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Review

Common pathological processes in Alzheimer disease and type 2 diabetes: A review

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ABSTRACT

Alzheimer disease (AD) and type 2 diabetes mellitus (T2DM) are conditions that affect a large number of people in the industrialized countries. Both conditions are on the increase, and finding novel treatments to cure or prevent them are a major aim in research. Somewhat surprisingly, AD and T2DM share several molecular processes that underlie the respective degenerative developments. This review describes and discusses several of these shared biochemical and physiological pathways. Disturbances in insulin signalling appears to be the main common impairment that affects cell growth and differentiation, cellular repair mechanisms, energy metabolism, and glucose utilization. Insulin not only regulates blood sugar levels but also acts as a growth factor on all cells including neurons in the CNS. Impairment of insulin signalling therefore not only affects blood glucose levels but also causes numerous degenerative processes. Other growth factor signalling systems such as insulin growth factors (IGFs) and transforming growth factors (TGFs) also are affected in both conditions. Also, the misfolding of proteins plays an important role in both diseases, as does the aggregation of amyloid peptides and of hyperphosphorylated proteins. Furthermore, more general physiological processes such as angiopathic and cytotoxic developments, the induction of apoptosis, or of non-apoptotic cell death via production of free radicals greatly influence the progression of AD and T2DM. The increase of detailed knowledge of these common physiological processes open up the opportunities for treatments that can prevent or reduce the onset of AD as well as T2DM.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic disorders, and its prevalence increases with age. Insulin resistance or T2DM is often associated with the most commonly occurring metabolic and physiologic problems, including elevated blood pressure, cardiovascular disease, dyslipidemia (high triglyceride levels and low levels of high-density lipoproteins), and high cholesterol levels. Together with visceral obesity, this clustering of risk factors is known as the metabolic syndrome (Ahmed and Goldstein, 2006; Levine, 2006). Recent evidence has identified T2DM as a risk factor of Alzheimer's disease (AD). AD, a progressive neurodegenerative disorder of hitherto unknown etiology leading progressively to severe incapacity and death, has been described as the pandemic of the 21st century (Jellinger, 2006). Familial AD is caused by mutations in the amyloid precursor protein (APP) and presenilin genes, both linked to Aβ synthesis. The etiology of the sporadic form of Alzheimer's disease (SAD) is complex, with an interaction of both genetic and environmental risk factors (Blennow et al., 2006). A key event in AD pathogenesis is the conversion of Aβ from its soluble monomeric form into various aggregated forms in the brain. Preventing aggregation of Aβ is being actively pursued as one therapeutic strategy for treating AD (Liu et al., 2005).

2. Similarities between physiological processes underlying T2DM and AD

Several studies have shown that there are many similarities between T2DM and AD, and that both conditions underlie common physiological processes. These include aging-related processes, degeneration, high cholesterol levels, metabolic disorders and degenerative processes, β-amyloid aggregation, and also second messenger system abnormalities such as glycogen synthase kinase 3 (GSK3) overactivity, and deregulated protein phosphorylation (Doble and Woodgett, 2003; Ristow, 2004), association with cardiovascular disease, blood vessel abnormalities (Brands et al., 2004), increased oxidative stress and increased inflammation response (de la Monte and Wands, 2006; Haan, 2006), correlation with the Apolipoprotein E (APOE) ε4 allele (Qiu and Folstein, 2006), and glyceraldehyde-derived advanced glycation end products (AGEs). These common properties of both conditions will be described in detail in this review. One important aspect that links AD with T2DM is the fact that insulin receptors are not only expressed in the peripheral system but are also found on neurons in the CNS (Havrankova et al., 1981; Havrankova et al., 1978a,b; Havrankova et al., 1978a,b). Insulin receptors not only regulate blood sugar levels but also have growth factor properties and regulate neuronal differentiation, stem cell and progenitor cell proliferation, dendritic sprouting, and cellular repair mechanisms (Gispen and Biessels, 2000; Hoyer, 2004; Northam et al., 2006; Steen et al., 2005).

AD is characterized by intracellular neurofibrillary tangles (NFTs), containing an abnormally hyperphosphorylated form of tau protein, and extracellular senile plaques (SPs), mainly composed of aggregated β-amyloid. Both of the pathologic hallmarks of AD are also found in T2DM (Churcher, 2006; Glabe, 2006). Another property common to both conditions is the loss of cells and associated degenerative changes. AD is the most common neurodegenerative disease with extensive neuronal loss. T2DM is also a degenerative disease that results from the selective destruction of pancreatic β cells and associated neuropathies (Brands et al., 2004; Ristow, 2004; Roche et al., 2005). Studies have shown that a higher serum insulin level in prediabetes and early T2DM has been associated with impaired cognitive function (Stolk et al., 1997). Mechanistically, this implies that elevation of Aβ levels is associated with elevated serum insulin content (Watson et al., 2003). The main physiological link between AD and T2DM is that both conditions are associated with peripheral and central insulin signalling abnormalities (Hoyer, 2004). These then lead to neurodegenerative processes and cognitive impairments (Sun and Alkon, 2006; Watson and Craft, 2004). The complex relationship between insulin, cholesterol, and AD has been investigated by many groups (Nelson and Alkon, 2005). Insulin regulates cholesterol biosynthesis by stimulating activity of 3-hydroxy-3-methylglutaryl-CoA reductase, a rate-limiting enzyme in cholesterol biosynthesis. Cholesterol levels also play a crucial role in AD and high levels are considered a risk factor. Hypercholesterolemia is also a known risk factors of T2DM (Kompoti et al., 2006). High levels of cholesterol affect β-amyloid synthesis, APOEε4 has been shown to affect cholesterol transport and Aβ deposition, amyloid precursor protein (APP) metabolism is affected since cholesterol levels modulate gamma secretase activity and β-amyloid synthesis (Cole et al., 2005; Simons and Ehehalt, 2002). Common biochemical pathways found in the pancreas and in the brain also include shared enzymes that are involved in neurotransmitter synthesis: glutamic acid decarboxylase, tyrosine hydroxylase, and dopa

decarboxylase. Numerous growth factor receptors and hormones are also found in both β cells and in neurons; e.g., thyrotrophin-releasing hormone, P75 receptors, neuronal growth factor receptors and glucagon-like peptide-1 (Hoyer, 2004; Li, 2007; Mohanty et al., 2005; Perry and Greig, 2002). All those similarities support the assumption that common signalling mechanisms exist in response to similar physiological stimuli, and that the same signalling impairments can develop in both β cells and neurons. One could also conclude from this that β-cells resemble neurons in several aspects: they are electrically excitable, express the same types of ion channels, and respond to hormonal stimuli and glucose by depolarization and exocytosis, in a process that resembles neurotransmitter release from synaptic vesicles. The insulin-releasing mechanism is under the control of cAMP and IP_3 signalling (Green et al., 2004), as is the neurotransmitter release mechanism in neurons (Hölscher et al., 1999).

3. Epidemiological studies that link T2DM and AD

Numerous epidemiological studies have linked T2DM with an increased risk of developing AD (Haan, 2006). Recent evidence from a population-based study shows a link between T2DM and AD, with an incidence of AD as much as 2 to 5 times higher in population suffered from T2DM. Four risk factors (T2DM, hypertension, heart disease, and smoking) were attributed to a higher risk of AD. The risk of AD increased with accumulation of the associated risk factors (Luchsinger et al., 2005). An investigation in Sweden also showed that T2DM increased the risk of dementia. In this study, a dementia-free cohort of 1301 residents 75 years or older was longitudinally examined to detect dementia cases. During the following 6 years, 350 subjects developed dementia, including 260 AD. T2DM was associated with hazard ratios of 1.5 for general dementia and 1.3 for AD (Xu et al., 2004). In another survey of 683 subjects aged 65 years and older, hyperinsulinemia is associated with a higher risk of AD and a faster decline in memory. In this investigation, 149 persons developed dementia, including 137 cases of AD. The risk of AD doubled in the population that had hyperinsulinemia. The increased risk of developing AD when hyperinsulinemia or diabetes was present was 39% (Luchsinger et al., 2004). In a prospective population-based cohort study among 6370 elderly subjects, an increased risk of AD in T2DM cases was also observed. In all 6370 study participants, 692 (11%) were diagnosed with T2DM. During the follow-up period, 126 participants became demented and 89 (70% of dementia cases) were diagnosed with AD. 27% patients with dementia were diagnosed with T2DM. Diabetes mellitus almost doubled the risk of dementia and AD. Interestingly enough, patients treated with insulin were at highest risk of developing dementia (Ott et al., 1999). The authors suggest that diabetes has been contributing to the clinical syndrome in a substantial proportion of all dementia patients.

A different study evaluated the risk factor of T2DM alone or combined with the APOEε4 gene for developing dementia. A population-based cohort of 2574 Japanese-American men had been analysed. A regression analysis showed that T2DM was associated with AD development. Individuals with both T2DM and the APOEε4 allele had a higher risk for developing AD than those with neither risk factor. Furthermore, the patients with both T2DM and the APOEε4 allele had a higher number of plaques and NFTs in the cortex and hippocampus, and they also showed a higher risk of cerebral amyloid angiopathy. The association between T2DM and AD is particularly increased by the APOEε4 allele (Peila et al., 2002).

More epidemiologic inquiries have shown similar results. In a study of 1455 cases of T2DM followed for 7 years, 101 developed dementia, including 77 AD cases. Persons with T2DM exhibited significantly increased risk of developing dementia (Leibson et al., 1997). In a study over for 5.5 years, 127 out of 824 participants that were over 55 years old were diagnosed with T2DM, and 151 cases developed AD. After adjusting for age, sex, and educational level, those with T2DM had a 65% increase in the risk of developing AD (Arvanitakis et al., 2004).

In conclusion, the evidence presented by numerous epidemiological studies show a clear association between T2DM and an increased risk of developing AD.

4. Similarities between T2DM and AD: 1. Amyloid peptides

There is considerable evidence to suggest that the accumulation of Aβ is the cause of the neurodegeneration that occurs in AD (Hölscher, 2005; Small and Cappai, 2006). Similarly, loss of β cells in pancreas in T2DM is partly attributed to amyloid deposits in the islets (Clark et al., 1988). Aβ is a product from the cleavage of its precursor protein, APP. Similarly, islet amyloid is derived from islet amyloid polypeptide (IAPP) (Cooper et al., 1987). The 90% structural similarity between APP and IAPP strengthen the link between AD and T2DM and suggest similar physiological roles (Janson et al., 2004). AD is characterized by formation of SPs which consist of Aβ (Glenner and Wong, 1984). These plaques have toxic properties and are likely linked to the induction of inflammatory processes that cause neurotoxicity (Yan et al., 2003). IAPP aggregates are commonly observed in pancreatic islets of diabetic patients (Hoppener et al., 2000; Hoppener and Lips, 2006; Mosselman et al., 1988). The islet of Langerhans in T2DM is characterized by β-cell loss, and amyloid deposits contribute to this development (Westermark and Wilander, 1978). It was shown transgenic mouse models that overexpress IAPP and develop aggregates of IAPP in the pancreas also developed diabetes (Janson et al., 1996; Verchere et al., 1996). Conversely, targeted disruption of IAPP expression lead to enhanced insulin secretion and improved glucose tolerance (Gebre-Medhin et al., 1998). Considering the pathogenetic similarities and the 90% structural similarity between Aβ precursor protein and IAPP, it should not be surprising that AD seems to predispose for insulin resistance, insulin hypersecretion, and T2DM (Haan, 2006). As described above, individuals suffering from T2DM have a much higher likelihood of developing dementia (Biessels and Kappelle, 2005; Ott et al., 1999).

Great progress has been made in identifying IAPP and islet amyloid as potentially important contributors to the pathogenesis of the β-cell dysfunction of T2DM (Hull et al., 2004). The physiological role of IAPP include the regulation of food intake and body weight. An effect of inhibition of food intake

was shown after central or peripheral administration of IAPP in rats (Arnelo et al., 2000; Lutz et al., 1998). Conversely, an increase of food intake and body weight was induced by administered IAPP antagonist intracerebroventricularly (i.c.v.) (Rushing et al., 2001). IAPP-receptors are localized in the nucleus accumbens, area postrema, nucleus of the solitary tract, and various hypothalamic regions in rodents that mediate food intake and body weight effectively (Sexton et al., 1994). Moreover, effects of IAPP also include the regulation of renal filtration (Harris et al., 1997), calcium homeostasis (Alam et al., 1993), and vasodilatation (Chin et al., 1994). IAPP is involved in the pathogenesis of the islet-cell dysfunction in T2DM. Under physiological conditions, IAPP is synthesized, processed, and secreted from the β-cell along with insulin and does not accumulate as amyloid fibrils. However, misfolding of ICE occurs when β-cells are damaged (before the onset of T2DM) (Kahn, 2001). The misfolded and/or unprocessed (pro)IAPP in secretory granules is released from the β cell. The structure of this peptide is altered as it is exposed to an altered chemical environment (e.g. increased pH and decreased calcium concentration) as well as to other molecules (such as heparan sulfate and proteoglycans), and further amyloid fibril is formed. A different study showed an aggregation of pro-IAPP and IAPP in β-cell lysosomes in patients with T2DM and human IAPP expressing transgenic mice (de Koning et al., 1994). There is evidence that misfolded (pro)IAPP is more resistant to normal proteolytic processes by lysosomes. These amyloid fibrils facilitate or seed a second stage of rapid amyloid fibril accumulation. T2DM is associated with chronically elevated glucose and free fatty acids, both of which have been demonstrated to enhance amyloid fibril formation. The toxicity of amyloid peptides associated with T2DM have been well documented (Lorenzo et al., 1994; Yankner et al., 1990). IAPP induces apoptosis and cell death when incubated with isolated islets or islet cells (Lorenzo et al., 1994). In addition to inducing cell death, IAPP may also inhibit β cell replication (Lundmark et al., 2005). Formation and progression of islet amyloid may be concomitant with the pathogenesis (a worsening of β cell function and glucose homeostasis and a loss of islet-cell mass) of T2DM. It seems that aging is accompanied with islet amyloid formation. The latter was found in older individuals who do not have diabetes, but show elevated postprandial glucose levels (Chen et al., 1985). Thus, islet amyloid formation may play a role in the impaired glucose metabolism of aging. In addition to IAPP amyloid deposits also contain other components: APOE, heparan sulfate proteoglycans (HSPGs), and serum amyloid P component (Kahn et al., 1999). These peptides are found or play crucial roles both in T2DM and AD. As mentioned earlier, APOEε4 is an important risk factor for AD. HSPGs are associated with the earliest stages of the formation of Aβ in AD (Hamaguchi et al., 2006).

Alois Alzheimer was the first to describe the special histological hallmarks in AD: “distributed all over the cortex, but especially numerous in the upper layers, there are minute military foci which are caused by the deposition of a special substance in the cortex.” (Alzheimer, 1907; Alzheimer et al., 1907). It is now over two decades since component of this military foci was sequenced (Glenner and Wong, 1984). and identified as a 39- to 43-amino-acid peptide, named as β-amyloid peptide (Wong et al., 1985). Aβ is a cleavage product of the amyloid precursor protein (APP). Three secretases (α, β, and γ) are involved in the cleavage of APP. APP is cleaved by at least two pathways. In the α pathway, APP is cleaved by the enzyme α-secretase to produce the neuroprotective soluble APPα fragment. There is no Aβ formation in this pathway, since α-secretase cleaves APP within the beta-amyloid sequence. Aβ is formed in another pathway, in which APP is sequentially cleaved by β- and then γ-secretases. Aβ can evoke a series of pathophysiological processes and finally aggregate to produce senile plaques (SPs) (Hölscher, 2005; Turner et al., 2004). The amyloid cascade hypothesis has received a lot of support in the recent years. Aβ peptides impair neuronal activity in different ways, including the impairment of synaptic function and the induction of cell death (Small et al., 2001; Walsh and Selkoe, 2004). Yankner and colleagues showed neuronal degeneration in cultured hippocampal cells after applying Aβ (Yankner et al., 1989). Similar toxic effects of Aβ were observed after i.c.v. injection *in vivo* (Hölscher, 1998). The ability to memorize spatial tasks, synaptic plasticity, and neuronal survival was impaired after injection of Aβ into the hippocampus or cerebral cortex, even in the absence of neurotoxic effects (Gengler et al., 2007; Hölscher et al., 2007; Kowall et al., 1991). Interestingly enough, Aβ can be neurotrophic to undifferentiated hippocampal neurons at low concentrations and neurotoxic to mature neurons at higher concentrations in cultural neurons (Yankner et al., 1990). Aβ toxicity was increased by oxidative stress (Miranda et al., 2000) and by additional challenge by glutamate (Koh et al., 1998; Koh et al., 1990). Further analysis showed that sections on the β-amyloid peptide that facilitate the aggregation process are important for the cytotoxic effects. Fragments of the peptide that cannot aggregate were found to be non-toxic (Pike et al., 1995). The analysis of the tertiary configuration of β-amyloid further gave additional information on what crucial properties are linked with neurotoxicity. The monomeric alpha-helical conformation did not induce neuronal toxicity. Aβ became neurotoxic after β-sheet transformation and aggregation (Talafous et al., 1994). Aβ also increases neurotoxicity by increasing calcium influx, in part by activating calcium channels (Freir and Herron, 2003) and partly by activating neuronal metabotropic receptors, or even by forming ion channels in cell membranes (Hölscher, 1998, 2005). Recently, the focus has shifted from analysing the effects of amyloid plaques to investigating what effects small aggregates that are still soluble can have. It was found that such pre-aggregated oligomers (also called ADDLs) already have pronounced effects on neuronal transmission, memory formation, and cell survival (Gong et al., 2003; Walsh and Selkoe, 2004). These effects can be reversible (Gong et al., 2003; Hölscher et al., 2007) and might be the first stage in cascade that eventually leads to irreversible damage and cell loss.

The strongest support for the Aβ cascade hypothesis originates from investigations of familial AD. Three different genes related to familial AD have been linked to abnormal Aβ production or aggregation (Selkoe, 2001). Specific point mutations in the APP gene shift the processing of APP towards the Aβ pathway, e.g. by reducing the affinity to alpha-secretase, or increasing turnover by β-secretase (Almkvist et al., 1997). The fact that such simple point mutations greatly accelerate the development of AD support the concept that Aβ is the main cause of AD. Aβ accumulation on a large scale is seen only in

AD brains, and much less so in age matched control brains, which suggest that some abnormal factors facilitate the aggregation of Aβ in AD.

There is further evidence for a relationship between β-amyloid, AD, and T2DM. To determine whether insulin affected plasma Aβ levels, insulin and Aβ levels of AD patients had been compared with those of normal older adults after infusions of insulin. Results showed that AD patients had higher plasma insulin and Aβ levels vs. normal adults. Insulin infusion reduced the plasma Aβ levels in normal adults. In contrast, insulin raised plasma Aβ levels in AD patients (Kulstad et al., 2006). The results suggest that AD patients show reduced insulin clearance and insulin-provoked plasma Aβ elevation. Abnormal increase of peripheral Aβ by insulin may well contribute to AD.

Considering the importance of Aβ in the pathogenesis of AD, a lot of research is focused on developing therapies for AD by targeting amyloid production, aggregation, clearance or toxicity (Golde, 2006; Kennedy et al., 2007).

5. Similarities between T2DM and AD: 2. NFTs and hyperphosphorylated tau protein

Another pathologic hallmark of AD is the accumulation of intracellular neurofibrillary tangles (NFTs), containing a hyperphosphorylated form of tau protein. The activation of insulin receptors triggers tau phosphorylation: increasing the peripheral insulin level by insulin injection significantly increased tau phosphorylation at Ser^{202} in the brain within 10 min (Freude et al., 2005). Further, this study reported that insulin receptor signalling and tau phosphorylation was completely abolished under hyperinsulinemic conditions in the brains of mice lacking the insulin receptor, indicating that the cerebral insulin receptors are a direct target of peripherally administered insulin. Tau phosphorylation in AD and T2DM involves glycogen synthase kinase-3 (GSK-3) activation, a serine/threonine kinase that phosphorylates glycogen synthase in the rate-limiting step of glycogen biosynthesis (Doble and Woodgett, 2007; Phiel et al., 2003; Sivaprakasam et al., 2006). GSK-3, in particular the GSK-3β isoform, therefore is a crucial step in the formation of NFTs. Consequently, developing inhibitors of GSK-3 is an attractive research target in order to evolve new treatments for diseases such as T2DM and AD (Bhat et al., 2004; Cole et al., 2007) (Fig. 1).

A cell signaling pathway that has received increasing attention in the research of the dual pathogenicities underlying AD and T2DM is the Cdk5/P35/P25 signaling axis. The analysis of genome data sets for genes associated with T2DM has recently reported findings that associate this pathway with both diseases. Studies undertaken in the USA, Finland, Iceland, and the UK uncovered a strong association of Cdkal1 with T2DM (Helgason et al., 2007; Saxena et al., 2007; Steinthorsdottir et al., 2007; Zeggini et al., 2007). Cdkal1 is a homolog of Cdk5rap1, the Cdk5 regulatory subunit associated protein-1, an inhibitor of Cdk5 activities. P35 is an activating peptide of Cdk5, and is also involved in the impairment of insulin secretion by pancreatic beta cells in response to glucotoxicity. Studies further showed that inhibition of Cdk5 activity protects pancreatic beta cells from glucotoxicity (Ubeda et al., 2006). In addition, Cdk5 activity plays a role in AD development. Importantly, Cdk5 is involved in the hyper-phosphorylation of tau (Orellana et al., 2007; Wang et al., 2007). This might be due to abnormalities in the ratios of P25/P35 found in AD patients that control the activation of Cdk5, and cause hyper-phosphorylation of tau (Ubeda et al., 2004; Ubeda et al., 2006). It appears that the hyper-phosphorylation of tau is not directly caused by Cdk5 activity, but by the modulation of GSK-3β activity by Cdk5 (Plattner et al., 2006). Glucose-induced expression of the Cdk5 activator p35 involved in AD regulates insulin gene transcription, and therefore is involved in control of insulin signalling. The Cdk5 activator p35 can act as an activator of GSK-3 since it maintains the active form of GSK-3 by promoting its N-terminal cleavage (Goni-Oliver et al., 2007). Therefore, novel drugs that reduce Cdk5 activity are tested as potential treatments for AD and Parkinson's disease (Camins et al., 2006).

6. Similarities between T2DM and AD: 3. Insulin and AD

There is growing evidence that impairments in insulin signalling is partly responsible for the cognitive decline in AD (de la Monte and Wands, 2005; Gasparini and Xu, 2003; Watson and Craft, 2004). One impairment that has been described repeatedly is the observation that in AD, insulin resistance in the CNS develops due to alterations of insulin receptor sensitivity. This affects the expression and metabolism of Aβ and tau protein. Insulin and the insulin receptor (IR) are abundantly expressed in the rodent brain. They are highly expressed in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala, and septum (Watson and Craft, 2004; Zhao et al., 2004). Insulin acts also as a 'neuromodulator' in the regulation of food intake and body weight. It influences the release and reuptake of neurotransmitters, and also appears to improve learning and memory (Biessels et al., 2004; Gispen and Biessels, 2000). The insulin/IR distributed in the hypothalamus is involved in the regulation of the body energy homeostasis. The hippocampus- and cerebral cortex-distributed insulin/IR has also been shown to be involved in brain cognitive functions. Insulin can modulate activities of excitatory and inhibitory receptors, and trigger signal transduction cascades leading to long-term memory consolidation. It has also been demonstrated that insulin signalling plays a role in synaptic plasticity (Gispen and Biessels, 2000). Conversely, deterioration of insulin receptor signalling is involved in aging-related brain degeneration such as the AD and cognitive impairment in T2DM patients (Zhao et al., 2004). Furthermore, in the brains of AD and PD patients, a decrease of expression of IR has been described (Moroo et al., 1994; Steen et al., 2005). When comparing the expression of insulin and IR of AD patients in neocortical brain areas with aged matched controls, it was found that insulin and insulin receptor densities decrease with aging (Frolich et al., 1998a,b). Brain IR densities in AD are also decreased compared to aged matched controls (Hoyer, 1998). In addition to this, it has been discovered that IR receptors are not only desensitized in T2DM but also in the brains of patients with AD. This impairment in insulin signalling in the brain is considered unique in development and distribution and has been termed 'Type 3

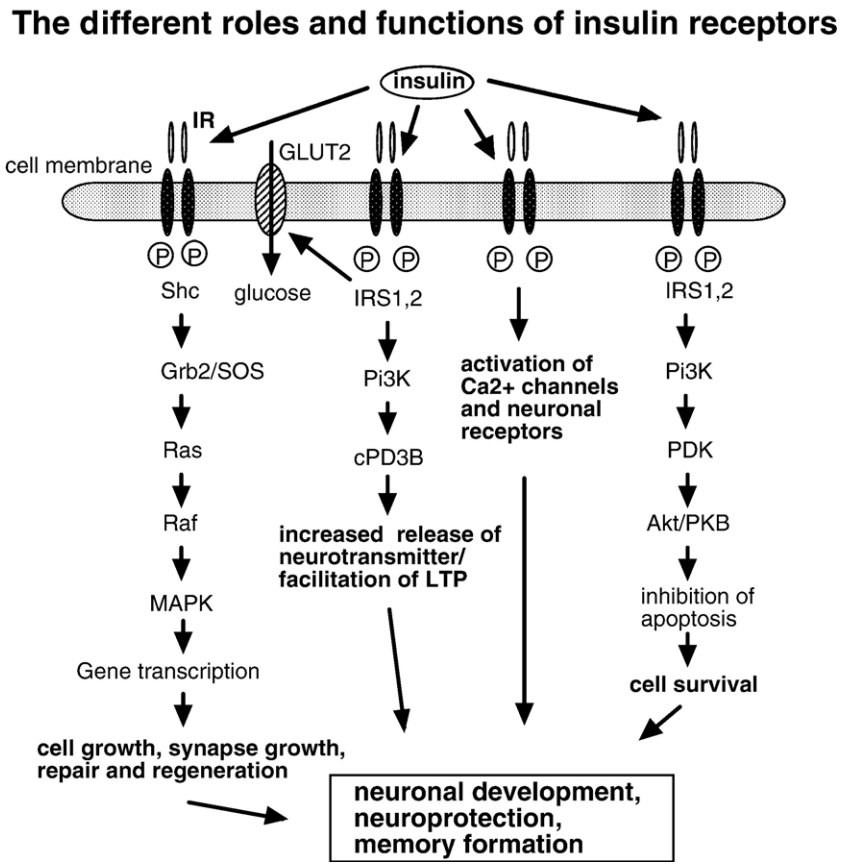

Fig. 1 – An overview of some of the diverse roles and functions that insulin receptors (IRs) play. Traditionally, insulin is associated with its blood glucose-lowering activity. This is achieved by activating a glucose uptake transporter, e.g. GLUT-2. This function is only one of many roles that IRs play. Recent research has uncovered a number of important roles in neuronal growth, synaptic development, and direct control of neurotransmitter release. During neuronal activity, insulin is released and it binds to the α-subunit of the receptor. This activates the tyrosine kinase phosphorylation of the β-subunit. Then, several second-messenger pathways can be activated: (1) Activation of the insulin receptor–Shc–MAP kinase pathway activates gene expression. The genes expressed include proteins that are required for cell growth, synapse growth, and for cell repair and maintenance. It is also required for repair and protection of cells against damaging influences such as oxidative stress (Biessels et al., 2006; Hoyer, 1997). (2) IR activation has a direct effect on neurotransmitter vesicle release, and primes synapses for induction of long-term potentiation of neuronal transmission (LTP). This pathway involves binding of insulin receptor substrate-1 (IRS1) and insulin receptor substrate-2 (IRS2) to phosphatidylinositol 3-kinase (PI3K). Then, the cyclic nucleotide phosphodiesterase 3B (cPD3B) is activated, and synaptic cAMP levels are reduced (Zhao et al., 2000). This primes the synapse for increased neurotransmitter vesicle release. This pathway can also induce the synthesis of NO via NOS activation (de la Monte and Wands, 2006). NO acts as a retrograde messenger for the modulation of neurotransmitter release and plays a role in memory formation (Hölscher, 1997). Modulation of neurotransmission will influence memory formation, information processing, and cognitive processes (Hölscher, 1999). Insulin can prevent impairments of LTP and memory formation in animal models of diabetes (Biessels et al., 2002; Gispen and Biessels, 2000). (3) IR furthermore modulates neurotransmission directly by altering glutamatergic and GABAergic receptor activity. NMDA glutamate receptors can be phosphorylated to increase the opening of the associated Ca^{2+} channel. Furthermore, IR signaling can change basic neuronal transmission and depolarization by influencing the internalization of AMPA receptors (Lin et al., 2000). This receptor drives synaptic membrane depolarization, required for LTP induction (Bliss and Collingridge, 1993; Zhao et al., 2004). IR activation also affects GABA transmission by recruiting functional GABA receptors to the postsynaptic site (Wan et al., 1997). (4) As a growth factor, insulin also suppresses the induction of apoptosis. This pathway involves stimulation of PI3K binding to IRS-1 and -2, activation of PI3K, PDPK, and protein kinase B (Akt/PKB), which suppresses the induction of apoptosis and thereby protects neurons (Eldar-Finkelman et al., 1999; Schubert et al., 2003a; Zhao et al., 2000). Abbreviations: Akt/PKB = protein kinase B complex. CPD3B = cyclic phosphodiesterase 3 beta. Grb2/SOS = growth factor receptor binding protein 2/son of sevenless protein. IRS = insulin receptor substrates that get phosphorylated after activation, MAPK = mitogen-activated protein kinase. PDK = phosphatidylinosite-dependent kinase. PI3K = phosphatidylinositol 3 kinase. Raf = regulation of alpha-fetoprotein. Ras = rat sarcoma virus peptide. Shc = Src homology collagen peptide.

Diabetes' by some (Lester-Coll et al., 2006). Others have called AD 'an insulin-resistant brain state' (Hoyer, 1998). Watson and Craft (2004) summarize the effects of insulin and glucose on memory formation in AD patients:

(1) AD is often associated with an impairment of glucose regulation because their plasma glucose and insulin levels in response to glucose and insulin administration increased, respectively.
(2) AD may worsen pre-existing insulin abnormalities.
(3) AD patients may have increased fasting plasma insulin levels, and/or a decreased cerebrospinal fluid insulin levels and/or a decreased cerebrospinal fluid-to-plasma insulin ratios.
(4) Acute glucose administration can facilitate memory of AD patients and healthy older adults; however, this effect is modulated by an individual's glucose regulatory efficiency and abolished by suppressing endogenous insulin secretion.
(5) Acute insulin administration facilitates memory of AD patients and healthy older adults when fasting plasma glucose is maintained. This effect occurs at lower insulin doses for healthy older adults than for AD patients and it is suppressed by insulin-induced elevations of Aβ in cerebrospinal fluid (Watson and Craft, 2004).

APOE not only is involved in AD but also moderates insulin activity and effects on memory for patients with AD. Patients without an APOEε4 allele have lower insulin sensitivity and develop insulin-induced memory facilitation at higher insulin doses. Conversely, patients with at least one APOEε4 allele show insulin-induced memory facilitation at lower insulin doses and reduced insulin-degrading enzyme levels. Hence, disturbances in cerebral insulin signalling pathways may be involved in AD and general aging processes of the brain (Zhao et al., 2004).

The relation between insulin and the metabolism of Aβ and tau is also receiving increasing attention. Insulin appears to stimulate Aβ secretion, and inhibits the extracellular degradation of Aβ by competing with Insulin-degrading enzyme (IDE) (Gasparini and Xu, 2003). IDE is the major enzyme responsible for insulin degradation. It cleaves several proteins that form β-pleated sheet-rich amyloid fibrils (e.g., Aβ, insulin, glucagon, amylin, atrial natriuretic factor, transforming growth factor alpha, and calcitonin) (Kurochkin, 2001). Two substrates of IDE, Aβ and insulin, connect AD and T2DM. IDE is regarded a principal regulator of Aβ levels in neuronal and microglial cells. An IDE deficient mouse model has been created to investigate the role of IDE in normal physiology. IDE deficiency resulted in a >50% decrease in Aβ degradation in both brain membrane fractions and primary neuronal cultures, and a similar deficit in insulin degradation in liver. Furthermore, the IDE KO mice showed increased cerebral accumulation of endogenous Aβ, hyperinsulinemia and glucose intolerance (Farris et al., 2003) (Fig. 2).

Hence, it seems that IDE hypofunction may underlie or contribute to some forms of AD and T2DM and provide an explanation for the relationship between hyperinsulinemia, T2DM, and AD. Indeed, a histopathological study of the hippocampus in AD patients showed marked reductions in IDE expression, and IDE mRNA levels, as compared to age-matched controls (Cook et al., 2003). Interestingly, this reduced expression only occurred in AD patients with the APOEε4 allele. As described above, APOEε4 greatly increases the risk of AD in T2DM patients (Peila et al., 2002).

The aging brain can be damaged by several toxic effects induced by hyperglycaemia, such as oxidative stress, the accumulation of advanced glycation end products and microangiopathy (Biessels et al., 2002), and the behavioural and neurophysiological consequences of diabetes are accentuated by aging (Kamal et al., 2000). Hyperglycaemic rodents, for example, express cognitive impairments and synaptic dysfunctions in the brain (Gispen and Biessels, 2000). Toxic effects of high glucose levels are mediated by an enhanced uptake of glucose. The increase in glucose metabolism via the polyol and hexosamine pathways leads to an imbalance in the generation and scavenging of reactive oxygen species. Additional processes involve the excessive glycation of important functional and structural proteins which impairs their functions (Brownlee, 2001).

It is plain to see that the continuous exposure of the brain to these processes will add up over time and will impair neuronal activity and regeneration, and thereby will increase the likelihood of developing AD. Neuronal insulin resistance contributes to defects in neuronal function, as demonstrated by the neuronal changes observed in insulin receptor knockout mice (Schubert et al., 2004). A complete loss of insulin-mediated activation of phosphatidylinositol 3-kinase and inhibition of neuronal apoptosis had been observed in these KO mice. As a result, phosphorylation of GSK-3 was markedly reduced, and consequently, the activity of GSK-3 and phosphorylation of tau protein was much increased. It is important to note that the alteration of neuronal proliferation and survival, memory formation, or basal brain glucose metabolism in the insulin receptor KO mice were not affected. This suggests a compensation of insulin receptor activity by other growth receptors (e.g. IGF-1) (Adamo et al., 1989). Clearly, other factors are also involved in the development of AD other than changes in GSK-3 activity and hyperphosphorylation of tau protein induced by lack of insulin signalling. Several studies show effects not only of insulin but also of IGF-1 on molecular and cellular mechanisms of AD (Gasparini and Xu, 2003). Similar to insulin and IR, IGF-1 and its receptors and IGF-1-binding proteins (IGFBPs) are also found in the rodent and human brain. Insulin and IGF-1 can cross the blood–brain barrier, and are also produced locally in the brain (Carro and Torres-Aleman, 2004; Carro et al., 2006; Schulingkamp et al., 2000). Sharing structural and functional homology, both insulin and IGF-1 bind to, and activate, both receptor types, and this cross talk suggests they play a similar role in neurophysiology and development. Hence, IGF-1 and its receptors modulate also neuronal activity, and are involved in AD. It was found that Aβ levels in the brain were elevated at an early age in mutant mice with low circulating IGF-1. Conversely, Aβ level of brain dropped in aging rats by increasing serum IGF-1 (Gasparini et al., 2002). A different study showed a similar effect of IGF infusion on Aβ level in the hippocampus in aging and young rats. It was observed that after IGF infusion, Aβ level of aging rats were reduced to those found in young rats (Carro et al., 2002).

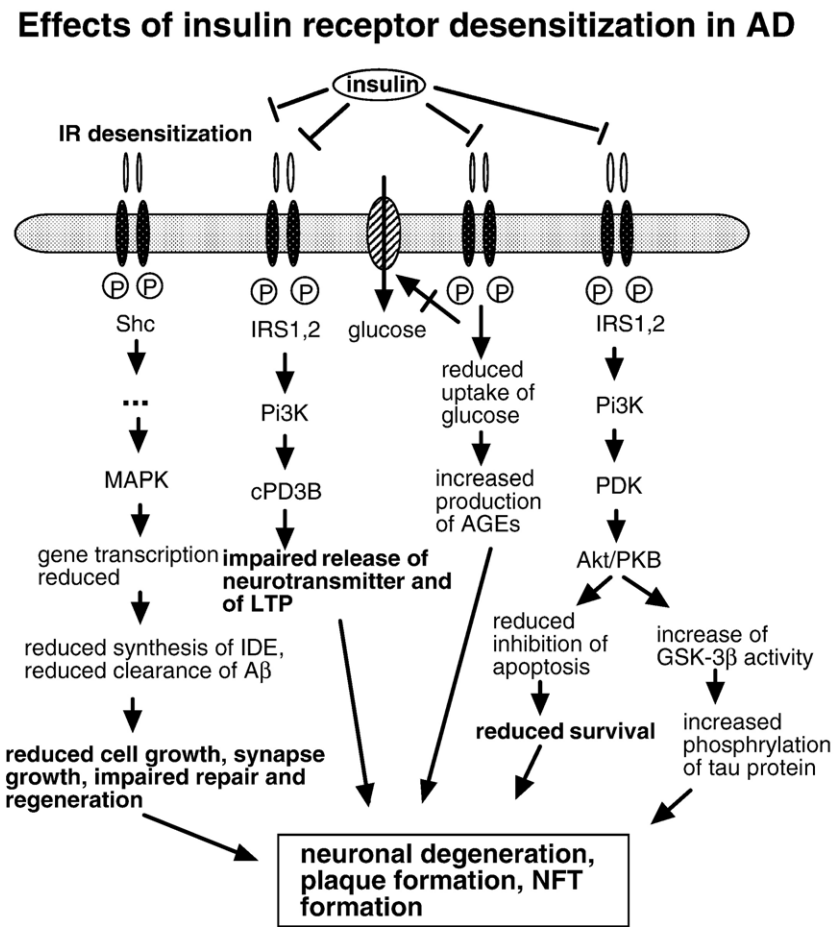

Fig. 2 – An overview of the effects that insulin receptor desensitization has on neuronal metabolism and on the development of AD. The growth factor activity of insulin on gene transcription and on the synthesis of housekeeping proteins is impaired, and reduces cell growth and regeneration. Among the proteins that are less synthesized is IDE (insulin-degrading enzyme), which also cleaves Aβ when aggregated in the beta-sheet formation. The metabolization of APP is shifted from α-secretase to β-secretase processing, and therefore towards Aβ formation. Furthermore, the clearance mechanisms for Aβ (e.g. transport systems at the blood brain barrier) are compromised. Synaptic transmission and LTP formation is impaired, which can have effects on memory formation and information processing in the brain. The higher levels of glucose in the system increase the formation of AGEs (advanced glycation end products) which have toxic properties. The pathway involving the stimulation of PI3K binding to IRS-1 and -2, activation of PI3K, PDPK, and protein kinase B (Akt/PKB), which suppresses the induction of apoptosis and thereby protects neuron inhibitory activity on apoptosis is reduced, and neurons are more prone to undergo apoptosis if damaged. Furthermore, the activity of GSK-3β is increased, which leads to the enhanced phosphorylation of tau protein and the formation of NFTs (neurofibrillary tangles), among other processes. Abbreviations are explained in Fig. 1, see also text for further details.

Activation of IGF receptors at the choroid plexus of the ventricles activates a carrier system that transports IGF-1, insulin and furthermore Aβ across the blood brain barrier. By this mechanism, IGF-1 can support the clearance of brain Aβ, by promoting transportation of proteins which act as a carrier for Aβ, or by transporting Aβ directly. Insulin and IGF-1 can also directly regulate the metabolism Aβ (Carro and Torres-Aleman, 2004; Carro et al., 2006, 2002).

In vitro studies showed a three- to fourfold increase of Aβ in extracellular levels in cultured cells that overexpressed the mutated human APP695 isoform, and in primary cultures of rat cortical neurons treated with insulin. The study also found a decrease of intracellular Aβ levels in cells overexpressing the human APP695 isoform. Furthermore, it was shown that insulin reduced Aβ in membrane fractions of cells, and that insulin-dependent secretion of Aβ and soluble βAPP was observed. This demonstrates that insulin stimulates Aβ and soluble APP trafficking within the cells. Insulin reduces intracellular Aβ and stimulates its secretion by increasing Aβ transport (Gasparini et al., 2001).

The observed modulation of tau phosphorylation by insulin and IGF-1 further demonstrates the connection between T2DM and AD. Insulin and IGF-1 were found to regulate the phosphorylation of tau in neuronal cell cultures (Lesort and Johnson, 2000) and also *in vivo* (Schubert et al., 2003a,b). Specifically, insulin and IGF-1 reduce tau protein phosphorylation and promote tau protein binding to microtubules in human neuronal cultures. Inhibition of GSK-3 prevents the IGF-1- or

insulin-induced increase in tau phosphorylation (Lesort and Johnson, 2000). The authors hypothesise that by increasing tau phosphorylation, insulin and IGF-1 may contribute to the reorganization of the cytoskeleton necessary for the development and growth of the neurites.

Insulin and IGF-1 increase tau phosphorylation on specific amino acid residues, indicating a regulation of the phosphorylation of tau protein by insulin signalling. Insulin and IGF-1 might also affect tau phosphorylation indirectly, via their effect on Aβ. In summary, decreased insulin and/or IGF-1 levels could elevate cellular Aβ burden and thus, indirectly increase AD pathology.

In conclusion, a therapy of AD by modulating the insulin/IGF-1 pathway appears promising. In addition to a direct effect on Aβ and tau protein, IGF-1 and insulin have neuroprotective effects, and can promote neurogenesis, synapse formation and glucose utilization throughout the brain (Mohanty et al., 2005; Venters et al., 2001). IGF-1 could be safely administered systemically. For insulin delivery, Born and colleagues suggested a route of intranasal administration to elevate its concentration in cerebrospinal fluid and prevent severe peripheral side effects (Born et al., 2002).

7. Similarities between T2DM and AD: 4. Glyceraldehyde-derived advanced glycation end products (AGEs) and O-linked *N*-acetylglucosamine acylation

Advanced glycation end products (AGEs) are a heterogeneous group of molecules that have side groups irreversibly added to them. AGEs are created from reactive derivatives by non-enzymatic glucose–protein condensation reactions, as well as from lipids and nucleic acids exposed to reducing sugars such as glucose (Yamagishi et al., 2002). In fact, the term AGEs is now used for a broad range of advanced products of the glycation process (also called the "Maillard reaction"). The product can form cross-links with and between amino groups. The formation and accumulation of AGEs in various tissues are known to progress during normal aging, and at an extremely accelerated rate in diabetes mellitus (Takeuchi and Yamagishi, 2004a,b; Yamagishi et al., 2003). Hyperglycemia is accompanied by an accelerated rate of AGE formation, and accelerated AGE formation can be also observed AD (Munch et al., 1998). AGEs are involved in the production of the pathologic hallmarks of AD: accumulation of Aβ is increased by Aβ glycation, and formation of NFTs from phosphorylated tau is accelerated by glycation of tau protein (Ledesma et al., 1994).

Six distinct AGEs groups have been identified (AGEs-1 to -6). The toxic AGEs (AGEs-2, -3, and AA-AGE), but not non-toxic AGEs (N-carboxymethyllysine, pentosidine, pyrraline, etc.) are likely to play an important role in the pathophysiological processes associated with AGEs formation (Takeuchi and Yamagishi, 2004a,b). AGEs and its receptor (RAGE) has been implicated in the development of diabetic vascular complications (Tan et al., 2006). Hyperglycaemia leads to the formation of AGEs. Chronic hyperglycemia in combination with oxidative stress result in the formation of advanced AGEs (Ma et al., 1997). The binding of AGE to RAGE induces the diabetic vascular complications (Singh et al., 2001).

AGE-related effects in diabetic complications include:

(1) Contribution to diabetic retinopathy: AGE-2 or AGE-3 up-regulate vascular endothelial growth factor mRNA levels; stimulate DNA synthesis and tube formation in microvascular endothelial cell; and induce *apoptosis* of retinal cells (Okamoto et al., 2002; Yamagishi et al., 2002).
(2) Induction of diabetic nephropathy: AGEs-2 and -3 not only disturb glomerular homeostasis by inducing *apoptosis* of human mesangial cells but also elicit hyperfiltration and microalbuminuria by stimulating secretion of VEGF and monocyte chemoattractant proteins, and thus are involved in the pathogenesis of the early phase of diabetic nephropathy (Yamagishi et al., 2002). AGEs inhibitors prevented renal tubular injury and tubulointerstitial fibrosis in an animal model of T2DM (Tsuchida et al., 1999).
(3) Contribution to diabetic neuropathic processes: the accumulation of AGEs was detected in the nerves of diabetics, and the inhibition of AGEs formation by anti-glycation agents improved neuropathic changes in experimental diabetic rats (Wada et al., 2001).

There is also evidence for the involvement of AGEs in the development of AD. Immunohistochemical studies showed the existence of AGEs in senile plaques and furthermore in NFTs. Cerebral amyloid angiopathy is also found in brain tissue of AD patients (Sasaki et al., 1998). In the hippocampus, immunoreactivity against Aβ, AGE, and ApoE was found in all types of plaques, diffuse plaques, early plaques, and dense core plaques. Most plaques showed both Aβ and AGE immunoreactivity, but surprisingly, some plaques showed only AGE immunoreactivity. In serial sections of leptomeningeal vessels and parenchymal vessels in the temporal lobe of AD brains, amyloid angiopathic sections were labeled by both anti-AGE and anti-ApoE. AGE immunoreactivity was also found in NFTs. In addition, Aβ-, AGE-1-, and RAGE-positive granules were present in hippocampal neurons (Sasaki et al., 1998; Sasaki et al., 2001). The glycation of IAPP in type 2 diabetes and AGE-modified IAPP is more amyloidogenic than the unmodified peptide (Kapurniotu et al., 1998). In neuronal cell culture studies, the cytotoxic effect of AGEs was completely prevented by the addition of the anti-AGE-2-specific antibody, but not by other types of anti-AGE antibodies (Takeuchi et al., 2000). Based on these results, it had been proposed that serum or CSF levels of AGEs could be a promising biomarker for early detection of AD (Sato et al., 2006).

In conclusion, the physiological activities of AGEs play a role in the pathogenesis of diabetic vascular complications and most likely in neurodegenerative disorders and angiopathies including AD (Takeuchi and Yamagishi, 2004a,b; Yamagishi et al., 2005; Yamagishi et al., 2003).

7.1. Glucose toxicity in diabetes and accelerating effects on AD development: the hexosamine biosynthetic pathway (HSP) and O-linked N-acetylglucosamine acylation (O-GlcNAc)

Chronically increased glucose levels can have toxic effects on cells, which is linked in part to the deregulated glycosylation of proteins. Glucose is used not only as a source of energy for

the cells but also for cell signalling and functional modulation of proteins such as enzymes and cell recognition molecules. The fine balance of such modulations by either phosphorylation or by O-GlcNAcylation can be disturbed by an increase or decrease of glucose concentrations. Hyperglycemia and hyperinsulinemia increases GlcNAcylation on many proteins in all cell types that have been examined. (Kudlow, 2006; Marz et al., 2006). A direct link between insulin resistance and conversion of glucose to glucosamine has been established (Marshall et al., 1991; McClain et al., 2002), and the importance of HSP and O-GlcNAc in diabetes has been described in detail (Hart et al., 2007; Love and Hanover, 2005). Increased GlcNAcylation directly blocks insulin signaling in adipocytes and muscle tissue, and the targeted over-expression of O-GlcNAc transferase (OGT) in muscle or fat cells caused diabetes in mice (McClain et al., 2002). Conversely, OGT is a substrate for the insulin receptor and is activated by tyrosine phosphorylation (Majumdar et al., 2004; Park et al., 2005; Vosseller et al., 2002). This suggests that OGT activity and insulin receptor activity are functionally connected via in a negative feedback and that they control the fine balance of activity within physiological levels. Chronic high glucose concentrations could destabilize this balance and contribute to the development of insulin signalling failure.

It has been hypothesized for several years that AD is accelerated by reduced glucose utilisation in the aging neuron. Studies of food deprived mice have shown hyperphosphorylated and hypo-O-GlcNAcylated Tau proteins appear. This effect is reversed by feeding (Li et al., 2006). Virtually all proteins involved in AD are regulated by O-GlcNAcylation or phosphorylation (Rudd et al., 2001). O-GlcNAcylation has been found to be reduced in brain tissue from AD patients (Yao and Coleman, 1998a,b). The reduced energy availability in cells would decrease UDP-GlcNAc pools, lower the normal levels of GlcNAc modification of neuronal proteins (Alexander et al., 2002) and lead to hyperphosphorylation of numerous peptides such as tau protein. Tau is extensively O-GlcNAcylated in normal brain samples but is much less O-GlcNAcylated and hyper-phosphorylated in AD (Arnold et al., 1996; O'Donnell et al., 2004). Other studies in neurons document the important interplay between O-GlcNAc and phosphorylation of Tau (Lazarus et al., 2006). Over-expression of the enzyme OGT in neurons increases Tau O-GlcNAcylation while decreasing Tau phosphorylation at sites that are important in AD development (Robertson et al., 2004). In a knock-down study that used a Cre-Lox brain-targeted deletion of OGT in mice, it was shown that Tau became hyper-phosphorylated prior to neuronal death (O'Donnell et al., 2004).

The APP molecule is furthermore O-GlcNAcylated at its cytosolic domain, indicating that the physiological role of cell signalling that APP plays is regulated by O-GlcNAc and can be compromised by de-regulation of O-GlcNAcylation (Griffith et al., 1995).

One of the functions of O-GlcNAc is to 'cap' phosphorylation sites that may not be needed in the adult. Excessive O-GlcNAcylation could block important phosphorylation sites that are needed for cell repair and development. Other functions include the regulation of the activities of promoters and gene transcription. For example, O-GlcNAc regulates the nuclear localization of NeuroD1 in response to glucose. NeuroD1 is a transcription factor that regulates insulin transcription in β-Cells (Andrali et al., 2007). GlcNAcylation of the transcription factor PDX-1 correlates with increased DNA affinity and insulin synthesis in β-cells (Gao et al., 2003). The OGase gene maps to 10q24.1, a locus that also maps the IDE gene and that is associated with sporadic or late onset AD, and OGT maps to X13, a Parkinson dystonia-associated locus (Bertram et al., 2000). Excess O-GlcNAc also inhibits transcription of SERCA2a, thereby contributing to diabetic cardiomyopathy (Brasse-Lagnel et al., 2003). Clearly, excessive O-GlcNAcylation has detrimental effects on the control of gene transcription, which could accelerate neurodegeneration by preventing the controlled activation of essential genes.

In addition, protein synthesis is modulated by O-GlcNAcylation. O-GlcNAcylation shuts off the proteasome, reducing protein synthesis and severely reducing the repair capacity of neurons (Hung et al., 2006; Zhang et al., 2003). Also, numerous synaptosomal proteins such as clathrins are dynamically O-GlcNAcylated, which could be important for synapse development if it involves survival factors such as Notch1, and could contribute to synapse loss in AD (Cole and Hart, 1999; Dimakopoulos, 2005; Yao and Coleman, 1998a,b).

O-GlcNAcylation furthermore plays an important role in the control of apoptosis (Zachara et al., 2004). The protein Ataxin-10 that is associated with neurodegeneration interacts with OGT in brain and increases O-GlcNAcylation (Marz et al., 2006). GlcNAcylation blocks Akt activation of eNOS and reduces the activation of glycogen synthase by insulin (Du et al., 2006a,b). These effects could greatly shift the balance between cell survival and apoptosis induction.

In conclusion, the deregulation of glucose levels in the body has a lot more effects on cellular metabolism than just the compromising of energy supply. Since O-GlcNAcylation plays a major role in cell signalling, the de-regulation of O-GlcNAcylation has important effects on cellular pathways and has the potential to greatly accelerate the development of AD. The impairment of cellular repair mechanisms, protein synthesis and gene transcription, and de-regulation of apoptosis induction, can add to ongoing degenerative processes or can even induce neuronal degeneration in chronic diabetes.

8. Similarities between T2DM and AD: 5. TGF-β

8.1. *Basic structure and biological activity of TGFs*

The Transforming growth factor group (TGF) has been identified two decades ago (Border and Noble, 1994). TGF and its receptor have been found in virtually every cell in the body, including epithelial, endothelial, hematopoietic, neuronal, and connective tissue cells (O'Connor-McCourt et al., 1987; Yamaguchi et al., 1990; Ziyadeh, 1994). The TGF group includes four major families: the Mullerian inhibitory substance (MIS) family, the inhibin/activin family, the bone morphogenetic protein (BMP) family, and the TGF-α and -β family (Bartram and Speer, 2004). Three structurally and functionally similar TGF-β isoforms (TGF-β 1, 2, and 3) have been identified. They are mapped by distinct genes on chromosomes 19q13.1–q13.3 19, 1q41 (Fujii et al., 1986) and 14q23–24 (Barton et al., 1988).

TGF-β levels are upregulated in some cancers, and play important physiological roles in tissue regeneration, cell differentiation, embryonic development, the regulation of the immune system and apoptosis. One of the specific functions of TGF-β that has been identified is the inhibition of the growth of most epithelial and hematopoietic cells, and to regulate the production of extracellular matrix by mesenchymal cells (Lim and Zhu, 2006). TGF-β1 is generally considered to be an immune regulatory cytokine with strong therapeutic potential for treatment of human autoimmune or chronic inflammatory diseases. In several animal models of human autoimmune disease, administration of TGF-β1 has demonstrated promising therapeutic applications (Braley-Mullen et al., 2001; Moritani et al., 1998; Piccirillo et al., 1998). TGF-β1-deficient mice express a severe inflammatory and autoimmune phenotype in multiple organs, underscoring the importance of TGF in the control of cell proliferation and immune response (Shull et al., 1992).

8.1.1. *Roles and functions of TGFs in T2D*

Elevations of plasma TGF-β1 have been reported in several human diseases or in animal models of disease (Yener et al., 2007). These include obesity with impaired insulin sensitivity (Romano et al., 2003) and both type 1 and type 2 diabetes (Esmatjes et al., 1999; Pfeiffer et al., 1996). It is known that hyperglycemia is one of the major triggers for TGF-β1 expression, and patients with diabetes have higher levels of TGF-β1 than healthy people (Yener et al., 2007). It is thought that the diacylglycerol–protein kinase C pathway, the glucosamine pathway and possibly the polyol pathway play important roles for the increased production of TGF-β1 in diabetes (Rossert et al., 2000). It was shown that rats with streptozotocin-induced diabetes had higher TGF-β1 expression during the first day of hyperglycemia (Shankland et al., 1994). Another study showed elevated plasma levels of TGF-β1 in T2DM and also demonstrated the association between metabolic control and TGF (Pfeiffer et al., 1996). Additionally, plasma and urinary TGF-β1 levels were significantly lower in controls than in patients with type 1 diabetes mellitus (Flores et al., 2004). This increase could be a response to the auto-immune process at the onset of type 1 diabetes, or an anti-inflammatory response, as these patients are known to have subclinical inflammation. The blockade of the renin–angiotensin system with ACE inhibitor therapy leads to a reduction in intra-renal TGF-β1 expression and activity in human diabetic nephropathy (Langham et al., 2001; Langham et al., 2006). Several studies in animal models have documented that not only is TGF-β expression increased in the diabetic kidney but that it is also present in the biologically active form (Gilbert et al., 1998). TGF-β1 induces the phosphorylation of the TGF-β receptor activated protein Smad2. In a histological study of Smad2 levels in the kidneys of diabetic patients, prominent nuclear staining of phosphorylated Smad2 was present in all diabetic biopsies, and a reduction was in those patients who had received ACE inhibitors over 2 years. In contrast to the reduction in TGF-β1 levels, expression of the TGF-β type II receptor was unaffected by ACE inhibitor therapy (Massague and Chen, 2000). Moreover, inhibition of TGF-β action has been shown to attenuate mesangial expansion and interstitial fibrosis in experimental diabetic nephropathy (Ziyadeh et al., 2000). In an animal model of type 1 diabetes, autoimmune diabetes mellitus development was completely prevented by TGF-β1 in both paracrine and autocrine fashions (Du et al., 2006a,b).

Using diabetic *db/db* mice, a model of obese type 2 diabetes, increases in renal expression of TGF-β1 was inhibited by a novel drug that improved diabetes in these mice (Ichinose et al., 2006). These results clearly demonstrate that induction and/or enhancement of TGF-β1 production produces a striking inhibitory effect on chronic inflammatory and autoimmune diseases (Faria et al., 2003; Roncarolo et al., 2001; Strobel, 2002).

8.1.2. *Functions of TGF in the brain*

The anti-inflammatory effects of TGF-β play also important roles in the brain. TGF-β expressed by neurons can protect from CNS inflammation and injury (Liu et al., 2006) and also play a pivotal role in regulating neuronal development and survival (Farkas et al., 2003). Furthermore, TGF-β1 promotes microglial amyloid-beta clearance and reduces plaque burden in a transgenic animal model of AD that expresses human APP and develops SPs (Wyss-Coray et al., 2001). Hence, improvement of TGF-β signalling may be a novel therapeutic approach to AD, simultaneously targeting a neurodegenerative pathway and preventing Aβ deposition. TGF-β1 is found within a subset of SPs, and TGF-β2 had been found in NFTs in AD brains (van der Wal et al., 1993). This suggests that TGF-β1 signalling may be increased by Aβ deposition and might play a role in cellular responses to clear Aβ and protect neurons, and that TGF-β2 plays a role in cellular responses to protect neurons against the effects of NFTs (Flanders et al., 1995) Neurons treated with TGF-β1 increased resistance to excitotoxicity and protected cortical neurons against ischemic injury in adult rodents (McNeill et al., 1994; Prehn et al., 1993) and rabbits (Gross et al., 1993). It was furthermore reported that TGF-β1 protected cultured embryonic human cortical neurons against Aβ toxicity (Chao et al., 1994). The possible mechanism of TGF-β1 protection is to increase expression of Bcl-2, which protects neurons from apoptosis, and stabilize calcium homeostasis in cultured neurons (Prehn et al., 1994). The TGF-β type II receptor is mainly expressed by neurons, and the levels of this receptor are reduced in human AD brain and correlate with pathological hallmarks of the disease. Reducing neuronal TGF-β signalling in mice resulted in age-dependent neurodegeneration and promoted Aβ accumulation and dendritic loss in a mouse model of AD. In cultured cells, reduced TGF-β signalling caused neuronal degeneration and resulted in increased levels of secreted Aβ and β secretase-cleaved soluble APP (Tesseur et al., 2006). Hence, reduced neuronal TGF-β signalling increases age-dependent neurodegeneration and AD-like symptoms. Increasing neuronal TGF-β signalling may thus reduce neurodegeneration and could be beneficial in the treatment of AD.

9. Similarities between T2DM and AD: 6. Evidence from animal models

Common processes that underlie both T2DM and AD are further shown by animal models of AD and diabetes. Various experimental models of AD have been developed, but none has been found to be truly representative of the sporadic type of AD (SAD), which cannot be directly linked to a specific gene

or mutation. Taken that SAD has now been recognized as an insulin-resistant brain state, it has been proposed that rats injected with streptozotocin (STZ) directly into the brain could be used as an experimental model of AD ('type 3 diabetes') (Lannert and Hoyer, 1998; Lester-Coll et al., 2006). STZ, a diabetogenic agent which selectively destroys the insulin producing pancreatic β-cells, is used to induce diabetes-like symptoms in animals (Meyerovitch et al., 1989). STZ decreases both insulin receptor autophosphorylation and intrinsic tyrosine kinase activity (Ar'Rajab and Ahren, 1993) and elevates the activity of phosphotyrosine phosphatase (Meyerovitch et al., 1992; Meyerovitch et al., 1989). In the mammalian brain, insulin is formed in pyramidal cells and its receptors are widely distributed in the brain (Banks, 2004; Begum et al., 1991). STZ was found to impair brain glucose and energy metabolism and to induce an impairment of learning and memory formation, and furthermore the decrease of choline acetyltransferase levels in the hippocampus (Hoyer, 1998; Lannert and Hoyer, 1998). Hence, the AD animal model of insulin signalling impairment in the CNS induced by STZ injection i.c.v. is considered a novel animal model of AD (Craft et al., 2000; Frolich et al., 1998a,b, 1999; Grunblatt et al., 2007; Lester-Coll et al., 2006; Mukai et al., 1980; Salkovic-Petrisic et al., 2006). This animal model does indeed show some of the hallmarks of SAD, e.g. the development of brain lesions (Craft et al., 2000; Frolich et al., 1998a,b; Frolich et al., 1998a,b; Mukai et al., 1980). In addition, the brains of STZ injected rats were reduced in size and exhibited neurodegeneration associated with cell loss, gliosis, and increased immunoreactivity for p53, activated GSK-3beta, and increased phospho-tau and Aβ levels (Lester-Coll et al., 2006). A different study also found an increase of phosphorylated GSK-3beta in the rat hippocampus, while Akt/PKB levels (which inhibit apoptosis) decreased after STZ treatment (Salkovic-Petrisic et al., 2006). It was furthermore shown that i.c.v. injection of STZ greatly affected behaviour and impaired learning over the period of 3 months (Lannert and Hoyer, 1998; Nitsch and Hoyer, 1991). Additionally, STZ i.c.v. injection produces oxidative stress in the brain of treated rats (Sharma and Gupta, 2001).

Therefore it might be concluded that the STZ-rat model for SAD does indeed demonstrates several key properties of Alzheimer's disease and of neurodegenerative processes in general. The impairment of insulin signalling in the brain results in the development of neuropathy, and therefore the STZ rat model is a valuable tool for basic research of the biochemical processes that underlie neurodegeneration (Grunblatt et al., 2006; Grunblatt et al., 2007).

For the purpose of this review, the fact that an animal model of diabetes can be modified to model key features of neurodegeneration as found in AD highlights the fact that both conditions underlie common biochemical pathways and processes.

10. Conclusion

The presented evidence highlights the wide range of common molecular mechanisms of degeneration that link T2DM with AD. While there are obvious differences between these two conditions, it is important to note the similarities in protein misfolding, insulin signalling impairments, and cytotoxic processes found in both diseases. Research to obtain detailed knowledge about the precise molecular processes can be of great help in the development of novel treatments and drug targets which can be of use to treat a much wider range of degenerative diseases than previously anticipated. The similarities between AD and T2DM have only been discovered fairly recently, and we are only at the very beginning of identifying the molecular pathways that are involved. It is therefore to be imagined that future research will present us with more information on the interactions between different diseases that hopefully will lead to novel treatments to improve or even prevent the molecular processes that underlie AD and T2DM.

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