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Crucial players in Alzheimer's disease and diabetes mellitus: Friends or foes?

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ABSTRACT

Alzheimer's disease (AD) and diabetes mellitus, especially type 2 (T2DM), are very common and widespread diseases in contemporary societies, and their incidence is steadily on the increase. T2DM is a multiple metabolic disorder, with several mechanisms including hyperglycaemia, insulin resistance, insulin receptor and insulin growth factor disturbances, glucose toxicity, formation of advanced glycation end products (AGEs) and the activity of their receptors. AD is the most common form of dementia, characterized by the accumulation of extracellular beta amyloid peptide aggregates and intracellular hyper-phosphorylated tau proteins, which are thought to drive and/or accelerate inflammatory and oxidative stress processes leading to neurodegeneration.

The aim of this paper is to provide a comprehensive review of the evidence linking T2DM to the onset and development of AD and highlight the unknown or poorly studied "nooks and crannies" of this interesting relationship, hence providing an opportunity to stimulate new ideas for the analysis of comorbidities between AD and DM. Despite, indication of possible biomarkers of early diagnosis of T2DM and AD, this review is also an attempt to answer the question as to whether the crucial factors in the development of both conditions support the link between DM and AD.

1. Introduction

Ageing populations at risk of neurodegenerative diseases such as Alzheimer's disease (AD) and metabolic disturbances as obesity and type 2 diabetes mellitus (T2DM); are posing enormous challenges for health care, cost of financing the treatment and for governments. This diseases share some common features as they both have long prodromal phases and are chronic, complex disorders. The difference between those two conditions occurs regarding disease-modifying or pharmacological treatments. While dementia has no proven or even modestly effective therapy, in T2DM, multiple pharmacological agents are available. In addition AD is a disorder of mainly a single organ - the brain, on the other hand diabetes mellitus (DM) is a widespread multiple organ damage. Although at first glance those two disorders seem to not have much in common but it seems that: impaired insulin signalling, chronic hyperglycaemia, glucotoxicity, inflammatory response, glycogen synthase kinase 3β (GSK3β) signalling mechanism, the accumulation of advanced glycation end products (AGEs), mitochondrial dysfunction and oxidative stress (OS); plays an essential role in the pathogenesis of both AD and diabetic complications (Kroner, 2009). Recent publications indicate that impaired insulin signalling may contribute to the AD development, leading to the idea that it's actually a neuroendocrine disease (Ribe and Lovestone, 2016; Schuh et al., 2011). Moreover, AD could be regarded as a "brain disorder" associated with insulin signalling that has attendant brain insulin deficiency state and/or chronic insulin resistance but there is absence of autoimmune destruction of pancreatic islet beta cells or metabolic disturbances (Ferreira et al., 2018). Shared molecular and cellular features supports the hypothesis of AD as specific form of brain diabetes with the name "Type-3-Diabetes" (T3DM) proposed by de la Monte group in 2005 year (Steen et al., 2005). Of the common features of AD and T2DM, the one most likely to be an etiological factor in AD is reduced cellular responsiveness to insulin. In post mortem study conducted in the Arnold Lab the causes and consequences of brain insulin resistance have been analysed in the hippocampal fields CA1–CA3, the dentate gyrus, and the subiculum, which develops marked pathology starting early; and in the cerebellar cortex, which develops limited pathology only late in AD. The state of brain insulin resistance appears to be an early and common feature in human AD patients (Talbot et al., 2012). The interrelation between diabetes and dementia exists, but data on specific mechanisms for its realization are insufficient and sometimes contradictory (Chatterjee and Mudher, 2018; Kandimalla et al., 2016; Salas and De Strooper, 2018).

The present review summarizes the evidences which establish the possible links between those two disorders and highlights the still unknown overlapping of factors and pathways responsible for

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neurodegenerative impairment which can play, in the same time, a crucial role in chronic hyperglycaemia. In our work we will consider the effect of diabetes mellitus on the β amyloid peptide (Aβ) and tau protein formation and theirs pathological modifications. We will mainly focus on the role of insulin and their receptors, elevated plasma glucose levels and AGEs and their impact on the Aβ and tau protein metabolism. What's more the resume of probable biomarkers of both diseases and metabolic interrelation points which are still missing the explanation are presented.

2. The comorbidity of chronic hyperglycaemia and neuropathological disorders

The prediction from the International Diabetes Federation is that 382 million people are living with diabetes in 2013 year which is a number previously forecast for 2030 year (Zimmet et al., 2014). DM is largely characterised by hyperglycaemia due to pancreas malfunction or disruption of the cellular response. There are two major clinical subtypes of DM: T1DM which is an insulin-depended diabetes and T2DM which is non-insulin-depended diabetes and accounts for the majority of the cases. Depending from the severity, the clinical presentations range widely from being asymptomatic to acute as polyuria and polydipsia to even coma and chronic as micro- and macroangiopathies. The main features of T2DM are high blood levels (hyperglycaemia) and relative lack of insulin and/or insulin resistance, which are the consequences of diminished susceptibility of targeted organs such as liver, adipose tissue, skeletal muscle and fat cells to insulin. In physiological conditions, pancreas activates the insulin production directly after a meal which induces the glucose uptake from the blood and promotes glycogenesis by intensification of gluconeogenesis and inhibition of glucose synthesis. Pancreatic β-cell malfunction is arising from formation and aggregation of amylin or human islet amyloid polypeptide (hIAPP) (DeFronzo et al., 2015; Yang and Song, 2013). This process is additionally accelerated by glucotoxic damage of pancreatic β-cells, which are strongly susceptible to adverse condition induced by strong hyperglycaemia, and especially due to their low efficiency of antioxidant systems. What's interesting, the molecular structure and morphology of hIAPP fibrils resemble those of Aβ fibrils in AD. Aβ can form early assembly intermediates and soluble hIAPP oligomers which are shown to induce β-cell apoptosis. The hIAPP exact physiological function is still unknown (Konarkowska et al., 2006; Lim et al., 2008; Meier et al., 2006).

Over the past decade, multiple studies supported the concept that AD represents a metabolic disease with subclinical symptoms in the brain such as deficits in glucose utilisation leading to the cognitive impairment (Caselli et al., 2008; Langbaum et al., 2010; Mosconi et al., 2008). Clinically, AD is characterised by worsening memory deficits and progressive cognitive decline. The main pathological features include intracellular neurofibrillary tangles (NFTs) consisted of abnormally hyperfosforylated axonal microtubule-associated protein - tau protein, and extracellular amyloid plaques with aggregated Aβ as a major component. The predominant protein constituent of senile plaques is a 4-kDa peptide formed during sequential cleavage of amyloid β precursor protein (APP) which can form large soluble assemblies of oligomers or goes through conformational changes leading to formation of amyloid fibrils. The second pathological hallmark which is accumulation of NFTs in neurons impairs axonal transport; disrupt synaptic plasticity and leads to dramatic apoptosis of neurones. Less than 1 per cent of people with Alzheimer's disease have an early-onset type associated with autosomal dominant missense gene mutations in presenilin 1 (PS1), presenilin 2 (PS2) or APP. The most common late-onset form does not show evident genetic or familial association and the prevalent form of AD is of unknown origin (Levy-Lahad et al., 1995; Rogaev et al., 1995; Selkoe, 1989). Alzheimer's disease is characterised also by diminished cerebral blood flow which as a consequence leads to lover oxygen, glucose and other nutrients levels in the brain. Hoyer et al. (Hoyer et al., 1991) have observed a severe imbalance between cerebral oxygen and glucose utilization in patient who had been clinically diagnosed as suffering from incipient late-onset dementia. As cognition and memory, metabolism and uptake of glucose in brain are regulated by insulin, malfunction of its signalling leads to energy imbalance manifesting in reactive oxygen species (ROS) production, DNA damage and mitochondrial dysfunction. Thus, as a consequence pro-apoptotic and pro-inflammatory cascades as well as APP pathological cleavage leading to Aβ formation are activated (de la Monte et al., 2009; Reddy, 2014). In addition to glucose metabolism distribution, some findings suggest that cognitive impairment can be observed after depletion of insulin and insulin growth factor (IGF) signalling mechanisms in in vivo model diabetes induced by intracerebral (*ic.*) injection of Streptozotocin (STZ) (Lester-Coll et al., 2006). What's interesting, this rats didn't manifest changes in pancreatic β cells morphology and metabolism or hyperglycaemia yet there was found apoptosis, gliosis and elevated immunoreactivity for phospho-tau and Aβ among others. These studies supports hypothesis of the important role of glucose and insulin signalling in the AD development. Because of insulin resistance the above stringent actions may take place and this would be one of the reason researchers termed this metabolic syndrome just as "Type-3-Diabetes".

A definite, albeit not clarified connection between diabetes and dementia has been studied by several neuropathological research groups. In the Hisayama study, it was suggested that AD histopathologic features are associated with DM or insulin resistance. Analysis of covariance and logistic regression analyses demonstrated association of hyperglycaemia and hyperinsulinemia with increased risk for amyloid plaques. Taking under consideration the genetic background, apolipoprotein E (APOE) epsilon 4 gene variant increased the risk for amyloid plaques formation (Matsuzaki et al., 2010). Other investigators found significantly fewer neurotic plaques and NFTs in the cerebral cortex and in the hippocampus were observed in diabetics (Beeri et al., 2005; Heitner and Dickson, 1997). In contrast, Aβ aggregation tended to be greater for untreated diabetic patients with dementia, while the number of microvascular infarcts was higher in patients with dementia whose diabetes was treated (Sonnen et al., 2009). Furthermore, individuals with DM were less likely to have amyloid plaques and tangle depositions but more likely to have ischemic cerebral infarcts (Ahtiluoto et al., 2010). There have been animal studies that have taken under investigation this two comorbid diseases (Gao et al., 2013; Kimura, 2016). An animal model of pre-diabetic type 2 conditions is transgenic BBZDR)/Wor rat strain. The diabetic male BBZDR/Wor rat is homozygous for the Zucker fatty (fa) gene mutation and shares the genetic background of the original Bio-Breeding strain. Obese juvenile BBZDR/Wor rats become insulin resistant, and ultimately develop hyperglycaemia. Similar to patients with clinical diabetes, the BBZDR/Wor rats develops complications associated with chronic hyperglycaemia. In BBZDR/Wor and type 1 BB/Wor rats, tau phosphorylation and amyloid accumulation seems to be correlated with insulin resistance and hypercholesterolemia (Li et al., 2007). Additionally, DM stimulates AD development via vascular inflammation leading to severe memory deficits and cognitive impairment (Takeda et al., 2010). Overall, epidemiological, clinical, and animal studies suggest that a possible mechanistic relationship underlies these two important clinical disorders.

3. The potential diagnostic markers of a very early stages of T2DM and AD

In the first clinical study performed in 1999 year, T2DM almost doubled the risk of dementia and patients who was treated with insulin had four times higher risk to develop dementia (Ott et al., 1999). The other studies have shown that risk of developing AD is increased by 50–60 per cent in case of T2DM patients (Janson et al., 2004; Kopf and Frölich, 2009; Talbot et al., 2012). There are only few studies trying to answer the question which molecules characteristic for onset of diabetes mellitus or Alzheimer's disease could be a possible biomarkers of

Table 1
The literature (till 20.02.19) on the probable biomarkers for both T2DM and AD.

Biomarker	Material/ Method	Diabetes mellitus	Alzheimer's disease	References
Amyloid β 1-42	cerebrospinal fluid	↑	↑	(Li et al., 2018)
Amyloid β autoantibody	serum	↑	↓	(Kim et al., 2010; Sohn, 2009)
Total tau	cerebrospinal fluid	↑	↑	(Lu et al., 2018; Moran et al., 2015)
Phospho-tau	cerebrospinal fluid	↑	↑	(Moran et al., 2015)
Brain derived neurotrophic factor	serum	↑	↓	(Suwa et al., 2006)
Brain derived neurotrophic factor	plasma	↓	↓	(Krabbe et al., 2007; Zhen et al., 2013)
Neuronal Butyrylcholinesterase	serum	↓	↓	(Rao et al., 2008)
sRAGE	serum	↑	↓	(Yamagishi, 2010)
Cerebral cortical amyloid β	PET imaging	↓	↑	(Li et al., 2018)
Apolipoprotein A1	serum	↓	↓	(Ankit et al., 2016; Kitamura et al., 2017)
Autotaxin	cerebrospinal fluid	↑	↑	(McLimans and Willette, 2017)
Cerebral cortical surface, volume and thickness	MRI	↓	↓	(Brundel et al., 2010; Schwarz et al., 2016)
Low density lipoprotein	serum	↑	↓ early in life	(Pappolla et al., 2003; Vergès, 2009)

sRAGE – soluble receptor for AGEs.

both illnesses with high predictive value. The asymptomatic period before the beginning of chronic diseases offer opportunities for disease prevention. The primary prevention is to avoid factors that activate the disease development while secondary prevention are treatments that modify the disease progression before the onset of clinical symptoms. Accurate prediction and identification using biomarkers will be useful for disease prevention and initiation of proactive therapies to those individuals who are most likely to develop the disease. Peer-reviewed journal articles describing the examples of potential biomarkers which levels changes during both T2DM and AD onsets, are presented below (Table 1).

4. The influence of insulin on amyloid β and tau proteins' metabolism

4.1. Amyloid β and insulin/insulin receptor interactions

The common features observed in T2DM and AD are deposition of Aβ plaques, mitochondrial malfunction and inflammatory stress in peripheral tissue but the way how they interact with disease development is still under question. There are few hypotheses on the possible role of elevated insulin levels in development of neuropathological processes (Fig. 1).

One is that peripheral hyperinsulinemia may invoke a signal that inhibits synthesis of insulin in the cerebral tissue. It is also proposed that low concentrations of insulin in the brain could reduce the release of Aβ and therefore accelerate its accumulation. Another hypothesis assumes that competition between amyloid and insulin for the insulin degrading enzyme (IDE) cause Aβ aggregation due to its higher secretion and reduced clearance. Another theory connects high insulin levels with activation of neuronal hypersensitisation to amyloid beta toxic forms and phosphorylated tau protein (Kroner, 2009). While the concentrations of glucose and insulin in peripheral as well as in cerebral tissues are pivotal for understanding the interrelation between DM and AD, another question lies in unveiling the ways of glucose transport via blood brain barrier (BBB) and its depends from insulin. Initial studies supported the concept that glucose transporters - GLUT-1 and GLUT-3 as well as cerebral glucose uptake are not insulin depended (Seaquist et al., 2001). The investigators reported neuronal ubiquitous expression of insulin-sensitive glucose transporter 4 and 8 (GLUT-4 and GLUT-8), the presence of insulin and insulin receptors (IR) in the rat and mouse neuronal cells and at the BBB. Insulin levels in hippocampus, hypothalamus, cortex and in substantia nigra can be 10–100 higher than those observed in plasma (Sankar et al., 2002; van der Heide et al., 2006).

Many studies have been devoted to investigation of mechanism underlying the interrelation between Aβ pathogenesis and insulin/IGF dysfunction. IGF, insulin and their receptor modulates cell growth and repair in cerebral tissues, synaptic maintenance and neuroprotection as well as dendritic sprouting (Kleinridders et al., 2014; Stockhorst et al., 2004). There were observed hyperphosphorylation and reduced sensitivity of brain IR, attenuated insulin and IGF receptor expression in AD patients (Steen et al., 2005). In a study by Ohno group, the authors found that insulin is elevating expression of enzyme responsible for natural amyloid protein precursor (APP) cleavage - β-secretase, thus leading to the inhibition of AβPP processing (Devi et al., 2012), In vivo studies indicate that insulin hastens AβPP/Aβ transport from the endoplasmic reticulum and trans-Golgi network to the plasma membrane. In the consequence Aβ plaques are generated also by inhibition of its clearance via a metalloprotease enzyme responsible for insulin degradation and the main soluble Aβ degrading enzyme at neutral pH - insulin-degrading enzyme The affinity of this enzyme to insulin is very high due to which the Aβ gets assembly. Due to competitive inhibitor nature of insulin for IDE, it would leave Aβ to accumulate. The consequences are hyperinsulinemic condition and IDE deficiency (Vekrellis et al., 2000). Furthermore, with aging the level of substrate increases and the production of IDE decline. In primary cultures of rat cortical neurons and in N2a neuroblastoma cells that overexpress wild-type APP insulin promote aggregation not only of Aβ 1–40 and Aβ 1–42 but also the soluble APPα (Gasparini et al., 2001). Interestingly, mice with three mutations associated with familial Alzheimer's disease (APP Swedish, MAPT P301 L, and PSEN1 M146 V) known as 3xTg-AD and mice with human transgenes for both APP bearing the Swedish mutation and PSEN1 containing an L166 P mutation; analysed 7 days after an Aβ oligomers intracerebroventricular (*icv.*) injection presented insulin resistance and impaired peripheral glucose tolerance comparable to that verified in mice submitted to a high-fat diet for a week. After endoplasmic reticulum stress hindrance the observed deregulation of peripheral insulin signalling was attenuated suggesting that Aβ oligomers use a central route to disrupt metabolic control in peripheral tissues (Pandini et al., 2013). In other studies, it was found that in APP transgenic mice overexpression of Aβ-degrading proteases such as IDE or neprylisin in neurons notably diminish Aβ levels and hence blocks senile plaques formation (Leissring et al., 2003). In line with this, IDE knockout mice presented high Aβ concentrations in brain (Farris et al., 2003). In vivo studies on highly differentiated cultures of hippocampal

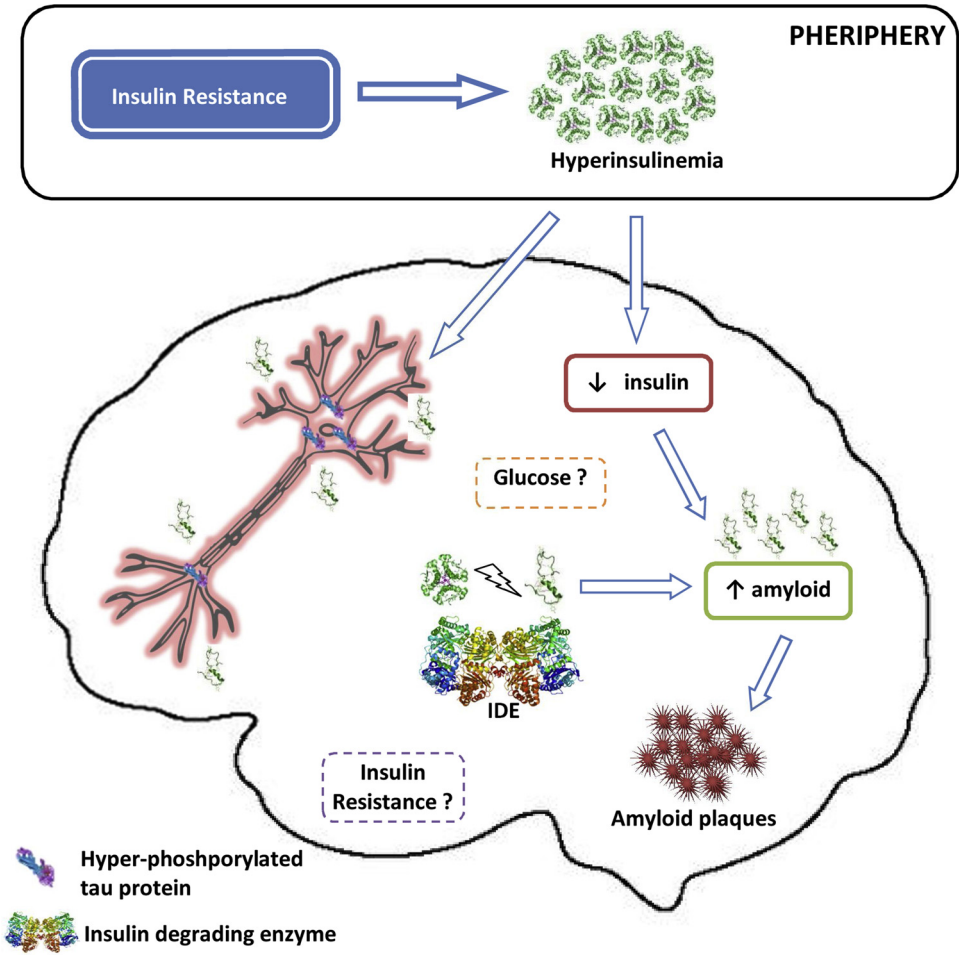

Fig. 1. A simplified schematic diagram representing the hypotheses on the possible role of insulin in development of amyloid pathological processes.

neurons shows that short-term exposure to synaptotoxic amyloid-beta derived diffusible ligands (ADDLs) induce reductions in dendritic IR levels and insulin-evoked tyrosine kinase activity. What's more, Western blots analysis revealed that even of the existence of hasty redistribution of surface IR rather than clear loss; there was no differences in total IR levels (Zhao et al., 2007). The soluble Aβ depended redistribution of IR is consistent with findings where the *N*-methyl-D-aspartate (NMDA) receptors subunits and EphB2 receptor tyrosine kinase also showed surface loss (Lacor et al., 2007). This hypothesis is supported by studies on AD brains and mice overexpressing a mutant form of APP (isoform 695) with the Swedish mutation (KM670/671 N L). It was shown that impaired insulin signalling corresponded with reduced IDE (Zhao et al., 2004). Further research in this field revealed that IR down-regulation and synaptic loss are considerably abolished by insulin treatment. Neuroprotective behaviour of insulin does not necessary comes from the fact of simple competition with amyloid for common binding sites on neuronal surface. It can be due to the fact that IR might down-regulate the binding sites via modulation of IR tyrosine kinase activity (De Felice et al., 2009). In rat astrocytoma cell line (C6) incubation for 24 h with STZ, resulted in significant decrease in IR mRNA and protein expression, phosphorylation of the insulin receptor substrate 1, the protein kinase B, the glycogen synthase kinase 3 α and β. Moreover, generates APP, the beta-secretase enzyme 1 and Aβ1–42 expression and significantly induce expression of the glial fibrillary acidic protein and phosphorylated P38 mitogen-activated protein kinases. STZ treatment triggered over expression of tumour necrosis factor α, interleukin 1β, cyclooxygenase 2, reactive oxygen species, the inducible isoform of nitric oxide synthase and caspase activation. Furthermore, insulin pre-treatment suppressed all above mentioned processes (Brown and Ransom, 2007; Rajasekar et al., 2014).

4.2. Tau protein and insulin/insulin receptor interactions

Over the last decade, there has been also considerable interest on the impact of insulin dysfunction and diabetes on tau pathology. Tau is an abundant neuronal protein expressed also at very low levels in central nervous system (CNS) astrocytes and oligodendrocytes. It arises as a product of alternative splicing from a single gene located on chromosome 17. Tau interacts with tubulin and is responsible for microtubulin polymerization and stabilization along with essential role in axonal homeostasis of organelles and biomolecules transport (Stokin et al., 2005). Under physiological conditions as well as in stress-induced responses tau activity is controlled by posttranslational modifications such as glycosylation, ubiquitination, glycation, nitration, oxidation, cleavage or truncation, and polyamination and sumoylation (Martin et al., 2011). This highly soluble and natively unfolded protein controls microtubule stability in two ways via isoforms and phosphorylation processes. Hyperphosphorylation of the tau protein can result in the self-assembly of tangles of paired helical filaments and straight filaments which is one of the crucial events in development of AD, frontotemporal dementia, and other taupathies patomorphological features. The process of binding tau to microtubule is controlled by GSK3β which activity is down regulated by insulin and IGF-1 because it's downstream event of the insulin-signalling pathway (Siddle et al., 2001). Stimulation of cultured human neuronal NT2N cells with insulin and IGF-1 diminish tau phosphorylation process, therefore leading to higher affinity of tau to microtubules. This process is due to the inhibition of GSK3β via the phosphatidylinositol 3-kinase/protein kinase B signalling

pathway (Hong and Lee, 1997) thus insulin deficiency or resistance may promote dephosphorylation and activation of GSK3β. The increasing data supports the hypothesis that the activity of GSK3β is enhanced in both types of diabetes mellitus, leading to the accumulation of hyper-phosphorylated tau. The evidence suggesting that IR signalling can influence tau production in the brain was presented by Plaschke et al. (Plaschke et al., 2011). Those investigations revealed that in AβPP Tg2576 mice *icv*. administration of STZ, among others, increased total tau protein which was associated with decreased GSK-3α/β ratio (phosphorylated/total). In other study, Swiss Webster mice with induced insulin-deficient diabetes presented significantly impaired learning capacity, reduced IDE expression diminished phosphorylation of GSK3β together with higher enzyme activity. This insulin depended features were associated with a concomitant escalation in tau phosphorylation. What's interesting, those changes wasn't observed in db/db mice, a model of type 2 diabetes after similar time of diabetes activation (Jolivalt et al., 2008). The same authors observed that phosphorylated tau immunoreactivity was increased in hippocampal neurons of hAPP mice with induced diabetes by overnight intraperitoneal injection of STZ. Moreover, there was observed co-incidence of activated GSK3β and increased tau phosphorylation (Jolivalt et al., 2010).

Mounting proofs obtained from human and animal models indicates that diabetes can promote aberrant tau modification. The fivefold average and detected with eight different phosphorylation-dependent tau antibodies increase in tau phosphorylation was found in cerebral cortex and hippocampus of 6–7 weeks old adult, male C57BL/6 mice within 3 days of insulin depletion by STZ treatment (Clodfelder-Miller et al., 2006). On a pre-existing tau pathology in the P301 L tau transgenic mice strain, insulin depletion by STZ administration generated massive deposition of hyper-phosphorylated, insoluble tau leading to NFTs formation (Ke et al., 2009). In a subsequent studies on THY-Tau22 transgenic mouse model developing progressive hippocampal tau pathology and spatial memory defects, revealed that early and progressive obesity potentiated hippocampal tau pathology at a later stage. Surprisingly, high fat diet didn't induced peripheral insulin resistance. Further, pathological worsening occurred while hippocampal insulin signalling was up regulated (Leboucher et al., 2013). In line, a detailed analysis of newly generated brain/neuron-specific insulin receptor knockout mice revealed abolition of IR expression, increased Tau phosphorylation connected to reduced phosphorylation of Akt and GSK3β in the presence of intact neurotrophic signalling. These mice are mainly characterized by hyperinsulinemia, mild insulin resistance, obesity and reduced fertility (Schubert et al., 2004). Similar study on three- to four-month-old, STZ *icv*-treated, male Wistar rats exhibited a statistically significant IR mRNA down-regulation in frontoparietal brain cortex and hippocampus together with marked increase in tau phosphorylation at Ser199, Thr212, Ser396, and PHF-1 sites as a long-term consequence of STZ administration. Also, levels of both GLUT1 and GLUT3, the protein *O* -GlcNAcylation as well as the microtubule-binding activity of tau enriched were markedly reduced (Grünblatt et al., 2007). Together, above mentioned studies suggest that insulin and IGF-1 regulate the level of tau phosphorylation, and therefore, disruption in proper insulin and IGF-1 signalling could play an important role in the onset and progression of tau pathogenesis. Animal models of insulin signalling dysfunction have provided additional evidence that insulin plays crucial role in the regulation of Tau phosphorylation in vivo. Those investigations are consistent with the hypothesis that insulin resistance alone is not sufficient for the development of overt neurodegenerative changes but facilitate abnormal hyper-phosphorylation of tau and neurofilaments and, consequently, neurofibrillary degeneration (Kim and Feldman, 2015; Peng et al., 2013).

Numerous studies have reported that T3DM rat models after iv STZ injections exhibit no alteration in both insulin and glucose levels but shows several neurochemical, structural and behavioural changes that are similar to cellular abnormalities observed in AD brains such as: brain atrophy, cell loss, neurodegeneration, a decrease in glucose utilization, induction of energy metabolism, an impairment in learning and memory, as well as a significant increase in OS (Duelli et al., 1994; Pathan et al., 2006; Sharma and Gupta, 2001; Yun et al., 2000). Other research in this field revealed that there was observed an increase in tau phosphorylation in 3xTg-AD mouse model after *icv.* injection of STZ. The 3xTg-STZ mice were produced by stereotaxic injection of STZ into the left lateral ventricle of the brain of 6 month old mice harbouring three mutant human transgenes $PS1_{M146V}$, APP_{SWE}, and tau_{P301L}; developing amyloid plaques, NFTs, and cognitive deficits in an age-dependent manner. Twenty-one days after injection, the mice were subjected to behavioural tests which lasted for 3 weeks than decapitated and the hippocampus, cerebral cortex, subcortical structures, cerebellum, and brain stem were dissected and stored for biochemical and histological analyses. The STZ injection caused a higher level of anxiety, exacerbates the short-term memory and spatial reference learning impairment. Immunohistochemical analysis reveals the increase in the phosphorylated tau in the hippocampus and the cerebral cortex of the 3xTg-STZ comparing to wild type and 3xTg-AD mice (Chen et al., 2014). According to other study performed by Plaschke et al. there wasn't detected any increase in the level of phosphorylated Tau in the brain of Tg2576 mice (Plaschke et al., 2011). Despite the inconsistency and heterogeneity of the available data (Table 2) considering differences in the rat strain used, the dose of STZ delivered, the age at STZ treatment and brain regions investigated; on the whole it can be considered that, brain insulin resistance might be one of a central events in AD development.

5. The influence of hyperglycaemia on amyloid β and tau proteins' metabolism

5.1. Amyloid β and hyperglycaemia

One of the most typical and critical pathological feature of diabetes patients is increased glucose concentrations in blood. In prospective, community-based cohort study Larson's group found that higher levels

Table 2
Studies performed on animal models analyzing the impact on insulin/IR on tau metabolism.

Experimental model	Method	Tau metabolism	References
3xTg-STZ mice	*icv*. injection of STZ	↑ phosphorylation	(Chen et al., 2014)
Tg2576 mice	*icv*. injection of STZ	↑ total tau	(Plaschke et al., 2011)
hAPP mice	i.p. injection of STZ	↑ phosphorylation	(Jolivalt et al., 2010)
P301 L mice	i.p. injection of STZ	↑ phosphorylation ↑ NFTs	(Ke et al., 2009)
THY-Tau22 mice	High fat diet	↑ phosphorylation	(Leboucher et al., 2013)
db/db mice	i.p. injection of STZ	No effect	(Jolivalt et al., 2008)
Wistar rats	*icv*. injection of STZ	↑ phosphorylation	(Grünblatt et al., 2007)
C57Bl/6 mice	i.p. injection of STZ	↑ phosphorylation	(Clodfelder-Miller et al., 2006)
Swiss Webster mice	i.p. injection of STZ	↑ phosphorylation	(Jolivalt et al., 2008)

STZ – streptozotocin; NFTs- neurofibrillary tangles.

of glucose connected with disrupted glucose homeostasis might play a causative role in increased risk of developing dementia and propensity to changeover from mild cognitive impairment (MCI) to AD (Crane et al., 2013). The transgenic AD mouse model APP/PS1 fed on high fat diet exhibited higher susceptibility to high fasting blood glucose, peripheral glucose intolerance and diet-induced body weight gain when compared to non-transgenic controls on high fat died (Ruiz et al., 2016). In other studies, it was found that glycated haemoglobin (HbA1c) level, a retrospective marker of glucose concentration could be associated with development of MCI or dementia in postmenopausal osteoporotic women primarily without diabetes. In non-diabetic non-demented elderly subjects, an increase in HbA1c over time is associated with cognitive decline and greater rate of brain atrophy (Enzinger et al., 2005; Ravona-Springer et al., 2012; Yaffe et al., 2006). In a population-based 12 year follow-up study the risk of AD or vascular dementia was increased by 63% by diabetes and is associated with low early insulin response but not with low insulin sensitivity (Rönnemaa et al., 2009). One of the hypothesis studied by Holtzman group is that hyperglycaemia modulates Aβ levels through the modulation of neuronal activity in APP/PS1 mice (Macauley et al., 2015). In this process are involved adenosine triphosphate-sensitive potassium channel which regulation seems to provide novel therapeutic approach for AD patients with metabolic disturbances. The contribution of the toxic effects of hyperglycaemia to Alzheimer's disease pathologic features can vary among patients depending on duration and magnitude of the hyperglycaemia. In another study, investigators examined the effect of high glucose on expression and metabolism of APP and on Aβ production in human neuroblastoma SH-SY5Y cells (Yang et al., 2013). They observed significantly increased levels of APP protein after incubation with 10 and 25 mM glucose solutions for 24 and 48 h. What's interesting, this effect was not the consequence of enhancement of APP gene transcription but resulted from low levels of its turnover rate. It can be also connected with the fact that APP degradation is proteasome and lysosome pathway depended and those mechanisms are also altered by hyperglycaemia (Peres et al., 2013; Queisser et al., 2010). Moreover, as APP proteolytic product C99 and Aβ are degraded through proteasome pathway, elevated protein C99 and Aβ levels seems to be natural repercussion of high glucose-induced proteasomal degradation (Tseng et al., 2008). In in vitro studies on human umbilical vein endothelial cells, Chao et al. observed significantly stimulated expression of full-length APP accompanied by heightened secretion of Aβ 1-42 after exposure to 30 mM glucose solution (Chao et al., 2016). In addition, hyperglycaemic state might have influence on APP glycation, phosphorylation and ubiquitination therefore, leading to alterations in intracellular trafficking and/or the conformation of the protein.

Normally in the brain, the increase of glucose uptake is a saturable process followed by upregulation of insulin receptors but when the receptor activity is inhibited it could create persistent hyperglycaemia. On the other hand, if the homeostasis between glucose levels entering the brain and the concentration of insulin is disturbed it could lead to the formation of advanced glycation and products. Acute insulin administration affects the cognition abilities while chronic administration can accelerate cognitive bias, activate insulin resistance, inflammation processes and hyperglycaemia. Moreover, it can diminish the insulin sensitivity at BBB and hence affects the glucose metabolism in brain. In this situation occurs the starvation in brain cells which is more pathologic situation as glucose - the energy fuel is available to the whole body but not available for brain cells (Convit, 2005). There are limited data explaining in details the glucose transport via BBB. It is coordinated by the family of GLUT transporters, which are highly expressed in the endothelial cells of the BBB. It is believed that under physiological conditions, the concentration of glucose in the brain is three times lower than in peripheral blood. Despite the GLUT pathway of establishing the glucose levels in the brain, there has to be other, not concentration gradient depended system involved in glucose transport. The studies of Seaquist et al. demonstrated the directly proportional correlation between peripheral and brain glucose levels after hyperglycaemic clamp. Using a novel technique of high-field 1H magnetic resonance spectroscopy they have directly and noninvasively examined the effect of insulin on the concentration of native glucose in the living human brain. It was shown that there is delay in the increase in brain glucose level following a rise in peripheral levels. Additionally, as the infusion of insulin was without significant effect on the in vivo glucose concentration, this findings support the hypothesis that cerebral glucose transport is an insulin-independent process (Seaquist et al., 2001). in vivo model of chronic hypoglycaemia induced in rats by constant infusion of insulin via osmotic minipumps; demonstrated increased expression of GLUT1 mRNA and protein at the BBB which seems to be responsible for compensatory increase in BBB glucose transport activity (Kumagai et al., 1995). Furthermore, in experimental diabetes model GLUT activity and its cerebral flow was 44% lower comparing to controls (Pardridge et al., 1990). Such findings indicated that the main factor responsible for regulation of glucose transport is the GLUT amount expressed at the BBB. During assessment of regional cerebral glucose metabolism by 18F-fluorodeoxyglucose (FDG) position emission tomography at resting state, it was shown reduced glucose uptake in regions vulnerable to AD pathology such as fronto-temporo-parietal and cingulate cortices (Herholz, 2010; Reiman et al., 2004). A similar situation was observed in patients with aging-associated cognitive decline (Hunt et al., 2007). A role of brain tissue glucose concentrations and assessment of glycolytic flux on severity of AD pathology and the expression of AD symptoms was investigated by Thambisetty group (An et al., 2017). They have shown that low levels of neuronal GLUT3 reflect greater severity of both amyloid plaque and neurofibrillary tangle pathology. Furthermore, longitudinal increases in fasting plasma glucose levels decades before death are associated with higher brain glucose (Mosconi et al., 2008).

5.2. Tau protein and hyperglycaemia

Multiple possible mechanisms may hence underpin the association between DM and AD, including direct effects of hyperglycaemia to the brain, neuronal insulin receptor desensitization, and insulin-induced Aβ amyloidosis. The brain is characterized for a high energetic consumption and therefore needs a large uptake of molecules capable of generating energy, mainly blood glucose. Furthermore, both neurons and astrocytes are highly susceptible to variations in glucose concentrations in blood. Researchers has consistently demonstrated that hyperglycaemia results in neuronal injuries, leading to neurons and supporting Schwann cells apoptosis and the development of diabetic neuropathy (Figueroa-Romero et al., 2008). Furthermore, genetically and nutritionally induced diabetic phenotypes in an AD background seem to aggravate and accelerate the pathological changes (Takeda et al., 2010). Devedjian et al. (Devedjian et al., 2000) observed sustained hyperglycaemia, hyperinsulinemia and insulin resistance in APdE9 mice crossed with mice over-expressing insulin growth factor 2 (IGF2) in the pancreas and fed with high fat diet.

In AD, abnormally phosphorylated tau aggregates into NFTs in the neuronal cell body and proximal dendrites. It seems that not only hyperphosphorylation but also tau cleavage, especially at Asp421 by caspase-3, can play an important role in the disease progression (Gamblin et al., 2003). Feldman and collaborators examined tau modification in STZ-injected and db/db mouse models of diabetes. The db/db mice develop hyperglycaemia at 3–4 week of age. The authors assumed that in T2DM, hyperglycaemia-mediated tau cleavage may contribute to AD. They have detected high levels of tau hyperphosphorylation and increase in cleavage rate in the cortex and hippocampus of T2DM mice model which was aggravated with age. In comparison, no cleavage and less hyperphosphorylated tau was discovered in STZ-injected mice (Kim et al., 2009). The in vitro studies on E15 rat embryonic cortical neurons and on db/db mice revealed that hyperglycaemic conditions induce tau cleavage and apoptosis. The

effect of glucose on the appearance of broken tau fragments was time- and concentration-dependent and well-correlated with the appearance of cleaved caspase-3 and apoptosis. Neurons treated concomitantly with Aβ and glucose had higher levels of apoptosis and tau cleavage comparing to those under hyperglycaemic conditions. Authors suggests that cleaved tau serves as a nucleation centre enhancing polymerization kinetics (Kim et al., 2013). Another pathway which has been associated with glucose toxicity and can influence tau pathology is O-GlcNAcylation - the addition of O-GlcNac to Ser/Thr residues in the tau protein. In tau protein Thr231, Ser396, and Ser422 phosphorylation sites are considered critical for tau's ability to bind. O-GlcNAcylation seems to have impact on tau phosphorylation, regulate cellular and microtubular structure and functionality (Gong et al., 2006; Lozano et al., 2014). In the work on hyperglycaemic and hyperinsulinemic rats that received the Aβ 24–35 peptide, investigators found a diminution in O-glycosyltransferase (OGT) expression and O-GlcNAcylation levels, and increased P-tau-Ser-396 phosphorylation. By high levels of GSK3β activity and OGT and O-GlcNAcylation inhibition in the hippocampal tissue, hyperglycaemia and hyperinsulinemia seems to modulate hippocampal damage and the development of AD (Lozano et al., 2017). There is difficulty in establishing appropriate animal model to study interrelation between chronic hyperglycaemia and neurodegenerative processes in vivo. Guo et al. (Guo et al., 2016) hybridized heterozygous knockout of pancreatic duodenal homeobox 1 ($Pdx1^{+/-}$) mice with APP/PS1 transgenic mice to generate $Pdx1^{+/-}$/APP/PS1 model. These animals exhibited a marked increase in blood glucose levels and substantial decreased serum insulin levels without insulin resistance. The increase of tau phosphorylated at the Thr205 and Ser396 sites in CA3 subfield of hippocampus was more apparent in the $Pdx1^{+/-}$/APP/PS1 mice than in the APP/PS1 mice and wild type mice. They also examined the change in protein phosphatase 2 (PP2) one of the most important phosphatase involved in tau dephosphorylation, specifically decreased in AD. Therefore, chronic hyperglycaemia might increase the risk or accelerate the AD development via the promotion of tau phosphorylation or exacerbation of tau hyperphosphorylation at critical, abnormal phosphorylation sites. Because of the lack of appropriate animal models, it remains to be confirmed whether chronic hyperglycaemia worsens tau protein pathology in vivo.

6. The influence of advanced glycation end products on amyloid β and tau proteins' metabolism

6.1. Amyloid β versus advanced glycation end products and their receptors

The pioneers of the theory connecting age-related decline in cell function and tissues with non-enzymatic glycation was Monnier and Cerami (Monnier and Cerami, 1981). They have proposed that AGEs can accelerate normal aging. This idea was confirmed by studies suggesting the correlation between AGEs and AD pathomorphology conducted in the mid 1990's (Vitek et al., 1994; Yan et al., 1996). In vivo, advanced glycation products are heterogeneous products of non-enzymatic modification of proteins by reducing sugars also known as Maillard reaction. This post-translational modification of proteins plays an important role in neuropathogenesis as AGEs accumulation rate notably rise in angiopathy in diabetic patients and AD (Takeuchi and Yamagishi, 2004; Yamagishi et al., 2003). AGEs are expressed in neurons, microglia astrocytes and in brain endothelial cells. In vitro studies where cortical neurons were incubated with distinct AGEs forms, enlighten the toxic impact of AGEs, especially AGE-2, on neuronal cells by inducing apoptotic cell death. Since the AGEs concentration in T2DM is elevated and extracellular accumulation of AGEs is known to have impact on Aβ plaques formation, so it could be another common link sheared by these two distinct diseases (Takeuchi et al., 2000; Takeuchi and Yamagishi, 2008). The accumulation of AGEs formation in different tissues is especially prominent in diabetes patients. AGEs can enter the cells, where they are metabolized, through the activation of the receptor for AGEs (RAGE), which are highly expressed in neurons and microglia (Sasaki et al., 2001). In subsequent studies it was shown that Aβ is a RAGE ligand and that this receptors are over-expressed in AD (Origlia et al., 2008). Experimental data indicate that insolubility and growth of amyloid plaques is accelerated by extensive covalent protein cross-linking and by formation of AGEs (Loske et al., 2000; Munch et al., 2003). An immunohistochemical study in human post-mortem samples of AD, T3DM, diabetic and nondemented controls demonstrated that hippocampus of ADD patients with AD and diabetes contained higher concentration of amyloid plaques, higher AGEs levels and RAGE-positive cells (Valente et al., 2010). RAGE are the receptors for multiple ligands, which interacts with Aβ leading to neuronal OS and inflammation processes activation (Li et al., 2009). Arancio et al. has demonstrated strong activation of NF-κB - inflammation factor as well as more subtle indications of neuronal malfunction (impaired spatial learning/memory), in generated mAPP/RAGE mice by 3–4 months of age way before the cerebral Aβ and plaque formation. Moreover, it seems that increased cellular RAGE renders neurons more vulnerable to Aβ-induced dysfunction (Arancio et al., 2004). Pentosidine levels (one of the class of AGEs), are significantly increased in serum from patients with AD and is useful for the diagnosis of AD (Meli et al., 2002). Glyceraldehyde-derived pyridinium (GLAP) is glyceraldehyde's-derived AGEs containing a pyridinium moiety, a predominant feature of toxic AGEs (TAGE) (Takeuchi and Yamagishi, 2008). The studies on this two AGEs: pentosidine and GLAP and theirs influence on beta-secretase 1 (BACE 1) expression were performed both in vivo (in STZ-treated rats) and in vitro (in differentiated SK-N-BE neuroblastoma cells) (Guglielmotto et al., 2012). They have shown that those AGEs can upregulate the key enzyme for amyloid-β production - BACE 1 through their binding with RAGE and the consequent activation of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB). Furthermore, the rate of microglial synthesis of the most abundant AGEs product in human AD brains, AGE-albumin is markedly increased by amyloid-β exposure and OS. It induce neuronal cell death by upregulation of RAGE, mitochondrial calcium influx, and mitogen-activated protein kinase (MAPK) - Bcl-2-associated X protein (Bax) pathway (Byun et al., 2012). As RAGE can bind Aβ and transduce signals leading to cellular activation, it could be important in cellular dysfunction that is prominent in AD pathology. For example, there was observed the presence of increased numbers of RAGE-immunoreactive microglia and neurons in the hippocampus, entorhinal cortex, and superior frontal gyrus of human post-mortem AD brains in comparison to nondemented individuals. Furthermore, the addition to or presence of Aβ 1–42 in cultured microglia derived from AD brains stimulates expression of macrophage colony-stimulating factor (M-CSF). The process was blocked after treatment with anti-RAGE $F(ab')_2$ (Lue et al., 2001; Miller et al., 2008). Similarly, RAGE levels are higher in the brains of early-onset familial AD transgenic model - Tg2576 mice as well as in cortical and hippocampal neurons and astrocytes of 3XTg AD mouse representing the full spectrum of AD neuropathology (Cho et al., 2009; Choi et al., 2014). The possible mechanism of interrelations between amyloid beta and AGE/RAGE is presented on Fig. 2.

There is a growing body of evidence to suggest that AGEs and/or RAGE can participate in transport of beta amyloid via BBB. This hypothesis is supported by studies on the murine mouse brain capillary endothelial cells line (bEnd.3), an in vitro model of BBB where Aβ treatment up-regulated the expression level of RAGE (Wan et al., 2015). In other study on the same cellular model AGE accelerated Aβ influx via BBB in concentration- and time-dependent manner. As a consequence there were observed higher RAGE and NF-κB p65 expressions (Chen et al., 2017). Further support for this link was provided by studies on Tg2576 mice fed with a high-AGEs diet for 8 months. This mouse shows spatial memory and learning impairments, higher Aβ and AGEs hippocampal levels. In addition there were observed the overexpression of RAGE, which binds to Aβ and regulates its transport across the BBB, suggesting a mediating pathway (Lubitz et al., 2016). Chronic

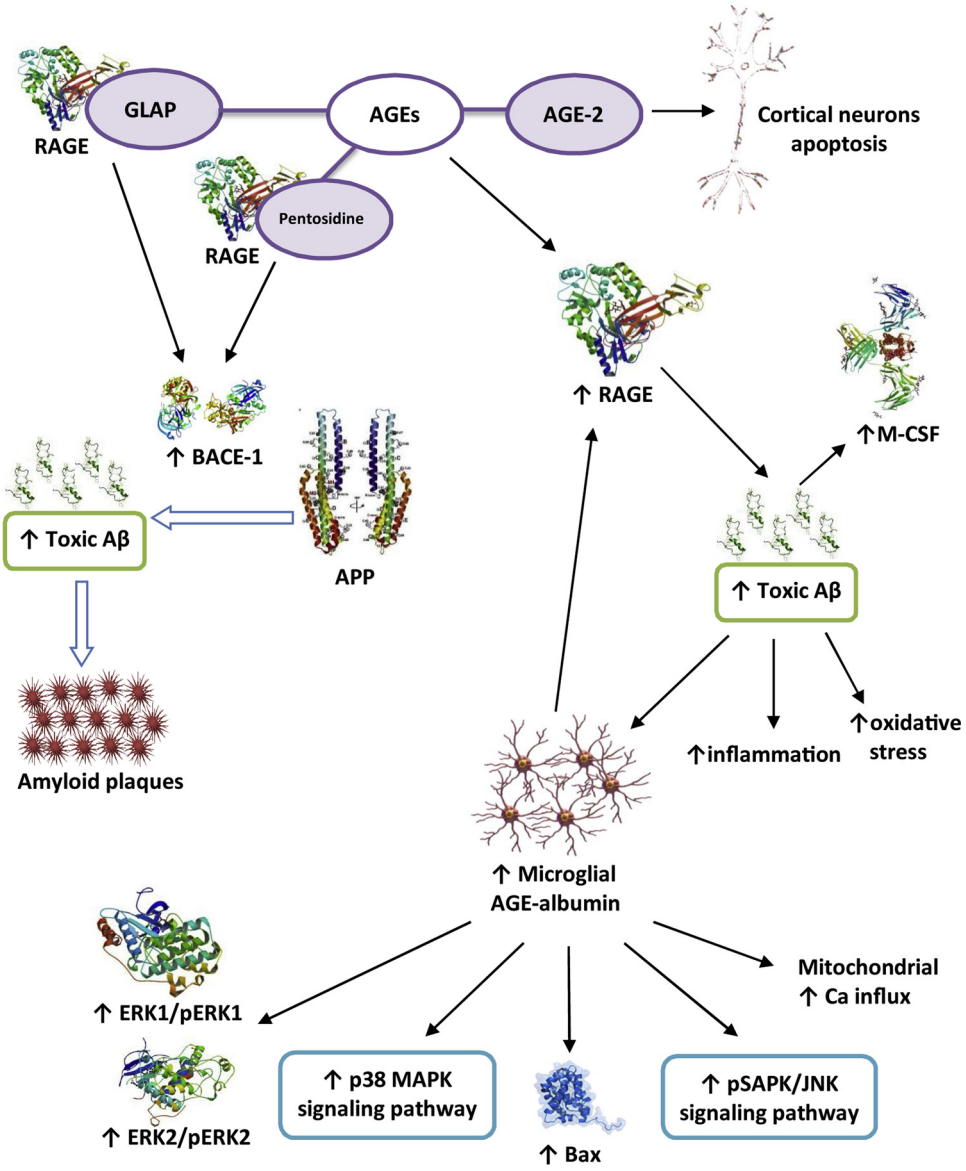

Fig. 2. The potential mechanism of interrelations among amyloid beta and AGE/RAGE.
AGEs- advanced glycation end products; AGE-2 - advanced glycation end product 2; RAGE-receptor for advanced glycation end products; GLAP- Glyceraldehyde-derived pyridinium; BACE-1 – beta-secretase 1; APP – amyloid precursor protein; M-CSF - macrophage colony-stimulating factor; Aβ – amyloid β, ERK1 - extracellular signal-regulated kinase 1; pERK1 – phosphorylated extracellular signal-regulated kinase 1; ERK2 - extracellular signal-regulated kinase 2; pERK2 – phosphorylated extracellular signal-regulated kinase 2; pSAPK/JNK- phosphorylated Stress-activated protein kinase/c-Jun NH(2)-terminal kinase; Bax - B-cell lymphoma 2 associated X protein; p38 MAPK – mitogen-activated protein kinases.

treatment with anti-diabetic drugs like metformin, glibenclamide and insulin for 6 weeks remarkably decreased influx of circulating Aβ across the BBB in a mouse model of type 2 diabetes, BKS.Cg-m$^{+/+}$ Lepr^{db}/J, commonly known as db/db mice (Chen et al., 2016).

Despite the well-established link between RAGE and the pathophysiology of T2DM and AD, the effects of soluble form of RAGE (sRAGE) on concurrent metabolic and cognitive derangement remain unknown. sRAGE a form of the extracellular receptor cleaved from the cell surface (via the action of different proteases) is an important metabolic mediator as it can act as an anti-inflammatory decoy ligand for full-length membrane-bound form RAGE and decoy receptor for Aβ (Cai et al., 2016). Thus, it can inhibit the binding of Aβ to RAGE and delay the development and progression of AD by hindering intracellular signaling pathways associated oxidative stress generation and inflammatory responses. Additionally, the binding of Aβ to sRAGE will benefit the Aβ clearance under blood circulation in liver and other organs (Fuller et al., 2018; Yamagishi, 2010). In the in vitro model of mice overexpressing human endogenous sRAGE and in RAGE-null mice the transition of 125I-labelled Aβ1–42 from circulation to brain parenchyma was considerably reduced in regions susceptible to amyloid pathological changes, in comparison to the effect observed in wild type mice (Sugihara et al., 2012). Reduced values of sRAGE observed with both obesity and impaired glucose tolerance patients seems to be associated with greater risk of developing T2DM (Miranda et al., 2017). Some studies showing elevated serum concentrations of sRAGE in patients with T2DM and their positive correlation with circulating AGEs levels (Nakamura et al., 2007; Tan et al., 2006). The reduction of blood sRAGE levels in MCI suggest a role of RAGE axis in the pathogenesis of the different types of dementia (Ghidoni et al., 2008). In AD patients the serum levels of sRAGE are associated with cognitive impairment and are attenuated as neuropathological changes occurs but it showed a low diagnostic accuracy and cannot be used to differentiate AD from vascular, mixed or other forms of dementia (He et al., 2016; Li et al., 2010; Liang et al., 2013). Fuller et al. (Fuller et al., 2018) in AD patients with or without diagnosed DM showed that such factors as BMI, fat mass, HOMA-IR, insulin, and amylin were all metabolic or anthropometric factors which significantly interacted with sRAGE profiles within AD subjects. Authors conclude that these characterizations of sRAGE contribute evidence to the link between impaired metabolism and cognitive decline due to AD and suggest that probably the attenuated plasma sRAGE seen in individuals with metabolic dysfunction may be contributing to AD due to a reduced capacity to scavenge RAGE ligands and attenuate RAGE signaling.

The deleterious effect of diabetes mellitus on peripheral nervous

systems is widely acknowledged. The “glycation theory of aging” unites some of the neuropathological and biochemical findings in AD to a general picture. AGEs may contribute to several mechanisms underlying dementia including the accelerated protein crosslinking with β amyloid. In addition, AGEs and other RAGE ligands including Aβ can lead to neuronal malfunction, therefore pharmaceutical interventions using antibodies against AGE/RAGE or its antagonists/inhibitors may be promising approach for minimising AGEs formation, one of the crucial elements in diabetes as well as neurodegenerative progression (Muronetz et al., 2017). Lately interesting hypothesis concerning the association of chronic exposure to some xenobiotics, such as arsenic, especially during development, with alterations of chemical transmission and demyelination, which result in cognitive deficits and peripheral neuropathies. In brains of male Wistar rats which were exposed to 3 ppm of inorganic arsenic in drinking water from fetal development until 4 months of age, significant increase of Aβ1–42 production and RAGE expression (both soluble and membral form) were observed (Nino et al., 2018).

6.2. Tau protein versus advanced glycation end products and their receptors

Other factors induced by diabetes might play an important role in tau pathogenic metabolism, such as AGEs and theirs receptors. It’s well known that AGEs accumulate during life and this process is accelerated under diabetic conditions. The intracellular AGEs are co-localized with NFTs, and treatment of SH-SY5Y neuroblastoma cells with glycated tau in culture leads to neural dysfunction and induce apoptosis, suggesting an intrinsic link of AGEs with tau (Yan et al., 1994). However, the direct in vivo evidence showing the effects of AGEs on tau phosphorylation is still missing. Post-mortem immunohistochemical studies revealed a significant increase of both RAGE-positive cells and the size of aggregated Tau-positive cells in hilus, pyramidal cells and granular layer of hippocampus of patients with diabetes and AD comparing to AD patients (Valente et al., 2010). Proteome measurements and quantitative analysis has convincingly demonstrated increased levels of RAGE, cathepsin B, and asparaginyl endopeptidase (AEP) correlating with higher levels of AGEs modified proteins and phosphorylated tau in brain homogenates from the temporal cortex of individuals affected by AD. As AEP is directly involved in tau hyper-phosphorylation, they also studied the AGEs-RAGE-dependent expression of this protein in primary cortical neurons. AGEs treatment enhanced tau phosphorylation, as evidenced by elevated phosphorylation at serine 396 of tau protein (Basurto-Islas et al., 2013; Batkulwar et al., 2018). Significant findings have provided substantial insight into how higher AGEs levels contribute to exacerbated tau phosphorylation. Li et al. (Li et al., 2012) demonstrated that treatment of the SK-N-SH cells, primary neurons, and rats with exogenous AGEs-modified BSA led to tau hyper-phosphorylation through RAGE-mediated GSK3 pathway. Targeting the RAGE/GSK-3 pathway could be a promising therapeutic strategy for preventing tau hyper-phosphorylation in response to increased AGEs levels. Targeting the RAGE/GSK-3 pathway could be a promising therapeutic strategy for preventing tau hyper-phosphorylation in response to increased AGE levels.

7. Future experimental directions

In this paragraph we would like to concentrate on novel correlations and possible pathways between diabetes mellitus and Alzheimer's disease that have not yet been deeply analysed, or about which there are limited data.

Firstly, we will consider the fact that protein glycation, including glyceraldehyde-3-phosphate dehydrogenase (GAPDH) by glyceraldehyde-3-phosphate (GADP) and the influence of this process on the neuropathological features characteristic for neurodegenerative diseases, is practically unstudied (Muronetz et al., 2017). The most widely known glycation is a nonenzymatic modification of proteins by reducing sugars. This process is a very slow and complex cascade of chemical transformations. GADP is an intermediate product of glycolysis capable of modifying proteins efficiently. A vicious circle is created when the more GAPDH activity decreases, the higher the concentrations of GADP and methylglyoxal, which glycate GAPDH, further reducing its activity. There is abundant data on the glycation of protein involved in the development of various neurodegenerative diseases such as prion protein, Aβ or α synuclein by methyglyoxal, but relatively little is known about the effects of protein glycation by GADP, and only a few studies examine the effect of glycation on the amyloid transformation of Aβ in vitro (Li et al., 2013; Iannuzzi et al., 2014). This way of glycation may cause the stabilization of amyloid oligomers and the acceleration of aggregation processes together with a break in the degradation system, and lead to complex neurological disorders. As a consequence of the excessive accumulation of active carbonyl compounds (e.g. GADP and methylglyoxal), GAPDH activity decreases. To our knowledge, there have so far been no studies on GAPDH glycation by GADP, and these aspects have not yet been studied in cellular models or in living organisms. The effect of GAPDH glycation on its non-glycolytic activities or catalytic functions in processes such as amyloidogenic transformations, apoptosis or DNA repair remains to be elucidated.

Furthermore, to our knowledge there are very few studies on the role of insulin or glucose on astroglial and neuron morphology such as e.g. spine density, synapse development, number and size, dendritic arbour morphology etc, on in vivo or in vitro models of Alzheimer's disease. One such study showed the crucial conservative role of the inositol requiring enzyme 1 (IRE1) in the regulation of dendritic morphogenesis in cultured rat hippocampal neurons, and as the authors showed, this effect can be abolished by reducing insulin/IGF signalling pathways (Salzberg et al., 2017). The second study verified, among other issues, whether the morphology of hypothalamic astrocytes was affected following the loss of IRs in vivo. The total number of hypothalamic glial fibrillary acidic protein (GFAP)-positive cells was unchanged after the postnatal ablation of insulin receptors in GFAP-expressing cells in mice (GFAP-IR KO). There was a difference in the quantity and length of hypothalamic primary astrocyte processes, which were shorter and less present in GFAP-IR KO mice compared to the wild type, indicating a potentially altered interaction with surrounding cells. Similar astrocyte load changes were observed in the hippocampus of GFAP-IR KO mice when compared to the control (García-Cáceres et al., 2016). As defective morphologies of different neuron types can have direct effects on its acquisition and the processing of distinct inputs leading to neuropathological disturbances, further studies contributing to the understanding of the role of insulin and glucose brain homeostasis in neuronal stability and development are definitely warranted.

Only one study has focused on the direct link between brain atrophy provoked by diabetes mellitus and subsequent conversion to AD. Fukuzawa et al. (Fukazawa et al., 2013) found a dementia subgroup within AD patients presenting typical diabetic metabolic abnormalities, which differed from the characteristics of AD. Further study is needed to determine the degree to which brain deficits elicited by diabetes might initiate or exacerbate the pathology of AD.

It is also of importance not to underestimate the influence of genetic and environmental factors such as lifestyle, metabolic disease and/or cumulative infections, as well as exposure to different xenobiotics, which might instigate a feed-forward cycle that contributes to the progression of both T2DM and AD (Heindel et al., 2017; Nicolia et al., 2015). In the search for explanations of the interplay between pathomechanisms it would also be worthwhile to deeply analyse the role of inheritance associated with epigenetic modifications of histone proteins and DNA by the modulation of acetylase and metylase activities (Rorbach-Dolata et al., 2017). These changes can have a deep impact on the onset of AD and T2DM, as well as on the influence of chronic hyperglycaemia conditions on typical neuropathological features in the

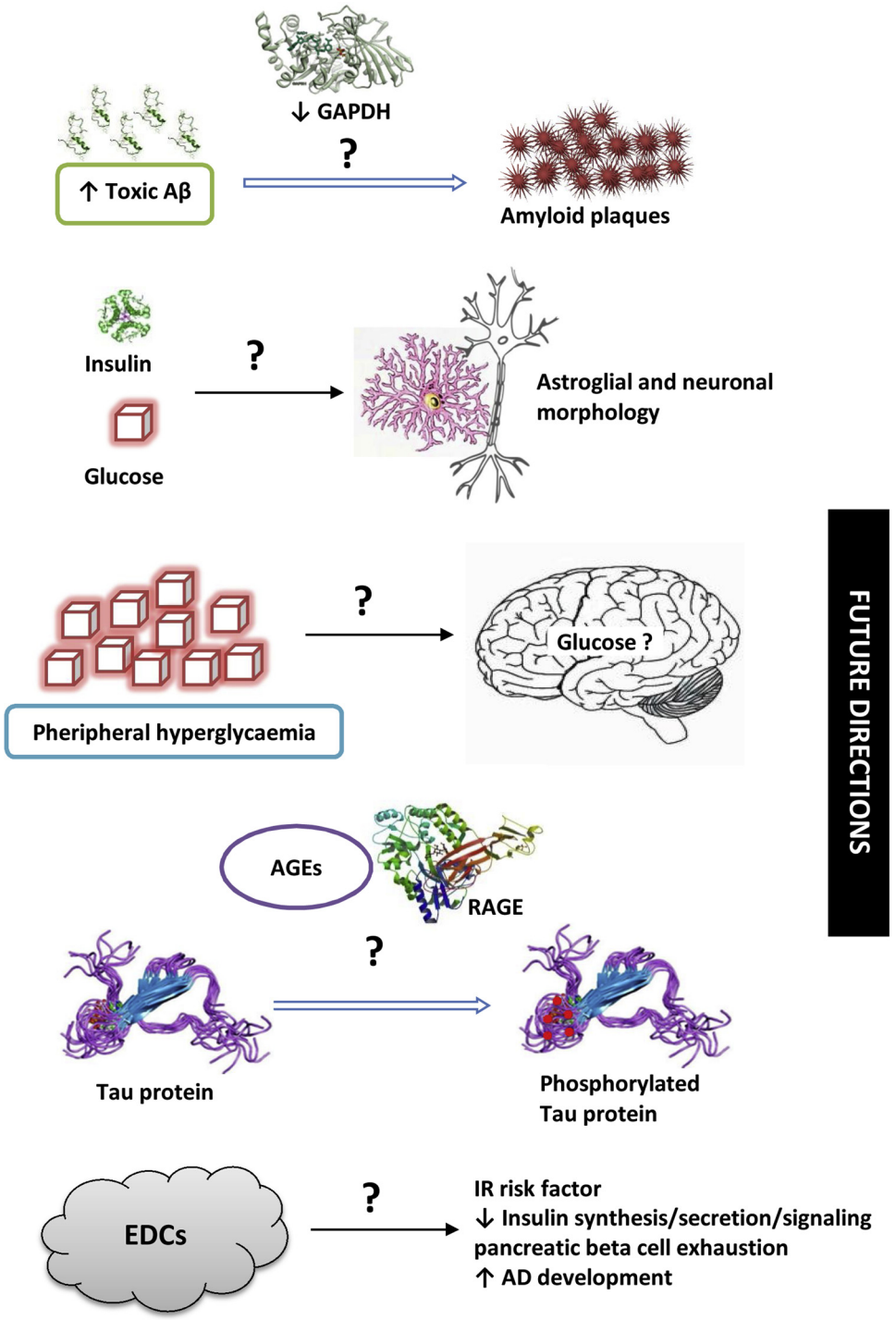

Fig. 3. Future experimental directions for a better understanding and explanation of common features of T2DM and AD.
GAPDH - Glyceraldehyde 3-phosphate dehydrogenase; Aβ- amyloid beta, AGEs - advanced glycation end products; RAGE- receptors for advanced glycation end products; IR- insulin resistance; EDCs -endocrine disrupting chemicals.

brain.

Increasing evidence supports the impact of irregularity in glucose concentrations on different pathways in AD pathogenesis, and therefore strategies focused on controlling glycaemic levels might be key etiopathogenic factors in AD managements. It is still under investigation whether abnormalities of cerebral glucose homeostasis in AD are dependent on peripheral glucose levels. Answering these questions is critical in order to establish whether central glucose homeostasis is a potential target for disease-modifying treatments in AD (Shah et al., 2012; Mergenthaler et al., 2013).

As may be noticed from paragraphs 5.2 and 6.2, there are limited data outlining the mechanisms by which tau truncation contributes to diabetes-induced cell damage, as well as synaptic and cognitive deficits. It remains to be determined whether diabetes can also enhance the degree of other post-translational modifications of tau, such as ubiquitination, nitration, polyamination and sumoylation, further solidifying its role as an important comorbid contributor to AD pathogenesis. The collected ideas could be a good source for future experimental directions (Fig. 3).

Another current and interesting problem refers to the observed

increased incidence of metabolic syndrome, obesity and diabetes as a result of exposition to xenoestrogens and others endocrine disrupting chemicals (EDCs) which the increased presence in the environment (especially for persistent organic pollutants) is still observed which should be considered as insulin-resistance risk factors and new diabetogenic agents (Chevalier and Fenichel, 2016; Fénichel and Chevalier, 2017). EDCs are found in everyday products (including food, plastic bottles, metal cans, toys, cosmetics, pesticides) and used in the manufacture of food. They interfere with the synthesis, secretion, transport, activity and/or elimination of natural hormones. Those interferences can block or mimic hormone actions and thus induce a wide range of adverse effects. For example in rodents, acute exposure to bisphenol A is responsible for modifications of insulin synthesis and secretion in pancreatic beta cells but also for modifications of insulin signaling in liver, skeletal muscle and adipose tissue, which both lead to insulin-resistance. In humans, some epidemiologic reports suggested a strong link between exposure to some persistent EDCs (as organochlorine pesticides, dioxins and polychlorinated biphenyl ethers) and T2DM and obesity, especially after acute exposure (Nadal et al., 2009; Paterni et al., 2017)

Xenoestrogens are different class of substance which can mimic of estrogen action by modulation of estrogen receptors (ER) action. Mainly ERα is overstimulated by an excess of endogenous (e.g. 17β-estradiol) as well as exogenous (e.g. bisphenol A) estrogens action, it will produce an excessive insulin signaling. This may provoke IR as well as beta-cell exhaustion and therefore, it may contribute to the development of T2DM (Nadal et al., 2009). Additionally it is indicates that estrogen receptors regulate the expression of IDE, which plays a significant role in the catalysis of the Aβ (Zhao et al., 2011). The great interest is focused on the use of natural xenoestrogens (some phytoestrogens) in the prevention and treatment of AD. Their application in animals models attenuated Aβ deposition and plaque formation in the brain in a female triple transgenic mouse model of AD (Zhao et al., 2013). Moreover the increased frequency of the AD in post-menopausal women suggests a negative role for estrogens in development of AD (Paterni et al., 2017). It is supposed that endocrine and metabolic disturbances induced by EDCs may not be associated only with T2DM onset but also result in an increase of AD incidence. In the light of persistent organic pollutants, which should now be considered as insulin-resistance risk factors and diabetogenic agents, it is especially noteworthy but only single studies are considering it in context of AD (Fénichel and Chevalier, 2017; Janicki and Schupf, 2010).

8. Conclusions

Substantial growth in in both diabetic numbers and the percentage of geriatrics in the overall population compels researchers to look for possible association between those two distinct disorders. The analysis of interrelation between amyloid β/tau protein and crucial players in diabetes mellitus type 2 helps to understand possible mechanisms linking those two important for society diseases but also helps to distinct and find the friends and foes of fatal processes. It seems that the toxic forms of amyloid beta are acquaintance with chronic hyperglycaemia and AGEs as from the above described data they are in positive correlation to each other. A definite, albeit not fully clarified role plays insulin homeostasis in regulation of neuropathological changes connected to Alzheimer's disease. Although some progress has been made, several hurdles still remains to be cleared before an effective insulin-sensitizing treatment strategy for AD is realized. Regarding the connection between tau phosphorylation and dephosphorylation processes and metabolic changes characteristic for diabetes the alliances are not understandable as there are the inconsistency of the available data and still missing some experimental evidences. The general view confirms the data obtained on amyloid progression analysis. There is a growing body of evidence to suggest that diabetes can promote aberrant tau modification, however, there are still lack of the profound knowledge how the particular mechanisms such AGEs metabolism or insulin/glucose concentration changes in the brain tissue can influence the stabilisation and binding to neurofilaments and cell organelles of neuronal and astroglial microtubules that is, processes dependent on the activity of the tau protein.

Despite the published data relating diabetes with AD, it is still necessary to conduct further research, ranging from basic models to clinical trials in order to help clarify a possible common pathophysiological mechanism and to implement improved therapeutic interventions for both conditions. Consequently, along with the results described above the paragraph describing unstudied, potentially critical pathways helps to project new experiments and analysis for better understanding of possible mechanistic relationships underlying these two important clinical disorders. The profound medical and economic impact that diabetes and AD have over society can be diminished by elucidating the molecular mechanism that mediate their associations and will allow the development of novel therapeutic strategies to modulate the onset and progression of either disorder.

9. Contributions

AK-K created the conception and wrote the manuscript with input from all authors. AR-D prepared graphical abstract, highlights and all graphs. AP did critical revision of the article and final approval of the version to be published.

Conflict of interest statement

The authors declare that they have no conflict of interest. All authors have contributed to the work equally. The work has not been published before nor is being considered for publication in another journal.

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