

Brain Energy Metabolism in Health and Disease

Felipe A. Beltrán, Aníbal I. Acuña,
María Paz Miró and Maite A. Castro*
*Instituto de Bioquímica y Microbiología, Facultad de Ciencias,
Universidad Austral de Chile, Valdivia,
Chile*

1. Introduction

Living cells require energy to perform work, to maintain their organized structures, to synthesize cellular components, to generate electric currents and many other processes. Energy metabolism is a highly coordinated cellular activity in which enzymes are organized into discrete metabolic pathways that cooperate in degrading energy-rich nutrients from the environment. Glucose is the principal metabolic substrate for living cells including brain cells. It is rich in potential energy and is also a versatile precursor, giving rise to metabolic intermediaries for biosynthetic reactions. Glycogen is a polymer of glucose and is the form in which glucose is stored. The mammalian brain contains glycogen, which is located predominantly in astrocytes (Brown & Ransom, 2007). In particular situations, substrates other than glucose can be utilized by the brain. β -hydroxybutyrate, acetoacetate and acetone are ketone bodies produced in the liver from Acetyl-CoA. Ketone bodies are an important source of brain energy in breast-fed neonates and during starvation when carbohydrates are scarce. However, it has been proposed that part of brain energy comes from the conversion of glucose to lactate at one location (within one cell) and part comes from the oxidation of lactate to pyruvate at another location (within the same cell or in a different cell).

The brain makes up 2% of a person's weight. Despite this, even at rest, the brain consumes 25% of the body's energy. Most of the energy consumed in the brain is attributable to restoration of the membrane gradient following neuronal depolarization. Neurotransmitter recycling, intracellular signaling and dendritic and axonal transport also require energy (Attwell & Laughlin, 2001). Even though neurons are responsible for massive energy consumption, the brain is made up of many cells, including neurons, glial and ependymal cells. Every brain cell has a specific function and thus every brain cell has different metabolic needs. Many of these specific functions are concerned with maintenance of neuronal transmission. For example, astrocytes play a central role in supporting neurons metabolically by producing lactate, through glycolysis and activation of glycogen catabolism (Brown & Ransom, 2007). Another critical factor for maintenance of neuronal

*Corresponding Author

transmission is an adequate supply of nutrients and oxygen from blood. Neurotransmitters stimulate neurovascular messenger production in astrocytes and neurons. These molecules induce the local constriction and dilation of smooth muscle around the neighboring arterioles (Attwell et al., 2010).

There have been several reports of metabolic impairment in a variety of neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis and Parkinson's disease, among others (Mosconi et al., 2005, Leenders et al., 1986, Kuwert et al., 1993, Hattingen et al., 2009). Because brain is an expensive organ in energetic terms, disruptions in energy production may affect neuronal transmission and thus, neuronal survival. Moreover, deregulation of energy metabolism could be implicated in an increased production of oxidative species. Indeed, oxidative damage has been proposed in such disorders (Mazziotta et al., 1987, Navarro et al., 2009).

2. Metabolic sources and principal metabolic pathways for brain energy metabolism

There are two barriers protecting the brain from toxic metabolites: the blood-brain barrier and the blood-CSF barrier formed by epithelial cells of the choroid plexus. These barriers protect the brain from possible changes in the concentration of blood metabolites. In the same way, they work as selective filters to allow for controlled delivery of metabolic substrates into the brain. These metabolic substrates are mainly glucose, ketone bodies and some metabolic intermediaries such as lactate and pyruvate.

2.1 Use of glucose in brain

Glucose is an essential energy source for the adult human brain. According to *in vivo* studies using labeled 2-deoxyglucose or 2-fluorodeoxyglucose there is a correlation between brain function and brain metabolism (Sokoloff et al., 1977). Glucose is rich in potential energy and thus, it is a good metabolic fuel. In any tissue glucose can follow several metabolic pathways. In brain, glucose is almost entirely oxidized through sequential glycolysis and the tricarboxylic cycle (TCA) associated with oxidative phosphorylation. Glucose can also be stored as the polysaccharide, glycogen. Glucose is not only an excellent energetic fuel, it is also a remarkably versatile precursor supplying metabolic intermediaries for biosynthetic reactions. In brain most of these intermediaries serve to synthesize neurotransmitters and gliotransmitters, as well as other molecules of biological significance. Glucose oxidation via glycolysis provides metabolic intermediaries besides producing ATP. Glucose can be oxidized through an alternative pathway: the pentose phosphate pathway (PPP). Glucose oxidation through PPP provides 5-carbon monosaccharides for nucleic acid synthesis and NADPH for reductive biosynthetic processes and for maintenance of the redox balance in the cell.

2.1.1 Glycolysis

In glycolysis, a molecule of glucose is oxidized to two molecules of pyruvate. This oxidation occurs through ten enzyme-catalyzed reactions (Figure 1). The first step in glycolysis is phosphorylation of glucose at C-6, by hexokinase, to yield glucose-6-phosphate. Most of the

glucose-6-phosphate is degraded to pyruvate. But glucose-6-phosphate can be used to generate glucose-1-phosphate, which in turn is used to synthesize glycogen (see below) or to generate NADPH and ribose-5-phosphate through PPP (see below). Myo-inositol is also synthesized from glucose-6-phosphate and serves as a precursor for phosphatidylinositide signaling molecules. The first step in glycolysis and the next nine enzymatic reactions occur in all brain cells (Lowry & Passonneau, 1964).

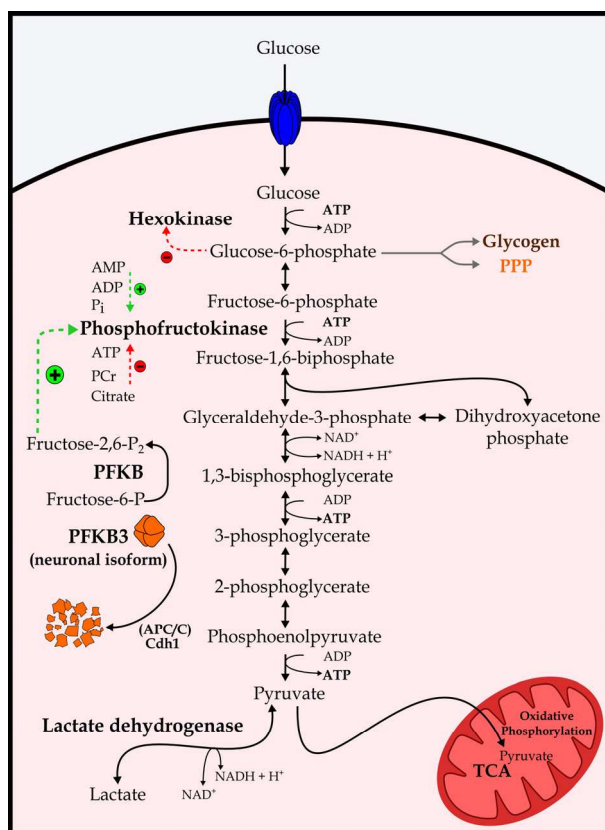


Fig. 1. Glycolysis. The first step in glycolysis is phosphorylation of glucose to glucose-6-phosphate by hexokinase, an enzyme inhibited by the same glucose-6-phosphate. Glucose must be phosphorylated to glucose-6-phosphate for it to enter glycolysis. The most important step in the control of glycolytic flux is a reaction catalyzed by phosphofruktokinase (PFK). PFK is inhibited by compounds that accumulate when energy status is high (ATP, citrate) and it is activated by products of functional metabolic activity (AMP, ADP). PFK1 in neurons is not activated by fructose 2,6-bisphosphate (Fructose-2,6-P₂) because the enzyme that catalyzes F2,6BP production is constantly degraded.

Major sites for the control of glycolytic flux are hexokinase (EC 2.7.1.1), phosphofruktokinase 1 (PFK1, EC 2.7.1.11) and pyruvate kinase (EC 2.7.1.40; Lowry & Passonneau, 1964). Hexokinase catalyzes the transfer of a phosphate group from one

molecule of ATP to glucose (Figure 1). Type-I hexokinase is the predominant isoenzyme in brain (Wilson, 1995). This reaction is irreversible under intracellular conditions. Type-I hexokinase is normally saturated with substrate and strongly inhibited by its product, glucose-6-phosphate (Wilson, 2003). Type-I hexokinase binds to the outer mitochondrial membrane via a hydrophobic N-terminal sequence (Wilson, 1997). Type-I hexokinase interacts with porin (also named voltage-dependent anion channel) which is a membrane protein located at the outer mitochondrial membrane. When type-I hexokinase binds to mitochondria, the K_i for glucose-6-phosphate is increased and the K_m for ATP is reduced, suggesting that the bound form is more active (Wilson, 2003). This association occurs alongside changes in the cellular metabolic state. It has also been proposed that type-I hexokinase can bind to microtubules in order to increase their activity. Indeed, under mitogenic stimulus, mitochondria and type-I hexokinase colocalization decreases, while tubulin and type-I hexokinase colocalization increases in glial cells (Sanchez-Alvarez et al., 2004). These changes in localization are accompanied by an increase in glucose transporters (GLUTs) and hexokinase expression (Sanchez-Alvarez et al., 2004). Therefore, hexokinase and GLUTs should be key factors in the regulation of glycolytic flux capacity.

All three isotypes of PFK1 (muscle [M], liver [L] and brain [B]) have been observed by immunohistochemical analysis in neurons and astrocytes. The three isoenzymes differ in their allosteric properties and their distribution in different brain cells. These differences might be important for regulation of brain glycolysis in the different cellular compartments. Regulation of PFK activity is a major control point for glycolysis (Passoneau & Lowry, 1964). PFK1 is inhibited by compounds that accumulate when energy status is high (ATP, citrate) and is activated by products of functional metabolic activity (AMP, ADP). The powerful allosteric activator of PFK1 is fructose 2,6-bisphosphate, which is produced by the enzymatic reaction catalyzed by phosphofructokinase 2 (PFK2 or PFKB, EC 2.7.1.105). PFKB3 is the main isoform expressed in brain. However, PFKB3 has been described as being constantly degraded via the E3 ubiquitin ligase anaphase-promoting complex/cyclosome (APC/C)-Cdh1 (Herrero-Mendez et al., 2009). Therefore, glycolysis in neurons is not activated. Indeed, when mitochondrial respiration is inhibited, astrocytes upregulate their glycolytic rates through fructose 2,6-bisphosphate production, while neurons die quickly. Thus glucose must be oxidized through other metabolic pathways, such as PPP, in neurons (see below).

Pyruvate kinase is expressed in neurons and astrocytes. But apparently, in brain, the reaction catalyzed by pyruvate kinase does not appear to be a major control point in glycolysis (Lowry & Passoneau, 1964).

2.1.2 Glycogen metabolism

Glucose can be stored in the form of glycogen in brain. Glycogen is synthesized from glucose-6-phosphate via glucose-1-phosphate and UDPglucose. Glycogen stores may only sustain brain metabolic turnover for a few minutes at most. Glycogen metabolism is regulated by two enzyme reactions, catalyzed by glycogen synthase and glycogen phosphorylase (Figure 2). Most, if not all, glycogen is localized in astrocytes (Vilchez et al., 2007). However, neuronal cells express enzymatic machinery for glycogen synthesis. Glycogen synthase is expressed in cultured neurons in a highly phosphorylated (inactive) state (Vilchez et al., 2007). Glycogen synthase phosphorylation is achieved by glycogen

synthase kinase 3 (EC 2.7.11.26). The abnormal activation of glycogen synthase is responsible for abnormal glycogen deposits in neurons, a feature observed in Lafora disease. Lafora disease is an autosomal recessive form of epilepsy which has been associated with mutations in malin and laforin genes. The malin-laforin complex induces the degradation of both PTG (regulatory subunit of protein phosphatase 1 that activates glycogen synthase) by dephosphorylation, and glycogen synthase. Interaction of malin and laforin is a regulated process that is modulated by the AMP-activated protein kinase (Solaz-Fuster et al., 2008).

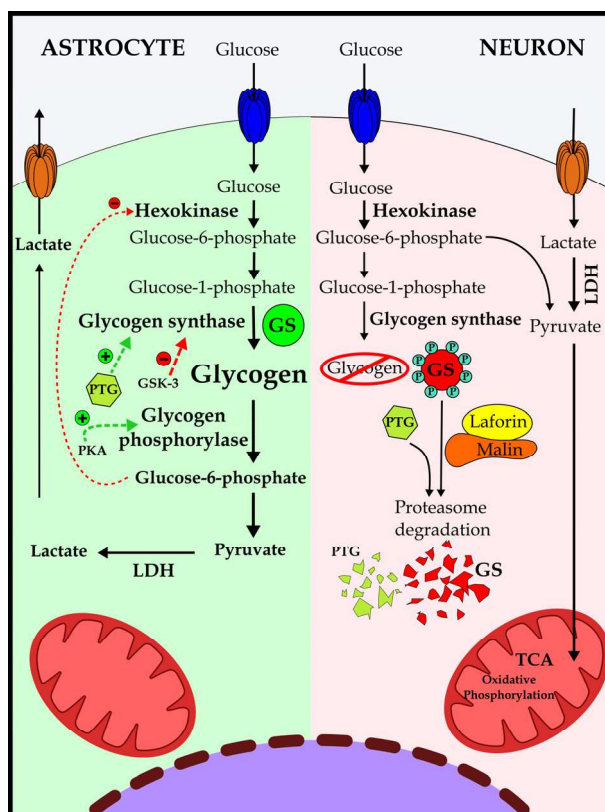


Fig. 2. Glycogen metabolism. Glycogen is synthesized in astrocytes by glycogen synthase (GS). Glycogenolysis is mediated by glycogen phosphorylase (GP). Both GS and GP are regulated in opposite directions by phosphorylation. GS is activated by protein phosphatase-1 and inhibited by GS kinase-3 (GSK-3). Both GS and protein phosphatase-1 interact with glycogen via protein targeting to glycogen (PTG). In neurons, GS is present in a highly phosphorylated, inactive state and, together with PTG, is targeted for proteasome-dependent degradation by the laforin-malin complex. Glycogenolysis in astrocytes depends on GP, which is activated by phosphorylation by several kinases, including the cyclic adenosine monophosphate (cAMP)-activated protein kinase A (PKA) in response to several neurochemical signals. Glycogenolysis in astrocytes leads to the production of lactate, which serves as an energy substrate for oxidative metabolism in the active neurons.

On the other hand, astrocytic glycogen is good for the brain. During synaptic activity, breakdown of astrocytic glycogen is stimulated by neurotransmitters such as glutamate and norepinephrine (Walls et al., 2008). Adrenergic agents cause protein kinase A (PKA) activation in astrocytes through metabotropic receptor binding. Glycogenolysis in astrocytes depends on glycogen phosphorylase, which is activated by phosphorylation of several kinases, including PKA (Benarroch, 2010). Glycogenolysis produces glucose-6-phosphate. It has been proposed that glucose-6-phosphate is used to produce metabolic substrates such as lactate, which can be exported from astrocytes to neuronal cells (Benarroch, 2010; Walls et al., 2008). It has also been proposed that glucose-6-phosphate from glycogen in astrocytes inhibits glycolysis (by hexokinase inhibition) and thus, glucose consumption is favored by neurons (DiNuzzo et al., 2011). In any case, glycogen is important for brain. Indeed glycogen metabolism in astrocytes only occurs in mature astrocytic cells.

2.1.3 Pentose phosphate pathway

The pentose phosphate pathway (PPP) generates NADPH and 5-carbon carbohydrates. PPP has two distinct phases (Figure 3). The first is the oxidative phase, in which NADPH is generated, and in the second phase, non-oxidative synthesis of 5-carbon carbohydrates occurs. Even if this pathway involves oxidation of glucose, its primary role is anabolic rather than catabolic. Glucose-6-phosphate dehydrogenase is the regulatory enzyme in PPP. It is regulated by the NADPH:NADP⁺ ratio and is allosterically stimulated by nicotinamide adenine dinucleotide phosphate (NADP⁺). The ratio of NADPH:NADP⁺ is normally high. Thus, this makes the cytosol a highly-reducing environment.

NADP⁺ is a coenzyme used in anabolic reactions, such as lipid and nucleic acid synthesis, which require NADPH as a reducing agent. Therefore, the PPP has a more prominent function in developing brain compared to adult brain due to lipogenesis and myelin formation during development. Astrocytes have a glucose-6-phosphate dehydrogenase K_i 10-times lower than glioma cells because PPP is an indicator of cellular biosynthesis, while glycolysis indicates cellular proliferation. However, adult brain slices from several age groups have shown similar PPP capacities. Thus, adult brain has a high PPP capacity. NADPH could be used for neurotransmitter and gliotransmitter turnover and to metabolize aldehydes and peroxides produced by monoamine oxidase, among other enzymes. In this way, NADPH is used to regenerate glutathione (GSH) from glutathione disulfide, which is a product of peroxide scavenging (Baquer et al., 1988).

As was mentioned previously, neurons are unable to increase glycolysis due to the lack of PFKB3. PFKB3 is constantly degraded in neuronal cells and thus glucose should be directed mainly to the PPP to generate NADPH and regenerate GSH (Bolaños et al., 2010). Recently, it has been demonstrated that glucose metabolism and glycogen utilization is impaired in astrocytes with a chronic GSH deficit (Lavoie et al., 2011). So, PPP activity is important in other brain cells besides neurons.

2.1.4 Tricarboxylic acid cycle and oxidative phosphorylation

The tricarboxylic acid (TCA) cycle, also called the citric acid cycle or Krebs cycle, includes eight enzyme-catalysed chemical reactions, which are of central importance in all living cells. The

purpose of the TCA is the complete oxidation of acetyl carbons from acetyl coenzyme A (Acetyl-CoA) with the subsequent formation of NADH and FADH₂ (Figure 4). The TCA cycle is closely linked to oxidative phosphorylation. In oxidative phosphorylation NADH and FADH₂ are reoxidized. NADH and FADH₂ electrons are transferred from electron

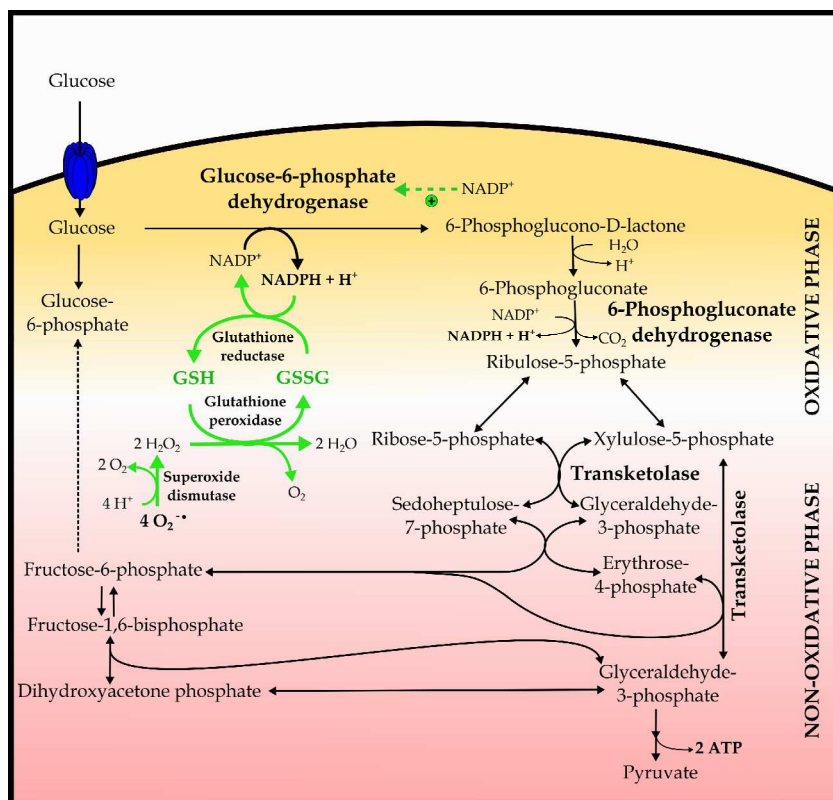


Fig. 3. The pentose phosphate pathway and glutathione. In the oxidative branch of the pentose phosphate pathway, two NADPH are generated per glucose-6-phosphate. The only limiting reaction of the pathway is catalyzed by glucose-6-phosphate dehydrogenase (G6PDH), which is allosterically activated by NADP⁺. G6PDH catalyzes glucose-6-phosphate oxidation and the production of the first NADPH. This NADPH is oxidized and thus glutathione is reduced. The second NADPH is generated through the oxidative decarboxylation of 6-phosphogluconate, a reaction catalyzed by glucose-6-phosphogluconate dehydrogenase. The nonoxidative branch of the pentose phosphate pathway provides a reversible link with glycolysis by regenerating the two glycolytic intermediates glyceraldehyde-3-phosphate and fructose-6-phosphate.

donors to consecutive electron acceptors, in which the last electron acceptor is oxygen (oxygen is reduced to H₂O, Figure 4). The energy released by electrons flowing through this electron transport chain is used to transport protons across the inner mitochondrial membrane, generating a potential energy (as an electrochemical gradient). This energy is

used to synthesize ATP in a enzyme reaction catalyzed by a large enzyme called ATP synthase.

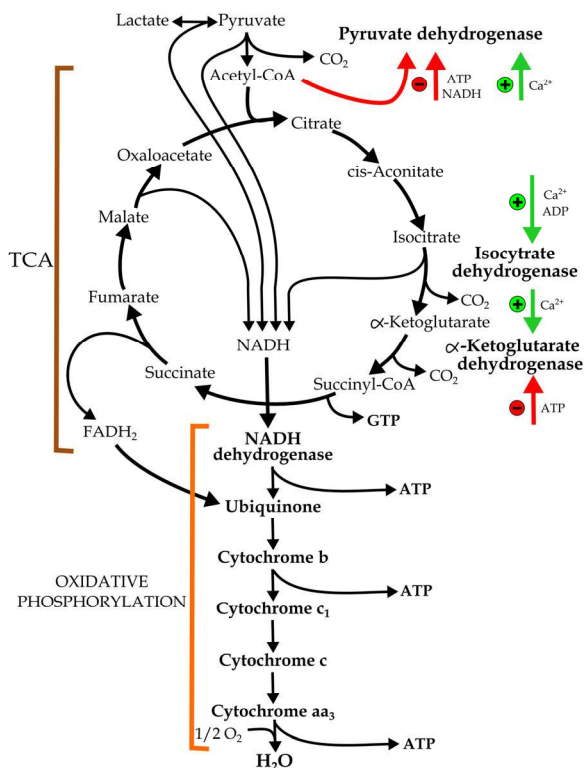


Fig. 4. The tricarboxylic acid cycle (TCA) and oxidative phosphorylation. Pyruvate entry into the cycle is controlled by pyruvate dehydrogenase activity that is inhibited by ATP and NADH. Two other regulatory steps in the cycle are controlled by isocitrate and α -ketoglutarate dehydrogenase, whose activity is controlled by the levels of high-energy phosphates. All dehydrogenases are stimulated by Ca^{2+} . NADH and FADH_2 produced in TCA are reoxidized by the donation of their electron to the electron transport chain, the final goal of which is reduction of oxygen to water. Electron flux is responsible for the necessary energy to drive ATP synthesis.

2.1.4.1 Formation of Acetyl-CoA

Acetyl-CoA is produced mainly from pyruvate, the product of glycolysis. Pyruvate enters the mitochondrion and it is oxidized via an enzyme reaction catalyzed by the pyruvate dehydrogenase complex. This is composed of three different enzymes that catalyze seven reactions in order to oxidize pyruvate to Acetyl-CoA. Pyruvate dehydrogenase complex K_m for Acetyl-CoA is approximately 0.05 mM, which is similar to pyruvate concentrations in brain. The enzyme complex also requires a variety of substrates and cofactors: pyruvate, NAD^+ , thiamine pyrophosphate, FAD, lipoic acid and coenzyme A. Activity of pyruvate

dehydrogenase complex is regulated by phosphorylation state and Ca^{2+} concentration among other factors (Huang et al., 1998). Pyruvate dehydrogenase complex immunoreactivity has been observed in neuronal cells (Calingasan et al., 1994). A low pyruvate dehydrogenase complex enzyme activity and immunoreactivity has been described in neurons following ischemia and reperfusion. This could explain the reduced cerebral glucose and oxygen consumption that occurs after cerebral ischemia (Martin et al., 2005).

Although brain Acetyl-CoA is mainly derived from pyruvate, it can also be synthesized from fatty acids, ketone bodies (see below), monocarboxylate acids, such as lactate (see below) and acetate. Fatty acids are mainly oxidized inside the mitochondria through β -oxidation to produce Acetyl-CoA, NADH and FADH_2 .

2.2 Use of lactate and ketone bodies

The transport of lactate and ketone bodies is accomplished by the monocarboxylate transporters (MCTs). Although BBB cells express MCT1, monocarboxylates cross the BBB with poor efficiency under physiological conditions. Only under extreme conditions, like starvation or prolonged exercise, could these compounds be important exogenous sources of metabolic fuel for the brain (Quistorff et al. 2008).

2.2.1 Lactate formation and lactate oxidation

Normally, when the glycolysis rate exceeds the rate of triose entry into the TCA cycle, pyruvate can be reduced to lactate by lactate dehydrogenase (LDH, EC 1.1.1.27) which catalyzes a reversible reaction (Figure 1). Lactate must be released because local lactate accumulation would be an opposing driving force that would influence many reversible NAD^+/NADH -coupled redox reactions.

Extracellular lactate is transported into the cell and is oxidized to pyruvate because LDH catalyzes the reversible interconversion between pyruvate and lactate. Two distinct subunits combine to form the five tetrameric isoenzymes of LDH. The LDH-5 subunit (muscle type, also termed the A or M subunit) has a higher maximal velocity (V_{max}) and is present in glycolytic tissues, favoring the formation of lactate from pyruvate, while the LDH-1 subunit (heart type, also referred to as the B or H subunit) favors the reaction towards the production of pyruvate. The different catalytic properties of the five isoenzymes of LDH (H4 or LDH-1, H3M or LDH-2, H2M2 or LDH-3, HM3 or LDH-4, and M4 or LDH-5) are in proportion to the ratio of LDH-5 to LDH-1 subunits. It has been demonstrated that neurons contain predominantly LDH-1, while astrocytes express LDH-5 (Bittar et al. 1996). In this way, lactate synthesized within astrocytes and released into the interstitial space in brain may serve as energy fuel for neurons. Astrocytes release lactate at a greater rate than neurons and lactate is preferentially metabolized in neural cells to produce energy and in oligodendrocytes to synthesize lipids (to make myelin, Sanchez-Abarca et al., 2001).

2.2.2 Ketone bodies formation and oxidation

Glucose is the main energetic fuel for brain. However, under certain conditions the brain can meet its energetic needs using ketone bodies. During ketosis, glucose brain consumption decreases by about 10% per each mM of plasma ketone bodies (LaManna et al., 2009). Ketone bodies are produced from Acetyl-CoA. Lipids are not a major energy source for the

brain. Astrocytes are able to oxidize fatty acids and ketone bodies, while neurons and oligodendrocytes can only use ketone bodies.

Ketone bodies are synthesized mainly in the liver. Ketone body synthesis is activated after exhaustion of cellular carbohydrate stores (glycogen). Fatty acids are broken down via β -oxidation to Acetyl-CoA, NADH and FADH₂. Normally, Acetyl-CoA is completely oxidized via the TCA cycle. However, if the amount of Acetyl-CoA generated in fatty-acid β -oxidation increases disproportionately, the processing capacity of the TCA cycle will start to drop due to low levels of intermediates. Acetyl-CoA will then be used instead for biosynthesis of acetoacetate, β -hydroxybutyrate and acetone (ketone bodies) through four enzymatic reactions (Figure 4). The utilization of ketone bodies is controlled by leptin through AMPK inhibition in the hypothalamic region (Narishima et al., 2011).

During starvation, during chronic feeding with high fat/low carbohydrate or in pathophysiological conditions as diabetes, glucose stores are depleted and ketone body synthesis is stimulated. Under these conditions, the concentration of ketone bodies in blood increases and MCT expression increases at the blood brain barrier. Within the brain, ketone bodies may be used because all brain cells express MCTs and because the enzymatic reactions of ketone body synthesis are reversible (except for spontaneous decarboxylation of acetoacetate to acetone). Thus brain cells obtain Acetyl-CoA from ketone bodies and Acetyl-CoA may be oxidized for those cells through the TCA cycle. The starving brain also extracts fatty acids from blood. Astrocytes can degrade fatty acids by β -oxidation to provide neurons with ketone bodies (Edmond, 1992). Moreover, ketone body oxidation must be important during the first postnatal period. Knockout animals for the ketolytic enzyme succinyl-CoA:3-oxoacid CoA-transferase exhibit normal prenatal development, but develop ketoacidosis, hypoglycemia, and reduced plasma lactate concentrations within the first 48 h of birth (Cotter et al., 2011).

A ketogenic diet has been proposed for treatment of epilepsy. This diet is a strict high fat, low protein, low carbohydrate diet, and is anticonvulsant in many drug-resistant epileptic children. The diet is also effective in mice. The mechanism by which this diet controls intractable seizures is unknown. The diet does not affect behavioral performance or synaptic plasticity. Ketone bodies not only function as an energy substrate, but also as intermediates for the synthesis of lipids and neurotransmitters. Because of this, a link has been proposed between ketone bodies, brain function and polyunsaturated fatty acids (Pifferi et al., 2008). Another proposed mechanism to explain the neuroprotective effect of the ketogenic diet is via mitochondrial improvement by scavenging of reactive species and regulation of gene expression to increase neuronal survival (Beskow et al., 2008). Ketone bodies are also proposed as protectors from neurotoxicity in other pathologies, such as Parkinson's disease and Alzheimer's disease (Kashiwaya et al., 2000).

3. Metabolic pathways during brain activation

The resting brain is not really at rest. It demonstrates continuous cognitive and sensory activity. For example, when we listen music, auditive areas of the brain are selectively activated. Over 120 years ago, brain activation was shown to produce an increase in blood flow in specific brain areas. The increased blood flow has been shown to be accompanied by an increase in glucose utilization (Sokoloff et al., 1977). A mechanism that couples neuronal

metabolism with blood flow should thus exist. An increase in extracellular K^+ , adenosine, and lactate and related changes in pH are all a consequence of increased neuronal activity. All of them have been considered mediators of neurovascular coupling because they have vasoactive effects (Villringer & Dirnagl, 1995). Astroglial cells seem to be protagonists in the coupling of neuron metabolism and blood flow. Astrocytes, like neurons, are organized into networks, although glial cells are organized as a syncytium, linked to each other by gap junctions (Giaume et al., 2010). Neuronal cells exchange information through chemical and electrical synapses. Astrocyte gap junctions are regulated by extra- and intracellular signals. Astrocytes release molecules that induce local constriction or dilation of smooth muscle cells surrounding endothelial cells forming arterioles (Attwell et al., 2010). Astrocytes also release molecules in response to neuronal activation. These molecules can modulate synaptic transmission and neuronal excitability (a concept referred to as the tripartite synapse, Perea & Araque, 2010). So, during brain activation, blood flow is increased due to several interactions between brain cells. We will discuss below the metabolic pathways that function during brain activation in neuronal and astroglial cells. We will then discuss the neuroglial interaction and molecular mechanisms that modulate the interaction.

3.1 Neuron metabolism during activity periods

In a chemical synapse, neurotransmitters released from the presynaptic neuron bind to ionotropic receptors in the postsynaptic membrane increasing the open probability of these ion channels. The ion flow can produce membrane depolarization (excitatory action potentials) or hyperpolarization (inhibitory action potentials). Excitatory action potentials are produced by the sequential opening of voltage-sensitive Na^+ channels, followed by the delayed opening of K^+ channels. This permits movement of positive charges from and into the neuronal cytosol. According to the biophysical properties of neuronal membranes, a theoretical minimum positive charge transfer (carried by Na^+) was predicted per propagating action potential of 121 nC/cm². This was corroborated by Alle and colleagues (2009) who calculated that charging of membrane capacitance requires 153 nC/cm² only 1.3 times more than the theoretical minimum. Action potentials are thus energy-efficient, minimizing their contribution to activity-dependent metabolism. But human brain has billions of neurons and each neuron maintains a large number of synaptic connections to other neurons. Even though action potentials are energy-efficient, this is consistent with the fact that neuronal activity accounts for 80% of brain energy consumption (Sibson et al., 1998). Most of the energy consumed in the brain is attributable to restoration of the membrane resting potential following depolarization. This is accomplished by the Na^+/K^+ -ATPase (EC 3.6.1.3, Attwell & Laughlin, 2001). Other energy-consuming processes are neurotransmitter recycling and axonal and dendritic transport (Ames, 2000). Because glutamate synapses represent at least 80% of cortical synapses, glutamate-mediated neurotransmission consumes most of the energy expended in the brain.

Electrical stimulation opens Na^+ channels in neuronal populations. An increase in intracellular Na^+ concentration activates the Na^+/K^+ -ATPase at its Na^+ -sensitive intracellular site. The activation of Na^+/K^+ -ATPase is accompanied by a decrease in the ATP/ADP ratio and glycolysis activation (Figure 6, probably via allosteric activation of PFK1 by ADP). Glycolysis activation is accompanied by a Ca^{2+} increase and an increase in pyruvate and NADH/NAD⁺ concentrations. TCA and oxidative phosphorylation are also

stimulated (Figure 6). Indeed, mitochondrial dehydrogenases are activated by an increase in intracellular Ca^{2+} (Figure 4). During glutamatergic activity, glutamate binds to ionotropic receptors and metabotropic channels in these cells. Both produce an increase in intracellular Ca^{2+} . Glucose oxidation (determined by CO_2 production) has been shown to be produced by an increased intracellular Na^+ concentration in neuronal-enriched cultures. However, neuronal cells are unable to stimulate glycolysis via fructose 2,6-bisphosphate (see above, Herrero-Mendez et al., 2009). It has thus been proposed that, when energy needs are overcome by glycolytic activity stimulated by ADP, neuronal cells preferentially consume lactate. Astrocytes release lactate in response to synaptic activation (see below, Magistretti et al., 2000) and neuronal cells oxidize this lactate through the TCA and oxidative phosphorylation via a mechanism named the neuron lactate shuttle hypothesis (ANLSH, see below, Magistretti et al., 1999; Allaman et al., 2010). To facilitate lactate use, glycolysis must be inhibited. We will discuss below the details of neuron-glia coupling and the inhibition of glucose use.

The pentose phosphate pathway (PPP) supplies red blood cells with NADPH, which in turn maintains the reduced state of glutathione (GSH). GSH has antioxidant properties since the thiol group in its cysteine moiety is a reducing agent and can be reversibly oxidized and reduced. In cells, GSH is maintained in the reduced form by the enzyme glutathione reductase. Regeneration of reduced GSH requires NADPH. Therefore, PPP is important for maintenance of adequate levels of GSH (Figure 6). Neurons are thought to be particularly vulnerable to damage by reactive oxygen and nitrogen species. Nitrogen species stimulate the PPP rate (Bolaños et al., 2010). The brain is a specific source of oxidative species such as those coming from metabolism of excitatory amino acids and neurotransmitters. During glutamatergic activity, glutamate binds ionotropic receptors and metabotropic channels in these cells. Both produce an increase on intracellular Ca^{2+} . The high and constant use of oxygen results in oxidative stress through the production of superoxide. Finally, other sources of free radicals are produced by Cytochrome P450 and monoamine oxidase activity. It is thus not surprising that neuronal cells oxidize glucose through the PPP (Figure 5 and Figure 6), especially, considering that neurons are unable to increase glycolysis activity via allosteric activation of PFK1 by fructose 2,6-bisphosphate (Figure 1, Herrero-Mendez et al., 2009).

3.2 Metabolic activation in astrocytes

Extracellular K^+ activates the Na^+/K^+ -ATPase via its extracellular K^+ -sensitive site in cultured astrocytes but not in neurons (Grisar et al. 1979; Hajek et al. 1996). Na^+/K^+ -ATPase activation produces a decrease in the ATP/ADP ratio, and thus glycolysis activation (see above, Figure 7, Sokoloff et al., 1996). Extracellular K^+ concentrations of between 5 and 12 mM increase glucose phosphorylation in cultured astrocytes (Hof et al., 1988). The Na^+/K^+ -ATPase can also be activated by increased intracellular Na^+ concentration (Denton et al., 1988). An increase in intracellular Na^+ concentration in astrocytes can be stimulated by the presence of glutamate. Glutamate uptake is carried out by excitatory amino acid transporters. This transport by excitatory amino acid transporters is dependent on the electrochemical gradient of sodium ions. Glutamate uptake can induce metabolic activation in astrocytes and can also be used as energetic fuel. Glutamate can be transformed into α -ketoglutarate through a reaction catalyzed by the enzyme aspartate amino transferase (EC 2.6.1.1, Fonnum, 1967) and thus, glutamate carbons can be oxidized through the TCA.

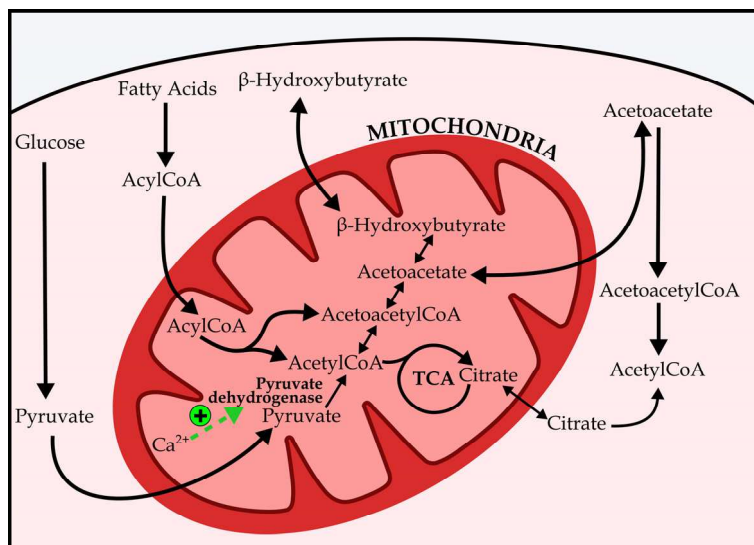


Fig. 5. Relationship between lipid metabolism and the TCA cycle. Under particular dietary conditions, such as lactation in newborns or fasting in adults, the ketone bodies acetoacetate and β -hydroxybutyrate and circulating fatty acids can provide substrates to the TCA cycle after their conversion to Acetyl-CoA. Carbon atoms for lipid synthesis can be provided by glucose through citrate produced in the TCA cycle, a particularly relevant process for the developing brain.

Glycogen stores may also be mobilized during astrocytic activation (Figure 7). During brain activation, neurotransmitters such as noradrenaline can stimulate PTG expression and thus, glycogen synthesis (Allaman et al., 2010). However, at the same time, Na^+/K^+ -ATPase activation induces a decrease in the ATP/ADP ratio and glycogen catabolism activation. Serotonin and other neurotransmitters induce an increase in intracellular concentrations of Ca^{2+} (via IP_3 production) and thus, activate glycogenolysis (Chen & Hertz, 1999). Activation of glycogen synthesis and degradation is termed the glycogen shunt (Walls et al., 2008). Glucose-6-phosphate from glycogen can be oxidized through glycolysis to produce lactate which is exported to neurons (Figure 7). It has, in fact, been demonstrated that glycogen is required for sustaining glutamatergic neurotransmission and for long-term memory formation (Suzuki et al., 2011).

Besides glutathione, the brain also uses ascorbic acid to protect itself from oxidant species. Ascorbic acid is highly concentrated in brain (Kratzing et al. 1982). In aqueous solutions, ascorbic acid is a powerful reductant and is oxidized to dehydroascorbic acid. The regeneration of ascorbic acid from dehydroascorbic acid is not spontaneous. Reduction is mainly an enzymatically catalyzed reaction, which may be glutathione-dependent (Ishikawa et al. 1998). Astrocytes are thought to be involved in ascorbic acid recycling (Figure 10, Astuya et al. 2005). During synaptic activity, ascorbic acid is released from intracellular reservoirs (O'Neill et al., 1984; Ghasemzadeh et al., 1991; Yusa, 2001). The molecular basis of ascorbic acid efflux is not yet well known. Neurons can take up ascorbic acid efficiently because they express SVCT2 (Castro et al., 2001). Ascorbic acid is oxidized within neurons

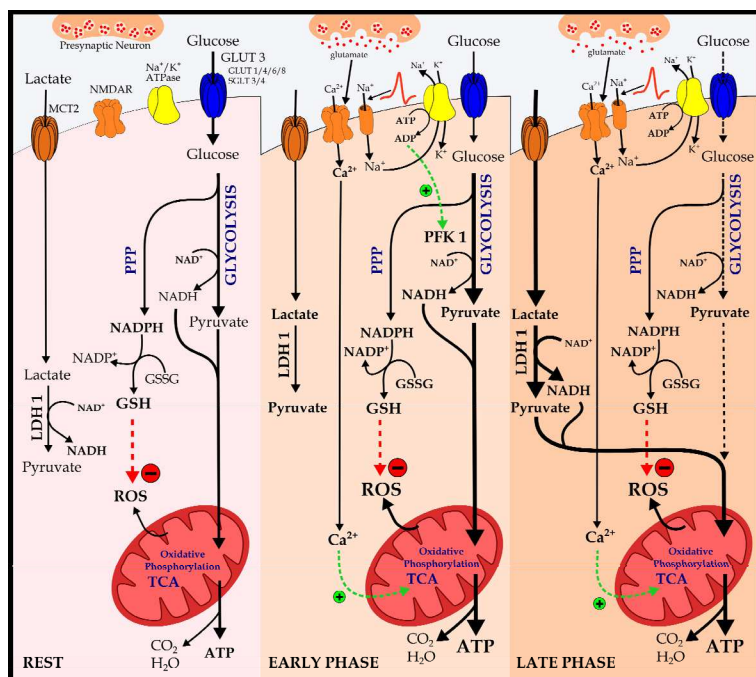


Fig. 6. Neuron metabolism during synaptic activity. Electrical stimulation opens Na^+ channels in neuronal cells. An increase in intracellular Na^+ concentration is able to activate $\text{Na}^+\text{K}^+-\text{ATPase}$ at its Na^+ -sensitive intracellular site (early phase). This activation produces a decrease in ATP/ADP ratio and thus, glycolysis activation by allosteric activation of PFK1 by ADP . Glycolysis activation is accompanied by Ca^{2+} increase and therefore, mitochondrial oxidative metabolism activation. In the late phase of synaptic activation, glycolysis activity is inhibited and lactate uptake is stimulated (see Figure 10 for details of inhibition of glucose utilization and stimulation of lactate transport in synaptically-active neurons). PPP is always present in neuronal cells because NADPH is required to maintain the redox balance in these cells. During synaptic activity, PPP becomes more important because synaptic activity produces oxidant species. NADPH is used to regenerate GSH and thus, to reduce oxidant species.

because during synaptic activity many oxidant species are generated. Neuronal oxidized ascorbic acid (dehydroascorbic acid) can be released through glucose transporters, GLUT1 or GLUT3 (because dehydroascorbic acid is a substrate for GLUTs ; Vera et al., 1993). Astrocytes uptake dehydroascorbic acid through GLUT1 and thus, they reduce dehydroascorbic acid to ascorbic acid through mechanisms that require GSH . GSH regeneration and PPP activation under synaptic transmission conditions should thus be important for astrocytes (Figure 7, Figure 10).

Astrocytic cells also express metabotropic glutamate receptors (mGluRs). Thus, during excitatory brain activation, glutamate is not only taken up by excitatory amino acid transporters, but glutamate activates mGluRs , which produce and increase intracellular Ca^{2+}

and the production of arachidonic acid and prostaglandins. These substances stimulate dilation or constriction of adjacent arterioles and permit that the correct nutrients and oxygen supply are present in order to sustain neurotransmission (Peppiatt & Attwell, 2004).

3.3 Neuron-glia metabolic coupling

As we discuss above, the key to neuron-glia metabolic coupling is the excitatory neurotransmitter glutamate and a rise in extracellular K^+ . Glutamatergic synaptic activity is necessary to maintain a low glutamate concentration in the extracellular space for efficient and successful synaptic transmission to occur and to prevent excitotoxicity. Glutamate uptake in astrocytes occurs via excitatory amino acid transporters. Within the cell, glutamate is then converted to glutamine by glutamine synthetase (EC 6.3.1.2). Glutamine is released into the extracellular space and is taken up by adjacent neurons that synthesize glutamate from glutamine in a reaction catalyzed by glutaminase (EC 3.5.1.2). This recycling of glutamate is named the glutamate–glutamine cycle (Figure 10, Sibson et al., 1997).

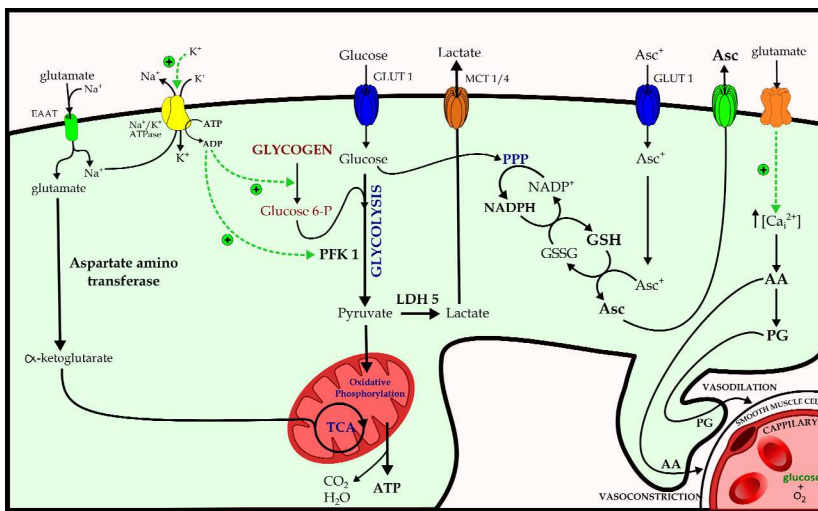


Fig. 7. Metabolic activation of astrocytes. Synaptic activity produces an increase in extracellular K^+ , which stimulates Na^+K^+ -ATPase by binding of its extracellular K^+ -sensitive site. The excitatory neurotransmitter glutamate is taken up by astrocytes through excitatory amino acid transporters. This kind of transport produces an increase in intracellular Na^+ , which stimulates Na^+K^+ -ATPase by binding of its intracellular Na^+ -sensitive site. Na^+K^+ -ATPase activation produces a decrease in ATP/ADP ratio and, thus glycolysis and glycogenolysis activation. In addition, glucose is oxidized by PPP to produce NADPH and to maintain the redox balance, reducing glutathione and ascorbic acid (Asc). Ascorbic acid released by astrocytes is taken up by neurons to protect themselves from oxidant species (ascorbic acid is oxidized in neurons). Oxidized ascorbic acid (dehydroascorbic acid, Asc^+) is released from neurons and taken up by astrocytes through GLUT1. Finally, in astrocytes, glutamate is able to bind ionotropic receptors, which are predominantly calcium channels. This Ca^{2+} increase cooperates with TCA activation and produces arachidonic acid (AA) and prostaglandin (PG) which stimulate the constriction and dilation of capillaries, respectively.

According to ANLSH, glutamate uptake also stimulates glucose uptake (Pellerin & Magistretti, 1994), glycolysis and lactate release in astrocytes (Pellerin & Magistretti, 1994; Demestre et al., 1997). In a similar way, glycolysis and glucose uptake is activated by an increase in the extracellular concentration of K^+ (Pellerin & Magistretti, 1994; Gegelashvili et al., 2007). An increased extracellular K^+ concentration stimulates 2-deoxyglucose phosphorylation (Hof et al., 1988) and lactate formation and release of lactate (Walz & Mukerji, 1988) in cultured astrocytes. Neurons take up the lactate released from astrocytes (Figure 10, Magistretti et al., 2000; Allaman et al., 2010). Lactate flow happens would be possible because there are a differential MCTs and LDH isoenzymes expression between neuronal and astroglial cells. However, use of neuronal lactate has been strongly debated in studies that support the idea that glucose is the main metabolic substrate for these cells (Chih & Roberts, 2003; Dienel, 2009; Gjedde, 2002; Hertz, 2004; Hertz et al., 2007; Mangia et al., 2003; Mangia et al., 2009).

Activation of glycolysis produces an increase in pyruvate and proton concentrations that are accompanied by a decrease in the $NAD^+/NADH$ ratio. Neuronal LDH1 should catalyze reduction of pyruvate to lactate. So, lactate utilization by neurons would only be possible if the consumption of glucose, either at the transport or the glycolysis stage, were inhibited. To explain this, at least four different (though coexistent) ideas have been proposed (Figure 10). Firstly, using real-time microscopy, glucose transport inhibition by glutamate has been demonstrated in neurons co-cultured with astrocytes (Porrás et al., 2008). But because these experiments were performed with co-cultures, it is not possible to discard the possibility that astrocytic stimulation by glutamate may induce the release of substances which inhibit glucose uptake in neurons. In other words, it is possible that the effect of glutamate on neuronal glucose uptake may be indirect. The second mechanism is explained by the redox switch/redox coupling hypothesis (Cerdan et al., 2006). This idea embraces a mechanism in which two different pyruvate pools exist: one is thought to operate in exchange with extracellular lactate or pyruvate and the other, thought to be derived from glycolytic activity. This mechanism considers a lactate/pyruvate redox shuttle, which is able to transfer lactate from astrocytes to neurons. So, high cytosolic lactate inhibits neuronal glycolysis at the glyceraldehyde- 3-phosphate dehydrogenase (EC 1.2.1.12) step by competing with cytosolic NAD^+ , favoring oxidation of extracellular lactate. The third mechanism is our own theory. We have demonstrated that neuronal intracellular ascorbic acid inhibits glucose utilization in neurons (Castro et al., 2009) through GLUT3 inhibition (Figure 8, Beltrán et al., 2011). This mechanism is supported by the idea of ascorbic acid recycling in brain (see above, Figure 10, Astuya et al., 2005). Using primary cultures of cortical neurons treated with a specific shRNA (to block GLUT3 expression) and a fluorescent glucose analogue, we have shown that this transporter is important, using real-time experiments (Figure 7). At the same time, intracellular ascorbic acid is able to stimulate lactate transport in neurons and in cells that express GLUT3 (Figure 9, Castro et al., 2008). Because ascorbic acid is able to change metabolic substrate preferences, we have termed this mechanism the ascorbic acid metabolic switch (Castro et al., 2009). The fourth proposed mechanism relates to the inability of neuronal cells to overactivate glycolysis (Herrero-Mendez et al., 2009; Bolaños et al., 2010). This idea is supported by elegant experimental data that demonstrate that in neurons, it is not possible to produce the allosteric activator of PFK1 (and therefore glycolysis activator) fructose 2,6-bisphosphate. The enzyme that catalyzes fructose-2,6-bisphosphate in neurons, PFK3B, has a very short half-life as it is being constantly degraded (Herrero-Mendez et al., 2009). This mechanism does not exclude basal glycolytic activity however.

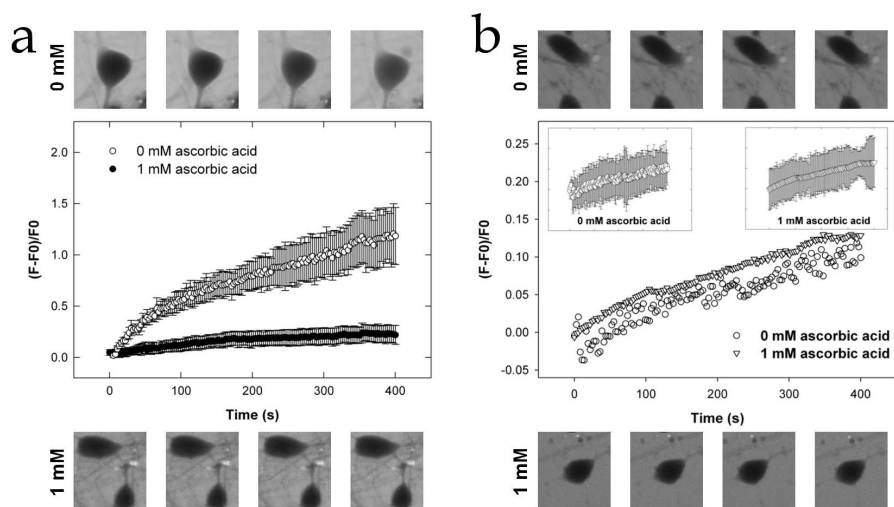


Fig. 8. Intracellular ascorbic acid only inhibits transport of 2-NBDG in cells expressing GLUT3. A: Time course of uptake of 2-NBDG (2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-2-deoxyglucose). 2-NBDG transport in cortical neurons in the presence (closed circles) or absence (open circles) of intracellular ascorbic acid. B: Time course of uptake of 2-NBDG transport in neuronal cells treated with shRNA to knock down GLUT3 expression in the presence (triangles) or absence (circles) of intracellular ascorbic acid. The data represent the mean \pm SD of four experiments (14 control cells and 10 shRNA-treated cells). The images represent one control experiment and one experiment with shRNA-treated cells, in the presence or absence of ascorbic acid. Adapted from Beltran et al. (2011) with permission of the publisher.

4. Metabolic failure in neurodegenerative diseases

Neurodegenerative disease is a broad term for a range of conditions which primarily affect neurons in the brain. Progression of neurodegenerative diseases is accompanied by loss of neuronal cell structure and function and even cell death. These diseases have many similarities at a sub-cellular level including atypical protein assemblies, failure of normal protein degradation pathways, induced cell death, impaired axonal transport and metabolic failures (Rubinsztein et al., 2006; De Vos et al., 2008; Bredesen et al., 2006; Lin & Beal, 2006). A better knowledge of how these failures arise may offer fresh hope for development of therapies that improve treatment of these diseases.

Directly or indirectly, energy is necessary for many, if not all, cellular processes. It is thus possible to speculate that metabolic failure is an early event in neurodegenerative disease. Indeed, there are neurodegenerative diseases caused by a deficiency of metabolic enzymes. One of these is pyruvate dehydrogenase complex deficiency (Brown et al., 1994). This condition has similar characteristics to those of other neurodegenerative diseases. Several neurodegenerative disorders, such as Alzheimer's disease, Huntington's disease and Parkinson's disease, show metabolic failure represented by altered patterns of expression of nutrient transporters, metabolic enzymes and molecular components of cellular respiration.

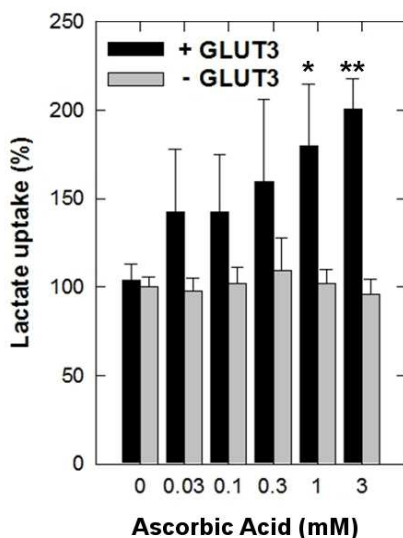


Fig. 9. Intracellular ascorbic acid stimulates lactate uptake in cells expressing GLUT3. Substrate dependence for the inhibition of 0.1 mM lactate transport (10 s, 20 °C) by intracellular ascorbic acid (cells were preloaded with ascorbic acid at the concentrations indicated) in cultured cortical astrocytes (gray bars) and cultured cortical astrocytes expressing GLUT3-EGFP (black bars). Cortical astrocytes were transfected through electroporation. The data represent the mean \pm SD of three experiments.

Metabolic failure is also represented by altered activities of the enzymes involved in energy metabolism. Mitochondria are the main platform for oxidative metabolism. They participate in cell metabolism, they produce ATP and they are important regulators of cytosolic calcium, which in turn, is related to whether or not programmed cell death occurs. Neurodegenerative diseases trigger programmed cell death and thus the role of mitochondria is key, from beginning to end of the disease, from the initial failure in energy metabolism to the later onset of cell death.

4.1 Alzheimer's disease

Alzheimer's disease is the most common cause of dementia. It is characterized by progressive cognitive dysfunction. The Alzheimer's disease brain appears atrophied. The temporal lobe, parietal lobe, frontal cortex and cingulate gyrus show degeneration and loss of cellular mass (Wenk, 2003). Parkinson's disease is characterized by loss of neurons and synapses in the cerebral cortex and in some subcortical regions. Genetically, Alzheimer's disease is heterogeneous and complex, showing no simple mode of inheritance. The causes of most Alzheimer's disease cases are still unknown, though in 1-5% of cases, genetic differences have been described. There are two neuropathological changes that can be correlated with an Alzheimer's disease diagnosis. First of all, neurofibrillary tangles (NFTs) accumulate in neuronal cytosol. And secondly, extracellular amyloid deposits appear in the form of senile plaques containing amyloid peptide (Duyckaerts et al., 2008).

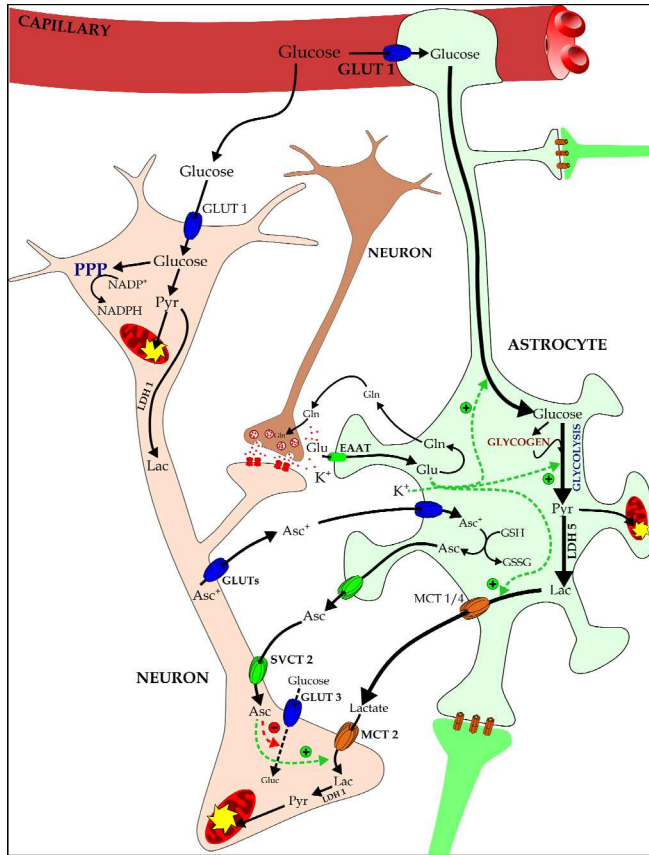


Fig. 10. Neuron-glia metabolic coupling. During glutamatergic synaptic activity, increases in extracellular glutamate and K^+ concentration are produced. This metabolically activates these cells (see Figure 7 for details of astrocytic metabolic activation). Astrocytes uptake glutamate and convert it into glutamine. Glutamine is released and taken up by neuronal cells to glutamate resynthesis (glutamate-glutamine shuttle). Metabolic activation of astrocytes produces an increase in glycolysis, glycogenolysis activities and lactate production. Lactate is taken up by neurons to support their energetic needs (astrocyte-neuron lactate shuttle). Lactate uptake and lactate oxidation in neurons is possible because these cells are not able to activate glycolysis through fructose 2,6-bisphosphate production (see Figure 6 for details of metabolism in synaptically-active neuronal cells). Glutamate also stimulates ascorbic acid release from astrocytes. Neuronal cells take up ascorbic acid through SVCT2. Intracellular ascorbic acid inhibits glucose transport through GLUT3 inhibition and stimulates lactate transport (ascorbic acid metabolic switch). Synaptic activity is accompanied by production of oxidant species. Thus ascorbic acid is oxidized to reduce that species. Dehydroascorbic acid (oxidized ascorbic acid, Asc^+) is released by neurons and taken up by astrocytes through GLUT1. Astrocytes reduce dehydroascorbic acid to ascorbic acid via glutathione-dependent reductases (ascorbic acid recycling). Glu: glutathione, Gluc: glucose, Gln: glutamine, Lac: lactate, Pyr: pyruvate.

Type 2 diabetes mellitus appears to be a significant risk factor for Alzheimer's disease (Bosco et al., 2011). Alzheimer's disease is characterized by a significant and pre-symptomatic reduction of brain glucose utilization (Table 1, Ferreira et al., 2010). Indeed, it has been proposed that early diagnosis of Alzheimer's disease will be rendered possible through a combination of imaging modalities (such as *magnetic resonance imaging*, MRI and *positron emission tomography*, PET; Mosconi et al., 2005). There is a correlation between impairment of glucose cerebral metabolism, decreased GLUT expression and cerebral spinal fluid tau protein levels. (Liu et al., 2008; Cavarolo et al., 2008). Indeed, patients show decreased GLUT3 levels (Liu et al., 2008, Harr et al., 1995). A decrease in glycolytic enzyme levels and activity, PFK1 and glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.12) has also been described. Decreased glycolysis could be related to an increase in glycogen synthesis. Pharmacological glycogen synthase kinase 3 inhibition improves behavioral dysfunction and decreases tau phosphorylation (Onishi et al., 2011). A spatial correlation between brain glycolysis without oxidative mitochondrial metabolism and amyloid deposition has been described (Vlassenko et al., 2010). Aggregate forms of amyloid can modify glucose metabolism and oxidative stress in astrocytes, affecting neuronal cells and probably contributing to neuronal death (Allaman et al., 2010). Indeed, reduction of GLUT1 and MCT expression, as well as the retraction of astrocyte endfeet occurs in Alzheimer's disease producing uncoupling of the neurovascular unit (Merlini et al., 2011). The activity of PPP is increased in Alzheimer's disease. Increased oxidative stress markers in Alzheimer's disease samples correlated with enhanced PPP activity suggesting that PPP activity could play a role in the response against brain pro-oxidant activity in Alzheimer's disease. Finally, mitochondrial dysfunction (Schapira et al., 2006), decreased expression of oxidative phosphorylation and reduced activity of cytochrome oxidase were all observed in Alzheimer's disease.

4.2 Huntington's disease

Huntington's disease is a progressive, autosomal dominant, neurodegenerative disorder. It can affect individuals of all ages, from infancy to old age and develops over a period of 15-20 years. Motor dysfunction and cognitive abnormalities are common symptoms. The disease is caused by an expanded polyglutamine (polyQ) stretch in the corresponding causal gene. Huntington's disease represents one of a growing number of polyQ repeat diseases that cause region-specific neuronal degeneration, including spinobulbar muscular atrophy and spinocerebellar ataxias (Pennuto et al., 2009). In Huntington's disease, polyQ expansion affects the *Huntingtin* gene, resulting in major cell loss in the striatum, a region of the basal ganglia that integrates cortical information for behavioral output. Huntington's disease is characterized by widespread neurodegeneration with preferential deterioration of medium-sized spiny neurons (MSSNs) in the striatum (Penney & Young, 1998). The major excitatory input to MSSNs comes from the cortex (corticostriatal pathway) and the thalamus. Huntington's disease also causes dysfunction and subsequent death of neurons in other brain regions, including the cortex.

The *Huntingtin* gene codes for a protein called the huntingtin protein (Htt). It is a soluble 384 kDa protein, essential for embryogenesis, and ubiquitously expressed in moderate amounts in the nervous system as well as in other systems (Cattaneo et al., 2001). Htt is associated with various intracellular organelles, including the nucleus, endoplasmic reticulum, Golgi

complex, microtubules and endosomal compartments. Wild-type (normal) huntingtin has an important role in the intracellular transport of vesicles, organelles and traffic of proteins to the cell surface (Caviston et al., 2009). Expansion of a glutamine stretch within the Htt protein to more than 40 repeats appears to confer a dominant toxic property that is deleterious to neurons and detrimental to normal Htt biological activities. The precise actions of the mutant huntingtin are still not clearly understood.

Huntington's disease is characterized by a failure in brain energy metabolism (Table 1). Defects in energy metabolism may even extend to presymptomatic subjects. Positron emission tomography studies have demonstrated marked reductions in glucose metabolism in the basal ganglia (Mazziotta et al., 1987), and in the cerebral cortex of symptomatic Huntington's disease patients (Leenders et al., 1986; Kuwert et al., 1993). However, Oláh and colleagues (2008) described an increase in several glycolytic enzymes and ATP production in brain from Huntington's disease animals. By contrast, the same authors described a marked decrease in glyceraldehyde-3-phosphate dehydrogenase activity. An impairment in enzyme activity of the TCA cycle (Lim et al., 2008) and oxidative phosphorylation has also been described. A key role for proliferator-activated receptor gamma coactivator-1 α has been proposed in the control of energy metabolism in the early stages of Huntington's disease pathogenesis. Proliferator-activated receptor gamma coactivator-1 α is a transcriptional coactivator that regulates several metabolic processes, including mitochondrial biogenesis and oxidative phosphorylation (Finck & Kelly, 2006). Although the origin of metabolic impairment is unknown, it is proposed that a systematic downregulation of peroxisome proliferator-activated receptor- γ plays a critical role in the deregulation of energy homeostasis observed in Huntington's disease (Chiang et al., 2010). Metabolic failure in Huntington's disease not only occurs in brain. Htt is a ubiquitous protein and thus energetic failure may also be observed in peripheral tissues. Huntington's disease patients do show progressive weight loss and development of diabetes (Aziz et al., 2010). These symptoms may be related to an impairment of insulin secretion (Smith et al., 2009).

Finally, oxidative damage has been shown (Mazziotta et al., 1987), as well as impaired SOD activity (Mazziotta et al., 1987) and impaired ascorbic acid homeostasis (Rebec et al., 1994) in Huntington's disease animal models. Our group has been making steady progress with respect to the function of ascorbic acid in neuronal metabolism (Castro et al., 2008; Castro et al., 2009; Beltrán et al., 2011, see above). Ascorbic acid, the reduced form of vitamin C, modulates neuronal metabolism between resting state and brain activation periods.

4.3 Parkinson's disease

Parkinson's disease is the most common neurodegenerative movement disorder of central nervous system. Clinical symptoms are due to the progressive degeneration of dopaminergic neurons in the substantia nigra and other monoaminergic neurons in the brainstem (Braak et al., 2003). The pathology of this disease is characterized by the accumulation of α -synuclein into inclusions called Lewy bodies in neurons. Although Parkinson's disease is a sporadic condition of uncertain etiology, there is some evidence that mitochondrial dysfunction considerably contributes to the pathogenesis of this disorder (Schapira, 2008). Mutations in several genes are found in Parkinson's disease. Point mutations, duplications and triplications in the α -synuclein gene and mutations in the leucine-rich repeat kinase 2 (LRRK2). Mutations have also been described in genes coding

CNS DISEASE	METABOLIC FAILURE	REFERENCES
Alzheimer's Disease (AD)	Reduced glucose metabolism in AD patients and animal models via measurement of CMRgl by FDG-PET. Early hypometabolism in posterior associative cortical areas and prefrontal areas. Increased activity of G6PDH in temporal cortex of AD patients. Increased G6PDH levels in pyramidal neurons from hippocampus. Mitochondrial dysfunction including: mtDNA mutation, decreased mRNA levels for complex I-IV subunits of the electron transport chain. Decreased activities of glycolytic enzymes, lower pyruvate synthesis, lower pyruvate dehydrogenase activity, lower Acetyl-CoA production and impaired cyclooxygenase activity. Decreased expression of GLUT1 and MCT1 in blood brain barrier of AD animal models, decreased GLUT1 and GLUT3 in AD brains. Decreased amount of GLUT-1 transporter in the hippocampus and cerebral cortex of AD patients.	Browen et al., 1979 Ferreira et al., 2010; Harr et al., 1995; Hooijmans et al., 2007; Horwood & Davies, 1994; Kalaria & Harik, 1989;; Langbaum et al., 2009; Liu et al., 2008; Merlini et al., 2011; Mooradian et al., 1997;; Nicholson et al., 2010; Ojaimi et al., 1999; Parker et al., 1994; Schapira et al., 2006; Shima et al., 2011; Simpson et al., 1994; Sims et al., 1983; Sorbi et al., 1983; Villain, 2010.
Huntington's disease (HD)	Reduced glucose metabolism in the basal ganglia and cerebral cortex of symptomatic HD patients. Deficiency in activities of respiratory chain complexes II, III and IV in caudate nucleus. Decreased cAMP levels in HD postmortem brain and Hdh ^{Q111} striatum. Decreased ATP and ATP/ADP ratio. Defective mitochondrial oxidative phosphorylation. Cytochrome oxidase subunit I (COI) mRNA levels are reduced within neurons of the putamen and globus pallidus. Expression of mHTT in hypothalamus causes metabolic imbalance in mice. Decreased GLUT1 and GLUT3 transporter expression in caudate of postmortem HD brains.	Gamberino & Brennan, 1994; Gourfinkel-An et al., 2002; Gu et al., 1996; Hult et al., 2011; Kuwert et al., 1990; Kuwert et al., 1993; Leenders et al., 1986; Lim et al., 2007; Mann et al., 1990; Martin et al., 1992; Mazziotta et al., 1987;
Parkinson's disease (PD)	Hypometabolism in striatal, thalamic, and motor regions in PD animal models with significant alterations in striatal and cortical function (FDG-PET). PD patients showed patterns of decreased metabolism in bilateral inferior, medial frontal and right parietal lobes, caudate nucleus and visual cortex. Deficiency in the activity of complex I in mitochondria of substantia nigra. Glucose metabolism is decreased in the caudate, putamen and thalamus in a primate PD model.	Bohnen et al., 2011; Borghammer et al., 2011 Brownell et al., 2003; Feng et al., 2008; Hattingen et al., 2009; Hou et al., 2010; Hyu Lee et al., 2009; Lee et al., 2010; Lyoo et al., 2008; Pernecky et al., 2008; Schapira et al., 1989.

Table 1. Metabolic failures in neurodegenerative diseases.

for Parkin, DJ-1, PINK1 and ATP13A2 (Biskup et al., 2008). The exact role of α -synuclein remains unknown, but it is thought to participate in maintenance of vesicle pools. Parkin directs ubiquitination of α -synuclein (Haywood & Staveley, 2004). Ubiquitin tagged α -synuclein is directed to proteasome and degraded. The parkin protein thus promotes Parkinson's disease by enhancing the failure in normal protein degradation. Mutations in PINK1 and DJ1 genes are related to mitochondrial dysfunction in Parkinson's disease. Oxidative stress also occurs in Parkinson's disease. Dopamine metabolism produces oxidant species. In this way, the α -synuclein mutation contributes to oxidative stress because in the presence of mutated α -synuclein, dopamine remains in the cytosol instead of being loaded into synaptic vesicles (Henchcliffe, 2008).

A hypometabolism of glucose has been described in Parkinson's disease patients (Huang et al., 2007; Yong et al., 2007; Perneczky et al., 2008; Hosokai et al., 2009; Lee et al., 2008; Lee et al., 2010; Bohnen et al., 2011; Borghammer et al., 2011). However, there is only limited molecular evidence to support this feature. Defects in oxidative phosphorylation with a decreased activity of complex I have been reported (Navarro et al., 2009; Hattingen et al., 2009). This evidence leads us to speculate that in Parkinson's disease, mitochondrial dysfunction by redox imbalance precedes metabolic failure. However, a role for glycogen synthase kinase 3- β , an enzyme participating in glycogen metabolism (see below) has been proposed in Parkinson's disease pathogenesis (as for Alzheimer's disease pathogenesis, Nagao et al., 2008; Garcia-Gorotiaga et al., 2009).

5. Conclusions

The metabolic cost of brain activity is high. Neuronal activity accounts for 80% of brain energy consumption. Glucose is an essential energy source for the adult human brain. It can be used to obtain energy and to produce metabolic intermediaries for biosynthesis of compound of biological interest. Glucose can also be stored in brain, in the form of glycogen. Glucose oxidation via glycolysis occurs in all brain cells. However, the ability of neuronal cells to activate this metabolic pathway is poor. Astrocytic glycolysis and glycogenolysis is activated in response to synaptic activation with the subsequent formation of lactate. Thus, during glutamatergic synaptic activity neurons preferably consume lactate released from glia. The energetic coupling between neuronal and astroglial cells is essential to meet energy brain needs in an efficient way. Astrocytes interact with each other and with endothelial cells from the blood brain barrier and smooth muscle cells surrounding arterioles. Under fasting conditions, during intense exercise and in suckling infants, ketone bodies are a significant source of energetic fuel for brain. Metabolic failure has been described in several neurodegenerative diseases. These diseases present atypical protein assemblies, failures in normal protein degradation pathways, induced cell death, impaired axonal transport and metabolic failures. Almost all cellular processes need energy. It is thus possible that metabolic failure is an early event in these pathologies. This hypothesis is supported by evidence that shows metabolic failure in pre-symptomatic patients suffering from diseases such as Alzheimer's disease and Huntington's disease.

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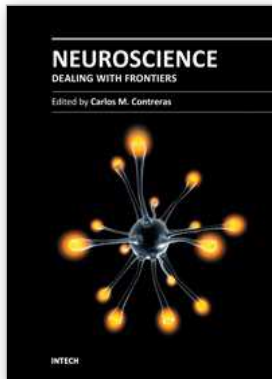
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The Neuronal Doctrine recently reached its 100th year and together with the development of psychopharmacology by the middle of 20th century promoted spectacular developments in the knowledge of the biological bases of behavior. The overwhelming amount of data accumulated, forced the division of neuroscience into several subdisciplines, but this division needs to dissolve in the 21st century and focus on specific processes that involve diverse methodological and theoretical approaches. The chapters contained in this book illustrate that neuroscience converges in the search for sound answers to several questions, including the pathways followed by cells, how individuals communicate with each other, inflammation, learning and memory, the development of drug dependence, and approaches to explaining the processes that underlie two highly incapacitating chronic degenerative illnesses.

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Slavka Krautzeka 83/A
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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