Review

CrossM.

other hand, patients with AD more frequently present an impaired glucose metabolism or T2DM [11]. These observations raise questions thus far unanswered: whether T2DM is a cause, consequence, or compensatory counterregulation to neurodegeneration, and whether neuronal insulin resistance indeed represents a risk factor for AD? Alternative mechanisms might be directly related to insulin/IGF-1 signaling, suggesting a common pathogenic cerebral signaling pathway in T2DM and neurodegeneration, including AD.

On a molecular level, several targets of the insulin machinery with potential in uence on the development of neurodegenerative disease have been identi ed. Insulin and IGF-1 have intense effects in the CNS, regulating key processes such as energy homeostasis, neuronal survival, longevity, learning and memory [12,13]. Insulin and IGF-1 bind to the tyrosine kinase receptors, IR, and IGF-1R, which share a high degree of identity in their structure and function [12,13]. IR and IGF-1R are selectively distributed in the brain with a higher density in the olfactory bulb, hypothalamus, as well as in two of the main brain areas affected by AD pathology, i.e., hippocampus and cerebral cortex [12,13]. Binding of insulin or IGF-1 induces a conformational change of the receptor leading to their auto-phosphorylation on speci c tyrosine residues on the -subunit with the consequent recruitment of the insulin receptor substrate-1 (IRS-1) [12,13]. This latter, in turn, activates two main signaling pathways: (i) the PI3K pathway, which, among other functions, is involved in the maintenance of synaptic plasticity and memory consolidation [14], A -induced memory loss [15], and synthesis of nitric oxide (NO), which in turn plays a role in learning and memory processes [16]; and (ii) the MAPK cascade, which is responsible both for the induction of several genes required for neuronal and synapse growth, maintenance and repair processes, as well as serving as a modulator of hippocampal synaptic plasticity that underlies learning and memory [3]. Importantly, neurons are vulnerable to excitotoxic stress, and with some notable exceptions, there is a slow rate of neurogenesis in the brain. Hence, neurons remain post-mitotic, and any increased stress or reduced repair mechanism can accumulate over time. The impairment of insulin signaling in the brain could well play a role in the development of neurodegenerative disorders, as it leaves neurons more exposed to toxic in uences.

2. Insulin resistance: a cross-talk between AD and T2DM

Insulin resistance is clinically de ned as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population [17]. Historically, insulin was long considered to be a hormone that primarily exerts its in uence in the periphery [18]. While in the past years, the signaling mechanism and the biological effects of insulin have been studied mainly in classical insulin target tissues, such as skeletal muscle, fat and liver, with respect to glucose uptake, regulation of cell proliferation, gene expression and the suppression of hepatic glucose production, recently, it has become clear that insulin also produces similar effects in the central nervous system (CNS). Indeed, insulin is a peptide secreted by pancreatic beta cells and is readily transported into the CNS across the blood brain barrier (BBB) by a saturable, receptor-mediated process [19,20]. Here, insulin binds to and activates the IR (Fig. 1), that is, as cited above, widely distributed in the brain [21..23].

In 1978, Havrankova et al. showed that insulin is present in rat brain in high concentration, and it is independent of peripheral insulin levels [24]. Thus, although pancreatic-derived insulin crosses the BBB and reaches the brain, a portion of the insulin in the CNS is locally produced, based on the detection of c-peptide (which is an integral part of the proinsulin molecule) and insulin mRNA in the brain [25].

Due to the well-known role of insulin in learning and memory processes[25..27]

or organelle membranes directly (e.g., through lipid peroxidation), or reacting with metals, nitrogen or carbon to form intermediates that react with proteins (e.g., through nitration, carbonylation, nitrosylation or reactive alkenals by Michael addition) [48,49]. Oxidation of amino acids can lead to the formation of advanced glycation end products (AGEs), advanced oxidation protein products (AOPPs), peroxides and

Several studies were conducted on murine models to demonstrate that mitochondrial failure may represent a functional link between both pathologies. A study on a rat model of sporadic AD generated by the intracerebroventricular (icv) injection of a sub-diabetogenic dose of streptozotocin (STZ) demonstrated that the insulin-resistant brain state is accompanied by the occurrence of mitochondrial abnormalities [63], while STZ-induced T1DM rats showed no signi cant changes in mitochondrial function and synaptic integrity as result of compensation mechanisms, although reverted by insulin administration [64]. The comparison 3xTg-AD mice with sucrose-treated WT mice reported by Carvalho and colleagues [65] showed a similar impairment of mitochondrial respiratory chain and phosphorylation system, as well as oxidative imbalance and increased A levels, consistent with the notion that mitochondrial metabolic alterations associated with diabetes contribute to the development of AD-like pathologic features. In agreement with this notion, comparison of 11-month-old T2D and AD mice showed, in addition to increased A levels, similar behavioral and cognitive anomalies characterized by increased fear and anxiety and decreased learning and memory abilities [66]. In addition, diabetic and non-diabetic rats infused with A had both profound decreased energy intake, activity and fat oxidation and increased carbohydrate oxidation and energy expenditure; however, these effects were aggravated by 10% to 20% in the diabetic rat group [67].

In a recent study on microvascular endothelial cells from rat

oxidative damage. Strong indications suggest that OS occurs before the onset of symptoms in AD and that oxidative damage is found before robust A plaque formation, supporting a causative role of mitochondrial dysfunction and OS in AD [42,46,105]. Within this context, data supporting protein oxidation in the presence of insulin resistance and reduced glucose utilization suggest the potential presence of a vicious cycle among these events that eventually culminate with AD pathology (Fig. 1). Consistent with this notion, studies on T2DM subjects demonstrated increased levels of PCO AOPPs, AGEs, oxLDL, 8-OHdG, MDA, NOx, and insulin resistance compared with control together with a signi cant drop in plasma \ SH groups, free radical scavenging capacity and de cits in the antioxidant defenscj /T1_T*yHs andamin

long-term diabetic users of metformin [155,156], thus questioning the effective protective role for this drug. Consequently, both pre-clinical and clinical of metformin suggest that further investigations are necessary to fully determine whether thus mTOR inhibition has promise in treatment AD patients with diabetes.

4.2. Sulfony(s)s.

[198] . The results showed that in severe hypoglycemia (serum glucose concentration below 1.0 mM) the lipoperoxidation in brain tissue expressed as the level of MDA was higher in comparison with normoglycemic controls (glycemia around 3.7 mM) as well as in comparison with the levels of MDA during moderate hypoglycemia (glycemia ranging between 1 and 2 mM). This indicates the enhance-

Saxagliptin (0.25, 0.5 and 1 mg/kg, for 60 d) exerted complete rever-

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