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Diabetes drugs in the fight against Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most prevalent form of dementia, particularly in old age subjects. Hyperinsulinemia and insulin resistance, which are known as pathophysiological features of Type 2 Diabetes Mellitus (T2DM), have also been demonstrated to have a significant impact on cognitive impairment. Studies have shown that an altered insulin pathway may interact with amyloid-β protein deposition and tau protein phosphorylation, both leading factors for AD development. Drugs used for T2DM treatment from insulin and metformin through dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists may represent a promising approach to fight AD. With this review from animal to human studies, we aim at responding to the reasons why drugs for diabetes may represent potential treatments for AD.

1. Introduction

Alzheimer's Disease (AD) and Type 2 Diabetes Mellitus (T2DM) undoubtedly represent two of the most prevalent disorders affecting old age subjects. AD is the most prevalent major neurocognitive disorder and the most common cause of dementia in the old population, accounting for 60% to 80% of all causes (de Matos et al., 2018). Clinically, AD is characterized by a progressive memory loss and a gradual decline in cognitive functions, leading to the premature death of the individual, that occurs several years after the diagnosis. The most common pathological characteristics of AD are the abnormal accumulation into the brain of amyloid plaques, resulting from the aggregation of amyloid-β (Aβ) peptides, and neurofibrillary tangles (NFT), composed by hyperphosphorylated tau protein. Extensive research in vitro, in vivo (mainly in mouse models), and *in post-mortem* studies on human brain specimens revealed that, in addition to the presence of extracellular amyloid plaques, intracellular NFT, and neuronal loss, AD is associated with cellular damages mainly due to oxidative stress, mitochondrial structural and functional abnormalities, inflammatory responses and senescence (Kandimalla et al., 2017). This damage might be linked to a status of insulin resistance, which includes hyperinsulinemia, chronic hyperglycemia, inflammation and vascular changes- known conditions related to T2DM. About 80% of subjects with AD are affected by a state of insulin resistance or suffer from T2DM (de la Monte, 2014a, 2014b). The epidemiological connection between T2DM and dementia represents a significant public health challenge but also an opportunity to understand these conditions further. Based on these observations, several biological and clinical investigations have provided convincing evidence that AD could be considered as a metabolic disorder where brain glucose utilization and energy production are impaired. Thus, many studies and clinical trials have been conducted, and several are ongoing, to assess the potential neuroprotective effect of anti-diabetic medications and evaluate their direct and indirect mechanism of action. This narrative review, after a summary on linking mechanisms between T2DM and AD, will focus on the principal "anti-diabetic" drugs, acting as suitable candidates in the treatment of AD.

2. T2DM and AD principal discovered linking mechanisms

When considering the links between T2DM and AD, it is important to take into account the natural history that leads to the first disorder. There are two underlying mechanisms involved in T2DM, insulin resistance and inadequate insulin secretion from pancreatic β-cells. Initially, pancreatic β-cells increase insulin secretion in response to a state of insulin resistance, causing hyperinsulinemia, which can effectively maintain glucose levels below the T2DM range. When β-cell function begins to decline, insulin production is inadequate to overcome the insulin resistance, and blood glucose levels start to rise, resulting in prediabetes and subsequently in diabetes. T2DM is a complex metabolic disorder associated with several microvascular and macrovascular complications, which includes retinopathy, nephropathy, neuropathy, and cardiovascular diseases. While the mechanisms between diabetes and these complications are well established, the impact of diabetes on the brain, particularly about cognitive decline, is still

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unclear. Below are reported the most important identified pathophysiological mechanisms underlying the association between T2DM and AD that we are going to examine.

2.1. Impaired insulin signalling

Insulin is the principal regulator of energy homeostasis, food intake as well as a modulator of brain activity. Insulin in the brain contributes to the control of nutrient homeostasis and cognitive functions with neurotrophic, neuromodulatory, and neuroprotective effects (Blàzquez et al., 2014). However, whereas insulin is neurotrophic at moderate concentrations, high levels of insulin in the brain is associated with reduced amyloid-β clearance. The insulin-degrading enzyme (IDE) is required for both insulin and Aβ degradation in microglia and neurons. Since IDE is more selective for insulin than Aβ, under the hyperinsulinemic condition Aβ is deprived of its main clearance mechanism (S. Roriz-Filho et al., 2009). Thus, inevitably Aβ accumulates into the brain, promoting many of the pathological features associated with AD. Again, insulin increases tau phosphorylation and cleavage as shown both in vitro (Lesort and Johnson, 2000) and in vivo (Cheng et al., 2005) which leads to an increase in NFT formation and accumulation. Specifically, insulin receptor signalling leads to the activation of two major pathways, the mitogen-activated protein kinase (MAPK) pathway and the AKT signalling pathway, both implicated in AD pathogenesis. MAPK expression, regulating cell differentiation, cell proliferation, and cell death, is increased in the brains of patients with AD and it is positively associated with Aβ plaques and NFTs. Indeed, many studies indicate that this pathway is involved in neuroinflammation, tau phosphorylation and synaptic plasticity (Brazil and Hemmings, 2001; Luchsinger, 2010). AKT signalling involved in cell growth, cell proliferation and protein synthesis induces the inhibition of glycogen synthase kinase-3β (GSK-3β) which inactivates the key enzyme in glycogenesis, glycogen synthase. Thus, while under normal conditions, insulin-signalling leads to GSK-3β inactivation, insulin resistance leads to GSK-3β dephosphorylation and activation. Increased GSK-3β activation leads to higher Aβ production and subsequently increases tau phosphorylation associated with NFT formation.

2.2. Impaired glucose metabolism

The brain cannot synthesize glucose or even store it, thus requiring for its functions a continuous supply of glucose from the peripheral circulation. A strong connection has been found between T2DM, impaired glucose metabolism, and AD, suggesting that T2DM dysregulation between glucose metabolism and insulin signalling can be considered an additional risk factor for developing AD (Arnold et al., 2018; Janson et al., 2004). In subjects affected by AD, there is a significant decrease in the rate of glucose metabolism especially in the regions associated with memory processing, and learning (Mistur et al., 2009; Mosconi et al., 2008; Reiman et al., 2004) and such a dysregulation occur early and before the clinical manifestation of cognitive decline (Chen et al., 2010; Langbaum et al., 2010). This abnormal metabolism is shown also in PET scan of people who are at high risk for developing AD, where a decrease in the rate of glucose metabolism can be detected three decades before the appearance of AD symptom (Mosconi et al., 2010). Even if glucose represents the primary energy substrate of the brain, the occurrence of *chronic hyperglycemia* is one of the most critical determinants of cerebral damage in subjects with abnormal glucose metabolism (Kodl and Seaquist, 2008). Chronic hyperglycemia is mainly associated with advanced glycation end products (AGEs) accumulation and an increase in oxidative stress (Vlassara and Uribarri, 2014). AGEs are a group of molecules constituted by irreversible and non-enzymatic reactions between glucose and the free amino groups of proteins, lipids, and nucleic acids. AGEs accumulation play an important role in AD progression since AGEs induce Aβ and tau proteins glycation leading to Aβ aggregation and the formation of senile plaques and intracellular neurofibrillary tangles, neuropathological markers of AD (Iannuzzi et al., 2014; Sasaki et al., 1998; Vlassara and Uribarri, 2014). Hyperglycaemia also increases the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative stress, an important contributing factor for diabetic neuropathy (Fakhruddin et al., 2017). Oxidative stress and lipid peroxidation, induced by ROS, occur very early in the development of AD as also shown by the increased levels of oxidized proteins in the frontal and parietal lobes of the brain and the hippocampus of patients affected by initial cognitive impairment (Ansari and Scheff, 2010; Wang et al., 2014). These conditions contribute to a sustained inflammatory process as well as microvascular changes, leading to repeated microinfarcts and generalized brain atrophy, which in turn results in an "accelerated brain aging," characteristic in subjects affected by T2DM (S. Roriz-Filho et al., 2009). Repetitive episodes of moderate or severe drug-related *hypoglycemia* represent another potential etiology of cognitive dysfunction in diabetes. Prolonged and acute severe hypoglycemia lead to permanent brain damage, affecting respectively cognition and conscious level. It has been shown that most cognitive functions are impaired when blood glucose falls below 2.8 mMol/L while recurrent severe hypoglycemia causes repeated sub-clinical cerebral injuries and permanent cognitive impairment (Languren et al., 2013; Won et al., 2012). The cerebral regions more vulnerable to hypoglycemia are the cortex, basal ganglia, and hippocampus as shown in some human autoptic studies where laminar, multifocal or diffuse necrosis and gliosis of the cerebral cortex were found. Hypoglycaemia also may exert profound changes on the vasculature, especially when it is already compromised by macro and microangiopathy observed in T2DM (Languren et al., 2013). Recent studies show that impairment of cognitive performance in older diabetic patients is also associated with *daily glucose fluctuations*, independently of the primary markers of sustained hyperglycemia such as HbA_{1c}, postprandial glucose and fasting plasma glucose. Repeated daily glycemic fluctuations can generate higher circulating levels of inflammatory cytokines and ROS as compared high but even stable blood glucose level, leading to endothelial dysfunction as shown both in healthy control subjects and patients affected by T2D (Barbieri et al., 2013; Rizzo et al., 2010).

2.3. Neuro-inflammation

Neuro-inflammation is defined as an innate inflammatory response of the nervous system, mediated by cytokines, chemokines, reactive oxygen species, and related molecular processes. Neuro-inflammation contributes to AD pathology by promoting AβPP-Aβ accumulation (Tuppo and Arias, 2005), Tau hyperphosphorylation (Heneka et al., 2010a, 2010b), oxidative damage (Markesbery and Carney, 1999; Yin et al., 2016), and impairments in neuronal plasticity (Munoz and Ammit, 2010). Furthermore, inflammation exacerbates insulin resistance and ceramide accumulation, i.e., lipotoxicity, and insulin resistance, lipotoxic injury and cell death, in turn, worsen inflammation (de la Monte and Tong, 2014). Results of studies about the association between T2DM and AD show that insulin resistance in T2DM generates oxidative stress, which in turn causes mitochondrial dysfunction and activation inflammatory response. In these conditions, insulin resistance is associated with increased levels of many serum cytokines such as IL-6, IL-1β, and IL-18, tumor necrosis factor-alpha (TNF-α), alpha-1 antichymotrypsin, and C-reactive protein (Kandimalla et al., 2017).

2.4. Oxidative stress

Oxidative stress is a condition where ROS production exceeds the cellular antioxidant defense system. The brain is highly susceptible to an oxidative imbalance due to its high-energy demand, high oxygen consumption, an abundance of easily peroxidable polyunsaturated fatty acids as found AD brain (Mecocci et al., 2018). Oxidative stress causes

damage by lipid peroxidation of membranes, including mitochondrial membranes, or oxidation of structural and enzymatic proteins, with irreversible modification of their structures and function. Oxidized protein accumulation, in turn, has been demonstrated in the hippocampus, frontal and temporal lobes of mild cognitive impairment patients, suggesting an early impact of oxidative damage in AD development (Sims-Robinson et al., 2010). The above-mentioned overproduction of ROS and the general increase in oxidative stress are also characteristics of T2DM (Mule and Singh, 2018). Thus, antioxidant therapy in combination with AGE inhibitor therapy may be effective approaches for AD and diabetes-related complications.

2.5. Senescence

Ageing is the main risk factor for T2DM and AD, and both diseases can be considered as "syndrome of accelerated ageing." Numerous and sophisticated are the mechanisms involved in theageing process and a sustained DNA damage response, so-called *cellular senescence*, has been hypothesized as one of the most important contributing factors. Cellular senescence is essentially an irreversible growth arrest that occurs in response to many stressors, including telomere erosion, DNA damage, oxidative stress, inflammation, mitochondrial dysfunction and oncogenic activation (Hernandez-Segura et al., 2018). Senescent cells adopt unique identifying characteristics, such as a flattened morphology in culture, upregulation of cell cycle inhibitor proteins (such as p21 and p16), accumulation of DNA damage foci, reactive oxygen species production, and enhanced β-galactosidase activity. Although senescent cells are incapable of dividing, they are metabolically active with the release of pro-inflammatory cytokines, chemokines, and growth factors collectively known as the "SASP" or senescence-associated secretory phenotype. Thus, senescent cells might be a link between ageing and inflammation that contributes to the development and progression of type 2 diabetes as well as AD (Palmer et al., 2015). Therapeutic targeting of a basic ageing mechanism such as cellular senescence may have a large impact on diseases pathogenesis and could be more effective in preventing the progression of diabetes complications than currently available therapies that have limited impact on already existing tissue damage (Palmer et al., 2015).

2.6. The cholinesterase connection

Acetylcholinesterase (AChE) is the key enzyme in the cholinergic nervous system, and its levels are consistently decreased in the brain during AD development (García-Ayllón et al., 2010). The classic function of AChE is to hydrolyze acetylcholine and terminate impulse transmissions at the cholinergic synapse (Rosenberry, 2006). Both AChE and decreased acetylcholine (Ach) levels play a role in the occurrence of AD; in fact, an abnormal AChE expression in association with amyloid plaques and tangles has been found in the AD brain (Markowicz-Piasecka et al., 2017a). The enzyme butyrylcholinesterase (BuChE), instead, is a non-specific cholinesterase enzyme ubiquitously expressed throughout the human body including the liver, blood serum, pancreas, and the central nervous system, as well. It has been proposed that activities of AChE and BuChE are elevated in AD, which includes a low-grade systemic inflammation even when plasma, cerebrospinal fluid and tissue concentrations of some inflammatory molecules (such as C-reactive protein or Interleukin-6) are in the normal range (Das, 2012). Interestingly, the activities of both AChE and BuChE are higher in subjects affected by T2DM as compared withhealthy controls (Mushtaq et al., 2014). This means that abnormal plasma levels of AChE and BuChE may be involved in the development of T2DM and AD (Rao et al., 2007) and may serve as potential therapeutic targets.

2.7. Other common linking mechanisms

Cardiovascular risk factors, including diabetes and its complications, have not been consistently associated with an increased burden of AD pathology, rather with cerebrovascular disease (Richardson et al., 2012). These include obesity, heart disease or family history of heart disease, dyslipidemia as well as hypertension (Chatterjee et al., 2016) The World Alzheimer Report recently concluded that T2DM is a much stronger risk factor for vascular dementia than AD, where cerebrovascular disease is likely the main mechanism involved (Prince et al., 2016) and dementia susceptibility (Justin et al., 2013). T2DM is mainly characterized by three factors that strongly augment the dementia risk: endothelial dysfunction, prothrombotic and proinflammatory state. Altogether, they increase the risk of developing micro- and macrovascular complications leading to cerebrovascular diseases. These molecular processes affect several cells implicated in initiation, progression, and complexity of atherogenesis, such as endothelial cells, monocytes, macrophages, and smooth muscle cells. Vascular diseases, including increased carotid intima-media thickness (IMT) in subjects affected by diabetes, are also associated with systemic inflammatory markers, which can also lead to neuroinflammation. T2DM is also associated with a hypercoagulability state, characterized by increased concentrations in anti-fibrinolytic and other procoagulant factors, as well as by nitric oxide (NO) metabolism alterations. Inevitably, this hypercoagulability state is associated withan enhanced risk for thrombotic vascular events (de la Monte, 2014a, 2014b). Insulin resistance, in turn, is associated with higher plasminogen activator inhibitor-1 and antithrombin III levels, which inhibit fibrinolysis (Cesari et al., 2010). Some studies have further shown that procoagulant factors, such as factor VII, factor VIII, and von-Willebrand factor also increase with the degree of insulin resistance (Klein et al., 2014). Indeed, studies in diabetic patients showed both in vitro and in vivo the higher platelet aggregability and hyper-reactivity, explained by increased platelet response to ADP and elevation of thromboxane A2 concentrations (Cesari et al., 2010; Klein et al., 2014). All described mechanisms may contribute to repeated and sometimes unrecognized ischemic events leading to cerebral tissue alterations, which contribute to the impairment of cognitive performances.

3. Anti-diabetic drugs as potential treatments for AD

In light of the multiple links between T2DM and AD, it is not surprising that drugs currently approved for DM could also be useful in treating AD. Schematic representation of anti-diabetic drugs with potential beneficial effects in AD are presented in Fig. 1. Antidiabetic drugs improve hyperglycemia, insulin resistance, cell metabolism, and can counteract tissue inflammation and oxidative stress associated with a state of insulin resistance. They might also positively affect cell metabolism in the brain and improve cognition as well. Anti-diabetic drugs may be divided into two groups: 1) hypoglycemic agents, including insulin, sulphonylureas, and glinides and 2) anti-hyperglycemic agents, including metformin, thiazolidinediones, dipeptidyl peptidase (DPP) IV inhibitors, Glucagon-like peptide-1 (GLP-1)analogues, GLP-1 receptor agonists and Sodium-Glucose co-transporters (SGLT)-2 inhibitors. In Table 1 are summarized the main evidence of antidiabetic drugs effects on AD markers, from experimental and clinical studies, and discussed below.

3.1. Hypoglycemic agents

3.1.1. Insulin

Preclinical studies have shown that a single injection of insulin can reverse the high fat diet-induced increase in brain Aβ and ameliorate cognitive deterioration in a mouse model of AD (APPswe, PSIM146 V, tauP301 L) (Vandal et al., 2014). (Shingo et al., 2013) found that intracerebroventricular administration of an insulinanalogue recovered cognitive impairment in diabetic rats induced by streptozotocin (STZ). STZ is a naturally occurring chemical, a broad-spectrum antibiotic that is particularly toxic to the insulin-producing β-cells of the pancreas.

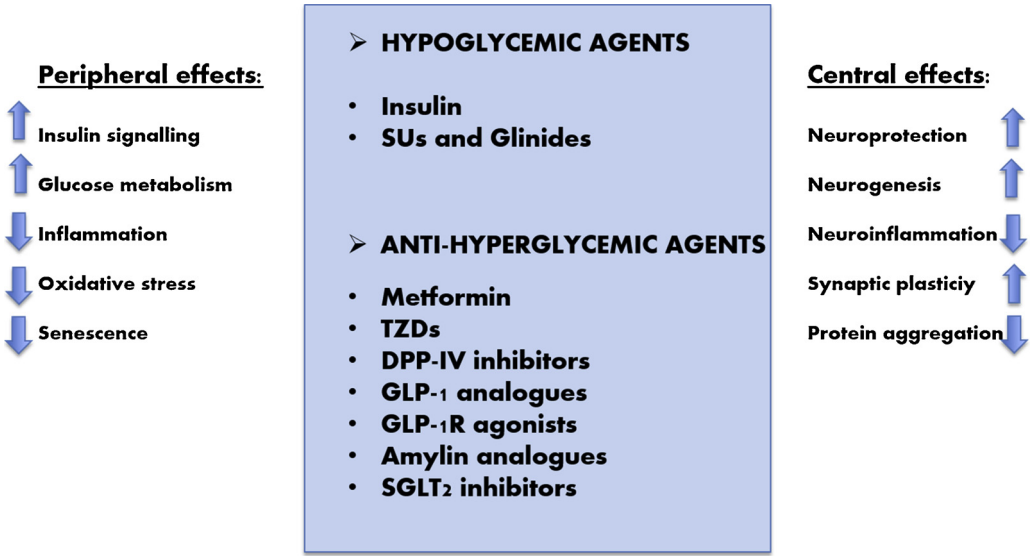

Fig. 1. Schematic representation of anti-diabetic therapies with beneficial effects in AD.
SUs: Sulphonylureas; TZDs: Thiazolidinediones; GLP-1: Glucagon-like peptide-1; GLP-1R: Glucagon-like peptide 1 receptors; DPP-IV: Dipeptidyl peptidase-IV; SGLT2: Sodium Glucose co-Transporters 2.

Another study demonstrated that intra-hippocampal insulin administration was able to reverse not only Aβ-induced memory impairment but also the activation of major hippocampal kinases (ERK and P38) implicated in the control of apoptosis (Ghasemi et al., 2014). A subsequent study also showed that basal insulin treatment (glargine) decreased hippocampal Aβ, suppressed neuronal apoptosis, and increased hippocampal synaptic plasticity in a mice model of diabetic dyslipidemia (db/db) (Chen et al., 2016). First clinical evidence, in humans, indicated that acute insulin administration has protective effects in subjects affected by AD (Craft et al., 1999). A state of hyperinsulinemia, without hyperglycemia, enhances memory in adults with AD, suggesting an important role of this hormone in memory facilitation (Cholerton et al., 2013). However, the systemic administration of insulin is associated with an increased risk of hypoglycemia and related consequences. To overcome these issues, the intranasal administration of insulin has been tested in several studies, proving to be effective in directly targeting the brain. A small, randomized placebo-controlled trial showed that intranasal insulin of 20 IU twice daily throughout 21 days in early AD or amnestic MCI patients resulted in higher verbal information retention and superior attention as compared with controls (Reger et al., 2008). In subjects with initial AD/MCI and APOE4 negative intranasal insulin improves cognitive function at a lower dosage (Reger et al., 2006). In facts, the effects of insulin on cognition are dose-dependent, with a maximal effect at 20 UI. In a more recent randomized controlled trial of old AD/MCI subjects with a mean age of 74 years, positive effects have been shown in subjects treated with intranasal insulin (20 IU or 40 IU). Again, ameliorations in delayed memory were observed at lower doses (Craft et al., 2012). More recently, the insulin detemir has been tested for intranasal administration in AD and MCI, showing a significant positive effect for the memory composite outcome. Since intranasal insulin is a safe intervention, future studies should be conducted with larger doses and after the proper selection of patients and insulin types.

3.1.2. *Sulphonylureas*

Sulphonylureas (SUs) are an older class of anti-diabetic drugs that stimulate insulin secretion by interacting with ATP-sensitive potassium (KATP) channels in the pancreas. Interestingly, KATP channels are also found in neurons. A recent experimental study showed that glibenclamide treatment in db/db mice reduced hippocampal Aβ, inhibited neuronal apoptosis, and enhanced hippocampal synaptic plasticity (Chen et al., 2016). In a prospective cohort study, Hsu et al. (2011) showed that a combination of metformin and sulphonylurea decreased the risk of dementia by 35% throughout eight years. On the other hand, a population based-control study showed long-term use of SUs does not change the risk of developing AD in general (Imfeld et al., 2012). In a recent study, Exalto et al. (2012) reported that the incidence of dementia in SUs-treated T2D subjects was reduced. An initial clinical

Table 1
Anti-diabetic drugs and their main effects on AD markers from the main experimental and clinical studies.

Anti-diabetic drugs	Experimental studies (mice)	Clinical studies (humans)
Hypoglycemic agents	**Insulin.** Basal insulin injection: ↓ hippocampal Aβ, ↓neuronal apoptosis, ↑ hippocampal synaptic plasticity **Sulphonylureas.** Glibenclamide: ↓ hippocampal Aβ, ↓ neuronal apoptosis, ↑ hippocampal synaptic plasticity	**Insulin.** Intranasal insulin administration: ↑attention ↑ memory **Sulphonylureas.** Glipizide: ↑ verbal learning
Anti-hyperglycemic agents	**Metformin**: ↓ total tau, ↓ tau phosphorylation, ↓ hippocampal Aβ **Thiazolidinediones**. Pioglitazone and rosiglitazione: ↓hippocampal Aβ, ↓ neuronal apoptosis, ↑ hippocampal synaptic plasticity **DPP-IV inhibitors.** Sitagliptin: ↑ GLP-1 brain levels, ↓nitrosative stress, ↓ inflammation, ↓ Aβ deposits. Lingliptin: ↓amyloid beta, ↓tau phosphorylation, ↓neuroinflammation **GLP-1 analogues.** Lixisenatide and liraglutide: ↑ neurogenesis. Liraglutide: ↓ Aβ plaque in the cortex, ↓ inflammation, ↓tau hyperphosphorylation. **Amylin analogues.** Pramlintide: ↓oxidative stress, ↓neuroinflammation, ↑ memory tasks **SGLT2 inhibitors.** No experimental data.	**Metformin:** ↑ working memory, ↓ dementia risk **Thiazolidinediones**. Pioglitazone: No significant effects **DPP-IV inhibitors.** No clinical data **GLP-1 analogs.** Liraglutide: glucose metabolism and cognitive decline improvement. **Amylin analogues.** No clinical data **SGLT2 inhibitors.** No clinical data

study with glipizide treatment in subjects affected by T2DM showed amelioration in verbal learning (Gradman et al., 1993). Further investigation to clarify the molecular mechanisms of action of SUs (particularly in CNS and in AD-dementia type) is needed before assuming their anti-AD potentialities.

3.2. Anti-hyperglycemic agents

3.2.1. Metformin

Metformin is a biguanide that increases insulin sensitivity in peripheral tissues and suppresses hepatic gluconeogenesis. The mechanism of action is still not fully understood, but it has been shown that the antihyperglycemic effect of metformin is mainly due to the inhibition of hepatic glucose output (Song, 2016). Other mechanisms of action include decreased intestinal absorption of glucose, increased glucose uptake from the blood into the tissues, decreased glucose production in the liver, and decreased insulin requirements for glucose disposal. The exact mechanism of advantageous activityof metformin in AD is not fully understood, but scientists claim that activation of AMPK-dependent pathways in human neural stem cells might be responsible for the neuroprotective activity of metformin (reviewed in (Markowicz-Piasecka et al., 2017b). Metformin was also found to markedly decrease Beta-secretase 1 (BACE1) protein expression and activity in cell culture models and in vivo. BACE1 is involved in the cleavages of the amyloid precursor protein and the generation of β-amyloid (Aβ). Thereby reducing BACE1 cleavage products, theproduction of Aβ is controlled. Accordingly, it has been found that metformin treatment decreases hippocampal Aβ level and ameliorates cognitive decline in db/db mice (Chen et al., 2016). Metformin also improves oxygen-glucose deprivation-induced neuronal injury, which is associated with a decreased insulin receptor phosphorylation that is reversed by metformin resulting in improved neuronal survival (Łabuzek et al., 2010.). Treatment with metformin is able to resensitize insulin signalling and prevent the molecular and pathological changes observed in AD neurons as shown in vitro experiments on neuronal cell lines under prolonged hyperinsulinemic conditions (Gupta et al., 2011). Moreover, in murine primary neurons from wild type and tau transgenic mice, metformin treatment is also able to reduce tau phosphorylation (Kickstein et al., 2010). Again, in a murine model of leptin-resistant obese mice, systemic administration of metformin attenuates the increase of total tau and phospho-tau in the hippocampus without significant effects on cognitive tests investigating the ability of learning and memory (Li et al., 2012). There is also some evidence that metformin decreases the activity of AChE, which as reported above it is responsible for the degradation of acetylcholine, the principal neurotransmitter involved in the process of learning and memory (Bhutada et al., 2011). Considering the beneficial effects of metformin, its anti-inflammatory and anti-oxidative properties cannot be undervalued as confirmed by numerous in vitro and in vivo studies (Markowicz-Piasecka et al., 2017b). A clinical study conducted on subjects aged 50 years or older showed that metformin treatment compared with no medication, remarkably decreased the risk of dementia, after adjustment for cerebrovascular disease (Hsu et al., 2011). In a randomized, double-blind trial in older T2D subjects, metformin with add-on therapy with glibenclamide or rosiglitazone showed remarkable amelioration in working memory (Ryan et al., 2006). As already reported the combination of metformin and sulphonylurea reduced the risk of dementia (Hsu et al., 2011). However, the evidence for its use in AD is controversial, and a slight increase of AD was reported in chronically metformin-treated patients (Wang et al., 2017).

3.2.2. Thiazolidinediones

Thiazolidinediones work by activating peroxisome proliferator-activated receptor gamma (PPARs) and have anti-inflammatory and insulin-sensitizing effects, which may decrease and delay the risk of neurodegeneration (Heneka et al. 2001). They also improve the sensitivity of skeletal muscles and adipose tissue to insulin, inhibiting hepatic gluconeogenesis, improve glycemic control, and reduce circulating insulin levels. Currently, only pioglitazone is approved in DM therapy, while rosiglitazone has been withdrawn due to the high incidence of cardiovascular events. In a rat model of memory impairment induced by intracerebroventricular (ICV) injection of streptozotocin, pioglitazone was able to improve cognitive impairment. This was associated with a decrease in oxidative stress (Pathan et al., 2006). Both rosiglitazone and pioglitazone decreased hippocampal Aβ, suppressed neuronal apoptosis, and increased hippocampal synaptic plasticity in db/db mice. A recent study in vitro also found that pioglitazone reduced both phosphorylated and total tau levels, and inactivated glycogen synthase kinase 3β, a major tau kinase (Hamano et al., 2016). A pilot study with pioglitazone in AD patients with T2DM indicated that 15–30 mg of pioglitazone for six months improved cognition and cerebral blood flow in the parietal lobe as compared with controls. Another trial assessing pioglitazone safety in patients with AD without T2DM demonstrated that 18 months of treatment were well tolerated by subjects, even if no significant data on efficacy have been observed (Desouza and Shivaswamy, 2010). Another population based case-control study showed long-term use of TZDs, in general, does not alter the risk of developing AD (Imfeld et al., 2012). Indeed, a recent metanalysis on PPARγ agonists in subjects affected by AD suggests that pioglitazone may offer an improvement in the early stages of AD and mild-to-moderate AD (Cheng et al., 2016).

3.2.3. Dipeptidyl peptidase IV inhibitors

Dipeptidyl-peptidase IV (DPP-4) inhibitors suppress the degradation of the incretins, Glucagon-like peptide (GLP-1), and glucose-dependent insulinotropic peptide (GIP). Multiple oral DPP-4 inhibitors indirectly increasing endogenous GLP-1 levels have also been developed for T2DM therapy. The commonly available DPP-4 inhibitors include gliptin, saxagliptin, linagliptin, vildagliptin, and sitagliptin. DPP-4 inhibitors are generally well tolerated and can be administrated orally to decrease fasting and postprandial blood glucose, without notably affecting body weight or gastric emptying. DPP-4 inhibitors can be used either alone or in combination with other oral agents or insulin in diabetes management. DPP-4 inhibitors have a low risk of causing hypoglycemia, comparable to that of GLP-1R agonists, thereby constituting another advantage for their possible application in AD therapy. Experimental studies to investigate the effect of gliptins on cognition have been demonstrated to be beneficial. Sitagliptin and vildagliptin have been shown to prevent mitochondrial dysfunction in the brain and particularly in the hippocampus and improve learning behaviour in the high-fat diet (HFD) induced insulin resistant rats (Pintana et al. 2013). A previous study also showed that vildagliptin effectively attenuated the impaired cognitive function caused by an HFD and restored insulin signalling in the brain (Pipatpiboon et al. 2013). In a mouse model of AD, sitagliptin therapy increased the brain levels of GLP-1, reduced brain nitrosative stress and inflammation, prevented memory impairment, which was associated with a significant reduction in Aβ deposits (D'Amico et al., 2010). On the other hand, notably, a recent study suggested that sitagliptin could increase the risk of developing AD by measuring increased tau phosphorylation in the hippocampus of rats (Kim et al. 2012). Indeed, also linagliptin treatment for 8 weeks mitigates the cognitive deficits present in mice models of AD with the attenuation of amyloid beta, tau phosphorylation as well as neuroinflammation (Kosaraju et al., 2017). No clinical data are currently available for the potential effects of gliptins in AD patients.

3.2.4. Glucagon-like peptide 1 (GLP-1) analogues and GLP-1 receptor agonists

Glucagon-like peptide 1 (GLP-1) is an insulin tropic peptide that is generated by cleavage of the pro-glucagon protein, and secreted by small intestinal L cells, following meal intake. GLP-1 has a half-life of only a few minutes, and it is rapidly degraded by a dipeptidyl

peptidase-4 enzyme (DPP-4). GLP-1 has multiple actions and mainly stimulates insulin gene expression and secretion and suppresses glucagon in the pancreas. GLP-1 has glucose-lowering effects by reducing glucagon secretion, enhanced insulin secretion, increased satiety and insulin sensitivity in multiple tissues and delayed gastric emptying. Like insulin, GLP-1 stimulates neuritic growth in CNS neurons and exerts neuroprotective actions against glutamate-mediated excitotoxicity, oxidative stress, trophic factor with-drawl and cell death (Salcedo et al., 2012). In an animal study, it has been shown that GLP-1 protects neurons from oxidative stress, reduces apoptosis, inflammatory responses, and plaque formation, and preserves synaptic plasticity in the brain of a mouse model (reviewed in Athauda and Foltynie, 2016). Analogues of GLP-1, which are injectable and have prolonged half-lives have been developed and approved for T2D treatment including liraglutide and exenatide. One of the advantages of these drugs is that acting physiologically, they have a lower risk of hypoglycemia. In another study on AD transgenic mice, intraperitoneal injection of GLP-1 receptor agonist decreased the hippocampal burden and improved spatial memory (Bomfim et al., 2012). Lixisenatide and liraglutide, two GLP-1 receptor agonists, have been shown to activate cAMP in the brain and induce neurogenesis. This is significant because AD is associated with neuronal degeneration (Hunter and Hölscher, 2012). Also, liraglutide ameliorated memory impairments in object recognition and water maze tasks, in a mouse model of AD (McClean et al., 2011). This amelioration was associated with a decrease in Aβ plaque in the cortex, and suppression of inflammation. Subcutaneous administration of liraglutide restored both peripheral and brain insulin sensitivity and improved tau hyperphosphorylation in T2D rats (Yang et al., 2013). In brief, these agents, by enhancing neurogenesis and synaptogenesis and protecting against oxidative injury, act as growth factors in the brain and ultimately slow down the key neurodegenerative progression of AD. Results from preclinical studies results have been encouraging. In a 26-week randomized, placebo-controlled, double-blind study, it has been shown that liraglutide treatment improved glucose metabolism and cognitive decline in AD patients, as compared with the placebo group. However, no difference in Aβ deposition between the groups treated with liraglutide or placebo was found (Gejl et al., 2016). Another three-year trial on 230-patients randomized on a GLP-1 analogue, exenatide, is currently ongoing.

3.2.5. Amylin analogue

Amylin is released with insulin from the pancreatic beta cells in response to glucose intake (Qiu and Zhu, 2014). Within the pancreas, amylin restrains insulin and glucagon secretion, regulating the glucose level and slow the gastric emptying rate (Westermark et al., 2011). Human amylin hormone may lose its function by oligomerization. Amylin oligomerization and deposition is common in patients with obesity and pre-diabetic insulin resistance who have an increased secretion of this hormone. Over 95% of humans with T2DM are positive for amylin amyloid deposition in pancreatic islets, where it is believed to be cytotoxic, and lower plastic levels. In the brain, amylin and amyloid β may share similar pathophysiology. This hypothesis is suggested by the fact that both amylin and amyloid β form toxic oligomers and amyloid fibrils. Thus, its analogue pramlintide has been recently approved as a drug for the treatment of T2DM, to prevent the state of hyperamylasemia and following release of oligomerized amylin in the blood. This may also represent a new therapeutic target in the treatment of diabetic brain injury and AD. Administration of amylin analogue pramlintide in preclinical data of AD mouse models was found to reduce oxidative stress, neuroinflammation and enhance the memory (Grizzanti et al., 2018). No data are available in humans, and no trial is ongoing with such a molecule for AD treatment.

3.2.6. SGLT-2 inhibitors

Sodium-glucose co-transporters (SGLTs 1 and 2) promotes renal glucose reabsorption (mostly by SGLT-2). SGLT-2 is expressed exclusively in the kidney and its inhibition act as a therapeutic target in T2DM without risk of hypoglycemia since it increases renal excretion of glucose, without influencing insulin secretion, and under hyperglycemic conditions. SGLT2 inhibitors, also called gliflozin drugs, are a new class of diabetic medications indicated for the treatment of T2DM. Currently, there are three SGLT2 selective inhibitors approved by the Food and Drug Administration (FDA) for mono, dual, and triple therapy: canagliflozin, dapagliflozin, and empagliflozin. Recent studies (Rizvi et al., 2014) have explored the molecular interactions of the human brain AChE with these antidiabetic drugs. Results suggest that canagliflozin and dapagliflozin might act as an inhibitor of acetylcholinesterase. The evidence is still poor, and further investigations are needed to address the issue regarding their dual inhibitory roles against T2DM and AD. No trial is ongoing with such molecules for AD treatment.

4. Conclusions

T2DM and AD are majors age-related chronic conditions, which negatively impact on individual health and care system as a whole. So far, T2DM and AD have been considered as two independent disorders. However, nowadays, T2DM has been recognized as an important risk factor for developing cognitive decline and dementia. Despite the mounting evidence of a positive association between T2DM and AD- the most common single cause of dementia- some longitudinal clinical studies failed to find such an association (Abner et al., 2016; dos Santos Matioli et al., 2017). These results might be attributed to differences in study designs, diagnostic criteria, subtypes of dementia, neuroimaging information, regional and ethnicities characteristics of study subjects. Conversely, individuals affected by AD are also at an increased risk of suffering T2DM. Thus, we cannot rule out that the pathogenesis of the two disorders share common characteristics, including impaired insulin signalling, altered glucose metabolism, inflammation, increased oxidative stress, and premature senescence, strongly impacting on cognitive functions and dementia susceptibility. This is the reason why appropriate glycemic control for subjects affected by T2DM should be addressed, not only for cardiovascular protection but also for cognitive function preservation and brain health. Collectively, several anti-diabetic drugs, beyond peripheral effects, by different mechanisms and linking pathways, can impact on neuroprotection, neurogenesis, neuroinflammation, synaptic plasticity, and proteins aggregation as well. These suggest that the therapeutic potential for AD of such agents could be a property of the drugs rather than mere glycemic control. However, it remains to be determined which antidiabetic drugs is more effective when compared to the others, as well as there is no a definite consensus about the superiority of any type of diabetic treatment to prevent cognitive impairment in subjects affected by T2DM. Multiple antidiabetic approaches may be helpful in treating AD but, the safety should also be taken into consideration when used in the management. The findings reviewed in this article are highly clinically relevant and provide a strong rationale for hypothesizing that improving central insulin levels could be a promising method for the treatment of AD. Based on the preclinical studies, insulin sensitizers including DPP-4 inhibitors, GLP-1 analogues or GLP-1R agonists looks promising targets for neuroprotection, and in particular in old age subjects. DPP-4 inhibitors are generally safe, well tolerated and can be administrated orally to decrease fasting and post-prandial blood glucose, without notably affecting body weight or gastric emptying. DPP-4 inhibitors also have a low risk of causing hypoglycemia, as compared with other drugs (such as GLP-1 analogues or GLP-1R agonists), considering their physiological mechanisms of action, thereby constituting another advantage for their possible application in AD therapy. But evidence from clinical studies are still lacking and several trials are underway. Instead, encouraging results have been obtained by multiple clinical trials of intranasal insulin administration in AD, with no major side effects, making such a therapy an effective way to prevent or treat AD.

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