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Glucose transport in brain – effect of inflammation

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Glucose is transported across the cell membrane by specific saturable transport system, which includes two types of glucose transporters: 1) sodium dependent glucose transporters (SGLTs) which transport glucose against its concentration gradient and 2) sodium independent glucose transporters (GLUTs), which transport glucose by facilitative diffusion in its concentration gradient. In the brain, both types of transporters are present with different function, affinity, capacity, and tissue distribution. GLUT1 occurs in brain in two isoforms. The more glycosylated GLUT1 is produced in brain microvasculature and ensures glucose transport across the blood brain barrier (BBB). The less glycosylated form is localized in astrocytic end-feet and cell bodies and is not present in axons, neuronal synapses or microglia. Glucose transported to astrocytes by GLUT1 is metabolized to lactate serving to neurons as energy source. Proinflammatory cytokine interleukin (IL)-1β upregulates GLUT1 in endothelial cells and astrocytes, whereas it induces neuronal death in neuronal cell culture. GLUT2 is present in hypothalamic neurons and serves as a glucose sensor in regulation of food intake. In neurons of the hippocampus, GLUT2 is supposed to regulate synaptic activity and neurotransmitter release. GLUT3 is the most abundant glucose transporter in the brain having five times higher transport capacity than GLUT1. It is present in neuropil, mostly in axons and dendrites. Its density and distribution correlate well with the local cerebral glucose demands. GLUT5 is predominantly fructose transporter. In brain, GLUT5 is the only hexose transporter in microglia, whose regulation is not yet clear. It is not present in neurons. GLUT4 and GLUT8 are insulin-regulated glucose transporters in neuronal cell bodies in the cortex and cerebellum, but mainly in the hippocampus and amygdala, where they maintain hippocampus-dependent cognitive functions. Insulin translocates GLUT4 from cytosol to plasma membrane to transport glucose into cells, and GLUT8 from cytosol to rough endoplasmic reticulum to recover redundant glucose to cytosol after protein glycosylation. In autoimmune diseases, the enhanced glucose uptake was found in inflamed peripheral tissue, mainly due to proliferating fibroblasts and activated macrophages. In our experimental model of rheumatoid arthritis (adjuvant arthritis), enhanced 2-deoxy-2[F-18]fluoro-D-glucose was found in the hippocampus and amygdala two days after the induction of the disease which, similarly as in the peripheral joints, can be ascribed to the activated macrophages. The knowledge on the glucose transport and the role of glucose transporters in the brain during systemic autoimmune inflammation is still incomplete and needs further investigations.

Key words: glucose transporters, BBB, insulin signaling, neurons, astrocytes, interleukins, autoimmune diseases, sepsis

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Introduction

Glucose is a vital energy source for all mammalian cells. Since cell membrane is impermeable to free diffusion of hydrophilic substances, glucose is transferred across the cell membrane by special saturable transport systems. These systems include two different types of transporters: 1) sodium dependent glucose transporters (SGLTs) which transport glucose against its concentration gradient and 2) sodium independent glucose transporters (GLUTs), which transport glucose by facilitative diffusion along its concentration gradient. In the brain, both types of transporters are present in different brain structures in various densities, all serving to specific functions according to the demands of the organism.

The effort of this review is to present the current understanding of the individual types of glucose transporters in the brain, their physiological function and significance under the pathological situation of inflammation. Inflammatory insult triggers activation of immune cells and consequently upregulation of proinflammatory cytokines in the central nervous system and periphery. This situation places greater demands on glucose supply because: 1) the enhanced proliferation of immune cells causes higher glucose consumption and 2) cytokines directly affect glucose metabolism by their specific effects. Thus under the inflammatory conditions glucose transporters may represent the gate to cope with this intense metabolic challenges.

Characterization of glucose transporters

The facilitative glucose transporters GLUTs, gene symbol SLC2 (Solute Carrier Family 2), work as simple carriers of glucose and related hexoses across the plasma membrane downhill its concentration and electrochemical gradient, which makes them energy independent. GLUTs are membrane-integrated proteins with a common structural feature, a presence of 12 membrane-spanning regions with both amino- and carboxy-terminal ends located in the cytosol (Uldry and Thorens 2004). Amino acid sequence in individual GLUTs revealed conserved glycine and tryptophan residues, which are essential for the facilitative transporter function. To date 13 members of GLUT family have been identified. Based on their sequence similarities they have been divided into three subclasses that also share common sequence motifs. Class I comprises GLUT1, GLUT2, GLUT3, and GLUT4; class II GLUT5, GLUT7, GLUT9, and GLUT11; and class III GLUT6, GLUT8, GLUT10, GLUT12, and HMIT (H^+-myo-inositol cotransporter) (Joost and Thorens 2001; Joost et al. 2002).

The sodium dependent glucose transporters (SGLTs), gene names SLC5A (Solute Carrier Family 5A), transport glucose by secondary active transport mechanism. Glucose is transported thanks to the downhill Na^+ gradient created by the Na^+/K^+ ATPase pump. This ATPase pumps three Na^+ outwards and two K^+ inwards the cells. After Na^+ and glucose binding on SGLT, Na^+ is transported by electrochemical gradient along with glucose against the electrochemical gradient. The structure of SGLTs differs from GLUTs. SGLTs contains 14 transmembrane helices with both amino- and carboxy-terminals facing the extracellular space. Na^+ binds to the amino-terminal portion causing conformational changes of the transport protein and enables sugar binding and translocation. Sugar permeates through the carboxy-terminal domain (Wright 2001; Wood and Trayhurn 2003).

Blood brain barrier. Blood borne glucose provides the brain with about 98% of energy and as a hydrophylic compound it has first to be transported across the blood brain barrier (BBB). Brain capillaries are about 100 times tighter than peripheral microvessels due to the occurrence of tight junctions between the endothelial cells. These junctions are created by transmembrane proteins (claudins, ocludins) as well as junctional adhesion molecule JAM-A and cytoplasmic proteins. The membrane proteins of the tight junctions are bound to the cytoskeleton – actin filaments – via cytoplasmic proteins (zona occludens) ZO-1, ZO-2, and ZO3 (Engelhardt and Sorokin 2009). Thus, BBB has dynamic and static properties that enable endothelium to protect the brain microenvironment. Functional BBB is equipped with active transport mechanisms that ensure the transport of nutrients into CNS. Anatomical studies revealed close physical relationship of astrocytes with the brain capillaries. Astrocytes ensheath arterioles and capillaries through their processes forming rosette like structures, called end-feet, around the abluminal membrane of capillaries. On the other hand, astrocytes branch and synapse with neurons. The abluminal membrane of the mature capillaries is also surrounded by a large number of pericytes which are supposed to contribute to the maintaining the BBB integrity. These cells form a gliovascular unit through which glucose is transported to the brain (Engelhardt and Sorokin 2009). The gliovascular unit accounts for about 90% of glucose metabolism in the gray matter (Barros et al. 2007).

Neuron – glia interaction. The role of glial cells in the neuronal glucose metabolism has been first postulated as a "neuron – astrocyte lactate shuttle" (Pellerin and Magistretti 1994; Pellerin et al. 1998). These authors described that astrocytes consume glucose and via glycolytic pathway produce lactate, which they present to neurons as energy source. In more details, synaptic glutamate is a signal of neuronal activity and consequently for higher metabolic demands. Astrocytes take up more glutamate from synaptic cleft of the neurons through Na^+-dependent transporters that consume more ATP. This results in a higher glucose uptake through GLUT1 transporters. Intracellular glucose is phosphorylated and according to the metabolic demands either stored as glycogen or utilized to produce lactate. Lactate is then transported to the extracellular space by monocarboxylate transporter MCT1 and it enters neurons through MCT2 monocarboxylate transpoter (Stobart and Andrerson 2013). In neurons, lactate is converted into pyruvate via lactate dehydrogenase and pyruvate enters the tricarboxylic acid cycle to produce ATP. This mechanism has been later confirmed using NMR method (Bouzier-Sore et al. 2003). Subsequently, an opposite pathway has been described in which lactate is delivered to astrocytes by neurons called neuron – astrocyte lactate shuttle (Simpson et al. 2007). These authors have concluded that neurons metabolize glucose and are the main producers of lactate. More recently, Mangia et al. (2011) have supported the idea that under physiological conditions neurons take up the majority of glucose and that the overall contribution of lactate to cerebral glucose utilization is less significant.

Distribution and function of glucose transporters in the brain

GLUT1 – is the most abundant glucose transporter in the brain representing up to 30% of the brain glucose transporters (McAllister et al. 2001). Two isoforms of GLUT1, originating from the same gene, have been described in the brain. They are modified postranslationally and exert different function in the glucose transport. The heavier, more glycosylated form of GLUT1 (55-kDa form), is located at the endothelial cells of the blood microvasculature securing the transport of glucose across the BBB (Mc Ewen and Reagan 2004; Shah et al. 2012). The endothelial GLUT1 is asymmetrically distributed between the luminal and abluminal membranes with the ratio of approximately 4:1 in human, canine (Gerhart et al. 1989), and rabbit (Cornford et al. 1994) brain. In the rat, Farrell and Pardridge (1991) have found approximately 12% of GLUT1 in the luminal, 48% in abluminal membranes, and 40% in the cytosol. However, Barros et al. (2007), based on a number of *in vivo* observations, have created a model of endothelium with symmetric GLUT1 distribution. In this model, they have shown that glucose gradient between the intersticium and parenchymal cells is much lower (in the order of few μM) than that between blood and intersticium (4 mM). Therefore, the parenchymal permeability is higher than the endothelial permeability with five times more carriers in the parenchymal cells than in endothelium. Other authors (McAllister et al. 2001) have demonstrated in an *in vitro* BBB model that the asymmetry of luminal versus abluminal glucose concentration is due to the asymmetric distribution of hexokinases in the endothelial cells. Hexokinases occur near the abluminal membrane and cause a drop in glucose in the adjacent cytosol by glucose phosphorylation. Thereafter, glucose-6-phosphatase restores glucose and GLUT1 transports glucose across the abluminal membrane. In this way, the enzymes act as rectifier of glucose transport. Similar mechanism may act also in opposite direction. These authors have concluded that this mechanism may serve to prevent the excess of glucose accumulation in the intersticium. It can be supposed that blood glucose may regulate its uptake in brain via GLUT1, since hypoglycemia upregulates the endothelial GLUT1 concentrations, but hyperglycemia has no effect (Carruthers et al. 2009).

The lighter, less glycosylated GLUT1 isoform (45-kDa form) is located in astrocytic cell bodies and their endfeet, but not in axons, neuronal synapses, and microglia (Mc Ewen and Reagan 2004; Shah et al. 2012). The presence of GLUT1 in astrocytes supports the concept that astrocytes may convert glucose to lactate and present it to neurons in the situation of inadequate glucose supply. Under *in vitro* conditions, astrocytes exposed to hypoxic stress produce significantly more GLUT1 in comparison with control astrocytes (Iwabuchi and Kawahara 2011).

GLUT2 – is a high capacity and high affinity transporter abundantly expressed in pancreas and liver, where it serves as glucose sensor. In pancreas, the glucose oxidation product ATP closes the K_{ATP} channel leading to reduction of K^+ efflux and depolarization of pancreatic β-cell membrane. This allows a calcium influx that triggers the insulin secretion. The presence of sulfonylurea receptor Kir6.2, the pore forming subunit of the K_{ATP} channel, is critical for the functioning of K_{ATP} channel and insulin secretion. GLUT2 is also highly expressed

in CNS, particularly in the hypothalamic nuclei where specific group of neurons express sulfonylurea receptors. It highlights the role of GLUT2 as glucose sensor in hypothalamus (Levin et al. 2001). The immunohistochemical and electron microscopic studies have shown localization of GLUT2 in cell bodies of the hippocampus and hypothalamic lateral and arcuate nuclei. More detailed immunocytochemical analyses revealed the presence of GLUT2 in a number of dendrites and nerve terminals in the hypothalamic arcuate, paraventricular, supraoptic, and lateral hypothalamic neurons as well as in astrocyte processes and Gomori positive astrocytes in the arcuate nuclei (Arluison et al. 2004a,b; Young and McKenzie 2004). These authors have hypothesized that neuronal GLUT2 may also regulate synaptic activity and neurotransmitter release and that glial cells may use GLUT2 to release glucose for neuronal consumption. The high mRNA expression of glucokinase along with the mRNA expression of GLUT2 in the hypothalamic arcuate and ventromedial nuclei underline the regulatory role of these hypothalamic areas in the central glucose sensing and regulation of the food intake (Li et al. 2003). The role of the central GLUT2 in insulin regulation has been experimentally confirmed by administration of antisense oligodeoxynucleotide to GLUT2 into the hypothalamic arcuate nucleus, which induced reduction in body weight. Antisense oligodeoxynucleotide to GLUT2 administration did not enhance the insulin release after intracarotid glucose administration. In rats without GLUT2 elimination, the intracarotid glucose injection has elicited sharp insulin response (Leloup et al. 1998). This finding has also confirmed the role of GLUT2 in the direct autonomic signaling to pancreatic β-cells. Similar experiments have shown that elimination of central GLUT2 by antisense treatment prevented increased food intake in response to glucoprivic feeding (Wan et al. 1998). In GLUT2 null mice, feeding behavior was not reduced by glucose administration, neither it was enhanced by 2-deoxy-glucose administration which demonstrated loss of feeding control in absence of GLUT2 (Kady et al. 2006). Transgenic mice with a GLUT2-loop domain that blocked the detection of glucose, but at the same time left the GLUT2-mediated glucose transport active, augmented daily food intake, whereas plasma levels of insulin, ghrelin, and leptin remained unaffected (Stolarczyk at al. 2010).

GLUT3 – is, besides the GLUT1 the most abundant facilitative glucose transporter distributed throughout the whole brain. Immunochemistry and electron microscopic studies have described its presence mainly along axons and dendrites in neuropil, very little in the cell bodies, and none in microglia (Mc Ewen and Reagan 2004). Kinetic studies have shown that GLUT3 transports extracellular glucose about seven times faster than GLUT1 does (Maher et al. 1996). This fact together with high density of GLUT3 in neurons underline the pivotal role of GLUT3 in the energy supply to maintain neuronal activities. The presence of GLUT3 has also been identified in the endothelial cells of BBB, although in much lower quantity than GLUT1 (Gerhard at al. 1992). More recently, very low level of GLUT3 expression was observed in the primary astrocytic cultures received from neonatal rats. However, during experimental ischemia induced by oxygen-glucose deprivation, mRNA for both GLUT1 and GLUT3 were significantly enhanced (Iwabuchi and Kawahara 2011). These authors further found that the transcription of mRNAs for both GLUT1 and GLUT3 was mediated by NF-κB. Because the higher glycogen content found in astrocytes after reperfusion was suppressed by inhibition of GLUT3 mRNA, enhanced GLUT3 is presumed to increase glycogen, which protects astrocytes from hypoxic stress damage (Iwabuchi and Kawahara 2011). In hypoxic conditions, increased uptake of glucose by astrocytes may lead to an enhanced level of lactate to be presented to neurons as energy substrate for their recovery after hypoxia. Other authors have shown an enhanced glucose transport to neurons and astrocytes, but with higher expression of GLUT3 only in neurons in acute anoxia after hypoxic preconditioning (Yu et al. 2008).

The physiological significance of GLUT3 in brain has been demonstrated by the fact that its density and distribution correlated with the local cerebral glucose utilization. In addition, a long-term local upregulation of GLUT3 was observed as a result of higher glucose demands during hypoglycemia induced by continuous insulin infusion. Even though the brain glucose utilization was lower under these conditions, GLUT3 was upregulated (Duelli and Kuschinsky 2001). On the other hand, in adult rats malnourished during suckling period (12 pups per litter), GLUT3 expression was significantly reduced in brain and the activity of acetylcholinesterase which breaks down acetylcholine, was enhanced. This fact may contribute to cognitive impairment (de Vasconcelos et al. 2012). Furthermore, GLUT3 deficiency in null heterozygous mice resulted in compensatory GLUT1 overexpression in brain, but these mice showed electroencephalographic seizures and cognitive impairment. These findings have demonstrated that preserving

glucose transport across BBB or its presence in astrocytes is not sufficient for maintenance the neuronal functions (Zhao et al. 2010). Other authors have found that GLUT3 null mice did not survive intrauterinally, but their heterozygous (GLUT3$^{+/-}$) littermates had normal body weight gain and brain glucose uptake when measured by micro PET imaging and *in vitro* immunoblot method, indicated that 50% decrease of GLUT3 does not impair the process of the brain transport (Stuart et al. 2011). However, these experiments have not been supported by any behavioral studies.

GLUT5 – is a small facilitative hexose transporter which was first isolated from the jejunum and later identified in various tissues, including brain. Further analyses have revealed that GLUT5 serves as a fructose transporter with lower capacity to transport glucose (Burant et al. 1992). Because of the predominant function to transport of fructose, GLUT5 serves mainly to directly absorb fructose in small intestine and to recover fructose from glomerular filtration in the kidney. Though the circulating fructose in comparison to glucose is low (ten to twenty times lower), GLUT5 has been identified in different cell types in brain such as cerebellar Purkinje cells in human fetus, human BBB cells, or rat hippocampus (Douard and Ferraris 2008). In human and rodent brain GLUT5 is specifically expressed in microglia (Payne et al. 1997), and GLUT5 immunolabeling can serve as a good marker for both resting and reactive microglia (Horikoshi at al. 2003). Interestingly, it is the only hexose transporter found in microglia (Yu and Ding 1998; Shah et al. 2012). It has been found also in macrophages of peripheral organs. Differentiation of monocytes to macrophages is also associated with increased fructose consumption and GLUT5 mRNA expression (Malide et al. 1998; Fu et al. 2004). Studies dealing with the effect of fructose on the hippocampal function revealed that mice fed 3 months with high fructose improved cognitive abilities such as learning of operant bar pressing. But there were no differences found in GLUT5 concentrations in hippocampus, sensorimotor cortex, frontal cortex, or cerebellum compared to controls, indicating that the fructose improved learning did not occur due to the upregulation of GLUT5 (Messier et al. 2007). On the contrary, short term i.e. 7 days lasting high fructose diet enhanced the expression of GLUT5 in rat hippocampus (Shu et al. 2006); however, these authors did not further analyze the cell types expressing GLUT5. Experimental inflammation induced by lipolysaccharide or tumor necrosis factor-α (TNF-α) treatments led to an inhibition of the GLUT5 expression and activity in intestine (Douard and Ferraris 2008). However, the question on the role and regulation of GLUT5 during microglia activation as for example in the case of brain inflammation remains open.

GLUT6 – Since the first report on the expression of GLUT6 in the brain (Doege et al. 2000), its role in the glucose transport and its regulation has not been elucidated. In adipocytes, GLUT6 has been shown to be located predominantly intracellularly, but insulin had no effect on its translocation (Lisinski et al. 2001). Recently, Stuart et al. (2011) have discovered that in the brain GLUT6 is predominantly located in nerve cells. However, these authors did not observe any changes in this transporter in mice expressing 50% of GLUT3 in the brain. Thus, the physiological role of GLUT6 in brain awaits further investigations.

Insulin-dependent glucose transporters GLUT4, GLUT8

Insulin receptors (IRs) – The studies on the mechanisms of central insulin action have been substantiated by the discovery of IRs in brain by Havrankova et al. (1978). Later on, it was found that insulin actively penetrates BBB via a receptor-saturable transport. This process involves three steps: 1) receptor-mediated endocytosis at the blood site of the BBB, 2) diffusion through the endothelial cell cytosol, 3) exocytosis at the abluminal membrane to the parenchyma of the brain. Thus, unlike glucose transport, which is mediated via GLUT1, insulin crosses the BBB via receptor-mediated transcytosis (Pardridge 1993; Banks et al. 1997). The IRs are present in the hypothalamus, olfactory bulb, and hippocampus in high density showing higher concentration in neurons than in glia (Stockhorst et al. 2004).

The IR monomer is composed of α- and ß-subunits bridged by an intrinsic disulfide bond. The monomer dimerizes with another insulin monomer receptor or with insulin-like growth factor (IGF) receptor. Both homodimer and heterodimer components form functional IR. The homodimer is present in two isoforms IRα and IRβ. The homodimer of the IRα form is the most prevalent form of IR present in neurons, mainly synapses. The IR signaling activated by ligand binding initiates autophosphorylation of ß-subunit, which stimulates two downstream pathways: phospho-inositid-3 kinase (PI3K)/Akt and Ras/mitogen-activated protein kinase (MAPK) pathways. The PI3K/Akt pathway activates glucose metabolism via regulation of GLUT4 and GLUT8

transporters (Chiu and Cline 2010). The IRs together with GLUT4 and GLUT8 are closely localized in the brain areas with high glucose metabolism, such as the cerebellar cortex, hypothalamus, and hippocampus (McEwen and Reagan 2004).

GLUT4 – is the principal insulin-regulated glucose transporter located mainly in the neuronal cell bodies and proximal dendrites at the synaptic level in the cortex, amygdala, hippocampus, hypothalamus, and cerebellum. Some GLUT4 immunoreactivity has been also observed in the endothelial cell of microvessels. It is intracellularly present on the membranes of transport vesicles, Golgi apparatus, and rough endoplasmic reticulum. The insulin-regulated translocation of GLUT4 to plasma membrane via PI3/Akt kinase mechanism has been first described in muscle and fat. The same mechanism has been also observed *in vitro* in human neuroblastoma cell line (Alquier et al. 2006). More recently, Grillo et al. (2009) have demonstrated that central administration of insulin increased phosphorylation of Akt along with translocation of GLUT4 into hippocampal plasma membranes, which could be prevented by PI3 kinase inhibitor. Thus, insulin induced glucose transport in hippocampus occurs via similar mechanisms as in peripheral tissue and possibly provides neurons with energy during enhanced neuronal activity associated with cognitive tasks.

It has been shown that insulin regulates aminopeptidase (IRAP), which is colocalized with GLUT4 in specialized vesicles of adipose tissue and is implicated in the regulation of GLUT4 vesicles trafficking. Fernando et al. (2008) have investigated the presence of this mechanism in various mouse brain structures. These authors have shown a clear-cut colocalization of IRAP and GLUT4 in the hippocampal pyramidal neurons, septum, olfactory bulb, and cortex. They have also shown the involvement of IRAP together with GLUT4 in stimulated ^{3}H-2deoxyglucose uptake when using hippocampal slices received from IRAP knockout mice. However, these authors did not clearly confirm the importance of insulin in IRAP – GLUT4 activation that may suggest that also other factors, independent of insulin signaling, can mobilize GLUT4.

GLUT8 – likewise GLUT4, GLUT8 has been expressed in several brain areas including cortex, hippocampus, amygdala, and hypothalamus with highest levels in hippocampus and amygdala. The expression of GLUT8 is principally neuronal (Reagan et al. 2002). It is located in high-density microsomes mainly near the rough endoplasmic reticulum, but it has not been detected in Golgi apparatus (Piroli et al. 2002). Its physiological role is not yet fully understood. The only situation when insulin induced the translocation of GLUT8 to plasma membranes has been shown in mouse blastocytes (Carayannopoulos et al. 2000), and this process has not been observed in any mature cells. In hippocampal neurons increased peripheral insulin levels have stimulated the translocation of GLUT8 from light- to high-density microsomes indicating that insulin redistributes GLUT8 from cytoplasm to the membrane of rough endoplasmic reticulum (Piroli et al. 2002; Schmidt et al. 2009). These authors have hypothesized that GLUT8 may catalyze the transport of glucose after the glycolysation process of proteins from rough endoplasmic reticulum to cytosol. In this way glucose can be used to provide cells with energy. In the hippocampus of diabetic rats with hyperglycemia, hypoinsulinemia reduced GLUT8 was found in the high-density microsomal fraction that was even more pronounced in combination with stress. It indicated that insulin might regulate the redistribution of GLUT8 from cytoplasm to the membrane of rough endoplasmic reticulum (Piroli et al. 2004). In the absence of insulin action the glucose imbalance and stress makes the hippocampal neurons more vulnerable. More recently, GLUT8 knockout mice showed hyperactivity when locomotion and voluntary wheel running were measured which could be ascribed to an altered metabolic activity of hippocampus (Schmidt et al. 2008). Other pathophysiological situations have not been studied yet.

Sodium-coupled glucose transporters in the brain

At present, the physiological significance of SGLTs is unknown. The question of brain needs of energetically demanding glucose transport in the presence of a number of facilitative glucose transporters remains open. One of the sensitive approaches to measure glucose metabolism in the brain is the positron emission tomography (PET) measuring the uptake and accumulation of 2-deoxy-2[F-18]fluoro-D-glucose (FDG). However, FDG binds only to GLUTs, and its accumulation reflects only facilitated glucose transport. Recently, Yu et al. (2010) have described two other tracers, 4[α-methyl-4-[F-18]fluoro-4-deoxy-D-glucosepyranoside (highly specific substrate for SGLT) and 4[F-18]fluoro-4-deoxy-D-glucose, which is transported by both GLUTs and SGLTs, to visualize the distribution of SGLTs in the rat brain. These authors have found high

florizin sensitive uptake in the brain sections from the hippocampus, amygdala, and hypothalamus, while no uptake in brain capillaries that proved specific presence of functional SGLTs in neurons of these brain structures. Their role may lay in the protection of neurons during hypoglycemia and anoxia by pumping glucose into neurons against the concentration gradient. In this way, the presence of SGLTs may represent a normal part of physiological regulations of glucose uptake in special areas of the brain.

Glucose transport in response to proinflammatory cytokines

***In vitro* studies.** The effect of cytokines on glucose utilization appears to be predominantly stimulatory in various tissues and under different experimental conditions. Transforming growth factor-β1 (TGF-β1) activates glucose uptake, GLUT1 mRNA, protein, and protein glycosylation in cultured Swiss mice fibroblasts (Kitagawa et al. 1991; Masumi et al. 1993). Similar effect has also been observed in kidney messangial cells (Inoki et al. 1999). Glucose uptake as well as glucose transporters were stimulated by IL-1β in human and porcine fibroblasts (Bird et al. 1990) and rat adipocytes (Garcia-Welsh et al.1990). In human articular chondrocytes, IL-1β, TNF-α, and IL-6 accelerated glucose uptake and IL-1β-increased GLUT1 mRNA, GLUT1 protein as well as its glycosylation (Shikhman et al. 2001).

Exposure of brain capillary endothelial cells to hypoxia enhanced IL-1β expression, NO production, and cell permeability as well as expression of the GLUT1 mRNA (Yamagata et al. 2004) demonstrating easier influx of glucose to brain during hypoxic stress. In the primary culture of mouse astrocytes, the adding of either IL-1β or TNF-α enhanced glucose utilization. Further analysis has shown that the effect of both IL-1β and TNF-α required PI3 kinase transduction pathway and the action of IL-1β used also MAPK pathway (Vega et al. 2002). Another report has shown that endotoxin lipopolysaccharide (LPS) enhanced GLUT3 along with glucose uptake in rat astrocytic culture (Cidad et al. 2001). Astrocytes cultured with conditioned medium harvested from LPS-activated microglia or with a mixture of IL-1β and TNF-α showed enhanced permeability, activated uptake of the fluorescent glucose derivatives and at the same time reduced intercellular glucose diffusion (Retamal et al. 2007). This may play a role in metabolic state of astrocytes during inflammation. Similarly, astrocytes cultivated with either IL-1β, IL-6, TNF-α or IFγ enhanced glucose utilization, IL-1β and TNF-α reduced glycogen stores, but the levels of lactate remained unaltered. Combination of proinflammatory cytokines potentiated or had additive effect on astrocytes and conversely, antiinflammatory cytokines attenuated these effects. Interestingly, in this experiment neurons did not show any changes in glucose or lactate uptake (Belanger et al. 2011). Another series of experiments have demonstrated that IL-1β and TNF-α induced neuronal cell death along with enhanced glutamate levels in primary neuronal cell culture. Pharmacological blockade of glutamate alleviated neurotoxicity of these cytokines (Ye et al. 2013).

***In vivo* studies.** Inflammation is usually accompanied with anorexia and hypoglycemia. Under experimental conditions, in LPS-induced inflammation, hypoglycemia is accounted for by the action of IL-1α and IL-1β release (Oguri et al. 2002). Mice bearing IL-1β producing tumor developed hypoglycemia without any profound affection of insulin levels, depletion of liver glycogen, reduction of liver gluconeogenetic enzymes as well as reduction of liver GLUT2. At the same time, enhanced GLUT3 in liver and enhanced 2-deoxy[^{3}H]-glucose uptake in heart, intestine, brain, spleen, and lung has been observed (Metzger et al. 2004) indicating the capacity of this cytokine to stimulate glucose uptake in various tissues as it was shown in *in vitro* experiments. Subsequent studies have shown that peripherally administered IL-1β induced hypoglycemia has been counteracted by centrally administered IL-1 antagonist. This demonstrated that central IL-1β contributes to peripheral hypoglycemia directly, independently from insulin and occurred in spite of the enhanced glucostimulatory hormones such as corticosterone, glucagon or catecholamines. The authors of these studies have concluded that IL-1β can induce a change of the set point for glucose homeostasis in favor of the glucose supply of tissue and lymphoid cells with higher energy demands. In this way, the organism may adapt to the inflammatory stress (del Rey et al. 1998; 2006; Besedovsky and del Rey 2010).

Glucose transport after peripheral inflammation and sepsis

Endotoxemia and sepsis are associated with profound changes in the glucose metabolism. In rat model of endotoxic shock, an enhanced utilization of glucose in the skeletal muscle, liver, and fat has been observed. Administration of Salmonella enteritidis endotoxin to

suckling rats elicited higher glucose uptake in liver and fat along with enhanced GLUT1 mRNA, while both glucose uptake and GLUT1 in the brain remained without any effect (Battelino et al. 1996). The same treatment of mature rats caused profound peripheral hypoglycemia, mRNA overexpression of GLUT1 in muscle, fat, and liver and GLUT4 in muscle (Zeller et al. 1991). However, it has to be taken into account that in *in vivo* studies, glucose uptake and changes of GLUTs in various organs can be confounded by active immune cells, especially macrophages, which show marked increase in the glucose utilization during inflammation (Meszaros et al. 1987).

Systemic inflammation has long been known to slow down mental processes, impair cognition, and attention in both humans and rodents that points to the profound effect of systemic inflammation on brain metabolism. Peripheral administration of LPS to rats resulted in a reduced cerebral blood flow, reduced uptake of [^{18}F]-fluorodeoxyglucose (FDG) in all neocortical areas, and decrease in the number of total and neuronal cells in cortex and hippocampus, increased microglia in the cortex, while number of astrocytes remained unchanged. Neuronal cell death and reduced neuronal activity correlated with increased expression of TNF-α, TGF-ß, and IL-1ß in the whole brain lysate supporting the involvement of these cytokines in the brain metabolism impairment and neuronal damage (Semmler et al. 2005). Astrocytes have been proposed to contribute to energy supply in form of lactate to hippocampal neurons in memory processing and memory consolidation. Inhibition of glycogenolysis, lactate production, and transport decreased spatial working memory in rats (Stobart and Anderson 2013). Thus, glycogen-derived lactate is important energy source for memory formation in healthy brain, but the question whether this mechanisms is sufficient to meet the demands of neurons under inflammatory insult remains open. Low dose of LPS injected i.v. to healthy human volunteers produced lack of interest, enhanced depressive score, and the symptoms correlated with plasma peak of the proinflammatory cytokines and lower [^{18}F]FDG uptake in anterior right cingulate cortex (Hannestad et al. 2012). Taken together, these findings indicate that local proinflammatory cytokines may play a role in the impaired brain glucose uptake. The fact that other organs enhance glucose uptake along with the activation of appropriate GLUTs when exposed to cytokines, brain neurons seem to react differently. The question whether the reduced glucose uptake is a result of lower cerebral blood flow, or whether impaired neuronal functioning results from insufficient glucose uptake due to subnormal glucose transport, remains open. In addition, brain is highly susceptible to oxidative stress because its oxygen consumption is relatively high and is less equipped with antioxidant mechanisms (Weinstock and Shoham 2004). Inflammatory environment is known to enhance oxidative stress to neurons, which contributes to neuronal apoptosis (Semmler at al. 2005). For example, in humans who died from septic shock, neuronal apoptosis was observed which correlated with the enhanced production of NO radical (Polito et al. 2011).

Glucose transport in autoimmune diseases

The most frequent type of autoimmune disease in humans is rheumatoid arthritis (RA), a chronic inflammatory disease in which small hand and feet joins are first affected. The study of glucose metabolism in RA has mainly been focused on the inflamed joints. In cultured human synovial cells obtained from RA patients, the glucose uptake was higher than in cell culture obtained from non-RA patients. The glucose uptake was IL-1ß dependent and not influenced by the presence of insulin (Hernvann et al. 1991; Hernvann et al. 1996). The useful noninvasive approach to study the rate of glucose metabolism *in vivo* is the uptake of [^{18}F]FDG. Enhanced glucose metabolism, i.e. enhanced hexokinase activity along with the activated glucose transporters, are typical for tumor tissue and inflamed joints. In murine collagen-induced arthritis, one of the most frequent model of RA, the main cell types accumulating [^{18}F]FDG proved to be proliferating fibroblasts and activated macrophages, but not T-cells in the hypoxic environment of the inflamed joint (Matsui et al. 2009). Under hypoxic conditions, macrophages start glycolytic metabolism and produce more TNF-α (Scannell 1996). In turpentine oil-induced experimental arthritis, the uptake of [^{18}F]FDG peaked in inflamed tissue 4 days after inoculation, whereas no significant uptake in muscle or blood was observed in this time interval. In experimental monoarthritis, induced by antibodies to glucose-6-phsphate-isomerase to mice, the affected joint revealed enhanced uptake of [^{18}F]-fluorothymidine already 1 day after inoculation (Fuchs et al. 2013). Also in patients with RA, 2.5 times higher [^{18}F]FDG uptake has been observed in painful swollen joint than in non-swollen joint (Kubota et al. 2011).

Similarly, in patients with systemic lupus erythematosus, the most intense [^{18}F]FDG uptake has been

seen in lymphoid organs. On the other hand, glucose hypometabolism has been observed in brains of these patients that presumably occurred due to neuropathy and disease related brain injury (Curiel et al. 2011). When studied the ^{14}C-2deoxyglucose uptake in brain of rats with monoarthritis, significantly higher uptake occurred in subcortical regions, including basolateral amygdala and cortex as early as 2 days after inoculation (Neto et al. 1999). The activated glucose metabolism in the basolateral amygdala, a region related to emotion and receiving information from hippocampus, suggests also emotional and cognitive components of monoarthritis. Patients with RA often manifest cognitive impairment as well as depression and anxiety (Lorton et al. 2008). In rat with adjuvant-induced polyartritis, we have recently shown an enhanced anxiety on day 2 and 4 after the inoculation, the time interval when no swelling related pain stimuli interfered with the effect of inflammation (Skurlova et al. 2011). Our recent experiments have shown higher [^{18}F]FDG uptake in the hippocampus and amygdala 2 days after induction of the disease. In this series rats received 50 MBq of [^{18}F]FDG into the tail vein under isoflurane anesthesia. The accumulation of [^{18}F]FDG was measured using micro PET scanner (eXplore VISTA SrT GE) in a dynamic mode: Ten times after 1 min, five times after 5 min, two times after 10 min, and one time after 15 min, together 70 min. The measurements were performed in five animals 2 days before the inoculation (control scan) and 2 days after the arthritis induction. The distribution of [^{18}F]FDG is expressed as a percentage of radioactivity administered to the animal relative to 1 g of tissue (Fig. 1). As we have previously shown (Skurlova et al. 2011), the expression of IL-β mRNA was again upregulated in the hipocampus (Fig. 2). Because the expression of IL-β was measured in the hippocampi without previous perfusion, it has to be taken into account that besides activated astrocytes and microglia also blood borne activated leucocytes invading the tissue may contribute to its higher level. Similarly, the enhanced [^{18}F]FDG uptake in brain structures may reflect an enhanced glucose uptake in all immune cells present in the brain during inflammation.

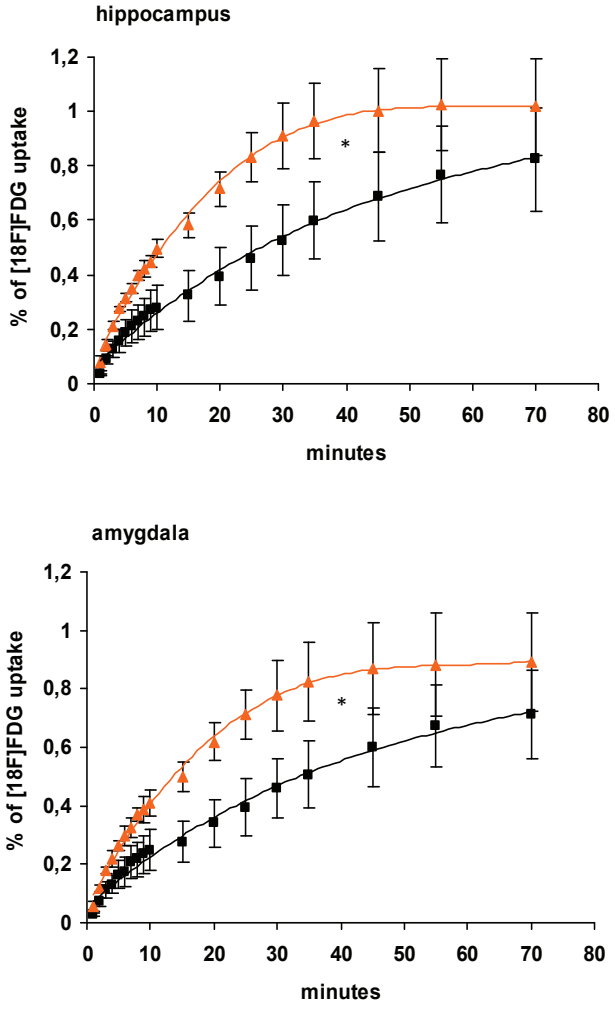

Fig. 1. Accumulation of [^{18}F]-fluorodeoxyglucose (FDG) in rat hippocampus and amygdala in male Lewis rats (n=4) before induction of the adjuvant arthritis (square points) and two days after induction of the disease (triangular points). * p<0.05

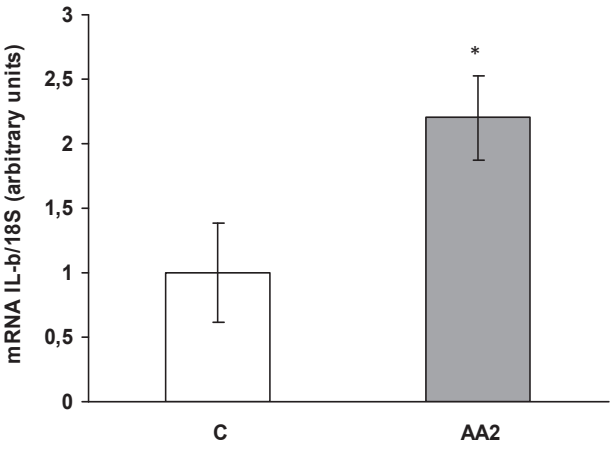

Fig. 2. Expression of interleukin-1β (IL-1β) mRNA in the hipppocampus of intact control male Lewis rats (n=8) (C) and two days after induction of the adjuvant arthritis (n=8) (AA2). * p<0.05

Future perspectives

As it is shown in this review, there is a lot of information on glucose transporters and glucose metabolism in the brain, particularly in astrocytes, which contributes to the understanding of the pathophysiological mechanisms of glucose metabolism in the brain. Although RA is not a typical CNS disease, approximately 30% of rheumatics have impaired cognitive functions and incidence of depression and/or anxiety is about 20%. It has been known that peripheral cytokines open BBB, invade brain, and trigger local cytokine production. This situation gives rise to oxidative stress and makes the neurons more vulnerable. Extensive investigation of the glucose metabolism and glucose transporters functioning in arthritic brain could contribute to better understanding of the impaired brain functions in patients suffering from RA.

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