*Review*

**Focus: Metabolism**

# Brain metabolism in health, aging, and neurodegeneration

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## Abstract

Brain cells normally respond adaptively to bioenergetic challenges resulting from ongoing activity in neuronal circuits, and from environmental energetic stressors such as food deprivation and physical exertion. At the cellular level, such adaptive responses include the "strengthening" of existing synapses, the formation of new synapses, and the production of new neurons from stem cells. At the molecular level, bioenergetic challenges result in the activation of transcription factors that induce the expression of proteins that bolster the resistance of neurons to the kinds of metabolic, oxidative, excitotoxic, and proteotoxic stresses involved in the pathogenesis of brain disorders including stroke, and Alzheimer's and Parkinson's diseases. Emerging findings suggest that lifestyles that include intermittent bioenergetic challenges, most notably exercise and dietary energy restriction, can increase the likelihood that the brain will function optimally and in the absence of disease throughout life. Here, we provide an overview of cellular and molecular mechanisms that regulate brain energy metabolism, how such mechanisms are altered during aging and in neurodegenerative disorders, and the potential applications to brain health and disease of interventions that engage pathways involved in neuronal adaptations to metabolic stress.

## Introduction

The higher cognitive functions of the human brain depend upon the expansion and increased density and complexity of the neocortex during evolution (Rakic, 2009). The enhanced abilities of the human brain to plan complex behaviors, make decisions, and process emotional and social contexts came with hefty energy requirements. Although it is only 2% of the total body weight, the brain accounts for 20% of an individual's energy expenditure at rest (Kety, 1957; Sokoloff, 1960). Among brain cells, neurons expend 70–80% of the total energy, with the remaining portion being utilized by glial cells

(astrocytes, oligodendrocytes, and microglia) (Harris *et al*, 2012; Hyder *et al*, 2013). Organisms allocate their available energy among the competing needs of maintenance, growth, reproduction, and, particularly in primates, higher cortical functions (communication, imagination, and creativity). A growing body of evidence suggests that metabolic adaptations within the brain and whole body played important roles in the expansion of the cerebral cortex during primate evolution. Several studies comparing the expression of genes and regulatory regions in brains of various primates have shown an up-regulation of genes and metabolites involved in oxidative metabolism and mitochondrial functions in human brains (Grossman *et al*, 2001, 2004; Cáceres *et al*, 2003; Uddin *et al*, 2004; Haygood *et al*, 2007). Furthermore, recent evidence indicates that an increase in metabolic rate, coupled with a higher predisposition to deposit fat and changes in the allocation of energy supplies, was crucial for the evolution of brain size and complexity (Pontzer *et al*, 2016). Understanding the metabolic signatures of different brain cells, and their metabolic interactions, will not only advance our understanding of how the brain functions and adapts to environmental demands, but may also elucidate the propensity of the human brain to age-related neurodegenerative disorders. In recent years, it has become evident that metabolic alterations strongly influence the instigation and progression of many neurodegenerative disorders. Decreases in glucose and oxygen metabolic rates of brain cells occur during normal aging (Hoyer, 1982a) and are further exacerbated in disorders such as Alzheimer's (AD), amyotrophic lateral sclerosis (ALS), Parkinson's (PD), and Huntington's (HD) diseases (Hoyer, 1982b).

In this review article, we summarize the current knowledge of neural cell energy metabolism in the contexts of normal brain function, adaptive neuroplasticity, and the pathogenesis of neurodegenerative disorders.

## Brain barriers and metabolite transporters

Neurons in the adult brain rely mostly on glucose as an energy source (Kety, 1957; Sokoloff, 1960). However, in some circumstances neurons can use substrates other than glucose. For example, ketone bodies are utilized during brain development and in the adult during prolonged fasting periods (Owen *et al*, 1967; Nehlig & Pereira de Vasconcelos, 1993), while lactate utilization is increased

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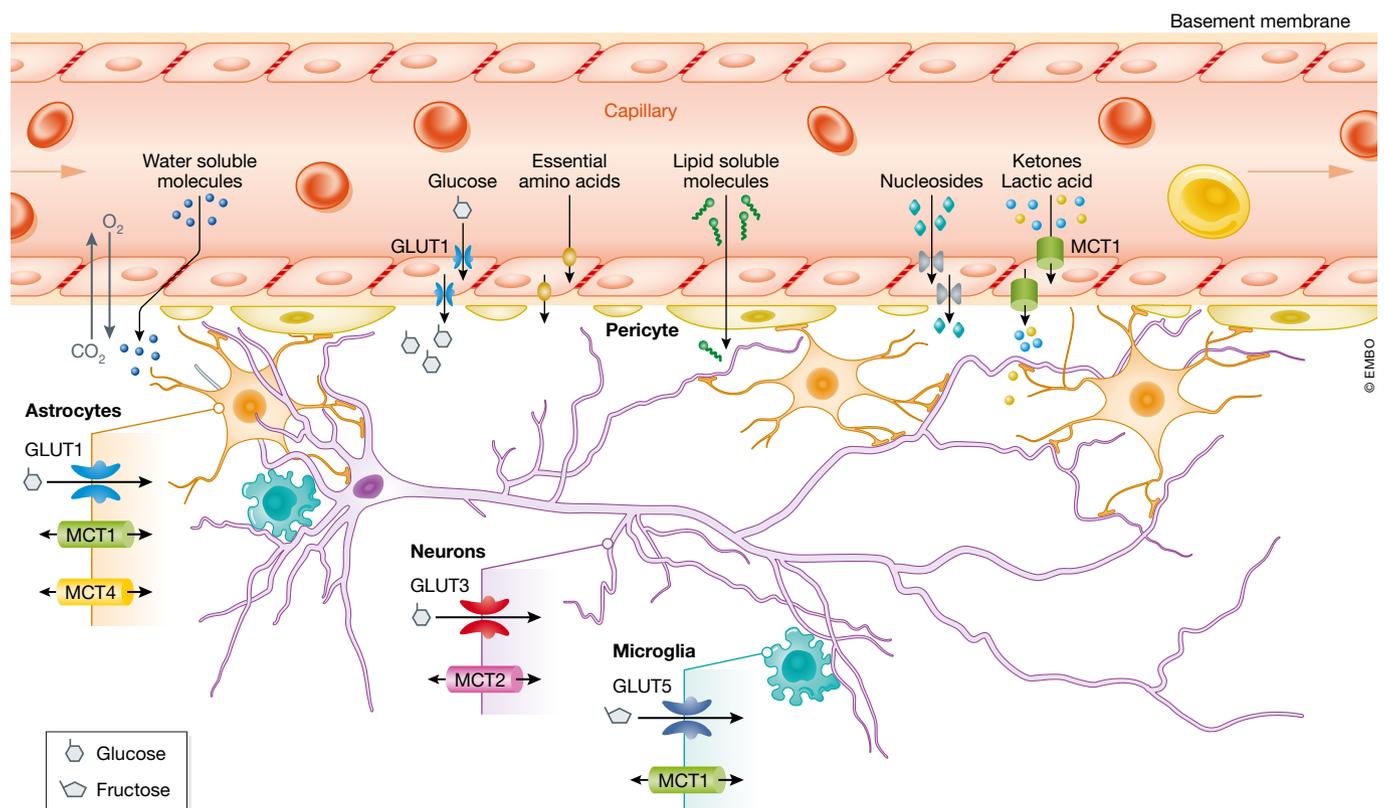1 Laboratory of Neuroscience, National Institute on Aging, Baltimore, MD, USA
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during intense physical activity (Dalsgaard *et al*, 2003; van de Hall *et al*, 2009). Given its high metabolic demands and negligible intrinsic energy stores, the brain depends upon a continuous influx of substrates from the blood. In order to protect the brain from fluctuations in the blood composition that could impact its milieu and functions, the exchanges of molecules between blood and cerebral fluids are regulated by the blood–brain barrier (BBB), and the blood–cerebrospinal fluid barrier (BCSFB). The main function of the these barriers is to limit the free diffusion of solutes between blood and brain fluids, and to selectively transport essential nutrients, ions, and signaling molecules, while removing metabolic waste products. The BBB separates the brain interstitial fluid from the blood and is formed by capillary endothelial cells interconnected by tight and adherens junctions, their underlying basement membrane, pericytes, and the "end feet" of astrocytes (Fig 1). The BBB controls the influx of metabolites such as glucose, amino acids, and ketones from the blood into the brain, while preventing the access of blood-borne molecules and cells (e.g., lymphocytes) that could be detrimental for neuronal functions. The BCSFB is formed by the modified epithelial cells of the choroid plexus which separates the peripheral blood from the CSF, and the arachnoid epithelium separating the cerebral blood from the CSF. In addition to filtering functions similar to the BBB, the epithelial cells of the BCSFB are also responsible for producing the CSF.

The modalities by which specific molecules cross through the BBB depend upon the nature of the solutes (Fig 1). Passive partition is limited to small nonpolar lipid-soluble molecules, and to diffusible gases such as oxygen and carbon dioxide according to their concentration gradients. The presence of tight junctions restricts paracellular diffusion of polar molecules such as proteins (Zlokovic *et al*, 1985a,b; Zlokovic & Apuzzo, 1997), which cross the BBB by interacting with receptors or transporters expressed on both the luminal and abluminal membranes, or selectively on one side (Zloković *et al*, 1987; Zlokovic *et al*, 1990; Abbott *et al*, 2010). Large peptides and proteins such as hormones, growth factors, and neuroactive peptides are transferred via receptor-mediated, adsorptive-mediated, and carrier-mediated transport (Zlokovic, 1995, 2008). Based on the requirement or not to hydrolyze ATP to move the solute across the membrane, two major families of transporters have been identified in the BBB: the ATP-binding cassette (ABC) proteins and the solute carrier (SLC) proteins. The ABC transporters include multidrug resistance-associated proteins (MRPs, ABCB1-6), P-glycoprotein, and breast cancer resistance protein (BRPC) (Begley, 2004). These transporters function as efflux pumps that couple ATP hydrolysis to move lipid-soluble molecules against their concentration gradient. The solute carrier proteins comprise a large superfamily of more than 300 members; they are instrumental for ensuring a stable supply of carbohydrates, amino acids,



**Figure 1.  Nutrient transport across the blood–brain barrier.**
The blood–brain barrier is formed by capillary endothelial cells surrounded by basement membrane, pericytes, and the astrocyte perivascular end feet. The presence of tight junctions between the endothelial cells strongly inhibits the penetration of water-soluble molecules. Passive diffusion is limited to gases and small nonpolar lipids. All other nutrients require passive or active mediated transporters. GLUT1-5, glucose transporter 1-5; MCT1-4, monocarboxylic acid transporter 1-4.

monocarboxylic acids, nucleotides, fatty acids, and organic anions and cations (Abbott *et al*, 2010).

Among the SLC carriers, those that transport hexose and pentose sugars (glucose transporters; GLUTs) and monocarboxylates (monocarboxylic acid transporters; MCTs) are particularly important for brain metabolism. The intake of glucose into the brain is mediated by GLUT1, which is expressed as a 55-kD isoform in endothelial cells of the BBB. A second 45-kD GLUT1 isoform ensures delivery of glucose to glia, ependymal cells, and the choroid plexus. GLUT3 mediates uptake of glucose in neurons; GLUT3 is mainly concentrated in axons and dendrites. GLUT3 has a higher glucose affinity and transport capacity compared to other transporters, and so ensures that neurons receive a constant supply of glucose even when interstitial glucose concentrations are low. Other members of the glucose transporter family are expressed at much lower levels compared to GLUT1 and GLUT3 in specific cell types and/or in specialized brain regions. For example, the insulin-sensitive GLUT4 is present in astrocytes, neurons, and endothelial cells (Kobayashi *et al*, 1996), and GLUT8 is located in the cytoplasm of neurons mostly in the hippocampus, amygdala, cerebellum, and hypothalamus (Reagan *et al*, 2001; Ibberson *et al*, 2002). GLUT2 is expressed in a subset of glutamatergic neurons in the hypothalamus and has recently been identified as a brain glucose sensor that triggers sugar seeking behavior under hypoglycemic conditions (Labouèbe *et al*, 2016). GLUT6 has been detected in neurons (Doege *et al*, 2000) and GLUT7 in astrocytes (Maher *et al*, 1994). In microglia, the most abundant transporter is GLUT5 which has a very low affinity for glucose and mostly fluxes fructose (Mantych *et al*, 1993).

The predominant roles of GLUT1 and GLUT3 in efficiently moving glucose from the blood across the BBB and into neurons have been clearly demonstrated in studies of gene knockout mice. GLUT1$^{+/-}$ mice have a reduced brain size and abnormal motor behavior (Wang *et al*, 2006), reminiscent of the phenotypes observed in human GLUT1 deficiency syndrome patients (De Vivo *et al*, 1991). GLUT3$^{+/-}$ mice exhibit abnormal spatial learning and working memory, in addition to perturbed social behavior (Zhao *et al*, 2010). GLUT8-null homozygous mice have modest reductions of hippocampus volume (Membrez *et al*, 2006), and locomotion (Schmidt *et al*, 2008). In addition to facilitative glucose transporters, the endothelial cells of the BBB also express sodium-dependent unidirectional transporters that are members of the solute carrier 5 family (SGLT) 1 and 2. These carriers couple the sodium electrochemical gradient to transfer glucose against its concentration gradient across the membrane. Their role under physiological conditions is not clear, but they appear to be functional during conditions of oxygen/glucose deprivation or ischemia (Yu *et al*, 2010). Because GLUT1 and GLUT3 transporters are constitutively located on the plasma membrane and do not respond to stimulation with insulin, brain glucose uptake is believed to be insulin-independent.

There are 14 MCTs with particular affinities for one or more substrates. MCTs 1–4 are expressed in cells of the BBB (Fig 1) and are responsible for bidirectional passive proton-linked transport of lactate, ketone bodies (i.e., acetoacetate and 3-β-hydroxybutyrate), and pyruvate. MCT1 has high affinity for pyruvate and also transports lactate and ketone bodies; it is present in endothelial cells (Gerhart *et al*, 1997), astrocytes (Bröer *et al*, 1997), oligodendrocytes (Lee *et al*, 2012), and microglia (Moreira *et al*, 2009). Only a few specific subsets of hypothalamic neurons express MCT1
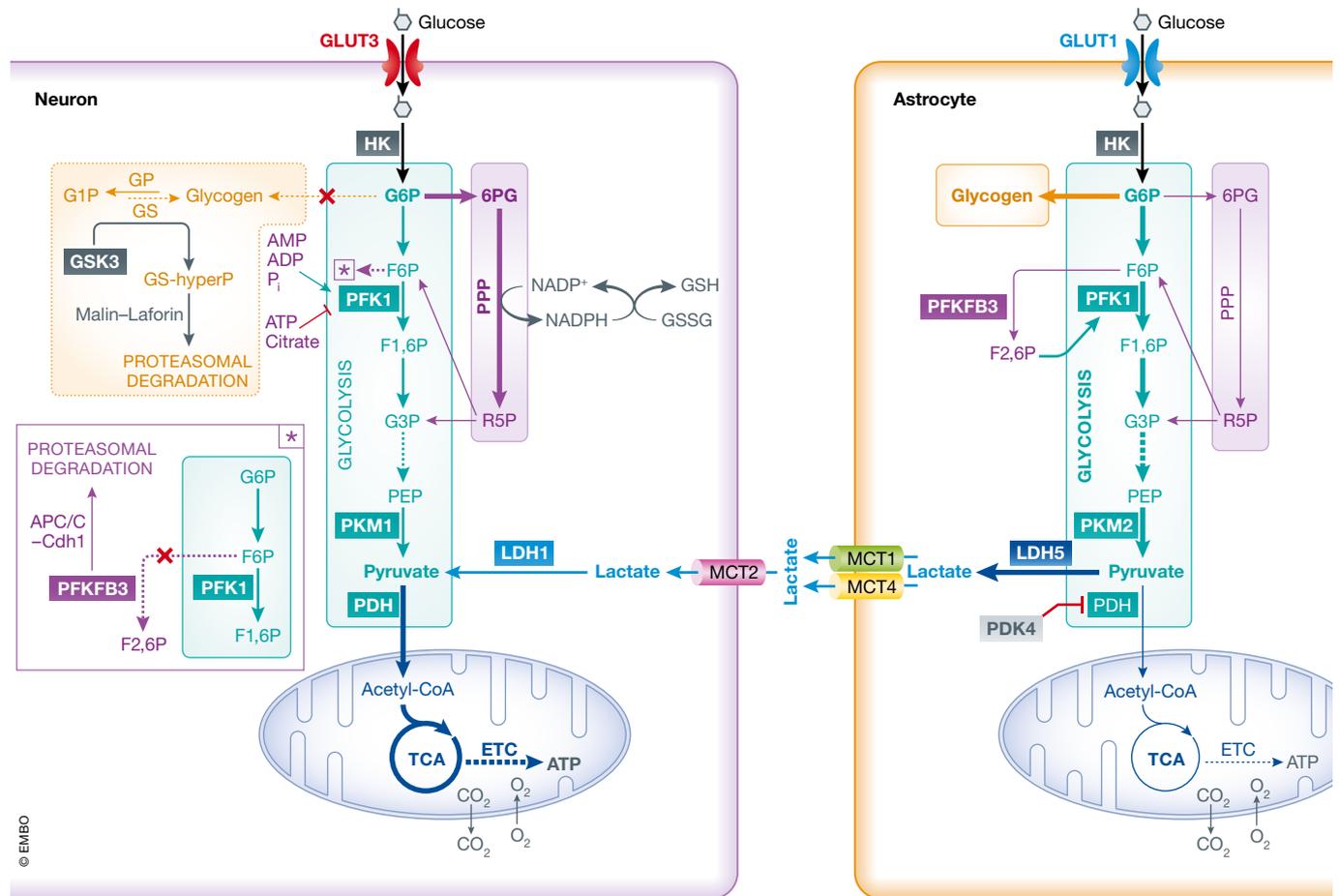
(Carneiro *et al*, 2016). MCT2 is the major transporter in neurons (Pierre *et al*, 2002), and compared to MCT1 has an overall higher affinity for all the substrates (Bröer *et al*, 1997). MCT2 is concentrated in dendritic spines where it associates with postsynaptic density proteins, as well as the AMPA receptor subunit Glur2 (Bergensen *et al*, 2005). MCT3 transports lactate and is only expressed in the retinal epithelium and the choroid plexus epithelium (Philp *et al*, 2001). MCT4 carries lactate and is exclusively expressed in astrocytes (Pellerin *et al*, 2005). The specific cell distribution patterns and substrate affinities of MCTs in the brain suggest that MCTs play fundamental roles in shuttling energy substrates among different brain cell types.

## Glucose metabolic pathways in neurons and astrocytes

The metabolic fate of glucose in the brain depends upon the cell type and the selective expression of metabolic enzymes. Neurons are predominantly oxidative, while astrocytes are mostly glycolytic (Hiden & Lange, 1962; Hamberger & Hyden, 1963). In addition to the production of adenosine-5′-triphosphate (ATP), glucose is also used to generate metabolic intermediates for the synthesis of fatty acids and other lipids required for membrane and myelin synthesis (Ramsey *et al*, 1971; Jones *et al*, 1975); amino acids for protein synthesis and neurotransmitter production (Vrba *et al*, 1962; Gaitonde & Richter, 1966); and 5-carbon sugars for the synthesis of nucleotides (Gaitonde *et al*, 1983); and to produce glycogen in astrocytes.

In neurons, each molecule of glucose is oxidized via glycolysis, the pentose phosphate pathway (PPP), the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation, with the production of carbon dioxide, water, and 30–36 molecules of ATP depending upon the rates of proton leakage in the mitochondria (Fig 2). The glycolytic process metabolizes glucose to pyruvate, which can be actively transported into the mitochondria where it is converted to acetyl coenzyme A (acetyl-CoA). Acetyl-CoA is complexed with citrate which undergoes a series of regenerative enzymatic reactions producing reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2) in the TCA cycle. The NADH and FADH2 produced during glycolysis and the TCA cycle are subsequently re-oxidized in the electron transport chain (ETC). ETC. utilizes the energy produced by the transfer of electrons through its various complexes to transport protons across the inner mitochondrial membrane into the intermembrane space. The flux of protons back into the mitochondrial matrix is mediated by the enzyme ATP synthase, which utilizes the energy to generate ATP from ADP. Once inside the cell, glucose is irreversibly converted to glucose-6-phosphate (G6P) by hexokinase (HK). G6P can then be further metabolized via glycolysis or the pentose phosphate pathway (PPP) or can be used for glycogen synthesis.

Although negligible compared to peripheral energy deposits, glycogen represents the largest energy reserve in the brain. Glycogen metabolism is regulated by two key enzymes, glycogen synthase (GS) and glycogen phosphorylase (GP). The reason why glycogen is produced and stored exclusively in astrocytes (Magistretti *et al*, 1993) is because in neurons GS is maintained in a constitutively inactive state by hyperphosphorylation via glycogen synthase kinase 3 (GSK3), and subsequent ubiquitin-dependent proteasomal

**Figure 2. Metabolic pathways of glucose utilization in neurons and astrocytes.**

In neurons after entering the cell via glucose transporter 3 (GLUT3), glucose is phosphorylated by hexokinase (HK) to glucose-6-phosphate (G6P), which is subsequently routed in the glycolytic pathway and the pentose phosphate pathway (PPP). The end product of glycolysis is pyruvate that enters the mitochondria where it is metabolized through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation in the electron transport chain (ETC.), generating adenosine-5'-triphosphate (ATP) and carbon dioxide ($CO_2$) while consuming oxygen ($O_2$). Pyruvate can also be generated from lactate dehydrogenase 1 (LDH1)-dependent conversion of lactate. In the PPP, G6P is converted to 6-phosphogluconate (6PG) that is transformed in ribulose-5-phosphate (R5P), with the concomitant production of reduced nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is utilized to regenerate oxidized antioxidants such as glutathione (GSH) and thioredoxin. Neurons are not able to store glucose in the form of glycogen due to constitutive degradation of glycogen synthase (GS) via glycogen synthase kinase 3 (GSK3) phosphorylation, and subsequent ubiquitin-dependent proteasomal digestion mediated by the malin–laforin complex. In astrocytes, glucose is imported trough glucose transporter 1 (GLUT1) and preferentially stored as glycogen, or metabolized via glycolysis. The pyruvate generated is converted to lactate thanks to the expression of lactate dehydrogenase 5 (LDH5), and pyruvate dehydrogenase kinase 4 (PDK4)-dependent inhibition of pyruvate dehydrogenase (PDH). The presence of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (Pfkfb3) allows astrocytes to generate fructose-2,6-bisphosphate (F2,6P) that acts as an allosteric modulator of PKF1 boosting glycolysis. Abbreviations are as follows: F6P, fructose-6-phosphate; PKF1, phosphofructokinase 1; F1,6P, fructose-1,6-diphosphate; G3P, glyceraldehyde-3-phosphate; Mit, mitochondrion; PEP, phosphoenolpyruvate; PKM1, pyruvate kinase M1; PKM2, pyruvate kinase M2; G1P, glucose-1-phosphate; GP, glycogen phosphorylase; APC/C-Cdh1, anaphase-promoting complex C/cytosome-Cdh1; MCT, monocarboxylic acid transporter.

degradation mediated by the malin–laforin complex (Vilchez *et al*, 2007) (Fig 2 inset). A similar degradation process also occurs for protein targeting to glycogen (PTG), the regulatory subunit of protein phosphatase 1 that is able to activate GS by dephosphorylation, thus preventing the accumulation of glycogen in neurons (Vilchez *et al*, 2007). The preferred route of G6P metabolism in neurons is the PPP, an anabolic metabolic pathway that converts G6P into 5-carbon sugars utilized for the biosynthesis of nucleotides with generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH). Based on the cellular requirements, a portion of ribulose-5-phosphate (R5P) can be converted back into the glycolytic intermediates fructose-6-phosphate (F6P) and glyceraldehyde-3-phosphate (G3P). In neurons, this conversion is minimal, and

NADPH is utilized as a cofactor for synthesis of fatty acids and myelin, for neurotransmitter turnover, and to maintain redox homeostasis. The maintenance of neuronal antioxidant potential relies on the use of NADPH as cofactor to regenerate reduced glutathione (GSH) (Fig 2) and thioredoxin by glutathione and thioredoxin reductase, respectively.

The balance between glycolysis and PPP rates in neurons is very important, and diversion of glucose utilization toward exclusive glycolysis can result in decreased availability of NADPH, increased oxidative stress and cell death (Herrero-Mendez *et al*, 2009). The preferential use of G6P in the PPP in neurons, as well as their inability to up-regulate glycolysis, is due to the selective expression of enzymes favoring such a metabolic route coupled with the absence

of specific glycolysis modulators. In addition to the HK step mentioned above, the glycolytic flux is regulated by phosphofructokinase 1 (PKF1) and pyruvate kinase (PK) (Lowry & Passonneau, 1964). PKF1 catalyzes the phosphorylation of F6P to fructose-1,6-bisphosphate (F1,6P). Its activity is inhibited by metabolites associated with a high energy state (i.e., ATP, citrate) and enhanced by those resulting from high metabolic activity (i.e., ADP, AMP, phosphate), as well as by fructose-2, 6-bisphosphate (F2,6P). It was recently shown that neurons lack the enzyme responsible for the generation of F2,6P, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (Pfkfb3) due to continuous ubiquitin-dependent proteasomal degradation (Herrero-Mendez *et al*, 2009) (Fig 2 inset). While neurons lack Pfkfb3, they express pyruvate kinase M1 (PKM1) (Zhang *et al*, 2014), a constitutively active enzyme with a very high affinity for phosphoenolpyruvate (PEP), thereby favoring the generation of high levels of pyruvate. This, in association with the expression in neurons of the low-pyruvate-affinity isoform of lactate dehydrogenase (LDH1), prevents pyruvate conversion to lactate and favors its entrance into the TCA cycle (Fig 2). Further metabolic bias toward the TCA cycle results from the lower levels of expression in neurons of pyruvate dehydrogenase kinase 4 (PDK4) which controls the activity of pyruvate dehydrogenase (PDH), and therefore the decarboxylation of pyruvate to acetyl-CoA.
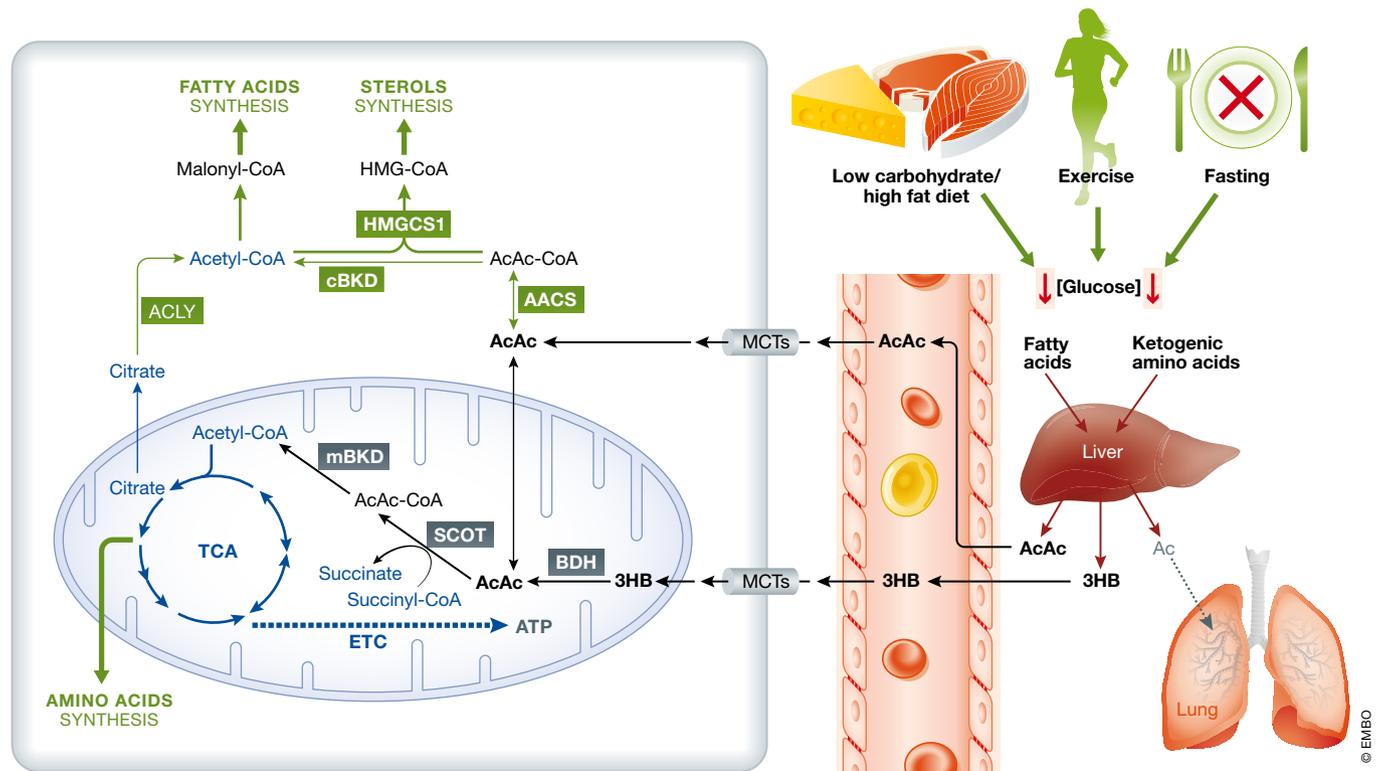
Astrocyte utilization of glucose is complementary to that of neurons. A portion of G6P is channeled into glycogen synthesis and PPP, but its predominant metabolism occurs via glycolysis with production of lactate and very low rates of mitochondrial oxidation (Itoh *et al*, 2003). This metabolic phenotype of astrocytes is the result of their unique expression of various enzymes and transporters. In contrast to neurons, astrocytes express very high levels of Pfkfb3 which favors glycolysis via allosteric activation of PFK by F2,6P (Herrero-Mendez *et al*, 2009). Furthermore, under basal conditions the levels of PDH phosphorylation are high (Halim *et al*, 2010) thanks to elevated expression of PDK4 (Zhang *et al*, 2014), efficiently limiting the conversion of pyruvate to acetyl-CoA (Fig 2). Astrocytes also express low levels of mitochondrial aspartate/glutamate carrier (AGC) decreasing the import of reduced equivalents (NADH) from the cytosol (Ramos *et al*, 2003). The expression of LDH5, which has a high affinity for pyruvate, rather than LDH1, ensures its conversion to lactate with concomitant oxidation of NADH to NAD$^+$ thus maintaining high rates of NAD$^+$/NADH that further favor aerobic glycolysis. The presence of PKM2 instead of PKM1 also enables astrocytes to easily up-regulate the rate of glycolysis to increase the production of lactate, if needed.

## Monocarboxylic acid metabolism

Over the past few decades, it has become clear that in addition to glucose, neurons can utilize alternate fuels, namely lactate and ketone bodies. Seminal *in vitro* studies of McIlwain in the 1950s demonstrated that in human cerebral cortex slices, both pyruvate and lactate could replace glucose to support respiration under basal conditions, and during electrical stimulation (McIlwain, 1953). Neurons *in vitro* have a preference for lactate over glucose when both substrates are provided (Itoh *et al*, 2003; Bouzier-Sore *et al*, 2006). However, clear evidence for a role for lactate in brain metabolism *in vivo* has been obtained only recently. The cell type-specific distribution of MCTs, and the intrinsic

metabolic properties of astrocytes and neurons, led to the hypothesis that lactate is shuttled between the two cell types to support neuronal metabolism (Pellerin & Magistretti, 1994) (Fig 2). Such metabolic coupling of astrocytes and neurons is supported by optogenetic studies showing an *in vivo* lactate gradient from astrocytes to neurons (Mächler *et al*, 2016). Furthermore, pharmacological inhibition or genetic targeting of MCT2 irreversibly impairs long-term memory in mice (Newman *et al*, 2011; Suzuki *et al*, 2011). Long-term memory impairment can be reversed by intrahippocampal administration of lactate, but not glucose, in MCT4-deficient mice (Suzuki *et al*, 2011). Targeted disruption of MCT1 and MCT2 impairs memory consolidation/reconsolidation in cocaine-induced conditioned place preference and self-administration (Zhang *et al*, 2016). Heterozygous MCT1 knockout mice have impaired inhibitory avoidance memory (Tadi *et al*, 2015). Altogether, these results strongly suggest that the neuronal uptake of lactate is important for the establishment of long-term memories. The overall contribution of lactate to brain metabolism varies with its availability. Studies in conscious humans have shown that under resting conditions, lactate uptake by the brain provides about 8% of its energy requirements (van de Hall *et al*, 2009). The percentage increases up to 20% under conditions of high plasma levels of lactate such as during intense exercise (van de Hall *et al*, 2009). Furthermore, at various exercise intensities the metabolism of lactate in the brain is higher in trained subjects compared to controls (Kemppainen *et al*, 2005). This suggests the possibility of adaptive mechanisms allowing the brain to respond to changes in substrate availability. Notably, in rodents acute exercise induces brain region-specific up-regulation of MCTs (Takimoto & Hamada, 2014) and enhances oxidative capacity of cells in the motor cortex (McCloskey *et al*, 2001).

In addition to lactate, brain cells can metabolize the ketone bodies 3-β-hydroxybutyrate (3HB) and acetoacetate (AcAc). Ketones are recognized as an essential energy substrate for the brain during development, delivering up to 30–70% of its energy requirement (Nehlig, 2004); compared to the adult, the immature brain has high activity and levels of MCTs (Gerhart *et al*, 1997; Pellerin *et al*, 1998). Also, in rodents the brain activity of enzymes involved in ketone metabolism increases steadily through the suckling period, and then drops after weaning (Page *et al*, 1971; Middleton, 1973). The high level of ketone utilization during development is necessary to support energy metabolism, as well as the amino acid and lipid biosynthesis required for brain maturation (De Vivo *et al*, 1975; Yeh *et al*, 1977). In rats, incorporation of 3HB into amino acids is two- to threefold higher than glucose during the nursing period (De Vivo *et al*, 1975). Similarly, lipid synthesis, fundamental for myelination, is preferentially sustained by the use of ketones as precursors during the suckling period (Yeh *et al*, 1977). In addition to anabolic functions, the oxidation of ketones is also important during the early postnatal period (Fig 3). Mice with succinyl-CoA-3-oxoacid CoA transferase (SCOT) deficiency have normal prenatal development, but right after birth they become ketotic, with reduced plasma levels of glucose and lactate (Cotter *et al*, 2011). In the adult brain, the utilization of ketones is greatly reduced in the fed state, but can increase considerably under conditions of limited glucose availability as occurs during fasting, starvation, low carbohydrate/high fat intake, and prolonged or intense exercise bouts (Fig 3). Under such conditions, the liver generates ketone bodies from fatty acid and ketogenic amino acid oxidation. Among brain cells, only astrocytes

**Figure 3. Schematic of ketone body oxidative and anabolic utilization in brain.**
Under conditions of reduced glucose availability such as low carbohydrates/high-fat diet, exercise, or fasting, the liver utilizes fatty acids mobilized from adipose tissue and ketogenic amino acids (i.e. leucine, lysine, phenylalanine, isoleucine, tryptophan, tyrosine, threonine) to produce acetoacetate (AcAc), 3-β-hydroxybutyrate (3HB), and acetone (Ac). Acetone is considered to have negligible metabolic significance and rapidly eliminated through urine and lungs. Ketone bodies cross the blood–brain barrier via monocarboxylate transporters (MCTs). Inside the cells, they may be directed toward anabolic or oxidative pathways depending on the developmental stage and cellular requirements. In the anabolic pathway taking place in the cytosol, acetoacetate is converted into acetoacetyl-CoA (AcAc-CoA) by acetoacetyl-CoA synthase (AACS). AcAc-CoA can be condensed with acetyl-CoA to generate the precursor of sterols, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) by 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1). The acetyl-CoA produced from AcAc-CoA by cytosolic β-ketothiolase (cBKD), or from citrate by ATP-citrate lyase (ACLY), can be transformed in malonyl-CoA for fatty acid synthesis. Amino acid can be synthesized utilizing intermediates of the TCA cycle. Oxidation of ketones occurs in the mitochondria (Mit) where AcAc directly taken up or generated from 3HB by 3-β-hydroxybutyrate dehydrogenase (BDH) is transformed into acetyl-CoA via succinyl-CoA-3-oxoacid CoA transferase (SCOT), and mitochondrial β-ketothiolase (mBKD). The complete oxidation of AcAc yields 23 molecules of ATP, while 3HB generates 26 molecules of ATP.

are equipped to generate ketone bodies from fatty acid β-oxidation (Edmond, 1992), but the rates of fatty acid transport are very low compared to those in the liver. All brain cell types are, however, able to uptake ketones, mostly 3HB and AcAc, via MCTs; the ketones are then metabolized to acetyl-CoA to support the cell energy and biosynthetic needs (Fig 3). In adults, the activity of ketone-metabolizing enzymes is high enough that it would easily permit a complete switch from glucose to ketones to support brain energy needs (Krebs *et al*, 1971). Because ketones are never produced at saturating concentrations, the brain rate of utilization is strictly regulated by their blood concentration (Sokoloff, 1973). Indeed, during ketosis the brain glucose utilization has been shown to decrease by about 10% for each millimole of plasma ketones (LaManna *et al*, 2009). During medically supervised starvation of obese patients, ketones provide up to 60% of the energy utilized by the brain (Owen *et al*, 1967).
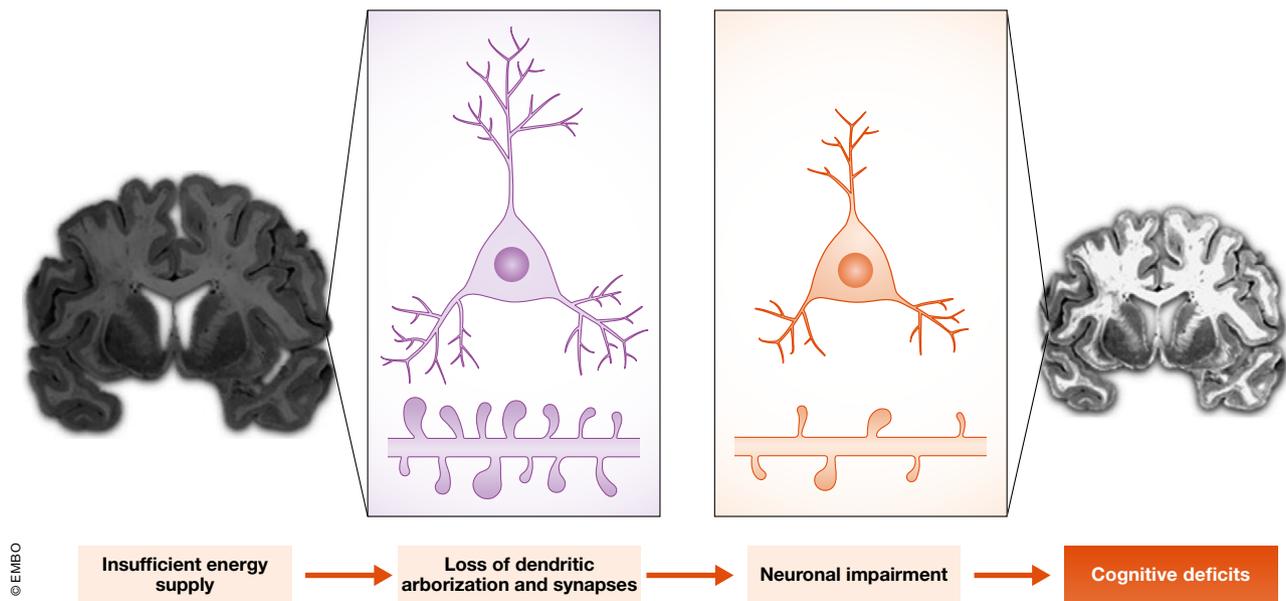
## Brain metabolism in aging

About 20–40% of healthy people between 60 and 78 years old experience discernable decrements in cognitive performance in several

domains including working, spatial, and episodic memory, and processing speed (Mattay *et al*, 2006; Glisky, 2007). Semantic memory and knowledge show no decline until very late in life, while emotional, automatic, and autobiographic memory are not impacted by aging (Hedden & Gabrieli, 2004). These cognitive alterations correlate with neuroanatomical changes, including an age-dependent decrease in gray matter volume not related to pathological conditions (Resnick *et al*, 2003). This thinning of the cortex is not uniform, with some regions such as the prefrontal cortex, medial temporal lobe, and hippocampus being more impacted by aging; other regions, such as the cingulate gyrus and the occipital cortex, remain relatively unaffected (Sowell *et al*, 2003). The loss of gray matter does not appear to be the result of neuronal loss, but instead involves a gradual decline of dendritic arborization and synapse numbers (Nakamura *et al*, 1985; Page *et al*, 2002). Aging also reduces white matter density and increases the number of white matter lesions (Guttmann *et al*, 1998), mostly in the prefrontal cortex and the anterior corpus callosum (O'Sullivan *et al*, 2001). By altering the interactions between prefrontal cortex and structures such as the hippocampus and striatum, white matter abnormalities result in poor performance in tasks requiring

processing speed and immediate or delayed memory (Glisky, 2007). The brain undergoes a gradual decline in energy utilization during aging (Hoyer, 1982a). Functional neuroimaging studies have shown that glucose hypometabolism and mitochondrial dysfunction are early indicators of age-related functional changes during normal brain aging (De Leon *et al*, 1983; Small *et al*, 2000: Mosconi *et al*, 2008). Positron emission tomography analyses of fluorodeoxyglucose uptake into brain cells in human subjects of different ages have revealed age-related decrements in glucose utilization in several different brain regions (Zuendorf *et al*, 2003). Regional analyses revealed age-related metabolic declines in temporal, parietal, and cerebral cortex, with a particularly rapid decline in the frontal cortex (Kuhl *et al*, 1984a). In rats, age-dependent reduction in brain cell energy metabolism (glucose utilization) in the hippocampus and prefrontal cortex is associated with impaired performance in learning and memory tests (Gage *et al*, 1984). The current resolution of functional brain imaging is insufficient to establish a temporal sequence between hypometabolism and neuroanatomical changes. It is however tempting to speculate that the increased mitochondrial capacity and oxidative metabolism that appear to have driven expansion of the cerebral cortex during human evolution (Grossman *et al*, 2001, 2004; Cáceres *et al*, 2003; Uddin *et al*, 2004; Haygood *et al*, 2007; Pontzer *et al*, 2016) may have also rendered the brain susceptible to cognitive decline in aging. Synaptic spines are the site of neurotransmission, and thus fundamental for forms of synaptic plasticity such as long-term potentiation and long-term depression. Excitatory synapses are subcellular sites with very high rates of energy consumption as large amounts of ATP are required to support the activities of neurotransmitter transporters, and

membrane $Na^+$ and $Ca^{2+}$ pumps that rapidly restore gradients of these ions after synapse activation (Attwell & Laughlin, 2001; Alle *et al*, 2009; Harris *et al*, 2012; Rangaraju *et al*, 2014). Accordingly, when the ability of neurons to generate sufficient ATP is compromised (e.g. aging, ischemia, and neurodegenerative disorders), synapses are vulnerable to dysfunction and degeneration (Harris *et al*, 2012) (Fig 4). Many factors likely contribute to the age-dependent brain hypometabolism. Clinical studies have shown a negative correlation between cerebral blood flow and age (Schultz *et al*, 1999; Fabiani *et al*, 2014). In addition, the permeabilities of the BBB and BCSFB are greater in older compared to younger individuals (Rosenberg, 2012). Brain hypoperfusion and loss of BBB integrity can result in diminished import of nutrients, and/or removal of toxins. Furthermore, a compromised BBB allows the parenchymal accumulation of blood-derived proteins (e.g., fibrinogen, immunoglobulins, albumin, thrombin, hemoglobin), and immune cells which can cause inflammation (Zlokovic, 2011). Studies of humans and animals have clearly shown reduced expression of glucose transporters in the brain with aging (Ding *et al*, 2013), as well as changes in the expression of key enzymes involved in glycolysis and oxidative phosphorylation (Meier-Ruge *et al*, 1980; Ulfert *et al*, 1982; Bowling *et al*, 1993). Studies of mice have shown that levels of ATP are reduced in white matter during aging, in correlation with ultrastructural alterations in mitochondria, and a reduced association of mitochondria with endoplasmic reticulum (Stahon *et al*, 2016). NAD levels are critical for mitochondrial function and ATP production (Bai *et al*, 2011; Pittelli *et al*, 2011). An increase in the levels of NADH, with decreased total NAD and $NAD^+$ levels, has been shown in human brain during normal aging (Zhu *et al*,



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| Insufficient energy supply | → | Loss of dendritic arborization and synapses | → | Neuronal impairment | → | Cognitive deficits |

**Figure 4.  Age-related cognitive decline as a result of neuroanatomical changes driven by decreased energy supply.**
The neuronal firing patterns that play an important role in normal cognitive processing rely on the neurons' ability to exchange information across synapses. Compared to young neurons (left), aging neurons (right) are characterized by a significant reduction of the dendritic tree, as well as changes in spines size, shape, density, and turnover. Age-dependent diminished nutrient import, as well as changes in glycolytic and oxidative phosphorylation efficiency, results in decreased ATP production. The reduced energy availability impairs the ability of aging neurons to preserve synapse homeostasis. The resulting structural changes lead to perturbations in neuronal function, and impairments in memory and learning.

2015). Experimental evidence supporting a causative role for hypometabolism in cognitive impairment comes from recent studies showing that mice with reduced GLUT1 levels display an age-dependent decrease in cerebral capillary density, reduced cerebral blood flow and glucose uptake, and increased BBB leakage (Winkler *et al*, 2015). These metabolic and vascular alterations precede dendritic spine loss in CA1 hippocampal neurons, and associated behavioral impairments (Winkler *et al*, 2015).

Although we tend to think of age-related metabolic decline as a "malfunction" of the brain, it is possible it represents an evolutionary adaptation. Human physiology is the result of millions of years of evolution under challenging environmental conditions and limited food availability. The drastic rapid changes in the lifestyle of modern human societies have led to an increased incidence of metabolic disorders (i.e., diabetes, obesity, metabolic syndrome, hyperlipidemia) that may be explained from an evolutionary perspective by the so-called thrifty genotype hypothesis (Neel, 1962). The positive natural selection of genes that decreased metabolic rates while maintaining cognitive efficiency would have allowed individuals to survive times of limited food availability, but such genes may be detrimental when food is abundant (Nesse & Williams, 1998). Indeed, as described in the section on "healthy habits for a healthy brain" below, the fundamental bioenergetic challenges that were a driving force for brain evolution (i.e., fasting/starvation, and physical mental exertion) are exactly those that engage adaptive signaling pathways that promote optimal brain health, and resistance to brain injury and neurodegenerative disorders in modern humans.

## Altered metabolism in neurodegenerative disorders

Neurodegenerative brain disorders are a broad spectrum of fatal conditions characterized by progressive neuronal dystrophic structural changes and loss of function. AD and PD are the most common neurodegenerative disorders, with ALS and HD being less prevalent. These diseases share several mechanistic similarities at the subcellular levels including atypical protein aggregation, failure of protein degradation pathways, impaired axonal transport, mitochondrial dysfunction, and programmed cell death (Mattson *et al*, 1999). Increasing evidence suggests that metabolic alterations strongly influence the initiation and progression of neurodegenerative disorders. Positron emission tomography imaging studies have documented reduced glucose utilization in brain regions affected in patients with AD, PD, ALS, and HD (Hoyer, 1982b). Epidemiological studies indicate that diabetes, obesity, high blood pressure, and atherosclerosis are all risk factors for dementia (Kivipelto *et al*, 2006). Because each of the latter disorders involves impaired energy metabolism, and/or adverse changes in the cerebral vasculature, reduced energy availability to neurons in the brain may contribute to increased vulnerability of the brain to cognitive impairment and dementia. Considerable evidence suggests that the BBB integrity is compromised in AD patients (Glenner, 1979, 1985; Powers *et al*, 1981; Zipser *et al*, 2007; Zlokovic, 2011). In patients with mild cognitive impairment, or early stages of AD, the age-dependent changes of the BBB permeability are accelerated compared to neurological normal individuals (Montagne *et al*, 2015; van de Haar *et al*, 2016). This suggests that neurovascular dysfunction may be an early occurrence in the pathogenesis of AD. Additionally, changes in

nutrient transporter and metabolic enzyme expression levels, and/or activities, have been reported in AD. For example, levels of GLUT1 and GLUT3 are reduced in the brains of AD patients (Simpson *et al*, 1994; Harr *et al*, 1995) and correlate with diminished brain glucose uptake and subsequent cognitive decline (Landau *et al*, 2010). A precipitous loss of activities of phosphofructokinase (PFK), phosphoglycerate mutase, aldolase, glucose-6-phosphate isomerase, and lactate dehydrogenase occurs in brain tissue samples of AD patients compared to age-matched controls (Iwangoff *et al*, 1980). The activities of pyruvate dehydrogenase complex (Perry *et al*, 1980; Sorbi *et al*, 1983), cytochrome oxidase (Kish *et al*, 1992), and α-ketoglutarate dehydrogenase complex (Gibson *et al*, 1988) are also decreased in the brains of AD patients. In mouse models of AD, reduction of GLUT1 levels worsens amyloid pathology, neurodegeneration, and cognitive function (Winkler *et al*, 2015), while ketone and nicotinamide supplementation reduces Aβ and p-Tau pathologies and improves behavioral outcomes (Kashiwaya *et al*, 2013; Liu *et al*, 2013).

Glucose hypometabolism in the brains of patients with PD has been documented using magnetic resonance imaging and positron emission tomography methods (Kuhl *et al*, 1984b; Borghammer *et al*, 2010). Decreased levels of the PPP key enzymes glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase occur at early stages in the putamen and cerebellum of PD patients (Dunn *et al*, 2014). The glycolytic enzyme glucose-6-phosphate isomerase that catalyzes the conversion of G6P to F6P has been recently identified as a conserved modifier of dopamine metabolism, protein aggregation, and neurodegeneration in *Caenorhabditis elegans*, *Drosophila melanogaster,* and murine neurons (Knight *et al*, 2014). Furthermore, it was recently shown that plasma levels of α-synuclein regulate glucose uptake in adipocytes (Rodriguez-Araujo *et al*, 2013). Importantly, mutations in multiple genes that cause early-onset inherited forms of PD (α-synuclein, Parkin, PINK1, LRRK2, DJ-1) result in mitochondrial dysfunction (Pickrell & Youle, 2015). Moreover, interventions that bolster mitochondrial bioenergetics can ameliorate neuropathology and motor deficits in animal models of PD (Tieu *et al*, 2003; Yang *et al*, 2009).

ALS patients are hypercatabolic and have increased energy expenditure at rest (Desport *et al*, 2001; Funalot *et al*, 2009). Glucose intolerance (Pradat *et al*, 2010), insulin resistance (Reyes *et al*, 1984), and hyperlipidemia (Dupuis *et al*, 2008) have all been reported in ALS patients. At a cellular level, ALS patients exhibit altered endothelial transporter proteins (Niebroj-Dobosz *et al*, 2010), astrocyte end feet degeneration (Miyazaki *et al*, 2011), increased permeability of the BBB/BCSFB resulting in abnormal levels of blood proteins in the CSF (Leonardi *et al*, 1984; Annunziata & Volpi, 1985), and IgG and complement deposits in the spinal cord and motor cortex (Donnenfeld *et al*, 1984). In superoxide dismutase 1 mutant mice and rats, BBB/BCSFB breakdown occurs prior to motor neuron degeneration and inflammation (Garbuzova-Davis *et al*, 2007; Zhong *et al*, 2008; Nicaise *et al*, 2009; Miyazaki *et al*, 2011). Collectively, these findings strongly suggest that altered metabolic homeostasis plays a major role in ALS insurgence and progression.

HD is a genetic disorder caused by trinucleotide repeat (CAG) expansions in the *huntingtin* gene that causes early degeneration of medium spiny neurons in the striatum, resulting in continuous involuntary motor movements. Striatal metabolism is decreased

well prior to atrophy, and the progression of the disease is more strongly correlated with glucose hypometabolism than the number of CAG repeats (Mazziotta *et al*, 1987; Grafton *et al*, 1992; Antonini *et al*, 1996). HD patients at early stages of striatum degeneration have normal total levels of glucose transporters (Gamberino & Brennan, 1994), but diminished glucose uptake in the brain (Kuhl *et al*, 1982; Ciarmiello *et al*, 2006). Immunohistochemical analysis utilizing antibody raised against an extracellular epitope of GLUT3 recently showed a diminished cell surface expression in the striatum and cortex of HD mice compared to wild-type mice (McClory *et al*, 2014). The diminished ability of neurons to uptake glucose can explain the characteristic hypometabolism that precedes neuronal loss. Interestingly, higher copy numbers of SLC2A3 (*Glut3*) delay the age of onset in HD patients (Vittori *et al*, 2014). In fruit fly models of HD, overexpression of GLUT3, PFK, and G6PD protects against HD phenotypes and increases survival (Vittori *et al*, 2014; Besson *et al*, 2015). Evidence suggests that the lysine deacetylases sirtuin 1 (SIRT1) and sirtuin 3 (SIRT3) can preserve mitochondrial function and protect striatal neurons against dysfunction and degeneration (Jeong *et al*, 2011; Jiang *et al*, 2011; Fu *et al*, 2012). Agents that increase SIRT1 activity (e.g., SRT2104) attenuate degeneration of striatal neurons and improve functional outcome in huntingtin mutant mice (Jiang *et al*, 2014). It was also reported that an agent that increases SIRT3 levels (viniferin) protects neural cells against the toxicity of mutant huntingtin (Fu *et al*, 2012). Collectively, the emerging data suggest that interventions that bolster neuronal bioenergetics may delay disease onset or slow the progression of HD.

## Healthy habits for a healthy brain

In the not too distant past, our ancestors were regularly challenged to locate and acquire food, while avoiding hazards. Assumedly, individuals whose brains and bodies functioned well/optimally when they were in a fasted state (i.e. when they had to make critical decisions on how to acquire food) had a survival advantage over those whose brains functioned less well in a state of prolonged negative energy balance. This bioenergetic challenge-based hypothesis of brain evolution is supported by empirical evidence that dietary energy restriction/fasting and exercise enhance synaptic plasticity, neurogenesis, and cognitive performance in animals (Mattson, 2015a). For example, running wheel exercise and food restriction each increase dendritic spine density in hippocampal neurons, and the combination of food restriction and running results in even greater increases of spine density (Stranahan *et al*, 2009). Hippocampal neurogenesis is also increased in response to exercise and intermittent fasting (van Praag *et al*, 1999; Lee *et al*, 2002). In *Drosophila melanogaster*, associative learning is performed in fasted animals. One single training is sufficient for the flies to create a "pleasant" association between a certain scent and food. However, sequential multiple trainings are needed to establish an "aversive" association between an odorant and an unpleasant stimulus (electric shock). Fasting before training has been shown to increase long-term memory formation for both "pleasant" and "aversive" experiences (Hirano *et al*, 2013). The duration of fasting appears to be crucial in determining the ability of the brain to prioritize the type of memory to establish/consolidate, based on the available energy

and the most pressing survival need. Short-term fasting results in increased long-term memory (Hirano *et al*, 2013), while protracted fasting prevents "aversive", but not "pleasant", memory formation (Hirano *et al*, 2013; Placais & Preat, 2013). From an evolutionary point of view, it makes sense that starving flies would channel their remaining energy in finding food, ignoring aversive/safety issues. These findings support the idea that intermittent bioenergetic challenges are beneficial for brain performance.

In this section of our article, we highlight the importance of "cerebro-bioenergetic resiliency", the ability of the brain to respond adaptively to bioenergetic challenges, in promoting optimal brain function and resistance to stress, injury, and disease throughout life.

Cells and organisms have evolved the ability to respond adaptively to stress by activating intra- and intercellular signaling pathways that increase their resistance to that specific type of stress, and stress in general. This property of biological systems is fundamental to the concept of "hormesis" which is defined by a biphasic dose–response curve in which low doses induce a stimulatory/beneficial response, while high doses are damaging/toxic (Mattson, 2008, 2015b). Numerous studies have shown that when neurons and the organism in which they reside are subjected to mild metabolic challenges, brain function is improved and resistance to dysfunction and degeneration is increased compared to those that are unchallenged. For example, when cultured neurons are first subjected to a mild metabolic stress (e.g., glutamate, 2-deoxyglucose, or mitochondrial uncoupling agents), they become resistant to subsequent exposure to a high level of stress (e.g., metabolic, excitotoxic, or oxidative stressor) that would have killed them had they not been previously exposed to the mild stress (Marini & Paul, 1992; Lee *et al*, 1999; Liu *et al*, 2015). A classic example of neuroprotection via hormesis *in vivo* is ischemic preconditioning in which rats or mice that are subjected to a mild cerebral ischemia prior to full-blown ischemic stroke exhibit reduced brain cell damage and improved functional outcome compared to animals not subjected to the preconditioning ischemia (Dirnagl *et al*, 2009). Similar to ischemic preconditioning, treatment of mice or rats with 2-deoxyglucose, an analog of glucose that induces cellular metabolic stress, can protect neurons in the brain and improve functional outcome in models of ischemic stroke, excitotoxic seizures, and PD (Duan & Mattson, 1999; Lee *et al*, 1999; Yu & Mattson, 1999).

Lifestyle factors appear to be crucial to determine how healthily our brain will age. Lack of physical activity, excessive calorie intake, and cognitive apathy negatively influence brain aging (Mattson, 2015a) and are predisposing factors for neurodegenerative disorders, such as AD and PD (Mattson, 2015a). Conversely, healthy lifestyle habits including dietary energy restriction, macro- and micronutrient diet composition, physical and mental exercise, and reduction of life stress boost cognitive function (Mattson, 2015a).

Regular aerobic exercise improves executive function, attention processing, speed memory, and learning (Colcombe & Kramer, 2003; Curlik & Shors, 2013; Dresler *et al*, 2013). Neuroimaging studies have shown that exercise targets specific brain areas, namely prefrontal and medial temporal cortices (Berchicci *et al*, 2013), and hippocampus (Kerr *et al*, 2010; Erickson *et al*, 2011, 2014). Elderly people that regularly exercise have increased brain volumes in these critical network areas, compared to sedentary subjects that instead undergo a significant volume decline (Colcombe *et al*, 2006; Erickson *et al*, 2009; Kerr *et al*, 2010). Epidemiological and

interventional studies in humans have shown that exercise can increase one's resistance to anxiety and depression, and possibly AD and PD; exercise lessens symptoms in individuals suffering from these medical conditions (Tordeurs *et al*, 2011; Mattson, 2012; Paillard *et al*, 2015). The results of studies of animal models of anxiety, depression, AD, PD, stroke, and traumatic brain injury have established broad preventative and therapeutic benefits of aerobic exercise (Greenwood & Fleshner, 2008; Yuede *et al*, 2009; Egan *et al*, 2014; Mattson, 2014; Holland & Schmidt, 2015; Ryan & Kelly, 2016). The dysfunction and degeneration of neurons in these different disorders involves impaired neuronal bioenergetics, whose onset and progression varies markedly with regard to severity and duration (insidious in AD and depression, and acute and dramatic in stroke and traumatic brain injury) (Dirnagl *et al*, 2009; Marazziti *et al*, 2011).

A second lifestyle modification that promotes brain health is dietary energy restriction that can be achieved by caloric restriction, or by intermittent fasting (IF). IF can be operationally defined as an eating pattern that includes extended periods of time (e.g. 16 h daily or 24 h twice a week) during which no or very little food is consumed. Most animal studies of IF have used alternate-day fasting (ADF, alternating days of complete fasting and *ad libitum* feeding). Mice or rats maintained on ADF exhibit reduced brain neuropathology and improved functional outcomes in models of stroke, AD, PD, HD, and epilepsy (Bruce-Keller *et al*, 1999; Duan & Mattson, 1999; Halagappa *et al*, 2007).

Age-related cognitive decline can also be counteracted by interventions stimulating brain activity. Engaging in intellectual challenges "exercises" and reinforces neuronal circuitries. Different types of cognitive training have been shown to improve specific cognitive aspects such as learning (Bailey *et al*, 2010), executive functions (Basak *et al*, 2008), and fluid intelligence (Jaeggi *et al*, 2008). In animal studies, environmental enrichment enhances cognitive performance by promoting neurotrophin production, synaptogenesis, dendrite formation, and arborization (van Praag *et al*, 2000; Fratiglioni *et al*, 2004). Neuroimaging studies in humans have shown that memory training increases hippocampal volume (Engvig *et al*, 2012), as well as the thickness of brain areas involved in decision-making processing (i.e., lateral and fusiform orbitofrontal cortex) (Engvig *et al*, 2010).

The importance of exercise, diet, and intellectual and social stimulation in brain aging is emphasized by the results of a recent study showing that changes in diet, exercise, and cognitive training slow cognitive decline in elderly subjects (Ngandu *et al*, 2015). An additional advantage of this healthy lifestyle habit is that their combination appears to provide synergistic benefits (Schneider & Yvon, 2013). For example, adopting an exercise routine together with cognitive training promotes memory performance (Fabre *et al*, 2002; Oswald *et al*, 2006). A recent study in elderly subjects exposed to either moderate aerobic exercise or cognitive training, or to a combination of both, showed a greater improvement in working memory, long-term memory, and reaction times in the cohort exposed to both trainings (Shatil, 2013).
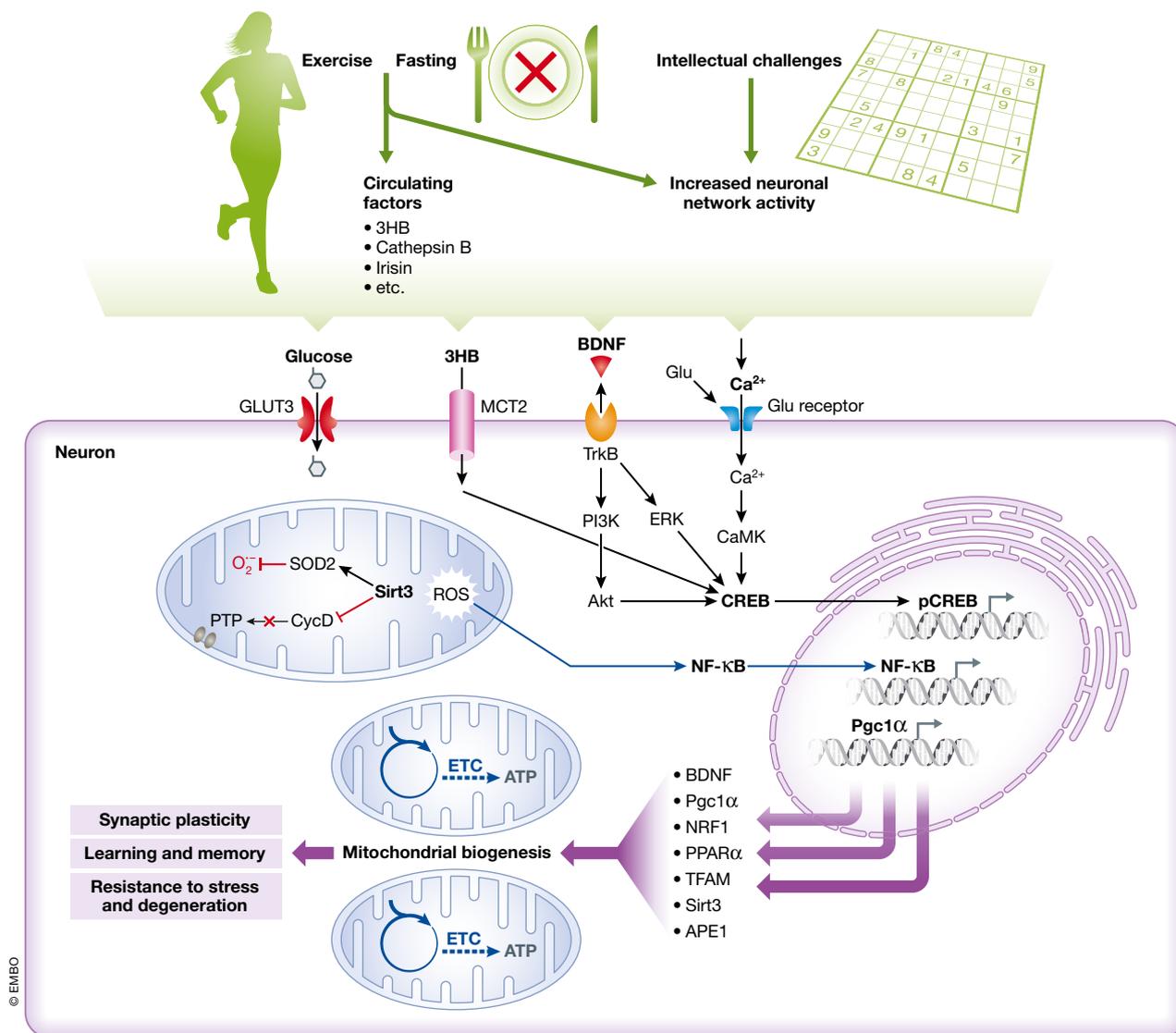
Studies of cell culture and *in vivo* models of bioenergetic stress-induced neuroprotection have begun to elucidate the molecular pathways that bolster neuronal resilience. They include activation of transcription factors such as cAMP response element-binding protein (CREB), nuclear factor κB (NF-κB), and nuclear factor erythroid-derived 2 (NRF2) and induction of the expression of genes encoding proteins that counteract cellular stress at multiple subcellular sites, and by different mechanisms (Mattson, 2012) (Fig 5).

Exercise and IF can up-regulate the expression of various proteins including antioxidant enzymes such as glutathione peroxidase, superoxide dismutase 2 (SOD2), and heme oxygenase 1; anti-apoptotic proteins such as B-cell lymphoma 2 family members; proteins involved in mitochondrial biogenesis and stress resistance; protein chaperones such as heat-shock protein 70 and glucose-regulated protein 78; neurotrophic factors such as brain-derived neurotrophic factor (BDNF); and fibroblast growth factor 2 (Marosi *et al*, 2012; Mattson, 2012). Secreted neurotrophins can in turn activate cytoprotective signaling pathways in adjacent or distant neurons, thereby propagating adaptive cellular stress responses to cells that themselves had not experienced the same metabolic stress (Madinier *et al*, 2013). BDNF may play a significant role in several neuronal activity-mediated effects of exercise and IF on neuronal bioenergetics and stress resistance. BDNF stimulates neuronal energy metabolism by increasing the expression of GLUT3, sodium-dependent amino acid transport and protein synthesis (Burkahalter *et al*, 2003), and ketone utilization via MCT2 (Robinet & Pellerin, 2010). Furthermore, running and BDNF induce the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) to increase mitochondrial biogenesis (Steiner *et al*, 1985; Cheng *et al*, 2012). Interestingly, exercise, moderate levels of glutamate receptor activation, and BDNF also induce the expression of the DNA repair enzyme apurinic/apyrimidinic endonuclease 1 (APE1), which plays a critical role in repairing oxidatively damaged DNA and protecting neurons against metabolic and excitotoxic stress (Yang *et al*, 2010, 2014).

Peripheral signals elicited in response to vigorous exercise and energy restriction/fasting may mediate some of the effects of these bioenergetic challenges on neuroplasticity and stress resistance. In addition to being used by neurons as an energy substrate, the ketone body 3HB also boosts the function, plasticity, and stress resistance of neurons in the brain by inducing the expression of BDNF *in vivo* (Sleiman *et al*, 2016) and *in vitro* (Marosi *et al*, 2016). 3HB mechanisms of action involve the generation of mitochondrial ROS and activation of the transcription factor nuclear factor κB (NF-κB) (Marosi *et al*, 2016) (Fig 5), as well as the inhibition of histone deacetylases (Sleiman *et al*, 2016). Metabolic challenges also trigger peripheral cells to release into the circulation proteins that enter the brain where they elicit adaptive responses in neurons. Levels of cathepsin B, a predominantly lysosomal protein, are increased in skeletal muscle and plasma in response to running in mice (Moon *et al*, 2016). Cathepsin B induces the expression of BDNF in hippocampal neural progenitor cells, and the abilities of running to induce hippocampal neurogenesis and improve learning and memory performance are attenuated in cathepsin B-deficient mice (Moon *et al*, 2016) (Fig 5). Another muscle-derived factor that has been suggested to mediate beneficial effects of exercise on neuroplasticity is irisin, which was reported to increase BDNF levels in the brain (Wrann *et al*, 2013). It is therefore becoming clear that bioenergetic challenges educe a complex array of brain-intrinsic and peripheral signaling mechanisms that coordinate adaptive responses of neurons and neural progenitor cells so as to optimize brain function and protect the brain against injury and disease.

It seems unlikely that drugs can be developed that trigger the complex, evolutionarily conserved mechanisms by which

**Figure 5.  Signaling pathways mediating adaptive responses of neurons to bioenergetic challenges.**
Exercise and fasting affect subcellular processes in neurons by brain-intrinsic mechanisms mediated by increased neuronal network activity, and via signals coming from the periphery including 3-β-hydroxybutyrate (3HB), cathepsin B, and irisin. Intellectual challenges involve increased neuronal network activity and consequent activation of calcium-responsive pathways. BDNF expression is up-regulated by neuronal network activity, as well as 3HB, cathepsin B, and irisin, and BDNF is known to mediate, at least in part, the enhancement of neuronal plasticity and stress resistance by exercise, fasting, and intellectual challenges. Exercise, fasting, and intellectual challenges result in the activation of glutamate receptors at excitatory synapses, $Ca^{2+}$ influx, and activation of $Ca^{2+}$ calmodulin-dependent protein kinase (CaMK) which, in turn, activates the transcription factor cyclic AMP response element-binding protein (CREB). CREB can directly and indirectly modulate mitochondrial biogenesis via expression of several genes (i.e. BDNF, PGC-1α, NRF1, PPARα, and TFAM). Activation of glutamate receptors also induces the expression of the mitochondrial protein sirtuin 3 (SIRT3) which can protect neurons by deacetylating superoxide dismutase 2 (SOD2) to increase its enzymatic activity, and thus reduce mitochondrial oxidative stress, and by inhibiting cyclophilin D (CycD), a protein involved in the formation of membrane permeability transition pores (PTP). 3-β-Hydroxybutyrate (3HB) can induce BDNF expression in neurons via the $Ca^{2+}$–CREB pathway, and a pathway involving mitochondrial reactive oxygen species (ROS) and activation of the transcription factor nuclear factor κB (NF-κB). BDNF is released from neurons and activates the receptor tropomyosin receptor kinase B (TrkB), on the same neuron and adjacent neurons, engaging downstream intracellular pathways which activate transcription factors that induce the expression of genes encoding proteins involved in synaptic plasticity, learning and memory, and neuronal stress resistance. Abbreviations are as follows: Pgc1a, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; NRF1, nuclear regulatory factor 1; PPARα, peroxisome proliferator-activated receptor α; TFAM, mitochondrial transcription factor A; GLUT3, glucose transporter 3; MCT2, monocarboxylic acid transporter 2; PI3K, phosphoinositide 3 kinase; Akt, protein kinase B; ERK, extracellular signal regulated kinase; ETC., electron transport chain; ATP, adenosine-5′-triphosphate; APE1, apurinic/apyrimidinic endonuclease 1.

bioenergetic challenges promote brain health. However, preclinical findings and the results of some clinical trials suggest the potential for pharmacological interventions able to activate some of signaling pathways induced by exercise, fasting, and intellectual challenges. Ketogenic diets, ketone precursors (medium chain triglycerides),

and 3HB have been reported in clinical studies of subjects with cognitive impairment, and AD (Reger *et al*, 2004; Henderson *et al*, 2009; Rebello *et al*, 2015), or PD patients (Vanitallie *et al*, 2005). It is not known whether improvements in cognitive function in the latter studies result from the utilization of 3HB as an energy

substrate and/or the activation of adaptive stress response signaling in neurons. Caffeine, by stimulating $Ca^{2+}$ release from the endoplasmic reticulum and increasing cyclic AMP levels, activates CREB (Connolly & Kingsbury, 2010) and has been shown to enhance memory consolidation in humans (Borota *et al*, 2014). Bitter chemicals that function as natural pesticides/antifeedants activate NRF2 and have demonstrated efficacy in animal models of stroke, AD, and PD; examples include sulforaphane, curcumin, and plumbagin (Son *et al*, 2008, 2010; Mattson, 2015b). Randomized controlled trials of such chemicals in human subjects with neurological disorders remain to be performed. Transcranial direct current or magnetic stimulation modulates BDNF levels (Müller *et al*, 2000) and can improve cognitive performance in healthy subjects and relieve symptoms in patients with depression and AD (Hsu *et al*, 2015; Brunoni *et al*, 2016). Noninvasive brain stimulation is a very exciting area because of its safety and potential for selective activation or inhibition of neuronal circuits in a brain region-specific manner.

Although promising, such approaches should not be considered as substitutes for exercise, energy restriction, and intellectually challenging lifestyles. The adaptive cellular and molecular responses to these physiological challenges are finely tuned and are centrally and peripherally coordinated. They involve metabolic stress that occurs predominantly in excitable cells—skeletal muscle, cardiac myocytes, and neurons—and results in the activation or inhibition of numerous signaling pathways in cells throughout the brain. There is much that remains to be learned about these pathways: how they are activated, their molecular components, and how they interact to promote neuroplasticity and stress resistance. We also have little information concerning the intensities and durations of exercise and energy restriction that promote optimal brain health, nor how such regimens might vary depending upon one's age, metabolic status, or neurological disorders.

## Conclusions and future directions

Emerging findings suggest that optimal brain health is promoted by intermittent bioenergetic challenges that increase activity in neuronal circuits, including intellectual challenges, restriction of energy intake, and physical exercise. Studies of animal and cell culture models have shown that such intermittent bioenergetic challenges activate signaling pathways in neurons that bolster mitochondrial health by, for example, stimulating mitochondrial biogenesis and mitophagy. The neuronal activity-dependent and cellular stress-responsive neurotrophic factor BDNF appears to play key roles in the neuroplasticity-enhancing and neuroprotective actions of bioenergetic challenges. Signals from peripheral organs to brain cells may also contribute to the beneficial effects of exercise and fasting on cognitive function and neuronal resilience. During normal aging, there are decrements in the functionality of several energy metabolism-related pathways in brain cells including glucose transport, mitochondrial electron transport, DNA repair, and neurotrophic factor signaling. Epidemiological, clinical, and experimental evidence points to important roles for impaired neuronal bioenergetics and reduced adaptation to stress in normal aging, and preclinical stages of neurodegenerative disorders such as AD and PD.

There is considerable complexity in the signaling pathways that integrate cellular energy metabolism with adaptive structural and functional responses of neuronal circuits to neuronal network activity. Future studies should be aimed at elucidating such intercellular and subcellular pathways. As new mechanisms emerge, it will be important to determine whether and how environmental and genetic factors that positively or negatively impact brain health influence brain cell energy metabolism. Translational research on cellular energy metabolism and brain health has been meager compared to efforts that focus on individual disease-specific molecular targets. The drug development approach has thus far failed for AD, PD, and stroke. Indeed, the number of individuals living until they are in the age range for neurodegenerative disorders is rapidly increasing. The kinds of evidence from preclinical studies and human subjects described above provide a rationale for moving forward with randomized controlled trials of intermittent bioenergetic challenges achieved physiologically (e.g. intermittent fasting and exercise) or pharmacologically (e.g. mitochondrial uncoupling agents) in humans at risk of or in the early symptomatic stages of a neurodegenerative disorder, or during recovery from a stroke. As elaborated elsewhere (Mattson, 2012), it would also seem prudent to incorporate intermittent exercise and fasting protocols into physician training and healthcare practice, for disease risk reduction and early intervention in acute and chronic neurodegenerative conditions.

## Conflict of interest

The authors declare that they have no conflict of interest.

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