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BRAIN GLUCOSE TRANSPORTER PROTEIN 2 AND SPORADIC ALZHEIMER'S DISEASE

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Abstract

Sporadic Alzheimer's disease (sAD) is associated with decreased glucose/energy metabolism in the brain. The majority of glucose utilization in the brain appears to be mediated through glucose transporter protein 1 and 3 (GLUT1 and GLUT3). Deficiency of GLUT1 and GLUT3 in the brain has been found in sAD patients post mortem; however this is not unique to the disease as it is associated with different clinical syndromes as well. In line with recent findings that insulin resistant brain state precedes and may possibly cause sAD, an experimental sAD model based on the central application of the streptozotocin (STZ-icv rat model), which is a selective GLUT2 substrate, has drawn attention to the possible significance of the brain GLUT2 in sAD etiopathogenesis. Important steps in the GLUT2 and sAD interplay are reviewed and discussed. It is concluded that increased vulnerability of GLUT2 expressing neurons may be involved in development of sAD.

Keywords

Glucose transporter protein 2 • Sporadic Alzheimer's disease • Streptozotocin Intracerebroventricular administration • Animal model

1. Introduction

The late-onset, sporadic type of Alzheimer's disease (sAD) is associated with decreased glucose metabolism in all cortical areas, especially in the parietotemporal and frontal association cortices and is particularly pronounced in structures with both high glucose demands and insulin sensitivity [1]. Predominant abnormalities of cerebral glucose metabolism were seen as reduced glucose utilization and altered activities of key glycolytic enzymes [1]. Although still not well understood, the impairment of cerebral glucose uptake/metabolism in sAD appears to be a cause, rather than a consequence of neurodegeneration found in sAD.

2. Glucose transporters in the brain

The entry of glucose into cells throughout the brain is enabled by a family of facilitative glucose transporter (GLUTs) proteins [2]. The role and mechanism of GLUTs regulation have been well known at the periphery, but far less so within the central nervous system [3]. The majority of glucose utilization in the central nervous system appears to be mediated through GLUT1 (expressed in the endothelial cells of the blood-brain barrier; responsible for glucose transport from blood into the extracellular space of the brain) and GLUT3 (expressed in neurons; responsible for glucose transport from extracellular space into the neuron) [3,4]. GLUT4 is an insulin-sensitive transporter whose mRNA and protein expression have also been detected in the brain, including the cerebellum, granule cells of the olfactory bulb, dentate gyrus of the hippocampus, the pituitary, the hypothalamus and microvessels [3]. It has been suggested that its role is in rapidly providing additional glucose to neurons under conditions of high-energy demand. Plasma membrane association of GLUT4 is altered in the hippocampus of diabetic rats [5], suggesting insulin induced stimulation of GLUT4 translocation in the brain. Experiments with rats demonstrated that insulin-mediated translocation of GLUT4 in the hippocampal neurons possibly provide a mechanism through which hippocampal neurons rapidly increase glucose utilization during increases in neuronal activity associated with hippocampal-dependent learning [6]. Furthermore, the selective presence of GLUT4 in cholinergic cells within the basal forebrain suggests the specific vulnerability of these cells to a lack of glucose supply [7]. GLUT8 is a novel isoform, found to be primarily expressed in neuronal cell bodies and in the most proximal dendrites of excitatory and inhibitory neurons in the rat hippocampus, and whose role has been suggested to be one of support for metabolic requirements [3]. It is localized in the cytoplasm and endoplasmic reticulum under basic conditions, and acute glucose administration followed by subsequent insulin secretion stimulates its redistribution to the rough endoplasmic reticulum in the hippocampus, suggesting

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that insulin-sensitive GLUT8 plays a prominent role in maintaining neuronal glucose homeostasis [8]. While GLUT2 is of extreme importance at the periphery for glucose sensing by the insulin producing/secreting cells, it remains a poorly investigated GLUT isoform within the brain. It is a low affinity, high-volume glucose transporter, which at the periphery is localized mainly on the membrane of the pancreatic β cells; coupling with glucokinase causes a glucose-sensing mechanism providing high-capacity glucose transport into cell and triggers insulin secretion [9]. Low levels of GLUT2 have also been found in the mammalian brain [3,10]. GLUT2-immunoreactive signalling was found throughout the brain especially in limbic areas and related nuclei, and appeared to be most concentrated in the ventral and medial regions close to the midline [11]. Few oligodendrocyte and astrocyte cell bodies were found to be labelled with GLUT2 in large myelinated fibre bundles, whereas the reactive glial processes have more numerous amounts and are often localized in the vicinity of nerve terminals and/or dendrites or dendritic spines forming synaptic contacts [12]. As a result, it has been suggested that GLUT2 might participate in the regulation of neurotransmitter release and, perhaps, in the release of glucose by glial cells. Nerve cell bodies immunostained for GLUT2 are scarce (although numerous in the dentate gyrus granular layer); whereas in the periphery, numerous nerve cells are labelled for this transporter [12]. The latter are clustered in the dorsal endopiriform nucleus and neighbouring temporal and perirhineal cortex, in the dorsal amygdaloid region, and in the paraventricular and reuniens thalamic nuclei, and only a few in the hypothalamus. It has been hypothesized that GLUT2, at least partially, is involved in cerebral glucose sensing [13]. The phenotype of glucose sensing neurons is similar to the pancreatic β cells in that these specialized neurons express sulfonylurea receptors, the pore forming subunit of the ATP-sensitive K^+ channel and glucokinase, all allowing speculation that GLUT2 may serve a similar role in pancreatic β cells and in glucose sensing neurons, including the induction of insulin secretion [14]. This hypothesis is supported by the finding that the release of insulin from brain synaptosomes is stimulated by glucose [15]. Therefore, it seems likely that cerebral GLUT2 might also be involved in initiation of the insulin-induced actions within the brain. GLUT2 mRNA distribution in the adult rat brain appears not to be entirely parallel to that of glucokinase [16], suggesting participation of brain GLUT2 in functions other than glucose sensing and insulin secretion, which remain to be explored. Beside GLUTs 1-4 and partly GLUT8, the role of other GLUT isoforms in the brain has been far less explored and understood [3].

3. Brain insulin system

Among other factors, cerebral glucose uptake/metabolism seems to be under the control of the neuronal insulin signal transduction system, as briefly mentioned above. The effect of insulin on cerebral glucose metabolism in humans has been extensively studied during the last two decades, but still remains controversial. In the mature adult brain the majority of insulin originates from the periphery, crossing the blood-brain barrier, while a smaller proportion of insulin is produced within the brain itself, as reviewed elsewhere [17,18]. Insulin in the brain binds to the neuronal insulin receptors which are abundantly but selectively distributed, with the highest concentration in the nerve terminals of key brain regions, such as the olfactory bulb, hypothalamus, cerebral cortex, cerebellum and hippocampus [19-22]. Neuronal insulin receptor is a tyrosine kinase receptor and shares a huge similarity in signalling pathways with the peripheral insulin receptor, by activating two parallel functional signal transduction cascades: the phosphatidylinositol-3 kinase (PI3K) pathway, and the mitogen activated protein kinase pathway [23]. The activation of the PI3K pathway subsequently activates protein kinase B (Akt/PKB) which triggers GLUT4 translocation and consequently increases cellular glucose uptake [5,23]. By transducing the signal to the glycogen synthase kinase 3β (GSK-3β), Akt/PKB activation also leads to the regulation of tau protein phosphorylation status, resulting in hyperphosphorylation of tau protein in case of the brain insulin receptor signalling dysfunction, i.e. insulin resistant brain state which has been found in sAD and its rat model [24,25]. Furthermore, brain insulin and neuronal insulin receptors are functionally linked to improved cognition, in particular general and spatial memory [26-29]. Although the exact mechanism(s) by which insulin could affect learning and memory is unclear, several pathways have been suggested; for example, those related to glucose metabolism and the modulation of different neurotransmitter functions [28]. The overlapping distributions of insulin, neuronal insulin receptor and the insulin-sensitive GLUT isoforms support the hypothesis of insulin stimulated glucose uptake in selective brain regions, particularly in the hippocampus [3,7]. Since hippocampal glucoregulatory activities contribute to cognitive function [30], insulin modulation of glucose metabolism in this structure appears to be one of the key components of hippocampal vulnerability.

4. Brain glucose transporters and Alzheimer's disease

Humans. The pathophysiology of GLUT isoforms in sAD is not well understood as there are only few literature reports on this issue. Reduced densities of GLUT1 and GLUT3 have been consistently found post-mortem in the brain of AD patients [31-35]. It has been suggested that the decrease in GLUT1 and GLUT3 levels in AD patients may result from down-regulation of hypoxia-inducible factor-1 (HIF-1) in AD patients, as it is involved in the regulation of GLUT1 and GLUT3 expression [34]. Furthermore, the decrease in GLUT1 and GLUT3 levels have been correlated to a decrease in 0-GlcNAcylation and to the hyperphosphorylation of tau protein in 7 AD brains post mortem with Braak stage V-VI [34]. This is in line with a previous finding that 0-GlcNAcylation and phosphorylation of tau regulate each other reciprocally [36]. Interestingly, in the brain of AD patients no change in GLUT4 levels and a significant increase in GLUT2 levels were found [38]. The

authors proposed that this GLUT2 increase be caused by astrocyte activation as seen in AD brain. Since this is the only report on GLUT2 and GLUT4 isoforms in AD patients, further research is needed to confirm these findings and to clarify the development and functional consequences of these GLUTs alterations.

Animal models. Due to the specific nature of AD, the exploration of onset and progression of the biochemical changes in the brain is difficult, if not almost impossible to perform during a patient's life-time. Therefore, one has to rely on in vivo experimental models although it is even more difficult to find an animal model that would be a true representative of human sAD. The most frequently exploited AD animal models are transgenic Tg2576 mice which overexpress the Swedish mutation of the human amyloid precursor protein and demonstrate a progressive, age-related cortical and hippocampal deposition of β-amyloid plaques [37]. It has been demonstrated that impairment of the cerebral cortical glucose metabolism in this model occurs only due to the long lasting high β-amyloid burden, i.e. as a consequence of β-amyloid pathology [38]. This results from a reduction in glycolytic activity in β-amyloid plaque-associated neurons and a concomitant up regulation in reactive, plaque-surrounding astrocytes. In the Tg2576 transgenic mice model of AD, GLUT1 has been investigated only as a marker of cortical vascular endothelial cells [39]. In another transgenic AD mice model (APP/PS1 transgenic mice) reduced levels of GLUT1 were found in the hippocampus (highest in the dentate gyrus) at age of 18 months with no differences in capillary density; while at 8 months, no differences were observed [40]. The authors concluded that the GLUT-1 amount and capillary density in both wild type and transgenic mice decreased due to ageing and that β- amyloid load in the hippocampus preceded the reduction of GLUT-1. Similar reduction in GLUT1 levels was found in brain homogenates of NSE/APPsw transgenic AD model which was normalized by exercise training [41]. No other GLUT isoforms have been investigated in transgenic mice models of AD. Recently, a new animal model has been proposed to more adequately represent the sporadic form of AD, as due to the amyloid-related genes manipulation, the transgenic mice models represent the rare, familial form of AD. Rats treated intracerebroventricularly with the drug streptozotocin (STZ-icv rat model) have been demonstrating long-term and progressive cognitive deficits in learning and memory; as well as deficits in cerebral glucose and energy metabolism and alterations of key glycolytic enzymes in the brain, similar to those found in human AD [42]. Furthermore, the STZ-icv rat model resembles sAD in the development of cerebral cholinergic deficits, oxidative stress and insulin resistant brain state, respectively, as reviewed elsewhere [43,44]. Recent data suggests that the development of an insulin resistant brain state subsequently causes hyperphosphorylation of tau protein and some structural changes, manifested as pathological amyloid aggregation in meningeal capillaries [45,46]. Currently in the literature, there is only one report on brain GLUTs in STZ-icv model [46]. Namely, quantitative receptor autoradiography revealed significant increase in (3H)cytochalasin-B binding levels in the hippocampal CA1-CA4 subfields (30%) and dentate gyrus (12%). GLUT3 mRNA was the only brain GLUT investigated but no changes were observed in STZ-icv rats. However, in regards to glucose transporters in the brain, the STZ-icv rat model is particularly important because the STZ chemical structure and its mechanism of action, enables this model to provide indirect data on GLUT2-associated impairments in the brain.

5. Peripheral administration of streptozotocin and glucose transporters

Streptozotocin (STZ, chemically (2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose)) is a betacytotoxic drug which has been widely used to induce experimental diabetes mellitus for more than 40 years. Following intravenous or intraperitoneal administration at high doses, STZ selectively destroys insulin producing/secreting β cells in the pancreas, and causes type I diabetes mellitus in adult animals [48]. Type II diabetes can also be induced in rats by parenteral injections of STZ on the day of birth, resulting in a mild basal hyperglycemia and an impaired response to the glucose tolerance test [48]. Treatment with low to moderate doses of STZ in short-term experiments causes insulin resistance [49] via a decrease in autophosphorylation [50] and an increase in the total number of insulin receptors, but with little change in the phosphorylated insulin receptor-β subunit [51]. Selective toxicity for insulin producing/secreting cells in the pancreas is related to the selective uptake of STZ *via* the glucose transporter GLUT2, which is predominantly located on the pancreatic β cell membrane [48]. The important role of GLUT2 has been confirmed with reports of the prevention of STZ-induced diabetogenic action by reduction of GLUT2 expression [52,53]. In line with that, the sensitivity of pancreatic β cells to STZ toxicity seems to be species-specific, and related to species-dependent difference in the levels of GLUT2 expression. Namely, human β cells express lower levels of GLUT2 than rodent islets and are much more resistant to STZ than mice and rats [54]. Furthermore, STZ has been shown to be a substrate for GLUT2-type only, as *in vitro* culture of islets of transgenic mice expressing only GLUT1-type has been shown to be insensitive to STZ toxicity [55]. However, not only has STZ been a selective substrate for GLUT2, but *in vitro* studies have also demonstrated that GLUT2 itself is a key target molecule for STZ, as the drug reduces GLUT2 protein expression in a concentration-dependent manner [56]. Once STZ has entered the cell, this nitrosourea drug is metabolized to liberate nitric oxide which is further involved in DNA alkylation and fragmentation followed by the unfavourable activation of the nuclear poly(ADP-ribose) polymerase, resulting in depletion of cellular NAD+ and ATP stores [48,57]. Based on these proposed mechanisms of STZ-induced damage, GLUT2 expressing cells at the periphery, D-glucose analogs like 5-thio-D-glucose (5-TG) and 3-0-methyl-D-glucose (3-0MG), compete with STZ for GLUT2 transport and, in a way, act like GLUT2 inhibitors [58,59], while drugs like 3-aminobenzamide and nicotinamide, act like strong inhibitors of poly(ADP-ribose) synthase [60,61]. Both have been found to prevent STZ-induced β cell toxicity [58-61].

6. Central administration of streptozotocin and brain glucose transporters

Considering the presence of insulin (both from periphery and brain) and insulin receptors in the brain, an experimental rat model was developed by applying STZ intracerebroventricularly (icv) in doses of up to 100 times lower (per kg body weight) than those used peripherally, to induce an insulin resistant brain state, as reviewed by Šalković-Petrišić & Hoyer [43,46]. Central STZ administration causes neither systemic metabolic changes nor diabetes mellitus but induces specific, region-dependent neurochemical changes within the brain [43]. Identical biochemical changes were found in the left and right striatum after administration of STZ to the right lateral cerebral ventricle only, suggesting that STZ-icv induced effects have not been related to the direct non-specific toxic effect of STZ at the site of drug administration [62]. The exact mechanism of central STZ action and its target cells/molecules in the brain have not yet been elucidated, but similarity to the mechanism of the peripheral STZ-induced toxicity seems very likely. Namely, GLUT2 with its regionally specific distribution in the mammalian brain [10-12,63,64] may enable the uptake of STZ into the GLUT2-expressing cells and be responsible for the STZ induced, regionally-specific effects in the brain including the subsequent extensive intracellular STZ-icv induced depletion of ATP (up to 80%) [42,65-67] and insulin receptor signalling dysfunction [45,46]. It may seem logical to assume that if GLUT2 is responsible for the subsequent STZ-induced toxicity within the brain, central application of compounds which compete with STZ for GLUT2 transport (i.e. GLUT2 inhibitors) would prevent STZ-icv induced effects. However, the results of our experiments with GLUT2 inhibitors in STZ-icv rat model were surprising. Initially the effect of central administration of the GLUT2 inhibitor (5-TG) alone was evaluated and compared to the STZ-icv induced effects. A single 5-TG-icv treatment induced long-lasting neurochemical effects in the insulin receptor signalling cascade in the hippocampus, which mostly resembled those induced by STZ-icv treatment [45]. These results are congruent with the findings of other authors in that 3 weeks after STZ-icv injection, the ultrastructure of rat frontoparietal cortical neurons was similar to that observed after intravenous application of non-metabolizable glucose analogue 2-deoxyglucose which competed with the glucose uptake [68].

Our experiments also showed that cognitive performance measured by the Morris Water Maze Swimming Test in 5-TG-icv treated rats demonstrated deficits in learning and memory functions manifested as decreased time spent in search for the removed platform and number of mistakes made during this search, similar to those found in STZ-icv rats [45]. After such a surprising finding, it was questioned whether GLUT2 inibitors would be capable of preventing the STZ-icv induced cognitive deficits. Our preliminary results demonstrated that pre-treatment with 5-TG did not prevent STZ-icv induced cognitive deficits in a Morris Water Maze Swimming Test, but surprisingly, deteriorated learning and memory functions in some parameters, in comparison to the STZ-icv treatment alone (Šalković-Petrišić M, unpublished data). Pretreatment with 5-TG and 3-0MG has also been found ineffective in normalizing decreased antioxidant capacity found in STZ-icv treated rats [69,70]. At first, these results tend to argue the similarity of the peripheral and the central mechanism of STZ action, since only its peripheral toxicity can be prevented by GLUT2 inhibitor pretreatment. However, one must remember that glucose represents the primary energy source for the brain and that brain neurons are unable to synthesize or store glucose but depend on glucose transport across the blood-brain barrier and then into the neurons. Therefore, impairment of glucose uptake may have far reaching consequences in the brain than in the periphery. It might be speculated that by blocking intracellular glucose uptake and consequently its intracellular metabolism and possible glucose sensing, 5-TG induces local conditions in the brain that might be similar to the cerebral glucose metabolism impairment found in human sAD [1] and its STZ-icv model [66,67]. However, one should be aware that there is no substrate selectivity of 5-TG and 3-0MG for the GLUT2 isoform among other GLUTs [71]. As a result, 5-TG and 3-0MG may compete with glucose transport via other GLUT isoforms (like GLUT1 and GLUT3 [71]) in addition to GLUT2, and consequently cause more extensive intracellular glucose deprivation which is spread not only to the GLUT2 expressing cells (as in the case of STZ-icv treatment) but to the much larger population of neurons and other cell types within the brain. This may offer a plausible explanation of the synergistic detrimental effect of STZ and 5-TG/3-0MG combined icv treatment on cognitive performance (Šalković-Petrišić M, unpublished data) and antioxidant status [69,70].

7. Concluding remarks on GLUT2 and sAD interplay

What might connect brain GLUT2 and Alzheimer's' disease? To hypothesize their interplay, several factors mentioned in this text must be taken into account:

(I) the function of neurons and other brain cell types depends on various GLUT isoforms, some of them being insulin-sensitive (II) GLUT2 seems to have a similar role both at the periphery and in the brain, particularly playing an important role of glucose-sensing within the brain; subsequently glucose stimulates synaptosomal insulin release (III) insulin binds to the brain insulin receptor and downstream its signalling cascade stimulates GLUT4-induced intraneuronal glucose uptake (possibly GLUT8 as well), and keeps the tau protein phosphorylation status balanced (IV) insulin-resistant brain state leads to a decrease in glucose/energy metabolism and to the hyperphosphorylation of tau protein, found both in sAD patients and in its representative model, STZ-icv treated rats (V) GLUT2 is the only GLUT isoform which selectively transports STZ into the cell, enabling thus selective STZ-induced toxicity of GLUT2 expressing neurons only, which results in AD-like cognitive, neurochemical and structural alterations. Therefore, it may be speculated that other substances which would have a structure similar to STZ regarding a selective GLUT2 substrate specificity, and

would additionally induce intracellular ATP depletion and cell damage as well as the insulin receptor signalling dysfunction, could also have a potential to induce sAD. Although this may seem impossible in real life, it fits quite well into the hypothesis that environmental toxins might play a significant role in the sAD etiopathogenesis [72]. Moreover, recent data demonstrating that environmental and food contaminant exposures to low, submutagenic levels of nitrosamines, compounds structurally related to STZ, may induce insulin resistant brain state, AD-type neurodegeneration and cognitive impairment in rats, strongly supports our hypothesis [73,74]. In line with the experimental data that reduced GLUT2 levels are responsible for STZ insensitivity [54], the only published data on increased GLUT2 levels found in AD patients post mortem due to astrocyte activation [34] may suggest increased sensitivity and vulnerability of GLUT2 expressing neurons in AD. The research in progress will hopefully elucidate the pathophysiological role of GLUT2 in sAD etiopathogenesis.

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