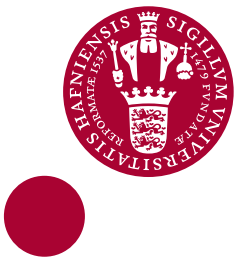

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REVIEW

The energetic brain – A review from students to students

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Abstract

The past 20 years have resulted in unprecedented progress in understanding brain energy metabolism and its role in health and disease. In this review, which was initiated at the 14th International Society for Neurochemistry Advanced School, we address the basic concepts of brain energy metabolism and approach the question of why the brain has high energy expenditure. Our review illustrates that the vertebrate brain has a high need for energy because of the high number of neurons and the need to maintain a delicate interplay between energy metabolism, neurotransmission, and plasticity. Disturbances to the energetic balance, to mitochondria quality control or to glia–neuron metabolic interaction may lead to brain circuit malfunction or even severe disorders of the CNS. We cover neuronal energy consumption in neural transmission and basic ('housekeeping') cellular processes. Additionally, we describe the most common (glucose) and alternative sources of energy namely

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Abbreviations used: AD, Alzheimer's disease; ADP, adenosine diphosphate; AGE, advanced glycation end product; AIS, axon initial segment; ALS, amyotrophic lateral sclerosis; AMP, adenosine monophosphate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPK, adenosine monophosphate-activated kinase; ANLS, astrocyte-neuron lactate shuttle; AP, action potential; APP, amyloid precursor protein; ATP, adenosine triphosphate; ATPmit, mitochondrial adenosine triphosphate; ATPpresyn, presynaptic adenosine triphosphate; Aβ, amyloid-beta; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CBF, cerebral blood flow; CMR_{glu}, cerebral metabolic rate of glucose; CNS, central nervous system; CoA, coenzyme A; DA, dopaminergic; DJ1/PARK7, protein deglycase DJ-1/Parkinson disease protein 7; Drp1, dynamin-related protein 1; EAAT 1/2, excitatory amino acid transporter 1/2; EEG, electroencephalography; ER, endoplasmic reticulum; ETC, electron transport chain; FDG, fluorodeoxyglucose; FRET, fluorescence resonance energy transfer; G6P, glucose-6-phosphate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GDH, glutamate dehydrogenase; GDNF, glial cell line-derived neurotrophic factor; GLS, glutaminase; GLUT, glutamate transporter; GPR120, G protein-coupled receptor 120; GS, glutamine synthase; GSH, glutathione; GSSG, glutathione disulfide; GTP, guanosine triphosphate; H–H model, Hodgkin–Huxley model; IGF-1, insulin-like growth factor-1; K_m, Michaelis–Menten constant; LDH, lactate dehydrogenase; LPL, lipoprotein lipase; LRRK2, leucine-rich repeat kinase 2; LTP, long-term potentiation; MAS, malate-aspartate shuttle; MCH, melanin-concentrating hormone; MCTG, medium chain triglyceride; MCT, monocarboxylic acid transporter; Mfn1/2, mitofusin 1/2; mRNA, messenger ribonucleic acid; MS, multiple sclerosis; mtDNA, mitochondrial deoxyribonucleic acid; NAD^+, oxidized nicotinamide adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NBCe1, electrogenic sodium bicarbonate cotransporter 1; NE, norepinephrine; NMDA, *N*-methyl-D-aspartate; NMR, nuclear magnetic resonance; NO, nitric oxide; OPA1, optic atrophy type 1; OxPhos, oxidative phosphorylation; PC, pyruvate carboxylase; PDGFRβ, platelet-derived growth factor receptor β; PDH, pyruvate dehydrogenase; PD, Parkinson's disease; PET, positron emission tomography; PFK, phosphofructokinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PINK1, PTEN-induced kinase 1; PPAR, peroxisome proliferator-activated receptor; PPP, pentose phosphate pathway; PSC, postsynaptic current; REM, rapid eye movement; ROS, reactive oxygen species; SAT, system A transport; SIRT1, sirtuin-1; SLC family, solute carrier family; SLC1A5, neutral amino acid transporter B(0); SLC38A1, sodium-coupled neutral amino acid transporter 1; SLC6A8, sodium- and chloride-dependent creatine transporter 1; SN-1, system n transport-1; SNpc, substantia nigra pars compacta; SPECT, single-photon emission computed tomography; SWS, slow wave sleep; T2DM, type 2 diabetes mellitus; TBI, traumatic brain injury; TCA, tricarboxylic acid; TGF-β, transforming growth factor β; VIP, vasoactive intestinal polypeptide; V_{max}, maximum rate in Michaelis–Menten kinetics; α-KG, α-ketoglutarate; β-OHB, β-hydroxybutyrate.

glutamate, lactate, ketone bodies, and medium chain fatty acids. We discuss the multifaceted role of non-neuronal cells in the transport of energy substrates from circulation (pericytes and astrocytes) and in the supply (astrocytes and microglia) and usage of different energy fuels. Finally, we address pathological consequences of disrupted energy homeostasis in the CNS.

Keywords: ANLS hypothesis, energy homeostasis, metabolism, neurometabolic coupling, neuronal energetic cost, synapse.
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Read the Preface for this article on page 137.

Why does the brain have high energy expenditure?

The brain is a highly active and plastic organ with outstanding energetic needs. Thus, the title of this review shall reflect both the dynamic and adaptive nature of the brain with its intense parallel information processing as well as its specific metabolic energy demands.

In a majority of adult vertebrate species (excluding primates), the CNS uses 2–8% of the energy of total basal metabolism (Mink *et al*. 1981). The human brain, however, accounts for 20% of oxygen (O_2) consumption and 25% of glucose utilization, although it amounts to only 2% of body weight (Sokoloff *et al*. 1977). Is the high energetic expense of the human brain related to the higher cognitive abilities and wider range of behaviors expressed by humans as compared to other vertebrates? Is it a consequence of brain growth during evolution? During humanization, multifaceted social behaviors evolved, such as formation of complex social groups, long-term parental investment, and cooperative foraging strategies. These outstanding social skills correlated with increased intelligence and are highlighted as necessary for more effective foraging and the exploitation of high-energy food; however, at the same time, the evolvement of these capabilities also imposes higher nutrient requirements (summarized in Dunbar & Shulz, 2017). Traditionally, comparative studies of brain scaling take into account brain size and/or the body–brain mass ratio to delineate an evolutionary explanation for the supposed human brain exceptionality. While some authors consider the human brain as an outlier because it deviates from the expected value even if compared to anthropoid primates (Marino 1998; Jerison 2012), a more recent view, based on data obtained with isotropic fractionation (Herculano-Houzel and Lent 2005), puts in focus the absolute number of neurons relative to body–brain mass ratios. Studies on scaling brain metabolism according to brain size across species or to neuronal number and/or density in a given structure were carried out to examine this human brain peculiarity which could have implications in brain evolution and could have exerted constraints for wiring patterns. According to Karbowski's estimates, which are based on the assumption of uniform scaling of neuronal density across species, cerebral energy per neuron increases with brain size (Karbowski 2009). However, more recently, Herculano-Hozuel based her calculations on available glucose and O_2 metabolic rates in awake animals (mouse, rat, squirrel, macaque monkey, baboon, and human) and the total number of neurons determined by her group. She found that neuronal density in the whole brain does not scale with brain mass across species, and that the energy budget of the whole brain per neuron is fixed across species and brain sizes. Thus, the total glucose use by the brain is a linear function of the number of neurons, and the remarkable energy use in humans may be explained simply by its large number of neurons (Herculano-Houzel 2011).

Why do neurons have a high energetic demand? In addition to basic ('housekeeping') cellular activity such as turnover of macromolecules, axoplasmic transport, and mitochondrial proton leak, neurons are highly specialized cells to perform energy-demanding electrochemical signaling processes. Not only the generation of action potentials (AP), postsynaptic ion fluxes, presynaptic Ca^{2+} entry, transmitter reuptake, and vesicle cycling but also the maintenance of the resting potential is a costly cellular neuronal function. In the following sections, we will provide a detailed description and explanation of each of the above-mentioned processes, which altogether account for the neuronal energy demand.

Energy use in synaptic transmission and synaptic plasticity

Synaptic transmission imposes a large metabolic demand which is met through activity-driven regulation of glycolysis and mitochondrial function (Rangaraju *et al*. 2014). Plasticity of synapses can be mediated by changes in Ca^{2+} concentration and/or the number of neurotransmitter receptors. Upon synaptic activity or plasticity, most of the adenosine triphosphate (ATP) is consumed when pumping ions to maintain resting membrane potential, vesicle filling, vesicle transport, vesicle recycling, and enzymatic processing of synaptic transmitter within synapses (Harris *et al*. 2012) (Fig. 1).

Presynaptic terminals

Activated presynaptic terminals are expected to place high ATP demands on energy supplies. The presynaptic ATP (ATPpresyn) levels are mainly consumed by the Na^+/K^+ pump (Na^+/K^+-ATPase), the Ca^2-ATPases in the plasma membrane and endoplasmic reticulum, the vacuolar H^+-ATPase, motor proteins (Attwell and Laughlin 2001; Lennie 2003), and protein disassembly machineries (Ly and Verstreken 2006; Rangaraju *et al*. 2014). The Na^+/K^+-ATPase imports two K^+ and exports three Na^+ ions involved in generating the AP and powers Ca^{2+}

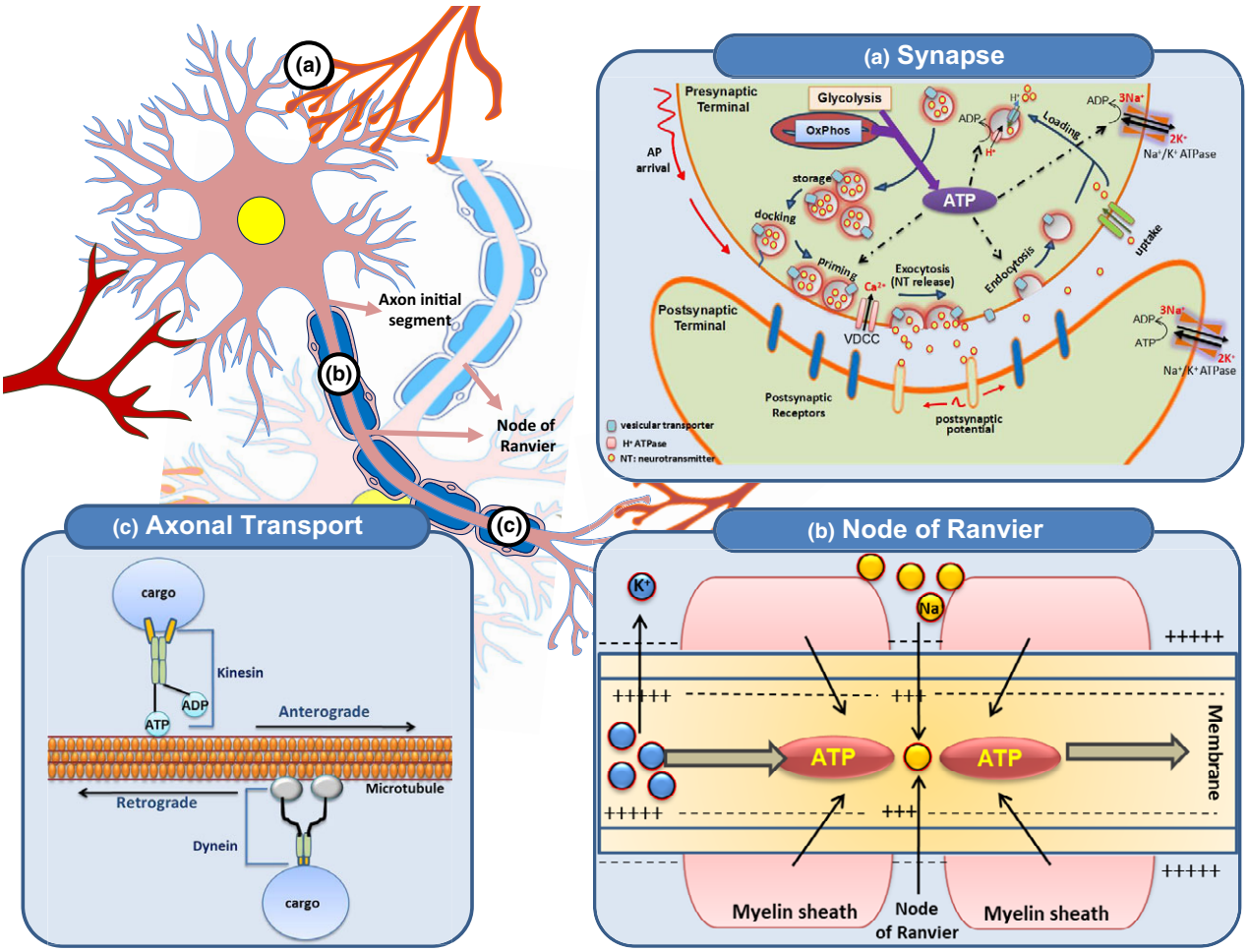

Fig. 1 Schematic representation of the main adenosine triphosphate (ATP) consuming processes in neurons. (a) At the synapse, most of neuronal signaling-related ATP is utilized by the Na^+/K^+-ATPase and in the synaptic vesicle cycle. The Na^+/K^+-ATPase restores membrane potential after depolarization and maintains the electrochemical gradient of Na^+ used in the removal of Ca^{2+} by the Na^+/Ca^{2+} exchanger and in the uptake of neurotransmitters (i.e., monoamines, GABA, glycine, and glutamate). The synaptic vesicle cycle uses ATP for neurotransmitter loading by vacuolar H^+-ATPase and for protein disassembly machineries during docking and priming. Also, extrusion of elevated cytosolic Ca^{2+} after exocytosis by the Ca^{2+}-ATPase (not shown) needs ATP. (b) Action potential (AP) generation and propagation at the axon initial segment and the nodes of Ranvier as well as reversing the ion fluxes after depolarization are also linked to high signaling-related ATP expenditure by Na^+/K^+-ATPase. (c) Basic cellular processes, such as axonal transport involved in the trafficking of vesicles, mitochondria, and other cargo within the neurites, require motor proteins that hydrolyze ATP.

removal by Na^+/Ca^{2+} exchange, while Ca^{2+}-ATPases in the plasma membrane and endoplasmic reticulum reduce the elevated cytosolic Ca^{2+} concentration after membrane depolarization. Vacuolar H^+-ATPase energizes vesicular transmitter uptake and the motor proteins are involved in intracellular transport of mitochondria and vesicles (Fig. 1).

ATPpresyn levels are reduced by insufficiency of either glycolysis or mitochondrial function, indicating the requirement of activity-driven ATP synthesis to meet the energy demands of synaptic function. Most ATP produced in response to increased neuronal activity is generated by mitochondria (Lin *et al*. 2010; Hall *et al*. 2012), highlighted by the positive correlation between the signaling-related energy usage predicted by Attwell and Laughlin (2001) and the distribution of mitochondria inside a cell, which was demonstrated to be higher in soma plus dendrites (62%) than in axon terminals (36%) (Wong-Riley 1989). In light of the distal location of nerve terminals from cell bodies, synapses must rely on local ATP supplies, leaving them highly susceptible to mitochondriopathies. Studies in *Drosophila* mutants affecting the mitochondrial localization as well as the mitochondrial ATP/adenosine diphosphate translocase confirmed the importance of mitochondria in synaptic function (Trotta *et al*. 2004; Guo *et al*. 2005; Verstreken *et al*. 2005).

ATPpresyn concentration is about 1.4 mM (corresponding to ~ 10^6 molecules for a typical presynaptic varicosity) and

ATP synthesis occurs through feedforward stimulation of both glycolysis and oxidative phosphorylation (OxPhos) via electrical activity-driven Ca^{2+} influx (Rangaraju *et al*. 2014). Completely blocking exocytosis does not significantly affect Ca^{2+} influx during neuronal APs, suggesting that the synaptic vesicle cycle consumes most ATPpresyn. The monitoring of ATPpresyn during AP firing in the absence of external Ca^{2+} revealed that ATP utilized by the Na^+/K^+-ATPase alone represents a relatively small energy burden compared to downstream vesicle cycle processes at presynaptic terminals and that AP firing can persist even during phases of acute ATP synthesis blockade. Inhibition of glycolysis is accompanied by a reduction in endocytosis and a shift in remaining vesicular pH to more alkaline values. The arrest of endocytosis at energy deficit conditions depends on the mechanochemical enzyme dynamin, which mediates membrane fission and depends cooperatively on synthesized guanosine triphosphate using ATP (Rangaraju *et al*. 2014). By contrast, compromised ATP synthesis does not immediately impact exocytosis. Therefore, ATPpresyn demand and activity-induced ATP synthesis should be synchronous and are essential for the maintenance of normal synaptic plasticity function. Any discrepancy or pathological condition disturbing these metabolic functions will ultimately affect synaptic strength and plasticity.

Postsynaptic terminals

At postsynaptic sites, ATP is mainly used for counterbalancing the ion fluxes through postsynaptic receptors and, to a lesser extent, on rebounding Ca^{2+} to intracellular stores and on mitochondrial trafficking. In inhibitory synapses, less energy is utilized to reverse postsynaptic Cl^- fluxes as the chloride reversal potential is close to the resting potential (Attwell and Laughlin 2001; Howarth *et al*. 2010, 2012). The number of activated receptors, channel open time, channel conductance, and consequently ATP usage is different at synapses throughout different regions of the brain (Spruston *et al*. 1995; Silver *et al*. 1996; Markram *et al*. 1997). Based on analysis of Attwell and Laughlin (2001), when a glutamatergic vesicle is released on a dendritic spine from non-cortical neurons, the number of activated *N*-methyl-D-aspartate (NMDA) receptors is less than that of non-NMDA receptors (Spruston *et al*. 1995; Silver *et al*. 1996; Markram *et al*. 1997). However, because NMDA receptors have longer open times and higher conductance than non-NMDA receptors, the ion influxes through those activated channels lead to hydrolysis of 5% more ATP molecules by the Na^+/K^+-ATPase, including the 3 Na^+/Ca^{2+} exchange, for extrusion. Moreover, activation of postsynaptic G protein-coupled receptors, such as metabotropic glutamate receptors (mGluR), triggers downstream events, which constrain ATP usage. However, the level of ATP consumption during G protein signaling is approximately 95% smaller than during NMDA and non-NMDA receptor activation (Attwell and Laughlin 2001).

Synaptic plasticity

Synaptic plasticity, increasing or decreasing of synaptic strength, can impact energy expenditure. For example, long-term potentiation (LTP), which can be triggered by activation of the postsynaptic NMDA receptors and insertion of more α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors into the postsynaptic membrane, enhances ATP supplement to potentiated synapses and energy consumption at postsynapses (Wieraszko 1982). It is suggested that induction of LTP, which is assumed as a fundamental mechanism of learning and memory, is accompanied by increased energy usage at activated synapses. Additionally, the level of lactate derived from glycogen in astrocytes is increased in response to energy demand in animals performing learning and memory tasks (Newman *et al*. 2011; Suzuki *et al*. 2011).

Mitochondrial ATP (ATPmit) production is noted to be essential for synaptic plasticity. Inhibition of ATPmit production interfered with synaptic accumulation of mitochondria and subsequently abolished synaptic potentiation at the *Drosophila* neuromuscular junction (Tong 2007). Additionally, mutations in *Drosophila* dynamin-related protein 1 (Drp1) depleted mitochondria from motor nerve terminals and interfered with mobilization of the reserve pool of synaptic vesicles and maintenance of neurotransmission (Verstreken *et al*. 2005). Moreover, transmission failure was rescued at high stimulation frequencies by adding ATP exogenously and provided evidence that the reserve pool recruitment depends on ATPmit production downstream of PKA (protein kinase A) signaling.

Action potential (AP) generation and propagation

The brain uses rapid electrical signaling in the form of APs as the primary means of communication between neurons. This signaling is associated with substantial energetic costs (Kole *et al*. 2008; Hallermann *et al*. 2012). Two sites, important for AP generation and maintenance, due to their lowered excitation threshold, are the axon initial segment (AIS) and the nodes of Ranvier (Fig. 1), the sites between adjacent myelinated axonal segments (Peters 1966; Palay *et al*. 1968). It has been estimated that after one AP, rodent cortical neurons require between ~ 4–8 × 10^8 ATP molecules to restore the Na^+ and K^+ gradient through the Na^+/K^+-ATPase, suggesting the metabolic cost of AP signaling is the second largest after synaptic transmission (Lennie 2003; Hallermann *et al*. 2012). However, energy usage within the brain depends in part on the AP rate. Moreover, because synaptic energy cost is proportional to the transmitter release probability by an AP and to the number of postsynaptic channels activated by transmitters, the estimated numbers for the synaptic cost vary in the literature. The estimation of relative contributions of AP generation and postsynaptic currents (PSC) to energy expenditure in the mammalian brain has varied in the literature: while the classical Hodgkin–Huxley model for AP generation in the squid axon and a number of assumptions such

as treating all neurons as identical (Attwell and Laughlin 2001) led to an assumed energy expenditure ratio for AP and PSC of 58 : 42%, direct experimental data in rat hippocampal non-myelinated mossy fibers showed a minimal temporal overlap between the entry of Na^+ and the outflow of K^+ during an AP which results in one-third less energy necessary to elicit depolarization than in the Hodgkin–Huxley model, pointing to an AP : PSC ratio of 20 : 80% (Alle *et al*. 2009).

The approximately 50-fold higher densities of voltage-gated Na^+ channels at AIS and nodes of Ranvier, when compared to the soma and dendrites, are vital for producing the adequate local current necessary to overcome membrane resistance and capacitance as well as to initiate and propagate self-regenerating APs (Zhou *et al*. 1998; Kole *et al*. 2008). Moreover, it has been shown that excess axonal Na^+ influx at the AIS and nodes of Ranvier is critical for AP conduction at high frequencies (Kole *et al*. 2008). Therefore, the high metabolic cost of AP initiation by the AIS and propagation down the axon by nodes of Ranvier is seen as a trade-off between minimizing energy costs and maximizing the conduction velocity of APs (Hallermann *et al*. 2012).

Maintaining resting potential

Beyond spiking activity, a large portion of the energy sources in the brain is spent on maintaining resting potential and non-signaling ('housekeeping') processes. Na^+/K^+-ATPases are recruited to compensate non-zero cell membrane conductance for K^+ and Na^+. Attwell and Laughlin (2001) calculated that at physiological spiking rate of 4 Hz, 15% of the total ATP in the gray matter is needed to maintain the resting potential of a typical neuron and an associated glial cell (Attwell and Laughlin 2001). Lennie (2003) estimated that the spike-related energy expenditure is only 13% of total energy usage in human neocortex, attributing 28% and 10% to maintain the resting potential in neurons and glia, respectively, and the remaining to non-signaling ('housekeeping') processes (Lennie 2003). Maintaining resting potential is estimated to take 30% and ~ 44% of the total energy used in partially and fully myelinated white matter, respectively (Harris and Attwell 2012), 34% in the cerebellum (Howarth *et al*. 2010), and 16% to ~ 68% of total energy used in the olfactory glomerulus, depending on the number of activated olfactory receptor neurons (Nawroth *et al*. 2007).

Non-signaling ('housekeeping') processes

In the vertebrate brain, a majority of the total energy is spent on the removal of Na^+ ions from cells by Na^+/K^+-ATPases (Attwell and Laughlin 2001; Lennie, 2003; Harris and Attwell 2012). Metabolic turnover is reduced by both Na^+/K^+-ATPase inhibition (Whittam, 1962; Astrup *et al.,* 1981; Shibuki, 1989) and deep anesthesia (Astrup *et al*. 1981; Sibson *et al.,* 1998; Du *et al.,* 2008). The residual energy expenditure persisting after the suppression of spiking and/or Na^+/K^+-ATPase was attributed to non-signaling, or 'housekeeping', processes (Attwell and Laughlin 2001; Du *et al.,* 2008; Harris and Attwell 2012; Engl and Atwell 2015). Using ^{13}C nuclear magnetic resonance spectroscopy, Sibson *et al*. (1998) estimated that roughly 16% of total glucose oxidation in the rat cortex are independent of synaptic activity. The cerebral ATP metabolic rate is roughly reduced by half when rats are deeply anesthetized and the electroencephalogram reads as 'silent', as compared with light anesthesia using isoflurane (Du *et al*. 2008). Calculations for rodent brains attribute 25% of energy used in the gray matter to 'housekeeping' processes (Attwell and Laughlin 2001; Lennie 2003; Harris *et al*. 2012), and ~ 63% and ~ 56% in partially or fully myelinated white matter, respectively (Harris and Attwell 2012). The 'housekeeping' functions account for 19% in the cerebellum (Howarth *et al*. 2010), and between 3 and 25% in the olfactory glomerulus (Nawroth *et al*. 2007). Particular non-signaling energy-consuming processes are now under debate.

Actin cytoskeleton (re-)modeling underlies neuron morphology and modulates synaptic function and structural plasticity (Luo 2002; Cingolani and Goda 2008), requiring ATP hydrolysis (Wegner 1976; Carlier *et al*. 1988). Modeling and experimental estimates for energy costs of actin treadmilling range from less than 1% (Engl and Attwell 2015) of the total brain energy usage to half of the energy used in neuronal culture (Bernstein and Bamburg 2003). The dynamic instability of microtubules instead requires energy in the form of guanosine triphosphate (Margolis 1981; Zakharov *et al*. 2015).

Protein and phospholipid synthesis were estimated theoretically to account for no more than 2% (Rolfe and Brown 1997; Attwell and Laughlin 2001) and 2–25% (Purdon and Rapoport 1998, 2007; McKenna *et al*. 2012) of the total ATP consumption in the brain, respectively. Purdon and Rapoport (2007) estimated that ~ 26% of the energy taken by phospholipid metabolism in the rat brain is spent on fatty acid turnover, phosphatidylinositol phosphorylation state and phospholipid bilayer asymmetry maintenance, and on *de novo* synthesis of phosphatidylinositol and ether phospholipids (Purdon and Rapoport 2007). Engl *et al*. (2017) provided first experimental single-assay measurements of energy consumption by actin cycling, microtubule restructuring, and protein as well as phospholipid metabolism (Engl *et al*. 2017). They applied specific blockers of these processes to resting (i.e., without evoked signaling activity) hippocampal slices of developing rat brains and traced the resulting changes in O_2 consumption. O_2 consumption decreased by 25% after actin cycling blockade (much higher than previously modeled by the same group but lower than previous estimates), by 22% after microtubule turnover blockade, and by 18% after lipid and protein metabolism blockade. However, blocking protein metabolism alone did not change the O_2 consumption significantly.

Proton leak across the inner mitochondrial membrane (IMM) uncoupled from ATP synthesis was documented in isolated brain mitochondria (Rolfe *et al*. 1994); though, its contribution was not quantified. The proton leak mechanism remains under debate. It may be attributed to the proton conductance through the lipid bilayer, which depends on the fatty acid composition of the mitochondrial membrane, to the non-specific proton conductance of IMM carrier proteins such as adenine nucleotide translocase (Brand *et al*. 2005), or to the functioning of the brain-specific uncoupling proteins UCP4 and UCP5 (Sanchis *et al*. 1998; Mao *et al*. 1999). Deficits in mitophagy genes like in the PTEN-induced kinase 1 (PINK1) knockout mouse also result in increased proton leak (Villeneuve *et al*. 2016).

Finally, axonal transport contributes to 'housekeeping' energy expenditure (Lennie 2003; Harris *et al*. 2012) (Fig. 1). Maday *et al*. (2014) calculated, as one kinesin-1 motor spends one ATP molecule for every elementary 8 nm step (Maday *et al*. 2014), the anterograde transport of a vesicle along an average 40 mm axon would require $\sim 5 \times 10^6$ ATP, which is small compared to the $\sim 1 \times 10^8$ ATP consumed by the propagation of a single spike along the same axon. However, this estimated cost of the axonal transport does not account for tug-of-war events (Soppina *et al*. 2009; Hendricks *et al*. 2010) and dynein retrograde transport. Further modeling is needed to estimate the actual energetic cost of axonal transport processes.

The negligible gluconeogenesis activity of the brain raises the question of how the brain uses energy in different physiological states and the importance of additional sources of energy other than glucose.

Brain metabolism in sleep versus wakefulness

Energy sources in the body are stored mainly in skeletal muscle, liver, and adipose tissue and maintain the reserve of energy during wakefulness (Brown and Ransom 2007). The neurons of the lateral hypothalamus that express melanin-concentrating hormone (MCH) and orexin/hypocretin regulate body energy metabolism and the sleep–wakeful cycle. During a high level of energy resources, MCH neurons are activated and promote the conservation of energy by inducing sleep, whereas a low level of glucose diminishes the excitability of MCH neurons and promotes wakefulness. Alternatively, excitation of orexin neurons induces wakefulness, while inhibition or loss of orexin neurons promotes sleep. Thus, MCH and orexin neurons have opposing effects on sleep and wakefulness (Burdakov *et al*. 2005; González *et al*. 2016).

Neuronal tissues are supplied with different sources of energy, such as glucose, lactate, and acetate, through regulated mechanisms. Neurometabolic coupling is the mechanism by which the brain energy metabolism and cerebral blood supply are modulated locally to meet the needs of neuronal activity. The energy requirement of neurons can change rapidly during wakefulness after sensory or motor stimulations, in sleep/waking and waking/sleep transitions (Petit and Magistretti 2016). Different sleep stages can be distinguished based on cortical activity, muscle tone, and eye movements. Deep sleep, also called slow wave sleep (SWS), is characterized by decreased heartbeat, breathing, and body temperature and reduced cortical activity typically showing high-amplitude, low-frequency (0.5–4 Hz) electroencephalography activity. In rapid eye movement (REM) sleep, cortical theta activity (4–11 Hz) is dominant (Niethard *et al*. 2016). Studies have shown that the energy demand diminishes during SWS; thus, the utilization of glucose and O_2 is reduced. Moreover, non-REM sleep promotes anabolic processes such as biosynthesis of proteins, glycogen, and fatty acids (Dworak *et al*. 2010). In contrast, sleep deprivation affects metabolic coupling and reduces glucose uptake in all brain areas in humans and rodents and decreases ATP levels by enhancing energy expenditure. Moreover, chronic sleep fragmentation reduced the uptake of 2-deoxyglucose in cortex and hippocampus and decreased lactate levels in the cortex (Baud *et al*. 2016). These results highlight the importance of non-REM sleep to restore brain energy levels (Dworak *et al*. 2010) because it is during the non-REM sleep when the increase in ATP and glycogen biosynthesis occurs; while REM sleep utilizes similar cerebral glucose as during wakefulness (Maquet *et al*. 1990).

Thus, synaptic potentiation, during the wakeful condition, increases the consumption of ATP by activating glycolysis, fatty acid oxidation, and glucose uptake; while during non-REM sleep, ATP consumption decreases and leads to energy conservative processes, such as synaptic scaling.

Sources of brain energy

Several regulatory mechanisms operate to regulate the production and usage of energy in the brain. Although the brain requires a high amount of energy, it possesses minimal energy reserve which can only satisfy a small portion of its energy demand and is dependent on the supply of energy substrates from the blood through the blood–brain barrier (BBB). Under normal physiological conditions, the major energy fuel for the brain is glucose (Dienel 2012a). However, several studies have shown that the brain can use alternative energy substrates such as lactate, medium chain triglycerides (MCTGs), and ketone bodies, during development and when glucose availability is limited (Owen *et al*. 1967; Hasselbalch *et al*. 1994; Ebert *et al*. 2003).

Specific transporters allow the uptake of energy substrates, such as glucose and monocarboxylic acids (lactate, pyruvate, β-hydroxybutyrate, acetoacetate, and acetate) from the circulation across the endothelial cell membrane and into brain cells. The uptake of energy substrates by brain cells is dependent on the type and distribution of transporters unique to each cell type and transport rate, on the number of transporters, and the catalytic activity of each transporter. In the brain, several

isoforms of the glucose transporter (GLUT) and the monocarboxylic acid transporter (MCT) have been identified.

Glucose

Glucose metabolism provides the fuel for physiological brain function through the synthesis of ATP via glycolysis, the pentose phosphate pathway (PPP), and the tricarboxylic acid (TCA) cycle which serves as the basis for neuronal and non-neuronal cellular maintenance as well as neurotransmitter and gliotransmitter production. Cells of the BBB, mainly astrocytes and pericytes, act as the gatekeepers for glucose entry into the brain. Glucose enters the brain tissue from the plasma by transport across the BBB mediated by the GLUTs. The cytoarchitectural presence of astrocytic end feet enriched in the 45 kDa-isoform of GLUT1 makes astrocytes an ideal cell type for the uptake of glucose. Glucose enters neurons *trans*-cellularly through astrocytes via GLUT1 or directly via GLUT3, a neuronal GLUT (Maher *et al*. 1994) (Fig. 2).

Astrocytes are considered highly glycolytic due to low expression and activity of the E3 ubiquitin ligase APC/C-Cdh1, which in neurons mediates proteasomal degradation of the glycolytic key enzyme phosphofructokinase (PFK) (Herrero-Mendez *et al*. 2009). Thus, high expression and activity of PFK in astrocytes results in glucose and glucose-6-phosphate (G6P) mainly being metabolized via the glycolytic pathway (Bélanger *et al*. 2011). Moreover, the expression of lactate dehydrogenase (LDH) 5, which favors the conversion of glycolytically derived pyruvate to lactate regenerating oxidized nicotinamide adenine nucleotide (NAD^+) that is required as substrate in the reaction of glyceraldehyde-3-phosphate dehydrogenase, also contributes to the high glycolytic activity of astrocytes (Pellerin and Magistretti 2004; Hirrlinger and Dringen 2010).

Unlike glycolytic astrocytes which synthetize lactate in aerobic conditions, neurons rely on oxidative metabolism through the TCA cycle for their high energy needs. Neuronal activity increases neurotransmitter concentration in the synaptic cleft (i.e., glutamate) and extracellular K^+. This is met by intense mitochondrial activity putting neurons in risk of oxidative stress, glutamate excitotoxicity, and apoptotic death. Increased glycolysis in the brain can induce glutathione oxidized (glutathione disulfide) accumulation. Glutathione is a tripeptide that serves not only as a scavenging antioxidant but also has been proposed as a reservoir for glutamate (Koga *et al*. 2011). Therefore, as a neuroprotective mechanism, neurons down-regulate glycolysis and the use of glucose to maintain an antioxidant reduced glutathione pool. Additionally, glucose is used by neurons to restore reducing equivalents of reduced nicotinamide adenine dinucleotide phosphate (NADPH) used in glutathione regeneration via the PPP which cannot be fueled by lactate (Gavillet *et al*. 2008; Bolaños *et al*. 2010).

Moreover, glutamate released from presynaptic terminals into the synapse during neuronal activation is taken up by astrocytes together with Na^+ ions. Furthermore, it stimulates both glucose uptake and glycolytic processing as well as lactate release in an ATP-dependent manner, and as such plays a significant role in neuroenergetics (Magistretti *et al*. 1999). Astrocytes convert glutamate to glutamine by glutamine synthetase (Norenberg and Martinez-Hernandez 1979), which is then taken up by neurons and converted back to glutamate by phosphate-activated glutaminase (GLS) (Fig. 2), completing the glutamate–glutamine cycle (Laake *et al*. 1999). Conversely, glutamate can be oxidized to enter into the TCA cycle (Bak *et al*. 2006). Interestingly, astrocytes have the anaplerotic enzyme pyruvate carboxylase (Yu *et al*. 1983), which carboxylates pyruvate to generate oxaloacetate. This process is crucial to replace lost TCA cycle intermediates used in the synthesis of neurotransmitters. Although sodium-coupled uptake of glutamate by astrocytes and the ensuing activation of the Na^+/K^+-ATPase may trigger glycolysis (Fox *et al*. 1988; Magistretti 2006) in a time scale of minutes, extracellular K^+ was demonstrated to stimulate astrocytic glycolysis *in vitro* within seconds using a genetically encoded fluorescence resonance energy transfer-based nanosensor for glucose (Bittner *et al*. 2011), an effect mediated by the Na^+/HCO_3^- cotransporter electrogenic sodium bicarbonate cotransporter 1 (Ruminot *et al*. 2011). This K^+-mediated mechanism was suggested to be a general hallmark of neurometabolic coupling, as K^+ is released not only by the postsynaptic terminal during glutamatergic neurotransmission but also at nodes of Ranvier during AP propagation, at serotonergic synapses, or at the cholinergic neuromuscular junction.

Glutamate

Glutamate acts as the major excitatory neurotransmitter in brain. As mentioned above, it plays a role as a trigger in stimulating glucose utilization when taken up by astrocytes leading to lactate production, acts as a recycled precursor for the neuronal neurotransmitter pool and as an energy substrate in astrocytes. Hans Krebs was the first who recognized glutamate as a brain energy substrate capable of increasing respiration in rabbit brain cortex in the absence of glucose (Krebs, 1953). Later, his group discovered that, in the absence of glucose, extracellular glutamate was metabolized and mostly converted into aspartate in rat brain homogenate (Haslam and Krebs, 1963). Further research discovered that glutamate is not only the co-substrate in the aminotransferase catalyzed interconversion reaction into aspartate but also into alanine, leucine, isoleucine, and valine (McKenna 2012; Schousboe *et al*. 2014). Astrocytes convert the glutamate taken up from the extracellular milieu to α-ketoglutarate (α-KG) either primarily by the glutamate dehydrogenase-catalyzed energy-producing reaction or by transamination reactions in astrocytes (Bergles *et al*. 1999; Zaganas *et al*. 2012). Furthermore, the formed α-KG is metabolized into the

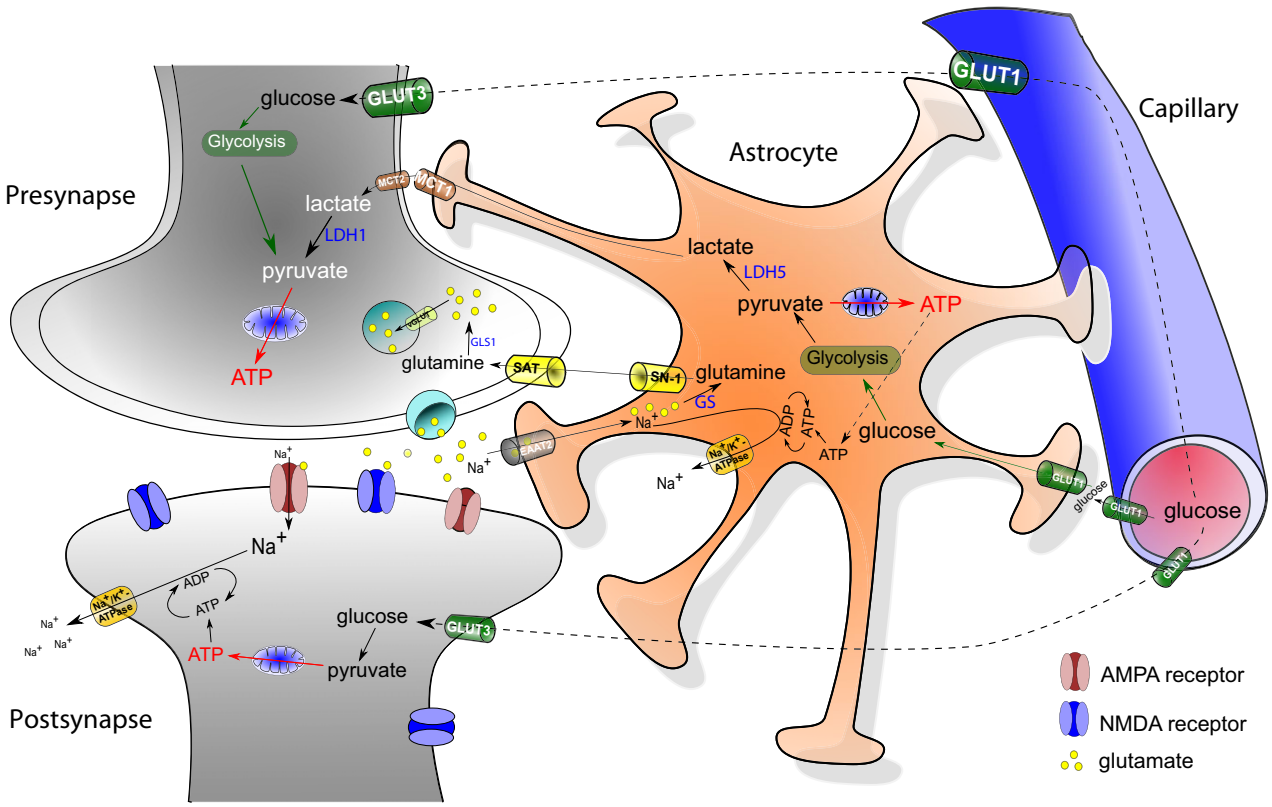

Fig. 2 Schematic representation of the neurometabolic coupling illustrating the energy expenditure in a glutamatergic synapse and the astrocyte-neuron lactate shuttle (ANLS) hypothesis. Glutamatergic vesicular release activates postsynaptic receptors [α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA), blue and red, respectively] and depolarizes the membrane by opening channels, in turn triggering the influx of Na^+ ions that constrain the use of adenosine triphosphate (ATP) when they are pumped out. Glutamate in the synaptic cleft is taken up into astrocytes via excitatory amino acid transporter 2 (EAAT2) and metabolized via glutamine synthase. Glial glutamine is released via the system N transport-1 (SN-1) in astrocytes, taken up by neurons via the system A transport (SAT) to replenish glutamate pools via glutaminase 1 (GLS1) and vesicular reuptake via vesicular glutamate transporter (vGLUT). Most of the energy required by those presynaptic and postsynaptic processes comes from glucose metabolism. However, neurons can use alternative sources of energy. According to the ANLS hypothesis, astrocytes take up glucose from the blood via glucose transporter 1 (GLUT1) and convert it into lactate through lactate dehydrogenase 5 (LDH5) that is released and taken up by neurons through monocarboxylic acid transporters (MCT). In neurons, lactate is converted to pyruvate by LDH1, enters the tricarboxylic acid cycle, and is metabolized via oxidative phosphorylation in the mitochondria.

four-carbon compound oxaloacetate through sequential reactions of the TCA cycle and eventually harvests nine ATP molecules (McKenna 2013).

Uptake of extracellular glutamate is an expensive process as astrocytes utilize one ATP for the transfer of one glutamate. Evidence from *in vitro* and *in vivo* studies suggests that mitochondrial mechanisms and multiprotein complexes are tightly associated with glutamate uptake by astrocytes. Glial glutamate transporters are coupled to the first step in glycolysis mediated by hexokinase, which ensures the oxidative energy metabolism of glutamate in mitochondria yielding ample energy that pays the cost of glutamate uptake from the synaptic cleft (Genda *et al*. 2011; Whitelaw and Robinson 2013). Oxidative metabolism of glutamate by astrocytes, which results in complete glutamate oxidation and energy generation, has been reported by several *in vitro* and *in vivo* studies (McKenna 2013). Studies based on substrate competition indicated that oxidation of glutamate in astrocytes as a source of energy is preferred compared to glucose and other substrates (Fig. 2), which suggests the robustness of glutamate use as a substrate for energy in these cells (McKenna *et al*. 2012).

The steady and dynamic connection between the pre- and postsynaptic neuron and astrocytes is efficiently involved in maintaining the low extracellular resting glutamate concentration of ~ 1–10 μM to avoid excitotoxicity and maintain healthy brain states (Hertz 1979; Schousboe 1981; Waagepetersen *et al*. 1999). *In vitro* experiments in primary cultured neurons indicate that 10 mM of extracellular glutamate causes profound neuronal cell death under normoglycemic and normoxic conditions (Murphy *et al*. 1990; Khanna *et al*. 2003). However, when glucose is removed from media, extracellular glutamate (10 mM) no longer induces cell death (Rink *et al*. 2011).

Lactate and the Astrocyte–Neuron Lactate Shuttle hypothesis

Despite glucose being the major source of energy in the brain, under various circumstances, lactate serves as an alternative energy substrate. Since lactate cannot diffuse passively across the BBB, it needs to be produced *in situ* within the brain and efficiently transported between cells (Fig. 2). Additionally, as lactate cannot be utilized directly, conversion of lactate to pyruvate, catalyzed by LDH, is essential as it then provides 18 ATPs via OxPhos (Pellerin and Magistretti 1994; Magistretti 2006). The identification of MCTs further strengthens the presence of lactate release and uptake in brain cells (Bröer *et al*. 1999; Pellerin *et al*. 2005). MCTs operate depending on the association with the glycoproteins basigin (MCTs 1, 3, 4) or embigin (MCT2) and the concentration gradients of monocarboxylates across the plasma membrane (Halestrap 2013). While MCT2 and MCT4 are selectively expressed by neurons and astrocytes, respectively, MCT1 is expressed in astrocytes, oligodendrocytes, and endothelial cells of blood vessels (Debernardi *et al*. 2003; Pierre and Pellerin 2005; Rinholm *et al*. 2011). Hence, lactate secreted by astrocytes through MCT1 and MCT4 is assumed to be transported by MCT2 into neurons, where it can be converted to pyruvate (Fig. 2). Then, pyruvate can either enter the TCA cycle via pyruvate dehydrogenase and be metabolized via OxPhos in mitochondria to generate ATP or be converted to lactate or alanine by LDH or aminotransferase, respectively. The distribution pattern of the LDH isoforms (high expression of LDH5 in astrocytes and LDH1 in neurons) further provides evidence for this concept. Furthermore, the muscle-type LDH5 having a greater V_{max} is better equipped at converting pyruvate to lactate and supports higher glycolytic rates, but LDH1 exhibits a lower K_m and is inhibited by low concentrations of pyruvate and by lactate. Thus, efficient conversion of lactate to pyruvate and clearance of pyruvate are essential for the enzymes to function properly. In summary, higher expression of LDH5 suggests a higher rate of glycolysis in astrocytes and higher expression of LDH1 suggests lactate utilization as an energy source in neurons. These data support the astrocyte-neuron lactate shuttle (ANLS) hypothesis postulated in 1994 (Pellerin and Magistretti 1994). According to this, astrocytes serve as a 'lactate source' whereas neurons serve as a 'lactate sink' (Fig. 2).

In this context, when neuronal activity intensifies, astrocytes increase their glucose uptake, thus increasing the rate of glycolysis and lactate release into the extracellular space. Increased neuronal activity corresponds to an increased release of glutamate from presynaptic vesicles into the synapse. Excessive glutamate is sensed and taken up by astroglial glutamate transporters (i.e., excitatory amino acid transporter 1 and 2). A sodium gradient drives this glutamate exchange, where one glutamate is co-transported with three Na^+ ions, thereby increasing the concentration of Na^+ within astrocytes. Glutamate uptake triggers glucose uptake by the astrocytes in a stoichiometric ratio of 1 : 1. A higher Na^+ concentration within astrocytes leads to the activation of the α_2 subunit of the Na^+/K^+ -ATPase which results in glycolysis stimulation (Mason 2017). This stimulation leads to the production of lactate which is used as a substitute energy substrate by neurons. Thus, lactate plays a role as an alternative to meet the energetic demands of the CNS.

In opposition to the ANLS hypothesis, Bak and colleagues argue that oxidative metabolism of lactate within neurons only occurs during repolarization (and in the period between depolarizations) rather than during neurotransmission activity (Bak *et al*. 2009); and that neurons use lactate as an 'opportunistic' substrate when it is present (Bak and Walls 2018). In synaptic terminals, the use of lactate as energy source is tightly coupled to the activity of the malate-aspartate shuttle (MAS), since its inhibition decreases the rate of lactate oxidation (McKenna *et al*. 1993). According to the model proposed by Bak *et al*., elevated neurotransmission may not increase oxidative metabolism of lactate; it decreases possibly because of a depolarization-induced increase in intracellular Ca^{2+} concentration and a putative limitation of the MAS, which transfers the reducing equivalents from the NADH produced during glycolysis into mitochondria. Thus, when the activity of the MAS is limited (due to Ca^{2+}-induced activation of the α-KG dehydrogenase, which competes with the malate/α-KG carrier for substrate), NAD^+ cannot be regenerated for glycolysis and NADH is not further oxidized in the electron transport chain (ETC), leading to an increase in cytosolic NADH concentration and a decrease in glycolysis and OxPhos. At this point, pyruvate is further converted into lactate with the concomitant regeneration of NAD^+ for glycolysis; and it is during repolarization (when cytosolic Ca^{2+} is low and the MAS is no longer limited) when accumulated lactate is oxidized (Bak *et al*. 2009).

The ANLS concept explains the role of lactate as an important energy source for brain function as well as defines the strong metabolic association between astrocytes and neurons. It is suggested that most of the neurodegenerative diseases, as well as any other adverse changes in the brain, have notable changes in the ANLS and lead to imbalances in neurometabolic coupling (Bélanger *et al*. 2011). However, the ANLS concept has been critically viewed and challenged due in part to contradictory results obtained in different experimental settings, and to the lack of a consensus-based method for real-time monitoring of metabolic dynamics at cellular resolution. For example, while some authors argue that neurons prefer lactate over glucose (Bouzier-Sore *et al*. 2003); others claim neurons are well equipped to metabolize glucose in an activity-dependent manner (Bak *et al*. 2009), which clearly opposes to the tight coupling of astrocytes to synaptic activity (Ruminot *et al*. 2017). To further build upon these findings, for both research and diagnose purposes, positron emission tomography (PET) with the glucose analog

^{18}F fluorodeoxyglucose (FDG) is commonly used as clinical diagnostic measure for local glucose metabolism. Further development of fluorescent protein-based sensors for specific, real-time readouts of metabolites will fill this current technological gap (Zhang *et al*. 2018) and shed light on this hypothesis which has long been a subject of debate (Chih and Roberts 2003; Dienel 2012b; Bak and Walls 2018; Barros and Weber 2018a, 2018b). However, based on the accumulated evidence in favor compared to that against this postulation, the ANLS hypothesis seems now to be broadly accepted.

Glucose versus Lactate at rest and while exercising

At rest, the predominant energy source for the brain is glucose (McEwen and Reagan 2004; Dienel 2012b). Strenuous physical activity increases O_2 demand by the skeletal muscles leading to increased heart rate and respiration. However, due to unmet O_2 demand, plasma lactate levels are enhanced by conversion of pyruvate to lactate, which is an important step to regenerate NAD^+, an essential substrate to carry out glycolysis and release ATP in the muscle (Lucas-Cuevas *et al*. 2015). Rigorous physical activity increases lactate plasma levels from 0.6 mmol/L to around 2–3 mmol/L, which then crosses the BBB via MCTs (Ide *et al*. 1999). The cerebral uptake of lactate is thought to be twofold higher than that of glucose. While performing extensive physical exercise, the cerebral metabolic ratio for carbohydrates, defined as cerebral molar uptake of (O_2/(glucose + 1/2 lactate)), decreases from a resting value of 6 to < 2 (Smith *et al*. 2003; Quistorff *et al*. 2008). Furthermore, a clinical study involving administration of sodium lactate reported a three- to fourfold increase in plasma lactate levels along with an average of 17% reduction in the rate of cerebral glucose uptake, indicative of a preferential cerebral uptake of lactate over glucose (Smith *et al*. 2003). Lactate is thought to be a favored cerebral energy source since the conversion of lactate to pyruvate does not require ATP and is thermodynamically preferable compared to glucose that needs two molecules of ATP (Quistorff *et al*. 2008; Dienel 2012b).

Induced alteration in metabolic substrate concentration, through voluntary exercise, has been shown to enhance metabolic enzymes involved in glycolysis, ATP synthesis, ATP transduction, and glutamate turnover (Ding *et al*. 2006). Preclinical studies report exercise training in mice augmented the expression of metabolically relevant genes (i.e., peroxisome proliferator-activated receptor gamma coactivator 1-alpha, sirtuin-1, and citrate synthase) as well as increased mitochondrial DNA (mtDNA), suggestive of mitochondrial biogenesis in most brain regions studied (Steiner *et al*. 2011). These results together with several converging lines of evidence suggest a critical role for alterations in global and regional brain metabolism in the pathogenesis of neurodegenerative diseases, indicating that physical activity could provide clinical benefit. However, the mechanisms involved in exercise-induced cerebral mRNA expression of metabolically relevant genes and mitochondrial biogenesis are not fully understood and need further investigation.

Ketone bodies

Ketone bodies provide the brain with an alternative source of energy during periods of prolonged fasting and starvation. Under normal physiological conditions, monocarboxylates cross the BBB with poor efficiency, but under starvation, the amount of ketones present in the blood and expression of MCTs in cells forming the BBB are increased (Hasselbalch *et al*. 1995). Additionally, mild elevation of blood ketone bodies occurs during the process of normal aging (Sengupta *et al*. 2010).

β-Hydroxybutyrate (β-OHB) is a metabolic intermediate that constitutes ~ 70% of ketone bodies produced in liver mitochondria mainly from the oxidation of fatty acids released from adipose tissue (Persson 1970). The concentration of β-OHB in plasma under healthy, fasted conditions is relatively low with reference values reported ~ 0.04 mM–0.08 mM (Hansen and Freier 1978). This may increase by fasting or starvation to 5–6 mM (Owen *et al*. 1967), and to ~ 25 mM by dietary intervention or diabetic ketosis (Garber *et al*. 1974; Saudubray *et al*. 1981; Bonnefont *et al*. 1990; Mitchell *et al*. 1995). In non-diabetic subjects, a 3-day fast increases the concentration of β-OHB from an average of 0.03–3.15 mM in plasma, and from 0.05 to 0.98 mM in the brain (Pan *et al*. 2000). Normal serum levels of ketone bodies can be defined as < 0.5 mM, hyperketonemia in excess of 1.0 mM, and ketoacidosis over 3.0 mM (Mitchell *et al*. 1995).

Regulation of ketone body metabolism is different in astrocytes and synaptic terminals. Inhibition of the MAS and other transaminase reactions on the oxidation of energy substrates increases the oxidation of lactate and β-OHB in astrocytes, but has no significant effect on the rates of β-OHB oxidation and decreases the rate of lactate oxidation by synaptic terminals (McKenna *et al*. 1993). Additionally, ketone bodies neither alter the plasma membrane potential of presynaptic terminals nor the pH of synaptic vesicles. β-OHB supports synaptic vesicle recycling, but reduces both endocytosis and, to a smaller extent, exocytosis (Hrynevich *et al*. 2016).

MCTGs as alternative brain energy fuel

MCTGs are fatty acids with 7–12 carbon chain length; the most common MCTGs include heptanoate (C7), octanoate (C8), and decanoate (C10) (Schönfeld and Wojtczak 2016). Owing to their smaller size, MCTGs can readily diffuse into the brain as they do not require carnitine transporters unlike long chain fatty acids (Oldendorf 1973; Kuge *et al*. 1995). Additionally, even MCTGs can be degraded in the liver to the four carbon (C4) ketone β-OHB. C4 ketones and MCTGs can be further metabolized to acetyl-coenzyme A (CoA) and enter into the TCA cycle, primarily in astrocytes (Edmond

et al. 1987; Marin-Valencia et al. 2013). Octanoate was shown to promote ketogenesis in astrocytes (Thevenet et al. 2016) and to inhibit brain glycolysis in mice (McDonald et al. 2014) by reducing the maximal activity of the rate-limiting enzyme PFK (Tan et al. 2017). Decanoate facilitates glycolysis and lactate formation in astrocytes thereby providing fuel to neurons (Thevenet et al. 2016) and improving mitochondrial energy metabolism (Tan et al. 2017).

The odd chain MCTGs are unique because they can be β-oxidized to deliver propionyl-CoA and acetyl-CoA. Additionally, they can be metabolized in the liver to 5 carbon (C5) ketone bodies β-ketopentanoate and β-hydroxypentanoate (Kinman et al. 2006; Deng et al. 2009). Triheptanoin, a triglyceride of heptanoate, generates three molecules of heptanoate upon hydrolysis. Heptanoate can directly enter into the brain or can be degraded into C5 ketones in the liver (Marin-Valencia et al. 2013). The C5 ketones get converted into propionyl CoA, an anaplerotic molecule which can be carboxylated to succinyl coenzyme A (CoA) to feed the TCA cycle. Anaplerosis is the process by which TCA cycle intermediates are restored to permit continuous function which is necessary during neurotransmission. Triheptanoin was shown to partially replenish TCA cycle intermediates in epileptic mice (Hadera et al. 2014). Additionally, numerous studies have demonstrated the beneficial effects of MCTGs as energy substrates in several neurological disorders such as epilepsy (Willis et al. 2010; Wlaź et al. 2012; Chang et al. 2013; Tan et al. 2017), amyotrophic lateral sclerosis (Zhao et al. 2012; Tefera et al. 2016), stroke (Schwarzkopf et al. 2015), and cognitive impairments (Wang and Mitchell 2016). Overall, these studies corroborate the importance of alternative fuels as a source of energy to improve brain energy metabolism with respect to pathoconditions.

The role of non-neuronal cells in brain energy metabolism

Pericytes

The perivascular location and morphology of pericytes led to the suggestion that they may be contractile cells involved in regulation of capillary blood flow in response to vasoactive agents and neural activity (Sweeney et al. 2016). They may also be found around the lymphatic capillaries in cases of developmental abnormalities (Petrova et al. 2004). Additionally, pericytes exhibit macrophage-like activity, as shown by the presence of numerous lysosomes within their cytoplasm (Allt and Lawrenson 2001), their efficient uptake capacity for soluble tracer compounds (delivered into the blood, in the ventricular cerebrospinal fluid, or in the extracellular fluid by direct injection into the tissue) (Rucker et al. 2000), their phagocytic activity (Thomas 1999), and their capability to present antigens (Rustenhoven et al. 2017).

Role of pericytes in the BBB and glucose homeostasis

Pericytes are imperative for normal CNS functioning and have important roles in angiogenesis, vessel stabilization, endothelial cell regulation, and maintenance of the BBB (Fisher 2009; Hill et al. 2014). These functions of pericytes are vital in maintaining the homeostasis of the perivascular environment (Vezzani et al. 2016). Moreover, glucose intake of pericytes is four times higher than of endothelial cells, but similar to that of astrocytes, suggesting potential astrocyte/pericyte complementary roles in maintaining glucose homeostasis in the brain. Furthermore, astrocytes and pericytes express comparable amounts of GLUT1 and GLUT4 (Castro et al. 2018).

As endothelial cells comprise a portion of the BBB that regulates CNS transport of energy metabolites, ions, and clearance of neurotoxic metabolites (Zhao et al. 2015), and since there is a strong interaction between pericytes and endothelial cells by means of tight and gap junctions found at their contact sites (Cuevas et al. 1984) allowing physical communication and molecule exchange between these cells, pericytes have also been reported to play an important role in the BBB (Daneman et al. 2010). Additionally, the stabilization of these contact sites by adhesion plaques between the cells and fibronectin from the extracellular matrix supports the fine-tuned distribution of the contractile force caused by vascular smooth muscle cells (Vezzani et al. 2016). Reports suggest that the pericyte–endothelial interaction regulates the basement membrane (Stratman et al. 2009, 2010) and the anatomical proximity between pericytes and endothelial cells indicates a probable role of pericytes in paracrine or juxtacrine signaling, as pericytes have been proposed to be involved in several signaling pathways including Angiopoietin-1, transforming growth factor β, and platelet-derived growth factor receptor β (Gaengel et al. 2009).

Astrocytes

Astrocytes are the most abundant glial cells in the brain and display a number of active roles critical for CNS function (Nedergaard et al. 2003; Barros et al. 2018b), including regulation of neurotransmitters (Anderson and Swanson 2000), supplying substrates to neurons for OxPhos (Pellerin et al. 1998), maintaining water homeostasis (Simard and Nedergaard 2004; Salman et al. 2017a), and regulating blood supply to meet neuronal energy demand (Zonta et al. 2003; Takano et al. 2006; Gordon et al. 2008). Additionally, astrocytes play a major role in synapse formation, maintenance, and plasticity during brain development and in adulthood (Araque et al. 1999; Han et al. 2013; Kim et al. 2017). Astrocytes have extensive processes originating from the soma; some of these ensheath synapses (Ventura and Harris 1999) forming the 'tripartite synapse', while others known as 'endfeet' surround the brain arteries and capillaries (Araque et al. 1999; Oberheim et al. 2006; Barros et al. 2018b).

An intricate link exists between blood flow, glucose utilization, synaptic plasticity, and neuronal activity. This neurometabolic coupling is a salient physiological characteristic of the brain function and has formed the basis for understanding neuroenergetics. Astrocytes take up glucose via GLUT1 located at the endfeet covering brain microvessels (Mathiisen *et al*. 2010) (Fig. 2). Following this, glucose is rapidly phosphorylated to G6P by hexokinase I (Tabernero *et al*. 2006; Brown and Ransom 2007). G6P can then be channeled into the glycolytic pathway to produce pyruvate, metabolized to glucose-1-phosphate for the synthesis of glycogen (Cataldo and Broadwell 1986; Dienel and Cruz 2015), or used in the PPP (Dringen *et al*. 2007). While the PPP is only a minor contributor to the total glucose oxidation, it generates NADPH, an important molecule for maintaining the antioxidant-reduced glutathione, as well as precursors for nucleotide synthesis (Dringen *et al*. 2007). In addition to glucose, astrocytes can efficiently use alternative energy substrates, such as mannose (Dringen *et al*. 1993); however, other carbohydrates like fructose or galactose are considered to be poor substrates in astrocytes (Dringen *et al*. 1993).

Glycogen metabolism

Alternatively, G6P can be used for the synthesis of glycogen, the main storage form of glucose in the brain (Hertz and Dienel 2002). Glycogen is predominantly found in astrocytes and seems to be connected to specific organelles and non-randomly distributed (Calì *et al*. 2016). The glycogen pool is dynamic and rapidly responds to changes in cerebral energetic demands by undergoing constant degradation and resynthesis (Swanson 1992), facilitated by glycogen synthase and glycogen phosphorylase expressed by astrocytes (Pellegri *et al*. 1996; Brown and Ransom 2007). Utilization of glycogen stores allows astrocytes to quickly increase glycolytic flux independent of glucose availability and hexokinase activity in response to local energy demands (Brown and Ransom 2015). Astrocytic glycogenolysis is activated by extracellular increase in neurotransmitter concentrations as well as changes in the K^+ homeostasis following neuronal activity (Hof *et al*. 1988; Sickmann *et al*. 2009; Wang *et al*. 2012). Interestingly, vasoactive intestinal polypeptide as well as norepinephrine induce glycogenolysis in murine cortex (Magistretti *et al*. 1981). This signal-induced regulation of glucose supply is thought to act in a complementary way; while vasoactive intestinal polypeptide acts locally within cortical columns, norepinephrine can control glycogen metabolism across adjacent columns. Glycogen can also be mobilized under conditions such as glucose deprivation (Dringen and Hamprecht 1992) or elevated cellular Ca^{2+} levels (Hamprecht *et al*. 1993). Functionally, glycogenolysis in astrocytes and the subsequent release of lactate have been shown to play a crucial role in formation of LTP and memory (Suzuki *et al*. 2011; Duran *et al*. 2013). The important role of glycogen in supporting neuronal signaling is highlighted by the glycogen shunt, where part of the glucose that enters the astrocyte is converted into glycogen before entering the glycolytic pathway, despite this being energetically unfavorable compared to classical glycolysis (Walls *et al*. 2009). Furthermore, astrocyte glycogen plays an important role in maintaining neuronal survival during conditions of hypoglycemia *in vitro* (Swanson and Choi 1993) and *in vivo* (Suh *et al*. 2007).

Oligodendrocytes

Oligodendroglia are specialized cells in the CNS that are responsible for generation and maintenance of myelin sheath that surrounds CNS axons (Bradl and Lassmann 2010; Nave 2010). Myelin acts as an electrical insulator by increasing the membrane resistance and decreasing membrane capacitance, resulting in increased conduction velocity while reducing axonal size requirements and neuronal metabolic demand. Moreover, myelin enables rapid saltatory propagation between nodes of Ranvier, allowing fast and efficient transduction of electrical signals in CNS (Ransom and Sontheimer 1992; Edgar and Garbern 2004; Harris *et al*. 2012).

While myelination is the primary function of oligodendrocytes, they also provide trophic support to neurons by secreting a wide variety of neurotrophins, including insulin-like growth factor-1, glial cell line-derived neurotrophic factor, and brain-derived neurotrophic factor (Bradl and Lassmann 2010; Saab *et al*. 2013). Moreover, though astrocytes play a critical role in sustaining energy substrates through their glycogen stores and production of lactate through glycolysis, recent evidence suggests that oligodendroglia are a prominent site of lactate export to neuronal axons (Saab *et al*. 2013).

Oligodendrocytes as energy consumers

As outlined above, CNS white matter, primarily composed of myelinated axons, is estimated to consume one-third of the energy of gray matter. Conversely, myelination is energetically costly and the metabolic costs of generating enough lipid and protein for myelin synthesis may be higher than the energy saved by accelerated axonal conduction (Nave and Werner 2014). It has been reported that during peak myelination, oligodendrocytes increase their weight threefold per day (McLaurin and Yong 1995; Ludwin 1997). Remarkably, in the optic nerve, it has been estimated the initial energetic costs of myelin formation during development can be repaid by 1–2 months normal activity (Harris and Attwell 2012). However, the ATP needed to maintain myelin throughout life, including the cost of maintaining oligodendroglia resting potential, likely negates the energy saved (Harris and Attwell 2012). Therefore, the primary function of myelination is not to save energy, but rather to allow fast

nerve conduction, thereby increasing information processing and improving cognitive power (Harris and Attwell 2012; Nave and Werner 2014).

Microglia

Microglia are cells of mesodermal origin that migrate into the CNS during embryonic development (Hickey and Kimura 1988). As immune cells, microglia serve both a supportive and a protective function within the CNS. In their resting state, microglia act as the CNS's surveillance system, equipped with a wide range of receptors (i.e., neurotransmitter, cytokine, chemokine, pattern recognition) (Kettenmann *et al*. 2011). Microglia interact with neurons (i.e., scanning synapses) and thus contribute to the structure of neuronal networks and connectivity (Kettenmann *et al*. 2011). When activated, as indicated by a change in morphology toward an increased soma size and thicker proximal ramifications, microglia can migrate to the site of injury and proliferate (Bernhart *et al*. 2010). Microglia can mount a molecular defense through the production of bioactive molecules that can be beneficial in some circumstances (i.e., phagocytosis of aberrant cells posing a threat to the CNS) and detrimental in others (i.e., when remaining primed in a disease state and being dysfunctional in response to a secondary injury, which can lead to loss of neural circuits) (Kettenmann *et al*. 2011; Daneman 2012; Koss *et al*. 2019). Proteomic changes in activated microglia involve several glycolytic enzymes leading to enhanced ATP production; highlighting the necessity of enhanced cellular metabolism to regulate their adaptability (Bernhart *et al*. 2010).

Microglial energy sources and metabolism

Microglia and macrophages within the CNS have a high energetic demand to function as they monitor for abnormalities and make connections with neurons. The three major energy substrates in microglia are glucose, fatty acids, and glutamine. Glucose is imperative for microglia survival and can enter microglia via transporters GLUT1, GLUT3, GLUT4, and GLUT5 (Payne *et al*. 1997; Wang *et al*. 2019). Conversely, GLUT5, exclusively expressed in microglial cells of the human and rat brain, is a very poor transporter of glucose and has been shown to facilitate the passage of fructose across the plasma membrane (Payne *et al*. 1997; Horikoshi *et al*. 2003). After uptake, glucose undergoes glycolysis and full aerobic breakdown or is used for formation and secretion of lactate.

Fatty acids are an alternative source of energy for microglia. After uptake by lipoprotein lipase, long chain fatty acyl-CoA synthetase catalyzes the formation of fatty acyl-CoA, which can only enter the mitochondria together with the carrier protein carnitine. Once inside the mitochondria, fatty acyl-CoA is β-oxidized into acetyl-CoA, which enters the TCA cycle and subsequently the ETC in order to generate ATP. G protein-coupled receptor 120 is known to bind unsaturated fatty acids and is possibly involved in their anti-inflammatory effects (Kalsbeek *et al*. 2016). Microglia highly express all components of the NADPH oxidase complex, which has been shown to be stimulated by fatty acids to increase the production of reactive oxygen species (ROS) in macrophages.

Finally, glutamine is used as an energy substrate by microglia (Kalsbeek *et al*. 2016). The glutamine transporters SLC1A5 and SLC38A1 are expressed by microglia and enable microglia to take up glutamine. Inside the mitochondria, glutamine is converted to glutamate and ammonia (NH_4^+) by the GLS, glutamate is further metabolized by glutamate dehydrogenase 1 to α-KG, which can enter the TCA cycle. Both microglial-produced glutamate and NH_4^+ have been shown to have neurotoxic effects, which may contribute to neuronal cell death in inflammatory, infectious, ischemic, and neurodegenerative diseases. Infection, for example, increases the demand of energy of microglia (Kalsbeek *et al*. 2016). Tissue damage releases ATP which attracts microglia at the site of infection and consumes a vast amount of energy (Engl and Attwell 2015). Activation of microglia by ROS, especially nitric oxide (NO), modulates metabolic assembly based on glucose uptake and upregulates both anaerobic glycolysis and OxPhos of PPP. Thus, NO plays a central role in the energy metabolism of microglia (Gimeno-Bayón *et al*. 2014).

Disturbed energy homeostasis as a hallmark of CNS disorders and brain aging

Energy homeostasis is essential in maintaining a healthy state of the brain. Disrupted energy homeostasis may either be a cause or an effect of a disease or a disease-like condition (i.e., unhealthy aging). Metabolic changes not only contribute to the pathology of neurodegenerative diseases, traumatic brain injury, or stroke but also cause neurological symptoms of diabetes mellitus, and accompany normal aging.

Aging

During human brain development, energy metabolism declines with aging. Studies calculating brain glucose utilization over the course of human development, from birth to adulthood, have identified that energy metabolism peaks during early childhood (Kuzawa *et al*. 2014a) and declines during aging (Kuzawa *et al*. 2014a, 2014b; Skoyles 2014). A recent study from Goyal *et al*. (2017) showed that age-related decline in brain glucose uptake exceeds that of O_2 utilization, causing a loss of brain aerobic glycolysis.

A suggestion for the decline in energy metabolism is the progression of metabolic deficiency resulting in the age-associated cognitive decline and general brain function disturbance (Yin *et al*. 2014; Ivanisevic *et al*. 2016). Metabolomics analysis-based studies have identified compromised cellular energy status with metabolic imbalances suggesting a failure to maintain metabolite homeostasis (Yin

et al. 2014). These studies have identified increased adenosine monophosphate (AMP), ATP, purine, and pyrimidine levels (Ivanisevic *et al*. 2016) with the accumulation of these metabolites as hallmarks of multiple neurodegenerative diseases (Nyhan 2005; Yin *et al*. 2014).

A recent study has identified metabolism-regulating peroxisome proliferator-activated receptor (PPAR) transcription factors as possible energetic metabolic switches during adult neurogenesis (Di Giacomo *et al*. 2017). PPAR transcription factors have been shown to be widely distributed within the mammalian brain and to be involved in regulating the expression of genes involved in energy metabolism (Woods *et al*. 2003; Cimini *et al*. 2005; Cimini and Cerù 2008), making them strong candidates for possible key regulators of metabolic pathways impacted by brain aging.

Of note, impaired energy metabolism accompanying aging is a distinguishing factor of neurodegeneration, highlighting aging as a predisposition destabilizing the "healthy" brain energetics, and making it more prone to neurodegenerative diseases.

Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a complex metabolic disease more prevalent with aging. It is characterized by chronic elevated blood glucose levels. Although glucose is the main energy substrate of the brain, chronic elevated blood glucose is not advantageous for the brain, thus untreated T2DM can lead to severe cognitive dysfunction, termed diabetic encephalopathy. Impeded cerebral glucose metabolism has been found in patients with T2DM; a condition commonly observed in Alzheimer patients (see below) (Mosconi *et al*. 2008; Baker *et al*. 2011). This inadequate glucose metabolism can arise from disruptions in supply, transport, or utilization, which likely all contribute to T2DM (Wardelmann *et al*. 2019). Furthermore, cognitive impairment in T2DM patients is suspected to arise due to hippocampal insulin resistance, which leads to several deleterious effects (Sims-Robinson *et al*. 2010; Correia *et al*. 2012; Biessels and Reagan 2015). Interestingly, a specific hippocampal decrease in glutamate and glutamine metabolism was recently described in a mouse model of T2DM (Andersen *et al*. 2017b), supporting that metabolic changes at the interface of glucose and neurotransmitter conversion may mediate cognitive hippocampal deficits in T2DM.

Brain mitochondrial function was also found to be altered in T2DM (Sims-Robinson *et al*. 2010; Correia *et al*. 2012). Several studies have documented deleterious effects on mitochondrial bioenergetics in mice models of T2DM, including altered activity and expression of components of the ETC (Ernst *et al*. 2013; Andersen *et al*. 2017a); highlighting mitochondrial deficits play a role in the decline of cerebral health in T2DM.

In addition to elevated plasma levels of glucose, increased amounts of ketone bodies, acetoacetate, and β-OHB are observed in T2DM model mice (Vannucci *et al*. 1997; Poplawski *et al*. 2011). Along this line, it has been shown that cerebral fatty acids and β-OHB metabolism are elevated in a mouse model of T2DM (Makar *et al*. 1995; Andersen *et al*. 2017a). These observations correlate with an increased capacity of ketone body transport into the brain (Pierre *et al*. 2007) and indicate that alternative substrates might be able to compensate for the diminished glucose metabolism in T2DM.

Diabetic conditions can have a disease-modifying effect for progressive neurodegenerative disorders of the brain like Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or multiple sclerosis, all of which involve diverse molecular and cellular mechanisms, yet despite unrelated aetiology, they all share a metabolic component which may be a consequence of the disorder or even causally contribute to its occurrence.

Alzheimer's disease

Alzheimer's disease (AD) is the most common chronic progressive neurodegenerative disorder that causes dementia. There are two hypotheses of AD pathogenesis. On the one hand, the amyloid hypothesis proposes that the presence of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles causes brain atrophy and leads to nerve cell death (Bhardwaj *et al*. 2017). On the other hand, the mitochondrial cascade hypothesis unifies the biochemical, histological, and clinical features of sporadic AD (Swerdlow and Khan 2004).

T2DM is a risk factor for the development of AD (Ott *et al*. 1996; Exalto *et al*. 2012; Crane *et al*. 2013). Indeed, increased brain Tau phosphorylation has been shown in T2DM mouse models (Kim *et al*. 2009; Ramos-Rodriguez *et al*. 2013). It has been suggested that T2DM accelerates AD development through perturbations in brain energy metabolism, advanced glycation end product and ROS production, and synaptic degeneration (Correia *et al*. 2012; Duarte 2015).

As dysfunctions in cerebral energy metabolism are considered a hallmark of AD, their detection represents a tool for AD diagnosis and understanding of pathophysiological mechanisms (Ferris *et al*. 1980; Mosconi 2013). As mentioned above, glucose metabolism can be assessed by ^{18}FDG uptake by PET. This technique has revealed a marked reduction in FDG labeling that correlates with AD progression and is more prominent in brain areas most affected by the disease, including the temporal and occipital lobes (Marcus *et al*. 2014).

One possible explanation for brain energetic impairment in AD could be reduced glucose uptake. It has been observed that expression of GLUT1 and GLUT3 is reduced in AD brains (Simpson *et al*. 1994). Furthermore, extracellular Aβ binds to several membrane receptors, such as the NMDA

receptor (De Strooper and Karran 2016). This interaction leads to an impaired activity of AMP-activated kinase (AMPK), a protein that is normally induced by high AMP/ATP ratios. Furthermore, AMPK inhibition promotes a reduction of GLUT3 and GLUT4 in plasma membranes of hippocampal neurons, reducing ATP production (da Silva *et al*. 2017). Additionally, Aβ oligomers reduce hexokinase activity and ATP levels in neuronal cultures (da Silva *et al*. 2017). Thus, extracellular Aβ contributes to the impairment of the energetic metabolism.

As aging is a major risk factor for the onset of neurodegenerative diseases like AD, the mitochondrial cascade hypothesis (Swerdlow and Khan 2004) suggests that accumulated mutations in mtDNA caused by ROS play a pivotal role in mitochondrial dysfunction (Lin and Beal 2006), which can be an early event in AD (Nunomura *et al*. 2001). Amyloid precursor protein forms can accumulate in protein import channels of mitochondria of human AD brains and thus contribute to mitochondrial dysfunction (Devi *et al*. 2006). These alterations promote a reduction in energetic metabolism in neurons (Caspersen *et al*. 2005). Though, some of these effects could be associated with variations in protein levels related to mitochondrial dynamics (Itoh *et al*. 2013). It has been demonstrated that protein levels of Drp1 are increased in AD and potentiate cell death (Park *et al*. 2014). This protein is important for mitochondrial quality surveillance and induces mitochondrial fission, which as a consequence reduces the protein levels of mitofusin (MFN) 1/2 and optic atrophy type 1 (OPA1); GTPases that promote the fusion process (Baek *et al*. 2017). Additionally, the inhibition of Drp1 ameliorates Aβ deposition and synaptic impairment. Therefore, reduction of mitochondrial fission leads to increased occurrences of mitochondrial fusion and results in neuroprotective effects in AD models (Itoh *et al*. 2013; Park *et al*. 2014; Baek *et al*. 2017).

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by a loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) and the presence of Lewy bodies (with α-synuclein inclusions) in the substantia nigra (Sveinbjornsdottir 2016). Interestingly, in a large retrospective cohort study, a higher prevalence of PD in patients with T2DM was detected (De Pablo-Fernandez *et al*. 2018).

However, dysfunctions in energy and/or redox homeostasis, along with oxidative stress leading to mitochondrial dysfunction, are considered the initiators of a chain of events that result in synaptic dysfunction, neuronal degeneration, and motor disabilities in PD (Saravanan *et al*. 2006; Schapira and Jenner 2011). However, the observation that Lewy bodies are not found in all neurons or are randomly expressed in the brain, as less than 1% of brain neurons are affected through the mid-stages of the disease, raised the question of why SNpc DA neurons are the most vulnerable. It was proposed that there are intrinsic neuronal features of generating and handling APs that render DA SNpc neurons more susceptible to mitochondrial dysfunction related to PD (Surmeier *et al*. 2012).

Indeed, candidate gene and genome-wide association studies identified many genetic mutations/polymorphisms associated with PD (i.e., in genes like PINK1, Parkin, protein deglycase DJ-1/Parkinson disease protein 7, and leucine-rich repeat kinase 2) that compromise mitochondrial function and dynamics (Coleman 2012). DA neurons lacking the mitochondrial fusion gene MFN2 display fragmented mitochondria and their transport within the axon is hindered (Anh *et al*. 2012). Mutation in MFN2 leads to severe locomotory behavioral deficits, which is accompanied by loss of striatal DA efferents. Moreover, altered mitochondrial fission may result in synaptic loss and DA neuronal cell loss (Berthet *et al*. 2014). In human patients, two heterozygous missense mutations in the mitochondrial fusion promoter OPA1 protein show slow symptoms of PD and dementia (Carelli *et al*. 2015).

Studies in various animal models of PD reveal that mitochondrial dysfunction in the brain is linked to alterations in mitochondrial morphology, dynamics, mutation of mtDNA, increased proton leak (Villeneuve *et al*. 2016), and decreased rates of electron transfer (Golpich *et al*. 2017; van der Merwe *et al*. 2017). These impairments in mitochondria are associated with: accumulation of oxidation products of phospholipids and proteins, increased ROS production, increased lipid peroxidation, decreased respiration and membrane potential, decreased capacity for ATP production, and neuronal degeneration due to oxidative damage and energy defects in the aged mammalian brain (Navarro and Boveris 2010).

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurologic disorder, primarily characterized by the selective death of lower and upper motor neurons in the spinal cord and cortical regions which finally leads to muscle denervation, weakness, and paralysis. Several pathogenic mechanisms are believed to contribute to motor neuron death, including abnormal protein aggregation (Bruijn *et al*. 1997), oxidative stress (Barber *et al*. 2006), glutamate excitotoxicity (Rothstein 1995), and impaired energy metabolism (Dupuis *et al*. 2011).

Numerous preclinical investigations *in vitro* and *in vivo* as well as in patients have revealed metabolic irregularities in ALS brains which include reductions in glucose uptake (Miyazaki *et al*. 2012) and reduced gene expression of enzymes involved in glycolysis (Ferraiuolo *et al*. 2011), PPP (Kirby *et al*. 2005), and TCA cycle (D'Arrigo *et al*. 2010), as well as the ETC (Ferraiuolo *et al*. 2011). These metabolic defects, which comprise also disrupted metabolic interactions between neurons and glial cells (reviewed in Tefera and Borges 2017), result in impaired mitochondrial oxidative

phosphorylation, declined generation of ATP, and subsequent death of neurons as well as non-neuronal cells.

Given the impairments in energy metabolism in ALS, several metabolic agents aimed at correcting metabolic irregularities have been examined in ALS mouse models and/or patients, including the ketogenic diet (Zhao *et al*. 2006), dichloroacetate (Miquel *et al*. 2012), caprylic triglyceride (Zhao *et al*. 2012), triheptanoin (Tefera *et al*. 2016), and others (reviewed in (Tefera and Borges 2017). These metabolic substrates were able to modify ALS disease progression to varying degrees, signifying the contribution of CNS energy metabolism toward the pathogenesis of the disease and the need for further studies to correct metabolic defects.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic autoimmune neurodegenerative disease characterized by axonal demyelination and impaired remyelination (Aslani *et al*. 2017). Activated T-cell-mediated autoimmune destruction of CNS myelin has been highlighted as the major underlying cause, yet genetic predisposition, oxidative stress, mitochondrial dysfunction, and energy failure likely contribute to accelerate the disease. Axonal energy failure and disrupted mitochondrial energetics, especially in white matter astrocytes, have been implicated in MS (Cambron *et al*. 2012), highlighted by the absence of β2-adrenoreceptors in the astrocytes of MS patients (Cambron *et al*. 2012), which impairs the noradrenaline-mediated glycogenolysis necessary to exploit this energy reservoir for neurons and their axons, thus leading to disrupted ion gradients that disturb the excitability of axons. Also, disrupted metabolic support from oligodendrocytes contributes to axonal damage and disease progression (summarized in (Philips and Rothstein 2017)).

Functionally, energy crisis-driven impaired ATP generation may lead to the failure of important pumps and exchangers like the Na^+/K^+-ATPase maintaining the Na^+ concentration within the axon, which is ATP dependent, and the Na^+/Ca^{2+} exchanger, which further sustains calcium homeostasis. This leads to an increased Na^+ and Ca^{2+} influx in axons and disrupted membrane potential. Intra-axonal accumulation of calcium activates phospholipases and proteases like calpain, which bring about axonal disintegration, and further leads to energy failure via mitochondrial disruption (Pennisi *et al*. 2011).

Traumatic brain injury (TBI) and stroke

Brain injury occurring under ischemic, hemorrhagic, or traumatic conditions is characterized by metabolic and energy imbalances within cerebral cells. Structural damage causes reduced cerebral blood flow and cell membrane disruption and is accompanied by mitochondrial dysfunction, inflammatory responses and oxidative stress, ionic gradient breakdown, glutamate-mediated excitotoxicity, stress signaling, and ultimately cell death (Lo *et al*. 2003; Malik and Dichgans 2018). In addition, the integrity of the BBB is adversely affected due to the disruption of tight junctions (Chodobski *et al*. 2011).

Autoradiographic studies have shown a transient increase followed by a prolonged decrease in cerebral glucose metabolism (measured as cerebral metabolic rate of glucose) in rodent models as well as in human patients with head injury (Glenn *et al*. 2003). It is postulated that the acute phase of hyperglycolysis occurs in order to compensate the increased cellular energy requirement to restore the ionic imbalance and membrane potential (Karelina and Weil 2016). The following long-term depression of cerebral metabolic rate of glucose, indicating reduced glucose uptake and utilization, suggests the inability of the injured brain to meet the increased metabolic demands which could be due to reduced glucose supply (as a consequence of hindered cerebral blood flow, CBF), defects in glucose transporter systems, and/or reduced need for glucose. However, changes in CBF in patients with TBI show a strong heterogeneity with some patients showing significantly reduced CBF, while in others, normal CBF values can be seen that persist for days to weeks after injury (Bouma *et al*. 1991; Marion *et al*. 1991). Nonetheless, the increased glucose metabolism despite the low CBF during acute phase after TBI indicates that the metabolic crisis is not likely caused by the reduced cerebral glucose supply. The other possibility includes the reduced glucose uptake due to impaired glucose transport systems following TBI. Preclinical studies have shown a decreased GLUT1 immunoreactivity indicating less transport of glucose molecules into the brain. However, the data are highly variable requiring further studies. Finally, shunting of glucose to other metabolic pathways within the cell may contribute to the energy crisis after TBI. An animal study has shown an upregulation of the PPP with a 12% increase in cerebral glucose levels that is shunted toward the synthesis of pentose 24 h after the injury (Bartnik *et al*. 2005). Moreover, a reduction in glucose-metabolizing enzymes (such as pyruvate dehydrogenase) and cofactors (NAD^+) indicating decreased efficiency of mitochondria to process glucose for oxidative metabolism in rats (Xing *et al*. 2009).

Altered ionic balance results in a calcium influx (Kitchen *et al*. 2015b), which in turn leads to the depolarization of the mitochondrial membrane due to the opening of the mitochondrial permeability transition pore and cytochrome c-mediated caspase-dependent apoptosis. Elevated levels of NO have been observed in animal models of head trauma (Görlach *et al*. 2015). NO hampers the enzymatic activity of the mitochondrial complex IV and thus interferes with energy metabolism, too.

Brain edema, which is a hallmark of TBI and stroke, occur when water enters the CNS via astrocytes at the BBB, primarily through the aquaporin 4 channel (Amiry-Moghaddam and Ottersen 2003; Kitchen *et al*. 2015a). There is an increased interest in applying therapeutic measures that could

target TBI and stroke through decreasing the energy need of the brain as well as act on limiting the devastating effects of edema (Salman *et al*. 2017b). Therapeutic hypothermia is gaining popularity to prevent or improve a wide range of neurological morbidities (Yenari and Han 2012; Salman *et al*. 2017a). The neuroprotective effect of therapeutic hypothermia, which potentially involves the restoration of the BBB, the preservation of high-energy phosphate compounds, and cellular metabolism, has been confirmed in a number of clinical trials investigating the outcomes of patients suffering from neonatal hypoxia–ischemia (Gluckman *et al*. 2005; Shankaran *et al*. 2005) and cardiac arrest (Bernard *et al*. 2002).

Brain metabolism produces oxygen molecules that are converted into hydrogen peroxides and finally to hydroxyl radicals (·OH). During normal physiological conditions, these highly reactive free radicals are quenched by the cellular antioxidant defense systems. However, during brain injury, the levels of free radicals overwhelm the scavenging systems and result in oxidative damage. OH has been shown to increase immediately after injury and peak at 30 min in severely injured mice (Hall *et al*. 1993). In addition, lipid peroxidation, a marker of increased oxidative metabolism, has been shown to increase up to 24 h post-injury (Hall *et al*. 1993).

Moreover, TBI is characterized by the presence of high lactate concentrations in the extracellular fluid, clearly indicating increased rates of glycolysis, mitochondrial impairment, and/or hypoxia. A high lactate/pyruvate ratio (i.e., < 25) has been well reported for TBI patients (Patet *et al*. 2016). TBI is frequently accompanied by ischemia and hypoxia, major but not the only causes of mitochondrial dysfunction after injury (Carpenter *et al*. 2015; Patet *et al*. 2016).

Concluding remarks

Costly human brain: evolutionary implications

In humans, the brain consumes more energy relative to the rest of the body and has a higher relative size than in other animals. However, the relative basal metabolism does not correlate with the relative size of the brain (Navarrete *et al*. 2011). Some studies connected the possibility of having such a costly brain with the relative reduction of gut (Aiello and Wheeler 1995) or skeletal muscles (Leonard *et al*. 2003) in volume or with the decrease of energy spent on locomotive tasks (Navarrete *et al*. 2011). According to this, the high energetic demands of the human brain are met not due to elevated basal metabolism, but rather due to the energy redirection from other metabolically expensive tissues. New findings highlight the existence of molecular mechanisms of energy redirection. As shown by Pfefferle *et al*. (2011) comparing GLUT1 and 4 expression patterns in apes, monkeys, and humans, the energy trade-off between the brain and other organs may be achieved by redistribution of glucose uptake systems. GLUT1 expression in human brain was found to be much higher as compared to chimpanzee and macaque brains, but GLUT4 expression is higher in chimpanzee skeletal muscle than in human and macaque muscle. Another system of fueling energy to tissue that likely facilitated the evolution of the costly human brain is the phosphocreatine pathway (Pfefferle *et al*. 2011). The expression of the active creatine transporter SLC6A8 and the brain-type cytosolic creatine kinase are higher in humans than in chimpanzees and rhesus macaques in cerebral cortex and cerebellum, but not in skeletal muscles (Pfefferle *et al*. 2011). Thus, shifts in the expression pattern of metabolic pathway players could account for primate brain divergence in evolution.

The importance of maintaining brain energy homeostasis

The existence of many alternative energy sources to fuel the brain as well as the pathological consequences of disturbed regional/global brain metabolism and energetics highlight the importance of maintaining brain energy homeostasis. Glucose metabolism is connected to cell death pathways by glucose-metabolizing enzymes. Thus, disruption of glucose delivery and metabolism can lead to debilitating brain diseases. Furthermore, other molecules that provide fuel or metabolic intermediates for the brain, for example, ketones, are used under pathological (diabetic ketosis) or physiological conditions such as fasting, starvation, or aging, and lactate during extensive physical exercise. A complex interplay exists between the brain, in particular the hypothalamus, and peripheral systems that control glucose uptake and supply to the brain (Lam *et al*. 2009), utilization, and feeding (Wu *et al*. 2009; Joly-Amado *et al*. 2012). When the body undergoes glucose deprivation, fatty acids are broken down into ketones in the liver and the permeability of the BBB to monocarboxylic acids increases in parallel; all of which allow ketone body utilization. Long chain fatty acids, in contrast, do not serve as fuel for the brain because they are bound to albumin in the plasma and do not traverse the BBB.

A non-neurocentric view for neuroenergetics

Neuronal cells together with glia orchestrate the metabolic reactions to maintain the energy demand and redox balance of neuronal activity. Glial cells are highly specialized in their roles within the brain. Moreover, neurodegenerative disorders are not exclusively restricted to neurons but glial cells are indeed a pivotal player. Future research is needed in order to illuminate the roles of the individual glial cells in brain health and disease as there are still many molecular mechanisms to define. For example, utilizing a combination of optogenetic stimulation, electrophysiological recordings, and bioenergetic readouts (Barros *et al*. 2018a) as well as further development of non-invasive imaging of brain metabolism with high-field nuclear magnetic resonance spectroscopy, PET, or single-photon emission computed tomography (Hyder and Rothman 2017). Further studies are warranted, not only because of the high prevalence of

metabolic syndrome, but additionally for a detailed understanding of brain energy metabolism and the link between mental and physical health.

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