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Does hyperglycemia downregulate glucose transporters in the brain?

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A B S T R A C T

Diabetes is a metabolic condition associated with hyperglycemia manifested by the elevation of blood glucose levels occurring when the pancreas decreases or stops the production of insulin, in case of insulin resistance or both. The current literature supports that insulin resistance may be responsible for the memory decline associated with diabetes. Glucose transporters (GLUTs) are a family of proteins involved in glucose transport across biological membranes. GLUT-1 and GLUT-3 are involved in glucose delivery to the brain. Evidence suggests that both transporters are downregulated in chronic peripheral hyperglycemia. Here we show the mechanisms of glucose transport and its influence on cognitive function, including a hypothesis of how peripheral hyperglycemia related genes network interactions may lead to glucose transporters downregulation and its possible consequences.

Introduction

According to WHO Global Report on Diabetes, the number of adults living with this disease is 422 million, and in 2016, an estimated 1.6 million deaths were directly caused by diabetes [1,2]. In 2019, the global diabetes prevalence was 463 million people, rising to 578 million by 2030 and to 700 million by 2045 [3]. Diabetes is a chronic metabolic condition associated with hyperglycemia manifested by the elevation of blood glucose levels when pancreas decreases the production or stops producing insulin (type 1 diabetes) or in cases of the cells' insulin resistance (type 2 diabetes) or both [4,5]. Insulin resistance or deficiency is associated with impairments in glucose metabolism disrupt brain energy balance increasing oxidative stress, reactive oxygen species production that leads to DNA damage, and mitochondrial dysfunction, all of which drive pro-apoptosis, pro-inflammatory, and the amyloid beta protein cascades [6].

Two different family types of glucose transporter are found in the neurovascular unit at the blood–brain barrier. The sodium-dependent unidirectional transporters (SLC5), which 12 isoforms (SGLTs 1–12) have been identified. However, the most prevalent transporters are the sodium-independent bidirectional GLUT [7–9]. Glucose transporters (GLUT) are a family of integral membrane proteins that provide bi-directional transport of D-glucose and its analogues without consuming energy and are based on the glucose concentration gradient across cell membrane [10]. In humans, 14 different GLUTs have been identified. Under basal metabolic conditions, most of these transporters, especially the GLUT-4 strongly relies on insulin dependent mechanisms and presents a major role on glucose uptake of adipocytes, cardiac and skeletal muscle cells and plays an important function in whole-body glucose homeostasis [11,12].

In the last decade, studies have shown that diabetes is associated with an increased risk of cognitive decline [13,14], affecting learning, working and episodic memory, cognitive flexibility and speed processing [15–18]. Cognitive impairment related to diabetes is traditionally associated with atherosclerosis, since diabetes has an influence in peripheral vascular disease and dyslipidemia that may lead to small vessel disease in the brain, which in turn may cause vascular dementia. Although, dyslipidemia has been also related to amyloid beta protein production [19–20]. However, more recent studies suggest that the binding mechanisms between diabetes and dementia are related to hyperinsulinemia and consequent insulin resistance, and this will cause dementia due to Alzheimer's disease (AD), not vascular dementia [21–24]. In fact, in type 2 diabetes, insulin is not capable to reduce the levels of blood glucose after a meal. In most cases the reason for this is that the insulin messenger signal no longer triggers the cellular cascade of events that leads to an increased uptake of glucose by cells [25].

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The human brain is almost entirely dependent upon glucose as an energy source, taking in around 100–150 g of glucose per day [26]. Due to the restrictive permeability of the blood–brain barrier (BBB) and the relative lack of local brain carbohydrate storage, the CNS heavily relies upon BBB expression of transporters for the delivery of key nutrients and solutes to the brain [27]. The delivery of blood glucose to the brain requires crossing of glucose mediated by glucose transporter proteins. Within the central nervous system, GLUT-1, mostly expressed in red blood cells and endothelial cells in heavily glycosylated form (55 kDa) and in astrocytes in low glycosylated form (45 kDa), involves glucose movement across the BBB's endothelial cells [28]. Furthermore, the GLUT-3 aids glucose to pass through the neural cell membrane [29,30]. Studies have shown that chronic hypoglycemia upregulates the GLUT-1 and GLUT-3 gene expression and increases their protein abundance. However, whether the expression of GLUT-1 and GLUT-3 is reduced in diabetes is unclear and is controversial. Any deficiency in GLUT transporter proteins leads to a major impact on brain energy metabolism [31,32].

Studies have shown that vascular endothelial cells exposed to high glucose levels downregulate the rate of glucose transport by reducing GLUT-1 mRNA and protein expression, as well as GLUT-1 plasma membrane localization [33,34]. In response to these recent findings, a couple of interesting questions arose: 1] could hyperglycemia be a cause of downregulation of GLUT transporters in the brain? 2] if the downregulation of GLUTs occurs in the brain, could it be one of the mechanisms related to AD? Therefore, the aim of this study is to hypothesize a cause-effect relationship of hyperglycemia and AD based on GLUT transporters downregulation. Available bioinformatic data were used as guidance to establish the hypothesis. In order to develop a working model, this article was organized in the following sections: i) The basis of glucose transport in the peripheral tissues, ii) The basis of glucose transport in the brain, iii) Gene network analyses, iv) Genes network model and hypothetical influence of peripheral hyperglycemia on downregulation of GLUT transporters in the astrocytes and neurons and its relationship with dementia, and v) Final considerations.

The basis of glucose transport in the peripheral tissues

Glucose cellular uptake is an essential physiological process. The maintenance of a relatively constant blood glucose concentration is necessary in order to sustain cerebral metabolism and the delivery of glucose to peripheral tissues for energetic storage and utilization. Indeed, glucose transport across cell membranes plays an important role in physiological regulation and control of metabolic processes [35].

Cell membranes are impermeable to glucose, so the transport of glucose across biological membranes must be mediated by specialized protein transporters. In the 1970s, glucose uptake into liposome was reconstituted with proteins partially purified from red blood cells [36–37]. This specific type of glucose transporter was later named as GLUT-1. Subsequently, glucose transporters were recognized from different tissues, GLUT-2, GLUT-3 and GLUT-4 [38–40]. Research development during the following years lead to the discovery of tissue distribution of subtypes of GLUTs, biochemical characterization of transport functions, and the formulation of the correlation between mutation or dysregulation of GLUTs and specific diseases [41–43].

Among the GLUT family, GLUT-4 is an insulin-stimulated transporter and it is primarily localized intracellularly in peripheral tissues when not stimulated and can be acutely redistributed to the plasma membrane in response to insulin and other stimuli. GLUT-4 is primarily expressed in adipose tissues, skeletal and cardiac muscle, and it facilitates the diffusion of circulating glucose across its gradient into muscle and fat cells [44]. Upon binding of insulin, the insulin receptor kinase is activated, and it promotes the activation of downstream targets and progression of signaling cascade leading to the translocation of GLUT-4 from intracellular pool to cell surface where it facilitates glucose entry inside the cell [45,46]. The central role of GLUT-4 in glucose homeostasis is strongly implicated by a variety of genetically engineered mouse models. Dysfunctional GLUT-4 in skeletal muscle is the main cause of peripheral insulin resistance [47,48].

The basis of glucose transport in the brain

Glucose availability in the CNS is critical for neuronal function, and glucose levels in the brain regulate local neuronal activity and whole-body energy metabolism [49]. Among the membrane transport proteins, GLUT-1 is known to be a key transporter of glucose transport into the brain across the BBB acting to maintain central nervous system glucose homeostasis. Expression of different isoforms of the GLUT has also been identified at BBB endothelial cells although with relative lower levels of GLUT-3 and GLUT-4 [50]. Considering the distribution and properties of GLUT transporters, GLUT-1 and GLUT-3 will be treated together as they are both particularly involved in delivery of glucose to the brain. As glucose is the obligatory substrate for cerebral metabolism under normal conditions, glucose transport is fundamental in this organ [51,35].

Glucose transport into the brain is a complex process involving the endothelial cells of small blood vessels, glial cells, particularly astrocytes and neurons. GLUT-1 is highly expressed in the endothelial cells of the microvasculature of the brain and is responsible for glucose transfer across the BBB. The transport of glucose to neurons is mediated by astrocytes [52], which also express GLUT-1. GLUT-1 is localized to both luminal and abluminal membranes of the BBB endothelial cells with the ratio of 1:4 respectively, and approximately 40% of the total cellular GLUT-1 resides in intracellular membrane [53–56].

Once glucose enters the brain extracellular space, it is rapidly taken up by the different brain cells. The neuron glucose uptake to support energy metabolism is mediated by GLUT-3. GLUT-3 has higher "affinity" and higher glucose transporter capacity compared to GLUT-1 [44,57]. Interestingly, during a high cognitive demand, astrocytes' glycolysis results in lactate production which will be delivered to activated neurons and used as energetic substrate [58]. Therefore, a continuous supply of glucose is required for brain function.

Gene network analyses

To explore proteins-related genes associated to hyperglycemia and AD, the GeneCards database (https://www.genecards.org) was used. Based on An et al. [59] who have investigated the relationship between hyperglycemia and Alzheimer's disease (AD), the following terms were inserted at GeneCards to search for genes related cellular receptors, hormones, proteins, and amino acids associated glucose metabolism and AD. Such cellular and molecular structures searched were: GLUT-1, GLUT-3, insulin, alanine, hexokinase, amyloid beta protein, apolipoprotein E, tau protein, and phosphofructokinase. Several genes were retrieved from GeneCards, as follow: *SLC2A1* (GLUT-1) and *SLC2A3* (GLUT-3), *INS* (insulin), *GPT* (alanine), *HK1/HK2/HK3* (hexokinase 1, 2, and 3), *GCK* (glucokinase), *APP* (amyloid precursor protein), *APOE* (apolipoprotein E), *MAPT* (microtubule-associated protein tau), *PFKL/PFKP/PFKM* (phosphofructokinases), and *GRN* (granulins). Genes aforementioned were inserted in String database (https://string-db.org), which permits to explore genes and their interactions as a network. Our exploration of interactions was performed considering *Homo sapiens* as the studied species.

Many specific and non-specific (unclear) significant interactions (PPI Enrichment p-value < 0.01) [60] were found among genes in the network displayed at String (Fig. 1). In String, each protein–protein interaction is annotated with one or more 'scores'. The scores indicate how likely String judges an interaction to be true, given the available evidence. Interactions were explored when a combined score above 0.4, determined as medium confidence, was found. As the main question of this study was related to downregulation of GLUTs, only direct interactions with genes associated with these transporters (*SLC2A1* and

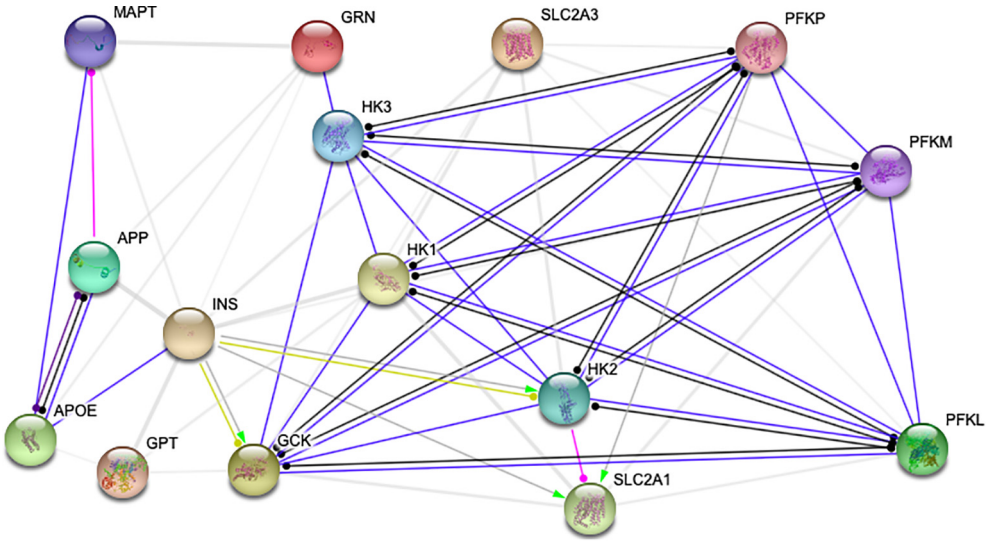

Fig. 1. Genes network found at String. Direct binding among genes *GRN*, *HK3*, *HK2*, and *SLC2A1* is shown. Color lines show molecular interactions, while grey lines show no molecular interactions but associations co-mentioned in PubMed abstracts. Arrows: activation. Circles: unspecified interaction.

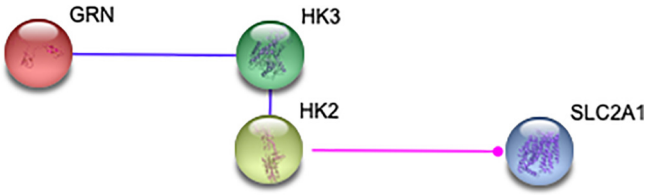

Fig. 2. Specific network among genes related GLUT-1 found at String. Blue lines mean direct binding among genes. Pink line: posttranslational modification. Circle: unspecified interaction.

SLC2A3) in the network were analyzed. Then, the following genes remained in the model: *GRN*, *HK3*, *HK2*, and *SLC2A1* (Fig. 2).

Genes network model and hypothetical influence of peripheral hyperglycemia on downregulation of GLUT transporters in the astrocytes and neurons, and its relationship with dementia

Diabetes is associated with hyperglycemia and it is caused by partial or total insulin insufficiency. Clinically, the rapid decline in blood glucose in patients with diabetes, even when the blood glucose is above normal, can lead to “hypoglycemia phenomenon”, including neuroglycopenia symptoms. The exact mechanism remains unclear, but it is possibly related to the downregulation of GLUT-1 and GLUT-3 expression in diabetes [61].

GLUT-1, which is expressed and localized at the endothelial cells of the BBB, is the first step in the transport of glucose from the blood into the tissue layers. Then, the glucose transport from extracellular space into neuronal cells is taken by GLUT-3, localized at the neuronal cell membrane. After it is within the cell, glucose is phosphorylated to glucose-6-phosphate by *HK*, a key enzyme for glucose utilization in the cell [62,63]. The downstream cascade of glucose breakdown is mainly mediated by *HK*, hence it is reasonable to hypothesize that any change in this enzyme could affect glucose metabolism.

Granulin (*GRN*) is a protein related to inflammation and wound repair originated from progranulin (PGRN). Mutations in PGRN genes are associated with neurodegenerative diseases, such as frontotemporal dementia [64]. PGRN was demonstrated to interact with the *HK3*. Autopsy studies had shown associations of PGRN and beta-amyloid plaques [65,66]. PGRN plaques were most dense in medial temporal and frontal regions and predominated over aggregated amyloid beta protein. At this moment, physiological significance of this interaction is not known [67]. However, according to our genes network model, bindings among granulin, *HK3* and *HK2* exist. In addition, a post-translational interaction between *HK2* and *SLC2A1* is present in the network. Hence, dysfunctional granulin, which is an important cell growth factor associate to wound repair and inflammation, could affect *HK3* and *HK2* interactions and the synthesis of GLUT-1. Dysfunctional *HK3* and *HK2* and attenuated synthesis of GLUT-1 could result in glucose excess in the extracellular space in the brain, causing a down-regulation of GLUT-1 and GLUT-3 transporters. In summary, these mechanisms would affect astrocytes and neurons metabolism.

Evidence suggests that chronic hyperglycemia reduces intracellular glucose transport in diabetes [35]. As a protective mechanism, the decreased glucose influx can diminish the cytotoxic effect of the high sugar content. It has been suggested that the reduction of glucose transport is related to a downregulation of 55 kDa isoform GLUT-1 (presented in microvessels) and GLUT-3 in patients with AD, which are the principal factors affecting glucose transport and metabolism in the brain [41,68]. In a study with diabetic rat model, chronic hyperglycemia downregulated GLUT-1 and GLUT-3 gene expression levels in the brain [61]. The downregulation of GLUT-1 and GLUT-3 expression might be the adaptive reaction of the body to prevent excessive glucose entering the cell that may lead to cell damage [61].

It is well known that glucose transport from the peripheral circulation across the BBB and capillary endothelial cells into the interstitial fluid and brain tissue are largely insulin-independent processes. Many epidemiological studies indicate that peripheral insulin resistance and diabetes are risk factors for AD [69–74], however, it is not known whether brain glucose dysregulation is a key feature of AD and is related to severity of AD pathology or symptom expression [75].

In patients with AD, several components of the insulin signaling pathway are abnormal, including genes encoding insulin, IGF-1, and IGF-2 peptides and their receptors [76,77]. Evidence suggests that abnormal insulin signaling contributes to clinical trials targeting abnormalities in patients with mild cognitive impairment and AD, but implications of these abnormalities are yet to be elucidated [78,79]. Some studies have shown reduced brain glucose uptake in regions vulnerable to AD pathology [80–82]. It is unclear whether an overall failure in the regulation of brain glucose metabolism is a key aetiopathogenic factor in AD and whether abnormalities of brain glucose homeostasis in AD are related to peripheral glucose concentration.

Since dysfunctional granulin could affect *HK3* and *HK2* interactions, it could also result in glucose excess in extracellular space in the brain. These mechanisms would lead to GLUT-1 downregulation affecting

astrocytes and neurons. Furthermore, changes in *HK3* and *HK2* also seem to affect GLUT-1 expression through *SLC2A1* posttranslational modification. Therefore, it makes sense to develop a hypothetical model which peripheral hyperglycemia triggers a downregulation of GLUT transporters in the brain. This hypothetical model highlights two consequences: 1) hyperglycemia in the brain could trigger neuroinflammation, especially influenced by pro-inflammatory cytokines [83], downregulating GLUT; and 2) fuel to neurons could be limited due to few GLUT-1 transporters, leading them to apoptosis.

Final considerations

Glucose is the primary energetic fuel of brain tissue, the availability of glucose and its transport into the brain across the BBB and into brain cells plays a key role in normal physiological function and energy metabolism. This mechanism is mediated by two GLUT transporters: GLUT-1 and GLUT-3. GLUT-1 transporter presents on both the luminal and abluminal membranes of the BBB endothelial cells, also in astrocytes. GLUT-3 is located in neurons. Studies showed that chronic hypoglycemia enhances the GLUT-1 and GLUT-3 gene expression. Also, the expression levels of both transporters are downregulated in chronic peripheral hyperglycemia, suggesting that GLUT-1 and GLUT-3 expression might be the adaptive reaction of the body to prevent cell damage. However, molecular mechanisms that lead to GLUT-1 and GLUT-3 reductions in AD remain unknown. The present hypothesis is based on molecular and clinical findings and presents the consequences of GLUTs downregulation that could be related events leading to neuronal damage, neurodegeneration, cognitive decline and AD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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