

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

Edna Soares  
Sara Nunes  
Flávio Reis  
Frederico C Pereira

Laboratory of Pharmacology and  
Experimental Therapeutics/IBILI,  
Coimbra University, Coimbra,  
Portugal

**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  $\beta$ -cells fail to secrete sufficient amounts of insulin to maintain normoglycemia and/or when (2) there is a resistance to insulin's actions.<sup>1,2</sup> The prevalence rates of DM have risen markedly in recent years (International Diabetes Federation [IDF]),<sup>3</sup> 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.<sup>4</sup> This in turn leads to an increased insulin release, followed by its inadequate secretion.<sup>5</sup> 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  $\beta$ -cell dysfunction, increased hepatic glucose production and increased IR, primarily in skeletal muscle.<sup>6</sup> 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.<sup>5,6</sup> In addition, people with metabolic syndrome have a fivefold-greater risk of developing T2DM.<sup>7</sup>

---

Correspondence: Frederico Pereira  
Laboratory of Pharmacology and  
Experimental Therapeutics, IBILI,  
Medicine Faculty, Sub-Unit I (Pólo III),  
Coimbra University, Coimbra 3000-548,  
Portugal  
Tel +351 239 480 071  
Fax +351 239 480 065  
Email fredcp@ci.uc.pt

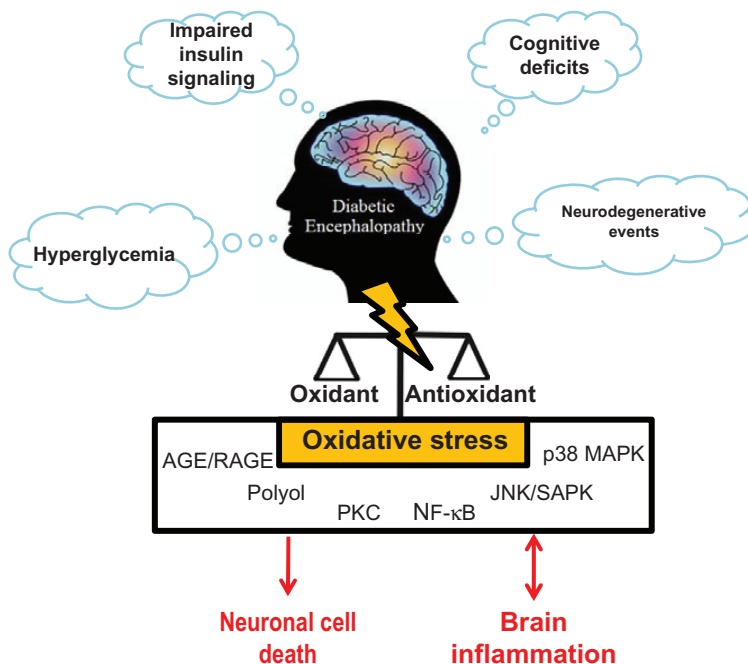
T2DM is associated with the occurrence of some complications, commonly divided into macrovascular – such as coronary artery disease, peripheral arterial disease, and stroke – and microvascular, such as diabetic nephropathy, neuropathy, and retinopathy.<sup>8</sup> There is accumulating evidence identifying the brain as a relevant site of T2DM damage, partly independent of atherosclerotic disease.<sup>9</sup> Central nervous system (CNS) lesions in T2DM subjects can be referred to as diabetic encephalopathy.<sup>11</sup> This relatively unknown DM complication is characterized by electrophysiological and structural CNS changes,<sup>11,12</sup> and diabetic encephalopathy together with chronic hyperglycemia and dyslipidemia compose the most relevant risk factors for cognitive dysfunction.<sup>4,13,14</sup> Indeed, several studies have established the relationship between T2DM and cognitive deficits,<sup>15,16</sup> showing an increased incidence of dementia.<sup>13,17</sup> 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).<sup>18–21</sup> 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.<sup>6</sup> However, a chronic increase in blood glucose levels, even in the absence of DM symptoms, will eventually lead to brain damage.<sup>1</sup> Thus, hyperglycemia-induced neurotoxicity is pointed out as one of the main causes of diabetic encephalopathy.<sup>6</sup> The advanced glycation end product (AGE)/AGE receptor (RAGE) axis and the polyol pathways may represent molecular mechanisms of glucose neurotoxicity.<sup>6,22,23</sup> 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- $\kappa$ 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, NH<sub>2</sub>-terminal Jun kinases/stress-activated protein kinases; MAPK, mitogen activated protein kinase; NF- $\kappa$ 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.<sup>1,24</sup> Finally, all these three pathways can either induce reactive oxygen species (ROS) or can be fueled by oxidative stress triggered by hyperglycemia.<sup>24–27</sup>

### AGE/RAGE pathway

AGE accumulation occurs through the CNS and is one of the consequences of poor glycemic control.<sup>23,28</sup> AGEs result from the nonenzymatic reaction between sugars and proteins, lipids, or nucleotides as a consequence of brain oxidative stress.<sup>29</sup> 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.<sup>13</sup> 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- $\kappa$ B), causing pathological changes in gene expression, including RAGE and inflammatory cytokines.<sup>30</sup> Additionally, increased RAGE expression is seen in brain regions affected by AD (including the hippocampus), and its overexpression accelerates AD pathology and cognitive impairment.<sup>20</sup> 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.<sup>26</sup>

### 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.<sup>24</sup> Furthermore, the aldose reductase pathway facilitates the generation of key potent glycation compounds, leading to an increase in AGEs and RAGE upregulation.<sup>31</sup> Additionally, stress-sensitive signaling pathways, including p38 mitogen-activated protein kinase (MAPK) and JNK, are strongly activated by sorbitol.<sup>24</sup>

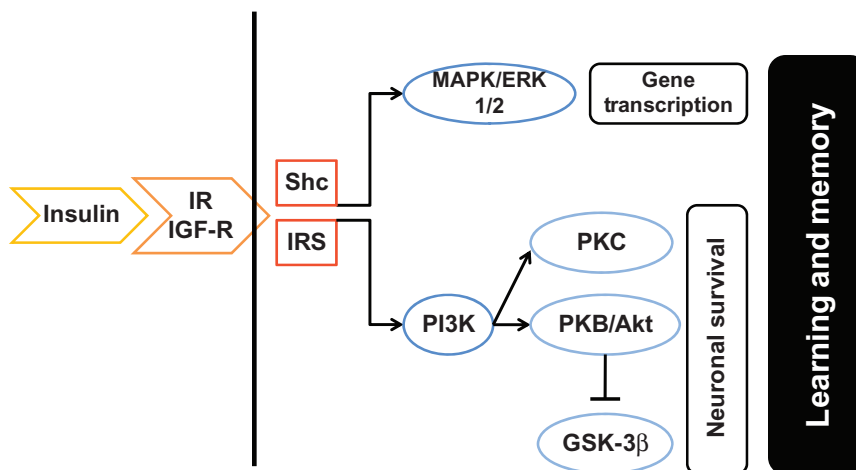
## Insulin-related mechanisms

Insulin is one of the most important anabolic hormones identified to date, since almost all cell types are sensitive to this peptide.<sup>18</sup> 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.<sup>33</sup> Furthermore, insulin plays a critical role in numerous mechanisms in the brain, such as metabolic, neurotrophic, neuromodulatory, and neuroendocrine,<sup>34</sup> as well as in memory and learning processes.<sup>35,36</sup> 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).<sup>37,38</sup> Once bound to these receptors, insulin triggers signaling cascades that include phosphoinositide 3-kinase (PI3K) and MAPK,<sup>39,40</sup> which are the most relevant ones involved in learning and memory processes (Figure 2).<sup>5,34,41</sup>

Brain insulin derives primarily from pancreatic  $\beta$ -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.<sup>42,43</sup> 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: insulinopenia) showed an increased saturable transport of insulin across the BBB.<sup>44</sup> 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.<sup>45</sup> 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.<sup>2,11</sup>

## 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.<sup>24</sup> 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.<sup>46–50</sup> 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.<sup>51</sup>



**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 $\beta$ , which is involved in the triggering of the apoptotic cascade.

**Abbreviations:** GSK-3 $\beta$ , 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.<sup>52,53</sup>

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  $\beta$ -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.<sup>54</sup> 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.<sup>55</sup>

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.<sup>56</sup> 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.<sup>57</sup>

Holloway et al demonstrated that raising plasma free fatty acids not only decreased myocardial phosphocreatine but also reduced cognition in healthy human subjects.<sup>58</sup> 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.<sup>59</sup>

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.<sup>60</sup> This is of relevance, since impaired neurogenesis has been associated with cognitive impairments and with diabetic encephalopathy.<sup>61,62</sup>

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.<sup>63</sup>

## Oxidative stress

Increased oxidative stress is usually accompanied by an augmented production of free radicals or impaired antioxidant defenses.<sup>64,65</sup> There is an increasing body of evidence indicating that oxidative stress induced by hyperglycemia and FFA causes insulin resistance,  $\beta$ -cell dysfunction, and late DM complications, thus playing a role in development as well as in progression and subsequent DM complications.<sup>26,53,66</sup> Furthermore, there is recent evidence suggesting a relationship between oxidative stress, cognitive decline, and neurodegenerative disorders (Figure 1).<sup>67–69</sup> 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- $\kappa$ B, p38 MAPK, JNK/stress-activated protein kinases, AGE/RAGE, and protein kinase C.<sup>26</sup> 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).<sup>26</sup> Among all these oxidative damage mechanisms, protein oxidation seems to be the most highly associated with cellular dysfunction underlying cognitive decline.<sup>69–71</sup>

## 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.<sup>72</sup> 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.<sup>34,35</sup> 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 $\beta$ ) exposure, among others.<sup>73–77</sup>

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

underlying cognitive deficits.<sup>79,80</sup> Another link between insulin and oxidative stress stems from impaired insulin-signaling activity acting unfavorably on the expression and translocation of NF- $\kappa$ B, which is also a modulator of ROS production.<sup>80</sup>

## 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.<sup>81</sup> There is an increasing body of neuropsychological studies showing brain structural changes and behavioral deficits,<sup>82–85</sup> such as cognitive decrements,<sup>15,85</sup> as well as learning and memory impairments,<sup>4</sup> thus confirming this early proposal.<sup>4</sup> 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.<sup>10,85–87</sup> 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.<sup>12</sup>

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.<sup>9</sup> Moreover, recent studies have found that specific verbal-memory impairments accompany hippocampal volume reductions among T2DM individuals.<sup>9,10</sup> Coherently, diabetic animal models exhibit impairments in spatial learning in association with distinct changes in hippocampal synaptic plasticity.<sup>15</sup> 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.<sup>60,61</sup>

### 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.<sup>34</sup> For instance, midbrain dopaminergic neurons express transcription factors involved in  $\beta$ -cell development, such as Foxa2.<sup>88</sup> Furthermore, brain cells share common features with  $\beta$ -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.<sup>89,80</sup> Therefore, it is plausible to admit that neurodegenerative diseases and diabetic encephalopathy have a genetic and biochemical common ground.<sup>4</sup>

### 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.<sup>90,91</sup> 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 $\beta$  protein, a cleaved product of amyloid precursor protein (APP).<sup>92</sup> Somewhat surprisingly, both of these pathologic hallmarks of AD are also found in T2DM.<sup>93</sup> 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 $\beta$ .<sup>94,95</sup> 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.<sup>35,96,97</sup> In fact, large population studies confirm such an association between T2DM and AD.<sup>17,98</sup> It has also been demonstrated that AD patients often have hyperinsulinemia and exhibit both peripheral and central IR and hyperglycemia.<sup>35</sup>

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

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

## Neuroinflammation in type 2 diabetes mellitus

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

Commonly, systemic inflammation exacerbates CNS inflammation and correlates with cognitive decline.<sup>80</sup> 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 $\beta$ , TNF- $\alpha$ , 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.<sup>100</sup>

Along these lines, there is emerging evidence suggesting that inflammation and its consequent brain changes are key pathogenetic factors for neurodegenerative diseases, including AD.<sup>101</sup> In fact, AD patients have elevated concentrations of IL-6, F<sub>2</sub>-isoprostane (a lipid peroxidation marker) and TNF- $\alpha$  in CNS.<sup>102,103</sup> Since TNF- $\alpha$  inhibits A $\beta$  transport from brain to periphery, the increment in this cytokine may increase brain A $\beta$  accumulation. There is also evidence for the role of specific cytokines in hippocampal neurodegeneration and cognitive loss. For example, sustained expression of IL-1 $\beta$  in the hippocampus has been shown to impair long-term contextual and spatial memory in mice.<sup>104</sup>

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 $\beta$  (see section “Going from oxidative stress to insulin resistance and back again”)<sup>35</sup> and (2) activation of NF- $\kappa$ B expression. On the other hand, proinflammatory cytokines, including TNF- $\alpha$  and IL-1 $\beta$ , can further fuel NF- $\kappa$ B signaling.<sup>105</sup> Finally, the AGE-RAGE axis also represents a key mediator of inflammation in both diseases.<sup>106</sup>

## Potential for anti-inflammatory and antioxidant therapeutics in diabetic encephalopathy

### PPAR- $\gamma$ agonists

The peroxisome proliferator-activated receptor (PPAR)- $\gamma$  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.<sup>107</sup> Thiazolidinediones, which are PPAR- $\gamma$  agonists, appear as possible therapy to improve insulin sensitivity and reduce inflammatory markers, thus representing a putative anti-inflammatory strategy.<sup>108</sup> 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.<sup>108</sup>

PPAR- $\gamma$  influences neuron survival through anti-inflammatory actions in the CNS.<sup>109</sup> For example, troglitazone inhibits A $\beta$ -stimulated monocyte differentiation into macrophages, activation of microglia, and A $\beta$ -stimulated expression of the cytokine genes *IL6*, *TNFA*, and *COX2*.<sup>110</sup> However, PPAR- $\gamma$  effects on A $\beta$  processing and deposition are controversial. On one hand, some authors have reported that pioglitazone inhibits the secretion of A $\beta$  induced by proinflammatory cytokines from neuroblastoma cells stably transfected with APP.<sup>111</sup> Additionally, rosiglitazone is currently in phase III clinical trials in AD patients on account of its efficacy on reducing A $\beta$  pathology and inflammation.<sup>112</sup> Furthermore, this PPAR- $\gamma$  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- $\gamma$  activation (ciglitazone, prostaglandin J<sub>2</sub>) on the reduction of A $\beta$  secretion from cultured Chinese hamster ovary cells stably expressing APP751.<sup>113</sup> Therefore, further studies are warranted to clarify the role of PPAR- $\gamma$  on A $\beta$  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 $\beta$  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.<sup>115</sup>

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.<sup>114</sup>

## 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.<sup>36</sup> 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.<sup>32</sup> Furthermore, Sima and colleagues demonstrated that delivering C-peptide subcutaneously to a spontaneously diabetic animal model corrected the upregulation of RAGE and NF- $\kappa$ B activation in hippocampus, with beneficial downstream effects on proinflammatory factors such as TNF- $\alpha$  and interleukins.<sup>36</sup> 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.<sup>36</sup>

## GSK-3 $\beta$

Recently, GSK-3 $\beta$  has been implicated as a key regulator of the inflammatory response.<sup>116</sup> GSK-3 $\beta$  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.<sup>106,117</sup> In recent decades, small-molecule inhibitors of GSK-3 $\beta$  have been emerging as promising drug material for treatments against AD, diabetes, and cancer.<sup>118</sup>

## Insulin: a putative antioxidant

Insulin was proposed as a neuroprotective agent against neurodegenerative diseases, where oxidative damage plays a major role.<sup>119</sup> 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.<sup>118</sup> However, there is conflicting information on its putative role as antioxidant.<sup>119</sup> 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 $\beta$  inhibition.<sup>34</sup> 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.<sup>121</sup> These conflicting results on the effect of insulin as a possible antioxidant warrant further studies to cast light on this issue.<sup>121</sup>

## 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.<sup>122</sup> Furthermore, exercise could attenuate levels of proinflammatory cytokine in AD brain by reducing the load of A $\beta$ , 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- $\gamma$  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.

## References

- Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. *Diabetes Care*. 1990;13:610–630.
- Saltiel A. New perspectives into the molecular pathogenesis and treatment of type 2 diabetes. *Cell*. 2001;104:517–529.
- Idf.org [homepage on the Internet]. International Diabetes Federation: IDF Diabetes Atlas, 5th edn. Brussels, Belgium [updated 2011]. Available from: <http://www.idf.org/diabetesatlas>. Accessed on Aug 7, 2012.
- Ristow M. Neurodegenerative disorders associated with diabetes mellitus. *J Mol Med (Berl)*. 2004;82:510–529.
- van der Heide LP, Remarkers GMJ, Marten PS. Insulin signaling in the central nervous system: learning to survive. *Prog Neurobiol*. 2006;79:205–221.
- McCall AL. Cerebral glucose metabolism in diabetes mellitus. *Eur J Pharmacol*. 2004;490:147–158.
- Eckel Robert H. Mechanisms of the components of the metabolic syndrome that predispose to diabetes and atherosclerotic CVD. *Proc Nutr Soc*. 2007;66:82–95.
- Stratton I, Adler A, Neil A, et al. Prospective association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405–412.
- Gold S, Dziobek I, Sweat V, et al. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia*. 2007;50:711–719.
- Bruehl H, Wolf OT, Sweat V, Tirsi A, Richardson S, Convit A. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. *Brain Res*. 2009;1280:186–194.
- Mijnhout GS, Scheltens P, Diamant M, et al. Diabetic encephalopathy: a concept in need of a definition. *Diabetologia*. 2006;49:1447–1448.
- Brands A, Kessels R, de Haan E, Kappelle LJ, Biessels GJ. Cerebral dysfunction in type I diabetes: effects of insulin, vascular risk factors and blood-glucose levels. *Eur J Pharmacol*. 2004;490:159–168.
- Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol*. 2006;5:64–74.
- Hernández-Fonseca J, Rincón J, Pedrañez A, et al. Structural and ultrastructural analysis of cerebral cortex, cerebellum, and hypothalamus from diabetic rats. *Exp Diabetes Res*. 2009;2009:329632.
- Gispén WH, Biessels GJ. Cognition and synaptic plasticity in diabetes mellitus. *Trends Neurosci*. 2000;23:542–549.
- McNay EC and Recknagel AK. Brain insulin signaling: a key component of cognitive processes and a potential basis for cognitive impairment in type 2 diabetes. *Neurobiol Learn Mem*. 2011;96:432–442.
- Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam study. *Neurology*. 1999;53:1937–1942.
- Sima AAF, Zhan W, Kreipk CW, et al. Inflammation in diabetic encephalopathy is prevented by C-peptide. *Rev Diabet Stud*. 2009;6:37–42.
- Maiese K, Morhan SD, Chong ZZ. Oxidative stress biology and cell injury during type 1 and type 2 diabetes mellitus. *Curr Neurovasc Res*. 2007;4:63–71.
- Sima AA. Encephalopathies: the emerging diabetic complications. *Acta Diabetol*. 2010;47(4):279–293.
- Böni-Schnetzler M, Donath MY. How biologics targeting the IL-1 system are being considered for the treatment of type 2 diabetes. *Br J Clin Pharmacol*. Epub April 17, 2012.
- Baynes JW. Role of oxidative stress in development of complications in diabetes. *Diabetes*. 1991;40:405–412.
- Brownlee M. Negative consequences of glycation. *Metabolism*. 2000;49:9–13.
- Tomlinson D, Gardiner N. Glucose neurotoxicity. *Nature*. 2008;9:36–43.
- Folli F, Corradi D, Fanti P, et al. The role of oxidative stress in the pathogenesis of type 2 diabetes mellitus micro- and macrovascular complications: avenues for a mechanistic-based therapeutic approach. *Curr Diabetes Rev*. 2011;7:313–324.
- Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr Rev*. 2002;23:599–622.
- Giardino I, Edelstein D, Brownlee M. BCL-2 expression or antioxidants prevent hyperglycemia-induced formation of intracellular advanced glycation end products in bovine endothelial cell. *J Clin Invest*. 1996;97:1422–1428.
- Toth C, Martinez J, Zochodne D. RAGE, diabetes, and the nervous system. *Curr Mol Med*. 2007;7:1–11.
- Vincent A, Perrone L, Sullivan K, et al. Receptor for advanced glycation end products activation injures primary sensory neurons via oxidative stress. *Endocrinology*. 2007;148:548–558.



30. Bierhaus A, Humpert PM, Morcos M, et al. Understanding RAGE, the receptor for advanced glycation end products. *J Mol Med.* 2005;83: 876–886.
31. Gabbay KH, Merola LO, Field RA. Sorbitol pathway: presence in nerve and cord with substrate accumulation in diabetes. *Science.* 1966;151: 209–210.
32. Fulop T, Larbi A, Douziche N. Insulin receptor and aging. *Pathol Biol (Paris).* 2003;51:574–580.
33. Adamo M, Raizada MK, LeRoith D. Insulin and insulin-like growth factor receptors in the nervous system. *Mol Neurobiol.* 1989;3:71–100.
34. Cardoso S, Correia S, Santos R, et al. Insulin is a two-edged knife on the brain. *J Alzheimers Dis.* 2009;18:483–507.
35. de la Monte SM. Insulin resistance and Alzheimer's disease. *BMB Rep.* 2009;42:475–481.
36. Sima AA, Zhang W, Kreipke CW, Rafols JA, Hoffman WH. Inflammation in diabetic encephalopathy is prevented by C-peptide. *Rev Diabet Stud.* 2009;6:37–42.
37. Havrankova J, Roth J, Brownstein M. Insulin receptors are widely distributed in the central nervous system of the rat. *Nature.* 1978;272: 827–829.
38. Plum L, Schubert M, Bruning J. The role of insulin receptor signaling in the brain. *Trends Endocrinol Metab.* 2005;16:59–65.
39. Gasparini L, Xu H. Potential roles of insulin and IGF-1 in Alzheimer's disease. *Trends Neurosci.* 2003;26:404–406.
40. Wada A, Yokoo H, Yanagita T, Kobayashi H. New twist on neuronal insulin receptor signaling in health, disease, and therapeutics. *J Pharmacol Sci.* 2005;99:128–143.
41. Huang C, Lee C, Hsu K. The role of insulin receptor signaling in synaptic plasticity and cognitive function. *Chang Gung Med J.* 2010; 33:115–125.
42. Banks W, Jaspán J, Huang W, Kastin A. Transport of insulin across the blood brain barrier: saturability at euglycemic doses of insulin. *Peptides.* 1997;18:1423–1429.
43. Wallum BJ, Taborsky GJ Jr, Porte D Jr, et al. Cerebrospinal fluid insulin levels increase during intravenous insulin infusions in man. *J Clin Endocrinol Metab.* 1987;64:1190–1194.
44. Banks WA. The source of cerebral insulin. *Eur J Pharmacol.* 2004;490:5–12.
45. Kuwabara T, Kagalwala MN, Onuma Y, et al. Insulin biosynthesis in neuronal progenitors derived from adult hippocampus and the olfactory bulb. *EMBO Mol Med.* 2011;3:742–754.
46. Obici S, Feng Z, Morgan K, Stein D, Karkanias G, Rossetti L. Central administration of oleic acid inhibits glucose production and food intake. *Diabetes.* 2002;51:271–275.
47. López M, Lelliott CJ, Vidal-Puig A. Hypothalamic fatty acid metabolism: a housekeeping pathway that regulates food intake. *Bioessays.* 2007;29:248–261.
48. López M, Lage R, Saha AK, et al. Hypothalamic fatty acid metabolism mediates the orexigenic action of ghrelin. *Cell Metab.* 2008;7: 389–399.
49. Lam TK, Schwartz GJ, Rossetti L. Hypothalamic sensing of fatty acids. *Nat Neurosci.* 2005;8:579–584.
50. Poci A, Lam TK, Obici S, et al. Restoration of hypothalamic lipid sensing normalizes energy and glucose homeostasis in overfed rats. *J Clin Invest.* 2006;116:1081–1091.
51. Karmi A, Iozzo P, Viljanen A, et al. Increased brain fatty acid uptake in metabolic syndrome. *Diabetes.* 2010;59:2171–2177.
52. Bachmann OP, Dahl DB, Brechtel K, et al. Effects of intravenous and dietary lipid challenge on intramyocellular lipid content and the relation with insulin sensitivity in humans. *Diabetes.* 2001;50: 2579–2584.
53. Schenk S, Horowitz JF. Acute exercise increases triglyceride synthesis in skeletal muscle and prevents fatty acid-induced insulin resistance. *J Clin Invest.* 2007;117:1690–1698.
54. Martins AR, Nachbar RT, Gorjao R, et al. Mechanisms underlying skeletal muscle insulin resistance induced by fatty acids: importance of the mitochondrial function. *Lipids Health Dis.* 2012;11:30.
55. Martínez de Morentin PB, González CR, López M. AMP-activated protein kinase: 'a cup of tea' against cholesterol-induced neurotoxicity. *J Pathol.* 2010;222:329–334.
56. Karczewska-Kupczewska M, Kowalska I, Nikolajuk A, et al. Circulating brain-derived neurotrophic factor concentration is downregulated by intralipid/heparin infusion or high-fat meal in young healthy male subjects. *Diabetes Care.* 2012;35:358–362.
57. Montine TJ, Morrow JD. Fatty acid oxidation in the pathogenesis of Alzheimer's disease. *Am J Pathol.* 2005;166:1283–1289.
58. Holloway CJ, Cochlin LE, Emmanuel Y, et al. A high-fat diet impairs cardiac high-energy phosphate metabolism and cognitive function in healthy human subjects. *Am J Clin Nutr.* 2011;93: 748–755.
59. Charradi K, Elkahoui S, Karkouch I, Limam F, Hassine FB, Aouani E. Grape seed and skin extract prevents high-fat diet-induced brain lipotoxicity in rat. *Neurochem Res.* Epub June 9, 2012.
60. Park HR, Park M, Choi J, Park KY, Chung HY, Lee J. A high-fat diet impairs neurogenesis: involvement of lipid peroxidation and brain-derived neurotrophic factor. *Neurosci Lett.* 2010;482: 235–239.
61. Rodríguez JJ, Jones VC, Tabuchi M, et al. Impaired adult neurogenesis in the dentate gyrus of a triple transgenic mouse model of Alzheimer's disease. *PLoS One.* 2008;3:e2935.
62. Fazeli SA. Neuroprotection in diabetic encephalopathy. *Neurodegener Dis.* 2009;6:213–218.
63. Scherer T, O'Hare J, Diggins-Andrews K, et al. Brain insulin controls adipose tissue lipolysis and lipogenesis. *Cell Metab.* 2011;13: 183–194.
64. Baynes JW. Role of oxidative stress in development of complications in diabetes. *Diabetes.* 1991;40:405–412.
65. Saxena AK, Srivastava P, Kale RK, Baquer NZ. Impaired antioxidant status in diabetic rat liver. Effect of vanadate. *Biochem Pharmacol.* 1993;45(3):539–542.
66. Ceriello A. Oxidative stress and glycemic regulation. *Metabolism.* 2000;49:27–29.
67. Moreira PI, Santos MS, Oliveira CR, et al. Alzheimer disease and the role of free radicals in the pathogenesis of the disease. *CNS Neurol Disord Drug Targets.* 2008;7:3–10.
68. Su B, Wang X, Nunomura A, et al. Oxidative stress signaling in Alzheimer's disease. *Curr Alzheimer Res.* 2004;5:525–532.
69. Smith CD, Carney JM, Starke-Reed PE, et al. Excess brain protein oxidation and enzyme dysfunction in normal aging and in Alzheimer disease. *Proc Natl Acad Sci U S A.* 1991;88:10540–10543.
70. Sohal RS. Role of oxidative stress and protein oxidation in the aging process. *Free Radic Biol Med.* 2002;33:37–44.
71. Dalle-Donne I, Rossi R, Giustarini D, Milzani A, Colombo R. Protein carbonyl groups as biomarkers of oxidative stress. *Clin Chim Acta.* 2003;329:23–38.
72. Kyriakis JM, Avruch J. Sounding the alarm: protein kinase cascades activated by stress and inflammation. *J Biol Chem.* 1996;271: 24313–24316.
73. Paz K, Hemi R, Le Roith D, et al. A molecular basis for insulin resistance. Elevated serine/threonine phosphorylation of IRS-1 and IRS-2 inhibits their binding to the juxtamembrane region of the insulin receptor and impairs their ability to undergo insulin-induced tyrosine phosphorylation. *J Biol Chem.* 1997;272:29911–29918.
74. Qiao LY, Goldberg JL, Russell JC, Sun XJ. Identification of enhanced serine kinase activity in insulin resistance. *J Biol Chem.* 1999;274:10625–10632.
75. Chong ZZ, Kang JQ, Maiese K. Erythropoietin fosters both intrinsic and extrinsic neuronal protection through modulation of microglia, Akt1, Bad, and caspase-mediated pathways. *Br J Pharmacol.* 2003;138:1107–1118.
76. Kang JQ, Chong ZZ, Maiese K. Akt1 protects against inflammatory microglial activation through maintenance of membrane asymmetry and modulation of cysteine protease activity. *J Neurosci Res.* 2003; 74:37–51.

77. Martín D, Salinas M, López-Valdaliso R, Serrano E, Recuero M, Cuadrado A. Effect of the Alzheimer amyloid fragment Aβ<sub>25–35</sub> on Akt/PKB kinase and survival of PC12 cells. *J Neurochem*. 2001;78:1000–1008.
78. Hoyer S, Lee SK, Löffler T, Schliebs R. Inhibition of the neuronal insulin receptor. An in vivo model for sporadic Alzheimer disease? *Ann N Y Acad Sci*. 2009;920:256–258.
79. Chen GJ, Xu J, Lahousse SA, Caggiano NL, de la Monte SM. Transient hypoxia causes Alzheimer-type molecular and biochemical abnormalities in cortical neurons: potential strategies for neuroprotection. *J Alzheimers Dis*. 2003;5:209–228.
80. Sima AA. Encephalopathies: the emerging diabetic complications. *Acta Diabetol*. 2010;47:279–293.
81. Miles WR, Root HF. Psychologic tests applied in diabetic patients. *Arch Intern Med*. 1922;30:767–777.
82. Strachan M, Deary I, Ewing F, Frier B. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care*. 1997;20:438–445.
83. Biessels G, van der Heide L, Kamal A, Bleys R, Gispen W. Ageing and diabetes: implications for brain function. *Eur J Pharmacol*. 2002;441:1–14.
84. Winocur G, Greenwood C, Piroli G, et al. Memory impairment in obese Zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity. *Behav Neurosci*. 2005;119:1389–1395.
85. Reijmer Y, van den Berg E, Ruis C, Kappelle L, Biessels G. Cognitive dysfunction in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2010;26:507–519.
86. Hayashi K, Kurioka S, Yamaguchi T, et al. Association of cognitive dysfunction with hippocampal atrophy in elderly Japanese patients with type 2 diabetes. *Diab Res Clin Pract*. 2011;94:180–185.
87. Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *J Clin Exp Neuropsychol*. 2004;26:1044–1080.
88. Ang SL. Foxa1 and Foxa2 transcription factors regulate differentiation of midbrain dopaminergic neurons. *Adv Exp Med Biol*. 2009;651:58–65.
89. Anarkooli I, Sankian M, Ahmadpour S, Varasteh A, Haghiri H. Evaluation of Bcl-2 family gene expression and caspase-3 activity in hippocampus STZ-induced diabetic rats. *Exp Diabetes Res*. 2008;2008:638467.
90. Braak H, Braak E, Bohl J. Staging of Alzheimer-related cortical destruction. *Eur Neurol*. 1993;33:403–408.
91. Mattson MP. Pathways towards and away from Alzheimer's disease. *Nature*. 2004;430:631–639.
92. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297:353–356.
93. Glabe CG. Common mechanisms of amyloid oligomer pathogenesis in degenerative disease. *Neurobiol Aging*. 2006;27:570–575.
94. Neumann KF, Rojo L, Navarrete LP, Farias G, Reyes P, Maccioni RB. Insulin resistance and Alzheimer's disease: molecular links and clinical implications. *Curr Alzheimer Res*. 2008;5:438–447.
95. Farris W, Mansourian S, Chang Y, et al. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proc Natl Acad Sci U S A*. 2003;100:4162–4167.
96. Li L, Hölscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. *Brain Res Rev*. 2007;56:384–402.
97. Kroner Z. The relationship between Alzheimer's disease and diabetes: type 3 diabetes? *Altern Med Rev*. 2009;14:373–379.
98. Leibson CL, Rocca WA, Hanson VA, et al. The risk of dementia among persons with diabetes mellitus: a population-based cohort study. *Ann N Y Acad Sci*. 1997;826:422–427.
99. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol*. 2009;6:399–409.
100. Dinel AL, André C, Aubert A, Ferreira G, Layé S, Castanon N. Cognitive and emotional alterations are related to hippocampal inflammation in a mouse model of metabolic syndrome. *PLoS One*. 2011;6:e24325.
101. Leonard BE, Myint A-M. Inflammation and depression: is there a causal connection with dementia? *Neurotox Res*. 2006;10:149–160.
102. Montine TJ, Kaye JA, Montine KS, McFarland L, Morrow JD, Quinn JF. Cerebrospinal fluid Aβ<sub>42</sub>, tau, and f<sub>2</sub>-isoprostane concentrations in patients with Alzheimer disease, other dementias, and in age-matched controls. *Arch Pathol Lab Med*. 2001;125:510–512.
103. Tarkowski E, Blennow K, Wallin A, Tarkowski A. Intracerebral production of tumor necrosis factor-α, a local neuroprotective agent, in Alzheimer disease and vascular dementia. *J Clin Immunol*. 1999;19:223–230.
104. Moore AH, Wu M, Shaftel SS, Graham KA, O'Banion MK. Sustained expression of interleukin-1β in mouse hippocampus impairs spatial memory. *Neuroscience*. 2009;164:1484–1495.
105. Barnes PJ, Karin M. Nuclear factor-κB: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med*. 1997;336:1066–1071.
106. Bhat NR. Linking cardiometabolic disorders to sporadic AD: a perspective on potential mechanisms and mediators. *J Neurochem*. 2010;115:551–562.
107. Whitehead JP. Diabetes: new conductors for the peroxisome proliferator-activated receptor γ (PPARγ) orchestra. *Int J Biochem Cell Biol*. 2011;43:1071–1074.
108. Pipatpiboon N, Pratchayasakul W, Chattipakorn N, Chattipakorn SC. PPARγ agonist improves neuronal insulin receptor function in hippocampus and brain mitochondria function in rats with insulin resistance induced by long term high-fat diets. *Endocrinology*. 2012;153:329–338.
109. Watson GS, Craft S. Insulin resistance, inflammation, and cognition in Alzheimer's disease: lessons for multiple sclerosis. *J Neurol Sci*. 2006;245:21–33.
110. Combs CK, Johnson DE, Karlo JC, Cannady SB, Landreth GE. Inflammatory mechanisms in Alzheimer's disease: inhibition of beta-amyloid-stimulated pro-inflammatory responses and neurotoxicity by PPARγ agonists. *J Neurosci*. 2000;20:558–567.
111. Sastre M, Dewachter I, Landreth GE, et al. Nonsteroidal anti-inflammatory drugs and peroxisome proliferator-activated receptor-γ agonists modulate immunostimulated processing of amyloid precursor protein through regulation of beta-secretase. *J Neurosci*. 2003;23:9796–9804.
112. Yoon SY, Park JS, Choi JE, et al. Rosiglitazone reduces tau phosphorylation via JNK inhibition in the hippocampus of rats with type 2 diabetes and tau transfected SH-SY5Y cells. *Neurobiol Dis*. 2010;40:449–455.
113. Sagi SA, Weggen S, Eriksen J, Golde TE, Koo EH. The non-cyclooxygenase targets of non-steroidal anti-inflammatory drugs, lipoxigenases, peroxisome proliferator-activated receptor, inhibitor of kappa B kinase, and NF kappa B, do not reduce amyloid beta 42 production. *J Biol Chem*. 2003;278:31825–31830.
114. Hölscher C. The role of GLP-1 in neuronal activity and neurodegeneration. *Vitam Horm*. 2010;84:331–354.
115. Ramirez SH, Fan S, Zhang M, et al. Inhibition of glycogen synthase kinase 3β (GSK3β) decreases inflammatory responses in brain endothelial cells. *Am J Pathol*. 2010;176:881–892.
116. Balaraman Y, Limaye AR, Levey AI, Srinivasan S. Glycogen synthase kinase 3β and Alzheimer's disease: pathophysiological and therapeutic significance. *Cell Mol Life Sci*. 2006;63:1226–1235.
117. Jacobs KM, Bhawe SR, Ferraro DJ, Jaboin JJ, Hallahan DE, Thotala D. GSK-3β: a bifunctional role in cell death pathways. *Int J Cell Biol*. 2012;2012:930710.
118. Schmidt RE, Dorsey DA, Beaudet LN, Peterson RG. Analysis of the Zucker diabetic fatty (ZDF) type 2 diabetic rat model suggests a neurotrophic role for insulin/IGF-I in diabetic autonomic neuropathy. *Am J Pathol*. 2003;163:21–28.

119. Bélanger A, Lavoie N, Trudeau F, Massicotte G, Gagnon S. Preserved LTP and water maze learning in hyperglycaemic-hyperinsulinemic ZDF rats. *Physiol Behav.* 2004;83:483–494.
120. Krogh-Madsen R, Plomgaard P, Keller P, Keller C, Pedersen BK. Insulin stimulates interleukin-6 and tumor necrosis factor- $\alpha$  gene expression in human subcutaneous adipose tissue. *Am J Physiol Endocrinol Metab.* 2004;286:E234–E238.
121. Bender K, Newsholme P, Brennan L, Maechler P. The importance of redox shuttles to pancreatic  $\beta$ -cell energy metabolism and function. *Biochem Soc Trans.* 2006;34:811–814.
122. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci.* 2007;30:464–472.

### International Journal of Interferon, Cytokine and Mediator Research

Dovepress

#### Publish your work in this journal

The International Journal of Interferon, Cytokine and Mediator Research is an international, peer-reviewed, open-access, online journal. The focus of the journal is to publish original research, reports, editorials, reviews and commentaries on all aspects of interferon, cytokine and mediators of inflammation from labora-

tory science to therapeutic indications and clinical studies. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/international-journal-of-interferon-cytokine-and-mediator-research-journal>