Neurotoxicity Research
https://doi.org/10.1007/s12640-021-00393-3

REVIEW ARTICLE

Potential Glioprotective Strategies Against Diabetes-Induced Brain Toxicity

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Received: 20 April 2021 / Revised: 30 June 2021 / Accepted: 5 July 2021

Abstract

Astrocytes are crucial for the maintenance of brain homeostasis by actively participating in the metabolism of glucose, which is the main energy substrate for the central nervous system (CNS), in addition to other supportive functions. More specifically, astrocytes support neurons through the metabolic coupling of synaptic activity and glucose utilization. As such, diabetes mellitus (DM) and consequent glucose metabolism disorders induce astrocyte damage, affecting CNS functionality. Glioprotective molecules can promote protection by improving glial functions and avoiding toxicity in different pathological conditions, including DM. Therefore, this review discusses specific pathomechanisms associated with DM/glucose metabolism disorder–induced gliotoxicity, namely astrocyte metabolism, redox homeostasis/mitochondrial activity, inflammation, and glial signaling pathways. Studies investigating natural products as potential glioprotective strategies against these deleterious effects of DM/glucose metabolism disorders are also reviewed herein. These products include carotenoids, catechins, isoflavones, lipoic acid, polysaccharides, resveratrol, and sulforaphane.

Keywords Astrocytes · Diabetes · Glucose metabolism disorders · Glioprotection · Gliotoxicity · Natural compounds

Introduction

Astrocytes are essential cells for central nervous system (CNS) homeostasis, presenting a refined cytoarchitecture that results in close contacts with synapses, blood vessels, and other glial cells (Allen and Eroglu 2017). Indeed, astrocytes actively participate in the regulation of neurotransmitter systems, energy metabolism, antioxidant defenses, and inflammatory responses (Bolaños 2016; Sofroniew 2020). Thus, astrocytes are associated with both physiological and pathological conditions of the CNS.

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia resulting from a failure in glucose transport and utilization in the tissues. In type 1 DM, hyperglycemia is caused by autoimmune destruction of the pancreatic β cells, leading to insulin insufficiency. Type 2 DM is associated with peripheral insulin resistance, which is eventually accompanied by insulin deficiency (Van Harten et al. 2006; Jing et al. 2013; Semwal et al. 2021). DM impacts not only the peripheral of the body, but also the CNS (Van Harten et al. 2006). Several neuroendocrine and metabolic factors regulate the actions of insulin and glucose in the CNS (Jing et al. 2013), which can result in neurotoxicity with significant impact on astrocytes (Nardin et al. 2016; Zanotto et al. 2019). Glucose is the main energy substrate of the CNS, and astrocytes support neurons through metabolic coupling of synaptic activity with glucose utilization (neurometabolic coupling) (Bélanger et al. 2011). In this regard, numerous recent publications have shown that DM induces astrocyte damage, which plays a key role in the pathophysiology of neurodegenerative disorders (González-Reyes et al. 2016; Acosta et al. 2017).

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Published online: 14 July 2021

Changes in astrocyte functions are closely related to gliotoxicity, a condition that involves cellular, molecular, and neurochemical alterations in glial cells and can affect neurons and/or other glial cells. Accordingly, DM can induce gliotoxicity (Fig. 1). On the other hand, glioprotection refers to the glial cell–mediated protection of neuronal cells and/or other glial cells, particularly after CNS injury and damage (Quincozes-Santos et al. 2014). Glioprotective molecules, therefore, can promote protection by improving glial functions and avoiding toxicity. Our research group has shown that resveratrol, lipoic acid, and sulforaphane mediate glioprotection in several experimental models of gliotoxicity (Bellaver et al. 2016; Bobermin et al. 2013, 2018, 2019, 2020; Quincozes-Santos et al. 2013a, b; Santos et al. 2015); moreover, some natural products may also serve as potential therapeutic strategies to ameliorate the consequences of DM in the CNS. Thus, the main objective of this review is to discuss natural products that may represent glioprotective strategies against DM-induced gliotoxicity. The main topics of this review are (I) astrocytes; (II) astrocytes and glucose metabolism disorders; (III) associations between glucose metabolism, redox homeostasis, and mitochondrial dysfunction, with a focus on astrocytes; (IV) astrocytes, glucose metabolism disorders, and inflammation; (V) glucose metabolism disorders and trophic support; (VI) glucose metabolism disorders and glial signaling pathways; and (VII) natural products as potential glioprotective molecules.

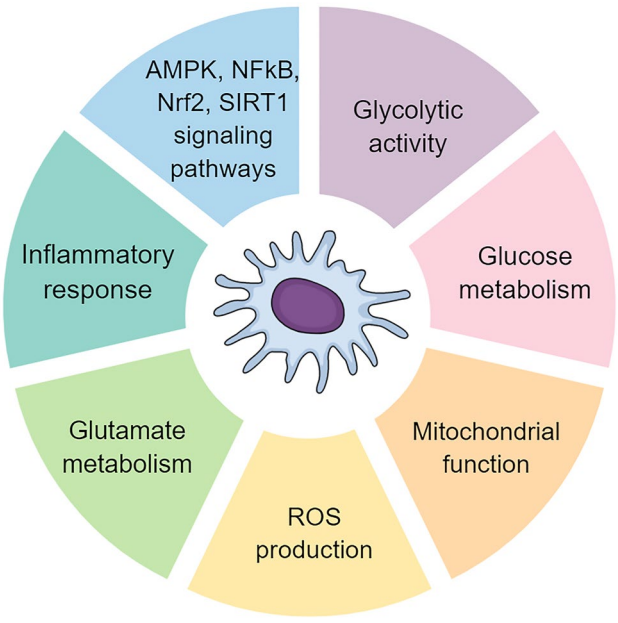

Fig. 1 Neurochemical changes induced by glucose metabolism disorders in astrocytes. DM can affect glycolytic activity, glucose metabolism, mitochondrial function, ROS production, glutamate metabolism, and inflammatory response, and several signaling pathways can be affected in astrocytes. These harmful effects that are associated with glucose metabolism disorders can induce gliotoxicity, affecting the morphofunctional properties of astrocytes. The cell in the center of the figure represents a reactive astrocyte. AMPK AMP-activated protein kinase, Nrf2 nuclear factor erythroid-derived 2-like 2, NFκB nuclear factor kappa B, SIRT1 sirtuin 1

Astrocytes

Astrocytes, the major class of glial cells, can serve as "bridges for passing information" between blood vessels and neurons, as well as between central and peripheral systems, coordinating metabolic substrates, hormonal signaling, and oxygen delivery according to the demands of specific brain regions (Bélanger et al. 2011; García-Cáceres et al. 2019). Indeed, the CNS has a high energy demand, and glucose is the obligatory metabolic substrate for the adult brain (Bélanger et al. 2011). Therefore, astrocytes are critical cells for the supply of glucose requirements, since tight regulatory mechanisms exist between astrocytes and neurons (astrocyte-neuron coupling) to maintain neuronal activity.

Although neurons consume more energy, the astrocytes are the major cells responsible for glucose uptake into the brain, and thereby the transfer of metabolic substrates to neurons (Nehlig and Coles 2007). The transport of glucose into cells occurs through specific carriers — glucose transporters (GLUTs) (Koepsell and Vallon 2020). Astrocytes express the glucose transporter 1 (GLUT1) isoform, which is also expressed in the endothelial and choroid plexus cells that form the BBB. Since astrocytes can cover more than 90% of non-fenestrated capillary vessels, they have a key role in the entry and distribution of glucose in the brain. In addition, these cells can participate in the regulation of blood glucose levels and glucose tolerance (García-Cáceres et al. 2019). After the transport of glucose into cells, it is phosphorylated in a rate-limiting step catalyzed by hexokinase. In astrocytes, glucose-6-phosphate can be used for glycogen synthesis, in the pentose phosphate and in hexosamine pathways, and to generate energy through glycolysis (Gonçalves et al. 2019). The activity and regulation of glycolytic enzymes in astrocytes suggest that they present a high glycolytic activity (Bolaños et al. 2010). On the other hand, although astrocytes are able to fully metabolize glucose through oxidative metabolism, an amount of pyruvate generated from glycolysis is converted to lactate, which is released by monocarboxylate transporters and can be used as an energy source by other cells, including neurons (Bélanger et al. 2011).

The metabolic activity of astrocytes may be reprogrammed in response to redox and inflammatory challenges (Robb et al. 2020), and changes in glucose levels induce redox and inflammatory responses (Quincozes-Santos et al. 2017), demonstrating that astrocytes display intrinsic regulatory functions. Moreover, astrocytes form/reform and maintain the BBB, which may restrict or allow the entry of metabolites and inflammatory and trophic factor

mediators into the CNS. Astrocytes also synthesize and release a wide range of trophic factors, including brain-derived neurotrophic factor (BDNF), glial cell line–derived neurotrophic factor (GDNF), S100B, vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF1), and transforming growth factor-β (TGF-β), among others, which support neuronal survival, function, and plasticity (Matias et al. 2019). These trophic factors can also target glial and endothelial cells, regulating differentiation, activation, metabolism, angiogenesis, and BBB integrity (Farina et al. 2007). Accordingly, the pathophysiological roles of astrocytes have become a primary focus of investigations regarding numerous diseases and have emerged as a target for preventive/therapeutic strategies for these diseases.

Astrocytes and Glucose Metabolism Disorders

Glucose metabolism disorders induce a number of astrocytic responses, including increased BBB permeability, inflammatory response, redox imbalance, and up- or downregulation of several signaling pathways that significantly impact brain homeostasis (Ying et al. 2015; Quincozes-Santos et al. 2017). In vivo and in vitro experimental models, as well as positron emission tomography (PET) and magnetic resonance imaging (MRI) from patients with DM, have shown a decreased metabolic rate of glucose consumption (Van Harten et al. 2006), in response to hyperglycemia. Additionally, significant alterations in classical astrocytic markers have been reported following hyperglycemia, including increased glial fibrillary acidic protein (GFAP) and glutamate transporter activity and decreased S100B release and glutamine synthetase (GS) activity (Nardin et al. 2007; Quincozes-Santos et al. 2017; Richa et al. 2017). Patients with long-term hyperglycemia present brain complications, including an increased risk of brain atrophy and white matter lesions (Van Harten et al. 2006), leading to functional and behavioral consequences, such as cognitive dysfunction, dementia, and movement disorders (Van Harten et al. 2006; Richa et al. 2017). Therefore, DM or high glucose levels induce brain damage that may result in cognitive dysfunction and cerebrovascular diseases.

With regard to the entry of glucose into the CNS, while in vivo evidence has suggested that DM is associated with an increased permeability of the BBB in rats (Zanotto et al. 2017), other studies have observed downregulation or absence of alterations in glucose uptake (Gjedde and Crone 1981; Nardin et al. 2016). Similarly, variable expressions of GLUT1 (downregulation or upregulation) depend on the model (Pardridge et al. 1990; Nardin et al. 2016). In addition, the metabolism of glycogen is also affected in DM; several studies in rodents and humans have reported lower quantities of brain glycogen, predominantly in astrocytes (Sickmann et al. 2010; Öz et al. 2012). Moreover, insulin can increase glucose uptake and S100B release and has other metabolic effects in astrocytes (Wartchow et al. 2016; García-Cáceres et al. 2016); therefore, deficiency/changes in insulin production or signaling underlying DM can impact astrocyte metabolism. Importantly, inadequate management of insulin therapy or diet can induce episodes of hypoglycemia, with serious detrimental effects on astroglial metabolism (Quincozes-Santos et al. 2013a, b). It has also been shown that fluctuations in glucose concentration (e.g., hyperglycemic spikes and hypoglycemic troughs) can be worse than constant hyperglycemia for astroglial and CNS metabolism, contributing to DM complications (Quincozes-Santos et al. 2017).

Besides glucose metabolism, astrocytes also actively participate in other important metabolic cooperations between astrocytes and neurons, such as glutamate-glutamine cycle and glutathione (GSH) synthesis (Bélanger et al. 2011). Glutamate uptake decrease was observed in the hippocampus of rats submitted to an in vivo experimental model of DM, without affecting the protein levels of glutamate transporters (Nardin et al. 2016; Zanotto et al. 2017). In contrast, in vitro studies reported an increased glutamate uptake in astroglial cells exposed to high glucose (Tramontina et al. 2012; Quincozes-Santos et al. 2017). Moreover, different studies have shown up- or downregulation of the expression and activity of the astrocytic enzyme GS, depending on the brain region and DM experimental model (Son et al. 2015; Zheng et al. 2016). GS activity was decreased in astroglial cells exposed to a high-glucose medium (Tramontina et al. 2012; Quincozes-Santos et al. 2017), whereas primary astrocytes presented an increase in GS activity (Son et al. 2015).

Another important fate of glutamate in astrocyte metabolism is the synthesis of GSH, an essential molecule for cellular antioxidant defense and the detoxification process that confers neuroprotection (Dringen et al. 2015). Decreased GSH levels are a remarkable feature associated with DM and hyperglycemia, both in the brain of DM-induced animals (Gurel-Gokmen et al. 2018) and in astroglial cells exposed to a high-glucose medium (Tramontina et al. 2012; Quincozes-Santos et al. 2017). Overall, DM seems to impair important metabolic parameters in astrocytes, representing a mechanism that may underlie DM-induced brain dysfunction.

Correlation Between Glucose Metabolism, Redox Homeostasis, and Mitochondrial Dysfunction: Focus on Astrocytes

Oxidative stress induction in astrocytes has been shown to play a significant role in the pathophysiology of DM. Hyperglycemia-induced reactive oxygen species (ROS) generation occurs via different mechanisms that include glucose autoxidation, increased metabolic flux of the polyol (sorbitol) pathway, production of advanced glycation end products (AGEs),

and mitochondrial dysfunction, potentially leading to astrogliosis, neuronal damage, and BBB dysfunction (Giacco and Brownlee 2010; Liyanagamage and Martinus 2020). Moreover, AGEs are responsible for glycation reactions with lipids, nucleic acids, and proteins, which affect cell metabolism and can induce further disruption in redox homeostasis (Srikanth et al. 2013; Allaman et al. 2015; Maessen et al. 2015).

Increases in polyol pathway flux, caused by hyperglycemia-induced ROS, may deplete NADPH levels due to the NADPH-dependent conversion of glucose to sorbitol by aldose reductase. Since NADPH is a cofactor of glutathione reductase, which recycles oxidized glutathione (GSSG) to GSH, decreased NADPH causes alterations in cellular antioxidant systems. Another phenomenon related to disturbances in the polyol pathway, and subsequent oxidative stress, is the increased production of NADH by sorbitol dehydrogenase that stimulates ROS generation via NADH oxidases (Giacco and Brownlee 2010; Apostolova et al. 2020).

In addition, AGEs are formed by the non-enzymatic reaction of glucose with proteins and are found at high levels in the tissues and plasma of patients with DM. Besides incurring protein dysfunction, AGEs may also bind to their receptor (receptor for advanced glycation end products, RAGE), activating the pleiotropic transcription factor, nuclear factor kappa B (NFκB). Thereafter, this factor promotes the production of cytokines and ROS that may trigger neuroinflammation (Paul et al. 2020), indicating that oxidative stress is strongly connected with the inflammatory response, both of which are associated with the pathogenesis of DM.

Hyperglycemia also induces mitochondrial dysfunction with intracellular and extracellular production of ROS. High levels of glucose induce the elevation of the reducing equivalents, NADH and $FADH_2$, and a consequent increase in electron transfer through the mitochondrial respiratory chain. The voltage gradient across the mitochondrial inner membrane then increases, reaching a critical threshold limit that damages the respiratory chain and causes the incomplete reduction of O_2 and consequent production of superoxide (Giacco and Brownlee 2010). In addition, fluctuations in glucose levels induce a decrease in mitochondrial membrane potential and an increase in cellular superoxide levels, ROS production, and nitrite levels (Quincozes-Santos et al. 2017). Moreover, this hyperglycemia-induced redox imbalance may also be associated with genotoxicity in astroglial cells (Quincozes-Santos et al. 2017).

DM affects a plethora of signaling pathways, and these have a significant impact on redox homeostasis and mitochondrial dysfunction, consequently participating in DM-induced brain damage. In addition, epigenetic adjustments are engaged with these signaling pathways and can also cause oxidative stress/brain damage. The phenomenon, described as metabolic memory, is related to the deleterious effects of hyperglycemia on tissues, even when there is strict glycemic control. Thus, regulatory pathways involving microRNAs, histone modifications, DNA methylation, and the sirtuin-histone functions can act as epigenetic modifiers and modulators to induce redox homeostasis impairment (Li et al. 2017; Shafabakhsh et al. 2019).

Astrocytes, Glucose Metabolism Disorders, and Inflammation

Neuroinflammation is an important feature of DM and is thought to play critical roles in its complications in the CNS, such as neuropathic pain (Rosenberger et al. 2020), cognitive decline (Chen et al. 2017), retinopathy (Rübsam et al. 2018), and the development of neuropsychiatric disorders (Zhou et al. 2017). Moreover, neuroinflammation has emerged as a possible link between DM and Alzheimer's disease (De Felice and Ferreira 2014). Several studies have demonstrated that DM animal models are associated with elevated brain levels of pro-inflammatory cytokines and chemokines (Oliveira et al. 2016; Kiguchi et al. 2017). Moreover, DM upregulates cyclooxygenase 2 (COX-2) and complement component 3 (C3), promotes NFκB activation (Oliveira et al. 2016), and modifies immune cell populations in the brain (Wanrooy et al. 2018). However, it is difficult to pinpoint the cellular origin of pro-inflammatory mediators within the brain, since both microglia and astrocytes can participate in inflammatory responses, and many studies have shown that DM induces GFAP expression, a hallmark of astrogliosis (Kiguchi et al. 2017), suggesting a role of astrocytes in DM-associated neuroinflammation.

In astrocytes, in particular, high glucose also induces inflammatory responses, by upregulating and/or increasing the release of TNF-α, IL-1β, IL-4, IL-6, VEGF, and complement C3 (Quincozes-Santos et al. 2017; Wang et al. 2012; Zhao et al. 2018), and decreasing anti-inflammatory cytokine IL-10 (Quincozes-Santos et al. 2017). Of note, it is also well established that AGEs can trigger inflammatory responses, due to their interaction with RAGE (Chu et al. 2016). Moreover, there is a connection between immune and metabolic functions that has been called "immunometabolism," in which inflammatory stimuli are able to positively modulate glucose uptake and associated metabolic pathways, including those in astrocytes (Robb et al. 2020). Metabolic changes, in turn, support the energy expenditure for immune responses. Importantly, NFκB signaling is at the center of the DM/hyperglycemia-induced neuroinflammation (Quincozes-Santos et al. 2017; Wang et al. 2012), links inflammation and oxidative stress (Aguilera et al. 2018), and mediates immunometabolic changes (Robb et al. 2020). This tissue will be further discussed in this review.

Experimental studies focusing on obesity and aging have shown that the hypothalamus undergoes a pro-inflammatory activation, which also involves astrocytes (Santos et al. 2018;

Tang et al. 2015). Hypothalamic inflammation has been recognized as a key component of metabolic syndrome disorders, and it is able to cause systemic glucose intolerance and peripheral insulin resistance (Tang et al. 2015) with a notable role for NFκB signaling. Therefore, it is conceivable that, in addition to being affected by DM and hyperglycemia, astrocytes (particularly hypothalamic astrocytes) may also be involved in the pathogenesis of type 2 DM.

Glucose Metabolism Disorders and Trophic Support

The production and release of trophic factors is another important function performed by astrocytes. Reductions in brain BDNF levels have been observed in animal models of type 1 and 2 DM and associated with synapse and cognitive dysfunctions (Rozanska et al. 2020). Interestingly, BDNF may influence diabetes pathogenesis beyond the CNS, since low plasma levels of BDNF have been correlated with impaired glucose metabolism and insulin resistance (Rozanska et al. 2020). Of note, the brain is considered the primary source of BDNF in the peripheral circulation, and the cerebral output of BDNF can be inhibited by hyperglycemia (Krabbe et al. 2007).

Reductions of IGF1 and NGF in the brain have also been observed in animal models of DM (Hamed 2017; Vines et al. 2019). In addition, lower serum S100B concentrations are reported in type 2 diabetic subjects (Hovsepyan et al. 2004), while the release of S100B by astrocytes is decreased by high glucose levels (Nardin et al. 2007). Excess TGF-β, however, has been associated with hyperglycemia and glucose metabolism, since it can induce hypothalamic stress and, consequently, inflammation, glucose intolerance, and insulin resistance (Yan et al. 2014). In contrast, GDNF ameliorates cell apoptosis in the hippocampus of rats with streptozotocin-induced diabetic encephalopathy (Cui et al. 2016). In this regard, impairment in trophic factor support can affect neuronal activity and survival, contributing to DM-related complications in the CNS. Thus, raising trophic factor levels from endogenous sources, which include astrocytes, may be a promising protective strategy.

Glucose Metabolism Disorders and Glial Signaling Pathways

DM and high glucose exposure have been shown to modulate several signaling pathways in astrocytes. Insulin and IGF1 can affect astrocyte metabolism via their receptors (insulin receptor and IGF1R), which trigger phosphatidylinositol 3-kinase (PI3K) signaling pathway (Kleinridders et al. 2014; Hong et al. 2017). It is important to note that the impairment in insulin and IGF1 signaling has been associated with cognitive deficits and may represent a link between DM and Alzheimer's disease (Talbot et al. 2012; Bassil et al. 2014). In brains of DM and Alzheimer's disease patients, downregulation of the PI3K/Akt signaling pathway could increase the activity of glycogen synthase kinase-3β (GSK-3β), leading to Tau protein phosphorylation (Xu et al. 2018). Moreover, disturbances in PI3K/Akt/GSK-3β have been associated with neuroinflammation, oxidative stress, and alterations in neurotransmitter systems (Datusalia and Sharma 2014). Mechanistic/mammalian target of rapamycin (mTOR) is a member of the PI3K-related kinases that, along with AMP-activated protein kinase (AMPK), acts as a metabolic sensor and plays a key role in energy homeostasis (Hardie et al. 2012; Saxton and Sabatini 2017). Physiologically, mTOR can positively regulate insulin signaling, but it has been reported that an overactivation of mTOR in type 2 DM, probably due to the excess of nutrients, exacerbates insulin resistance (Guillén and Benito 2018), representing another important link between DM and dementia. In addition, mTOR can regulate neuroinflammation in glial cells (Dasuri et al. 2016).

With regard to AMPK, this kinase supports the glycolytic nature of astrocytes, since it phosphorylates and activates the enzymes phosphofructokinase 1 (PFK-1) and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB-3) (Bolaños 2016). Therefore, hyperglycemia can activate AMPK, impacting astrocyte energy metabolism (Li et al. 2018). NAD-dependent deacetylase sirtuin 1 (SIRT1) is a well-characterized cellular energy sensor in peripheral tissues. It has recently been reported that SIRT1 signaling in astrocytes could contribute to metabolic regulation in mice (Choi et al. 2019). In DM models, a decreased expression of SIRT1 was observed (Kitada et al. 2019), while SIRT1 can prevent inflammation and DNA damage, which are closely related to DM. However, the activation of SIRT1 is able to exert neuroprotective effects, being associated with mechanisms of protective compounds, such as resveratrol. Therefore, it can act as a protective pathway in neurodegeneration and Alzheimer's disease (Chandrasekaran et al. 2019).

Several interconnected signaling pathways in astrocytes are also involved in the neuroinflammation and oxidative stress observed in DM; these include the mitogen-activated protein kinase (MAPK) pathways p38 and c-Jun-N-terminal kinase (JNK), further supporting evidence of a role of hyperglycemia in astrocytic redox/inflammatory processes (Chistyakov et al. 2019). Different studies have shown that high glucose increases astroglial levels and/or activation of p38 MAPK, extracellular signal-regulated kinase 1/2 (ERK1/2), and JNK (Quincozes-Santos et al. 2017; Bahniwal et al. 2017). NFκB is an important downstream factor of MAPKs and acts as a powerful regulator of both oxidative stress and inflammation, since it controls the gene expression of pro-inflammatory cytokines and other mediators (Singh and Singh 2020). In this context, abnormal MAPKs/NFκB signaling has been implicated in the mechanisms underlying diabetic neuropathy and several neurodegenerative diseases (Dewanjee et al. 2018).

In this regard, nuclear factor erythroid-derived 2-like 2 (Nrf2) transcription factor is able to counteract NFκB activation (Aguilera et al. 2018) and regulate the expression of metabolic, antioxidant, and detoxifying genes, including glucose-6-phosphate dehydrogenase, γ-glutamyl cysteine ligase (GCL), GSH synthase, and system xc (Escartin et al. 2011). In addition, Nrf2 induces the expression of heme oxygenase 1 (HO-1), an enzyme that confers cellular resistance against stressful conditions, such as oxidative stress and inflammation (Wakabayashi et al. 2010). Accordingly, in vitro studies have reported that hyperglycemia increased Nrf2 nuclear translocation in astrocytes, as well as HO-1 expression, probably as a compensatory mechanism to cope with the acute oxidative stress (Lind et al. 2013). In contrast, deficiencies in Nrf2 and HO-1 signaling have been reported in the brains of animals subjected to DM (Moreira et al. 2007; Sajja et al. 2017). Importantly, activation of Nrf2/HO-1 signaling has been suggested to be a potential mechanism of the neuroprotection that is mediated by natural products in DM (Pu et al. 2018; Wang et al. 2020). Therefore, as astrocytes have been suggested to be the predominant cell in which activation of Nrf2 occurs in the brain, they may represent interesting targets for protective strategies in DM (Liddell 2017).

Natural Products as Potential Glioprotective Molecules

Natural compounds, derived from plants, animals, fungi, and microorganisms, are crucial for the development of new drugs and medicinal supplements. These compounds can be used naturally, in nutraceutical foods, or included in the form of extracts or molecules isolated during the formulation of potential drugs and can have a direct action on, or interact with, specific receptors. In addition, natural products have been widely used in in vitro and in vivo experimental pre-clinical studies. As such, several pharmaceutical products that are currently available are structural derivatives of natural compounds found in medicinal plants that have been traditionally used for the treatment of various diseases. For example, metformin, one of the major antihyperglycemic compounds, was developed using the *Galega officinalis* plant (Ota and Ulrih 2017).

Moreover, the majority of studies investigating compounds associated with the prevention or treatment of DM have focused on the investigation of metabolic control or complications related to this disease (Infante-Garcia and Garcia-Alloza 2019; Semwal et al. 2021). As the complications generated by hyperglycemia are well established, the search for treatments has focused on specific targets, such as redox homeostasis, inflammatory response/neuroinflammation, neurodegeneration, and cognition, aiming to evaluate one or more factors that may interfere in the major pathways associated with these processes (Patil et al. 2020). Since some natural products may serve as potential therapeutic strategies for the consequences of DM in the CNS, we will summarize, hence on, specific natural compounds that can protect against neuropathologies associated with diabetic conditions and that may therefore represent potential glioprotective molecules. Table 1 displays the main references for the natural compounds reviewed here.

Carotenoids

Carotenoids are terpenoids that are produced by many species of bacteria, fungi, and plants (Keshavarzi et al. 2019). The antioxidant properties of these compounds are well known, but they are also able to prevent and/or ameliorate DM and its complications. It has been shown that dietary carotenoids and its plasma concentrations may be inversely associated with fasting plasma glucose concentrations, insulin resistance, and HbA_{1c} levels (Roohbakhsh et al. 2017). Astaxanthin and fucoxanthin, carotenoids found in marine algae, have antidiabetic/antihyperglycemic effects that may be related to the induction of PPARγ and GLUT4 expressions (Nishikawa et al. 2012). Moreover, astaxanthin decreased glucose tolerance, enhanced serum insulin levels, and attenuated blood glucose levels in db/db mice by protecting pancreatic β cells (Uchiyama et al. 2002).

With regard to the actions of carotenoids in the CNS, astaxanthin exerts positive effects by preventing cognitive and memory impairment, as well as by attenuating increased GSK-3β activity, TNF-α level oxidative stress, and factors related to the insulin substrate-1 (IRS-1) pathway, and neuronal insulin resistance in the hippocampus of Wistar rats (Rahman et al. 2019). Fucoxanthin reportedly elicits effects on the modulation of the AMPK/NFκB signaling pathways and inhibits the overexpression of pro-inflammatory cytokines in the hippocampus, frontal cortex, and hypothalamus of mice subjected to behavioral changes induced by an inflammatory lipopolysaccharide stimulus (Jiang et al. 2019). Lycopene, a carotenoid primarily found in tomatoes and other red fruits, attenuates diabetes-associated cognitive decline in rats (Kuhad et al. 2008) and displays neuroprotective activities against inflammation and oxidative damage, in addition to promoting the secretion of trophic factors, such as NGF and BDNF, from neural stem cells (Huang et al. 2018). These findings imply the importance of investigating similar effects and signaling pathways involved in the hyperglycemic processes in astrocytes.

Catechins

Catechins are the major bioactive polyphenols found in purified green tea extract. These compounds present neuroprotective effects that are mediated by their antioxidant and anti-inflammatory properties (Scapagnini et al. 2011).

Table 1 Biological effects of natural compounds on DM/glucose metabolism disorders

Natural compound	Biological effect	Reference
Carotenoids	Antidiabetic and antihyperglycemic effects; enhancement of serum insulin levels	Nishikawa et al. (2012) Uchiyama et al. (2002)
	Amelioration of hippocampal insulin resistance in Wistar rats and prevention of cognitive and memory impairments	Kuhad et al. (2008) Rahman et al. (2019)
	Protective activities against brain inflammation and oxidative damage; promotion of trophic factor release	Huang et al. (2018)
Catechins	Effects on insulin sensitivity mechanisms	Potenza et al. (2007)
	Improvement of cognitive disorders	Ettcheto et al. (2020)
Galega officinalis	Antihyperglycemic compound	Ota and Ulrih (2017)
Isoflavones	Antidiabetic and hypolipidemic effects	Mezei et al. (2003)
	Action on β-cell proliferation/glucose-stimulated insulin secretion	Gilbert and Liu (2013)
	Positive effects on glycemia in women with DM	Braxas et al. (2019)
Lipoic acid	Antioxidant activity and modulator of several signaling pathways	Lee et al. (2009) Yaworsky et al. (2000)
	Modulation of brain energy metabolism and insulin-related signaling	Jiang et al. (2013)
	Attenuation of glial reactivity against DM-induced brain damage	Baydas et al. (2004) Rodriguez-Perdigon et al. (2016)
Oligosaccharides	Action on neural regulation, insulin sensitivity, and glucose metabolism	Chan et al. (2016) Zhu et al. (2019)
Polysaccharides	Antihyperglycemic activity through inhibitory effects on α-amylase and α-glucosidase	Xu et al. (2019)
	Hypoglycemic potential	Xue et al. (2018)
	Drop in plasma glucose; increase in the levels of antioxidant enzymes	Kou et al. (2019)
Resveratrol	Control of inflammation and maintenance of redox homeostasis of cells	Tian et al. (2016) Wang et al. (2020)
	Improvement of homeostatic glucose balance in the body, mainly through the regulation of AMPK and SIRT1	Ding et al. (2020) Vlavcheski et al. (2020)
	Improvement of insulin sensitivity and glucose homeostasis	Knight et al. (2011)
	Attenuation of astrocytic activation in the hippocampus of diabetic rats	Jing et al. (2013)
	Effects on cognitive decline and neurodegeneration	Ma et al. (2020) Zeng et al. (2016)
	Prevention of neuronal apoptosis and memory impairment in diabetic rats	Wang et al. (2016) Tang et al. (2020)
	Protective effects on DM-related cognitive decline	Pu et al. (2018)
	Induction of Nrf2/HO-1 pathway in cells exposed to high glucose	Zhao et al. (2019)
Sulforaphane	Prevention of neuronal apoptosis and memory impairment in diabetic rats	Wang et al. (2016) Tang et al. (2020)
	Protective effects on DM-related cognitive decline	Pu et al. (2018)
	Induction of Nrf2/HO-1 pathway in cells exposed to high glucose	Zhao et al. (2019)

DM diabetes mellitus, *AMPK* AMP-activated protein kinase, *SIRT1* sirtuin 1 , *Nrf2* nuclear factor erythroid-derived 2-like 2, *HO-1* heme oxygenase- 1

Epigallocatechin-3-gallate (EGCG) is the most abundant catechin in green tea extract and reportedly affects insulin sensitivity mechanisms by modulating Nrf2 transcriptional activity (Potenza et al. 2007; Scapagnini et al. 2011) and Akt activation (Ettcheto et al. 2020), resulting in the reduction of insulin resistance and improvements in cognitive disorders, respectively. In addition, extracts of polyphenols, containing catechin and epicatechin, were found to attenuate nitric oxide synthase activation in astroglial cells subjected to oxygen–glucose deprivation and ischemic injury in vitro (Panickar et al. 2009). Epicatechin gallate (ECG) also improves glutamate uptake and S100B secretion in astroglial cells (Abib et al. 2008), potentially exerting a glioprotective role.

Isoflavones

Isoflavones are a subclass of flavonoids present in high concentrations in leguminous plants, such as soybeans. Genistein, followed by daidzein, glycitein, and aglycone, is the major bioactive form of this subclass (Ganai et al. 2015),

and several studies have demonstrated the beneficial effects of isoflavones, and/or their derivative compounds, against obesity, DM, and cardiovascular and neurodegenerative diseases. Genistein supplementation presented positive effects on glycemia, serum lipid profile, and antioxidant status in postmenopausal women with DM (Braxas et al. 2019) and on antioxidant defenses in knockout mice for low-density lipoprotein (LDL) receptors (Wang et al. 2008).

The beneficial effects of isoflavones are partially associated with their antioxidant and anti-inflammatory activities, as well as with estrogenic and hypocholesterolemic functions (Park et al. 2016). Notably, isoflavones act through estrogen receptors (ERs), due to their structural similarity to the estradiol hormone, and are considered to be phytoestrogens (Kuiper et al. 1998).

Isoflavones and genistein are able to control oxidative/nitrosative stress and inflammatory responses in numerous experimental models through signaling pathways, such as NFκB, PI3K/Akt (Qian et al. 2012), and peroxisome proliferator-activated receptors, PPARs (Mezei et al. 2003). They are also recognized as having antidiabetic properties, since they act directly on β-cell proliferation/glucose-stimulated insulin secretion and enzymes related to glucose metabolism (Gilbert and Liu 2013). Genistein can also relieve diabetic peripheral painful neuropathy and restore nerve NGF content (Valsecchi et al. 2011). Thus, these compounds may hold potential as glioprotective molecules, since they modulate specific activities associated with dysfunctions induced by DM in the CNS.

Lipoic Acid

Lipoic acid (LA) is a natural compound that can be endogenously synthesized in small amounts in the mitochondria. This compound is essential for the function of different oxidative metabolism enzymes and modulates the redox and energy status of cells. LA contains two thiol sulfur groups that act as antioxidants, particularly in GSH metabolism, and also as metal chelators, thereby modulating several signaling pathways (Lee et al. 2009; Gomes and Negrato 2014).

A number of studies have reported on the potential therapeutic actions of LA in chronic diseases, such as DM and its complications, hypertension, Alzheimer's disease, and cognitive dysfunction (Gomes and Negrato 2014). LA is able to restore glucose uptake impairment, mitochondrial dysfunction, and synaptic plasticity in the aging brain, through the modulation of insulin signaling (Jiang et al. 2013). In addition, LA can boost neurotrophic support in diabetic rats (Garrett et al. 1997). The protective effects of LA are related to NFκB inhibition, AMPK activation, and attenuation of inflammatory response and oxidative stress in peripheral and brain tissue (Ramamurthy and Ronnett 2012). With regard to glial cells, LA modulates glial parameters, such as glutamate uptake, GS activity, S100B secretion, GSH content, and inflammatory response, therefore attenuating glial reactivity (Bobermin et al. 2013; Kleinkauf-Rocha et al. 2013; Santos et al. 2015).

Polysaccharides

Mushrooms are rich in polysaccharides, especially β- and α-glucans, substances with antidiabetic properties (Dubey et al. 2019). Ethanolic extracts of the mushroom *Lactarius deliciosus* showed inhibitory effects on α-amylase and α-glucosidase (Xu et al. 2019), while polysaccharides isolated from *Inonotus obliquus* were demonstrated to strongly increase glucose consumption in insulin-resistant cells (Xue et al. 2018), demonstrating potential hypoglycemic activity in in vitro studies. Moreover, the polysaccharides of the mushroom *Grifola frondosa* also presented antidiabetic effects by decreasing glucose levels and increasing enzymatic antioxidant defenses (Kou et al. 2019).

Small molecules, such as functional oligosaccharides, have also been used as antidiabetic agents, as they present the ability to regulate insulin tolerance and glucose metabolism, by improving pancreas function, α-glucosidase inhibition, anti-inflammatory effects, and the regulation of gut microbiota (Chan et al. 2016; Zhu et al. 2019). Although studies about the possible effects of polysaccharides in the brain are lacking, these compounds can act as neuroprotective molecules, avoiding the deleterious effects of glucose in the CNS.

Resveratrol

Resveratrol is a natural polyphenol of the stilbene family that is synthesized by a variety of plants, such as grapes, peanut, and berries (Baur and Sinclair 2006). As a well-known phenolic and antioxidant compound, resveratrol prevents oxidative damage in various pathological situations, controlling inflammation and maintaining redox homeostasis of the cells, including astrocytes, where it is able to reduce glial activation, oxidative/nitrosative stress, and the inflammatory response (Bellaver et al. 2016; Bobermin et al. 2018, 2019; Quincozes-Santos et al. 2013a, b; Wang et al. 2020). Moreover, resveratrol is able to increase the release of trophic factors, particularly BDNF and GDNF, by astrocytes under an inflammatory stimulus (Bobermin et al. 2019).

Studies in diabetic animal models have demonstrated that resveratrol ameliorates the overall scenario of the disease via several mechanisms, such as improvement in sensitivity to insulin, a reduction in oxidative stress, an anti-inflammatory activity, and regulation of metabolic enzymes (Tian et al. 2016; Ota and Ulrih 2017). The glucose balance may be improved by resveratrol, modulating insulin secretion patterns, and maintaining metabolic processes, mainly through the regulation of AMPK, GLUT4 transporter levels, and

SIRT1 (Ding et al. 2020; Vlavcheski et al. 2020). Interestingly, the activation of SIRT1 by resveratrol in the hypothalamus improves insulin sensitivity and glucose homeostasis (Knight et al. 2011).

The effects of resveratrol on cognitive decline and neurodegeneration have been widely described (Jing et al. 2013; Ma et al. 2020). With particular regard to astrocytes, resveratrol was able to attenuate astrocytic activation in the hippocampus of diabetic rats (Jing et al. 2013) and improve brain levels of GSH (Ma et al. 2020) and also prevented retinal dysfunction by regulating specialized glial functions, such as the glutamate-glutamine cycle (Zeng et al. 2016). Considering these observations, resveratrol may hold potential for the prevention of diabetic encephalopathy, acting as a glioprotective molecule. It is important to note that resveratrol is able to modulate the Nrf2/HO-1 pathways, protecting glial cells against glucose-induced cytotoxicity.

Sulforaphane

Sulforaphane is a natural isothiocyanate found in cruciferous vegetables (e.g., broccoli, cauliflower, and cabbage) that has demonstrated a therapeutic potential due to its antioxidant and anti-inflammatory activities (Huang et al. 2019). Since sulforaphane is able to cross the BBB, it can protect neural cells in different experimental models of brain injuries, including DM. It has been shown that sulforaphane prevented neuronal apoptosis and memory impairment in diabetic rats, by regulating neurotrophic factors, Akt/GSK-3β pathway, and endoplasmic reticulum stress (Tang et al. 2020; Wang et al. 2016). Moreover, the protective effects of sulforaphane on DM-related cognitive decline are associated with its ability to improve Nrf2 signaling, increasing the expression of HO-1 in the brain (Pu et al. 2018). With regard to the neural cell types targeted by sulforaphane, its Nrf2/HO-1 pathway–inducing effects were observed in neuronal cells exposed to high glucose (Zhao et al. 2019) and in astroglial cells (Bobermin et al. 2020). In addition, sulforaphane modulates a wide range of astroglial functions, including glutamate uptake, GS activity, GSH metabolism, the release of GDNF, and the inflammatory response (Bobermin et al. 2020); these glioprotective mechanisms presumably mediate the beneficial effects of sulforaphane in a diabetic brain.

Concluding Remarks

DM is strongly correlated with brain disorders, which are mainly associated with obesity and aging. Moreover, DM affects astrocyte functions, particularly their glucose metabolism, in turn impairing CNS homeostasis. Therefore,

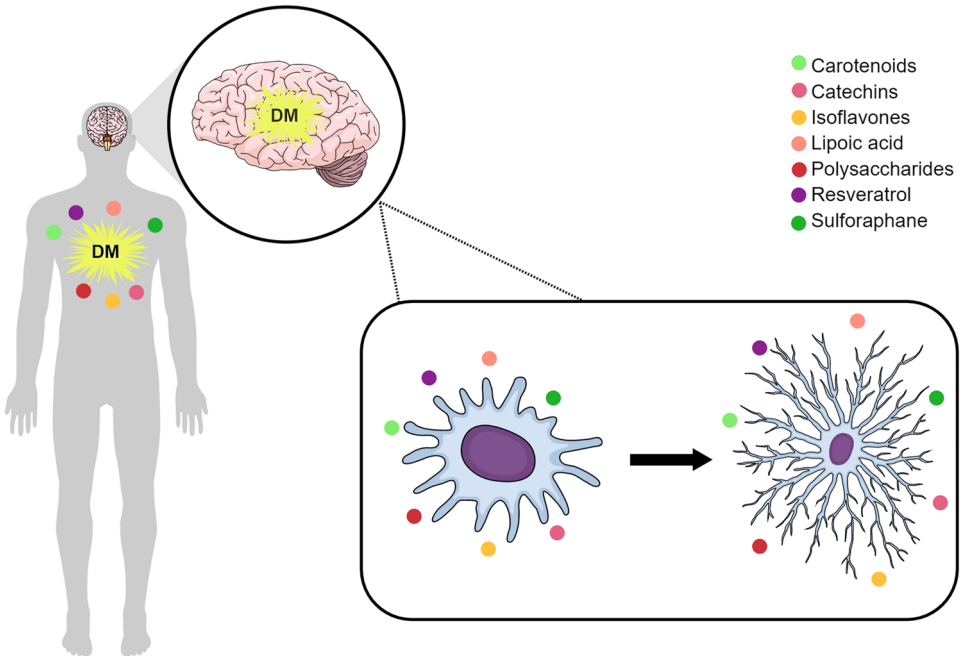

Fig. 2 Schematic illustration of the potential glioprotective effects of natural compounds. DM induces peripheral and central nervous system dysfunctions. Carotenoids, catechins, isoflavones, lipoic acid, polysaccharides, resveratrol, and sulforaphane can act as glioprotective molecules by attenuating and/or avoiding gliotoxicity. Glioprotective molecules can promote glioprotection in DM by the modulation of glycolytic activity, glucose metabolism, mitochondrial function, ROS production, glutamate metabolism, inflammatory responses, and several signaling pathways in astrocytes. The cell on the left represents a reactive (dysfunctional) astrocyte, while the cell on the right represents a ramified (functional) astrocyte. Colored circles represent the glioprotective molecules

astrocytes are a relevant target for preventive/therapeutic strategies for DM-induced gliotoxicity. Data from our group and others have highlighted natural compounds as glioprotective molecules that are able to improve specific astrocyte activities and thereby may prevent the brain damage that occurs in DM. Figure 2 depicts how natural compounds can act on astrocytes to promote glioprotection. The major mechanisms by which natural compounds exert glioprotection involve signaling pathways such as the AMPK, HO-1, Nrf2, NFκB, PI3K, and SIRT1 pathways. Accordingly, nutraceuticals such as catechins, lipoic acid, resveratrol, and sulforaphane have received substantial interest due to their potential nutritional and therapeutic effects on these pathways, including in DM. Since there is a lack of studies on human astrocytes and DM, the majority of studies cited herein were performed in animal models. In summary, the present review sheds light on the homeostatic ability of astrocytes, reinforcing natural products as potential glioprotective strategies against diabetes-induced gliotoxicity.

Author Contribution VS, LDB, IS, GL, and AQS conceived, wrote, and revised the manuscript. VS, LDB, and AQS designed and created the figures.

Funding The authors of this study are supported by the Universidade Federal do Rio Grande do Sul (UFRGS), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

Declarations

Conflict of Interest The authors declare no competing interests.

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