

Diabetic encephalopathy: the role of oxidative stress and inflammation in type 2 diabetes

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Abstract: Type 2 diabetes mellitus (T2DM) is a heterogeneous metabolic disorder associated with an increased risk for central nervous system disorders. Diabetic encephalopathy is a relatively unknown diabetes complication, characterized by electrophysiological, structural, neurochemical, and degenerative neuronal changes that lead to cognitive functioning limitations. Besides chronic hyperglycemia and dyslipidemia, diabetic encephalopathy represents the most relevant risk factor for cognitive dysfunction, increased incidence of dementia, and consequently Alzheimer's disease (AD), also referred to as "type 3 diabetes." There has been recent evidence suggesting that oxidative stress and inflammation are key pathogenic factors for T2DM, cognitive decline, and neurodegenerative diseases, including AD. Thus in this review we aim to ascertain brain mechanisms underlying the link between T2DM and AD with a focus on oxidative stress and inflammatory processes. We also intend to review the main antioxidant/anti-inflammatory therapeutic strategies targeting the brain and contributing to halt the progression from diabetic encephalopathy into AD.

Keywords: diabetic encephalopathy, oxidative stress, inflammation

Introduction

Diabetes mellitus (DM) is a complex and heterogeneous metabolic disorder, mainly characterized by an abnormal rise in blood glucose levels – hyperglycemia. This occurs when (1) pancreatic β -cells fail to secrete sufficient amounts of insulin to maintain normoglycemia and/or when (2) there is a resistance to insulin's actions.^{1,2} The prevalence rates of DM have risen markedly in recent years (International Diabetes Federation [IDF]),³ this pathology being one of the most common worldwide: it affects about 285 million people at present and with an estimated increase of 50% by 2030.

Insulin resistance (IR) is defined as a pathophysiological condition where insulin is unable or less effective to promote glucose uptake and/or usage by target tissues.⁴ This in turn leads to an increased insulin release, followed by its inadequate secretion.⁵ Elevated fasting glucose levels, as a consequence of IR, can then ultimately lead to the diagnosis of type 2 diabetes mellitus (T2DM), which is characterized by β -cell dysfunction, increased hepatic glucose production and increased IR, primarily in skeletal muscle.⁶ In most people with T2DM, there is a multiple set of risk factors that commonly appear together, depicting what is now known as metabolic syndrome. According to the IDF, this includes diabetes, raised fasting plasma glucose, abdominal obesity, high cholesterol, and high blood pressure.^{5,6} In addition, people with metabolic syndrome have a fivefold-greater risk of developing T2DM.⁷

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T2DM is associated with the occurrence of some complications, commonly divided into macrovascular – such as coronary artery disease, peripheral arterial disease, and stroke – and microvascular, such as diabetic nephropathy, neuropathy, and retinopathy.⁸ There is accumulating evidence identifying the brain as a relevant site of T2DM damage, partly independent of atherosclerotic disease.⁹ Central nervous system (CNS) lesions in T2DM subjects can be referred to as diabetic encephalopathy.¹¹ This relatively unknown DM complication is characterized by electrophysiological and structural CNS changes,^{11,12} and diabetic encephalopathy together with chronic hyperglycemia and dyslipidemia compose the most relevant risk factors for cognitive dysfunction.^{4,13,14} Indeed, several studies have established the relationship between T2DM and cognitive deficits,^{15,16} showing an increased incidence of dementia.^{13,17} Oxidative stress and inflammation, which underlie multiple cellular pathways that can ultimately lead to the onset and progression of subsequent complications of T2DM, are being envisioned as two key players in diabetic encephalopathy, an emerging and pressing type 2 diabetic complication

(Figure 1).^{18–21} Additionally a correlation was unequivocally drawn between hallmarks of T2DM, including hyperglycemia, impaired insulin signaling, free fatty acids (FFAs), oxidative stress, and inflammation.

The vicious triad in diabetic encephalopathy: glucose, insulin and free fatty acids

Hyperglycemia and glucotoxicity

The brain uses glucose as the main fuel to generate energy, primarily by oxidative metabolism.⁶ However, a chronic increase in blood glucose levels, even in the absence of DM symptoms, will eventually lead to brain damage.¹ Thus, hyperglycemia-induced neurotoxicity is pointed out as one of the main causes of diabetic encephalopathy.⁶ The advanced glycation end product (AGE)/AGE receptor (RAGE) axis and the polyol pathways may represent molecular mechanisms of glucose neurotoxicity.^{6,22,23} The hexosamine synthesis pathway is a minor contributor to overall glucose disposal by cells. However, an overproduction of glucosamine may

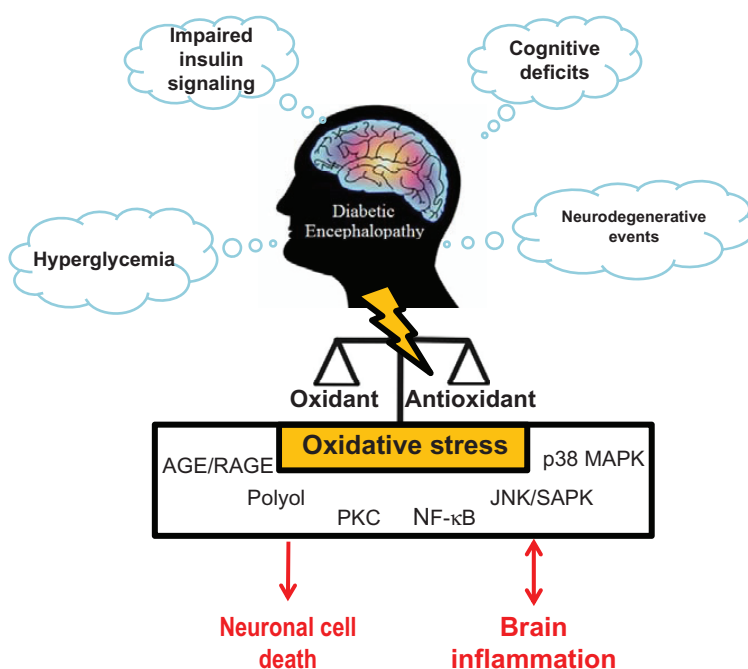


Figure 1 Mechanisms behind the relationship between diabetic encephalopathy and brain oxidative stress.

Notes: Diabetic encephalopathy refers to CNS damage as a diabetes complication. This may be the consequence of interplay between a disruption of insulin signaling and defective glucose metabolism (two key hallmarks of diabetes) that underlie dementia. Thus, the link between DM and neurodegenerative events is quite established, leading ultimately to cognitive deficits. A diabetic encephalopathy state is able to reverse the physiological redox equilibrium, which will lead to oxidative stress through increased production of free radicals or impaired antioxidant defenses. Oxidative stress is a widely accepted participant in the induction of multiple cellular pathways involved in DM development and progression or as a subsequent complication. Activation of transcription factors, AGE/RAGE, polyol, and PKC pathways seems to be the main mechanisms, related to glucotoxicity and/or insulin signaling deregulation. Recent evidence also suggests that stress-activated signaling pathways such as NF- κ B, p38 MAPK, and JNK/SAPK are involved. The ultimate consequence of such oxidative stress mechanisms related to DM is neuronal apoptosis and brain inflammation, which in turn are engaged with neurodegenerative events. Inflammation can further fuel oxidative stress–signaling pathways.

Abbreviations: AGE/RAGE, advanced glycation end products/AGE receptor; CNS, central nervous system; DM, diabetes mellitus; JNK/SAPK, NH₂-terminal Jun kinases/stress-activated protein kinases; MAPK, mitogen activated protein kinase; NF- κ B, nuclear factor kappa B; PKC, protein kinase C.

initiate endoplasmatic reticulum stress, which can promote a c-Jun N-terminal kinase (JNK)-dependent serine phosphorylation of insulin receptor substrate 1 (IRS-1). This may result in the suppression of the insulin receptor–signaling pathway.^{1,24} Finally, all these three pathways can either induce reactive oxygen species (ROS) or can be fueled by oxidative stress triggered by hyperglycemia.^{24–27}

AGE/RAGE pathway

AGE accumulation occurs through the CNS and is one of the consequences of poor glycemic control.^{23,28} AGEs result from the nonenzymatic reaction between sugars and proteins, lipids, or nucleotides as a consequence of brain oxidative stress.²⁹ Accumulated AGEs are present in normal aging brains as well as in certain pathological conditions, such as Alzheimer's disease (AD) and diabetes, and may affect neuronal function, either by modifying important functional proteins or by inducing ROS generation.¹³ AGEs bind to their cognate cell-surface receptor, RAGE, resulting in the activation of postreceptor signaling, inducing the production of ROS and the activation of pleiotropic transcription factor nuclear factor kappa B (NF- κ B), causing pathological changes in gene expression, including RAGE and inflammatory cytokines.³⁰ Additionally, increased RAGE expression is seen in brain regions affected by AD (including the hippocampus), and its overexpression accelerates AD pathology and cognitive impairment.²⁰ AGEs are not only markers but also act as mediators of late DM complications. Furthermore, administration of antioxidants to hyperglycemic patients can block free radical production and prevent the production of AGEs.²⁶

Polyol pathway

When intracellular glucose rises, aldose reductase activity is stimulated and catalyzes the formation of sorbitol, which can be oxidized to fructose by sorbitol dehydrogenase. Therefore, there is an accumulation of sorbitol, which leads to increased osmotic pressure, fructose accumulation, and a decrease of the reduced form of nicotinamide adenine dinucleotide phosphate. These alterations lead to the blockage of the reduction of glutathione disulfide (oxidized form) to glutathione, thereby promoting oxidative stress and causing cell damage.²⁴ Furthermore, the aldose reductase pathway facilitates the generation of key potent glycation compounds, leading to an increase in AGEs and RAGE upregulation.³¹ Additionally, stress-sensitive signaling pathways, including p38 mitogen-activated protein kinase (MAPK) and JNK, are strongly activated by sorbitol.²⁴

Insulin-related mechanisms

Insulin is one of the most important anabolic hormones identified to date, since almost all cell types are sensitive to this peptide.¹⁸ Although the brain was described before as an insulin-insensitive organ, there is now an increasing body of evidence demonstrating that insulin is widely distributed in this organ.³³ Furthermore, insulin plays a critical role in numerous mechanisms in the brain, such as metabolic, neurotrophic, neuromodulatory, and neuroendocrine,³⁴ as well as in memory and learning processes.^{35,36} Additionally, insulin operates in the CNS through binding to specific cell receptors – insulin and insulin growth factor 1 receptor (IGF-1R) – which are highly abundant and selectively distributed throughout the CNS (eg, hypothalamus, hippocampus).^{37,38} Once bound to these receptors, insulin triggers signaling cascades that include phosphoinositide 3-kinase (PI3K) and MAPK,^{39,40} which are the most relevant ones involved in learning and memory processes (Figure 2).^{5,34,41}

Brain insulin derives primarily from pancreatic β -cell secretion, being subsequently transported across the blood–brain barrier (BBB) by a saturable, insulin receptor–mediated transport process. In fact, there is a nonlinear correlation between cerebrospinal fluid and serum levels of insulin.^{42,43} Diabetes mellitus exerts a regulation on insulin BBB transport. For example, in contrast to the inhibition of insulin transport seen in an animal model of T2DM (obese Zucker rat [ZDF]: insulin resistance accompanying elevated levels of serum insulin), animal models of T1DM (alloxan or streptozotocin diabetes: insulionopenia) showed an increased saturable transport of insulin across the BBB.⁴⁴ AD also decreases insulin transport across the BBB. However, although this area remains controversial, there have been some recent findings suggesting that insulin could be produced in hippocampal pyramidal neurons.⁴⁵ IR may result in a modification of insulin transport into the brain, thus evoking a reduction in insulin signaling. This can be one of the underlying causes of diabetic encephalopathy.^{2,11}

Free fatty acids and brain neurotoxicity

The brain preferentially uses glucose as an energy source, and is not metabolically adjusted for the metabolism of FFAs.²⁴ However, recent evidence suggests that FFAs and specifically their intermediates could have a key role in the central control of energy-balance regulation and feeding.^{46–50} It was found that patients having metabolic syndrome have increased brain FFA uptake when compared with healthy subjects. Additionally, weight loss was able to partly reverse this abnormality.⁵¹

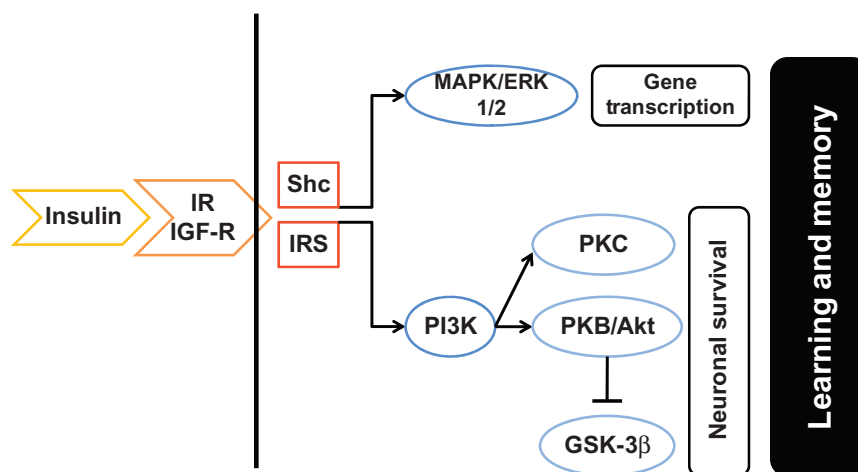


Figure 2 Scheme of the most relevant insulin signaling pathways in the brain.

Notes: Insulin binds to its specific cell receptors, such as IR and IGF-R, thereby activating endogenous substrates, mainly the IRS and the Shc, thus exerting its effects through several signaling cascades. PI3K and MAPK/ERK1/2 are the most relevant ones involved in learning and memory processes. PI3K also mediates the activation of PKB/Akt, favoring neuronal survival, and inhibits GSK-3 β , which is involved in the triggering of the apoptotic cascade.

Abbreviations: GSK-3 β , glycogen synthase kinase 3; IGF-R, insulin growth factor receptor; IR, insulin receptor; IRS, insulin receptor substrates; MAPK/ERK1/2, mitogen activated protein kinase; PI3K, phosphoinositide 3-kinase; PKB/Akt, protein kinase-B; Shc, Src-homology-2-containing protein.

It is well known that increasing the flux of fatty acids in lean individuals to rates similar to or greater than those seen in obese individuals (typically via a lipid-plus-heparin infusion) induces insulin resistance.^{52,53}

Activated fatty acids (ie, fatty acyl-CoAs) are “metabolized” primarily via one of two pathways – oxidation or storage. When fatty acid flux exceeds the ability of these pathways to dispose of fatty acyl-CoAs, intermediaries of fatty acid metabolism (eg, diacylglycerol, phosphatidic acid, lysophosphatidic acid, ceramide) accumulate. In turn, these molecules can negatively regulate insulin action through the activation of a number of different serine kinases. An inability to completely oxidize fatty acids through β -oxidation, which leads to an accumulation of acylcarnitines, has also been hypothesized to cause insulin resistance. For example, both in vivo and in vitro exposure of skeletal muscle and myocytes to physiological concentrations of saturated fatty acids is associated with insulin resistance.⁵⁴ Several mechanisms have been postulated to account for fatty acid-induced muscle insulin resistance, including glucose fatty acid (Randle) cycle, oxidative stress, and inflammation. These authors further proposed an integrative model placing mitochondrial dysfunction as an important and common factor in the other mechanisms. In brain, there is evidence suggesting that the impairment of lipid metabolism and accumulation of specific lipid species have deleterious effects in the hypothalamus through endoplasmic reticulum stress.⁵⁵

It was suggested that there is a potential link between raised FFA (obtained during intralipid plus heparin infusion

or a high-fat meal), insulin resistance, and neurodegenerative disorders.⁵⁶ For example, there is a body of evidence showing that oxidation products of two fatty acids, arachidonic acid and docosahexaenoic acid, are effectors of neurodegeneration as well as biomarkers of AD.⁵⁷

Holloway et al demonstrated that raising plasma free fatty acids not only decreased myocardial phosphocreatine but also reduced cognition in healthy human subjects.⁵⁸ Moreover, Charradi et al showed that brain lipotoxicity is linked to oxidative stress characterized by increased lipoperoxidation and carbonylation and inhibition of two key antioxidant enzymes: glutathione peroxidase and superoxide dismutase.⁵⁹

Finally, experimental studies indicated that increased plasma FFA (high-fat diet-induced) impaired neurogenesis through oxidative stress followed by the accumulation of peroxidized lipids, including malondialdehyde, and a decrease of brain-derived neurotrophic factor (BDNF) levels in the hippocampus.⁶⁰ This is of relevance, since impaired neurogenesis has been associated with cognitive impairments and with diabetic encephalopathy.^{61,62}

However, the role of FFA on diabetic encephalopathy was never systematically addressed. Interestingly, brain (particularly hypothalamic) insulin has a chief role in white adipose tissue (WAT) functionality, which plays a critical role in normal glucose and lipid homeostasis. In fact, Scherer and colleagues showed that mice lacking the neuronal insulin receptor exhibit unrestrained lipolysis and decreased de novo lipogenesis in WAT. Additionally, WAT dysfunction exerts a key influence on the pathogenesis of T2DM.⁶³

Oxidative stress

Increased oxidative stress is usually accompanied by an augmented production of free radicals or impaired antioxidant defenses.^{64,65} There is an increasing body of evidence indicating that oxidative stress induced by hyperglycemia and FFA causes insulin resistance, β -cell dysfunction, and late DM complications, thus playing a role in development as well as in progression and subsequent DM complications.^{26,53,66} Furthermore, there is recent evidence suggesting a relationship between oxidative stress, cognitive decline, and neurodegenerative disorders (Figure 1).^{67–69} This is of particular relevance to diabetic encephalopathy.

Recent studies further suggest that oxidative stress operates through the activation of stress-sensitive pathways, including NF- κ B, p38 MAPK, JNK/stress-activated protein kinases, AGE/RAGE, and protein kinase C.²⁶ This oxidative stress signaling has been envisioned to cause damage to cellular proteins, membrane lipids, and nucleic acids, eventually leading to apoptotic cell death and neural inflammation (Figure 1).²⁶ Among all these oxidative damage mechanisms, protein oxidation seems to be the most highly associated with cellular dysfunction underlying cognitive decline.^{69–71}

Going from oxidative stress to insulin resistance and back again

On one hand, oxidative stress specifically leads to insulin resistance through the activation of multiple serine kinase cascades that target insulin receptors as well as insulin receptor substrate–family proteins and Src-homology-2-containing protein.⁷² In fact, it has been demonstrated that increased phosphorylation on discrete serine or threonine sites in such proteins can evoke hampered insulin signaling, including impairment in PI3-K and protein kinase B (PKB) activation and in glucose transport.^{34,35} Interestingly, PKB is considered to be a central modulator in preventing apoptotic cell death. Indeed, increased PKB activity can promote cell survival during free radical exposure, oxidative stress, and beta-amyloid (A β) exposure, among others.^{73–77}

On the other hand, deficiencies in energy metabolism tipped by inhibition of insulin/IGF signaling increase oxidative stress.⁷⁸ For example, AD abnormalities are associated with inhibition of insulin/IGF-1 signaling, which negatively regulates glycogen synthase kinase 3 beta (GSK-3 β) via a PI3K-/Akt-dependent mechanism.³⁴ Furthermore, oxidative stress can trigger both GSK-3 β activation and an aberrant intraneuronal accumulation of hyperphosphorylated tau, thus contributing to neurodegeneration

underlying cognitive deficits.^{79,80} Another link between insulin and oxidative stress stems from impaired insulin-signaling activity acting unfavorably on the expression and translocation of NF- κ B, which is also a modulator of ROS production.⁸⁰

Brain: end-organ damage in type 2 diabetes mellitus

T2DM and cognitive deficits

The relationship between DM and cognitive dysfunction was proposed in 1922 by Miles and Root.⁸¹ There is an increasing body of neuropsychological studies showing brain structural changes and behavioral deficits,^{82–85} such as cognitive decrements,^{15,85} as well as learning and memory impairments,⁴ thus confirming this early proposal.⁴ Such cognitive impairments (that seem to be related to a chronic increase in intracellular glucose levels) are observed particularly in older diabetic adults, who apparently face a greater risk of vascular dementia.^{10,85–87} On the other hand, the differences in cognitive profile observed for both T1DM and T2DM suggest that SNC insulin-signaling impairment has a significant role in cerebral dysfunction.¹²

The hippocampus, an important player in learning and memory processes, was recently recognized as presenting a high degree of susceptibility to diabetes. Additionally, hippocampal damage and memory impairments are most probably the early brain complications of T2DM.⁹ Moreover, recent studies have found that specific verbal-memory impairments accompany hippocampal volume reductions among T2DM individuals.^{9,10} Coherently, diabetic animal models exhibit impairments in spatial learning in association with distinct changes in hippocampal synaptic plasticity.¹⁵ Additionally, increases in oxidative stress in rat hippocampus are associated with decreases in behavioral performance in hippocampal-dependent learning and memory tasks, such as the Morris water maze.^{60,61}

T2DM and neurodegenerative events

Diabetic and insulin-resistant subjects have been associated with a higher risk of developing such neurodegenerative diseases as AD, Parkinson's, and Huntington's disease.³⁴ For instance, midbrain dopaminergic neurons express transcription factors involved in β -cell development, such as Foxa2.⁸⁸ Furthermore, brain cells share common features with β -cells, such as high metabolic activity and low regeneration rate, which makes them extremely vulnerable to the environment and genetic effects. Apoptosis, which is one of the underlying mechanisms of numerous neurodegenerative diseases, can be

triggered by hyperglycemia and impaired insulin signaling in hippocampal neurons.^{89,90} Therefore, it is plausible to admit that neurodegenerative diseases and diabetic encephalopathy have a genetic and biochemical common ground.⁴

Alzheimer's disease – type 3 diabetes

AD is a neurological disorder characterized by profound memory loss and progressive cognitive and behavioral decline due to selective loss or dysfunction of neurons in specific brain regions/neural circuits, including the neocortex, hippocampus, and basal forebrain.^{90,91} Moreover, it is associated with consistent pathological findings, including intracellular neurofibrillary tangles (an accumulation of insoluble fibrous material, partly composed of an abnormally hyperphosphorylated form of tau protein) and extracellular senile plaques, mainly composed of aggregated A β protein, a cleaved product of amyloid precursor protein (APP).⁹² Somewhat surprisingly, both of these pathologic hallmarks of AD are also found in T2DM.⁹³ There are also other striking similarities between these two diseases, including elevated AGEs and oxidative stress, apoptosis-driven cellular injury, and impaired expression and activity of insulin-degrading enzyme, which is able to degrade both insulin and A β .^{94,95} Additionally, the increased incidence of this pathology in T2DM subjects seems to be related to hyperinsulinemia, insulin resistance, and hyperglycemia. Also, given that AD is usually accompanied by metabolic syndrome features such as hypercholesterolemia, hypertension, and obesity, this pathology is referred to as type 3 diabetes by some authors.^{35,96,97} In fact, large population studies confirm such an association between T2DM and AD.^{17,98} It has also been demonstrated that AD patients often have hyperinsulinemia and exhibit both peripheral and central IR and hyperglycemia.³⁵

This impaired insulin signaling is now thought to underlie diabetes-associated cognitive decline and dementia both by facilitating A β and tau protein accumulation and by exerting detrimental effects on neuronal function and survival.⁹⁴

In fact, there is clear evidence that hyperinsulinemia coupled with an insulin-resistant condition will foster an increment of extracellular A β by two independent mechanisms: (1) inhibition of extracellular degradation of A β by insulin-degrading enzyme or (2) stimulation of A β secretion by the enhancement of its trafficking from the endoplasmic reticulum and trans-Golgi network, the main site for A β generation, to the plasma membrane.³⁴ Therefore, these would enhance A β neurotoxicity and AD progression.⁹⁵

Neuroinflammation in type 2 diabetes mellitus

Chronic low-grade inflammation resulting from oxidative stress has been associated with the development and progression of T2DM.^{26,99} Furthermore, elevated levels of the proinflammatory cytokines tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6), and C-reactive protein have been shown in individuals with insulin resistance and diabetes.⁵³

Commonly, systemic inflammation exacerbates CNS inflammation and correlates with cognitive decline.⁸⁰ Recently, it was demonstrated that diabetic and obese mice (db/db) displayed impaired spatial-recognition memory (hippocampus-dependent task), which was associated with increased inflammatory cytokines (IL-1 β , TNF- α , and IL-6) and reduced expression of BDNF in the hippocampus. Interestingly, these animals also exhibited an increase in plasmatic IL-6 levels. These results strongly suggest an interaction between inflammation and memory impairment.¹⁰⁰

Along these lines, there is emerging evidence suggesting that inflammation and its consequent brain changes are key pathogenetic factors for neurodegenerative diseases, including AD.¹⁰¹ In fact, AD patients have elevated concentrations of IL-6, F₂-isoprostane (a lipid peroxidation marker) and TNF- α in CNS.^{102,103} Since TNF- α inhibits A β transport from brain to periphery, the increment in this cytokine may increase brain A β accumulation. There is also evidence for the role of specific cytokines in hippocampal neurodegeneration and cognitive loss. For example, sustained expression of IL-1 β in the hippocampus has been shown to impair long-term contextual and spatial memory in mice.¹⁰⁴

The triad composed of impaired insulin signaling, hyperglycemia, and increased free-fatty acids (which play a relevant role both in T2DM and in AD) triggers an inflammatory cascade essentially by two mechanisms: (1) a defective regulation of GSK-3 β (see section “Going from oxidative stress to insulin resistance and back again”)³⁵ and (2) activation of NF- κ B expression. On the other hand, proinflammatory cytokines, including TNF- α and IL-1 β , can further fuel NF- κ B signaling.¹⁰⁵ Finally, the AGE–RAGE axis also represents a key mediator of inflammation in both diseases.¹⁰⁶

Potential for anti-inflammatory and antioxidant therapeutics in diabetic encephalopathy

PPAR- γ agonists

The peroxisome proliferator-activated receptor (PPAR)- γ is a nuclear receptor that regulates fatty acid storage and

glucose metabolism by coordinating the expression of genes involved in lipid uptake, adipogenesis, and inflammation.¹⁰⁷ Thiazolidinediones, which are PPAR- γ agonists, appear as possible therapy to improve insulin sensitivity and reduce inflammatory markers, thus representing a putative anti-inflammatory strategy.¹⁰⁸ In fact, recently Pipatpiboon and colleagues demonstrated that rosiglitazone improved neuronal insulin receptor as well as brain mitochondria function in hippocampus from rats with insulin resistance induced by long-term high-fat diets.¹⁰⁸

PPAR- γ influences neuron survival through anti-inflammatory actions in the CNS.¹⁰⁹ For example, troglitazone inhibits A β -stimulated monocyte differentiation into macrophages, activation of microglia, and A β -stimulated expression of the cytokine genes *IL6*, *TNFA*, and *COX2*.¹¹⁰ However, PPAR- γ effects on A β processing and deposition are controversial. On one hand, some authors have reported that pioglitazone inhibits the secretion of A β induced by proinflammatory cytokines from neuroblastoma cells stably transfected with APP.¹¹¹ Additionally, rosiglitazone is currently in phase III clinical trials in AD patients on account of its efficacy on reducing A β pathology and inflammation.¹¹² Furthermore, this PPAR- γ was also shown to reduce tau phosphorylation through JNK inactivation in the hippocampus of rats with T2DM. On the other hand, others have found minimal effects of PPAR- γ activation (ciglitazone, prostaglandin J₂) on the reduction of A β secretion from cultured Chinese hamster ovary cells stably expressing APP751.¹¹³ Therefore, further studies are warranted to clarify the role of PPAR- γ on A β dynamics.

GLP-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that not only stimulates glucose-dependent insulin secretion and supports glucose homeostasis but also reduces the speed of nutrient absorption. Interestingly, GLP-1 shares with insulin growth factor-like properties and is neuroprotective. For example, GLP-1 and longer-lasting analogues (eg, liraglutide) protect neurons from apoptosis and oxidative stress, induce neurite outgrowth, protect synaptic plasticity and memory formation from A β detrimental effects, and reduce inflammatory response in brains of AD mouse models. Such peptides have two main advantages: not affecting blood sugar levels and crossing the BBB.¹¹⁵

Therefore, GLP-1 analogues that have been developed to treat T2DM can be envisioned as promising, novel treatment for AD or other neurodegenerative conditions. This is of major relevance to diabetic encephalopathy.¹¹⁴

C-peptide

Recent data suggest that insulin/C-peptide deficit may exert a key effect in diabetic encephalopathy, providing a basis for application of this peptide as a potentially effective therapy for DM and related complications.³⁶ In fact, its administration partially improves the deregulation of the IGF system in the brain (often associated with changes in insulin sensitivity) and prevents neuronal apoptosis in the hippocampus of diabetic patients.³² Furthermore, Sima and colleagues demonstrated that delivering C-peptide subcutaneously to a spontaneously diabetic animal model corrected the upregulation of RAGE and NF- κ B activation in hippocampus, with beneficial downstream effects on proinflammatory factors such as TNF- α and interleukins.³⁶ These findings are associated with a prevention of the proliferation of RAGE-positive astrocytes (glial cells that play a major role in synaptic transmission and energy supply) in hippocampus and prevention of deficits in spatial memory and learning.³⁶

GSK-3 β

Recently, GSK-3 β has been implicated as a key regulator of the inflammatory response.¹¹⁶ GSK-3 β is considered to be a therapeutic target for some neurodegenerative disorders, including AD, as its inhibition can increase cell survival during oxidative stress and inflammation.^{106,117} In recent decades, small-molecule inhibitors of GSK-3 β have been emerging as promising drug material for treatments against AD, diabetes, and cancer.¹¹⁸

Insulin: a putative antioxidant

Insulin was proposed as a neuroprotective agent against neurodegenerative diseases, where oxidative damage plays a major role.¹¹⁹ For example, Bélanger and colleagues suggested that the absence of cognitive and electrophysiological dysfunctions in ZDF rats (a T2DM model), might be due to protective action of hyperinsulinemia.¹¹⁸ However, there is conflicting information on its putative role as antioxidant.¹¹⁹ In fact, it was proposed that insulin per se or its signaling pathways can protect neurons against oxidative stress-induced apoptosis through Akt activation or GSK-3 β inhibition.³⁴ On the other hand, it was suggested that insulin has a dose-dependent dual role: (1) at low doses, it has anti-inflammatory effects during short-term inflammatory provocation, and (2) during chronic hyperinsulinemia or inflammation, it may exacerbate inflammatory responses and increase oxidative stress markers.¹²¹ These conflicting results on the effect of insulin as a possible antioxidant warrant further studies to cast light on this issue.¹²¹

Exercise

There are several studies that demonstrate that exercise targets many aspects of brain function, having broad effects on overall brain health. Learning and memory, protection from neurodegeneration, and alleviation of depression seem to be its main targets, particularly in elderly populations. The beneficial role of exercise might stem from its anti-inflammatory properties through modulating growth factors. In fact, BDNF, IGF-1 and vascular endothelial growth factor are the principal growth factors known to mediate the effects of exercise on the brain.¹²² Furthermore, exercise could attenuate levels of proinflammatory cytokine in AD brain by reducing the load of A β , which itself has proinflammatory effects.

Conclusion and future perspectives

The relationship of diabetic encephalopathy and AD is still a matter of intense debate. However, there is a growing body of evidence suggesting that T2DM is a setting where oxidative stress and brain inflammation engage in a spiraling and deleterious cross talk that leads to hippocampal damage and cognitive decline. This would underlie the increased incidence of AD in T2DM. One of the most promising avenues is to identify and biochemically characterize these early brain complications of T2DM, since it is when interventional therapy should have the greatest potential.

Several drugs have been developed to treat T2DM and may be instrumental to prevent the progression of AD in T2DM. For example, GLP-1 analogues, PPAR- γ agonists, C-peptide, and insulin should be particularly stressed as being promising candidates for successful pharmacological approaches to diabetic encephalopathy.

Disclosure

The authors declare no conflicts of interest in this work.

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