytes, ~ 90–100% of the glucose they consumed was released as lactate, and cells remained alive (Bolaños et al. 1994). These results suggest that OXPHOS inhibition invokes glycolysis as a survival pathway in astrocytes. In fact, endothelial cells-derived NO activates glycolytic lactate from neighbor astrocytes through hypoxia-inducible factor-1 (HIF-1)-mediated induction of glycolytic enzymes and monocarboxylate transporter-4 expression (Brix et al. 2012). Glycolytic ATP drives the reverse ATP synthase reaction, which pumps H+ into the intermembrane space, thus sustaining the mitochondrial membrane potential (ΔΨm) (Beltran et al. 2000; Almeida et al. 2001). As long as glycolytic ATP sustains ΔΨm astrocytes avoid apoptosis (Almeida et al. 2001), confirming that glycolysis is a survival pathway (Bolaños et al. 2010).
Neurotransmission-associated NH4⁺ formation acidifies the mitochondrial matrix in astrocytes leading to inhibition of pyruvate uptake (Lerchundi et al. 2015), which likely leads to TCA cycle impairment and mitochondrial energy stress, thus, contributing to glycolytic activation. Therefore, it is tempting to speculate that glycolysis is essential in astrocytes whereas OXPHOS is dispensable for the generation of energy associated with neurotransmission.

In contrast to astrocytes, neurons are highly vulnerable to the inhibition of the MRC. Incubation of neurons and astrocytes with NO or its derivative peroxynitrite anion causing identical degree permanent inhibition of cytochrome c oxidase and mitochondrial respiration in both cell types dramatically triggered neuronal death, whereas astrocytes remained intact (Bolaños et al. 1995; Almeida et al. 2001). Interestingly, under these conditions, neurons were unable to up-regulate glycolysis, and neuronal apoptosis was preceded by ΔΨm collapse and ATP depletion (Almeida et al. 2001). Furthermore, these features were mimicked by stimulation of glutamate receptors, which immediately caused ATP decline (Esteban et al. 2004) or glycolytic activation (Delgado-Esteban et al. 2000). Thus, during neuronal activity, neurons – in contrast to astrocytes – are tightly dependent on OXPHOS for energy generation and survival.

**Astrocytes are constitutively glycolytic**

Glycolysis is mainly regulated by the enzymatic activities of hexokinase, 6-phosphofructo-1-kinase (PFK1), and pyruvate kinase (PK). In resting astrocytes, PFK1 specific activity is fourfold that found in resting neurons, and the levels of PFK1 positive effector, fructose-2,6-bisphosphate (F2,6P2) is twofold (Almeida et al. 2004). There are four isoforms of the enzyme responsible for the synthesis of F2,6P2, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB). However, isoform 3 (PFKFB3) is, by far, the most abundant one found in astrocytes (Almeida et al. 2004). Interestingly, PFKFB3 has a high, ~700-fold kinase versus bisphosphatase ratio (Pilkis et al. 1995). Hence, PFKFB3 levels are directly proportional to F2,6-P2 synthesizing activity. PFKFB3 knockdown abolishes the ability of astrocytes to up-regulate glycolysis upon mitochondrial inhibition, suggesting that PFKFB3 is necessary and sufficient to maintain the glycolytic phenotype of astrocytes (Almeida et al. 2004) (Fig. 1).

The transcriptome of the brain has been analyzed at single-cell level by RNA-sequencing, and it was found that PFKFB3, PK muscle-2 isoform, lactate dehydrogenase B-isoform (LDHB), and pyruvate dehydrogenase kinase 4-isoform (PDK4) were highly expressed in astrocytes when compared with neurons (Zhang et al. 2014). This confirms previous findings on PFKFB3 levels and activity (Almeida et al. 2004), strengthening the notion that astrocytes are constitutively glycolytic (at the light of PFKFB3, PK muscle-2 isoform, and LDHB mRNA levels) and independent on the OXPHOS (as judged by the high mRNA levels of pyruvate dehydrogenase kinase 4-isoform, which phosphorylates and inhibits pyruvate dehydrogenase). In another study, the isoforms of LDH were shown to be differentially expressed in neurons and astrocytes, with neurons preferentially expressing LDH1 (mainly pyruvate-producing tissues) and astrocytes expressing LDH5 (associated with high lactate-producing tissues) (Pellerin et al. 1998). Furthermore, astrocytes were shown to express the monocarboxylate transporters-1 and -4 (MCT1 and MCT4), which are responsible for lactate efflux, whereas neurons express MCT2, which is specialized for lactate influx (Pierre and Pellerin 2005). These data, taken together, support the notion that astrocytes continuously produce lactate through glycolysis and explain the presence of an intracellular lactate reservoir in these cells (Sotelo-Hitschfeld et al. 2015), which is released through a channel upon extracellular rise in K⁺ or depolarization (Sotelo-Hitschfeld et al. 2015).

Upon cellular energy stress, 5'-AMP concentrations increase and facilitate activation 5'-AMP-activated protein kinase (AMPK) by phosphorylation of a Thr172 residue on its catalytic subunit by the liver kinase-1 (Sanders et al. 2007), which is a protein kinase with tumor suppression activity (Partanen et al. 2009). Active AMPK catalyzes the phosphorylation of several key metabolic regulatory enzymes, including PFKFB (Lage et al. 2008). In astrocytes, AMPK becomes phosphorylated, F2,6P2 levels elevated, and glycolysis activated within minutes of the inhibition of mitochondrial respiration by NO or cyanide (Almeida et al. 2004). Knockdown of the α1 subunit of AMPK, or PFKFB3, abolishes F2,6P2 elevation and glycolysis activation (Almeida et al. 2004). Thus, energy stress up-regulates glycolysis through AMPK-mediated activation of PFKFB3 in astrocytes. There is a likely possibility that the glycolytic activation caused by glutamate uptake (Pellerin and Magistretti 1994) occurs through this AMPK-PFKFB3 pathway, as suggested before (Ronnett et al. 2009), but this needs to be directly elucidated. Interestingly, the ATP/AMP ratio, as well as O2 levels and nutrients, such as glucose and amino acids, regulate the mammalian target of rapamycin (mTOR) (Wullschleger et al. 2006). Beside controlling key cellular functions, including energy metabolism or autophagy, mTOR regulates synaptic plasticity, memory storage, and cognition, this being the subject of a recent review (Bockaert and Marin 2015). Besides its critical importance in the tissue energy homeostasis, no evidence for the cellular localization and specific functions of mTOR on the bioenergetics and redox adaptations of brain cells to neural activity has been reported so far. The possible involvement of mTOR pathways in the control of brain energy metabolism during neural activity is therefore interesting and worthy of exploration.
Neurons are less glycolytic than astrocytes

While the widely spread notion is that glucose utilization through glycolysis by neurons is low and they depend on OXPHOS for energy generation (Knott et al. 2008), results obtained from different biologic preparations and brain regions are apparently controversial. Studies performed in rat cerebellar neurons in culture (Budd and Nicholls 1996), cortex synaptosomes (Kauppinen and Nicholls 1986; Choi et al. 2009), and retinal neurons (Xu et al. 2007; Bringmann et al. 2009) proposed glucose as the main energetic substrate. Noticeably, fast axonal transport of vesicles has a need for locally supplied ATP, which is met by glycolysis not mitochondria (Zala et al. 2013), and thus is a process that specifically requires glyceraldehyde-3-phosphate dehydrogenase. In addition, neurons have recently been reported to require glucose for synaptic activity (Lundgaard et al. 2015), although it remains unclear whether the metabolic fate of neurally used glucose is glycolysis or pentose-phosphate pathway (PPP) known to be essential for antioxidant protection (Herrero-Mendez et al. 2009) (see below). Moreover, there is question as to the reliability of the fluorescent probe, used in Lundgaard et al. (2015), to specifically assess glucose transport—in contrast to carrier endocytosis (Tadi et al. 2015). Furthermore, recently, using the genetically encoded lactate probe Laconic, it has been provided the first in vivo evidence for a lactate gradient from astrocytes to neurons (Maechler et al. 2016), a prerequisite for the occurrence of the ANLS. Accordingly, glucose does not seem to be used for the energy generation needed during neural activity, at least by cortical and hippocampal neurons, except for in fast vesicle transport through the axons (Zala et al. 2013).

Studies aimed at understanding why neurons do not rely on glycolysis for energy generation found PFKFB3 protein to be virtually absent in neurons (Almeida et al. 2004), both in culture and in vivo, because of the continuous destabilization by the ubiquitin-proteasome pathway (Herrero-Mendez et al. 2009). Thus, PFKFB3—not PFKFB1, -2 or -4—contains a 142Lys-Glu-Asn (KEN) box that targets it for ubiquitination by the anaphase-promoting complex/cyclosome (APC/C)-Cdhl (Herrero-Mendez et al. 2009), which is an E3 ubiquitine ligase known for its roles in the regulation of mitosis, meiosis (Pesin and Orr-Weaver 2008), tumor suppression, and genome stability (Garcia-Higuera et al. 2008). Besides these roles, APC/C-Cdh1 regulates important functions in neurons, such as axonal growth (Konishi et al. 2004; Harmey et al. 2009; Huyhn et al. 2009), cortical neurogenesis and size (Delgado-Esteban et al. 2013), and survival (Almeida et al. 2005; Stegmuller and Bonni 2005; Maestre et al. 2008). In cortical neurons, Cdh1 knockdown leads to PFKFB3 accumulation, which is sufficient to increase glycolysis (Herrero-Mendez et al. 2009). This was the first observation to describe a role for a cell cycle-related protein (APC/C-Cdh1) in metabolism, which was mimicked by PFKFB3 full-length cDNA over-expression (Herrero-Mendez et al. 2009). In contrast, Cdh1 protein levels and APC/C-Cdh1 ubiquitylating activity are very low in astrocytes, which explains their high levels of PFKFB3 and glycolytic activity (Herrero-Mendez et al. 2009) (Fig. 1).

Metabolic fate of neuronal glucose

The rate of [6-14C]glucose incorporated into 14CO2 (i.e., an index of glucose that is oxidized in the TCA cycle after having been converted into pyruvate) is negligible in cortical neurons when compared with astrocytes (Garcia-Nogales et al. 2003; Herrero-Mendez et al. 2009). Glucose is not actively transformed into lactate either, as judged by the low rate of [U-14C]glucose incorporation into 14C-lactate in neurons (Herrero-Mendez et al. 2009). Lastly, glycolytic rate, assessed as the rate of H2O formation from [3-3H]glucose and thus accurately reflecting the flux of glucose through glycolysis (Bouzier-Sore and Bolanos 2015), is ~4-5-fold lower in neurons than in astrocytes (Herrero-Mendez et al. 2009). It seems, therefore, likely that the neuronal ability to perform glycolysis is limited. Interestingly, over-activation of PFKFB3 leading to up-regulation of glycolysis causes oxidative stress and neuronal death (Herrero-Mendez et al. 2009), whereas over-activation of glutamate receptors, which inhibits APC/C-Cdh1 (Maestre et al. 2008), stabilizes endogenous PFKFB3 protein causing neuronal death that can be rescued by knocking down PFKFB3 (Rodriguez-Rodriguez et al. 2012). Together, these results strongly suggest that high glycolysis is not safe for neurons.

PPP converts glucose-6-phosphate (G6P) into ribulose-5-phosphate (R5P) in three consecutive steps, the first one catalyzed by G6P dehydrogenase (G6PD), which forms 6-phosphogluconolactone; 6-phosphogluconolactone is then converted into 6-phosphoglucuronate (6PG) by a lactonase, followed by its decarboxylation into R5P by 6PG dehydrogenase (Wamelink et al. 2008; Bouzier-Sore and Bolanos 2015). Two of these reactions (G6PD and 6PG dehydrogenase) occur, each, at the expense of one mole of NADPH(H+) regenerated per mole of substrate, and constitute the oxidative branch of the PPP. Thus, this branch of the PPP can regenerate 2 moles of NADPH(H+) per mole of G6P entering the pathway with the loss of one carbon atom as CO2. This branch (the non-oxidative branch) is followed by a series of reactions that produce, from three moles of R5P, one mole of the glycolytic intermediates fructose-6-phosphate (F6P) and glyceraldehyde-3-phosphate (Wamelink et al. 2008; Bouzier-Sore and Bolanos 2015). The oxidative PPP branch is therefore a process that conserves the glucose redox energy in reducing NADP+ to NADPH(H+), a necessary cofactor for antioxidant (GSH) regeneration (Wamelink et al. 2008).

G6PD catalyzes the PPP rate-limiting reaction (Eggleston and Krebs 1974). A large body of evidence now supports the
notion that the PPP has antioxidant and cytoprotective roles. In cortical neurons, exogenous H$_2$O$_2$ stimulates PPP activity and regenerates NADPH(H$^+$) and GSH, thus contributing to neuroprotection (Ben-Yoseph et al. 1996). By stimulating glutamate receptors in neurons, GSH becomes oxidized to oxidized glutathione, which triggers an increase in the rate of glucose oxidation through the PPP to regenerate neuroprotective NADPH(H$^+$) and GSH (Delgadox-Esteban et al. 2000). At low doses, peroxynitrite activates G6PD, causing an enhancement of neuroprotective PPP activity in neurons (Garcia-Nogales et al. 2003). Moreover, inhibition of APC/C-Cdh1 activity leading to PFKFB3 stabilization or PFKFB3 over-expression shifts glucose-6-phosphate utilization from PPP to glycolysis causing neuronal death (Herrero-Mendez et al. 2009). Taken together, these results strongly suggest that neurons use glucose through the PPP as an essential survival pathway (Vaughn and Deshmukh 2008; Herrero-Mendez et al. 2009). Thus, by using glucose preferentially through the PPP for antioxidant purposes (Herrero-Mendez et al., 2009), neurons can mainly rely on ANLS-derived lactate as metabolic fuel (Kasparov 2016; Maechler et al. 2016). Furthermore, APC/C-Cdh1 is likely to coordinate the metabolic adaptation of neurons and astrocytes to the astrocyte-neuronal lactate shuttle (Pellerin and Magistretti 1994, 2012; Bouzier-Sore et al. 2003; Magistretti 2006; Allaman et al. 2011) (Fig. 1).

An astrocyte-neuronal glutathione shuttle couples neural activity with redox balance

Neurotransmission unavoidably increases mitochondrial ROS in neurons, possibly because of mitochondrial Ca$^{2+}$ influx (Mattson and Liu 2002). However, neuronal antioxidant machinery is generally weak (Makar et al. 1994; Bolaños et al. 1995, 1996), albeit provided with some intrinsic defense (Papadia et al. 2008; Deighton et al. 2014; Baxter et al. 2015). The antioxidant defense of neurons is repressed because of continuous protein destabilization of the master antioxidant transcriptional activator, nuclear factor-erythroid 2-related factor-2 (Nrf2), by Cullin 3/Kelch-like ECH-associated protein 1 (Bell et al. 2015; Jimenez-Blasco et al. 2015). In contrast, Nrf2 is highly stable in neighbor astrocytes, which explains their robust antioxidant defense and resistance against oxidative stress (Habas et al. 2013; Jimenez-Blasco et al. 2015), although this notion has been disputed (Haskew-Layton et al. 2010). Moreover, astrocytes release GSH precursors, which neurons can use for the de novo GSH biosynthesis (Dingen et al. 1999), a system that contributes to neuroprotective ischemic preconditioning (Bell et al. 2011). However, a definitive answer as to whether astrocytes sense neurotransmission to activate the release of GSH precursors upon neuronal activity has long remained elusive. Like post-synaptic neurons, astrocytes express glutamate receptors (Conti et al. 1996; Schipke et al. 2001; Seifert and Steinhäuser 2001; Verkhovsky and Kirchhoff 2007; Lee et al. 2010; Palygin et al. 2011), though their function in these glial cells has been enigmatic.

Recently, it was shown that subtle and persistent stimulation of glutamate receptors in astrocytes, through a mechanism not requiring extracellular Ca$^{2+}$ influx, up-regulates a signal transduction pathway involving phospholipase C-mediated endoplasmic reticulum release of Ca$^{2+}$ and protein kinase C$\delta$ activation. Through phosphorylation, active protein kinase C$\delta$ promotes the stabilization of p35, a cyclin-dependent kinase-5 (Cdk5) cofactor. Active p35/Cdk5 complex in the cytosol phosphorylates Nrf2 at Thr$^{495}$, Ser$^{433}$, and Thr$^{439}$ that is sufficient to promote Nrf2 translocation to the nucleus and induce the expression of antioxidant genes. Furthermore, this Cdk5-Nrf2 transduction pathway boosts GSH metabolism in astrocytes efficiently protecting closely spaced neurons against oxidative damage. These results demonstrate that neural activity is coupled with astrocyte release of GSH for neuronal de novo GSH biosynthesis (astrocyte-neuronal glutathione shuttle or

**Fig. 2 Redox adaptation of astrocytes to neurotransmission.** Synaptic cleft glutamate (Glu) released by the pre-synaptic neuron acts on glutamate receptors (Glu-R) placed both in the post-synaptic neuron and astrocytes. Part of intracellular Ca$^{2+}$ at the post-synaptic neuron is removed from the cytosol by entering mitochondria, and this causes mitochondrial production of reactive oxygen species (ROS). Synaptic cleft glutamate interacts with its receptors placed in astrocytes, triggering a cascade of events via cyclin-dependent kinase-5 (Cdk5)-mediated phosphorylation of Nrf2 (nuclear factor-erythroid 2-related factor-2), which enters the nucleus (n.) and binds to the antioxidant responsive elements (ARE) to promote the expression of antioxidant genes (green arrowed lines). This pathway leads to the biosynthesis and release of glutathione (GSH), whose precursors are taken up by neurons for the de novo GSH biosynthesis necessary to detoxify neuronal activity-mediated mitochondrial ROS. Thus, through this astrocyte-neuronal glutathione shuttle, astrocytes sustain the redox status of neurons during neural activity. The stoichiometry of the reactions has been omitted for clarity. Likewise, additional factors involved in these adaptations could not be depicted herein and can be found in the main text.

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ANGS) as a strategy for balancing the neuronal redox status (Jimenez-Blasco et al. 2015) (Fig. 2).

**Pathophysiological implications of disruption in energy and redox adaptations of astrocytes**

Disruption of the metabolic and redox adaptations of astrocytes and neurons to neural activity cause neuronal death and is likely to play important roles in neurological diseases. A condition underlying several of these diseases is the excitotoxic phenomenon, in which there is a \( \text{Ca}^{2+} \)-dependent component following glutamate receptor over-activation-mediated neuronal death (Choi 1987). Besides the rapid increase in cytosolic \( \text{Ca}^{2+} \) by \( \text{N-methyl-D-aspartate} \) (NMDA) receptor over-stimulation, there is a delayed \( \text{Ca}^{2+} \) deregulation process, which persists even after glutamate removal from the synaptic cleft, which is responsible for the activation of secondary cascades, notably those involving calpain (Brustovetsky et al. 2010). Calpain triggers the proteolytic cleavage of the \( \text{Na}^{+}/\text{Ca}^{2+} \) exchanger, a major plasma membrane system for \( \text{Ca}^{2+} \) extruding, thus impairing \( \text{Ca}^{2+} \) homeostasis and leading to neuronal death (Bano et al. 2005; Brustovetsky et al. 2010). Furthermore, the increase in intracellular \( \text{Ca}^{2+} \) causes a mitochondrial \( \text{Ca}^{2+} \) overload responsible for enhanced ROS formation and cytochrome \( c \) release, both playing a crucial role in glutamate-induced excitotoxicity (Luetjens et al. 2000). Oxidative stress associated with excitotoxicity also leads to mitochondrial fragmentation, an observation that concurs in several neurodegenerative diseases (Knott et al. 2008; Nguyen et al. 2011). Moreover, mitochondrial dynamics imbalance can trigger NMDA receptor up-regulation, further contributing to propagate the excitotoxic process (Nguyen et al. 2011).

A bioenergetics-redox component in this excitotoxicity cascade has also been shown. Upon a glutamatergic excitotoxic \textit{stimulus} in cortical neurons, \textit{APC/C}\text{-Cdh1} is inhibited by \textit{Cdk5-mediated phosphorylation of Cdh1} (Maestre et al. 2008), a process that is triggered by \( \text{Ca}^{2+} \)-dependent calpain activation (Maestre et al. 2008). This leads to \textit{PFKFB3} stabilization triggering neuronal death as a consequence of the PPP inhibition that leads to oxidative stress (Rodriguez-Rodriguez et al. 2012). Interestingly, \textit{PFKFB3} knockout in cultured human astrocytes leads to extracellular \( \beta \)-amyloid accumulation (Fu et al. 2015). Moreover, \textit{PFKFB3} is increased in the astrocytes of an Alzheimer’s disease mouse model that over-expresses \( \beta \)-amyloid (Fu et al. 2015). Specific inhibition of GSH released from astrocyte triggers neuronal death in co-culture systems (Jimenez-Blasco et al. 2015), and disruption of astrocyte function in adult mice causes oxygen and nitrogen redox species imbalance of neurons in \textit{vivo} (Schreiner et al. 2015). Glucose metabolism is altered in the brains of Alzheimer’s disease patients (Silverman et al. 2001), and \( \beta \)-amyloid causes an enhancement in the flux of glucose utilization via the PPP (Soucek et al. 2003). Interestingly, increased \textit{G6PD} levels are found in the surviving pyramidal neurons of hippocampal slices from the post-mortem brains of Alzheimer’s disease patients (Palmer 1999; Russell et al. 1999). In a cell model of Huntington’s disease there is evidence for inhibition of the PPP and decreased mitochondrial \( \text{NADH(H)}^{+}/\text{NAD}^{+} \) ratio (Ferreira et al. 2011). Together, these findings strongly suggest that during the oxidative stress associated with human brain pathologies, the consumption of glucose through the PPP is critical for maintaining the neuronal antioxidant redox status and survival. Thus, besides their critical role in controlling energy metabolism, astrocyte redox metabolism is also adapted to protect neurons against oxidative stress and neurodegeneration, likely playing an important role in neurological disorders.

**Concluding remarks and perspectives**

Astrocytes and neurons are metabolically programmed to spatiotemporally deal with the energy and redox requirements of neural activity. Astrocytes show a prominent constitutive glycolytic metabolism whereas neurons do not, and this is coordinated by the E3 ubiquitin ligase APC/C-Cdh1 (Herrero-Mendez et al. 2009). High Cdh1 levels keep APC/C active, thus destabilizing the pro-glycolytic enzyme \textit{PFKFB3}; whereas low Cdh1 levels in astrocytes allows \textit{PFKFB3} stabilization responsible for the high glycolytic phenotype (Herrero-Mendez et al. 2009; Bolaños et al. 2010) (Fig. 1). In addition, messengers such as 'NO or \( \text{NH}_4^{+} \) also contribute to the glycolytic phenotype of astrocytes (Almeida et al. 2004; Brix et al. 2012; Lerchundi et al. 2015), and an appropriate redox balance is critically important to sustain antioxidant protection during neural activity. Neurons spare glucose for its oxidation through the PPP, which serves to regenerate GSH and exert protection against oxidative stress (Vaughn and Deshmukh 2008; Herrero-Mendez et al. 2009). In addition, neurons constitutively destabilize Nrf2, whereas astrocytes accumulate it (Jimenez-Blasco et al. 2015). Thus, neurons rely on astrocyte-derived precursors for \textit{de novo} GSH biosynthesis (Dringen et al. 1999), and in astrocytes neural activity triggers the signaling pathway needed to activate this redox regulatory system (Jimenez-Blasco et al. 2015) (Fig. 2). Such mechanisms do not exclude the occurrence of other, still unknown systems helping neural cells adapt their metabolism to the necessary rapid changes occurring during neural activity. These may include mTOR (Bockaert and Marin 2015) and/or hypoxia-inducible factor-1 (Brix et al. 2012) signaling pathways, the importance of which is still elusive. In any case, the metabolic status of neuronal cells would favor the necessary spatiotemporal changes in energy homeostasis following neural activity to satisfy neuronal needs. Recent studies in \textit{Drosophila} (Volkenhoff et al. 2015)
and in mice (Sada et al. 2015; Tadi et al. 2015) confirm the occurrence of the metabolic adaptations of astrocytes in vivo. The use of novel fluorescent probes has confirmed the key role of glycolytic-derived lactate from astrocytes during neural activity at a real-time resolution (Sotelo-Hitschfeld et al. 2015), suggesting dual roles for lactate as metabolic fuel (Pellerin and Magistretti 2012) and intercellular messenger (Barros 2013). Further advances in similar tools would be desirable to investigate roles for neuronal use of glucose through the PPP as an antioxidant strategy during neural activity (Bouzier-Sore and Bolanos 2015). Thus prominent neurochemical advances have been made over the past few decades in our understanding of the physiological mechanisms that coordinate the metabolic adaptations of neural cells to neurotransmission. Key conserved pathways have been identified that are regulated by specific molecules, the disruption of which causes neural problems. Therefore, it seems reasonable to move forward and develop therapeutic interventions aimed to interfere with these targets for the treatment of neurological disorders.

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