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DHA (omega-3 fatty acid) and estradiol: key roles in regional cerebral glucose uptake

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Abstract – Neurons have a high energy need, requiring a continuous supply of glucose from the blood. Tight regulation of glucose metabolism in response to stimuli is essential for brain physiology. Glucose metabolism and cerebral blood flow are closely coordinated during neuronal activity to maintain proper brain function. Glucose uptake across the blood-brain barrier is facilitated by a carrier protein: the GLUT-1 transporter. The first way the body meets urgent demand for glucose is to increase the blood flow through vasodilatory responses generated by nitric oxide. If that is insufficient, the second way is to increase the density of GLUT-1 through the translocation of this transporter from intracellular stores. The third pathway is to increase GLUT-1 synthesis by stimulating *SLC2A1* (GLUT-1 gene) transcription. A tandem of two key molecules, free estradiol and DHA, is involved in this critical regulation. Their relationship is synergistic and reciprocal: free estradiol with genomic and non-genomic actions *via* ERα, and DHA *via* the PPARα-RXRα and PPARɣ-RXRα heterodimers. We highlight several original mechanisms linking two main principles (neuronal stimulation and brain energy metabolism) with the fundamental roles played by DHA and free estradiol. In particular, it has been shown that from a certain level of chronic DHA deficiency, a permanent imbalance sets in with disturbances in glucose intake and brain metabolism. This DHA deficiency is an aggravating factor in some neuropathologies.

Keywords: Brain / glucose / DHA / estradiol / GLUT-1

Résumé – DHA (acide gras oméga-3) : un rôle clé dans l'absorption cérébrale du glucose. Dans le cerveau, les neurones présentent la plus forte demande énergétique et nécessitent un apport continu de glucose par le sang. Une régulation étroite du métabolisme du glucose, en réponse à des stimuli, est essentielle. Au cours de l'activité neuronale, le métabolisme du glucose et le flux sanguin cérébral sont étroitement coordonnés pour maintenir une fonction cérébrale appropriée. L'absorption du glucose à travers la barrière hémato-encéphalique est facilitée par le transporteur GLUT-1. La première façon de répondre aux demandes urgentes de glucose est d'augmenter le flux sanguin par le biais d'actions vasodilatatrices générées par le monoxyde d'azote. La deuxième consiste à augmenter la densité de GLUT-1 par translocation de ce transporteur à partir des réserves intracellulaires. La troisième consiste à augmenter la synthèse du GLUT-1 en stimulant la transcription du *SLC2A1* (GLUT-1 gène). Un tandem de deux molécules clés, l'estradiol libre et le DHA, est impliqué dans cette régulation. Leur interrelation est synergique et réciproque : l'estradiol libre avec des actions génomiques et non génomiques *via* ERα, et le DHA *via* les hétérodimères PPARα-RXRα et PPARɣ-RXRα. Avec cet article, nous mettons en évidence plusieurs mécanismes originaux reliant deux grands principes : la stimulation neuronale et le métabolisme énergétique cérébral, avec les rôles fondamentaux joués par le DHA et l'estradiol libre. En particulier, il montre qu'à partir d'un certain niveau de carence chronique en DHA, un déséquilibre permanent s'installe avec une perturbation de l'apport en glucose et du métabolisme cérébral. Cette carence en DHA est un facteur aggravant de certaines neuropathologies.

Mots clés : Cerveau / glucose / DHA / estradiol / GLUT-1

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1 Introduction

The mammalian brain depends on glucose as its primary source of energy. Neurons have the highest energy requirements of all of the human brain's components (Howarth *et al.,* 2012), requiring a continuous supply of glucose from the blood. Glucose metabolism provides energy for physiological brain function in the form of ATP, the basis for neuronal and non-neuronal cell maintenance, as well as through the production of neurotransmitters. Therefore, tight regulation of glucose metabolism in response to stimuli is essential for brain physiology. Disruption of this metabolism in the brain is the cause of several diseases affecting both the brain itself and the entire organism (Mergenthaler *et al.,* 2013).

Glucose metabolism and cerebral blood flow are closely coordinated during neuronal activity, to maintain proper brain function. Glucose transport across the blood-brain barrier (BBB) is facilitated by a single carrier protein, the GLUT-1 (glucose transporter). The delivery of this energy source is modulated by cerebral blood flow, which is one of the important factors in the regulation of brain function. The critical importance of controlling regional cerebral blood flow was reported as early as 1890 in a landmark publication (Roy *et al.,* 1890). Both regional cerebral blood flow and regional cerebral glucose utilization are reliable indices of synaptic function (Jueptner et al., 1995). Astrocytes play a key role in the regulation of regional cerebral blood flow and glucose uptake (Paulson *et al.,* 2010). An increase in synaptic activity leads to a dilation of local parenchymal arterioles that corresponds to the increase in metabolic demand. Cerebral blood flow and vascular smooth muscle tone are regulated by nitric oxide (NO) (Moncada *et al.,* 1991). The nitric oxide pathway is the first pathway for meeting urgent demand for glucose, as well as other nutrients, such as other nutrients, DHA (docosahexaenoic acid), ALA (linolenic acid), EPA (eicosapentaenoic acid), testosterone, estradiol, IGF-1, oxygen, etc. The second pathway for increasing glucose intake, as well as DHAA (dehydroascorbic acid), is to increase the density of GLUT-1 through the translocation of this transporter from intracellular stores. The third pathway is to increase GLUT-1 synthesis by stimulating *SLC2A1* (GLUT-1 gene) transcription (Majou, 2015). All steps in the process are complementary and highly regulated.

For glutamatergic neurons, studies have provided insight into the functional implications of the fundamental role of glucose metabolism in physiological and pathological brain function. In this opinion article, we highlight several original concepts linking two main principles: neuronal stimulation and brain energy metabolism, with the fundamental and synergic roles played by the DHA-estradiol tandem.

2 Neuronal metabolism: sources of energy

2.1 Energy in the form of ATP

ATP provides energy for the chemical reactions involved in metabolism through hydrolysis. ATP is a coenzyme for the transfer of phosphate groups associated with the kinases non-covalently. It cannot be stored in a raw state and is produced continuously. The body's ATP stocks do not exceed more than a few seconds of consumption. Important pathways by which eukaryotes generate ATP are the glycolysis (Embden-Meyerhof-Parnas pathway), the citric acid cycle (or the Kreb's cycle), and the electron transport chain (or the oxidative phosphorylation pathway). Together, these three stages are referred to as cellular respiration. Glycolysis is the metabolic pathway that converts glucose *via* a series of reactions to pyruvate. Pyruvate undergoes oxidative decarboxylation to produce acetyl-CoA. The acetyl-CoA is used as a substrate for the Kreb's cycle, which occurs in the mitochondria (Fig. 1).

2.2 The astrocyte-neuron lactate shuttle

Lactate is a ubiquitous metabolite that originates from glycolysis. Its role as an energy substrate in the brain, alongside glucose, has also been highlighted. Over the last 25 yr or so, the astrocyte-neuron lactate shuttle (ANLS) concept (Magistretti, 1997; Pellerin *et al.,* 2003) has become widely interpreted as meaning that the neuron's principal source of energy seems to be lactate from glucose. This process proposes that astrocytes play the key role in the coupling of neuronal activity and cerebral glucose utilization. According to this concept, astrocytes are the primary consumer of blood-borne glucose in the brain. Within astrocytes, glucose is metabolized glycolytically to lactate, which is then exported as the neuron's primary source of energy; this process is stimulated by glutamate. Astrocytes have a key role in maintaining the functionality of synapses and neuronal circuits, and store glucose in the form of glycogen (Rodriguez *et al.*, 2009). Astrocyte-to-neuron signaling in intact tissue contributes to synaptic plasticity (Fiacco *et al.*, 2004).

The two pyruvate molecules produced from one glucose molecule have two uses in astrocytes: (i) the reduction in lactate catalyzed by lactate dehydrogenase (LDH) (O'Brien *et al.*, 2007), (ii) their use as a substrate of the Kreb's cycle to enable the continued production of ATP molecules through oxidative phosphorylation (Pellerin *et al.,* 2003; Fig. 1). Astrocytes and neurons have different LDH isoforms: LDH5 is the main isoform expressed in astrocytes, and it converts pyruvate to lactate whereas LDH1 is the major isoform in neurons to convert lactate to pyruvate. The rate of pyruvate production exceeds the catalytic activity of pyruvate dehydrogenase, and lactate production occurs. The enzymatic activity of LDH is much higher than that of the pyruvate dehydrogenase.

Astrocytic lactate is an intermediate metabolite of energy storage in neurons. It is an element of the elasticity of energy metabolism. It compensates for the difference in speed between the pathways of glycolysis and aerobic production of ATP. At rest, neurons spend most of their energy production in aerobic glycolysis (>90%) for the maintenance of transmembrane ion concentration gradients through Na^+/K^+-ATPase. Aerobic glycolysis saturates quickly during prolonged stimulation (Fox *et al.*, 1988). A second energy pathway must quickly replace the first one to secure neuronal and synaptic function upon stimulation. This alternative route involves two main intermediaries: astrocytes and lactate. The transient formation of lactate during stimulation has been demonstrated in several studies (Prichard *et al.*, 1991; Sappey-Marinier *et al.*, 1992; Fellows *et al.*, 1993).

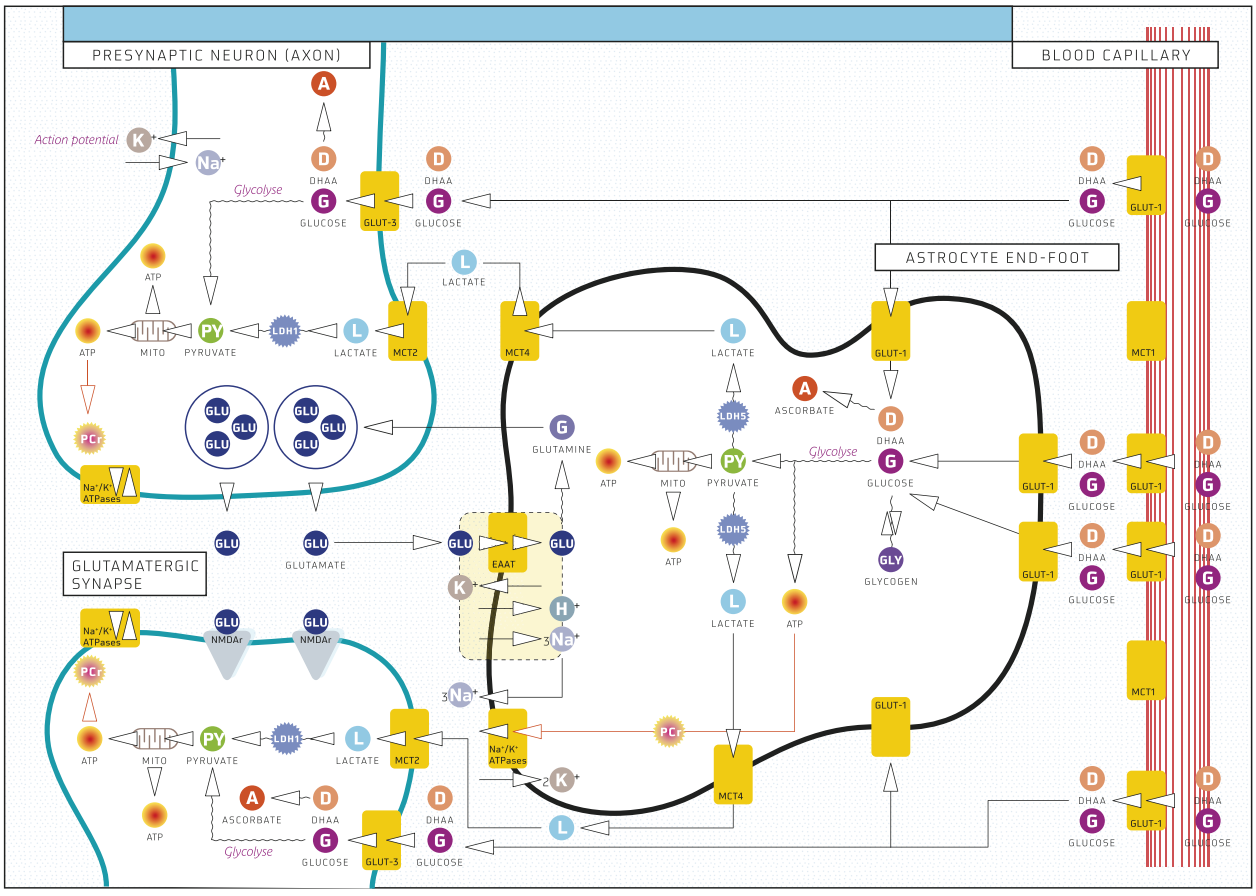

Fig. 1. Astrocyte – Neuron – Glucose flow sheet.

3 Sustaining ATP demand caused by glutamatergic stimulation

At the astrocyte, the flow of glucose, its concentration and the kinetics of ATP production are dependent on the stimulation mediated by glutamate for glutamatergic neurons with a pre- and postsynaptic synchronization (Magistretti, 2009). Glutamate is released into the synaptic cleft and activates ionotropic glutamatergic receptors, producing a postsynaptic depolarization. Astrocytic excitatory amino acid transporters (EAATs) are responsible for the uptake of a large fraction of glutamate at the synapse and they control glutamate homeostasis. EAAT2, which is concentrated in perisynaptic astrocytes, performs 90% of glutamate uptake. Glutamate is converted into glutamine by glutamine synthetase and shuttled back to neurons for glutamate synthesis (Allaman *et al.*, 2011). The glutamate-glutamine shuttle consumes two ATP molecules: one molecule of ATP for astrocytes to capture glutamate through the action of the Na^+/K^+-ATPase (Magistretti *et al.*, 1997; Schurr *et al.*, 1998), and one molecule of ATP to convert the glutamate to glutamine by glutamine synthase (Smith *et al.*, 1991). This energy consumption activates astrocytic glycolysis, its enzymatic chain and phosphorylation of glucose to glucose-6-phosphate by hexokinase to find equilibrium a balance between osmotic input and consumption.

In order to meet this need for glucose, different processes are mobilized according to different spatiotemporal modalities. The first way the body meets urgent demand for glucose is to increase the blood flow through vasodilatory responses generated by nitric oxide. If that is insufficient, the second way is to increase the density of GLUT-1 through the translocation of this transporter from intracellular stores. The third pathway is to increase GLUT-1 synthesis by stimulating *SLC2A1* (GLUT-1 gene) transcription.

4 Vasodilatation and glucose uptake

Nitric oxide (NO), produced by many cells in the body, relaxes vascular smooth muscle. It is produced by a group of enzymes called nitric oxide synthases (NOS). Three NOS isoforms have been identified: neuronal NOS (nNOS or NOS 1), endothelial NOS (eNOS or NOS 3), and an inducible NOS (iNOS or NOS 2). The expression of the iNOS is one of the direct consequences of an inflammatory process. iNOS is induced in astrocytes and microglia under pathological conditions; nNOS are localized in synaptic spines, astrocytes, and the loose connective tissue surrounding blood vessels in the brain; eNOS are present in cerebral vascular endothelial cells, motor neurons, dendritic spines (Caviedes *et al.*, 2017) and astrocytes (Wiencken *et al.*, 1999). During physiological processes, NO produced by both eNOS and

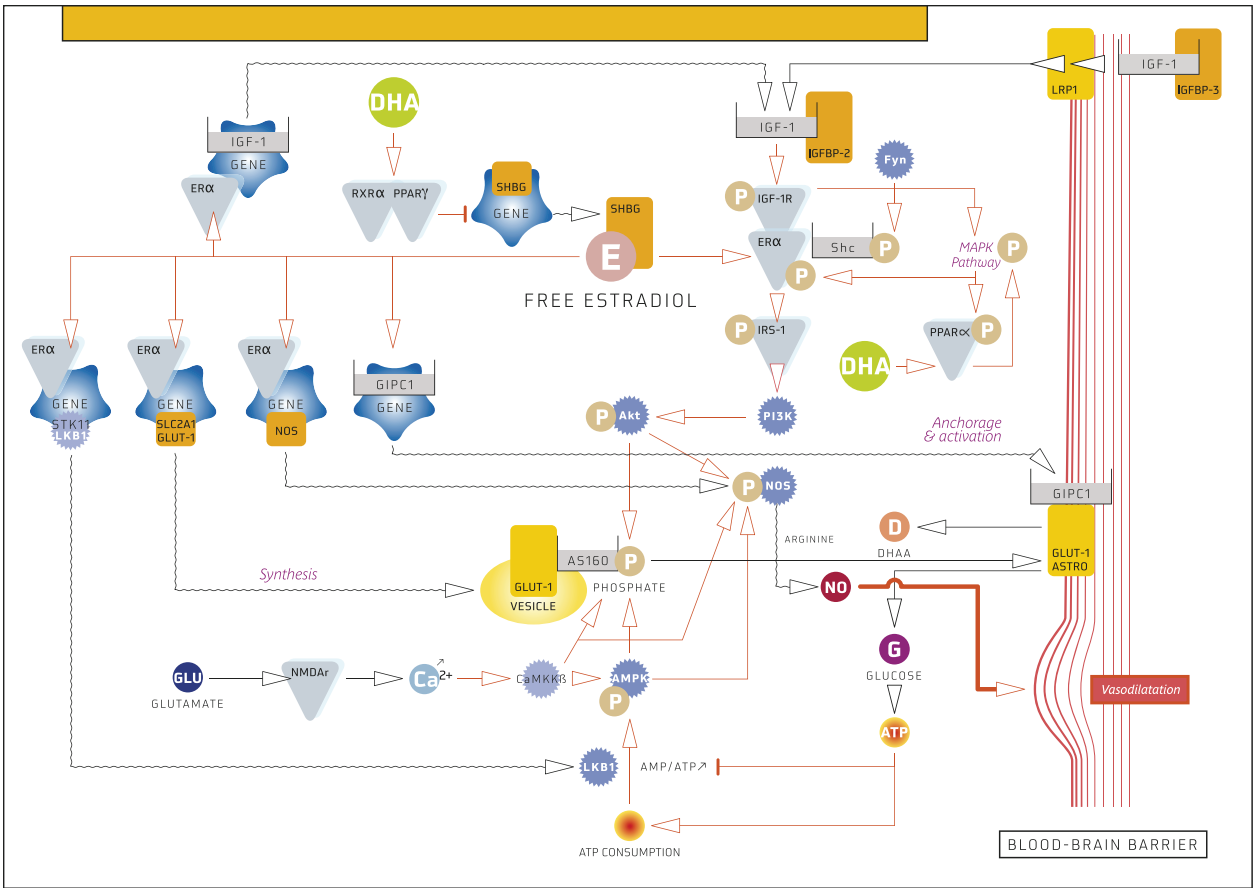

Fig. 2. Astrocytes – Up-regulation of GLUT-1 and NO.

nNOS controls blood flow activation through vasodilatory responses (Reis *et al.,* 2017). eNOS become more prominent at lower levels of neuronal activity and nNOS dominate at higher neuronal activation levels (de Labra *et al.,* 2009). As the intensity of stimulation increases (glutamate, Ca^{2+}), there is a parallel increment of NO production. Thus, eNOS is active at normal levels of stimulation; when levels of activity increase, there is a switch from eNOS to nNOS.

These enzymes, activated by phosphorylation, convert arginine into citrulline, producing NO in the process. Oxygen and NADPH are necessary co-factors. The phosphorylation of eNOS resembles that of AS160 (see mechanisms below) *via* the activation/phosphorylation of AMP-activated protein kinase (AMPK) or *via* the PI3K (phosphoinositide-3-kinase)/Akt signaling pathway (Fig. 2). The first one, *via* AMPK, is induced most commonly upon activation of the NMDA receptor (N-methyl-D-aspartate) subtype of the glutamate receptor, which results in calcium influx (Zonta *et al.,* 2003; Stobart *et al.*, 2013). Ca^{2+} binds to calmodulin-dependent protein kinase II (CaMKII), which phosphorylates and activates eNOS (Schneider *et al.*, 2003). In nNOS and eNOS, calmodulin binding is brought about by an increase in intracellular Ca^{2+}. When calmodulin affinity to NOS increases, it facilitates the flow of electrons from NADPH in the reductase domain to the haem in the oxygenase domain. Activation of eNOS and nNOS is thought to depend on the phosphorylation of serine 847 and serine 1412. A low glutamate concentration (30 µm glutamate) induces rapid and transient NMDA receptor-dependent phosphorylation of S1412 by Akt, followed by sustained phosphorylation of S847 by CaMKII of nNOS (Rameau *et al.,* 2007). But the phosphorylation of nNOS at S847 by CaMKII attenuates the catalytic activity of the enzyme (Komeima *et al.,* 2000). Moreover, an excitotoxic stimulus (150 µm glutamate) induced S1412, but not S847 phosphorylation of nNOS (Rameau *et al.,* 2007). In concert with CaMKII signaling in the post-translational activation of eNOS, the LKB1/AMPK/eNOS pathway is also activated by the depletion of ATP (Vázquez-Chantada *et al.*, 2009; Fig. 2). In addition, MAPK pathway (mitogen-activated protein kinase) works in synergy with and activates the PI3K/Akt signaling pathway (see mechanism below).

NO diffuses freely across membranes (it is a transient paracrine and autocrine signaling molecule) into smooth muscle cells surrounding arterioles. There it activates soluble guanylyl cyclase (sGC) (a heterodimer with a heme moiety as a prosthetic group) yielding cyclic GMP (cGMP) from guanosine triphosphate (GTP). The binding of NO to the ferrous (Fe^{2+}) center of the heme moiety induces a conformational change and leads to a several hundred-fold increase in cGMP

production (Shah *et al.,* 2018). Oxidation of the sGC heme to the ferric (Fe^{3+}) state desensitizes the enzyme to NO (Fernhoff *et al.,* 2012). cGMP binds and activates protein kinase G (PKG), resulting in an overall reduction in calcium influx, and an inhibition of calcium-dependent muscle contraction. PKG can also block other pathways that lead to muscle contraction (Guix *et al.,* 2005). The result is vasodilatation and increased blood flow. This pathway leads to a dilation of local parenchymal arterioles that meets the increased metabolic demand. NO is known as the endothelium-relaxing derived factor (ERDF). NO is synthesized at astrocytes and postsynaptic neurons (Galea *et al.*, 1992; Ko *et al.,* 1999). Endothelium-dependent vasodilation declines steadily with aging in healthy human subjects; in women, a steep decline commences at around the time of menopause (Celermajer *et al.,* 1994; Gerhard *et al.*, 1996; Fig. 2).

5 The key roles of transporters

5.1 Glucose and the fundamental role of GLUT-1 transporter

Glucose is transported across the BBB from the blood into the brain intercellular space. Intercellular glucose is then transported into neurons and astrocytes *via* a process of facilitated diffusion. Once the substrate is transported into the intracellular compartment, glucose is immediately phosphorylated into glucose 6-phosphate by a rate-limiting reaction catalyzed by the hexokinase enzyme (Purich, *et al.*,1973). This maintains the glucose concentration gradient and prevents glucose 6-phosphate retro-diffusion. This facilitated glucose transport is mediated by isoforms of a family of membrane-spanning glycoproteins called GLUTs (Joost, 2001). GLUT-1 and −3 are the two glucose transporter isoforms that are widely expressed by the mammalian brain. GLUT-1 transporters are present on astrocytes and on capillaries (Szablewski, 2017) with two significant types. GLUT-1 55kDa on capillaries is responsible for glucose transport across the blood-brain barrier (microvascular endothelial cells). For astrocytes, glucose is taken up especially by GLUT-1 45kDa at the astrocytic end-feet adjacent to the endothelial cells. Both isoforms of GLUT-1 are encoded by the same *SLC2A1* gene, and differ only in their degree of glycosylation (Kumagai *et al.,* 1994). There is approximately the same amount of GLUT-1 on astrocytes and endothelial cells. For example, the activation of the hippocampus, an area of the brain involved in memory processing, specifically increases *SLC2A1* gene and protein expressions of both endothelial and astrocytic isoforms (Choeiri *et al.*, 2005). For neurons, glucose is transported by GLUT-3 (*SLC2A3* gene) from the extracellular space. GLUT3 is mainly concentrated in axons and dendrites. GLUT-3 has a higher affinity for glucose than GLUT-1 (Custódio *et al.,* 2021) and its transportation capacity is at least five times greater. The combination of lower affinity constant and higher capacity gives neurons preferential access to available glucose from extracellular space (Simpson *et al.*, 2008). However, GLUT-3 is downstream of GLUT-1 55kDa. Regulation of GLUT-3 is dependent on the regulation of GLUT-1 55kDa, which allows glucose to enter the extracellular space (Fig. 1).

5.2 GLUT-1, transporter of dehydroascorbic acid (DHAA), and antioxidant defenses

Nerve endings in the brain contain the highest concentrations of L-ascorbic acid in the human body after the suprarenal and pituitary glands (Bourre, 2006). This concentration in the brain exceeds blood concentrations by at least tenfold. As an electron donor, L-ascorbic acid (vitamin C) has an antioxidant function in the brain. During reduction of free radicals, L-ascorbic acid is oxidized to dehydroascorbic acid (DHAA) by giving two electrons. DHAA, is reduced by glutathione, then the oxidized glutathione is reduced by the action of glutathione reductase in a reaction coupled with NADPH. The glutathione/oxidized glutathione redox state is coupled with the L-ascorbic acid/DHAA redox state by both enzymatic and non-enzymatic processes (Harrison *et al.,* 2009).

Working in synergy with the activity of the main free radical scavenging enzymes, copper/zinc superoxide dismutase, manganese superoxide dismutase, catalase, and glutathione peroxidase, L-ascorbic acid protects cellular components from free radical damage. It scavenges free radicals directly in the aqueous phases of cells and the circulatory system. L-ascorbic acid also protects membrane and other hydrophobic compartments from such damage by regenerating the antioxidant form of dietary vitamin E (Beyer, 1994). Vitamin E, localizes to lysosomes and mitochondria in primary neurons and astrocytes (Ulatowski *et al.,* 2022), inhibits lipid peroxidation, thus preventing membrane damage and the modification of low-density lipoproteins. Moreover, vitamin E and vitamin C work together to protect vulnerable polyunsaturated fatty acids such as omega-3s. And, as we shall see later, an omega-3 fatty acid, docosahexaenoic acid (DHA), is a key molecule in GLUT-1 transporter function. In fact, brain tissue is especially sensitive to oxidative injury because of its higher metabolic rate driven by glucose and oxygen (reactive oxygen species are generated continuously during oxidative metabolism), lower concentrations of protective antioxidants, and higher levels of polyunsaturated fatty acids that are susceptible to lipid peroxidation (Markesbery, 1999). The most reactive forms, such as the hydroxyl radical, are also capable of oxidizing proteins and nucleic acids.

Whereas most mammals synthesize L-ascorbic acid *de novo* in their liver, anthropoid primates, including humans, certain bats and guinea pigs, are incapable of doing so. This is due to a mutation in the L-gulonolactone oxidase enzyme gene (*GULO* gene), thought to have occurred during the late Eocene (Majou, 2018). These animals have an inactive form of the altered *GULO* gene (*GULO* pseudogene), which does not allow the enzyme to be synthesized (Ohta *et al.,* 1999). They must therefore regularly obtain it from dietary sources in oxidized form (DHAA). L-ascorbic acid is not transported across the capillary endothelial cells in the blood-brain barrier. DHAA is transported through the blood-brain barrier by GLUT-1 transporters (Rumsey *et al.*, 1997) and then immediately converted into L-ascorbic acid by enzymes, namely NADPH-dependent thioredoxin reductase, glutathione-dependent protein disulfide isomerase, and DHAA reductase (Agus *et al.*, 1997), particularly in astrocytes

(Daskalopoulos *et al.*, 2002). Being the transporter that enables glucose and DHAA to cross the blood-brain barrier, this further reinforces the essential role of GLUT-1. It allows the production of ATP, glutamate (Kreb's cycle), and glutathione from glutamate and L-ascorbic acid. These molecules are used in neurotransmission, energy production and the synthesis of antioxidants. GLUT-3 also mediates DHAA transport with a lower effect (Rumsey *et al.*, 1997). The release of ascorbate from astrocytes is associated principally with the activity of glutamatergic neurons (Castro *et al.*, 2009).

5.3 Translocation of GLUT-1 transporter from intracellular stores

We will describe the body's second pathway for increasing the uptake of glucose, as well as DHAA, namely to increase the GLUT-1 density by relocating this transporter from intracellular stores. Concentration changes in ATP and AMP are the main regulators of AMPKactivity. AMPK is a key sensor of cellular energy status based on the AMP/ATP ratio. It is activated by AMP allosterically and inhibited by ATP. The two nucleotides compete for the same binding site on the regulatory γ subunit (2 Bateman domains) (Adams *et al.*, 2004). Then, Thr172 of α subunit catalytic site is phosphorylated by Liver kinase B1 (LKB1). This phosphorylation is essential for the activity of AMPK. AMPK activity has been shown to increase in neuronal tissue in response to glucose deprivation, metabolic stress, hypoxia and ischemia (Culmsee *et al.*, 2001; Gadalla et *al.*, 2004; McCullough *et al.*, 2005). AMPK activation promotes the translocation of GLUT-3 storage vesicles on the surface of neuronal cells (Weisová *et al.*, 2009). Increasing the amount of GLUT-3 promotes the entry of glucose. At the astrocyte, AMPK activation promotes the translocation of GLUT-1 storage vesicles to the blood brain barrier (Cura *et al.,* 2012). This translocation of GLUT-1 is made from a reservoir of cytoplasmic vesicles (Widnell, 1995). AS160 (Akt substrate of 160 kDa), a Rab GTPase-activating protein that is widely expressed in vertebrates, is located on the membranes of these intracellular vesicles. In the absence of phosphorylation, it maintains these vesicles in the cytoplasm and inhibits its translocation. The phosphorylation of AS160 is dependent on PI3K/Akt pathway (Kim *et al.,* 2011). And remember that the MAPK pathway works in synergy with and activates the PI3K/Akt signaling pathway (see mechanism below). After the phosphorylation of AS160 (Treebak *et al.*, 2006), GLUT-1 translocates to and enters the BBB (Andrisse *et al.*, 2013; Fig. 2). The role of AS160 is mediated by its GTPase-activating domain and interactions with Rab proteins in vesicle formation, increasing GLUT-1 translocation when its GTPase activity is inhibited by AMPK phosphorylation. AS160 is not only an Akt substrate but also a substrate for other kinases such as AMPK (Sakamoto *et al.,* 2008). Phosphorylation appears to occur at different sites (Ser or Thr) (Chen *et al.*, 2008). Eight residues on AS160 (Ser318, Ser341, Thr568, Ser570, Ser588, Thr642, Ser666, Ser751) that can be phosphorylated have been identified. AMPK preferentially phosphorylates Ser588, with less phosphorylation of other sites (Geraghty *et al.*, 2007). These actions have been described for GLUT-1 and GLUT-4 (Sakamoto *et al.,* 2008; Marko *et al.,* 2020) in skeletal muscle. It can be assumed to apply to astrocytes and neurons, to GLUT-1 and GLUT-3 (Cura *et al.,* 2012; Fig. 2).

AMPK can also be phosphorylated and activated by the AMPK kinase Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ) (Hawley *et al.,* 2005) (Fig. 2). CaMKKβ is a serine/threonine-directed kinase that is activated following increases in intracellular Ca^{2+} concentrations. The level of glutamatergic activity determines the level of Ca^{2+} that enters astrocytes and postsynaptic neurons. A key receptor is involved, the NMDA receptor is a gateway for Ca^{2+}. NMDA agonists such as glutamate can cause a rise in intracellular Ca^{2+} levels within astrocytes (Lee *et al.*, 2010). NMDA receptors are Ca^{2+}-permeable and stimulate Ca^{2+} influx into the cell. The activation of CaMKKβ facilitates the translocation of GLUT-1 and GLUT-3 as described above. Thus, if the role of AMPK is to promote ATP conservation and production, AMPK does not just react to cellular energy depletion but also anticipates it *via* extracellular Ca^{2+} flux. AS160 also contains a calmodulin-binding domain, and this domain mediates phosphorylation (Kramer *et al.*, 2007); the calmodulin-dependent protein kinase II (CaMKII) is involved (Mohankumar *et al.*, 2012). The levels of phosphorylation of AS160 at its multiple phosphorylation sites may be such that AMPK-induced phosphorylation alone would limit its reaction speed. The coupling of the two means of phosphorylation (AMPK and calmodulin) would accelerate the kinetics.

5.4 Lactate and the role of monocarboxylate transporters (MCTs)

The transport of lactate from astrocytes to pre- and postsynaptic neurons by proton-linked monocarboxylate transporters (MCTs) (Halestrap *et al.,* 1999; Pérez-Escuredo *et al.*, 2016) has several advantages: (i) the removal of lactate and its proton avoids acidosis of astrocytic cytosol (low pH inhibits phosphofructokinase activity and slows or stops anaerobic glycolysis), (ii) the catabolism of lactate in neurons, once again *via* pyruvate. With lactate, neurons can respond faster to stimulation than they can with aerobic glycolysis from glucose. MCTs are found in many types of tissue, including the brain where three isoforms, MCT1, MCT2 and MCT4 (monocarboxylate transporters), have been described. Each of these isoforms exhibits a distinct regional and cellular distribution in rodent brains. At the cellular level, MCT1 is expressed by endothelial cells of microvessels, by ependymocytes, and by astrocytes. MCT4 expression appears to be specific to astrocytes. MCT2 is mainly expressed in neurons (Pierre *et al.*, 2005). Their anchorage and activity at the plasma membrane requires interaction with a chaperone protein, such as basigin (CD147) or embigin (gp70), which belong to the immunoglobulin superfamily. These proteins are anchored to the plasma membrane through a single transmembrane domain containing a conserved glutamate residue. Basigin (Muramatsu *et al.,* 2016) is more widely expressed cell tissue than embigin, and appears more frequently as the preferential partner for MCT1 and MCT4, whereas MCT2 preferentially interacts with embigin (Wilson *et al.*, 2005). Basigin expression (*BSG* gene) in the mouse uterine epithelium appears to be upregulated by estrogen *via* the estrogen receptor-α (ERα) (Chen *et al.*, 2010). Embigin expression

(*EMB* gene) in the amygdala of female mice is regulated by estradiol (Jasnow *et al.*, 2007).

Glucose and lactate provide a complementary supply of energy according to different spatiotemporal modalities. Thus, estradiol has an important role in the transport of lactate by MCTs, *via* basigin and embigin, which is similar to its role in the transport of glucose by GLUTs, whose mechanism will be detailed in the following sections of the article in addition to the synergistic interaction between estradiol and DHA.

6 Free estradiol as key regulator of regional cerebral glucose uptake

Baseline regional cerebral glucose metabolism differs between males and females (Gur *et al.*, 1995). Neuroimaging studies have demonstrated that both age and sex affect cerebral glucose metabolism (Kim *et al.*, 2009). Ovarian steroids may mediate alterations in glucose uptake because the highest glucose uptake occurs during pro-oestrus (Nehlig *et al.*, 1985), and cerebral glucose metabolism decreases in postmenopausal women who are not receiving estrogen replacement therapy (Rasgon *et al.*, 2005). Cerebral blood flow is diminished in hypoestrogenic women, with regional patterns resembling those of patients with mild to moderate Alzheimer's disease (Greene, 2000). Gender differences exist in the gene expression profiles of GLUT-1 in mouse tissues (Nagai *et al.,* 2014). Hormonal variation across the four stages of the rat oestrus cycle affects the abundance of mRNA of cerebral transporters GLUT-1 and GLUT-3 in the hypothalamus, hippocampus and prefrontal cortex (Harrell *et al.*, 2014).

6.1 Free estradiol and regional cerebral glucose flow regulation by GLUT-1 transporters

17β-estradiol (estradiol) is an estrogen hormone that plays an essential role in the up-regulation of GLUT-1 in the brain. It increases the number of GLUT-1 molecules on the astrocyte and capillary endothelial cell membranes in contact with the blood-brain barrier. Its intervention takes place in at least three stages (synthesis, translocation, and anchoring) to increase the flow of glucose and DHAA in response to stimulations (Majou, 2018).

The *SLC2A1* gene, which codes for GLUT-1, is an estrogen-regulated gene with transcription activation by estrogen receptors (ERs) (Wang *et al.*, 2004), which are also present on astrocyte membranes (Chaban *et al.*, 2004). *In vivo*, treatment with estradiol increases GLUT-1 protein concentration in the blood-brain barrier's endothelial cells, and GLUT-1 mRNA expression in correlation with the increase in glucose uptake (Shi *et al.,* 1997). The same effect also appears in fetal rat lungs (Hart *et al.*, 1998). This treatment induces a two- to fourfold increase in GLUT-3 mRNA levels and lesser but significant increases in GLUT-3 protein levels, as well as a 70% increase in parenchymal GLUT-1 mRNA levels in the primate cerebral cortex (Cheng *et al.*, 2001).

Once synthesized, GLUT-1 protein is stored in vesicles. As described above, AMPK activation promotes the translocation of GLUT-1 and GLUT-3 to the BBB. And estradiol allows the translocation of GLUT-1 vesicles to the cell membranes, favoring the phosphorylation of a vesicle protein (AS160) *via* the PI3K/Akt signaling pathway or *via* activation/phosphorylation of AMPK (Rogers *et al.*, 2009) by the LKB1 enzyme, coded by the *STK11* gene (Serine-Threonine Kinase 11). Estradiol also increases the expression of this *STK11* gene, an effect mediated by ERα (Mac Innes *et al.,* 2012). Lastly, the GLUT-1C terminus is anchored to the sub membranous actin cytoskeleton by a scaffolding protein known as GIPC1 (GAIP-interacting protein, C terminus) or GLUT-1CBP (GLUT-1 C-terminal binding protein) (Hernandez-Garzón *et al.,* 2016; Reed *et al.*, 2005). Estradiol increases the expression of GIPC1 mRNA (RGD). The highest amount of GIPC1 mRNA is observed in the brain (Bunn *et al.*, 1999). Blocking GLUT-1 interactions with GIPC1 disrupts normal GLUT-1 trafficking, leading to a reduction in the level of GLUT-1 in the plasma membrane and concomitant accumulation in internal membrane structures (Reed *et al.*, 2005). A GIPC1 deficiency decreases GLUT-1 surface levels and glucose uptake (Wieman *et al.*, 2009).

Thus, free estradiol – without its binding protein (sex hormone binding globulin, SHBG) – plays a significant role in the up-regulation of GLUT-1 during its synthesis by the expression of the *SLC2A1* gene, as well as translocation by activating AMPK *via* the *LKB1* gene and its anchor GIPC1 to increase the number of GLUT-1 molecules in astrocytes and capillary endothelial cells (Fig. 2). Therefore, if the concentration of free estradiol falls, there is competition between all estrogen receptors and SHBG (see below) and uses thereof will take place with a consequence on GLUT-1 activity kinetics (number of operational GLUT-1 per unit of time). This is demonstrated by the delayed response to cellular demand for glucose and DHAA, resulting in energy and antioxidant imbalance (FEDOX paradigm). If astrocytes are relatively well protected, the impact will be on pre- and postsynaptic neurons.

6.2 Free estradiol and free IGF-1: a synergistic effect

Free estradiol has a synergistic effect with free insulin-like growth factor-1 (IGF-1) – without its binding protein (insulin-like growth factor-binding proteins, IGFBPs) – which in humans is encoded by the *IGF-1* gene (Nelson *et al.,* 2014). For example, several studies have shown this interaction in different regions of the brain (Garcia-Segura *et al.*, 2006; Varea *et al.*, 2010; Park *et al.*, 2014; Huffman *et al.,* 2017) and in breast cancer cells (Song *et al.,* 2010). IGF-1 mRNA levels were significantly increased in primate cerebral cortical neurons treated with estradiol (Cheng *et al.*, 2001) and in the immortalized rat hippocampal cell H19-7. This increase in the number of copies of IGF-1 mRNA was accompanied by an increase inIGF-1 protein level (Shingo *et al.,* 2003). In uterus, this IGF-1 synthesis requires ERα, which binds directly to target DNA sequences (estrogen-responsive elements) (Hewitt *et al.*, 2010). IGF-1 is a protein that provides good neuroprotective effects. IGF-1 is produced by the liver as an endocrine hormone as well as in target tissues in a paracrine or autocrine fashion. IGF-1 is synthesized *de novo* or transported across the BBB. Local production of IGF-1 is believed to be the primary source for brain cells (Russo *et al.*, 2005). IGF-1 is particularly expressed in astrocytes (Chernausek, 1993; Madathil *et al.*, 2013). IGF-1 crosses the BBB from plasma *via* a saturable transport system.

In serum, only a small amount of IGF-1 circulates free. IGF-1 is sequestered into ternary complexes consisting of one molecule each of IGF-1, IGF binding protein-3 (IGFBP-3), and acid-labile subunit (ALS) (Nishijima *et al.,* 2010). The cleavage of IGFBP-3 by matrix metalloproteinase-9 (MMP9) allows the passage of serum IGF-1 through an interaction with the endothelial transporter lipoprotein related receptor 1 (LRP1) which is abundantly expressed in brain endothelium (Nishijima *et al.,* 2010). PPARγ-RXRα induces the expression of the *LRP1* gene (see mechanism below) (Wang *et al.,* 2016).

The anabolic actions of IGF-1 are mediated by the IGF-1 receptors (IGF-1Rs). When IGF-1 binds to the IGF-1R, it causes a conformational change to the receptor, inducing the autophosphorylation of tyrosine residues (Hubbard *et al.,* 2000). This leads to the recruitment of insulin receptor substrates (IRS-1 to IRS-4), which in turn phosphorylates the tyrosine residues of the IRSs. ERα regulates the IGF-1 signaling pathways (Kahlert *et al.,* 2000) through phosphorylation of ERK1/2 (extracellular signal-regulated kinases) and Akt, and the between ER and IGF-1R potentiates cell growth. Estradiol and IGF-1 stimulate translocation of ERs from the nucleus to the cytoplasm (Song *et al.*, 2010). Estradiol stimulates the rapid activation of the IGF-1Rs through phosphorylation *via* ERα and induces the formation of a ternary protein complex comprised of phosphorylated Shc protein, ERα and IGF-1R (Song *et al.*, 2004). Adapter protein Shc generally acts by activating MAPK and PI3K/Akt pathways (Gu *et al.,* 2000; Vindis *et al.,* 2003). The tyrosine phosphorylation of Shc is mediated by the tyrosine kinase Fyn (Src family kinase) associated with caveolin-1 (scaffolding protein) (Wary *et al.*, 1998). Upon integrin ligation, Fyn is activated and binds to Shc *via* its SH3 domain. Shc is subsequently phosphorylated at tyrosine 317 (Wary *et al.,* 1998). The activation of IGF-1Rs stimulates MAPK kinase and, consequently, the phosphorylation of ERK1/2. The activation of ERK1/2 may in turn lead to the phosphorylation of ERα (Kato *et al.,* 1995) (Russo *et al.*, 2002). Moreover, Shc is expressed in astrocytes (Cazaubon *et al.,* 1994). The activation of membrane ERα appears to be coupled to the MAPK pathway (Pawlak *et al.*, 2005). This process leads to the activation of two main downstream signaling pathways: PI3K/Akt and MAPK cascades (Zheng *et al.*, 2000). The interaction of the ER and IGF-1R is important for the non-genomic effects of ER. (Yu *et al.,* 2013; Fig. 2). It is also worth noting that the IGF-1R is capable of heteromeric assembly with the insulin receptor (IR). Heterodimers exhibit a similar affinity to IGF1 as IGF-1R homodimers but have a substantially lower insulin binding affinity (Bailyes *et al.,* 1997; Kleinridders, 2016), indicating that the action of IGF-1 is crucial for brain physiology. Indeed, IGF-1 is at least 10 times more potent than insulin in stimulating the rate of glucose uptake, showing that IGF-1, rather than insulin, is the physiological agonist regulating glucose transport in ependymal cells (Verleysdonk *et al.,* 2004). Insulin appears to stimulate brain glucose metabolism at physiological postprandial levels in patients with impaired glucose tolerance (diabetes), but not in healthy subjects (Hirvonen *et al.,* 2011), perhaps through glucagon-like peptide-1 (GLP-1) system (Sandoval and Sisley 2015).

6.3 Estradiol and regional cerebral glucose flow regulation by nitric oxide (NO)

The phosphorylation of eNOS resembles that of AS160 *via* the activation/phosphorylation of AMPK or *via* the MAPK and PI3K/Akt pathways (Fig. 2). In the LKB1/AMPK/eNOS pathway, estradiol induces transcription of the *LKB1* gene (Mac Innes *et al.,* 2012). The second pathway is a non-genomic interactive effect of free estradiol and free IGF-1, which rapidly phosphorylates eNOS *via* the PI3K/Akt dependent pathway (Dimmeler *et al.*, 1999). This activation is mediated by ERα (Gerhard *et al.*, 1996) localized to caveolae in endothelial cells lining cerebral capillaries (Isenovic *et al.*, 2003; Stirone *et al.*, 2005; Chambliss *et al.*, 2005). The process also requires phosphorylated Shc and Fyn (Src kinase) associated with caveolin-1 (Kim and Formoso, 2007). Moreover, Src kinase mediates ERβ-induced increases in phosphorylation levels of nNOS at S1412 and NO production by activating the PI3K/Akt pathway (Gingerich *et al.,* 2008; Fig. 2).

An increase in NO is also due to increases in *eNOS* and *nNOS* expression. The effects on eNOS and nNOS abundance are primarily mediated at the level of gene transcription. Estradiol is known to induce an upregulation of *eNOS* gene expression, through the binding of ERα to its *eNOS* promoter through the estrogen-responsive element (Min, 2007). Endogenous variations in estrogen levels during the estrous cycle also coincide with corresponding changes in the state of nNOS Ser1412 phosphorylation (Parkash *et al.,* 2010). Estradiol increases *nNOS* and *eNOS* expression and activity in the female hippocampus and thus improves hippocampal function (Grohe *et al.,* 2004). Both pregnancy and estradiol treatment increase the amount of NOS isozyme, eNOS and nNOS mRNA in skeletal muscle (Weiner *et al.,* 1994). Overall, estradiol stimulates the NO neuronal system. Reduced *eNOS* and *nNOS* expression have been associated with stroke and Alzheimer's disease, which is associated with neurovascular dysfunction (Thorns *et al.,* 1998; Tan *et al.,* 2015).

6.4 Astrocytes: endogenous and exogenous sources of estradiol

The supply of 17β-estradiol can have several origins depending on the quantities to be supplied and local consumption. As we will see, it will depend on the plasma concentrations of estradiol and testosterone, and their modulator, SHBG, at every stage of life (puberty, elderly, menstrual or estrous cycle, pregnancy), physiological status, or exogenous hormones (contraceptive pills, phytoestrogens, etc.). Thus, the action of estradiol is regarded as endocrine, autocrine and paracrine.

Estradiol may have three sources, including an exogenous source, directly from plasma through gonadal synthesis; the free form of estradiol crosses the BBB thanks to its lipid-permeable nature by a passive diffusion mechanism (Pardridge *et al.*, 1979). But the concentration of estrogens circulating in the blood may be much lower than that of local intra-tissue estrogen production, particularly in men and postmenopausal women (Simpson *et al.,* 2005). And a first local endogenous source, from testosterone from the plasma through gonadal synthesis. The free form of testosterone also crosses the BBB

thanks to its lipid-permeable nature. Testosterone is the precursor of estradiol by aromatization. The P450 aromatase (*CYP19* gene) is a microsomal enzyme of the cytochrome P450 family (Roselli *et al.*, 2009). Neurons, astrocytes and brain capillary endothelial cells express P450 aromatase. In astrocytes, estradiol concentrations are proportional to the activity and expression of aromatase (Saleh *et al.*, 2005).

The second local endogenous source is cholesterol, which is synthesized from acetyl-CoA, which may partly be produced from glucose and from fatty acids. The brain is a steroidogenic organ that expresses steroidogenic enzymes and produces neurosteroids. In studies on rat brains (Zwain and Yen 1999), astrocytes appear to be the most active steroidogenic cells. They express a cholesterol side-chain cleavage enzyme (P450scc) (mitochondrial enzyme), 17α-hydroxylase/C17,20 lyase (P450c17), 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-hydroxysteroid dehydrogenase (17β-HSD), and P450 aromatase and produce pregnenolone, progesterone, dehydroepiandrosterone (DHEA), androstenedione, testosterone, estradiol, and estrone.

A rate-limiting step in neurosteroid synthesis from cholesterol is the transport of cholesterol mediated by apolipoprotein E (ApoE). ApoE is expressed in such high concentrations that the brain is the organ with the second highest *ApoE* expression after the liver. *ApoE* is expressed within the brain predominantly by astrocytes, oligodendrocytes, microglia and epidermal layer cells (Orth *et al.,* 2012) while neurons preferentially express the receptors for ApoE. ApoE does not cross the BBB and, therefore, must be synthesized locally in the brain (Liu *et al.,* 2012). This protein is undoubtedly involved in brain cholesterol homeostasis. It transports cholesterol to neurons *via* ApoE receptors. Free 17β-estradiol regulates *ApoE* gene expression in a tissue-specific manner in mice, in particular free estrogen increases ApoE mRNA and protein expression in the brain (Srivastava *et al.*, 1996; Stone *et al.*, 1997) *via* the activation of ERα (Struble *et al.,* 2003; Wang *et al.,* 2006).

The other rate-limiting step in neurosteroid synthesis from cholesterol is the transport of cholesterol into the mitochondria. Steroidogenic acute regulatory protein (StAR) is the protein involved in this transport of cholesterol (Stocco, 2001). StAR transcripts are abundant in the cerebral cortex, hippocampus, dentate gyrus, olfactory bulb, cerebellar granular layer, and Purkinje cells. In addition its cellular distribution overlaps with that of P450scc and 3β-HSD (Furukawa et *al.,* 1998). These findings implicate StAR in the biosynthesis of neurosteroids. It is important to note that the expression of PPARγ-RXRα increases StAR-promoter activity in KK1 mouse granulosa cells and MA-10 mouse Leydig tumor cells (Kowalewski et *al.*, 2009), and DHA is a preferential ligand compared to PPARs and RXRs (de Urquiza *et al.*, 2000; Diep *et al.,* 2002; Deckelbaum *et al.,* 2006; Song *et al.*, 2017; Dziedzic *et al.,* 2018).

6.5 By binding to PPARy-RXRα, DHA therefore blocks transcription of SHBG gene and increases the quantity of free estradiol

However, the biologically active fraction of estradiol is its non-protein-bound, free fraction (Hammond, 2016). The role of binding proteins is essential in the modulation of the distribution of active molecules in space and over time, and in their protection against lysis. The regulation is dependent on the strength of the molecular bond; low affinity causes rapid action while high affinity allows a more progressive distribution compared to the "all or nothing" action of synthesis. Albumin and sex hormone-binding globulin (SHBG) modulate the availability of estradiol. SHBG, an extracellular glycoprotein, is produced mostly by the liver and is released into the bloodstream. Other sites that locally produce SHBG include the brain (Herbert *et al.,* 2005), uterus, testes and placenta. SHBG concentrations vary with age (Harman *et al.,* 2001; Maggio *et al.,* 2008). In adults, SHBG is on average twice as high in women than in men (Carlström *et al.*, 1990). Testosterone lowers SHBG levels, while inversely estradiol raises them (Carlström *et al.*, 1990; Cunningham *et al.,* 1984). For example, SHBG concentrations rise significantly under oral contraceptive treatment (Panzer *et al.,* 2006), as well as during pregnancy. Albumin has low affinity and high capacity for estradiol, contrary to SHBG which has high affinity and low capacity (stable binding constant for albumin: 4.21×10^4 L/mol, and for SHBG: 3.14×10^8 L/mol) (Södergard *et al.*, 1982; Cunningham *et al.*, 1984). All of the above are in a dynamic, competitive equilibrium. The "bioavailable fraction" is the sum of the "free fraction" and the albumin-bound fraction. The SHBG-bound fraction of estradiol is not biologically active. Thus, the SHBG concentration is decisive for the bioavailability of estradiol and its activity. The promoter region of the human *SHBG* gene contains PPRE. PPARy-RXRα represses the expression of SHBG in liver cells, while different PPARy-RXRα levels and activity contribute directly to the variations in plasma SHBG levels (Selva *et al.,* 2009). DHA is a preferential ligand in comparison to PPARs and RXRs. DHA increases the activity of PPARy (Hwang *et al.,* 2017; Naeini *et al.*, 2020; Song *et al.*, 2017). By binding to PPARy-RXRα, DHA therefore blocks transcription of *SHBG* gene, reduces the concentration of SHBG, and increases the quantity of free estradiol. This favors the activity of GLUT-1 and the flow of glucose and DHAA.

7 DHA as key regulator of regional cerebral glucose uptake

7.1 Gene transcription modulation by DHA

DHA also plays an essential role as a gene transcription modulator *via* transcription factors, in particular peroxisome proliferator activated receptors (PPARs) and retinoid X receptors (RXRs). These transcription factors take the form of PPAR-RXR heterodimers, located within the nucleus and activated by phosphorylation and their respective ligands, which modify their tertiary structures and enable them to bind to the PPRE located in the promoter region of target genes. In the absence of ligands, PPARs form complexes with corepressors such as NCoR, RIP140 or SMRT, which repress transcription through the recruitment of histone deacetylases. In the presence of ligands, coactivators such as p300, CBP, or SRC-1 become bound to the amino terminal of PPARs (Moreno *et al.,* 2010). As we will see later, the heterodimer bond on the PPRE activates the transcription of genes such as *FADS2* (Majou, 2021), *LRP1* (Wang *et al.,* 2016), *StAR*

(Kowalewski et *al.*, 2009), *eNOS* (Huang *et al.*, 2023), and represses the expression of genes such as *SHBG* (Selva et al., 2009). DHA is a preferential ligand in comparison to PPARs and RXRs (de Urquiza *et al.*, 2000; Diep *et al.,* 2002; Deckelbaum *et al.,* 2006; Song *et al.*, 2017; Dziedzic *et al.,* 2018).

7.2 Up-regulation of eNOS and nNOS by DHA

The consumption of fish or fish oil influences the expression of various vasoactive molecules and NO production by *nNOS* (Engström *et al.,* 2009) and *eNOS* gene expression in endothelial cells. Furthermore, DHA induces endothelium-dependent NO-mediated relaxation in the coronary artery. In cultured human coronary artery endothelial cells, DHA enhanced NO production and the activity of eNOS. In addition, it enhanced the expression of *eNOS* and phospho-eNOS. Specifically, DHA stimulated eNOS and PI3K/Akt activity, and induced NO bioavailability in response to Akt kinase activation (Stebbins *et al.*, 2008). eNOS activity in endothelial cells is modulated by DHA *via* MAPK pathway (Huang *et al.,* 2021; Fig. 2). p38 MAPK regulates both the activity and expression of *eNOS* by DHA (Huang *et al.*, 2023). PPARα and PPARγ induce activation of members of the MAPK family (p38 MAPK) (Gardner *et al.,* 2003). From all these converging experimental results, there is evidence that DHA, a preferential ligand for PPARs and RXRs, modulates eNOS activity *via* p38 MAPK. DHA treatment protects dopaminergic neurons in *substantia nigra* increasing nNOS in the experimental mice model of Parkinson's disease (Parlak *et al.,* 2018). So, it is plausible that the mechanisms are identical for nNOS.

7.3 Up-regulation of GLUT-1 transporters by DHA

DHA plays a major role in the up-regulation of GLUT-1. For example, in elderly monkeys, supply of DHA results in a significant increase in regional cerebral blood flow response to stimulation (Tsukada *et al.*, 2000). In humans, quantitative erythrocyte EPA/DHA levels are related to a higher regional cerebral blood flow in the brain (Amen *et al.*, 2017). *N*-3 PUFA deficiency specifically decreases the GLUT-1 protein content of both endothelial cells and astrocytes in rats (Pifferi *et al.*, 2005; Harbeby *et al.*, 2012). Lower levels of GLUT-1 transporters result from a reduction of the transcription of the *SLC2A1* gene encoding the two GLUT-1 isoforms (Harbeby *et al.,* 2012). This reduction in gene expression was also found during neuronal activation, supporting the hypothesis that the alteration of glucose uptake due to *n*-3 PUFA deficiency persists during brain activation (Harbeby *et al.,* 2012). Long-chain *n*-3 polyunsaturated fatty acid supplementation (mainly EPA and DHA) improves brain glucose uptake and metabolism in adult non-human primates (Pifferi *et al.*, 2015; Harbeby *et al.*, 2012). In primate studies, DHA levels are proportional to local cerebral metabolic rate of glucose uptake. This is correlated to a higher DHA concentration in cells and tissues, which associated with high energy consumption, consistent with high DHA levels in mitochondria and synaptosomes (Brenna *et al.,* 2007). In addition, the activity of the Na^+/K^+-ATPase pump is severely reduced in nerve endings in the whole brain of *n*-3 PUFA-deficient rats (Bourre *et al.*, 1989). These results confirm that physiological doses of DHA have a direct and positive effect on glucose transport and density of the two isoforms of GLUT1 (endothelial and astrocytic) (Pifferi *et al.,* 2010).

On the other hand, the specificity of the *n*-3 effect is highlighted by the absence of an effect on neuronal GLUT-3 glucose transporters. The expression of neuronal *GLUT-3* does not change (Pifferi *et al.,* 2005), supporting the concept that neurons are metabolically unable to increase their glucose uptake and utilization upon activation to sustain ATP demand (Choeiri *et al.,* 2005).

7.4 Origin and synthesis of DHA in the brain

Mammals are incapable of synthesizing α-linolenic acid, the precursor of the omega-3 polyunsaturated fatty acids, *de novo*. They are totally dependent on the intake of dietary precursors. The supply of DHA to the brain is thought to be governed by a principle of energy optimization. The brain is capable of autonomous DHA synthesis from α-linolenic acid (ALA, 18:3 n-3), the essential precursor for DHA. However, it prefers an exogenous source of DHA from the blood, *via* the blood-brain barrier.

This supply can come from four different, non-exclusive sources, depending on the concentrations of supply and consumption. Two sources are exogenous to the brain, from the blood: (i) directly from the diet in *via* the transport of lysophosphatidylcholine-DHA across the BBB most likely occurs through major facilitator superfamily domain-containing protein 2 (MFSD2) – a membrane transport protein that is expressed in the endothelium of the BBB (Nguyen *et al.,* 2014; Thies *et al.,* 1994) (ii) by synthesis in the liver from dietary ALA, the essential precursor for DHA - but less than 5% ALA is converted into DHA. This rate depends on the concentration of *n*-6 fatty acids and long chain polyunsaturated fatty acids in the diet (Brenna, 2002). The two other sources are: (i) from membrane phospholipids, which are a major component of all nerve cell membranes (Jump, 2002); the enzymes responsible for its release are intracellular phospholipases of the A_2 family as calcium-independent phospholipase A2 (iPLA2) that releases docosahexaenoic acid (DHA) from glycerophospholipids (Capper *et al.,* 2001; Rosa *et al.*, 1791) (ii) by synthesis in the astrocytes from dietary ALA *via* the blood-brain barrier. Neurons do not have the desaturases required to synthesize these omega-3 lipids (DHA). Astrocytes, on the other hand, elongate and desaturate the 18- and 20-carbon precursors. The majority of the long-chain fatty acids formed by astrocytes, particularly DHA, are released into the extracellular fluid for uptake by neurons (Moore *et al.*, 1991). The relationship between diet, blood synthesis and astrocyte synthesis are still a subject of debate (Bewicz-Binkowsha *et al.*, 2019). A more efficient route of incorporation of DHA into brain lipids is *via* DHA itself derived from food or phospholipids or by metabolism in the liver, rather than by metabolism from ALA in astrocytes (Sinclair *et al.,* 1972). However, when DHA levels in the brain decline, a secondary synthesis appears to take place in astrocytes in an attempt to offset dietary deficiencies and ensure neuronal DHA homeostasis (McNamara *et al.,* 2008).

The DHA synthesis pathway is known as Sprecher's shunt. From ALA found in the diet, a series of enzyme transformations, including two desaturases (Δ6-desaturase and Δ5-desaturase) and elongases in the endoplasmic reticulum, followed by peroxisomal β-oxidation, results in DHA (Voss *et al.*, 1991). Δ6-desaturase catalyzes two essential stages of DHA biosynthesis (Cho *et al.*, 1999; Stoffel *et al.*, 2008). As the second stage of desaturation by this enzyme is limiting, it makes Δ6-desaturase a key enzyme in DHA synthesis (Lattka *et al.*, 2010; Tosi et al., 2014; O'Neill *et al.,* 2017; Delplanque, 2017). The amount of DHA produced is directly linked to the level of Δ6-desaturase available, but also to the ALA content. The rate of conversion from ALA to DHA depends on the type of tissue. Astrocytes are believed to have exceptional productivity (Barceló-Coblijn *et al.*, 2005). The ratio of omega-3/omega-α6 fatty acids is also important for efficient conversion. Non-converted ALA undergoes aerobic β-oxidation in astrocyte mitochondria (Edmond et al., 1987) and is fully degraded into acetyl-CoA (Lynen's helix). In humans, the *FADS2* gene (*Δ6-desaturase* gene) is ubiquitously expressed, especially in the liver and brain (astrocytes) (Innis *et al.*, 2002; Nakamura *et al.*, 2004), as well as in the heart, skeletal muscle, kidney, lung, prostate, testes, adipocytes, ovary, uterus and sebaceous glands (Ge *et al.,* 2003; Nwankwo *et al.*, 2003; Pédrono *et al.*, 2010). The phosphorylated PPARα-RXRα heterodimer modulates the transcription of the *FADS2* gene (Tang *et al.*, 2003; Majou, 2021). Free estradiol induces the activation of PPARα *via* two pathways. The first, by transcription, through its genomic action on the *PPARα* gene, which is mediated by an estrogen receptor (Campbell *et al.*, 2003). The second involves a non-genomic effect which, through phosphorylation exclusively on serine residues, increases the transcriptional activity of PPARα, *via* the ERK1/2-MAPK pathway (Majou, 2021) with a strong functional cooperation with PGC-1, a known ligand-influenced PPARα coactivator (Barger *et al.,* 2001). The expression of Δ6-desaturase is retro-inhibited by intracellular free DHA (Matsusaka *et al.*, 2002; Gibson *et al.*, 2013; Bewicz-Binkowska *et al.,* 2019; Majou, 2021).

8. What are the relationships between the up-regulation of regional cerebral glucose uptake by free estradiol and by DHA?

There are close molecular relationships between the up-regulation of the GLUT-1 and NO pathways by free estradiol and by DHA. First, the interactions between DHA and estradiol occur in particular *via* the phosphorylated PPARs-RXRs heterodimers, one of whose preferential ligands is DHA (de Urquiza *et al.*, 2000; Diep *et al.,* 2002; Deckelbaum *et al.,* 2006; Song *et al.*, 2017; Dziedzic *et al.,* 2018). As described above, PPARγ-RXRα blocks the transcription of the *SHBG* gene, reduces the concentration of SHBG, and increases the quantity of free estradiol, and consequently DHA boosts the action of estradiol.

PPARα-RXRα and PPARγ-RXRα, with their ligand DHA, induce activation of members of the MAPK family (Gardner *et al.,* 2003) which activate the IGF-1/Estradiol/PI3K/Akt signaling pathway.

And, as we have already described, the PPARα-RXRα heterodimer modulates the transcription of the *FADS2* gene (Tang *et al.,* 2003). Free estradiol induces the activation of PPARα *via* two pathways: (i) transcription, through its genomic action on the *PPARα* gene, which is mediated by an estrogen receptor; (ii) a non-genomic effect that allows for phosphorylation and activates PPARα *via* the ERK1/2-MAPK pathway (Majou, 2021). As confirmation of this mechanism, observational evidence suggests that in populations that consume low levels of n-3 highly unsaturated fatty acids, women have higher blood DHA levels than men (Kitson *et al.,* 2010). Women of reproductive age are known to convert more ALA into DHA than men (Burdge *et al.,* 2002; Magnusardottir *et al.,* 2009). Estrogens cause higher DHA concentrations in plasma cholesteryl esters in women than in men by up-regulating synthesis from ALA. This difference is independent of dietary differences. Moreover, it has also been suggested that estradiol may increase the activity of the desaturation pathway because DHA synthesis is shown to be almost three times greater in women who use an oral contraceptive pill that contains 17-ethinylestradiol than in women who do not, whereas a testosterone stimulus induces a decrease in DHA status (Giltay *et al.*, 2004). This difference in conversion appears to be associated with estrogen and some evidence indicates that the expression of enzymes, including desaturases, involved in synthesizing DHA from ALA is higher in females (Kitson *et al.,* 2013).

9 Conclusion

During neuronal activity, glucose metabolism and cerebral blood flow are closely coordinated to maintain proper brain function. The uptake of glucose and DHAA across the BBB is facilitated by a single carrier protein, the GLUT-1 transporter. Then, lactate transport between astrocytes and neurons is achieved by MCT transporters. Cerebral blood flow is regulated by the nitric oxide pathway. All steps of the process are complementary and highly controlled in order to guarantee the kinetics at the synapses, according to the neuronal stimulations, and thus glutamate metabolism, neurotransmission and cell viability.

A tandem of two key molecules, free estradiol and DHA is involved in this critical regulation. Their relationship is synergistic and reciprocal: free estradiol with genomic and non-genomic actions *via* ERα, and DHA *via* the PPARα-RXRα and PPARγ-RXRα heterodimers. From a certain level of chronic DHA and free estradiol deficiency, a permanent imbalance is established with a disruption of glucose intake and cerebral metabolism. This depletion, particularly in DHA, is associated with pathologies of the central nervous system encompassing neurodegeneration and cognitive defects. It is an aggravating factor in certain pediatric neuropathologies such as hyperactivity, learning difficulties (Milte *et al.,* 2012), mental retardation (Neggers *et al.,* 2009), epilepsy (Emory University Health Sciences Center, 2004) and autism (Bent *et al.,* 2009; Sun *et al.,* 2018). In the elderly, DHA depletion is an aggravating factor in the etiology of Alzheimer's disease (Majou, 2015), for example. The origins of this deficiency are multiple: (i) a genetic polymorphism that has an impact on various proteins (transporters, enzymes, etc.), in particular the

FADS2 gene; (ii) diet, in particular insufficient intake of ALA, DHA and EPA; (iii) diabetes; (iv) age, due to changes in the concentrations of free steroid hormones such as estradiol and testosterone, with cumulative effects.

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