In: Glucose Uptake ISBN: 978-1-62618-670-5
Editors: Carter C. Johnson and Davis B. Williams © 2013 Nova Science Publishers, Inc.

Chapter 3

Expression and Regulation of Neuronal Glucose Transporters in Health and Disease

Aníbal I. Acuña, Angara Zambrano, Ilona I. Concha and Maite A. Castro*
Instituto de Bioquímica y Microbiología,
Facultad de Ciencias, Universidad Austral de Chile,
Valdivia, Chile

Abstract

The brain is an energy demanding organ and relies on glucose as its main energy source. Glucose is taken up by brain cells through glucose transporters, which are expressed in every cell of the central nervous system. Maintaining a constant influx of energetic substrates is necessary for the survival and function of every cell in the body. However, glucose uptake can be modified under different physiological and pathological conditions.

In this chapter we will discuss neuronal glucose transporter expression and function, with descriptions of neuronal glucose transport regulation during periods of both rest and activity.

We will give some insight into the signalling pathways involved in the regulation of glucose transporter function and availability. And finally, by focusing on neurodegenerative disorders, with special emphasis on Alzheimer's disease, we will describe glucose transporter function, regulation and signalling under disease conditions.

* Corresponding author: Dr. Maite A. Castro, Instituto de Bioquímica y Microbiología, Facultad de Ciencias, Universidad Austral de Chile, casilla 547, Valdivia, Chile. Tel: 56-63-221474, E-mail: macastro@uach.cl.

1. Introduction

While the brain represents only 2% of the body mass in an adult human, it accounts for 25% of the total (resting) body energy consumption (Siesjèo 1978). Brain activity is sustained on the energy provided by glucose. Most of the energy consumed in the brain is attributable to restoration of the resting membrane potential following neuronal depolarisation. Neuronal activity is responsible for 80% of brain energy consumption (Sibson et al., 1998; Rothman et al., 1999). Neuronal functions such as neurotransmitter recycling and axonal and dendritic transport also contribute to brain energy consumption (Ames 2000). When blood glucose levels decrease to 2-3 mM, some cognitive impairment can be observed. Below a level of 1 mM, mental confusion is evident (Cox et al., 2008; Dwyer 2002).

Glucose enters the brain through the blood-brain barrier (BBB, Huber et al., 1997; Boado and Pardridge 1994; Nualart et al., 1999). Glucose transport across the BBB is not affected by acute hyperglycaemia or hyperinsulinaemia (Hasselbach et al., 1999, 2005). The BBB permeability may be altered under starvation conditions, permitting entrance of other metabolic substrates in substantial quantities. Starvation induces higher concentrations of ketone bodies in the blood that correlates with an increased expression of monocarboxylate transporters, MCTs in the BBB (Hasselbach et al., 1995).

Neurons have a highly oxidative metabolism (Hertz 2008) and are able to utilise glucose because they possess glucose transporters and have glycolytic and tricarboxylic acid (TCA) cycle enzymes. Metabolism of glucose is tightly regulated to meet two main needs: the generation of ATP and the provision of carbon for biosynthetic reactions in conjunction with local functional activities. Glucose can also follow an alternative oxidative route, the pentose phosphate pathway (PPP), providing NADPH that is mainly used for regeneration of glutathione (Kletzien et al., 1994), thus conferring an antioxidant role upon neurons (Ben-Yoseph et al. 1996, Herrero-Mendez et al., 2009).

Maintaining an adequate glucose uptake is essential for the brain and for neurons. However, glucose transporter function and localisation can be modified under certain physiological and pathological conditions. In the following sections we provide an up-to-date review of: glucose transport in brain and neurons; neuronal glucose transport under conditions of synaptic activity; pathways involved in regulating the function and subcellular localisation of neuronal glucose transporters. For each section we will discuss the related pathological conditions.

2. Glucose Transport in Brain and Glucose Transporters

Glucose from the bloodstream can enter the brain through the blood brain barrier (BBB) because BBB cells possess GLUTs, facilitative glucose transporters (Agus et al., 1997, Pardridge et al., 1990, Nualart et al., 1999). All brain cells can uptake glucose because all of them express GLUTs (Table 1). Thus, glucose can reach intracellular compartments in brain and in this way be metabolised.

The *SLC2 family* of *GLUTs* currently has 14 members (Joost et al., 2002; Doege et al., 2001; Ibberson et al., 2000; Joost y Thorens, 2001; Lisinski et al., 2001; Phay et al., 2000; Rogers et al., 2002; Wu y Freeze, 2002), many of which are expressed in brain (Table 1). GLUTs have molecular sizes ranging from 45 to 55 kDa and they are only able to translocate glucose D-enantiomers across the plasma membrane. GLUTs are responsible for the facilitative transport of glucose across the plasma membrane (Muekler, 1994; Joost and Thorens, 2001).

Table 1. Glucose transporter expression in brain

TRANSPORTER	TISSUE EXPRESSION	FUNCTION	REFERENCES
GLUT1 55 kDa	Endothelial cells of the BBB.	Supplies basal glucose. Glucose entry in brain.	Agus et al., 1997; Boado and Pardridge, 1994; Bolz et al., 1996; Devraj et al., 2011; Pardridge et al., 1990; Nualart et al., 1999.
45 kD	Epithelial cells of the choroid plexus, ependymal cells, hypothalamic glial cells, glial cells, vascular feet of astrocytes.	Supplies basal glucose. Glucose entry in brain.	Aller et al., 1997; Chari et al., 2011; Nualart et al., 1999; Silva-Alvarez et al., 2005; Simpson et al., 1994.
GLUT2	Found in embryonic brain and hypothalamic ependymal cells.	Glucose sensing.	García et al., 2003; Nualart et al., 1999.
GLUT3	Predominant isoform in axons and dendrites of neurons.	Mediates glucose delivery to neurons.	Aller et al., 1997; Castro et al., 2007; Leino et al., 1997; Maher et al., 1999; Vanucci et al., 1997.
GLUT4	Slightly expressed in hippocampus and cerebellum.		Choeiri et al., 2002; Vannucci et al., 2000.
GLUT5	Embryonic cerebellum. Microglial cells.		Maher et al., 1994; Mueckler et al., 1994; Nualart et al., 1999.
GLUT6	Only GLUT6 mRNA has been localised in the brain.		Doege et al., 2000; Godoy et al., 2006.
GLUT8	Some neurons in the hippocampus and other brain areas.		Ibberson et al., 2000; Ibberson et al., 2002; Lisinski et al., 2001; Reagan et al., 2002.
GLUT13 (HMIT)	Primarily expressed in neurons.	Myoinositol and proton-coupled transport.	Augustin et al., 2010; Uldry et al., 2001.
SGLT1	Expressed in BBB. Expression is inducible by ischaemia.		Elfeber et al., 2004; Wright et al., 2011.
SGLT3	Expressed in hippocampus and cerebral cortex.		Enerson and Drenes, 2006; Vemula et al., 2008; Wright et al., 2011.
SGLT4	Expressed in hippocampus and cerebral cortex.		Wright et al., 2004.

Considering their primary structure, 12 transmembrane domains have been proposed for the GLUT transporter family (Uldry et al., 2001). GLUT1 is ubiquitous and thus this isoform should be responsible for basal glucose transport in many different cell types (Thorens et al., 1988).

In brain, GLUT1 exists as two different molecular weight forms (45 and 55 kDa). Both forms have similar kinetic properties (Birnbaum et al., 1986). The 55 kDa form has been described at the BBB, in endothelial cells from cerebral microvasculature (Nualart et al., 1999, Agus et al., 1997, Pardridge et al., 1990; Boado and Pardridge, 1994, Bolz et al., 1996). This form of GLUT1 is glycosylated (Maher et al., 1992).

Devraj and colleagues (2011) demonstrated that GLUT1 in luminal (blood-facing) and abluminal (brain-facing) endothelial cells is differentially phosphorylated.

A differential phosphorylation of the 55 kDa form has also been demonstrated, suggesting differences between GLUT1 expressed at the luminal and abluminal membranes of ependymal cells (Devraj et al., 2011). The 45 kDa form of GLUT1 is expressed in epithelial cells from choroid plexus, ependymal cells (Nualart et al., 1999; Silva-Alvarez et al., 2005), hypothalamic glial cells (Chari et al., 2011), astrocytes and neurons (Aller et al., 1997). Immunohistochemical analysis of GLUT1 suggests a correlation between the presence of GLUT1 and local cerebral glucose utilisation (Zeller et al., 1997). GLUT2 however has a low affinity for glucose and its expression is very limited in brain. It has been described in embryonic cerebellum (Nualart et al., 1999) and hypothalamus (García et al., 2003). GLUT3 is a major neuronal glucose-transporter isoform (Maher et al., 1996). It is a high-affinity transporter with a catalytic constant higher than that of GLUT1 (Nagamatsu et al., 1993).

Immunohistochemistry studies generally detect the most intense staining of GLUT3 in the neuropil, reflecting high concentrations in axons and dendrites (Aller et al., 1997; Leino et al., 1997; Vannucci et al., 1997, Maher et al., 1999; Castro et al., 2007). Inducible astrocytic GLUT3 expression during ischaemia has recently been reported (Iwabuchi and Kaeahara, 2011). GLUT4 has been described mainly in hippocampus and cerebellum (Choeiri et al., 2002). Neuronal GLUT4 expression was detected in Purkinje and granule cells from cerebellum, in granule cells from the olfactory bulb and in hippocampus (Vannucci et al., 2000). GLUT5 is predominantly a fructose transporter (Mueckler, 1994). Immunohistochemical methods detected GLUT5 in microglial cells (Maher et al., 1994) and embryonic cerebellum (Nualart et al., 1999). GLUT6 in brain has not been fully characterised. GLUT6 mRNA has been found in brain (Doege et al., 2000; Godoy et al., 2006), but protein expression has not yet been reported. GLUT8 is found in hippocampal neurons (Reagan et al., 2002) and in neurons from other brain areas (Ibberson et al., 2000; Lisinski et al., 2001; Ibberson et al., 2002).

This transporter has a dileucine motif, which targets the protein to insulin-regulated trafficking pathways (Manolescu et al., 2008). GLUT13 (HMIT), the proton-coupled myo-inositol transporter, is the only GLUT reported to use a proton gradient to energise substrate movement (Uldry et al., 2001). In brain, myo-inositol is a precursor for phosphatidylinositol, a key regulator for several signalling pathways. Because HMIT is predominantly expressed in brain, there is increasing interest in a possible role for HMIT in myo-inositol/ phosphatidylinositol physiology in neurons (Uldry et al., 2001; Augustin et al., 2010).

The sodium-dependent glucose co-transporters (SGLT) are responsible for the transport of glucose (and galactose) and sodium across the plasma membrane via a secondary active transport mechanism (Wright et al., 2011). SGLTs are mainly important for their role at

epithelial barriers such as the brush border membrane of mature enterocytes in the small intestine and the brush border membrane in renal tubules (Wright et al., 2004; Wright et al., 2011). Expression of five SGLT isoforms has been documented in brain (Table 1).

However, SGLT function in the nervous system is poorly understood. Ischaemia-induced SGLT1 expression was determined at the BBB (Elfeber et al., 2004). The presence of SGLT2 mRNA has been shown in rat brain (Enerson y Drenes, 2006) and SGLT2 activity has been measured at the BBB (Vemula et al., 2008). In cultured hypothalamic neurons, mRNA corresponding to SGLT1, SGLT3a and SGLT3b has been detected (O`Malley et al., 2006), while protein expression of SGLT4 and SGLT5 has been described in brain (Wright et al., 2004).

2.1. GLUT3 Localisation in the Plasma Membrane

Neurons are able to take up glucose from the extracellular space because they possess glucose transporters, mainly the neuronal glucose transporter, GLUT3 (Carruthers 1990; Maher et al., 1992; Nagamatsu et al., 1993; Simpson et al., 2007). The neuronal glucose transporter GLUT3 can be observed in intracellular compartments as well as at the cell surface. This transporter has been shown to be targeted to the apical membranes of polarised cells by the presence of a targeting signal in the C-terminal cytosolic tail domain (Harris et al., 1992; Inukai et al., 2004). Intracellular localisation of GLUT3 is proposed to be within synaptic-like vesicles that are distinct from classic synaptic vesicles (Thoidis et al., 1999). A similar localisation was observed in platelets, where GLUT3 vesicles translocate after thrombin treatment (Heijnen et al., 1997). GLUT3 was observed to be localised in fluid membrane domains (Sakyo et al., 2002; Sakyo et al., 2007) and caveolin-rich detergent-resistant membrane domains (Rauch et al., 2007). Therefore it is possible that GLUT3 membrane localisation depends on cell type and cell requirements. Using Total Internal Reflection Microscopy, we have observed that treatment of a neuronal cell line with the cholesterol sequestering compound methyl-β-cyclodextrin and cholesterol loading methods have different effects on cell surface localisation of GLUT1 and GLUT3 (unpublished data, Figure 1). In the absence of cholesterol, GLUT3 appears to be misplaced and even loses its surface localisation. This effect can be reversed by loading with cholesterol. On the other hand, GLUT1 surface localisation seems to increase in cells depleted of cholesterol, an effect that is unaltered by later addition of cholesterol.

Although GLUT1 has been observed in detergent-resistant domains (Sakyo et al., 2007; Rauch et al., 2006), cholesterol depletion triggers GLUT1 translocation (Caliceti et al., 2012) and stimulates glucose uptake (Barnes et al., 2004) in leukaemia cells and liver epithelial cells respectively. Further studies are required to investigate glucose transporter trafficking as well as the subcellular and membrane localisation of transporters in neurons. However, glucose uptake and glucose transporters have been studied under resting and active neuronal conditions because of the high energetic requirements of neurons.

3. Neuronal Glucose Uptake during Periods of Rest and Activity

Under resting conditions neuronal cells take up glucose mainly through GLUT3. Extracellular brain glucose concentrations are considerably lower than normal blood glucose, reported to be around 2-3 mM (Silver and Erecińska 1994). A high affinity for glucose and a higher turnover number for GLUT3 transporters compared to astrocytic GLUT1 transporters ensures a constant supply of glucose (Maher et al., 1996). Glycolytic and oxidative metabolism are both active in neurons. Glucose taken up is rapidly phosphorylated by hexokinase-I in the first step of the glycolytic pathway.

Since hexokinase-I has an affinity constant for glucose that is one order of magnitude lower than that for the extracellular glucose concentration, glucose is readily phosphorylated and committed to neuronal metabolism (Lowry and Passonneau 1964).

Glucose follows different routes that are relevant for neuronal physiology. Glycolysis and the tricarboxylic acid cycle, coupled to oxidative phosphorylation, help to maintain ATP levels. The pentose phosphate pathway generates five-carbon sugars and NADPH for use in biosynthetic reactions. NADPH also restores the reduced form of the antioxidant glutathione and is favoured in neurons (Herrero-Mendez 2009).

Different approaches have been used to study neuronal glucose uptake in cell cultures and brain slices. Uptake of a fluorescent glucose analogue, 6-NBDG, has been observed to be higher in neurons than in astrocytes, although intracellular glucose levels measured with a FRET nanosensor increased faster in astrocytes than in neurons.

It has been suggested that kinetic differences between glucose transporter isoforms may account for the observed differences in glucose analogue uptake (Jakoby et al., 2012). A computer simulation study proposes an inverse correlation between 6-NBDG uptake and glycolysis rate (calculated for GLUT1 and hexokinase-I; Dinuzzo et al., 2013).

Radiolabelled glucose analogues have also been used to analyse glucose uptake in cultured neurons and to describe the kinetic properties of facilitative glucose transporters (Maher et al., 1996; Castro et al. 2007). Neuronal glucose uptake and usage was also measured indirectly, with electrophysiological recordings used to evaluate neuronal activity (Castro et al., 2007).Neuronal activity requires large quantities of ATP, with most energy being needed for processes that follow synaptic transmission, such as restoring the membrane gradient after neuronal depolarisation, neurotransmitter recycling and intracellular signalling (Attwell and Laughlin 2001; Ames 2000).

Neuronal energy substrate uptake and metabolism has to meet the increased energy demands that accompany brain activity and since neurons are unable to synthesise glycogen, substrates need to be taken up from the extracellular space. The increased blood flow observed with brain activity is accompanied by an increase in glucose utilisation (Sokoloff et al., 1977). Glutamatergic synaptic activity, which accounts for 80% of cortical synapse activity, increases glucose uptake via an up-regulation of surface GLUT3 expression, though functional glucose transport activity has not been evaluated (Weisová et al., 2009; Ferreira 2011). Although a previous study showed an increased ^{3}H-2-deoxyglucose uptake in 20 minute uptake assays after stimulation with glutamate, the fact that this increase might represent glycolytic activity, as 2-deoxyglucose is phosphorylatable by hexokinase, can not be ruled out (Ward et al., 2007).

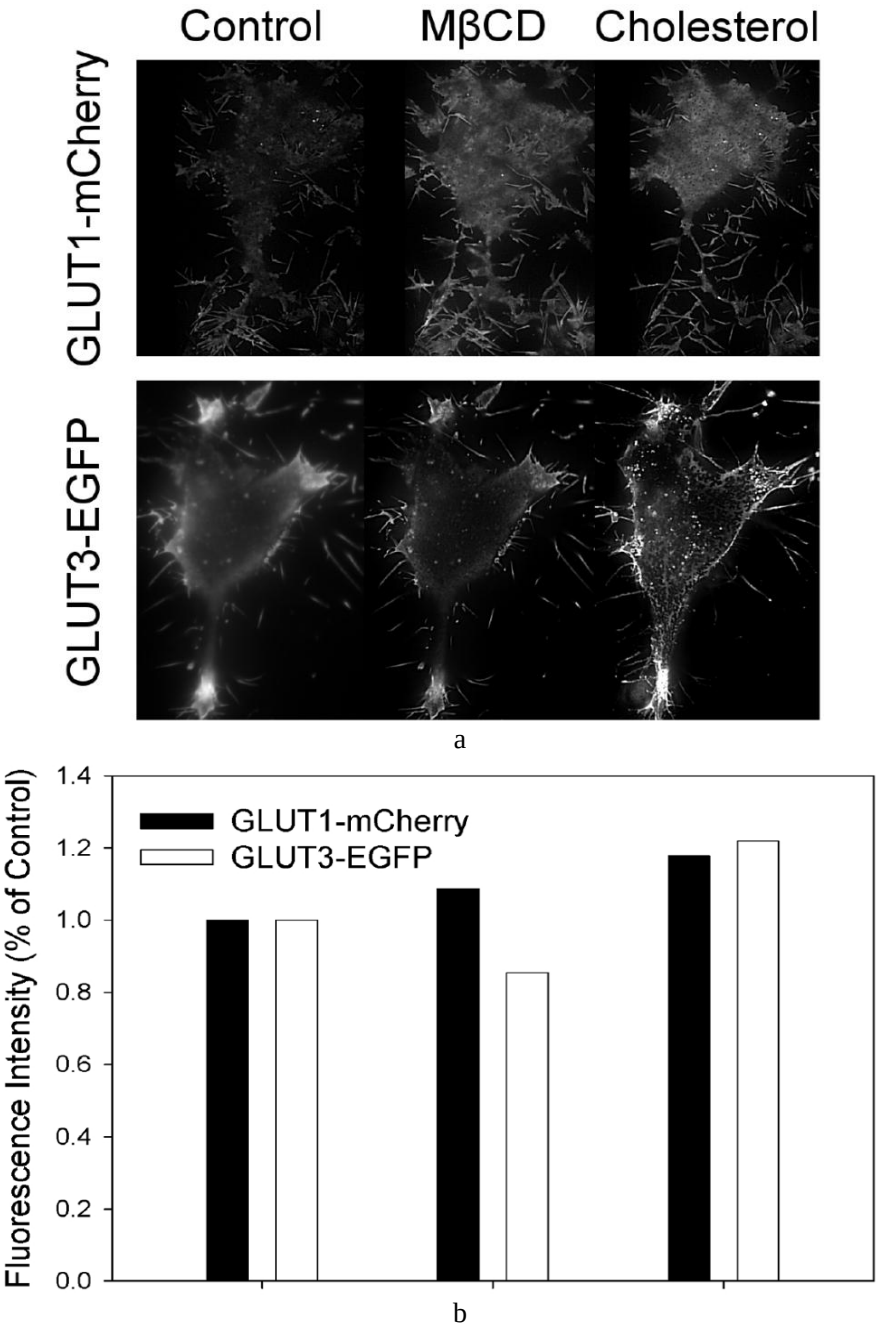

Figure 1. Cholesterol depletion induces a decrease in GLUT3 localisation at the plasma membrane. *Top:* Total internal reflection microscopy (TIRM) images from the neuronal cell line NG108 expressing GLUT1-mCherry and GLUT3-EGFP. Cells were incubated in serum-free media for 15 min (control). Following this, the same cells were treated with 10 mM methyl-β-cyclodextrin (MβCD), the cholesterol sequestering compound, for 15 min. Finally, cells were washed and treated with 30μg/ml Synthechol (cholesterol) for 20 min. *Bottom*: Bars plot graph for fluorescence intensity measured during the above-mentioned treatments. Data were acquired using an Olympus IX71 microscope equipped with an Olympus TIRF objective (60x, oil, NA 1.49). The evanescent field was 180 nm.

Neuronal lactate uptake has been a controversial topic for over 15 years (Allaman et al., 2010; Castro et al., 2009; Chih and Roberts, 2003; Dienel, 2009; Gjedde, 2002; Hertz, 2004; Hertz et al., 2007; Pellerin and Magistretti 1994; Pellerin and Magistretti 2012; Mangia et al., 2003; Mangia et al., 2009). However, the paradigm of glucose as the essential brain energy substrate remains firm. What is not clear, is whether glucose metabolised by astrocytes and released as lactate serves as an energy substrate for active neurons. Glycolysis and oxidation of lactate into pyruvate are not able to be activated simultaneously. Activation of glycolysis produces an increase in pyruvate levels and a decrease in NAD^+/NADH ratio, thus favouring lactate dehydrogenase catalysis of pyruvate to lactate.

Therefore, if neurons were to use lactate as the major energy source following synaptic activity, glycolysis or glucose uptake into neurons should be inhibited. There are various (coexisting) theories that have been proposed to explain this (For a review see Castro et al., 2009, Beltrán et al., 2012). Two hypotheses that involve glucose uptake inhibition have been proposed.

In the first, glutamate has been shown to inhibit glucose transport in neurons through single-cell time-lapse confocal microscopy in neuron-astrocyte co-cultures (Porras et al., 2008). Since these experiments were performed in co-cultures, the possibility that glutamate-treated astrocytes play a role in neuronal glucose uptake inhibition can not be excluded. Thus the effect of glutamate on neurons may be an indirect one. The second hypothesis demonstrates, using radiolabelled and fluorescent glucose analogues, that intracellular ascorbic acid inhibits glucose utilisation in neurons by inhibiting the neuronal glucose transporter GLUT3 (Castro et al., 2007; Castro et al., 2009, Beltrán et al., 2011). Astrocytes are thought to be involved in ascorbic acid recycling (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) and can be taken up by neurons efficiently because they express the ascorbic acid transporter SVCT2 (Castro et al., 2001). Intracellular ascorbic acid is also able to stimulate lactate transport in neurons and in cells that express GLUT3 (Castro et al., 2008). The specific nature of this mechanism relies on GLUT3 as a necessary component for inhibition. Ascorbic acid is unable to inhibit glucose uptake in neurons treated with a specific shRNA (to block GLUT3 expression) or in cells that do not express GLUT3.

The role of ascorbic acid as a regulator of metabolic substrate preferences has been termed the ascorbic acid metabolic switch (Castro et al., 2009; Beltrán et al., 2011). An *in vivo* study using two-photon microscopy revealed similar glucose uptake in astrocytes and neurons.

Following neuronal activity, glucose uptake was only seen to be increased in astrocytes (Chuquet et al., 2010). Lactate has been shown to sustain the energetic requirements during neuronal activation both *in vitro* and *in vivo* (Ivanov et al., 2011; Wyss et al., 2011). Neuronal glucose transporters are able to efficiently supply glucose to neurons.

However, during periods of brain activity, glucose uptake (or glycolysis) inhibition mechanisms are required in order to allow the uptake and utilisation of lactate as a faster energy source. This effect may occur in two steps. In the first, glycolysis and glucose uptake are increased to try and meet energetic demands.

In a later step, glucose uptake and utilisation are inhibited. Thus, lactate can be taken up by neurons and neuronal ATP levels replenished.

4. Regulation of Glucose Uptake in Neuronal Cells: Signalling Associated with GLUT Trafficking and Activation

Multiple organ systems, such as the central nervous system, liver, kidney, pancreas and intestine, participate in homeostatic feedback loops that work to maintain constant levels of nutrients in the bloodstream partly by altering nutrient transporter expression on the surface of their constituent cells (Edinger 2007, Zambrano et al., 2010 (1)).

The best known example of signal transduction that is related to GLUT expression at the plasma membrane is GLUT4. GLUT4 is not the most abundant GLUT isoform in the brain, but it is strongly insulin-sensitive, while other GLUT isoforms (GLUT1, GLUT3, GLUT8, GLUT12) are only weakly insulin-sensitive (Chua et al., 2012; Piper et al., 1991; Navarrete Santos et al., 2004; Stuart et al., 2009; Wilson et al., 1995).

For this reason, we will describe the regulatory mechanism of GLUT4 expression at the plasma membrane and then compare this mechanism with findings reported for neuronal glucose transporter GLUT3 expression at the cell surface.

4.1. Regulatory Mechanism of Glucose Uptake

Growth signals increase the transcription of nutrient transporter mRNAs. In contrast, much less is known about how signal transduction cascades affect the trafficking and degradation of these proteins, although some progress is being made in this field. For this reason, despite the fact that GLUT4 trafficking in response to insulin signalling has been very well studied, many molecular details are still lacking. Insulin stimulates glucose transport into muscle and adipose tissue 10- to 30-fold with a half time of 2-5 minutes. The major glucose transporter expressed in these tissues is GLUT4, which has received a great deal of attention. Much less is known about the regulation of other glucose transporters. Specifically, the mechanisms that govern insulin-stimulated glucose transport in muscle and fat cells have captured the interest of researchers for decades. New insights into insulin signalling reveal that phosphorylation events initiated by the insulin receptor regulate key GLUT4 trafficking proteins, including small GTPases, tethering complexes and the synaptic vesicle fusion machinery (Leto and Saltiel, 2012). Translocation of GLUT4 to the plasma membrane following insulin stimulation represents the convergence of two complex systems: signal transduction and vesicular transport (Stockli et al. 2011).

Following a meal, increased nutrients in the blood lead to secretion of insulin. In turn, this hormone prevents gluconeogenesis in the liver and promotes glucose uptake into muscle and adipose tissue through regulated trafficking of GLUT4 from intracellular stores to the plasma membrane (Saltiel and Khan, 2001). Glucose uptake is the rate-limiting step in glucose utilisation and/or storage and as such has a key role in the maintenance of glucose homeostasis. Insulin increases the steady-state plasma membrane GLUT4 levels by 5- to 30-fold. Three different features of GLUT4 trafficking have been implicated in this redistribution: an increase in the exocytosis rate constant, a decrease in the endocytosis rate

constant and an increased amount of GLUT4 in the cell surface recycling pool (Stockli et al. 2011).

In the absence of insulin, most GLUT4 is distributed between endosomes, the trans-Golgi network (TGN) and heterogeneous tubulovesicular structures comprised of endosomal sorting intermediates and specialised GLUT4 storage vesicles (GSVs). In the absence of insulin, only about 5% of the total transporter pool is found on the cell surface. Exclusion of GLUT4 from the cell surface depends on efficient sorting and sequestration into GSVs that do not readily cycle to the plasma membrane in the absence of stimulation but translocate to the membrane in response to insulin or exercise, which results in a ten-fold increase in glucose uptake (Leto and Saltiel, 2012). Specifically, insulin signals through TBC1D4 (TBC1 domain family member 4) and TBC1D1 (tre-2/USP6, BUB2, cdc16 domain family, member 1), both Akt substrates, to modulate Rab GTPases and through the Rho GTPase TC10α to act on other targets. GLUT4 is sorted into highly specialised store vesicles containing e.g. VAMP2 (vesicle-associated membrane protein 2). In stimulated cells these vesicles are mobilised to the plasma membrane where insulin is able to modulate the trafficking itinerary and endosome process (Bogan 2012).

Insulin is secreted by the pancreas and engages its receptor on the surface of myocytes and adipocytes, thereby activating the canonical PI3K-Akt pathway. Activation of this pathway is necessary and sufficient to trigger exocytosis of GSVs to the plasma membrane (Stockli et al., 2011). Oncogenic alleles of Akt can support growth factor-independent glucose transporter expression (Edinger and Thompson, 2002; Rathmell et al., 2003). Akt is a serine/threonine kinase that lies downstream from many growth factor receptors.

In addition to regulating glucose uptake, growth factors and Akt also affect the rate of glycolysis (Vander Heider et al., 2001; Plas et al., 2001). The ability of Akt to support growth-factor independent cell survival is completely dependent on the availability of extracellular glucose. While activated Akt protects from growth factor withdrawal-induced death, myristoylated Akt-expressing cells are as sensitive as control cells to glucose withdrawal (Edinger 2005).

Akt phosphorylates TBC1D4 (TBC1 domain family, member 4) at multiple sites, which results in 14-3-3 binding to TBC1D4 and the presumed inhibition of TBC1D4 GAP (GTPase-activating proteins) activity. This enables a large number of GSVs to move to, dock at and fuse with the plasma membrane (Sano et al., 2003; Ramm et al., 2006).

Insulin-dependent phosphorylation of a range of other molecules also plays a key regulatory role in GLUT4 translocation: ESYT1 (Extended synaptotagmin-1) and TC10 (Rho-related GTP-binding protein RhoQ) phosphorylation by CDK5 (Cyclin-dependent kinase 5); MYO1C (Unconventional myosin-1c) and MYO5 (Myosin-5) phosphorylation by CamKII (Calcium/calmodulin-dependent protein kinase II); RIP140 (NRIP1, nuclear receptor interacting protein 1) and SEC5 (Exocyst complex component 2) phosphorylation by PKC (Protein kinase C); and PIKFYVE (1-phosphatidylinositol 3-phosphate 5-kinase), AS250 (250kDa substrate of Akt) and MYO5 phosphorylation by Akt.

Akt is the principal insulin-regulated signal transducer for GLUT4 translocation and several steps in the GLUT4-trafficking pathway are regulated by insulin, including the approach, tethering, docking and fusion of vesicles at the plasma membrane (for review see Stockli et al., 2011). Likewise, mTOR appears to lie downstream of Akt in the growth factor signal transduction cascade. Treatment of cells with rapamycin (specific inhibitor of mTOR

complex) blocked the growth factor-independent expression of nutrient transporters supported by activated Akt (Edinger 2005).

The PI3K-dependent signalling pathway is also initiated after insulin binds to its cognate Tyr kinase receptor on the cell surface, leading to recruitment and Tyr phosphorylation of the insulin receptor substrate (IRS) family of adaptor proteins (Myers and White, 1996). Tyr-phosphorylated IRS proteins serve as docking sites for the SH2 domain of the p85 regulatory subunit of class I PI3K, and the interaction of IRS proteins and PI3K results in PI3K activation and the subsequent synthesis of phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P3) from PtdIns(4,5)P2 at the plasma membrane. PtdIns(3,4,5)P3 in turn serves as a docking site for several PH domain-containing Ser/Thr kinases that are implicated in glucose uptake, including phosphoinositide-dependent kinase 1 (PDK1) and Akt. PDK1 and mTORC2 activate Akt through dual Ser/Thr phosphorylation (Leto and Saltiel 2012).

AMPK (5'-adenosine monophosphate-activated protein kinase) is a serine/threonine kinase that plays a crucial role in regulating energy homeostasis, acting as an integrator of cellular and organismal energy balance and energy-dependent responses. AMPK also functions at tissue and organism levels to promote context-specific responses to physiological signals of metabolic status.

AMPK modulates many aspects of cellular metabolism. AMPK was first known to be activated by ATP depletion (increased AMP/ATP ratio) and related stimuli (exercise, starvation, hypoxia, cellular pH and redox status, increased creatine/phosphocreatine ratio; Kahn et al., 2005; Hardie 2007).

However, certain drugs, hormones, and cellular stressors that do not alter AMP/ATP ratio also activate AMPK. Thus, AMPK in various cells and tissues senses both physiological and pathophysiological stimuli. AMPK stimulates catabolism by activating glucose uptake (GLUT4 translocation), glycolysis [activating 6-phosphofructo-2-kinase kinase (PFK-2)], glucose oxidation, and fatty acid oxidation (by relieving CPT-1 inhibition by malonyl-CoA; Ramamurthy and Ronnett 2012).

4.2. Regulation of Glucose Uptake in Neuronal Cells

Despite the critical importance of glucose for brain function, little is known about the molecular events regulating normal glucose uptake. It has been shown that the distribution of glucose transporters exposed to the cell surface is a major regulator of glucose uptake, so that trafficking of glucose transporters between the cytosol and the plasma membrane is under strict control (Pessin and Bell, 1992). As described previously, this has been studied extensively for the adipocyte and muscle cell-specific transporter isoform GLUT4, the trafficking and consequent cell glucose uptake of which are under the control of insulin. Neuronal glucose uptake relies on GLUT3 at the plasma membrane but very little is known about regulation of the subcellular localisation of this transporter. Nor is it well understood just how translocation of the neuronal glucose transporter isoform GLUT3 vesicles to the plasma membrane occurs, as well as how they fuse with the membrane. Reports show that GLUT3 in PC12 cells colocalises with SNARE complex proteins SNAP-25 and syntaxin 1, suggesting that fusion of GLUT3-containing vesicles with the plasma membrane may be mediated by these proteins. In addition, GLUT3 vesicle fusion would seem to be regulated, as depolarisation increases GLUT3 insertion into the plasma membrane. In both PC12 cells and

neurons, GLUT3 is present in a distinct population of small vesicles that have many vesicular proteins in common with synaptic vesicles (Weisova 2009).

Depolarisation of neurons by high extracellular K^+ acutely increases glucose uptake and increases the amount of GLUT3 exposed to the extracellular surface (Uemura and West Greenlee, 2001). Therefore, regulation of glucose uptake in neurons would seem to rely, in part, on regulated, Ca^{2+}-dependent exocytosis of GLUT3 vesicles at the plasma membrane.

In the brain, glutamate is the major neurotransmitter mediating most of the occurring synaptic transmission. Glutamate excitation produces an increase in the surface expression of GLUT3 that persists for hours following the initial glutamate treatment. Increased GLUT3 surface expression was mediated by AMPK, as inhibition of AMPK, either through knockdown or pharmacological inhibition, blocked the GLUT3 response to glutamate (Amato and Man, 2011)**.** Glutamate excitation induced a rapid alteration in the AMP:ATP ratio associated with activation of the AMPK. Pharmacological activation of AMPK with AICAR (5-aminoimidazole-4- carboxamide riboside) alone also increased GLUT3 surface expression, with a hyperpolarisation of mitochondrial membrane potential that was evident in many neurons (Weisova, 2009).

Additional studies suggest that synaptic activity increases surface expression of GLUT3 leading to an elevation of intracellular glucose. This effect was blocked by the NMDA receptor (NMDAR) and by neuronal nitric oxide synthase (nNOS) inhibition. Interestingly, the Akt inhibitor I (Akt-I) blocked NMDAR-induced GLUT3 surface expression while a nNOS-phosphomimetic mutant (S1412D) enhanced GLUT3 expression at the cell surface. These results suggest that NMDAR/Akt-dependent nNOS phosphorylation is coupled to GLUT3 trafficking. The NMDAR-induced increase in surface GLUT3 may represent a novel pathway for control of energy supply during neuronal activity (Ferreira et al., 2011)

It is important to add that GLUT3 is upregulated in response to many stressors, such as hypoxia, hypoglycaemia, insulin and IGF-1. HIF-1α, a transcription factor that mediates adaptive responses to changes in tissue oxygenation, can stimulate GLUT3 expression. In addition, GLUT3 is regulated by some other transcription factors such as SP1, SP3, MSY-1 and CREB, etc (Rajakumar et al., 2004).

In peripheral tissues, insulin is a key signalling component in glucose uptake, while the regulation of neuronal glucose influx has traditionally been viewed as an insulin-insensitive process. However, there is evidence to suggest that both the insulin and insulin-like growth factor 1 (IGF1) signalling pathways are involved in glucose uptake in the brain. Insulin treatment in cultured hippocampal neurons facilitates GLUT3 membrane translocation, which requires membrane depolarisation for the final fusion of GLUT3-carrying vesicles with the plasma membrane in order to facilitate glucose uptake (Amato and Man, 2011). In addition to its varied role in peripheral tissues, insulin has profound effects in the CNS, where it regulates various key physiological functions, such as food intake, energy homeostasis, reproductive endocrinology, sympathetic activity, peripheral insulin actions, and even learning and memory (Gupta and Dey, 2012).

Insulin markedly potentiates Ca^{2+}-dependent neuronal glucose uptake induced by KCl, an effect that coincides with increased immunolabelling of the exofacial epitope of GLUT3. The increase in glucose uptake is due to increased fusion of GLUT3 vesicles with the plasma membrane, resulting in more GLUT3 being exposed to the extra-cellular surface (Uemura and Greenlee, 2001). Insulin potentiation of glucose uptake stimulated by depolarisation with KCl

is probably a result of increased numbers of docked GLUT3 available for fusion with the plasma membrane.

This neuronal glucose uptake is regulated by at least two separable factors: the promotion of GLUT3 translocation to the plasma membrane and a membrane depolarisation that induces fusion of GLUT3 vesicles with the plasma membrane.

High extracellular K^+ is known to double the rate of neuronal glucose oxidation, although this K^+ effect is secondary to cell depolarisation and reflects the high-energy demand for Na^+ extrusion. Thus, insulin promotion of GLUT3 translocation to the plasma membrane may be an important regulatory mechanism that modulates neuronal glucose uptake in response to the metabolic demands of neurons (Uemura et al., 2006).

The insulin-like growth factor (IGF-1) is homologous to insulin and acts through its own, but closely related tyrosine kinase receptor that shares many signalling components and cellular responses with the insulin receptor (Treins et al., 2005). The IGF-1 receptor is widely distributed in the brain and has been shown to induce GLUT3 expression, with SP1 participating in this pathway. Both receptors, IGF-1 and insulin, are homologous with identical signal-transducing domains controlling most of the same intracellular pathways. The IGF-1 receptor plays a critical role in brain glucose metabolism. It activates phosphatidylinositol 3-kinase, PI3K/Akt and extracellular signal-regulated kinase (ERK) pathways which mediate cell proliferation and/or survival (Mairet-Coello et al., 2009). Several cytokines, including IGF-1, have also been reported to modulate HIF-1α protein expression or stability through PI3K/Akt/mTOR and/or ERK pathways (Fukuda et al., 2002; Slomiany and Rosenzweig, 2006). Expression of GLUT3 in response to IGF-1 was dependent on PI3K and mTOR activity and required the transcription factor HIF-1α (Yu et la., 2012).

5. Neuronal Glucose Transporters and Neurodegenerative Diseases

According to the World Health Organization, there were more than 35.6 million people worldwide living with dementia in 2010. The most common form of dementia is Alzheimer's disease, which probably contributes to 60–70% of cases (WHO, 2012).

The impact of neurodegenerative diseases on the society and economy will continue to increase as the population ages. Neurodegenerative diseases are chronic, progressive neurological disorders associated with neuronal loss.

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 and Beal, 2006).

As discussed above, glucose is an essential substrate for the maintenance of brain and neuronal activity. Neurons are particularly sensitive to fluctuations in energy levels. Energy deficiency is tightly related to neuronal survival and viability and also contributes to age-related disorders. Alterations in uptake and/or utilisation of glucose can thus be associated with pathological conditions.

Several neurodegenerative diseases show metabolic failure that includes alterations in the expression of glucose transporters, altered expression of metabolic enzymes and altered

activity of the enzymes involved in energy metabolism. Whether these metabolic alterations contribute to the onset and progression of the disease or whether they are a consequence of the disease is not yet fully understood. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (PD) and amyotrophic lateral sclerosis (ALS) are neurodegenerative diseases that present metabolic failure.

Parkinson's disease is the most common neurodegenerative movement disorder of the central nervous system. Clinical symptoms arise from a progressive degeneration of dopaminergic neurons in the substantia nigra and other monoaminergic neurons in the brainstem (Braak et al., 2003). Studies have found that mitochondrial dysfunction contributes to the pathogenesis of PD and is thought to be related to mutations in PINK1 and DJ1 genes (Schapira, 2006; Wallace, 2005). Hypometabolism of glucose has been described in PD patients (Huang et al., 2007; Yong et al., 2007; Perneczy 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 symptom. Neuronal cell cultures with PINK1 deficiency associated with reduced neuronal glucose uptake had their uptake restored to control levels by scavenging or inhibiting ROS species (Gandhi et al., 2009)

Amyotrophic lateral sclerosis is the third most common human adult-onset neurodegenerative disease. ALS is a progressive and severely disabling neurological disease characterised by muscle atrophy, spasticity, eventual paralysis and death.

A progressive degeneration and elimination of upper motor neurons in the cerebral cortex occurs as well as in the lower motor neurons of the brainstem and spinal cord (Rowland and Shneider, 2001; Sathasivam et al., 2001).

Research has revealed that mitochondrial dysfunction, including abnormalities of mitochondrial morphology and function, are associated with ALS, (Sasaki and Iwata, 1999; Menzies et al., 2002; Martin, 2012). Cu/Zn-SOD in transgenic mice presented decreased levels of glucose transport in cerebral cortex synaptic terminals (Guo et al., 2000). An upregulation of Glut3 was observed *in vivo* in motor neurons from $SOD1^{G93A}$ mice that could be reproduced *in vitro* when non-transgenic motor neurons were grown on $SOD1^{G93A}$ primary astrocytes. This suggests that a dysregulated energy provision by mutant SOD1 astrocytes occurs in response to motor neurons (Ferraiuolo et al., 2011).

Huntington's disease (HD) is a progressive, autosomal dominant, neurodegenerative disorder. Its common symptoms are motor dysfunction and cognitive abnormalities. The disease is caused by an expanded polyglutamine (polyQ) stretch in the Huntingtin gene, resulting in major cell loss in the striatum, a region of the basal ganglia that integrates cortical information for behavioural output. HD is characterised by widespread neurodegeneration with preferential deterioration of medium-sized spiny neurons (MSSNs) in the striatum (Penney and Young, 1998). The major excitatory input to MSSNs comes from the cortex (corticostriatal pathway) and the thalamus. HD also causes dysfunction and subsequent death of neurons in other brain regions, including the cortex. Defects in energy metabolism may even extend to presymptomatic subjects. Decreased GLUT1 and GLUT3 transporter expression has been shown in the caudate of postmortem HD brains (Gamberino and Brennan, 1994). This decrease in glucose transporter expression correlates with positron emission tomography studies that have demonstrated marked reductions in glucose metabolism in basal ganglia (Mazziotta et al., 1987) and in cerebral cortex of symptomatic Huntington's disease patients (Leenders et al., 1986; Kuwert et al., 1993). However, Oláh et

al. (2008) described an increase in several glycolytic enzymes and in ATP production in brain from animals with Huntington's disease.

The same authors described a marked contrasting decrease in glyceraldehyde-3-phosphate dehydrogenase activity. Impairment in enzyme activity of the TCA cycle (Lim et al., 2008) and in oxidative phosphorylation has also been described. A key role for proliferator-activated receptor gamma coactivator-1α has been proposed for the control of energy metabolism in the early stages of Huntington's disease (Finck and Kelly, 2006). Metabolic abnormalities are not limited to the nervous system as for many neurodegenerative diseases (AD, PD, HD and ALS) and have been associated with type II diabetes or insulin resistance (Bruce et al., 2001; Sandyk 1993; Podolsky et al., 1972; Ristow 2004; Pradat et al., 2010). Given the higher incidence of AD and increasing research efforts that aim to better understand these disorders, we will further discuss the findings related to alterations seen in glucose uptake in AD.

5.1. Failure of Glucose Uptake Associated with Alzheimer's Disease

Growing evidence supports the notion that Alzheimer's disease could be conceptualised as a metabolic disease with progressive impairment of the brain's capacity to utilise glucose and to respond to insulin and insulin-like growth factor (IGF) stimulation (de la Monte 2012). Inhibition of neuronal glucose utilisation may decrease neuronal activity and precede neuronal degeneration. Restrictions to glucose availability increase the sensitivity of primary neurons to glutamate excitation. It has been suggested that the impairment of neuronal glucose utilisation in the brain of AD patients may precede neuronal degeneration (Ogawa et al., 1996; Ferreira et al., 2010; Zhang et al., 2012). AD is known to be associated with abnormalities in energy metabolism, including decreased insulin sensitivity, compromised mitochondrial activities and impaired lipid metabolism (Amato and Man, 2011).

In AD there is a severe reduction of glucose uptake and metabolism (Hoyer, 2004; Jagust et al. 1991; Minoshima et al., 1995; Nicholson et al., 2010). A decreased brain glucose metabolism has been observed even before the onset of the disease in several groups of at-risk individuals (Petersen et al., 1999; Kennedy et al., 1995; Mosconi et al., 2006; Reiman et al., 2004; Mosconi et al., 2007, Small et al., 2000). This suggests that the impairment of glucose uptake/metabolism is a cause of neurodegeneration or is involved in the pathogenesis of AD. The reduction in glucose uptake is accompanied by a decrease in GLUT1 and GLUT3 in the brains of patients with AD (Simpson et al., 1994; Simpson and Davies, 1994; Harr et al., 1995). This decrease in glucose transporters was found to be correlated with tau hyperphosphorylation, with a higher density of neurofibrillary tangles and a downregulation of HIF-1 in human AD brains (Liu et al., 2008). A recent study reveals a mechanism that might be responsible for the altered GLUT3 expression in AD. The study shows that the promoter of human GLUT3 contains three potential cAMP response elements (CRE)-like elements, two of which (CRE-2 and CRE-3) are required to promote GLUT3 expression. In AD, CRE-binding protein (CREB) would be proteolysed by calpain I thus decreasing GLUT3 expression and impairing glucose uptake and metabolism in AD brain (Jin et al., 2013).

In AD, beta-amyloid (βA) deposits are one of the fundamental causes of the disease. Several growth factors, such as IL-3, that increase glucose uptake, can rescue neuronal cells

neuronal glucose uptake. It has been suggested that βA decreases glucose uptake by inhibiting fusion of these vesicles (Uemura and Greenlee, 2001). Likewise, it has been shown that βA impairs glucose uptake in cultured hippocampal neurons and astrocytes. Deposits of βA are correlated with a decreased GLUT1 expression in the hippocampus (Hooijmans et al., 2007). Exposure of neurons to βA also leads to impaired mitochondrial activity, suppressed production of ATP, and ultimately neuronal cell death. It is not known whether βA affects glucose uptake in the brain of AD patients. However, *in vitro* studies suggest that βA inhibition of neuronal glucose uptake precedes neuronal degeneration and may thus contribute to changes in glucose utilisation observed in the brain of AD patients.

Research has demonstrated that βA inhibition of neuronal glucose uptake is mediated by a G protein and cAMP. βA transiently increased intracellular cAMP and either forskolin or dibutyryl cAMP (Bt2cAMP) also inhibited neuronal glucose uptake, suggesting that cAMP plays a role in inhibiting neuronal glucose uptake. It is of interest to note that βA-mediated inhibition of neuronal glucose uptake occurs despite a significant increase in GLUT3 translocation to the plasma membrane and an upregulation of GLUT3 mRNA transcription. Further, βA inhibited a K^+-induced increase in GLUT3 at the extracellular surface, suggesting that βA inhibits neuronal glucose uptake by inhibiting fusion of GLUT3-containing vesicles with the plasma membrane (Prapong et al., 2002).

Several additional studies have indicated that neurons are insulin-resistant in AD and that their glucose uptake is decreased. The expression levels of insulin and insulin-like growth factor (IGF-1) proteins and their receptors, as well as expression of insulin receptor substrate-1/2 proteins, are significantly reduced in AD brains. These studies indicate that the insulin/IGF signalling pathway is clearly compromised and that neurons had become insulin-resistant in AD. Streptozotocin (STZ)-treated mice show decreased levels of GLUT1 and GLUT3 rat brain. This decrease might arise from STZ-induced impaired insulin signalling (Deng et al., 2009).

Further, AD-like alterations in protein kinase B and glycogen synthase kinase-β in hippocampus and frontal cortex were seen in STZ-treated rats (Salkovic-Petrisic et al., 2006). Treatment with flavonoids (hesperetin and hesperidin) reverted the effect of βA on GLUT3 expression and PI3K signalling. Thus an increased GLUT3 expression and Akt phosphorylation were observed (Huang et al., 2012). However, AMPK signalling provides an alternative pathway for regulation of glucose uptake. It seems that AMPK may be a major regulator of energy metabolism in neurons, whereas the insulin/IGF pathway might play a more significant role in regulation of neuronal growth and survival (Salminen 2011).

Conclusion

Glucose is an essential energy source for the adult human brain. The brain constitutes only 25% of the adult body weight but it utilises 50% of the total glucose supply. Neuronal activity accounts for 80% of brain energy consumption. Therefore, regulation of the expression and sub cellular localisation of the neuronal glucose transporter GLUT3 is key to the regulation of neuronal energy supply. GLUT3 is expressed at cholesterol-rich domains in the plasma membrane and synaptic-like vesicles in the intracellular space. GLUT3

translocation to the plasma membrane is induced by at least three signalling pathways (Figure 2).

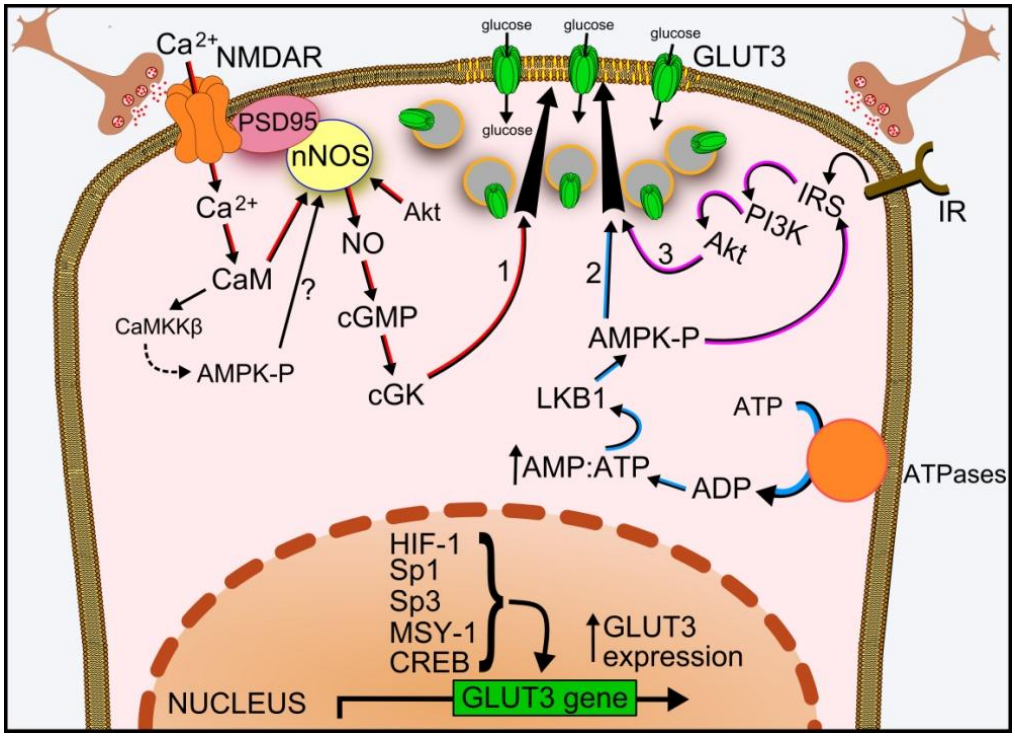

Figure 2. Multiple pathways may contribute to increased GLUT3 expression at the cell surface. GLUT3 is the predominant glucose transporter isoform expressed in neurons. It is expressed at cholesterol-rich domains in the plasma membrane and in synaptic-like vesicles. Expression of GLUT3 at the plasma membrane may be induced by at least four pathways. These pathways should coexist thus assuring efficient glucose uptake in neuronal cells. First (red arrows): An increase in intracellular Ca^{2+} induced by NMDAR activation might lead to nNOS activation and GLUT3 translocation to the plasma membrane. Second (blue arrows): Synaptic activity induces an increase in the AMP:ATP ratio because activation of ATPases is necessary to restore ion gradients. An increase in AMP:ATP ratio induces AMPK activation and GLUT3 translocation to the plasma membrane. Third (purple arrows): Insulin receptor activation leads to GLUT3 translocation to the plasma membrane in an Akt-dependent manner. Fourth: GLUT3 expression is upregulated in response to many stressors mediating adaptive responses to oxygen deprivation and hypoglycaemia, among others. Several transcription factors can induce GLUT3 expression. Akt: protein kinase B; AMPK-P: activated (phosphorylated) AMP kinase; CaM: calmodulin-dependent protein; CaMKKβ: calmodulin-dependent protein kinase kinase β; cGK: cGMP-dependent protein kinase; cGMP: cyclic guanosine mono phosphate; CREB: *cAMP* response element-binding protein; GLUT3: glucose transporter isoform 3; HIF-1: hypoxia-inducible factor-*1*; IR: insulin receptor; IRS: insulin receptor substrate; LKB1: serine/threonine kinase LKB1; MSY-1: transcription factor MSY-1; NMDAR: NMDA receptor; nNOS: neuronal nitric oxide synthase; PI3K: phosphoinositide 3-kinase; PSD95: postsynaptic density protein 95; Sp1: transcription factor SP1; Sp3: transcription factor SP3.

Glutamatergic synaptic activity induces NMDAR activation, increased intracellular Ca^{2+} concentration and nNOS activation causing GLUT3 translocation to the cell surface. Synaptic activity in general induces activation of ATPases because restoration of the ion gradient is essential for successful synaptic transmission. ATPase activation induces an increase in the

AMP:ATP ratio, AMPK activation and thus, GLUT3 translocation to the plasma membrane. Insulin receptor activation can also induce GLUT3 translocation to the cell surface via activation of the PI3K/Akt pathway.

However, neuronal cells can respond to several stressors in an adaptive manner, producing transcription factors which are able to stimulate GLUT3 expression. There are several reports of metabolic impairment in various neurodegenerative disorders such as AD, HD, ALS and PD. Indeed, many of these impairments are related to failures in glucose uptake. 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 that also affects neuronal survival.

Acknowledgments

TIRFM experiments were performed at Dr. S. Brauchi's laboratory (Instituto de Fisiología, UACh). This work was supported by Chilean grants FONDECYT 1110571 (M.A.C.) and 1110508 (I.I.C.), DID-UACh.

References

Agus, D. B., Gambhir, S. S., Pardridge, W. M., Spielholz, C., Baselga, J., Vera, J. C., and Golde, D. W. (1997). Vitamin C crosses the blood-brain barrier in the oxidized form through the glucose transporters. *The Journal of clinical investigation* 100, 2842-2848.

Allaman, I., Belanger, M. and Magistretti, P. J. (2011). Astrocyte-neuron metabolic relationships: for better and for worse. *Trends in neurosciences* 34, 76-87.

Aller, C. B., Ehmann, S., Gilman-Sachs, A., and Snyder, A. K. (1997). Flow cytometric analysis of glucose transport by rat brain cells. *Cytometry* 27, 262-268.

Amato, S. and Man, H. Y. (2011). Bioenergy sensing in the brain: the role of AMP-activated protein kinase in neuronal metabolism, development and neurological diseases. *Cell cycle* 10, 3452-3460.

Ames, A., 3rd (2000). CNS energy metabolism as related to function. *Brain research Brain research reviews* 34, 42-68.

Astuya, A., Caprile, T., Castro, M., Salazar, K., Garcia Mde, L., Reinicke, K., Rodriguez, F., Vera, J. C., Millan, C., Ulloa, V., et al. (2005). Vitamin C uptake and recycling among normal and tumor cells from the central nervous system. *Journal of neuroscience research* 79, 146-156.

Attwell, D. and Laughlin, S. B. (2001). An energy budget for signaling in the grey matter of the brain. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 21, 1133-1145.

Augustin, R. (2010). The protein family of glucose transport facilitators: It's not only about glucose after all. *IUBMB life* 62, 315-333.

Barnes, K., Ingram, J. C., Bennett, M. D., Stewart, G. W., and Baldwin, S. A. (2004). Methyl-beta-cyclodextrin stimulates glucose uptake in Clone 9 cells: a possible role for lipid rafts. *The Biochemical journal* 378, 343-351.

Beltrán, F. A., Acuna, A. I., Miro, M. P., Angulo, C., Concha, I. I., and Castro, M. A. (2011). Ascorbic acid-dependent GLUT3 inhibition is a critical step for switching neuronal metabolism. *Journal of cellular physiology* 226, 3286-3294.

Beltrán, F. A., Acuña, A. I., Miro, M. P., and Castro, M. A. (2012). Brain Energy Metabolism in Health and Disease. In: *Neuroscience - Dealing With Frontiers*, C. M. Contreras, ed. (InTech).

Ben-Yoseph, O., Boxer, P. A. and Ross, B. D. (1996). Assessment of the role of the glutathione and pentose phosphate pathways in the protection of primary cerebrocortical cultures from oxidative stress. *Journal of neurochemistry* 66, 2329-2337.

Birnbaum, M. J., Haspel, H. C. and Rosen, O. M. (1986). Cloning and characterization of a cDNA encoding the rat brain glucose-transporter protein. *Proceedings of the National Academy of Sciences of the United States of America* 83, 5784-5788.

Biskup, S., Gerlach, M., Kupsch, A., Reichmann, H., Riederer, P., Vieregge, P., Wullner, U., and Gasser, T. (2008). Genes associated with Parkinson syndrome. *Journal of neurology* 255 Suppl. 5, 8-17.

Boado, R. J. and Pardridge, W. M. (1994). Measurement of blood-brain barrier GLUT1 glucose transporter and actin mRNA by a quantitative polymerase chain reaction assay. *Journal of neurochemistry* 62, 2085-2090.

Bogan, J. S. (2012). Regulation of glucose transporter translocation in health and diabetes. *Annual review of biochemistry* 81, 507-532.

Bohnen, N. I., Koeppe, R. A., Minoshima, S., Giordani, B., Albin, R. L., Frey, K. A., and Kuhl, D. E. (2011). Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study. *Journal of nuclear medicine: official publication, Society of Nuclear Medicine* 52, 848-855.

Bolz, S., Farrell, C. L., Dietz, K., and Wolburg, H. (1996). Subcellular distribution of glucose transporter (GLUT-1) during development of the blood-brain barrier in rats. *Cell and tissue research* 284, 355-365.

Borghammer, P., Hansen, S. B., Eggers, C., Chakravarty, M., Vang, K., Aanerud, J., Hilker, R., Heiss, W. D., Rodell, A., Munk, O. L., et al. (2012). Glucose metabolism in small subcortical structures in Parkinson's disease. *Acta neurologica Scandinavica* 125, 303-310.

Braak, H., Rub, U., Gai, W. P., and Del Tredici, K. (2003). Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *Journal of neural transmission* 110, 517-536.

Bredesen, D. E., Rao, R. V. and Mehlen, P. (2006). Cell death in the nervous system. *Nature* 443, 796-802.

Bruce, D. G., Harrington, N., Davis, W. A., Davis, T. M., and Fremantle Diabetes, S. (2001). Dementia and its associations in type 2 diabetes mellitus: the Fremantle Diabetes Study. *Diabetes research and clinical practice* 53, 165-172.

Caliceti, C., Zambonin, L., Prata, C., Vieceli Dalla Sega, F., Hakim, G., Hrelia, S., and Fiorentini, D. (2012). Effect of plasma membrane cholesterol depletion on glucose transport regulation in leukemia cells. *PloS one* 7, e41246.

Carruthers, A. (1990). Facilitated diffusion of glucose. *Physiological reviews* 70, 1135-1176.

Castro, M., Caprile, T., Astuya, A., Millan, C., Reinicke, K., Vera, J. C., Vasquez, O., Aguayo, L. G., and Nualart, F. (2001). High-affinity sodium-vitamin C co-transporters

(SVCT) expression in embryonic mouse neurons. *Journal of neurochemistry* 78, 815-823.

Castro, M. A., Angulo, C., Brauchi, S., Nualart, F., and Concha, I. I. (2008). Ascorbic acid participates in a general mechanism for concerted glucose transport inhibition and lactate transport stimulation. Pflugers Archiv: *European journal of physiology* 457, 519-528.

Castro, M. A., Beltrán, F. A., Brauchi, S., and Concha, I. I. (2009). A metabolic switch in brain: glucose and lactate metabolism modulation by ascorbic acid. *Journal of neurochemistry* 110, 423-440.

Castro, M. A., Pozo, M., Cortes, C., Garcia Mde, L., Concha, I. I., and Nualart, F. (2007). Intracellular ascorbic acid inhibits transport of glucose by neurons, but not by astrocytes. *Journal of neurochemistry* 102, 773-782.

Cox, D., Gonder-Frederick, L., McCall, A., Kovatchev, B., and Clarke, W. (2002). The effects of glucose fluctuation on cognitive function and QOL: the functional costs of hypoglycaemia and hyperglycaemia among adults with type 1 or type 2 diabetes. *International journal of clinical practice Supplement*, 20-26.

Chari, M., Yang, C. S., Lam, C. K., Lee, K., Mighiu, P., Kokorovic, A., Cheung, G. W., Lai, T. Y., Wang, P. Y., and Lam, T. K. (2011). Glucose transporter-1 in the hypothalamic glial cells mediates glucose sensing to regulate glucose production in vivo. *Diabetes* 60, 1901-1906.

Chih, C. P. and Roberts Jr, E. L. (2003). Energy substrates for neurons during neural activity: a critical review of the astrocyte-neuron lactate shuttle hypothesis. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 23, 1263-1281.

Choeiri, C., Staines, W. and Messier, C. (2002). Immunohistochemical localization and quantification of glucose transporters in the mouse brain. *Neuroscience* 111, 19-34.

Chua, L. M., Lim, M. L., Chong, P. R., Hu, Z. P., Cheung, N. S., and Wong, B. S. (2012). Impaired neuronal insulin signaling precedes Abeta42 accumulation in female AbetaPPsw/PS1DeltaE9 mice. *Journal of Alzheimer's disease: JAD* 29, 783-791.

Chuquet, J., Quilichini, P., Nimchinsky, E. A., and Buzsaki, G. (2010). Predominant enhancement of glucose uptake in astrocytes versus neurons during activation of the somatosensory cortex. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 30, 15298-15303.

De la Monte, S. M. (2012). Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. *Current Alzheimer research* 9, 35-66.

De Vos, K. J., Grierson, A. J., Ackerley, S., and Miller, C. C. (2008). Role of axonal transport in neurodegenerative diseases. *Annual review of neuroscience* 31, 151-173.

Deng, Y., Li, B., Liu, Y., Iqbal, K., Grundke-Iqbal, I., and Gong, C. X. (2009). Dysregulation of insulin signaling, glucose transporters, O-GlcNAcylation, and phosphorylation of tau and neurofilaments in the brain: Implication for Alzheimer's disease. *The American journal of pathology* 175, 2089-2098.

Devraj, K., Klinger, M. E., Myers, R. L., Mokashi, A., Hawkins, R. A., and Simpson, I. A. (2011). GLUT-1 glucose transporters in the blood-brain barrier: differential phosphorylation. *Journal of neuroscience research* 89, 1913-1925.

Dienel, G. A. and Cruz, N. F. (2009). Exchange-mediated dilution of brain lactate specific activity: implications for the origin of glutamate dilution and the contributions of glutamine dilution and other pathways. *Journal of neurochemistry* 109 Suppl. 1, 30-37.

Dinuzzo, M., Giove, F., Maraviglia, B., and Mangia, S. (2013). Glucose metabolism down-regulates the uptake of 6-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose (6-NBDG) mediated by glucose transporter 1 isoform (GLUT1): theory and simulations using the symmetric four-state carrier model. *Journal of neurochemistry*.

Doege, H., Bocianski, A., Scheepers, A., Axer, H., Eckel, J., Joost, H. G., and Schurmann, A. (2001). Characterization of human glucose transporter (GLUT) 11 (encoded by SLC2A11), a novel sugar-transport facilitator specifically expressed in heart and skeletal muscle. *The Biochemical journal* 359, 443-449.

Doege, H., Schurmann, A., Bahrenberg, G., Brauers, A., and Joost, H. G. (2000). GLUT8, a novel member of the sugar transport facilitator family with glucose transport activity. *The Journal of biological chemistry* 275, 16275-16280.

Dwyer, D. S. (2002). *Glucose Metabolism in the Brain* (London: Academic Press).

Edinger, A. L. (2005). Growth factors regulate cell survival by controlling nutrient transporter expression. *Biochemical Society transactions* 33, 225-227.

Edinger, A. L. (2007). Controlling cell growth and survival through regulated nutrient transporter expression. *The Biochemical journal* 406, 1-12.

Edinger, A. L. and Thompson, C. B. (2002). Akt maintains cell size and survival by increasing mTOR-dependent nutrient uptake. *Molecular biology of the cell* 13, 2276-2288.

Elfeber, K., Kohler, A., Lutzenburg, M., Osswald, C., Galla, H. J., Witte, O. W., and Koepsell, H. (2004). Localization of the Na+-D-glucose cotransporter SGLT1 in the blood-brain barrier. *Histochemistry and cell biology* 121, 201-207.

Enerson, B. E. and Drewes, L. R. (2006). The rat blood-brain barrier transcriptome. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 26, 959-973.

Ferraiuolo, L., Kirby, J., Grierson, A. J., Sendtner, M., and Shaw, P. J. (2011). Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis. *Nature reviews Neurology* 7, 616-630.

Ferreira, I. L., Resende, R., Ferreiro, E., Rego, A. C., and Pereira, C. F. (2010). Multiple defects in energy metabolism in Alzheimer's disease. *Current drug targets* 11, 1193-1206.

Ferreira, J. M., Burnett, A. L. and Rameau, G. A. (2011). Activity-dependent regulation of surface glucose transporter-3. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 31, 1991-1999.

Finck, B. N. and Kelly, D. P. (2006). PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. *The Journal of clinical investigation* 116, 615-622.

Fukuda, R., Hirota, K., Fan, F., Jung, Y. D., Ellis, L. M., and Semenza, G. L. (2002). Insulin-like growth factor 1 induces hypoxia-inducible factor 1-mediated vascular endothelial growth factor expression, which is dependent on MAP kinase and phosphatidylinositol 3-kinase signaling in colon cancer cells. *The Journal of biological chemistry* 277, 38205-38211.

Gamberino, W. C. and Brennan, W. A., Jr. (1994). Glucose transporter isoform expression in Huntington's disease brain. *Journal of neurochemistry* 63, 1392-1397.

Gandhi, S., Wood-Kaczmar, A., Yao, Z., Plun-Favreau, H., Deas, E., Klupsch, K., Downward, J., Latchman, D. S., Tabrizi, S. J., Wood, N. W., et al. (2009). PINK1-

associated Parkinson's disease is caused by neuronal vulnerability to calcium-induced cell death. *Molecular cell* 33, 627-638.

Garcia, M., Millan, C., Balmaceda-Aguilera, C., Castro, T., Pastor, P., Montecinos, H., Reinicke, K., Zuniga, F., Vera, J. C., Onate, S. A., et al. (2003). Hypothalamic ependymal-glial cells express the glucose transporter GLUT2, a protein involved in glucose sensing. *Journal of neurochemistry* 86, 709-724.

Ghasemzadeh, B., Cammack, J. and Adams, R. N. (1991). Dynamic changes in extracellular fluid ascorbic acid monitored by in vivo electrochemistry. *Brain research* 547, 162-166.

Gjedde, A., Marrett, S. and Vafaee, M. (2002). Oxidative and nonoxidative metabolism of excited neurons and astrocytes. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 22, 1-14.

Godoy, A., Ulloa, V., Rodriguez, F., Reinicke, K., Yanez, A. J., Garcia Mde, L., Medina, R. A., Carrasco, M., Barberis, S., Castro, T., et al. (2006). Differential subcellular distribution of glucose transporters GLUT1-6 and GLUT9 in human cancer: ultrastructural localization of GLUT1 and GLUT5 in breast tumor tissues. *Journal of cellular physiology* 207, 614-627.

Guo, Z., Kindy, M. S., Kruman, I., and Mattson, M. P. (2000). ALS-linked Cu/Zn-SOD mutation impairs cerebral synaptic glucose and glutamate transport and exacerbates ischemic brain injury. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 20, 463-468.

Gupta, A. and Dey, C. S. (2012). PTEN, a widely known negative regulator of insulin/PI3K signaling, positively regulates neuronal insulin resistance. *Molecular biology of the cell* 23, 3882-3898.

Hardie, D. G. (2007). AMP-activated/SNF1 protein kinases: conserved guardians of cellular energy. *Nature reviews Molecular cell biology* 8, 774-785.

Harr, S. D., Simonian, N. A. and Hyman, B. T. (1995). Functional alterations in Alzheimer's disease: decreased glucose transporter 3 immunoreactivity in the perforant pathway terminal zone. *Journal of neuropathology and experimental neurology* 54, 38-41.

Harris, D. S., Slot, J. W., Geuze, H. J., and James, D. E. (1992). Polarized distribution of glucose transporter isoforms in Caco-2 cells. *Proceedings of the National Academy of Sciences of the United States of America* 89, 7556-7560.

Hasselbalch, S. G., Knudsen, G. M., Capaldo, B., Postiglione, A., and Paulson, O. B. (2001). Blood-brain barrier transport and brain metabolism of glucose during acute hyperglycemia in humans. *The Journal of clinical endocrinology and metabolism* 86, 1986-1990.

Hasselbalch, S. G., Knudsen, G. M., Jakobsen, J., Hageman, L. P., Holm, S., and Paulson, O. B. (1995). Blood-brain barrier permeability of glucose and ketone bodies during short-term starvation in humans. *The American journal of physiology* 268, E1161-1166.

Hasselbalch, S. G., Knudsen, G. M., Videbaek, C., Pinborg, L. H., Schmidt, J. F., Holm, S., and Paulson, O. B. (1999). No effect of insulin on glucose blood-brain barrier transport and cerebral metabolism in humans. *Diabetes* 48, 1915-1921.

Heijnen, H. F., Oorschot, V., Sixma, J. J., Slot, J. W., and James, D. E. (1997). Thrombin stimulates glucose transport in human platelets via the translocation of the glucose transporter GLUT-3 from alpha-granules to the cell surface. *The Journal of cell biology* 138, 323-330.

Herrero-Mendez, A., Almeida, A., Fernandez, E., Maestre, C., Moncada, S., and Bolanos, J. P. (2009). The bioenergetic and antioxidant status of neurons is controlled by continuous degradation of a key glycolytic enzyme by APC/C-Cdh1. *Nature cell biology* 11, 747-752.

Hertz, L. (2004). The astrocyte-neuron lactate shuttle: a challenge of a challenge. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 24, 1241-1248.

Hertz, L. (2008). Bioenergetics of cerebral ischemia: a cellular perspective. *Neuropharmacology* 55, 289-309.

Hertz, L., Peng, L. and Dienel, G. A. (2007). Energy metabolism in astrocytes: high rate of oxidative metabolism and spatiotemporal dependence on glycolysis/glycogenolysis. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 27, 219-249.

Hooijmans, C. R., Graven, C., Dederen, P. J., Tanila, H., van Groen, T., and Kiliaan, A. J. (2007). Amyloid beta deposition is related to decreased glucose transporter-1 levels and hippocampal atrophy in brains of aged APP/PS1 mice. *Brain research* 1181, 93-103.

Hosokai, Y., Nishio, Y., Hirayama, K., Takeda, A., Ishioka, T., Sawada, Y., Suzuki, K., Itoyama, Y., Takahashi, S., Fukuda, H., et al. (2009). Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment. *Movement disorders: official journal of the Movement Disorder Society* 24, 854-862.

Hoyer, S. (2004). Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. *European journal of pharmacology* 490, 115-125.

Huang, C., Mattis, P., Tang, C., Perrine, K., Carbon, M., and Eidelberg, D. (2007). Metabolic brain networks associated with cognitive function in Parkinson's disease. *NeuroImage* 34, 714-723.

Huang, S. (2012). Inhibition of PI3K/Akt/mTOR Signaling by Natural Products. Anti-cancer agents in medicinal chemistry.

Huber, J. D., Egleton, R. D. and Davis, T. P. (2001). Molecular physiology and pathophysiology of tight junctions in the blood-brain barrier. *Trends in neurosciences* 24, 719-725.

Ibberson, M., Riederer, B. M., Uldry, M., Guhl, B., Roth, J., and Thorens, B. (2002). Immunolocalization of GLUTX1 in the testis and to specific brain areas and vasopressin-containing neurons. *Endocrinology* 143, 276-284.

Ibberson, M., Uldry, M. and Thorens, B. (2000). GLUTX1, a novel mammalian glucose transporter expressed in the central nervous system and insulin-sensitive tissues. *The Journal of biological chemistry* 275, 4607-4612.

Inukai, K., Shewan, A. M., Pascoe, W. S., Katayama, S., James, D. E., and Oka, Y. (2004). Carboxy terminus of glucose transporter 3 contains an apical membrane targeting domain. *Molecular endocrinology* 18, 339-349.

Ivanov, A., Mukhtarov, M., Bregestovski, P., and Zilberter, Y. (2011). Lactate Effectively Covers Energy Demands during Neuronal Network Activity in Neonatal Hippocampal Slices. *Frontiers in neuroenergetics* 3, 2.

Iwabuchi, S. and Kawahara, K. (2011). Inducible astrocytic glucose transporter-3 contributes to the enhanced storage of intracellular glycogen during reperfusion after ischemia. *Neurochemistry international* 59, 319-325.

Jagust, W. J., Seab, J. P., Huesman, R. H., Valk, P. E., Mathis, C. A., Reed, B. R., Coxson, P. G., and Budinger, T. F. (1991). Diminished glucose transport in Alzheimer's disease: dynamic PET studies. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 11, 323-330.

Jin, N., Qian, W., Yin, X., Zhang, L., Iqbal, K., Grundke-Iqbal, I., Gong, C. X., and Liu, F. (2013). CREB regulates the expression of neuronal glucose transporter 3: a possible mechanism related to impaired brain glucose uptake in Alzheimer's disease. *Nucleic acids research*.

Joost, H. G., Bell, G. I., Best, J. D., Birnbaum, M. J., Charron, M. J., Chen, Y. T., Doege, H., James, D. E., Lodish, H. F., Moley, K. H., et al. (2002). Nomenclature of the GLUT/SLC2A family of sugar/polyol transport facilitators. *American journal of physiology Endocrinology and metabolism* 282, E974-976.

Joost, H. G. and Thorens, B. (2001). The extended GLUT-family of sugar/polyol transport facilitators: nomenclature, sequence characteristics, and potential function of its novel members (review). *Molecular membrane biology* 18, 247-256.

Kahn, B. B., Alquier, T., Carling, D., and Hardie, D. G. (2005). AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell metabolism* 1, 15-25.

Kennedy, A. M., Frackowiak, R. S., Newman, S. K., Bloomfield, P. M., Seaward, J., Roques, P., Lewington, G., Cunningham, V. J., and Rossor, M. N. (1995). Deficits in cerebral glucose metabolism demonstrated by positron emission tomography in individuals at risk of familial Alzheimer's disease. *Neuroscience letters* 186, 17-20.

Kletzien, R. F., Harris, P. K. and Foellmi, L. A. (1994). Glucose-6-phosphate dehydrogenase: a "housekeeping" enzyme subject to tissue-specific regulation by hormones, nutrients, and oxidant stress. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology* 8, 174-181.

Kuwert, T., Lange, H. W., Boecker, H., Titz, H., Herzog, H., Aulich, A., Wang, B. C., Nayak, U., and Feinendegen, L. E. (1993). Striatal glucose consumption in chorea-free subjects at risk of Huntington's disease. *Journal of neurology* 241, 31-36.

Lee, F. J. and Liu, F. (2008). Genetic factors involved in the pathogenesis of Parkinson's disease. *Brain research reviews* 58, 354-364.

Lee, M. S., Lyoo, C. H., Ryu, Y. H., Lim, H. S., Nam, C. M., Kim, H. S., and Rinne, J. O. (2011). The effect of age on motor deficits and cerebral glucose metabolism of Parkinson's disease. *Acta neurologica Scandinavica* 124, 196-201.

Leenders, K. L., Frackowiak, R. S., Quinn, N., and Marsden, C. D. (1986). Brain energy metabolism and dopaminergic function in Huntington's disease measured in vivo using positron emission tomography. *Movement disorders: official journal of the Movement Disorder Society* 1, 69-77.

Leino, R. L., Gerhart, D. Z., van Bueren, A. M., McCall, A. L., and Drewes, L. R. (1997). Ultrastructural localization of GLUT 1 and GLUT 3 glucose transporters in rat brain. *Journal of neuroscience research* 49, 617-626.

Leto, D. and Saltiel, A. R. (2012). Regulation of glucose transport by insulin: traffic control of GLUT4. *Nature reviews Molecular cell biology* 13, 383-396.

Lim, D., Fedrizzi, L., Tartari, M., Zuccato, C., Cattaneo, E., Brini, M., and Carafoli, E. (2008). Calcium homeostasis and mitochondrial dysfunction in striatal neurons of Huntington disease. *The Journal of biological chemistry* 283, 5780-5789.

Lin, M. T. and Beal, M. F. (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 443, 787-795.

Lisinski, I., Schurmann, A., Joost, H. G., Cushman, S. W., and Al-Hasani, H. (2001). Targeting of GLUT6 (formerly GLUT9) and GLUT8 in rat adipose cells. *The Biochemical journal* 358, 517-522.

Liu, Y., Liu, F., Iqbal, K., Grundke-Iqbal, I., and Gong, C. X. (2008). Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer disease. *FEBS letters* 582, 359-364.

Lowry, O. H. and Passonneau, J. V. (1964). The Relationships between Substrates and Enzymes of Glycolysis in Brain. *The Journal of biological chemistry* 239, 31-42.

Maher, F. (1995). Immunolocalization of GLUT1 and GLUT3 glucose transporters in primary cultured neurons and glia. *Journal of neuroscience research* 42, 459-469.

Maher, F., Davies-Hill, T. M. and Simpson, I. A. (1996). Substrate specificity and kinetic parameters of GLUT3 in rat cerebellar granule neurons. *The Biochemical journal* 315 (Pt 3), 827-831.

Maher, F., Vannucci, S., Takeda, J., and Simpson, I. A. (1992). Expression of mouse-GLUT3 and human-GLUT3 glucose transporter proteins in brain. *Biochemical and biophysical research communications* 182, 703-711.

Maher, F., Vannucci, S. J. and Simpson, I. A. (1994). Glucose transporter proteins in brain. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology* 8, 1003-1011.

Mairet-Coello, G., Tury, A. and DiCicco-Bloom, E. (2009). Insulin-like growth factor-1 promotes G(1)/S cell cycle progression through bidirectional regulation of cyclins and cyclin-dependent kinase inhibitors via the phosphatidylinositol 3-kinase/Akt pathway in developing rat cerebral cortex. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 29, 775-788.

Mangia, S., Garreffa, G., Bianciardi, M., Giove, F., Di Salle, F., and Maraviglia, B. (2003). The aerobic brain: lactate decrease at the onset of neural activity. *Neuroscience* 118, 7-10.

Mangia, S., Simpson, I. A., Vannucci, S. J., and Carruthers, A. (2009). The in vivo neuron-to-astrocyte lactate shuttle in human brain: evidence from modeling of measured lactate levels during visual stimulation. *Journal of neurochemistry* 109 Suppl. 1, 55-62.

Manolescu, A. R., Witkowska, K., Kinnaird, A., Cessford, T., and Cheeseman, C. (2007). Facilitated hexose transporters: new perspectives on form and function. *Physiology* 22, 234-240.

Mazziotta, J. C., Phelps, M. E., Pahl, J. J., Huang, S. C., Baxter, L. R., Riege, W. H., Hoffman, J. M., Kuhl, D. E., Lanto, A. B., Wapenski, J. A., et al. (1987). Reduced cerebral glucose metabolism in asymptomatic subjects at risk for Huntington's disease. *The New England journal of medicine* 316, 357-362.

Menzies, F. M., Ince, P. G. and Shaw, P. J. (2002). Mitochondrial involvement in amyotrophic lateral sclerosis. *Neurochemistry international* 40, 543-551.

Minoshima, S., Frey, K. A., Koeppe, R. A., Foster, N. L., and Kuhl, D. E. (1995). A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. *Journal of nuclear medicine: official publication, Society of Nuclear Medicine* 36, 1238-1248.

Mosconi, L., Brys, M., Switalski, R., Mistur, R., Glodzik, L., Pirraglia, E., Tsui, W., De Santi, S., and de Leon, M. J. (2007). Maternal family history of Alzheimer's disease predisposes to reduced brain glucose metabolism. *Proceedings of the National Academy of Sciences of the United States of America* 104, 19067-19072.

Mosconi, L., Sorbi, S., de Leon, M. J., Li, Y., Nacmias, B., Myoung, P. S., Tsui, W., Ginestroni, A., Bessi, V., Fayyazz, M., et al. (2006). Hypometabolism exceeds atrophy in presymptomatic early-onset familial Alzheimer's disease. *Journal of nuclear medicine: official publication, Society of Nuclear Medicine* 47, 1778-1786.

Mueckler, M. (1994). Facilitative glucose transporters. *European journal of biochemistry / FEBS* 219, 713-725.

Myers, M. G., Jr. and White, M. F. (1996). Insulin signal transduction and the IRS proteins. *Annual review of pharmacology and toxicology* 36, 615-658.

Nagamatsu, S., Sawa, H., Kamada, K., Nakamichi, Y., Yoshimoto, K., and Hoshino, T. (1993). Neuron-specific glucose transporter (NSGT): CNS distribution of GLUT3 rat glucose transporter (RGT3) in rat central neurons. *FEBS letters* 334, 289-295.

Navarrete Santos, A., Tonack, S., Kirstein, M., Kietz, S., and Fischer, B. (2004). Two insulin-responsive glucose transporter isoforms and the insulin receptor are developmentally expressed in rabbit preimplantation embryos. *Reproduction* 128, 503-516.

Nicholson, R. M., Kusne, Y., Nowak, L. A., LaFerla, F. M., Reiman, E. M., and Valla, J. (2010). Regional cerebral glucose uptake in the 3xTG model of Alzheimer's disease highlights common regional vulnerability across AD mouse models. *Brain research* 1347, 179-185.

Nualart, F., Godoy, A. and Reinicke, K. (1999). Expression of the hexose transporters GLUT1 and GLUT2 during the early development of the human brain. *Brain research* 824, 97-104.

O'Malley, D., Reimann, F., Simpson, A. K., and Gribble, F. M. (2006). Sodium-coupled glucose cotransporters contribute to hypothalamic glucose sensing. *Diabetes* 55, 3381-3386.

O'Neill, R. D., Fillenz, M., Sundstrom, L., and Rawlins, J. N. (1984). Voltammetrically monitored brain ascorbate as an index of excitatory amino acid release in the unrestrained rat. *Neuroscience letters* 52, 227-233.

Ogawa, M., Fukuyama, H., Ouchi, Y., Yamauchi, H., and Kimura, J. (1996). Altered energy metabolism in Alzheimer's disease. *Journal of the neurological sciences* 139, 78-82.

Olah, J., Klivenyi, P., Gardian, G., Vecsei, L., Orosz, F., Kovacs, G. G., Westerhoff, H. V., and Ovadi, J. (2008). Increased glucose metabolism and ATP level in brain tissue of Huntington's disease transgenic mice. *The FEBS journal* 275, 4740-4755.

Pardridge, W. M., Boado, R. J. and Farrell, C. R. (1990). Brain-type glucose transporter (GLUT-1) is selectively localized to the blood-brain barrier. Studies with quantitative western blotting and in situ hybridization. *The Journal of biological chemistry* 265, 18035-18040.

Pellerin, L. and Magistretti, P. J. (1994). Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. *Proceedings of the National Academy of Sciences of the United States of America* 91, 10625-10629.

Pellerin, L. and Magistretti, P. J. (2012). Sweet sixteen for ANLS. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 32, 1152-1166.

Perneczky, R., Drzezga, A., Boecker, H., Ceballos-Baumann, A. O., Granert, O., Forstl, H., Kurz, A., and Haussermann, P. (2008). Activities of daily living, cerebral glucose metabolism, and cognitive reserve in Lewy body and Parkinson's disease. *Dementia and geriatric cognitive disorders* 26, 475-481.

Pessin, J. E. and Bell, G. I. (1992). Mammalian facilitative glucose transporter family: structure and molecular regulation. *Annual review of physiology* 54, 911-930.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., and Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of neurology* 56, 303-308.

Phay, J. E., Hussain, H. B. and Moley, J. F. (2000). Strategy for identification of novel glucose transporter family members by using internet-based genomic databases. *Surgery* 128, 946-951.

Piper, R. C., Hess, L. J. and James, D. E. (1991). Differential sorting of two glucose transporters expressed in insulin-sensitive cells. *The American journal of physiology* 260, C570-580.

Plas, D. R., Talapatra, S., Edinger, A. L., Rathmell, J. C., and Thompson, C. B. (2001). Akt and Bcl-xL promote growth factor-independent survival through distinct effects on mitochondrial physiology. *The Journal of biological chemistry* 276, 12041-12048.

Podolsky, S., Leopold, N. A. and Sax, D. S. (1972). Increased frequency of diabetes mellitus in patients with Huntington's chorea. *Lancet* 1, 1356-1358.

Porras, O. H., Loaiza, A. and Barros, L. F. (2004). Glutamate mediates acute glucose transport inhibition in hippocampal neurons. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 24, 9669-9673.

Pradat, P. F., Bruneteau, G., Gordon, P. H., Dupuis, L., Bonnefont-Rousselot, D., Simon, D., Salachas, F., Corcia, P., Frochot, V., Lacorte, J. M., et al. (2010). Impaired glucose tolerance in patients with amyotrophic lateral sclerosis. *Amyotrophic lateral sclerosis: official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases* 11, 166-171.

Prapong, T., Buss, J., Hsu, W. H., Heine, P., West Greenlee, H., and Uemura, E. (2002). Amyloid beta-peptide decreases neuronal glucose uptake despite causing increase in GLUT3 mRNA transcription and GLUT3 translocation to the plasma membrane. *Experimental neurology* 174, 253-258.

Rajakumar, A., Thamotharan, S., Raychaudhuri, N., Menon, R. K., and Devaskar, S. U. (2004). Trans-activators regulating neuronal glucose transporter isoform-3 gene expression in mammalian neurons. *The Journal of biological chemistry* 279, 26768-26779.

Ramamurthy, S. and Ronnett, G. (2012). AMP-Activated Protein Kinase (AMPK) and Energy-Sensing in the Brain. *Experimental neurobiology* 21, 52-60.

Ramm, G., Larance, M., Guilhaus, M., and James, D. E. (2006). A role for 14-3-3 in insulin-stimulated GLUT4 translocation through its interaction with the RabGAP AS160. *The Journal of biological chemistry* 281, 29174-29180.

Rathmell, J. C., Elstrom, R. L., Cinalli, R. M., and Thompson, C. B. (2003). Activated Akt promotes increased resting T cell size, CD28-independent T cell growth, and development of autoimmunity and lymphoma. *European journal of immunology* 33, 2223-2232.

Rauch, M. C., Ocampo, M. E., Bohle, J., Amthauer, R., Yanez, A. J., Rodriguez-Gil, J. E., Slebe, J. C., Reyes, J. G., and Concha, I. I. (2006). Hexose transporters GLUT1 and GLUT3 are colocalized with hexokinase I in caveolae microdomains of rat spermatogenic cells. *Journal of cellular physiology* 207, 397-406.

Reagan, L. P., Rosell, D. R., Alves, S. E., Hoskin, E. K., McCall, A. L., Charron, M. J., and McEwen, B. S. (2002). GLUT8 glucose transporter is localized to excitatory and inhibitory neurons in the rat hippocampus. *Brain research* 932, 129-134.

Reiman, E. M., Chen, K., Alexander, G. E., Caselli, R. J., Bandy, D., Osborne, D., Saunders, A. M., and Hardy, J. (2004). Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proceedings of the National Academy of Sciences of the United States of America* 101, 284-289.

Ristow, M. (2004). Neurodegenerative disorders associated with diabetes mellitus. *Journal of molecular medicine* 82, 510-529.

Rogers, S., Macheda, M. L., Docherty, S. E., Carty, M. D., Henderson, M. A., Soeller, W. C., Gibbs, E. M., James, D. E., and Best, J. D. (2002). Identification of a novel glucose transporter-like protein-GLUT-12. *American journal of physiology Endocrinology and metabolism* 282, E733-738.

Rothman, D. L., Sibson, N. R., Hyder, F., Shen, J., Behar, K. L., and Shulman, R. G. (1999). In vivo nuclear magnetic resonance spectroscopy studies of the relationship between the glutamate-glutamine neurotransmitter cycle and functional neuroenergetics. *Philosophical transactions of the Royal Society of London Series B, Biological sciences* 354, 1165-1177.

Rowland, L. P. and Shneider, N. A. (2001). Amyotrophic lateral sclerosis. *The New England journal of medicine* 344, 1688-1700.

Rubinsztein, D. C. (2006). The roles of intracellular protein-degradation pathways in neurodegeneration. *Nature* 443, 780-786.

Sakyo, T. and Kitagawa, T. (2002). Differential localization of glucose transporter isoforms in non-polarized mammalian cells: distribution of GLUT1 but not GLUT3 to detergent-resistant membrane domains. *Biochimica et biophysica acta* 1567, 165-175.

Sakyo, T., Naraba, H., Teraoka, H., and Kitagawa, T. (2007). The intrinsic structure of glucose transporter isoforms Glut1 and Glut3 regulates their differential distribution to detergent-resistant membrane domains in nonpolarized mammalian cells. *The FEBS journal* 274, 2843-2853.

Salkovic-Petrisic, M., Tribl, F., Schmidt, M., Hoyer, S., and Riederer, P. (2006). Alzheimer-like changes in protein kinase B and glycogen synthase kinase-3 in rat frontal cortex and hippocampus after damage to the insulin signalling pathway. *Journal of neurochemistry* 96, 1005-1015.

Salminen, A., Kaarniranta, K., Haapasalo, A., Soininen, H., and Hiltunen, M. (2011). AMP-activated protein kinase: a potential player in Alzheimer's disease. *Journal of neurochemistry* 118, 460-474.

Saltiel, A. R. and Kahn, C. R. (2001). Insulin signalling and the regulation of glucose and lipid metabolism. *Nature* 414, 799-806.

Sandyk, R. (1993). The relationship between diabetes mellitus and Parkinson's disease. *The International journal of neuroscience* 69, 125-130.

Sano, H., Kane, S., Sano, E., Miinea, C. P., Asara, J. M., Lane, W. S., Garner, C. W., and Lienhard, G. E. (2003). Insulin-stimulated phosphorylation of a Rab GTPase-activating

protein regulates GLUT4 translocation. *The Journal of biological chemistry* 278, 14599-14602.

Sasaki, S. and Iwata, M. (1999). Ultrastructural change of synapses of Betz cells in patients with amyotrophic lateral sclerosis. *Neuroscience letters* 268, 29-32.

Sathasivam, S., Ince, P. G. and Shaw, P. J. (2001). Apoptosis in amyotrophic lateral sclerosis: a review of the evidence. *Neuropathology and applied neurobiology* 27, 257-274.

Schapira, A. H. (2006). Mitochondrial disease. *Lancet* 368, 70-82.

Sibson, N. R., Dhankhar, A., Mason, G. F., Rothman, D. L., Behar, K. L., and Shulman, R. G. (1998). Stoichiometric coupling of brain glucose metabolism and glutamatergic neuronal activity. *Proceedings of the National Academy of Sciences of the United States of America* 95, 316-321.

Siesjo, B. K. (1978). Utilisation of substrates by brain tissues. In: *Brain energy metabolism* (New York: John Wiley and Sons), p. 308.

Silva-Alvarez, C., Carrasco, M., Balmaceda-Aguilera, C., Pastor, P., Garcia Mde, L., Reinicke, K., Aguayo, L., Molina, B., Cifuentes, M., Medina, R., et al. (2005). Ependymal cell differentiation and GLUT1 expression is a synchronous process in the ventricular wall. *Neurochemical research* 30, 1227-1236.

Silver, I. A. and Erecinska, M. (1994). Extracellular glucose concentration in mammalian brain: continuous monitoring of changes during increased neuronal activity and upon limitation in oxygen supply in normo-, hypo-, and hyperglycemic animals. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 14, 5068-5076.

Simpson, I. A., Carruthers, A. and Vannucci, S. J. (2007). Supply and demand in cerebral energy metabolism: the role of nutrient transporters. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 27, 1766-1791.

Simpson, I. A. and Davies, P. (1994). Reduced glucose transporter concentrations in brains of patients with Alzheimer's disease. *Annals of neurology* 36, 800-801.

Slomiany, M. G. and Rosenzweig, S. A. (2006). Hypoxia-inducible factor-1-dependent and -independent regulation of insulin-like growth factor-1-stimulated vascular endothelial growth factor secretion. *The Journal of pharmacology and experimental therapeutics* 318, 666-675.

Small, G. W., Ercoli, L. M., Silverman, D. H., Huang, S. C., Komo, S., Bookheimer, S. Y., Lavretsky, H., Miller, K., Siddarth, P., Rasgon, N. L., et al. (2000). Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America* 97, 6037-6042.

Sokoloff, L., Reivich, M., Kennedy, C., Des Rosiers, M. H., Patlak, C. S., Pettigrew, K. D., Sakurada, O., and Shinohara, M. (1977). The [14C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *Journal of neurochemistry* 28, 897-916.

Stockli, J., Fazakerley, D. J. and James, D. E. (2011). GLUT4 exocytosis. *Journal of cell science* 124, 4147-4159.

Stuart, C. A., Howell, M. E., Zhang, Y., and Yin, D. (2009). Insulin-stimulated translocation of glucose transporter (GLUT) 12 parallels that of GLUT4 in normal muscle. *The Journal of clinical endocrinology and metabolism* 94, 3535-3542.

Thoidis, G., Kupriyanova, T., Cunningham, J. M., Chen, P., Cadel, S., Foulon, T., Cohen, P., Fine, R. E., and Kandror, K. V. (1999). Glucose transporter Glut3 is targeted to secretory

vesicles in neurons and PC12 cells. *The Journal of biological chemistry* 274, 14062-14066.

Thorens, B., Sarkar, H. K., Kaback, H. R., and Lodish, H. F. (1988). Cloning and functional expression in bacteria of a novel glucose transporter present in liver, intestine, kidney, and beta-pancreatic islet cells. *Cell* 55, 281-290.

Treins, C., Giorgetti-Peraldi, S., Murdaca, J., Monthouel-Kartmann, M. N., and Van Obberghen, E. (2005). Regulation of hypoxia-inducible factor (HIF)-1 activity and expression of HIF hydroxylases in response to insulin-like growth factor I. *Molecular endocrinology* 19, 1304-1317.

Uemura, E. and Greenlee, H. W. (2001). Amyloid beta-peptide inhibits neuronal glucose uptake by preventing exocytosis. *Experimental neurology* 170, 270-276.

Uemura, E. and Greenlee, H. W. (2006). Insulin regulates neuronal glucose uptake by promoting translocation of glucose transporter GLUT3. *Experimental neurology* 198, 48-53.

Uldry, M., Ibberson, M., Horisberger, J. D., Chatton, J. Y., Riederer, B. M., and Thorens, B. (2001). Identification of a mammalian H(+)-myo-inositol symporter expressed predominantly in the brain. *The EMBO journal* 20, 4467-4477.

Vander Heiden, M. G., Plas, D. R., Rathmell, J. C., Fox, C. J., Harris, M. H., and Thompson, C. B. (2001). Growth factors can influence cell growth and survival through effects on glucose metabolism. *Molecular and cellular biology* 21, 5899-5912.

Vannucci, S. J., Reinhart, R., Maher, F., Bondy, C. A., Lee, W. H., Vannucci, R. C., and Simpson, I. A. (1998). Alterations in GLUT1 and GLUT3 glucose transporter gene expression following unilateral hypoxia-ischemia in the immature rat brain. *Brain research Developmental brain research* 107, 255-264.

Vannucci, S. J., Rutherford, T., Wilkie, M. B., Simpson, I. A., and Lauder, J. M. (2000). Prenatal expression of the GLUT4 glucose transporter in the mouse. *Developmental neuroscience* 22, 274-282.

Vemula, S., Roder, K. E., Yang, T., Bhat, G. J., Thekkumkara, T. J., and Abbruscato, T. J. (2009). A functional role for sodium-dependent glucose transport across the blood-brain barrier during oxygen glucose deprivation. *The Journal of pharmacology and experimental therapeutics* 328, 487-495.

Ward, M. W., Huber, H. J., Weisova, P., Dussmann, H., Nicholls, D. G., and Prehn, J. H. (2007). Mitochondrial and plasma membrane potential of cultured cerebellar neurons during glutamate-induced necrosis, apoptosis, and tolerance. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 27, 8238-8249.

Weisova, P., Concannon, C. G., Devocelle, M., Prehn, J. H., and Ward, M. W. (2009). Regulation of glucose transporter 3 surface expression by the AMP-activated protein kinase mediates tolerance to glutamate excitation in neurons. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 29, 2997-3008.

WHO [World Health Organisation] (2012). Dementia: A Public Health Priority (Geneva, Switzerland: WHO Press).

Wilson, C. M., Mitsumoto, Y., Maher, F., and Klip, A. (1995). Regulation of cell surface GLUT1, GLUT3, and GLUT4 by insulin and IGF-I in L6 myotubes. *FEBS letters* 368, 19-22.

Wright, E. M., Loo, D. D. and Hirayama, B. A. (2011). Biology of human sodium glucose transporters. *Physiological reviews* 91, 733-794.

Wright, E. M., Loo, D. D., Hirayama, B. A., and Turk, E. (2004). Surprising versatility of Na+-glucose cotransporters: SLC5. *Physiology* 19, 370-376.

Wright, E. M. and Turk, E. (2004). The sodium/glucose cotransport family SLC5. *Pflugers Archiv: European journal of physiology* 447, 510-518.

Wu, X. and Freeze, H. H. (2002). GLUT14, a duplicon of GLUT3, is specifically expressed in testis as alternative splice forms. *Genomics* 80, 553-557.

Wyss, M. T., Jolivet, R., Buck, A., Magistretti, P. J., and Weber, B. (2011). In vivo evidence for lactate as a neuronal energy source. *The Journal of neuroscience: the official journal of the Society for Neuroscience* 31, 7477-7485.

Yong, S. W., Yoon, J. K., An, Y. S., and Lee, P. H. (2007). A comparison of cerebral glucose metabolism in Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies. *European journal of neurology: the official journal of the European Federation of Neurological Societies* 14, 1357-1362.

Yu, J., Li, J., Zhang, S., Xu, X., Zheng, M., Jiang, G., and Li, F. (2012). IGF-1 induces hypoxia-inducible factor 1alpha-mediated GLUT3 expression through PI3K/Akt/mTOR dependent pathways in PC12 cells. *Brain research* 1430, 18-24.

Yusa, T. (2001). Increased extracellular ascorbate release reflects glutamate re-uptake during the early stage of reperfusion after forebrain ischemia in rats. *Brain research* 897, 104-113.

Zambrano, A., Jara, E., Murgas, P., Jara, C., Castro, M. A., Angulo, C., and Concha, I. I. (2010a). Cytokine stimulation promotes increased glucose uptake via translocation at the plasma membrane of GLUT1 in HEK293 cells. *Journal of cellular biochemistry* 110, 1471-1480.

Zambrano, A., Otth, C., Maccioni, R. B., and Concha, I. I. (2010b). IL-3 controls tau modifications and protects cortical neurons from neurodegeneration. *Current Alzheimer research* 7, 615-624.

Zambrano, A., Otth, C., Mujica, L., Concha, I. I., and Maccioni, R. B. (2007). Interleukin-3 prevents neuronal death induced by amyloid peptide. *BMC neuroscience* 8, 82.

Zeller, K., Rahner-Welsch, S. and Kuschinsky, W. (1997). Distribution of Glut1 glucose transporters in different brain structures compared to glucose utilization and capillary density of adult rat brains. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism* 17, 204-209.

Zhang, F., Wang, Y. Y., Liu, H., Lu, Y. F., Wu, Q., Liu, J., and Shi, J. S. (2012). Resveratrol Produces Neurotrophic Effects on Cultured Dopaminergic Neurons through Prompting Astroglial BDNF and GDNF Release. *Evidence-based complementary and alternative medicine: eCAM* 2012, 937605.