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Review Article

Glucose effects on the brain in the healthy and unhealthy individuals: metabolic and cognitive aspects

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Abstract

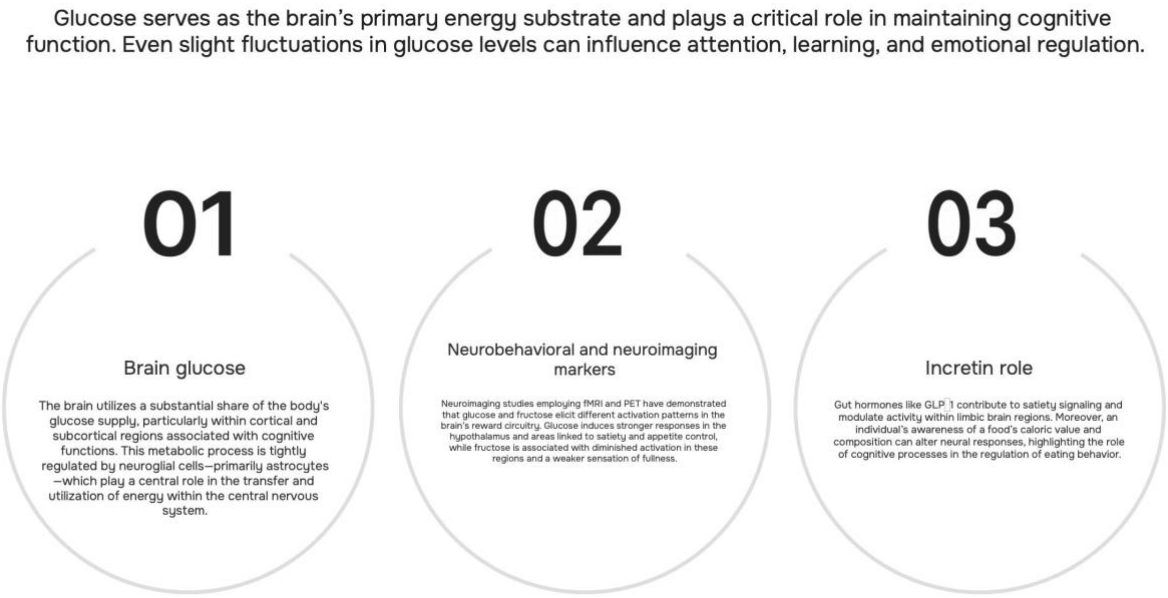
Introduction: Glucose serves as the brain's primary energy substrate and plays a critical role in maintaining cognitive function. Even slight fluctuations in glucose levels can influence attention, learning, and emotional regulation.

Materials and Methods: The authors organised a screening of PubMed and Google Scholar reference databases on relevant articles from 1995 till 2025 to perform a systematic review.

Results: Glucose metabolism and its regulation in the brain: The brain consumes a significant portion of the body's glucose, especially in cortical and subcortical regions involved in cognitive processing. Glucose regulation is mediated by neuroglia, particularly astrocytes, which are essential for energy transfer and utilization. Neurobehavioral and neuroimaging markers: Neuroimaging studies using fMRI and PET reveal distinct patterns of activation in the brain's reward system when comparing glucose and fructose consumption. Glucose more strongly activates the hypothalamus and regions related to satiety and appetite regulation, whereas fructose is associated with a reduced sense of fullness. Effects of sweet substances on cognitive function: Comparisons between glucose and non-caloric sweeteners (e.g., sucralose) highlight differences in the engagement of dopaminergic pathways and reward anticipation mechanisms. Glucose demonstrates a more stable effect on short-term memory and attention. Role of incretins and calorie awareness: Gut hormones such as GLP-1 are involved in satiety signaling and influence activity in limbic structures. Additionally, cognitive awareness of caloric content and food composition can modulate neural responses, underscoring the importance of cognitive factors in regulating eating behavior.

Conclusion: Understanding the differences in perception and processing of glucose, fructose, and non-caloric sweeteners is crucial for developing dietary strategies and interventions for metabolic and neuropsychiatric disorders. Further research into neuroenergetics and individual variability in nutrient responses may support more precise and personalized approaches in medicine.

Graphical Abstract



Keywords

neurochemistry, glycemic control, neurometabolism, energy balance, GLP-1, glucose transporters, cognitive function

Introduction

Glucose is a fundamental metabolic substrate for the human brain. This high demand reflects the brain's continuous need for energy to sustain neuronal firing, synaptic transmission, and overall cognitive performance. In healthy individuals, glucose homeostasis supports learning, memory, and attention, while even mild fluctuations can alter cognitive efficiency and emotional reactivity.

Emerging evidence suggests that the brain's perception and processing of caloric intake – particularly in relation to glucose and fructose – varies across individuals, potentially contributing to differences in eating behavior, satiety, and reward sensitivity. These effects are especially relevant in the context of increased consumption of processed foods and sweetened beverages, which may have long-term implications for metabolic regulation and brain health.

This review synthesizes current knowledge on how glucose metabolism interacts with brain function across both healthy and clinical populations. We explore underlying neural mechanisms, including astrocyte-neuron interactions, the role of gut-brain peptides like GLP-1. By examining these mechanisms, we aim to clarify the broader implications of sugar consumption and identify directions for future research.

Materials and Methods

The authors conducted a comprehensive screening of the PubMed and Google Scholar reference databases to identify relevant articles published between 1995 and 2025. This search aimed to gather all pertinent studies necessary for performing a systematic review. The selection process involved systematically searching for and extracting articles that met

predefined inclusion criteria related to the topic of interest (i.e. glucose metabolism, consumption, cognitive functioning affected by glucose consumption, cognitive impairment in diabetes type 1 and 2). Both databases were chosen to ensure a broad coverage of peer-reviewed biomedical literature as well as interdisciplinary research outputs. The time frame of 30 years was selected to encompass both foundational and the most recent studies, thereby providing a thorough and up-to-date synthesis of the available evidence. The screening process incorporated the use of specific keywords and subject filters to optimize the relevance and accuracy of the literature retrieved for subsequent qualitative analysis in the review.

Results

Glucose metabolism and its regulation in the brain

The brain consumes about 25% of the body's available glucose, despite its mass accounts for only 2% of the total body mass (Mansur et al. 2014). Glucose metabolism plays a key role in maintaining neuronal activity, supporting cognitive functions and neuroplasticity. Various types of neurons have different sensitivities to glucose levels. For example, glutamatergic neurons are characterized by high metabolic activity and require significant amounts of energy, whereas GABAergic neurons can use alternative substrates such as ketone bodies.

Astrocytes play an important role in the brain energy balance regulation by processing glucose, including through glycogen metabolism, and transferring metabolites to neurons. They participate in tripartite synapses, interacting with both presynaptic and postsynaptic membranes. This interaction enables astrocytic modulation of synaptic transmission: astrocytes suppress the release of neurotransmitters at low frequencies input and enhance signal transmission at high frequencies input (Gordleeva et al. 2012). This maintains neural homeostasis and the brain adaption to changing environment. In hypoglycemia or increased neuronal activity, glycogen is quickly converted into lactate, which is then transported to neurons and used as an energy source (Falkowska et al. 2015). Astrocytic glycogen acts as a protective mechanism, ensuring stable neuronal function even in glucose deficiency. Astrocytes secrete lactate via low-affinity peri-synaptic monocarboxylate transporters (MCT1 and MCT4). Neurons take up this lactate via the high-affinity MCT2 transporter and use it to synthesize ATP (Goit et al. 2022; Shima et al. 2022). This mechanism dysfunction leads to lactate accumulation in various brain regions, which may indicate a disruption of the lactate shuttle between astrocytes and neurons. High concentrations of extracellular lactate can produce a neurotoxic effect if neurons are unable to efficiently utilize it, leading to uncoupling of astrocyte and neuronal metabolism. The animal type 2 diabetes models demonstrated decreased expression of MCT1 and MCT4 in astrocytes, as well as MCT2 in neurons correlating with cognitive decline (Shima et al. 2018, 2022; Goit et al. 2022).

In addition to that, glycogen in astrocytes plays a key role in memory processes and long-term potentiation (Premi et al. 2017). Astrocytes express glucose transporters: GLUT1 and GLUT2, while neurons preferentially use GLUT3, which has a higher affinity for glucose (Simpson et al. 2007). These transporters regulate glucose entry into the brain and its distribution between the cells, and their dysfunction is associated with neurodegenerative diseases (Zhang et al. 2023). However, in type 2 diabetes mellitus, the expression of these transporters is reduced limiting the glucose flow to neurons (Simpson et al. 2009). The studies found a decrease in GLUT1 and GLUT3 levels in the brain of the T2DM and Alzheimer's disease patients contributing to cognitive impairment (Liu et al. 2009). The intranasal administration of insulin, a drug used to treat diabetes, demonstrated a positive effect on cognitive function in the patients with type 2 diabetes and Alzheimer's disease (McClure et al. 2022). In addition to that, insulin resistance in the brain, associated with impaired PI3K/AKT signaling, decreases glucose transport and neuronal activity. The studies of postmortem brain samples revealed that the insulin/PI3K/AKT signaling pathway is impaired in the patients with type 2 diabetes and Alzheimer's disease, with impairments being more pronounced in the patients with a combination of these diseases (DeBrosse et al. 2012).

Glucose metabolism is mediated by its further phosphorylation by hexokinase (HK) to produce glucose-6-phosphate (glucose-6P). This intermediate product can be processed through three main metabolic pathways. Glucose-6P can be metabolized via glycolysis to produce two pyruvate molecules, ATP and NADH. Pyruvate can then enter the tricarboxylic acid cycle and oxidative phosphorylation in the mitochondria to produce ATP and carbon dioxide with the consumption of oxygen. In oxygen deficiency, pyruvate is reduced to lactate by lactate dehydrogenase, which is then released into the extracellular space via monocarboxylic acid transporters. Complete glucose oxidation in the mitochondria provides significantly more energy in the form of ATP (30–34 molecules) compared to glycolysis (2

molecules) (Bélanger et al. 2011). Glucose-6P can also be processed via the pentose phosphate pathway to produce reducing equivalents in the form of NADPH. This pathway is linked to glycolysis at the level of glyceraldehyde-3-phosphate (GA3P) and fructose-6-phosphate. In astrocytes, glucose-6P can be used to store glucose units as glycogen.

In addition to lactate, other metabolites are also transferred between astrocytes and neurons. Glutamine, synthesized in astrocytes by glutamine synthetase (GS), is transferred to neurons, where it is converted to glutamate (an excitatory neurotransmitter) by glutaminase (GLS). Glutamate can then be converted to gamma-aminobutyric acid (GABA) by glutamate decarboxylase (GAD) (Crane et al. 2013). This process, known as the glutamate/GABA-glutamine (Glu/GABA-Gln) cycle, plays an important role in maintaining cognitive function (Dong et al. 2018; Huo et al. 2021). The diabetic animal models demonstrated decreased levels of glutamate and GABA with increased GS expression and decreased GLS and GAD activity. This cycle disruption of changes the energy exchange between astrocytes and neurons, which may contribute to neurodegeneration (Dong et al. 2018; Zheng et al. 2019; Huo et al. 2021).

During functional activation, local cerebral blood flow (LCBF) typically increases in parallel with an increase in local glucose metabolism (LGM), while oxygen consumption changes to a lesser extent. However, exceptions are possible: for example, peripheral somatosensory stimulation may result in a decrease in LCBF in the ipsilateral cortex despite an increase in LGM (Yeung and Wong 2020). The close correlation between LCBF and LGM requires dynamic mechanisms to adapt glucose and oxygen delivery. The traditional metabolic hypothesis of neurovascular coupling based on vasoactive metabolites (CO_2/H^+, lactate, adenosine) was replaced by the neuronal hypothesis. This hypothesis suggests that the energy needs of neurons are transmitted to the vessels (directly or via astrocytes) within the neurovascular complex via vasoactive neurotransmitters or synaptic activity products. (Mergenthaler et al. 2013; van Opstal et al. 2020; Yeung et al. 2020). This transmission occurs in advance, via a "feedforward" regulation mechanism, and causes vasodilation independently of the signals related to glucose metabolism (Mergenthaler et al. 2013; van Opstal et al. 2020; Yeung et al. 2020). This process prevents a potentially dangerous decrease in glucose and oxygen concentrations that could occur with purely metabolic regulation. However, the recent studies suggest that vasodilation accompanying neuronal activation may be determined not only by feedforward regulation mechanisms. A significant role is played by the changes in the lactate to pyruvate ratio and variations in the cytosolic $NADH/NAD^+$ ratio (Spagnuolo et al. 2020). The recent studies suggest that direct glucose sensing mechanisms are largely uninvolved in the regulation of activity-induced LCBF. Neither hyperglycemia nor mild hypoglycemia produce a significant effect on blood flow, but in acute hypoglycemia, resting LCBF levels increase following decreased blood and brain glucose level (Jacques et al. 2019).

The $NADH/NAD^+$ ratio represents the balance between the oxidized (NAD^+) and reduced (NADH) forms of nicotinamide adenine dinucleotide, a coenzyme that plays a key role in cellular redox reactions. A shift toward an increase in $NADH/NAD^+$ may indicate a change in the metabolic state of the cell and promote vasodilation. The glutamate-glutamine cycle (GGC) rate also helps to understand the imbalance between glucose and oxygen consumption as the GGC increases. This enables the use of the oxygen-glucose index in tissues to characterize different activation states. Glucose is taken up and metabolized according to the energy needs of the cells, and its distribution between different cell types does not depend significantly on the GGC rate. Moreover, both the direction and magnitude of lactate exchange between neurons and astrocytes depend on the relative glucose uptake by cells, while remaining relatively independent of the glutamate-glutamine cycle rate (Massucci et al. 2013). Therefore, neurovascular coupling, traditionally explained by the predominance of advanced signaling, is likely complemented or modulated by metabolically dependent mechanisms involving products of cellular metabolism, such as the lactate/pyruvate ratio and $NADH/NAD^+$ (Mergenthaler et al. 2013).

Impaired glucose metabolism leads to decreased synthesis of neurotransmitters such as acetylcholine, GABA, glutamate, and serotonin, which is associated with neuronal dysfunction. In the diabetic mice, decreased levels of glutamate, aspartate, ATP, and other energy metabolites were recorded at Week 9 of disease development, when pathological changes were already observed in the hippocampus (Dong et al. 2018). Reduced ATP synthesis in neurons leads to deterioration in the maintenance of ion gradients, which disrupts the action potentials' generation and conduction. The changes in the neuronal structure and function following ATP deficiency are the basis for the cognitive impairment in diabetes. Energy deficiency leads to a chain of destructive events, including calcium stress, apoptosis, microtubule disruption, and the accumulation of toxic protein aggregates. Decreased ATP levels in the diabetic brain can be considered the main mechanism of neuronal damage and cognitive deficits (Krishnaswamy et al. 2012; Oliveira et al. 2021). Glucose metabolism disorders are also closely associated with oxidative stress and inflammation. Glucose-6-phosphate dehydrogenase (G6PD) deficiency leads to decreased NADPH levels contributing to the reactive oxygen species accumulation (Pandolfi et al. 1995; Ulusu et al. 2003). In hyperglycemia,

mitochondrial dysfunction increases the reactive oxygen species production triggering inflammatory cascades and neuronal apoptosis. Activated microglial cells involved in the immune response contribute to increased inflammation aggravating neurodegenerative processes (Pandolfi et al. 1995; Ulusu et al. 2003).

In terms of influence of sugar on the brain and its health, the ketogenic diet is being explored as a supportive strategy in the treatment of neurodegenerative disorders, including Alzheimer's and Parkinson's diseases. It may help by improving mitochondrial function and offering an alternative energy source to glucose. While early results are promising, the clinical value of this approach remains uncertain, and further research is needed to clarify its effectiveness and long-term impact (Tao et al. 2022).

Glucose consumption and cognitive functioning

Burger KS (2017) revealed that daily consumption of sugar-sweetened beverages resulted in decreased dorsal striatum activation upon the receipt of the beverage and decreased ventromedial prefrontal cortex responses to the beverage logo anticipation. These changes correlated with increased behavioral disinhibition toward the beverage logo. In addition to that, the regular beverage consumption increased precuneus activation in response to logos suggesting a generalized effect across the beverage-related stimuli. There was a reduction in the hedonic value of the beverage consumed similar to that caused by the activation prior to consumption.

The studies examining the relationship between circulating glucagon-like peptide-1 (GLP-1) levels, striatal responsiveness to food stimuli, and food intake found that GLP-1 is involved in overeating regulation through the effects on mesolimbic structures that process food stimuli, including the dorsal striatum (Jones et al. 2021). Reduced GLP-1 secretion is observed in obese individuals with high sugar intake, which may contribute to altered food preferences and increased sensitivity to food stimuli. The studies revealed that the interaction between body mass index (BMI) and added sugar intake is associated with reduced postprandial GLP-1 secretion. The obese participants with high sugar intake had the smallest increase in the plasma GLP-1 levels after glucose intake. They also had increased dorsal striatal responses to low-calorie foods, whereas responses to high-calorie stimuli were reduced. This effect inversely correlated with the amount of sugar consumed in the buffet setting suggesting possible mechanisms of sugar- and obesity-related eating behavior.

Semaglutide, a GLP-1 analogue, was studied for its effectiveness in weight loss by targeting neural pathways that regulate appetite and energy balance. The studies demonstrated that semaglutide exerts its effects through multiple mechanisms, including receptor activation, food intake modulation and neural activity changes (Gabery et al. 2020). One of its key mechanisms of action is interaction with GLP-1 receptors in the brain. Unlike many other appetite regulators, it does not penetrate the blood-brain barrier, but acts on the central nervous system through the circumventricular organs – structures located along the borders of the third ventricle of the brain, where the blood-brain barrier is most permeable. Activation of GLP-1 receptors in areas such as the brainstem, hypothalamus, and septal nucleus contributes to the regulation of eating behavior and energy metabolism (Lu et al. 2020). Interestingly, semaglutide reduced alcohol consumption in the obese mice, presumably through interactions with the nucleus accumbens, suggesting its multi-level effects on neurobiological processes related to eating behavior (Vallöf et al. 2019; Aranäs et al. 2023).

Fructose intake, compared with glucose, elicits smaller increases in plasma insulin levels but results in greater brain responses to food stimuli in the visual cortex and left orbitofrontal cortex (Leo et al. 2015). Fructose intake increased hunger, increased desire to eat, and promoted preference for immediate rewards of high-calorie foods over long-term monetary rewards.

The research into the effects of sugar on cognitive function focused primarily on its possible beneficial effects on short-term memory. However, the findings remain contradictory: several studies demonstrated findings that suggest potential benefits of glucose and sucrose consumption for cognitive function (García et al. 2021; Sun et al. 2022). For example, sugar consumption affects the brain activity and the neural network connections: glucose consumption increases the hemodynamic response in the thalamus, while water consumption leads to an increase in the hemodynamic response in visual networks (Peters et al. 2020). In this case, glucose consumption did not produce a significant effect on cognitive functions, but additional analysis revealed that, performing more complex tasks, the participants who had received a placebo forgot more words compared to those who had taken glucose before and after training. Glucose consumption improved the performance of task with a high memory load, but did not produce a significant effect on the performance of tasks requiring a high cognitive load (Meikle et al. 2005). In a study with a single dose of 25 g and 60 g glucose, the

participants demonstrated better results in memorization, as well as in word recognition tasks and reaction time testing, but the accuracy of the tasks remained unchanged. Notably, participants with insufficient glycemic control demonstrated better results in recalling information after taking 25 g of glucose (Owen et al. 2013). No glucose effect on the task performance accuracy was demonstrated in other studies (Riby et al. 2011; Scholey et al. 2009).

The studies of fructose effects on cognitive function yielded conflicting results. Four studies assessed fructose intake from fruits and sugars. The studies involving the children, the mother-infant pairs, and the older adults found that fructose intake was associated with improved overall cognitive function (Øverby et al. 2013; Cohen et al. 2018). However, no such relationship was found in the study involving the young adults; in fact, increased fructose consumption was associated with decreased cognitive function (Ye et al. 2011). Total fructose consumption produced a beneficial effect on cognitive performance in the children (Naveed et al. 2020), but was associated with worse cognitive performance in the older adults (Chong et al. 2019). These differences may result from dietary differences: in the children, the main source of fructose is fruits and juices, while in the adults and the elderly, its consumption is more often associated with added sugars (Gillespie et al. 2023). In addition to that, the studies revealed that increased fructose consumption is associated with insulin receptors dysregulation in the brain, which may aggravate cognitive impairment and increase neurodegenerative disease risk (Jones et al. 2021). When consumed in excess, fructose enters the liver and brain, where it affects inflammation, mitochondrial function, and cognitive processes, leading to changes in the food intake and energy metabolism regulation (Jones et al. 2021).

Age-related changes in glucose metabolism are associated with decreased glucose utilization efficiency in the brain, which affects cognitive functions and increases neurodegenerative disease risk. At a young age, glucose is the main source of energy, providing high neural activity and cognitive productivity. However, with age, there is a decrease in glucose consumption in certain areas of the brain, which is accompanied by memory impairment and a cognitive processes slowdown (Goyal et al. 2017). The older adults had lower cognitive scores than the younger adults when given placebo ($p = 0.02$), but these differences disappeared following glucose intake. The older adults had poorer blood glucose control and a greater physiological response to glucose compared to the younger adults. Increased glucose sensitivity combined with impaired glucose regulation may indicate a decrease in the brain's resistance to blood sugar level fluctuations reflecting age-related changes in glucose metabolism (Peters 2020). At the same time, in the patients with worse glucose control, cognitive function improvement was observed at lower glucose doses (15 mg), whereas the patients with better glucose control required higher glucose doses (60 mg) for a similar result (Sünram-Lea 2011).

In addition to that, age-related decline in metabolic efficiency makes it difficult to restore energy reserves and reduces the adaptive capacity of neurons. In response to that, the aged brain begins to more actively use alternative energy sources, such as ketone bodies, which can provide up to 70% of energy needs with limited glucose supply. This mechanism is considered a strategy that partially compensates for the energy deficit (Mattson and Arumugam 2018; Cunnane et al. 2020). There are age-related changes in the glucose metabolism interaction with other metabolic pathways such as the glutamate-glutamine cycle, which plays a key role in neuronal energy supply. These changes may reduce the signal transmission efficiency in the nervous system and contribute to neurodegeneration.

Cognitive impairment and metabolic changes in diabetes mellitus type 1 and 2

Glucose intake, especially in the patients with diabetes, affects both metabolic and cognitive processes. These effects include direct mechanisms related to blood glucose levels and indirect factors related to diabetic complications.

Diabetes mellitus is a chronic disease associated with impaired glucose metabolism. It develops following insufficient insulin production (type 1 diabetes) or decreased tissue sensitivity to insulin (type 2 diabetes). Type 1 diabetes is most often diagnosed in childhood or adolescence and requires lifelong insulin administration. It accounts for about 5–10% of all cases of diabetes. Type 2 diabetes is much more common (90–95% of all cases) and mainly develops in adults, especially in the presence of obesity and a sedentary lifestyle.

Type 2 diabetes mellitus (T2DM) is associated with cognitive impairment and an increased risk of mild cognitive impairment (MCI) and dementia. A number of studies divide cognitive impairment in T2DM into three stages: 1) diabetes-associated cognitive deficits, 2) mild cognitive impairment (MCI), and 3) dementia. Biessels et al. (2014) indicate that cognitive impairment in T2DM should not be viewed as a linear continuum, but as a combination of factors.

Diabetes-associated cognitive deficits involve changes in motor function, executive abilities, information processing speed, verbal and visual memory, and attention (Palta et al. 2016). These changes can manifest themselves as early as in the early stages of the disease and progress twice as fast compared to the individuals without diabetes (Yaffe 2012; Bangen 2015; Biessels and Despa 2018; Jha et al. 2022).

Mild cognitive impairment (MCI) is considered an intermediate stage between normal cognitive functioning and dementia. It is characterized by a decline in cognitive ability in one or more areas while maintaining daily functioning. Mild cognitive impairment and dementia affect different age groups and demonstrate different mechanisms of development, depending on a combination of vascular and metabolic factors. For example, an association was found between glucose, insulin and glycated hemoglobin (HbA1c) levels and the risk of cognitive impairment, as well as the influence of age, disease duration, hypertension and microangiopathy (Crane et al. 2013; Mansur et al. 2014).

Dementia is a severe cognitive disorder that affects multiple cognitive domains and significantly reduces quality of life. The meta-analysis including 144 prospective studies found the relative risk of dementia in T2DM 1.43 (1.33–1.53) for all types of dementia, 1.43 (1.25–1.62) for Alzheimer's disease, and 1.91 (1.61–2.25) for vascular dementia. The risk of MCI in the patients with T2DM is 49% higher than in the individuals without diabetes (Xu et al. 2020). In addition to that, the studies revealed that the patients with type 1 diabetes exhibit decreased attention, psychomotor speed, cognitive flexibility, and visual perception compared to the healthy controls, while the patients with type 2 diabetes have higher rates of memory and learning impairments (McCrimmon et al. 2012). These cognitive impairments are a risk factor of dementia, including Alzheimer's disease, of which the patients with diabetes have a 50% higher risk (Cheng et al. 2012).

One hypothesis for cognitive impairment in diabetes involves abnormal neural networks synchronization similar to the changes seen in certain psychiatric disorders. Key factors contributing to cognitive decline are thought to include impaired glial function, microangiopathy, and imbalances in insulin homeostasis. On the one hand, this may explain the high comorbidity of diabetes and mental disorders, and, on the other hand, provide new insights into the pathogenesis of mental illnesses (Mansur et al. 2014). An interesting fact is that the patients with depression have impaired glucose metabolism, which may precede depression without an obvious connection with diabetes (Golden et al. 2008; Hamer et al. 2011). The depression in the patients with diabetes is an aggravating factor, since it worsens glycemic control and increases the risk of complications (Lustman et al. 2000).

Morphological and metabolic changes in diabetes mellitus type 1 and 2

The MRI studies found that cognitive impairment in the patients with type 2 diabetes mellitus (T2DM) is accompanied by atrophy of the hippocampus, a key structure responsible for memory processes (Hirabayashi et al. 2013). The studies revealed pronounced atrophy of the amygdala, the degree of which correlates with the disease duration (den Heijer et al. 2006). Diabetes-associated changes in the brain volume are equivalent to 4-5 years of normal aging (Biessels et al. 2014; Biessels and Despa 2018).

Hyperglycemia is a characteristic feature of diabetic changes in the brain. The studies revealed that the level of glucose in the brain increases linearly with the increase in the blood glucose level, making up 20-30% of the plasma concentration (Gruetter et al. 1998). However, the patients with type 2 diabetes demonstrate decreased glucose transport to the brain, which may limit its utilization by neurons (Shvyrkova 1995). Decreased cerebral glucose uptake is detected by positron emission tomography (PET) using 18F-FDG. The patients with T2DM and cognitive impairment have decreased metabolic activity in the frontal, parietal, and temporal regions, including the hippocampus (Baker et al. 2011). Similar changes were observed in animal models of T2DM, supporting their pathogenetic significance (Soares et al. 2013).

Hypoglycemia is also considered a significant risk factor for cognitive impairment. The introduction of insulin into clinical practice became a breakthrough in diabetes treatment, significantly improving the prognosis and quality of life of the patients. However, insulin therapy has a downside – the risk of iatrogenic hypoglycemia, which remains a serious treatment complication (Sherwin 2008). Hypoglycemia is a potent oxidative stressor that can exacerbate the cellular damage caused by chronic hyperglycemia. This process is accompanied by inflammation and damage to vulnerable neuronal structures and other target organs. The preclinical studies found that the recovery phase after hypoglycemia is characterized by intense reactive oxygen species production, which may exacerbate the long-term consequences of chronic hypoglycemia (McCrimmon 2021).

The studies of brain metabolism in type 1 diabetes discussed the role of brain glycogen supercompensation in the development of hypoglycemia unawareness. It was thought that

increased glycogen content could provide an additional energy reserve, supporting brain activity in hypoglycemia. However, the studies demonstrated that levels of newly synthesized glycogen are lower in the patients with type 1 diabetes compared to the controls, despite comparable blood glucose and insulin levels. This may indicate either lower brain glycogen content or a faster metabolic turnover in the healthy participants. The metabolic modeling revealed a trend toward lower brain glycogen levels in the patients with type 1 diabetes, indicating a lack of glycogen supercompensation in this group (Öz et al. 2012).

Insulin-independent mechanisms, known as "glucose efficiency," account for about 50% of total glucose utilization. Decreased efficiency plays a significant role in the development of diabetes. Although the exact mechanisms remain poorly understood, the evidence suggests that the brain is able to dynamically regulate this process, helping to improve or even normalize glycemic levels (Schwartz et al. 2013). The patients with T2DM have significantly reduced glycogen levels in the hippocampus and other brain regions, which correlates with cognitive impairment (Choi et al. 2003). This may result from a decreased expression of GLUT transport proteins and impaired insulin signaling.

Discussion

Sugar metabolism in the brain represents a highly intricate and multifaceted biochemical and physiological process that plays a crucial role in maintaining normal brain function as well as in the pathogenesis of several serious disorders, including diabetes mellitus and depression. Glucose is the primary energy substrate for the brain, and its metabolism underpins critical processes such as neurotransmission, synaptic plasticity, and overall neural homeostasis. Disruptions in cerebral glucose metabolism have been increasingly recognized as pivotal contributors to cognitive decline and neurodegeneration, particularly in metabolic and neuroendocrine disorders.

Further in-depth investigations into the specific pathways and regulatory mechanisms involved in brain glucose metabolism are essential for elucidating the early pathophysiological changes that result in cognitive impairment, especially in the preclinical or initial stages of diabetes. These early deficits in cognitive function often precede more overt clinical manifestations and are associated with impaired glucose uptake, altered insulin signaling, and mitochondrial dysfunction within neural tissues. A better understanding of these early changes may clarify why current therapeutic interventions frequently fall short in fully restoring cognitive function and highlight the challenges patients face in adhering to medical recommendations, particularly concerning obesity management and lifestyle modifications.

Moreover, the various biochemical components of brain glucose metabolism—including glucose transporters, key glycolytic enzymes, and secondary messengers—serve not only as metabolic intermediates but also as independent risk factors for the development and progression of cognitive dysfunction. Alterations in these components can exacerbate oxidative stress, neuroinflammation, and abnormal neurotransmitter release, further aggravating neurological outcomes in endocrine disorders. The data summarized in this review strongly underscore the necessity for refined characterization of these metabolic pathways at the molecular level to establish novel biomarkers and therapeutic targets.

In conclusion, advancing our knowledge of cerebral sugar metabolism will be instrumental in driving the next generation of pharmacological strategies aimed at mitigating cognitive deficits across a spectrum of endocrine and neurological conditions. Targeted interventions designed to normalize or enhance brain glucose utilization have the potential to improve clinical outcomes and quality of life for patients affected by these complex disorders. This approach promises to bridge existing gaps in treatment efficacy and foster more personalized, mechanism-based therapies for cognitive impairment in diabetes, depression, obesity, and related diseases.

Conclusion

Sugar metabolism in the brain is a complex and multifaceted process that affects both its functioning and the development of pathologies such as diabetes and depression. A further study of these mechanisms will help to explain the causes of cognitive impairment in the early stages of diabetes, the insufficient effectiveness of treatment for these disorders, as well as difficulties in following recommendations for the treatment of obesity. Various biochemical links of glucose metabolism in the brain act as independent risk factors of cognitive dysfunction. The data presented in this review indicate that a more precise understanding of brain glucose metabolism will lead to the development of new therapeutical targets and

pharmacological strategies for the cognitive impairment treatment in various endocrine and neurological diseases.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

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Data availability

All of the data that support the findings of this study are available in the main text.

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