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Inside the Diabetic Brain: Role of Different Players Involved in Cognitive Decline

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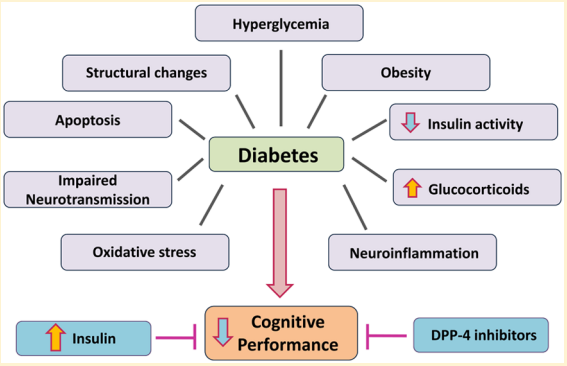
ABSTRACT: Diabetes mellitus is the most common metabolic disease, and its prevalence is increasing. A growing body of evidence, both in animal models and epidemiological studies, has demonstrated that metabolic diseases like obesity, insulin resistance, and diabetes are associated with alterations in the central nervous system (CNS), being linked with development of cognitive and memory impairments and presenting a higher risk for dementia and Alzheimer's disease. The rising prevalence of diabetes together with its increasing earlier onset suggests that diabetes-related cognitive dysfunction will increase in the near future, causing substantial socioeconomic impact. Decreased insulin secretion or action, dysregulation of glucose homeostasis, impairment in the hypothalamic−pituitary−adrenal axis, obesity, hyperleptinemia, and inflammation may act independently or synergistically to disrupt neuronal homeostasis and cause diabetes-associated cognitive decline. However, the crosstalk between those factors and the mechanisms underlying the diabetes-related CNS complications is still elusive. During the past few years, different strategies (neuroprotective and antioxidant drugs) have emerged as promising therapies for this complication, which still remains to be preventable or treatable. This Review summarizes fundamental past and ongoing research on diabetes-associated cognitive decline, highlighting potential contributors, mechanistic mediators, and new pharmacological approaches to prevent and/or delay this complication.



KEYWORDS: *Diabetes, hyperglycemia, insulinemia, obesity, brain, cognition, synapse*

Diabetes mellitus, the most common metabolic disorder worldwide, is increasing dramatically. It is estimated that 387 million people live with diabetes, of which nearly 50% are unaware they have the disease mostly due to the fact that diabetes can remain asymptomatic or be misdiagnosed for several years (IDF diabetes Atlas 2014).

The underlying determinants of diabetes are the same all over the world. Economic development is associated with increasingly "obesogenic environments", characterized by increasing access to energy-rich diets and decreased physical activity.

It is firmly established that diabetes causes micro- and macrovascular diseases.[1] Nevertheless, increasing evidence has also demonstrated that both type 1 and type 2 diabetes, in different degrees, result in complications in the central nervous system (CNS), with many brain structures being sensitive and responsive to changes in glucose homeostasis. Diabetes-associated cognitive decline (also known as diabetic encephalopathy) results from a complex interplay between direct and indirect metabolic consequences of long-term hyperglycemia, insulin deficiency, and additional components such as genetic and environmental factors.[2]

Diabetes-associated cognitive decline has been linked to learning and memory deficits, which in turn increase the risk for dementia, Alzheimer's disease, and affective disorders.[3,4] In this context, recent studies have shown that elevated body mass index, obesity, and insulin resistance are correlated with increased risk of dementia and cognitive impairment.[5,6]

The mechanisms by which cognitive abilities are impaired in diabetes have not been clearly identified. Nevertheless, it has been shown that altered neurogenesis, electrophysiological deficits, oxidative stress injury, neuroinflammation, and neuronal apoptosis can induce structural changes and be involved in brain dysfunction during the course of diabetes.[2,7]

This Review will give particular emphasis on the main factors underpinning type 1 and type 2 diabetic-related cognitive

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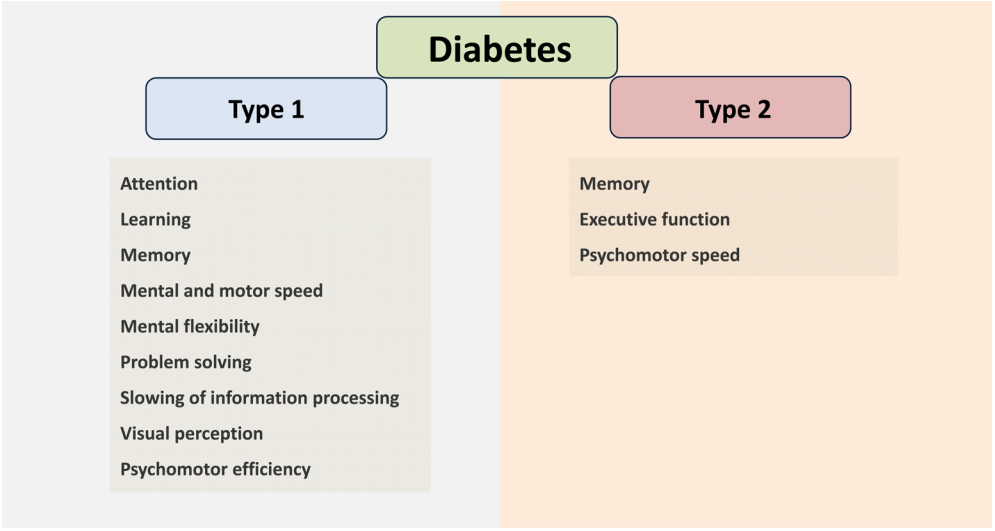

Figure 1. Diabetes-associated cognitive impairments described in type 1 and type 2 diabetic patients. Principal cognitive domains that have been found to be negatively affected in type 1 and type 2 diabetic patients.

deficits, highlighting recent advances on the treatment of diabetes-associated cognitive decline.

DIABETES AND COGNITIVE FUNCTION

Diabetes-associated cognitive decline has been associated with structural alterations in the brain, including brain atrophy, and electrophysiological deficits, that culminate in decreased memory and cognitive performance. The hippocampus, the brain region involved in memory formation and associative learning, is particularly affected by this pathology due to its sensitivity to changes in glucose and insulin homeostasis. The relative degree of cognitive dysfunction and the way cognitive abnormalities are manifested differs in both types of diabetes (Figure 1).[4,7−10]

Type 1 diabetic patients have impairments in learning and memory, problem solving, and mental and motor speed. Type 1 diabetic children show declarative memory deficits,[11] whereas young adults have mild central brain atrophy, associated with changes in intellectual performance, mainly on information processing speed, mental flexibility, and psychomotor functioning.[12,13] Moreover, 6 years after the onset of disease, children with type 1 diabetes have poorer performance on measures of intelligence, attention, processing speed, long-term memory, and executive skills comparing with control subjects.[14]

In animal models of type 1 diabetes, impaired performance in complex tasks, such as in Morris water maze or spatial-object learning task, has also been detected,[15−18] with the development of behavioral deficits being dependent on diabetes duration.[8,19] Intensive treatment with insulin[16] or lowering corticosteroid levels[17,20] prevents most of these deficits.

Patients with type 2 diabetes present moderate impairments in tasks involving verbal memory or complex information processing, increase in memory deficits, reduced frontal lobe/executive function, and reduction in psychomotor speed (Figure 1).[14,21]

In animal models of insulin resistance, in which rats are submitted to a high fat or high sugar diets, learning impairments are detected, as assessed by hippocampus-dependent water maze tests. Also, insulin ability to induce long-term depression (LTD) is reduced in CA1 hippocampal subregion, which correlates with peripheral insulin resistance.[22] Moreover, rats fed with high-fat diet during 3 months present cognitive deficits,[23] while rats fed during 8 months exhibit impaired spatial learning ability, and reduced long-term potentiation (LTP) at Schaffer collateral - CA1 synapses.[24] In Zucker rats, an animal model of genetic obesity and insulin resistance, impaired spatial memory was also detected.[25]

The differential effects induced by type 1 and type 2 diabetes on cognitive processes raise questions regarding the underlying causes and the progression of diabetes-associated cognitive decline.

MAIN CONTRIBUTORS TO DIABETES-ASSOCIATED COGNITIVE DECLINE

Hyperglycemia. Hyperglycemia is generally considered the major cause for diabetic complications, triggering several metabolic and molecular alterations that lead to progressive neuronal dysfunction.[26] Although the brain preferentially uses glucose as the main metabolic fuel source, under poor controlled diabetes (prolonged hyperglycemia), glucose transport is disturbed, which can lead to a dysregulation of brain metabolism and also to a dysregulation of osmolarity.[26−28]

Higher plasma glucose levels (yet within the normal range) were associated with greater atrophy of the hippocampus and amygdala,[29] and accordingly, a better control of blood glucose levels improves cognitive performance in type 2 diabetic patients.[21]

Elevated glucose levels trigger various processes and activate several biochemical pathways that ultimately induce cell dysfunction and eventually cell death, slowly conducting to progressive functional and structural abnormalities in the brain.[7] Dysfunctional glucose regulation elicits neuronal synaptic reorganization[30,31] and increases proliferation of astrocytes[32] in the hippocampus of streptozotocin (STZ)-induced diabetic animals. Synaptic reorganization includes depletion and dispersion of synaptic vesicles[31] and changes in the content of proteins involved in exocytosis[33,34] at presynaptic level, whereas an increase in postsynaptic density-95 (PSD-95) protein expression and changes in its distribution are described[30] at postsynaptic side. Nevertheless, hyperglycemia does not explain all the differences regarding neurological complications in type 1 and type 2 diabetes. In

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fact, only a partial benefit is achieved when normal glycemia is maintained.[35] Nowadays, it is accepted that several factors (besides hyperglycemia) can act in additive or synergistic ways to impair neuronal homeostasis and increase neuronal vulnerability, thus contributing to cognitive decline. However, the interplay between those factors and the development of CNS complications remain to be clarified. The complex pathophysiological features of diabetes (Figure 2) may include

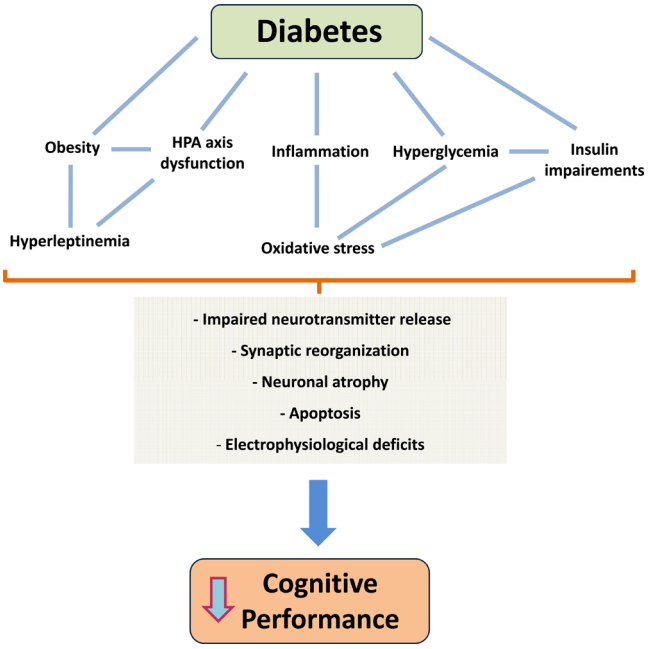

Figure 2. Main factors contributing to diabetes-induced brain dysfunction. The complex pathophysiological features of diabetes include decrease in insulin activity, impaired glucose homeostasis, and dysregulation of the hypothalamic−pituitary−adrenal axis function, among others. Changes observed in the brain under diabetic conditions include neuronal/dendritic atrophy, changes in synapse formation, impaired neurotransmitter release, and electrophysiological deficits.

not only a dysregulation of glucose homeostasis, but also decreased insulin secretion or action, impairment in the hypothalamic−pituitary−adrenal (HPA) axis, obesity, hyperleptinemia, oxidative stress, and inflammation.[2,7]

Insulin Signaling. Hyperinsulinemia and insulin resistance occurs in the prediabetes and in early stages of type 2 diabetes, whereas chronic hypoinsulinemia occurs in type 1 and in later stages of type 2 diabetes. Insulin receptors are expressed throughout the brain suggesting an important role of insulin in the physiology of the CNS.

Insulin promotes proper synaptic metabolism, protein synthesis, neuronal survival, and the establishment of LTP (Figure 3A). Particularly in the hippocampus, insulin is a regulator of energy and glucose homeostasis,[36] hippocampal neuronal plasticity and cognitive functions (potentiating LTD and LTP),[37−41] as well as neurogenesis.[42−44] Insulin and the closely related proteins insulin-like growth factor (IGF)-1 and IGF-2 mediate their biological effects through the activation of two highly related tyrosine kinase receptors: the insulin receptor and the IGF-1 receptor. Both insulin and IGF-1 receptors are expressed throughout the brain, and use similar intracellular signaling machinery.

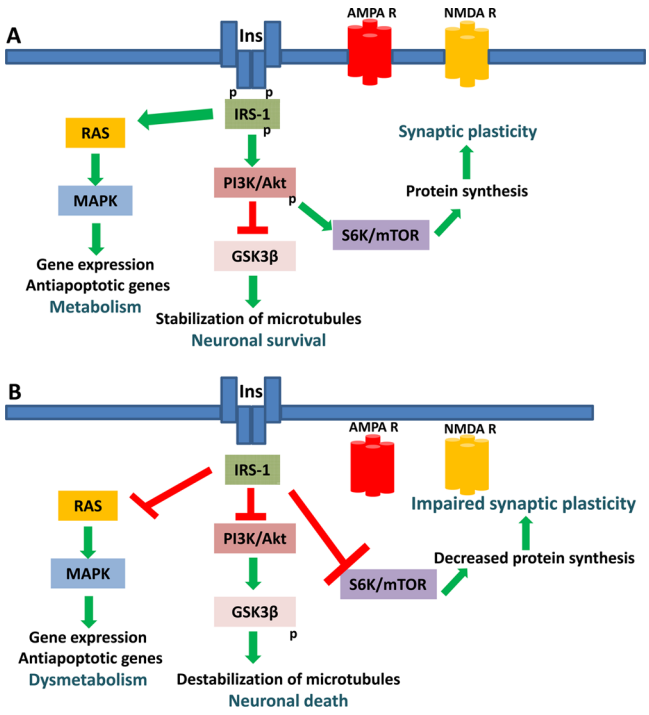

Figure 3. Neuronal insulin signaling. (A) Activation of insulin receptor leads to different signaling cascades with different physiological effects. Activation of MAPK signaling is responsible for the regulation of antiapoptotic gene expression and mitochondrial metabolism. Activation of Akt and consequently the inhibition of GSK-3β leads to a microtubule stabilization and neuronal survival. Akt phosphorylation also activates mTOR pathway that is responsible for protein synthesis and the increase in synaptic plasticity. (B) Dysfunctional insulin signaling leads to dysmetabolism, impaired synaptic plasticity, destabilization of microtubules, and changes in the expression of genes involved in the apoptotic pathway.

Insulin receptor is a tyrosine kinase that activates downstream targets by phosphorylation of insulin receptor substrate (IRS). Phosphorylation of IRS leads to activation of phosphatidylinositol-3 kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, which are involved in changes in hippocampal synaptic plasticity either by increasing protein synthesis or by stabilization of microtubules/axonal transport through GSK-3β. Emerging data have shown that insulin may participate in the strengthening of synaptic plasticity through the activation of canonical PI3K. However, insulin might also activate other pathways such as S6K/mTOR that are involved in neuronal survival and nutrient sensing.[41−43]

The multifactorial pathogenesis of diabetes-associated cognitive decline is not completely understood, but clearly shares features with brain aging and Alzheimer's disease.

In animal models of insulin resistance (high fat diet consumption), it has been described an impairment of insulin receptor function.[22] As a result, changes in cytoskeleton components occur, leading to synaptic injury and neuronal loss; synaptic transmission is reduced and an attenuation of insulin-induced LTD is detected[45] (Figure 3B). Deficits in insulin signaling increase tau phosphorylation,[46−48] a pathogenic feature detected in hippocampus of STZ diabetic mice and fatty Zucker rats, as well as in animal models of Alzheimer's disease.[49,50] In addition, insulin treatment is able to improve cognitive performance,[51] both in Alzheimer's disease[52] and in nondemented individuals.[53]

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Alzheimer's disease is associated with the accumulation of neurofibrillary tangles and amyloid fibers, which leads to neuronal loss. Islet amyloid polypeptide (IAPP), which is cosecreted with insulin by pancreatic beta cells, spontaneously forms amyloid aggregates in a similar way of amyloid beta peptide. Degeneration of pancreatic islets, observed in type 2 diabetes, is associated with the formation of neurofibrillary tangles. These similarities in the accumulation of neurofibrillary tangles implicate a close biological relationship of protein aggregation between type 2 diabetes and Alzheimer's disease.[54]

Several pieces of evidence indicate that insulin regulates the metabolism of amyloid beta and tau proteins. In the CNS, hypoinsulinemia can lower the levels of insulin-degrading enzyme (IDE), thereby impairing amyloid beta clearance. Also, chronic hyperinsulinemia in the peripheral circulation, along with decreased uptake of insulin into the brain, can lead to dysregulation of amyloid beta and inflammation.[55]

Growing evidence also indicates that insulin regulates the metabolism of amyloid beta and tau proteins.[56] The levels of IDE are unchanged in the brain of diabetic animals,[57] although the increase in nitrosative stress can inhibit IDE.[58] IDE is an enzyme involved in insulin and amyloid beta protein degradation (the main component of amyloid plaques in the Alzheimer's brain). Inhibition of IDE promotes an accumulation of amyloid beta protein and leads to increased insulin levels and consequently insulin resistance.[58]

Glucocorticoids. Although hyperglycemia and decreased insulin secretion or insulin activity are certainly central factors contributing to the complex pathophysiological characteristics of diabetes-associated cognitive decline, alterations in the HPA axis have also been shown to contribute for neuronal complications associated with diabetes. Elevated basal levels of glucocorticoids have been reported in patients with diabetes,[59,60] which may influence proper CNS function and contribute for the development of cognitive impairments.[61,62]A chronic increase in plasma glucocorticoids levels can aggravate symptoms induced by high blood glucose levels and enhance insulin resistance.[63] It was demonstrated that chronic elevation of corticosteroid levels induces changes in transcription of genes encoding corticotropin-releasing hormone receptors, suppresses dendritic arborization, and inhibits neurogenesis in the hippocampus.[64,65]

In diabetic rodents, high levels of corticosteroids contribute to the impairment in synaptic plasticity and neurogenesis,[17,41] induce depletion and clustering of synaptic vesicles in mossy fiber terminals,[31] and increase the expression and the redistribution of synaptophysin in the hippocampus.[30] Maintaining physiological corticosterone levels and replacing insulin in diabetic rats prevents plasticity changes in the hippocampus.[16,17]

Obesity and Hyperleptinemia. Both obesity and saturated fats are described to have damaging effects in the brain, being negatively correlated with cognitive performance. Obesity may contribute to dementia and other cognitive impairments by increasing the incidence of vascular pathologies,[6,61,66] brain atrophy,[6] and neuronal injury.[67]

Excessive intake of certain macronutrients, such as simple carbohydrates and fatty acids, may lead to metabolic dysfunction, resulting also in alterations in structural plasticity and neurogenesis in some brain regions. In fact, the relation between obesity and central neuropathology has been demonstrated by evidence that weight reduction improves cognition.[68]

In animals under high fat diet, a significant modification of neural and endocrine factors linked to energy and glucose homeostasis is observed. This, changes insulin action in the brain, even before the appearance of metabolic disease symptoms, therefore influencing the cognitive domain.[69]

An additional consideration in obesity phenotypes is the potential for the increase in plasma levels of adipocyte derived hormones, such as leptin, that may have harmful consequences to the brain.[5] Leptin receptors are abundantly expressed throughout the hippocampus, supporting a role for leptin in the facilitation of hippocampal synaptic plasticity under physiological conditions.[70] When directly administered in the CA1 hippocampal region, leptin improves memory processing and retention.[71] Treatment of acute hippocampal slices with leptin results in the conversion of short-term potentiation to LTP by enhancing Ca^{2+} influx through NMDA receptors.[70] Leptin also increases neurogenesis in the dentate gyrus of adult mice and plays a critical role in hippocampal neuronal survival by activating the PI3K/Akt and JAK2/STAT3 signal transduction pathways.[72,73] However, an increase in leptin levels observed under obesity induces long form receptor resistance thus impairing the signaling pathways and changing the normal synaptic plasticity.[74]

Genetic mutations that disrupt leptin signaling such as in the db/db mouse and the Zucker fa/fa rat are associated with a reduction in LTP and impaired performance of hippocampal-dependent tasks,[75] suggesting that impairments in leptin signaling and leptin resistance contribute to deficits in hippocampal synaptic plasticity.

Oxidative Stress. Oxidative stress is defined as an increase in the steady-state levels of reactive oxygen species (ROS). Increased oxidative stress in diabetes is thought to promote the development of several diabetic complications. Diabetes may cause ROS production through glucose auto-oxidation, increased flux through the polyol pathway, and increases in protein glycation.[26] ROS may also activate aldose reductase and protein kinase C (PKC) and increase advanced glycation end-products (AGEs) and diacylglycerol formation.

In the brain of diabetic animals, there is an increase in oxidative and nitrosative stress, which can contribute to morphological abnormalities, neuronal damage, and cognitive and behavioral deficits.[76] Increased oxidative stress might result, not only from the increased generation of free radicals, but also from an impairment of the antioxidant defense system, responsible for scavenging free radicals and maintaining redox homeostasis. It was reported that together with the increase in ROS production, there is a decrease in the activity of antioxidant enzymes, namely superoxide dismutase and catalase, in the brain of diabetic rats.[77]

Oxidative stress is linked to mitochondrial dysfunction that results in energy deficits and consequently neuronal damage and neurodegeneration.[78] Increasing evidence supports the idea that mitochondrial function declines with aging and with age related diseases; some authors consider brain mitochondrial dysfunction as the link between Alzheimer's disease and diabetes. Brain mitochondria isolated from STZ-induced diabetic rats have a lower content of CoQ9, which is a marker of antioxidant defense.[79] In a rat model of type 2 diabetes (Goto-Kakizaki), impairments in respiratory chain and oxidative phosphorylation in isolated brain mitochondria were reported.[80] Mitochondrial dysfunction in diabetes can be prevented/reduced by using antioxidants and insulin therapy.[79]

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Neuroinflammation. The increase in the expression of proinflammatory cytokines in the brain under diabetic conditions indicates that the innate immune system, and particularly microglial cells, are activated[81,82] and play an important role in neuronal damage in diabetic patients and animals.[83,84] The levels of proinflammatory cytokines are increased in the brain of patients and animal models with neuropathological disorders associated with cognitive function impairments, such as Alzheimer's disease and depression.[85,86] In human postmortem hippocampus, it was detected that the activation of microglia in diabetic patients is similar to what is observed in Alzheimer's patients.[87]

In the hippocampus of diabetic animals, the expression of tumor necrosis factor (TNF), interleukin-1β (IL-1β), IL-2, and IL-6 is increased.[81] The increase in the expression of proinflammatory mediators in diabetic animals is associated with the increase of nitric oxide (NO) levels, simultaneously with the upregulation of the inducible nitric oxide synthase (iNOS) isoform, receptor for AGEs and NF-κB.[82] High fat diet fed mice present increased TNF levels and microglia/macrophage activation in the brain and adipose tissue, supporting the hypothesis that high fat diet dependent obesity results in concomitant proinflammatory changes in brain.[88] In type 2 diabetes, it was demonstrated that diabetic and obese mice (db/db) display impaired spatial-recognition memory, which is associated with increased levels of proinflammatory cytokines (IL-1β, TNF, and IL-6) and reduced expression of BDNF in the hippocampus, thus suggesting an interaction between inflammation and memory impairment.[89]

Moreover, it was found that after 2 weeks of diabetes there is an activation of microglia and enhanced GFAP expression in the hippocampus of STZ-induced diabetic rats.[90] Additionally, after 6 weeks of diabetes, increased caspase-3 activity induces profound cell death. This cell damage mediated by caspase 3 was concomitant with activation of astrocytes and microglia. The authors therefore suggested that these events are linked which further underpin the progression and severity of brain disorders, resulting in cognitive and behavioral impairments.[90]

Inflammation, memory, and learning deficits are prevented in animals treated with antiinflammatory[83] and antioxidant[82] compounds, and also in animals receiving C-peptide (peptide that connects A-chain of insulin to B-chain in the proinsulin molecule);[81] however, the detailed molecular mechanism by which C-peptide has beneficial effects in the brain is still unclear. Recently, it was demonstrated that an antidepressant (Rolipram, phosphodiesterase-4 inhibitor) was able to decrease TNF levels and increase IL-10 levels, also preventing cognitive impairment in diabetic animals.[91]

A correlation between hyperglycemia, impaired insulin signaling, oxidative stress, and inflammation has been described. In diabetic encephalopathy, the physiological redox equilibrium is impaired leading to oxidative stress. This, in turn, is involved in multiple cellular pathways such as activation of transcription factors, AGE/RAGE, polyol, and PKC pathways, that are related to glucotoxicity and/or insulin signaling impairment. The ultimate consequence of such oxidative stress mechanisms related to diabetes is neuronal apoptosis and brain inflammation, which in turn are engaged with neurodegenerative events.[26]

Another link between oxidative stress and insulin arises from impaired insulin signaling activity acting unfavorably on the expression and translocation of NF-κB, which is also a modulator of ROS production. Activation of NF-κB also occurs in the presence of high glucose.[92] NF-κB regulates the expression of TNF and interleukins, playing a major role in the initiation of the inflammatory cascade. The upregulation of TNF has an inhibitory effect on insulin and IGF-1signaling, thereby providing a self-perpetuating loop. NF-κB signaling is also a modulator of apoptosis and ROS production and has been also associated with cognitive impairments.[82,93]

NEUROSTRUCTURAL, NEUROCHEMICAL, AND ELECTROPHYSIOLOGICAL ALTERATIONS

Although several brain areas contribute to the cognitive deficits associated with diabetes, hippocampal-dependent tasks seem to be particularly sensitive to this disease.[2,4,29,61,66,67] The multifactorial pathogenesis of diabetes-associated cognitive decline shares features with brain aging and Alzheimer's disease, such as alterations at neurochemical, structural, electrophysiological, and neurobehavioral levels. Altered regulation of the same intracellular signaling pathways was detected both in type 2 diabetes and in Alzheimer's disease. Based on these similarities, Alzheimer's disease is often referred as type 3 diabetes.

Structural Alterations and Neuronal Loss. The cognitive impairments in diabetic encephalopathy have been associated with structural alterations[94] and brain atrophy.[13,95] Cortical, subcortical, and hippocampal atrophy (particularly in the dentate gyrus) has been detected in type 2 diabetic patients by brain magnetic resonance imaging.[95−97]

In the STZ animal model of diabetes (type 1), swelling of neurons, glia, oligodendrocytes, synaptic boutons, and mitochondria has been reported in several brain regions.[94] Also, in the STZ animal model, diabetes reduces the density and length of neuronal dendrites[98,99] and induces remodeling of dendrites which may be associated with the shrinkage of hippocampus.[100] In obese Zucker rats, a significant increase in the number of glial fibrillary acidic protein (GFAP) immunoreactive astrocytes was detected the frontal and parietal cortex and also in the CA1 and CA3 subfields and dentate gyrus of the hippocampus, compared with the lean Zucker rats.[101] Alterations of neurogenesis have also been reported in STZ-induced diabetic animals,[102−105] and also in an animal model of type 2 diabetes (Goto-Kakizaki rats).[106]

Moreover, apoptosis has also been implicated in diabetic complications. In vitro studies have shown that high glucose induces cell death in neuronal cells,[107−109] and it was reported to occur in the hippocampus of diabetic animal models.[110,111,103,112] In type 1 diabetic BioBreeding/Worcester (BB/Wor) rats, apoptosis was detected in CA1 and CA2 hippocampal neurons, which was accompanied by impairments in Morris water maze performance.[110−112] Treatment with C-peptide was able to protect against hippocampal neuronal apoptosis, suggesting that cell death was in part caused by impaired insulin/C-peptide action/levels in BB/Wor rats.[111,112]

Apoptosis was also detected in a type 2 diabetes animal model, BioBreedingZucker diabetic rat/Worcester (BBZDR/Wor), but in a lesser extent than in type 1 model, being more severe in CA1 pyramidal cells.[112] An increase in caspase-3 activity and Bax expression, and a significant increase in the ratio of Bax/Bcl-2 and Bax/Bcl-xL (used as index of apoptotic cell death) in the hippocampus of diabetic animals were also reported.[113]

Changes in Synaptic Transmission and Plasticity. In hippocampus of diabetic animal models, changes at presynaptic sites have been reported, including depletion and dispersion of

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synaptic vesicles[31] and changes in the content of proteins involved in exocytosis.[33,34] In the postsynaptic terminal, it was detected an increase in PSD-95 protein expression, which may contribute to changes in the content and functional properties of glutamate receptors in the hippocampus of STZ diabetic rats.[30] PSD-95 controls the number of AMPA receptors at the synapses and participates in receptor delivery/stabilization during synaptic. Moreover, stronger synapses with increased PSD-95 levels showed enhanced LTD.[114]

Diabetes affects the synthesis and release of key neurotransmitters,[115−119] which may underlie cognitive deficits observed in diabetic animals. It was reported in type 1 animal models of diabetes, increased levels of dopamine in different brain areas,[120] decreased basal levels of serotonin and dopamine in the hippocampus, and also decreased basal levels of glutamate in dentate gyrus.[121] The basal levels of GABA in the hippocampus are not altered in STZ-induced diabetic animals.[119,122] However, under chronic hyperglycemia, extracellular brain levels of GABA and glutamate are decreased.[115] In addition, GABA receptors are downregulated in STZ-induced diabetic animals,[123] which may contribute to changes in inhibitory function and disruption of memory. Imbalances between excitatory and inhibitory neurotransmission are triggering factors for neurodegeneration and consequently may contribute to changes in cognitive processes.

Acetylcholine esterase has a fundamental role in cognitive processes, and any alterations in its activity, as well as in the neurotransmitter acetylcholine, are associated with cognitive deficits observed in patients and animal models of diabetes.[124] In the hippocampus of type 1 STZ diabetic animals, acetylcholine esterase mRNA expression increases, whereas choline acetyltransferase mRNA expression decreases, suggesting a reduction in cholinergic transmission in hippocampal neurons.[123]

ATP signaling is also compromised in the hippocampus of STZ-induced diabetic rats. There is a decrease in ATP release and a downregulation of synaptic P2 receptors.[125] Extracellular ATP plays a role in synaptic efficiency processes by the activation of P2 receptors at the presynaptic sites, to control the release of glutamate,[126] and at the postsynaptic cell facilitating the activation of ionotropic glutamate receptors.[127]

Alterations in Ca^{2+} homeostasis and Ca^{2+}-dependent forms of synaptic plasticity in the hippocampus of diabetic animals have been associated with alterations in neurotransmitter release and learning impairments. Increasing evidence reveals that both type 1 and type 2 diabetes impairs Ca^{2+} homeostasis;[128−130] small changes in free intracellular Ca^{2+} sustained over a period of time results in cellular damage.[130] Cellular Ca^{2+} homeostasis is required for proper neuronal function and mitochondria has a major role in regulating intracellular Ca^{2+}. In fact, excessive Ca^{2+} uptake into mitochondria has been shown to increase ROS production, inhibit ATP synthesis, and induce mitochondrial permeability transition (MTP). MPT results in mitochondrial swelling and can lead to the release of proapoptotic proteins. Mitochondrial dysfunction and the resulting energy deficit trigger the onset of neuronal degeneration and death.[78]

Furthermore, Ca^{2+} currents and the expression of voltage-sensitive Ca^{2+}channels[131−133] are increased in dorsal root ganglion neurons from BB/W and STZ-induced diabetic rats. In retinal neurons exposed to high glucose, the increase in the intracellular Ca^{2+} concentration evoked by cell depolarization is enhanced, and the recovery to basal Ca^{2+} levels is delayed comparing with control retinal neurons.[134]

Slow afterhyperpolarization (Ca^{2+}-dependent feature of synaptic transmission occurring following a sequence of action potentials) is increased in the hippocampus of diabetic rats.[128] In an established animal model of brain aging (F344 rats), high-fat diet exacerbates cognitive decline and the hippocampal Ca^{2+}-dependent afterhyperpolarization (a marker of age-dependent Ca^{2+} dysregulation).[135]

Diabetes-induced alterations in synaptic neurotransmission at pre- and postsynaptic level may lead to changes in synaptic plasticity (Figure 4). Impairments in hippocampal synaptic plasticity and cognition have been demonstrated in several animal models of diabetes, such as impaired LTP and enhanced LTD;[16,17,136,137] although in the STZ model, LTP does not occur in more than 50% of animals. Moreover, when LTP is induced in diabetic animals, the magnitude of the excitatory postsynaptic potential (EPSP) slope is slower and is not sustained comparing with control animals.[16]

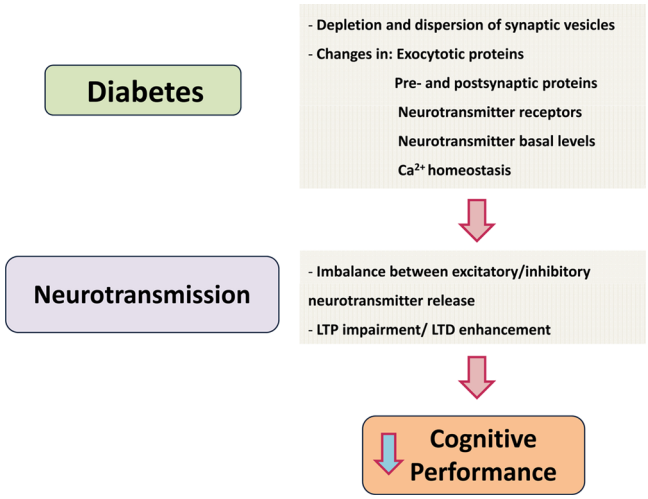

Figure 4. Neurotransmission impairment under diabetes correlates with decreased cognitive performance. Diabetes affects the synapse both at pre- and postsynaptic level, which may underlie changes in synaptic plasticity and consequently cognitive deficits that have been detected in diabetic patients and animal models.

LTP induction is regulated by postsynaptic NMDA receptors. NMDA receptors containing the NR2B subunit are decreased in the hippocampus of STZ-induced diabetic animals, causing a decrease in EPSPs.[138,139] Besides the reduction of the NR2B subunit, its phosphorylation by CaMKII also decreases in postsynaptic densities.[138] The affinity of glutamate for AMPA receptors, but not for NMDA receptors, is decreased in the hippocampus of STZ-induced diabetic rats.[140,141] In STZ-diabetic animals, the transient and the persistent sodium currents are decreased and the potassium currents are increased in hippocampal CA1 neurons, contributing to the decrease in membrane excitability. Moreover, the resting membrane potential of diabetic neurons was more positive than the control neurons.[10]

Taken together, changes reported in neurotransmitter release suggest the existence of an imbalance between excitation and inhibition, thus contributing to neuronal dysfunction and ultimately to memory impairments detected in diabetic animals and humans.

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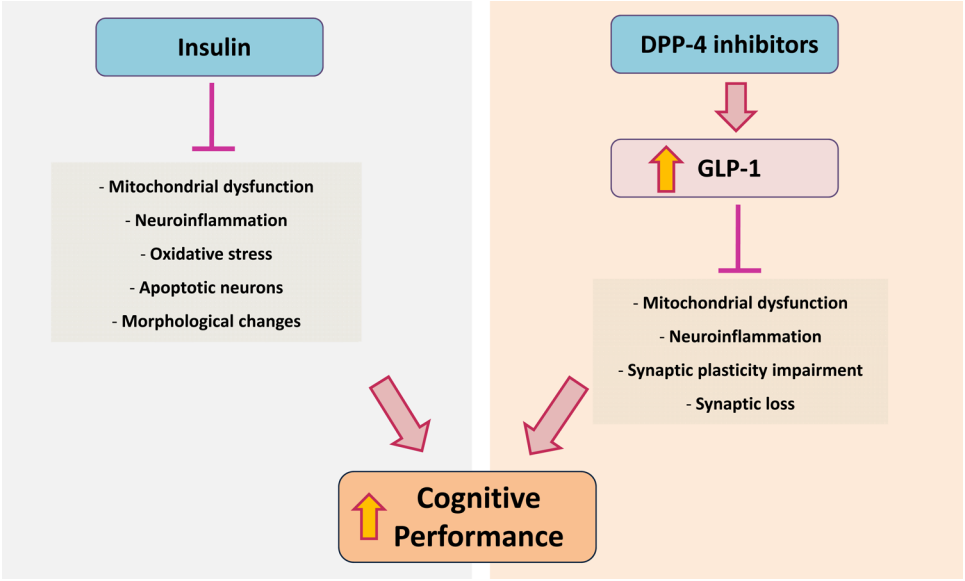

Figure 5. Pharmacological therapeutic strategies in diabetic encephalopathy. Insulin therapy and increasing GLP-1 levels using DPP-4 inhibitors can improve cognitive performance under diabetes through several mechanisms, attenuating brain mitochondrial dysfunction, neuroinflammation, and synaptic/neuronal loss, among others.

PHARMACOLOGICAL THERAPEUTIC STRATEGIES

Unraveling the pathogenesis of diabetes-triggered dysfunction in the brain will open new avenues for devising possible innovative pharmacological approaches to treat diabetes-associated cognitive decline. During the past few years, different strategies have been considered for the prevention or treatment of this complication; however, diabetic encephalopathy still remains to be preventable or treatable. Given the underlying mechanisms of diabetes-associated cognitive decline, the neuroprotective strategies have been focused mainly on the reduction of oxidative stress and the prevention of apoptosis to avoid neuronal loss.

Antioxidant and Neuroprotective Agents. As oxidative stress is one of the factors that can induce hippocampal dysfunction and consequently cognitive dysfunction, several studies have reported the protective effect of antioxidants in hippocampus of animal models of diabetes and obesity. Isoflavones have a metabolic action on energy balance and, due to its antioxidant properties, protects cultured primary hippocampal neurons from oxidative stress induced by exposure to glutamate and beta-amyloid. Treatment of STZ-induced diabetic animals with melatonin and vitamin E significantly ameliorates learning and memory performance, and can reverse lipid peroxidation and glutathione levels toward control values.[142]

Sesamol (3,4-methylenedioxyphenol) is a phenolic antioxidant and anti-inflammatory molecule that attenuates cognitive deficits and reduces acetylcholinesterase activity, oxidative stress, and inflammation in STZ-induced diabetic rats.[83] These authors also demonstrated that chronic treatment with curcumin, a well-established phenolic antioxidant and anti-inflammatory molecule, significantly attenuates cognitive deficits, oxidative stress, and inflammation in STZ-induced diabetic rats.[143]

Moreover, *N*-acetylcysteine administration for 8 weeks significantly ameliorates oxidative stress, improves lipid composition, and restores membrane fluidity and the activity of membrane bound enzymes in STZ-induced diabetic rats.[144] Another molecule, etomidate, significantly decreases nitrite levels in the rat cortex, hippocampus, cerebellum, brain stem, and spinal cord, demonstrating that etomidate can have neuroprotective effects on the neuronal tissue against the diabetic-induced oxidative damage.[145]

Insulin and C-Peptide. In the brain, insulin has neurotrophic and neuroprotective effects, facilitating synaptic plasticity in the hippocampus and enhancing memory function. Based on experimental and clinical studies that support important roles for insulin in several neuronal functions, particularly in plasticity events, insulin is currently being studied as a potential therapeutic strategy for cognitive deficits (Figure 5). Insulin is able to protect against oxidative stress and the reduction of mitochondrial oxidative phosphorylation efficiency induced by amyloid beta peptide in STZ rats.[79] Moreover, insulin treatment is able to prevent morphological changes in hippocampal CA3 subregion,[146] as well as the decrease in GFAP levels and the increase in glutamate uptake in diabetic animal models.[147] Moreover, replacement of insulin in type 1 diabetic rats protects against hippocampal damage and prevents cognitive deficits.[16]

Insulin and/or C-peptide prevent apoptotic neuronal cell death mediated by PI3-kinase stimulation. They also prevent the p38 activation and the disinhibition of NF-κB translocation[111,148] and the release of proinflammatory factors in the hippocampus of diabetic animals.[81]

Even though insulin therapy can be useful to prevent or slow the progression of diabetic complications, it is important to keep in mind that these hormone beneficial effects may be compromised by the increased risk of severe hypoglycemic episodes, which in turn are associated with increased neuronal and cognitive dysfunction. Alternatively, the use of insulin sensitizers may provide a reliable therapeutic alternative.

Dipeptidyl Peptidase-4 Inhibitors and GLP-1 Agonists. Glucagon-like peptide-1 (GLP-1) facilitates insulin release from the pancreas under hyperglycemic conditions. However, its short half-life is a limitation for its use as a therapeutic tool. Based on this, long-acting glucagon-like

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peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors have been developed as treatments for type 2 diabetes. These drugs increase insulin secretion and decrease glucagon production in a glucose-dependent manner without promoting hypoglycemia.GLP-1 analogues and DPP-4 inhibitors have protective effects in several tissues, including the brain (Figure 5).

GLP-1 receptors are expressed throughout the brain and GLP-1 can cross the blood-brain barrier (BBB), suggesting that they are promising therapeutic targets in neurodegenerative diseases, such as diabetes-associated cognitive decline and Alzheimer's disease.[149] Agonists of GLP-1R have anti-inflammatory and neurogenic effects, and are able to reduce beta-amyloid plaques preventing loss of synapses and memory impairments.[150−152]

Vildagliptin andl inagliptin (DPP-4 inhibitors) increase plasma and brain GLP-1 levels and restore insulin-induced long-term depression. They also restore neuronal insulin receptor phosphorylation, IRS-1 phosphorylation, and Akt/PKB-ser phosphorylation, attenuating the impaired cognitive function caused by high fat diet.[153,154] Vildagliptin and sitagliptin completely restore brain mitochondrial function and improve learning and memory behaviors in rats with high fat diet induced insulin resistance.[155] Liraglutide (long-acting GLP-1 agonist) prevents or attenuates type 2 diabetes associated neuronal and cognitive deficits,[151] possibly by a mechanism that promotes neurogenesis in dentate gyrus.[156] Liraglutide significantly affects brain neurotransmission and modulates synaptic plasticity enhancing LTP; it also protects against impairment in learning and memory in animal models of Alzheimer's disease and diabetes.[157] In a type 2 diabetic animal model, liraglutide normalizes brain metabolic homeostasis, decreases hippocampal lipid oxidation, improves brain mitochondrial regulation, and preserves synaptic plasticity (for a review, see ref 149). In line with these studies, two clinical trials are ongoing to analyze the effect of liraglutide as a neuroprotective drug in Alzheimer's disease.

CONCLUSIONS

Measurable manifestations of diabetic encephalopathy include impairment in cognitive functions and brain structural and electrophysiological changes. The precise mechanisms that underpin this pathology remain to be fully determined. Nonetheless, they are likely to involve impaired insulin signaling and increased inflammatory and oxidative stress pathways; these events occur early in the neurodegenerative process and share complex features with mechanisms of brain aging.

New treatment approaches for managing diabetes have shown some efficacy in reducing diabetes-induced neurodegeneration in animal studies, and promising drugs are being assessed to prevent or slow the progression of the disease. In addition, the management of diabetes can often involve a combination of treatments to control hyperglycemia and hyperinsulinemia, as well as treatments to improve peripheral insulin sensitivity. Advances in the understanding of the mechanisms underlying cognitive deficits pave the way to develop novel neuroprotective strategies aiming at preventing, delaying, and/or reversing the neurological consequences of diabetes.

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J.M.G. designed, wrote and edited the manuscript; F.I.B. wrote and critically reviewed the manuscript; M.P.M. and A.F.A. contributed to critical review of the manuscript.

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Notes

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ABBREVIATIONS

BDNF, brain derived neurotrophic factor; CA, *CornuAmmonis*; CNS, central nervous system; DPP-4, dipeptidylpeptidase 4; EPSP, excitatory postsynaptic potential; GFAP, Glial fibrillary acidic protein; GLP-1, glucagon-like peptide-1; HPA, hypothalamic-pituitary-adrenal; IDE, insulin degrading enzyme; IGF, insulin-like growth factor; IL, interleukin; LTD, long-term depression; LTP, long-term potentiation; NO, nitric oxide; ROS, reactive oxygen species; STZ, streptozotocin; TNF, tumor necrosis factor

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