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Alzheimer's Disease and Type 2 Diabetes: Different Pathologies and Same Features

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1. Introduction

Protein aggregation is a very fascinating matter due to its implication in many human neurodegenerative diseases and its relevance in food and pharmaceutical industries. In some cases, the aggregation of protein is a natural phenomenon occurring in living organisms. For example, in the reaction leading from the globular (G) monomeric actin to its polymeric fibrillar (F) structure (Morris et al., 2009):

$$n\ (\text{G-Actin}) \rightarrow (\text{F-Actin})_n$$

or the case of polymerization of tropocollagen to obtain collagen fibrils, a process leading, in the case of type I Collagen, to the formation of long fibrils having a wave pattern (Yadavalli et al., 2010).

In general, a non-physiological aggregation, that is an aggregation process not naturally occurring, starts from "activated" molecules having secondary and/or tertiary structures different from those corresponding to the "native state" (Manno et al., 2006, 2010; Morris et al., 2009). Increasing evidence suggests that the non-physiological aggregation of proteins such beta-amyloid, alpha-synuclein, huntingtin and ataxin, superoxide-dismutase 1 (SOD1), Tau and Amylin, is responsible for the onset of many neurodegenerative pathologies such as Alzheimer's, Parkinson's and Huntington's diseases, Amyotrophic Lateral Sclerosis, Frontotemporal Lobar Degeneration (Figure 1) and Type 2 Diabetes (or diabetes mellitus), respectively (Chiti & Dobson, 2006).

The question of what triggers the transformation of a biologically active protein into a "pathogenic agent" with high self-assembly propensity is still unanswered. Some of the proposed explainations include:

i. the propensity of some proteins to assume a pathological conformation which increases with aging (Uversky, 2007; Saraiva, 2001);
ii. the persistently high cellular or plasma concentrations (Singleton et al., 2003; Farrer et al., 2004);
iii. an amino acid mutation or a genetic expansion of DNA sequences encoding proteins, as in the case of Huntington disease (Cummings & Zoghbi, 2000);
iv. an abnormal post-traslational modification of the protein responsible for the disease (Goedert et al., 1993);

v. the proteolitic cleavage of the precursor protein, as in the case of Abeta-peptide;
vi. the influence of environmental factors.

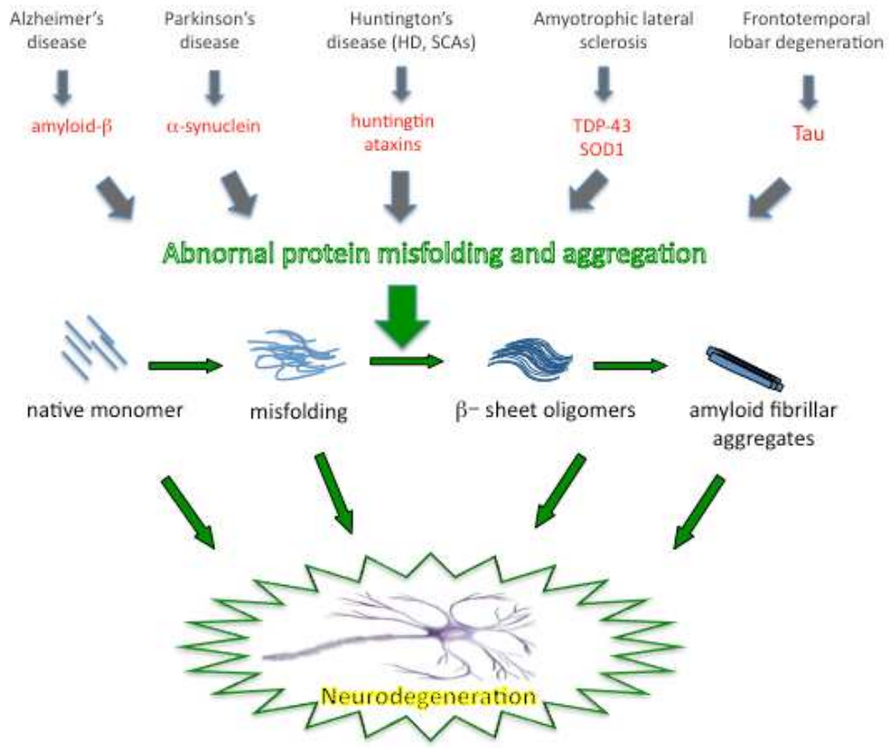


Fig. 1. *Protein misfolding and aggregation as the common molecular pathogenesis of neurodegenerative diseases*. Some genetic mutations responsible of neurodegenerative diseases render the causative proteins prone to misfold and to form beta-sheet-rich oligomers and amyloid fibrillar aggregates, resulting in their accumulation in the affected neurons and eventually leading to degeneration in the brain. This mechanism is retained common to a broad variety of neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington disease, Amyothophic Lateral Sclerosis and Frontotemporal Lobar degeneration.

Type 2 diabetes (T2D) is classified as a metabolism disorder and it is often associated with microvascular and macrovascular complications, including retinopathy, nephropathy, neuropathy and cardiovascular disease. A diabetes affected person has an elevated quantity of glucose in the blood (hyperglycemia) that is caused by the inability of the body either to produce any insulin or enough insulin, or by the inability of the cells to respond properly to the insulin producted in the pancreas. This excess blood glucose eventually passes out of the body in the urine. So, even though the blood has plenty of glucose, the cells are incapable of getting it for their essential energy and growth requirements. There are three main types of diabetes: Type 1 diabetes (T1D) (referred to as *insulin-dependent* diabetes and *juvenile* diabetes), results from the body's failure to produce insulin, and presently requires the person to inject insulin. Type 2 diabetes (referred to as *non-insulin-dependent* diabetes mellitus, and *adult-onset* diabetes.) is associated with a reduced ability of insulin to stimulate glucose utilization (insulin resistance) and sometimes it is combined with an absolute

insulin deficiency. The third type, gestational diabetes, is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy and it may precede development of T2D. Ninety percent of diabetes patients have T2D, which usually has its onset in adulthood. Diabetes is increasing and the World Health Organization estimates that there will be a doubling of cases by 2025, largely as a result of lack of physical activity and poor dietary habits, both of which are risk factors for the disease. Obesity, hypertension, hyper-cholesterolemia and hyperlipidemia are all associated with T2D (MedScape).

Alzheimer's disease (AD) is the most common form of dementia in the elderly. It is characterized by neuronal cell loss and increasing accumulation of neurofibrillary tangles (NTF) in neurons and amyloid fibers in neuritic plaques and in the walls of blood vessels (Wisniewski et al., 1997). Amyloid beta-peptides of varying length (39–43 residues) are produced by cleavage of a transmembrane protein, the amyloid beta-protein precursor (APP) (Wilquet & De Strooper, 2004). The 42 residue beta-peptide (Abeta-42) is the predominant form found in plaques and under physiological condition the ratio between Abeta42 and Abeta40 is about 1:10 (Iwatsubo et al., 1994). Abeta42 has a much greater neurotoxity than Abeta40 and its aggregation kinetics is faster than other beta-petides (Davis & Van Nostrand, 1996). The proteinaceous material is organized in structured linear aggregates (amyloid fibrils). A recent and now convincing belief is that small diffusible oligomers of Abeta-42, called ADDLs, are the determining pathogenic species causing synaptic dysfunction and eventually neuronal degeneration (Lambert et al., 1998; Picone et al., 2009)

AD accounts for 50–70% of all dementia cases and is characterized by cognitive deficits. This incurable, degenerative, and terminal disease was first described by the German psychiatrist and neuropathologist Alois Alzheimer in 1906. Several factors have been considered relevant for the AD pathogenesis and among these the most important is age. During life small variations occurring in cellular metabolism and structure can modify the functional state of susceptible neurons, leading to dramatic or even lethal changes. Thus, while the the monomeric Abeta is not neurotoxic, for not yet known reasons it starts to form supramolecular aggregates accumulating in the AD brain.

Familial AD is a rare form of dementia and is caused by autosomal dominant mutations in one or more of the genes encoding the amyloid precursor protein (APP), presenilin 1 or presenilin 2 (the latter two proteins form the catalytic core of γ-secretase) (Gotz et al., 2004). By contrast, late-onset AD might be caused by environmental and/or life style factors (Rocchi et al., 2003). Interestingly, late-onset AD is characterized not only by the neuropathological markers mentioned above, but also by vascular lesions, and hyperglycemia, hyperinsulinemia, insulin resistance, glucose intolerance, adiposity, atherosclerosis and hypertension (Haan, 2006).

Diabetes and AD are considered age-related diseases and are both increasing. In the USA, diabetes and AD affect ≈ 23.6 and ≈ 5.3 million people, respectively, and these numbers are projected to rise considerably. The Centers for Disease Control and Prevention predict that more than 29 million people in the US will be affected by diabetes by 2050, while the Alzheimer's association forecasts that by this date, 11–16 million Americans will have AD (Han & Li, 2010). Numerous studies report that patients with diabetes have an increased risk of developing AD compared with healthy individuals (Arvanitakis et al., 2004; Neumann et al., 2008; Roriz-Filho et al. 2009). In fact, some studies revealed that 80% of

patients with AD exhibited either impairments in glucose tolerance or frank diabetes (Schrijvers et al., 2010). In particular, similarities between T2D and AD include: aging-related processes, degeneration, high cholesterol levels, peripheral and CNS insulin resistance, dysfunctional IR and IR-mediated signaling pathways, decreased glucose transport and metabolism, despite the higher non-metabolized glucose levels in cerebral blood (Hoyer, 1998; Salkovic-Petrisic & Hoyer, 2007; Schulingkamp et al., 2000). The inbalance between low and high glucose levels in T2D patients may be responsible for brain vascular damage and neurodegeneration thus facilitating the AD onset.

2. Alzheimer's disease and type 2 diabetes: Two amyloidogenic pathologies

AD and T2D are two pathologies characterized by the presence of large insoluble aggregates having an amyloidogenic fibrillar conformation, amylin in T2D pancreatic islets and Abeta and the microtubule protein Tau in the brain of AD patients. In particular, amylin aggregation is associated with pancreatic b-cell loss, whereas Abeta and Tau aggregation is associated with neuronal cell loss and synaptic dysfunction (Lupi & Del Prato, 2008; Schroeder & Koo, 2005; Resende et al., 2008a). The formation of amyloid aggregate occurs both in the intra- and extra-cellular environments; further the proteinaceous aggregates are strictly bound with membranes and calcified. Despite their common secondary structure conformation, it is well accepted that a correlation does not exit between amino acid sequence and tendency to amyloid structure formation; thus it is assumed that amyloid formation is a generic properties of all polypeptides (Chiti & Dobson, 2006).
In particular, amyloid fibers share the following features (Xu, 2007):

- all have a rope-like appearance;
- all show a dominant beta-sheet structure;
- their formation can be enhanced either by the stirring or the presence of seeds;
- all aggregate starts from spherical oligomers that in turn self-assemble linearly;
- all can incorporate a special kind of dye molecules such as Congo Red or Thioflavin T.

On a molecular lengthscale, Abeta can form aggregates of different shape originated in vitro under different conditions. These structures include amyloid fibrils (Ban et al., 2004), small oligomers (Walsh et al., 1999), spherical amyloid oligomers (Westlind-Danielsson & Arnerup, 2001) and annular pore-forming structures (Lashuel et al., 2002), amyloid protofibrils (Harper et al., 1997), beaded chain protofibrils (Huang et al., 2000) and spherocylindrical micelles (Lomakin et al., 1996; Yong et al., 2002).
X-ray fiber diffraction showed that amyloid fibrils contain beta-sheet structure lying orthogonally to the major fibril axis (Serpell, 2000). In the early 2000s, Tycko's group (Antzutkin et al., 2000; Balbach et al., 2002) obtained, for the first time, evidence of an extended parallel beta-sheet organization for the Abeta40 fibrils using solid-state NMR. They showed that the methyl carbons of Ala-21 and Ala-30 must be placed in groups of at least four with internuclear distances of less than 5.5 Å. Although beta-sheets are the main constituent of the amyloid fibrils they are not the only structure present in the fibrils. Liquid state NMR, FTIR and CD measurements in Abeta40 have demonstrated the existence of a turn formed by the amino acids at position 26-29. Little information is known about the Abeta42 fibril structure and many mutant peptides have been synthetized to obtain an explanation about its secondary structure. The results have showed that the residues at positions 15–21 and 24–32 are involved in the beta-sheet formation and that the turn at positions 22 and 23 plays a crucial role in the aggregation of Abeta42.

The islet amyloid polypetide (IAPP), identified for the first time in 1987 (Westermark et al.) and also known as amylin, is secreted by the beta cells of the pancreatic islets of Langerhans, which also secrete the insulin. The occurrence of IAPP in the membranes of beta-cells and the presence of alterations in the membranes of the same cells (Lorenzo et al., 1994; Janson et al., 1999) suggest that this interaction is responsible for the cytotoxic effect of these formations. The primary sequence of the peptide is well conserved in organisms and, in particular human and mouse IAPPs differ by only six amino acids but the latter does not form fibrils neither in vitro nor in vivo. The development of IAPP deposits is deeply associated with T2D because more than 90% of T2D patients presents this type of amyloid formations as evidenced by autopsy and, further, the amount of aggregates appears to be correlated with the pathology seriousness.

Human IAPP (hIAPP) consists of 37 amino acids with a S-S bridge between the Cys 2 and Cys 7. As in Abeta, IAPP is non-toxic in its monomeric form but it exhibits high toxicity levels when it aggregates into beta-rich amyloid structures. As in other amyloid peptides, the mechanism of fibrillation occurs through the formation of nuclei with a lag phase whose duration is concentration-dependent and proceeds by addition of monomers or oligomers to both fibril terminals. The secondary structure of hIAPP mainly consists of unstructured regions, with small alpha-helical and beta-sheet components (Goldsbury et al., 2000). Recently has been suggested that hIAPP oligomers in presence of membranes could exhibit an alpha-helical structure (Knight et al., 2006).

The three dimensional structure of hIAPP has been extensively studied with different techniques and the results show that, similarly to other amyloid proteins, the amylin mature amyloid fibrils show a relevant amount of beta-structure (McLean, 1992; Goldsbury, 2000). Studies on the mechanism of hIAPP fibrillation indicate that during the process, hIAPP undergoes a conformational change from an unstructured peptide to beta-sheets and alpha-helical structures (Goldsbury, 2000).

The IAPP decapeptide sequence between residues 20-29 seems to play an important role in the fibrillization process (Westermark et al., 1990) even if it does not appear to be the only region involved in fibril formation. In fact, recent studies have evidenced the importance of the residues in position 13-18 in the interaction leading to the formation of fibrils (Gilead & Gazit, 2008). Also the aromatic-aromatic interactions between residues 15, 23 and 37 seem to be important in amyloid formation althought not essential for fiber formation as evidenced using IAPP with a triple mutation (Marek et al., 2007).

3. The effect of oxidative stress

The brain has a high energy demand and, although it represents only 2% of body weight, it accounts for 20% of total body oxygen consumption. This energy requirement is largely driven by neuronal request of energy to maintain the ion gradients across the plasma membrane, which are critical for the generation of action potentials. This intense energy requirement is continuous; even brief periods of oxygen or glucose deprivation result in neuronal death. Diabetes mellitus leads to functional and structural changes in the brain, which appear to be most pronounced in the elderly. Furthermore, increased age is associated with insulin resistance. Increasing data support the idea that mitochondrial function declines with aging and in age-related diseases such as diabetes and AD.

Normal glucose metabolism is required for the performance of cognitive functions, and impairments in glucose metabolism might contribute to cognitive dysfunction. Imaging

studies have revealed that patients with AD and individuals at risk of developing this disease typically have reductions in glucose metabolism in temporal and parietal brain regions and hippocampus (Garrido et al., 2002). Moreover, compared to healthy individuals, patients with AD often have increased plasma insulin levels and/or a decreased cerebrospinal fluid (CsF)-to-plasma insulin ratio. These findings indicates that glucose metabolism and insulin signaling are important in normal brain function. The negative effect of impaired glucose metabolism on cognitive functioning can be caused by an increase in oxidative stress that is associated with mitochondrial dysfunction.

Mitochondria are essential subcellular organelles for generating the energy that fuels normal cellular functioning. At the same time, the mitochondria have a strategic task because, depending on environmental factors, they can decide whether to continue the healthy life of the cell or to terminate it by apoptosis activation. Mitochondria are essential for neuronal function because the limited glycolytic capacity of these cells makes them highly dependent on aerobic oxidative phosphorylation for their energetic needs. However, oxidative phosphorylation is a major source of endogenous free radicals. A variety of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced in vivo through both enzymatic and non-enzymatic routes. ROS include hydrogen peroxide, hydroxyl radical, superoxide ion and singlet oxygen, products of normal cellular respiration. The hydroxyl radical is a highly reactive species and has a relatively short life time. It is abundantly produced in the mitochondria during respiration cycles and reacts with the proteins, lipids, and nucleic acids during their production. Peroxynitrous acid is one of the major RNS found intracellularly and it is involved in the rapid nitration of aromatic residues of proteins, such as tyrosine, to give 3-nitrotyrosine, which may alter the protein structure. Further it is also a marker of oxidative stress (Smith et al., 1997). Under normal conditions, antioxidant defenses can counteract oxidative stress damage. In the absence of an appropriate compensatory response from the endogenous antioxidant network, the system becomes redox imbalanced, leading to the activation of a stress-sensitive intracellular signaling pathway and, in extreme conditions, to apoptosis. Increased oxidative damage and impaired antioxidant defenses are prominent both in the onset of AD and diabetes (Smith et al., 1996; Evans et al. 2002). Abnormal glucose metabolism can also increase the production of free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). This overproduction of free radicals can exhaust the antioxidant capacity of the cell and lead to a condition known as oxidative stress, which is a hallmark of both T1D and T2D and a contributing factor to diabetic neuropathy (Russell et al., 2008; Vincent et al., 2004). Oxidative stress is not only associated with diabetes and its complications, but has been linked to insulin resistance, the subnormal response to a given amount of insulin (West, 2000).

ROS-induced and RNS-induced protein modifications and/or lipid peroxidations result in cell damage that can lead to cell death, and they are increased in patients with diabetes or AD compared with healthy controls (Pratico et al., 2004). Brain and cerebrospinal fluid (CSF) levels of lipid peroxidation biomarkers, including malondialdehyde and 4-hydroxynonenal (two highly toxic products generated in part by lipid oxidation and ROS), are both higher in individuals with AD and diabetes mellitus than in healthy people (Reddy et al., 2009; Slatter et al., 2000). Furthermore, levels of oxidized proteins are increased in the frontal and parietal lobes and in the hippocampus of patients with mild cognitive impairment compared with healthy controls, indicating that oxidative damage might occur early in the development of AD (Butterfield et al., 2007). ROS, as mentioned earlier, are also involved in the damage of

DNA. Minor modifications of the nucleic acid bases are repaired through base excision repair involving DNA glycosylase and AP endonuclease, which are located in nuclei and mitochondria. The progression of AD is associated with the diminished expression of these DNA repair enzymes (Nakabeppu et al., 2004). The accumulation of the oxidatively damaged nucleic acids and proteins likely exceeds the limit of cellular repair and detoxification mechanisms and leads to the onset or progression of diabetic and neurological pathologies. In general, accumulation of oxidatively damaged proteins, lipids, and nucleic acids correlates with the onset of age-related diseases, especially in diabetes and AD (Stadtman, 2001), indicative of a common pathological mechanism.
Oxidative stress and lipid peroxidation seem to be able to induce Abeta accumulation: studies in a mouse model of AD have demonstrated that brain lipid peroxidation increases before that Abeta levels increase (Pratico et al., 2001) and that the onset of Abeta deposition is associated with an increase in the level of RNS (Apelt et al., 2004). Further evidence supporting this hypothesis has been obtained from studies of a mouse model of AD in which mutations in the genes encoding APP and presenilin 1 cause an increase in Abeta42 production. In these animals, lipid and protein peroxidation is evident at the disease onset (Matsuoka et al., 2001). In a triple-transgenic animal model of AD, in which mice develop Abeta plaques, tangles and cognitive defects, a decrease in antioxidant capacity and an increase in lipid peroxidation were noted before the development of AD pathology (Resende et al., 2008). Oxidative stress seems to affect APP either directly, by increasing APP levels, or indirectly, by modulating APP processing, and both mechanisms could increase levels of Abeta. Studies in transgenic mice and postmortem brain tissue from patients with AD suggest also that an increase in Abeta production leads to a rise in the production of ROS and that oxidative stress occurs early in the development of the disease.

4. The mitochondrial dysfunction

Several studies are consistent with the view that diabetes-related mitochondrial dysfunction is exacerbated by aging and/or by the presence of neurotoxic agents, such as Abeta. This suggests that diabetes and aging are risk factors for the neurodegeneration induced by this peptide. Mitochondrial dysfunction could be one of the common underlying mechanisms explaining the association between diabetes and AD. Mitochondrial dysfunction and the resulting energy deficit trigger the onset of neuronal degeneration and death. Mitochondria serve also as high capacity Ca^{2+} sink, which allows them to follow the changes in cytosolic Ca^{2+} loads and helps in maintaining cellular Ca^{2+} homeostasis, required for normal neuronal function (Rizzuto et al., 2000). Conversely, excessive Ca^{2+} uptake inside mitochondria has been shown to increase ROS production, inhibit ATP synthesis, release cytochrome C, and induce mitochondrial permeability transition (Brustovetsky et al., 2002). The mitochondrial permeability transition (MPT) is defined as the sudden increase of inner mitochondrial membrane permeability to solutes of molecular mass lower than 1500 Da (Bernardi et al., 1994). Strong evidence now exists that the MPT is due to the opening of a nonselective megachannel (estimated to be 2–3 nm in diameter). Because the chemiosmotic theory is based on the impermeability of the inner mitocondrion membrane to solutes that are not specifically transported, MPT would collapse the mitochondrial membrane potential ($\Delta\Psi m$) and uncouple the electron transport system from the production of ATP. Additionally, MPT results in mitochondrial swelling and can lead to the release of proapoptotic proteins. Importantly, Ca^{2+}, P_i, oxidative stress, and low inner membrane potential promote the onset

of MPT, whereas cyclosporin A, Mg^{2+}, ADP, and the existence of a high membrane potential oppose the onset (Bernardi et al., 1994).
Increasing data support the idea that mitochondrial function declines with aging and in age-related diseases, such as diabetes and AD (Calabrese et al., 2001). Some data show the existence of an age-related impairment of the respiratory chain and an uncoupling of oxidative phosphorylation in brain mitochondria isolated from Goto-Kakizaki (GK) rats, as model of T2D (Moreira et al., 2003). Furthermore, aging exacerbates the decrease in the energetic levels promoted by diabetes. The maintenance of oxidative phosphorylation capacity is extremely important in the brain since a large amount of the energy required for the normal functioning of neurons is provided by mitochondria. Moreover, the CNS requires a large amount of ATP for the transmission of impulses along the neural pathway, thus indicating that mitochondrial function impairment can result in neurodegeneration and loss in neuronal metabolic control (Calabrese et al., 2001).

5. Advanced glycation end products (AGE)

Abnormal glucose metabolism and oxidative stress contribute to the formation of advanced glycation end products (AGE). This process occurs through the Maillard reaction or "non-enzymatic browning", a complex series of reactions between reducing carbohydrates with lysine side chains and N-terminal amino groups of proteins. This process initially leads to rather labile Schiff bases which as a rule rearrange to the more stable Amadori products. The Amadori compounds are slowly degraded, in complex reaction pathways via dicarbonyl intermediates, to a plethora of compounds (Ledl & Schleicher, 1990) designated summarily as "advanced glycation end products" (AGEs); this overall reaction sequence proceeds both in vitro and in vivo. In long-lived tissue proteins, these chemical modifications accumulate with age and may contribute to pathophysiologies associated with aging and long-term complications of diabetes and atherosclerosis (Lederer & Klalber, 2000).
Practically, AGEs comprise a heterogeneous group of molecules formed by irreversible, non-enzymatic reactions between sugars and the free amino groups of proteins, lipids and nucleic acids. Auto-oxidation of glucose leads to the formation of oxygen radicals, which are intermediates in the AGE pathway and the predominant source of endogenous AGEs. AGEs may exist as protein cross-links or as modification of the side chains of a single protein, and significantly alter protein conformations leading to protein inactivation. Numerous AGEs have been isolated and characterized by spectroscopic analysis after cleavage from the protein backbones. AGEs involving protein cross-links include: pentosidine, a dimer of arginine and lysine; methylglyoxal-lysine dimer (MOLD), a dimer of two lysine residues; and methylglyoxal-derived imidazolium cross-link (MODIC) and glyoxal-derived imidazolium cross-link (GODIC), dimers of arginine and lysine residues. Examples of AGEs resulting from the single protein modification are pyrraline and Nε -(carboxymethyl)lysine (CML), the lysine-residue modified products, and argpyrimidine, an arginine-residue modified protein. Although many other AGEs, including the hydroimidazolone adduct MG-H1, have been characterized in diabetes, some of them have common occurrence in AD (Rabbani et al., 2008).
The formation and accumulation of AGEs occur during normal aging; however, these processes are exacerbated in patients with diabetes and the binding of AGE to its receptor (receptor for AGEs or RAGE) induces a series of biological processes that cause further diabetic complications (Singh et al., 2001). AGE immunoreactivity is present in both Abeta

plaques and NFTs in patients with AD. Furthermore, hippocampal neurons from patients with this neurodegenerative disease contain Abeta-positive, AGE-positive and RAGE positive granules. (Sasaki et al., 2001). Whether the modifications of Abeta and tau by AGEs are a primary or secondary event in AD is a controversial topic. Nevertheless, AGEs are widely accepted to be active participants in the progression of AD, since AGE-induced glycation of Abeta and tau protein has been shown to cause the Abeta aggregation and the formation of NFTs, respectively (Ledesma et al., 1994). Moreover, diabetic mice with cognitive impairments exhibit increased RAGE expression in neurons and glia compared with wild-type control mice (Toth et al. 2006), and in one clinical study, AGE immunostaining was increased in postmortem brain slices from patients with AD and diabetes compared with non-diabetic patients with AD (Girones et al., 2004).

The question of whether AGEs are the cause or consequence of the pathology is not clear, although there is likely a primary role of oxidative stress in both pathologies. However, it should be pointed out that glycoxidation and oxidative stress are mutually dependent and reinforce each other. Thus, while the sources of oxidative stress may widely differ in diabetes and AD, and while a number of AGEs accumulate in both conditions, other AGEs found in diabetes have yet to be characterized in AD.

6. Antioxidant therapy in Alzheimer's disease and diabetes

Given the importance of mitochondria as the primary source of oxidative stress in AD and diabetes, the use of antioxidants may also be useful. However, the broad occurrence of both diseases, the non-regenerative nature of the CNS and the fact that AD diagnosis often does not occur until late in the disease progression, suggest that the ideal antioxidant should be used as a prophylactic treatment for the aged population. Oxidative stress is one of the earliest events in the neurological and pathological changes of AD, while the effects of oxidative stress are manifested in the slow accumulation of AGEs in diabetes. Thus, antioxidant therapy in combination with AGE inhibitor therapy may be effective approaches for AD and diabetes-related complications. Oxidative stress leads to irreversible protein aggregation and consequent neuronal degeneration in AD (Liu et al., 2007). Advanced lipoxidation products, such as HNE, bind to phosphorylated tau protein to form paired helical filaments, accelerating the formation of neurofibrillary tangles. Oxidative stress also results in the covalent crosslinking of tau filaments to form large aggregates that are resistant to proteolytic cleavage. Larbig and coworkers reported a series of inhibitors for tau protein aggregation (Larbig et al., 2007). Remarkably, thiazolium-based compounds, which are also AGE inhibitors and potentially useful for diabetic therapy, are effective inhibitors of tau aggregation.

Extensive studies of pharmacological interventions based on biological antioxidants have been carried out both for AD and diabetes (Lee et al., 2010; Maritim et al., 2002). Common antioxidants include the vitamins A, C, and E, glutathione, and the enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. Other antioxidants include lipoic acid, mixed carotenoids, coenzyme Q10, several bioflavonoids, antioxidant minerals (copper, zinc, manganese, and selenium), and the cofactors (folic acid; vitamins B1, B2, B6 and B12). They work in synergy with each other and against different types of free radicals. Vitamin E suppresses the propagation of lipid peroxidation; vitamin C, with vitamin E, inhibits hydroperoxide formation; metal complexing agents, such as penicillamine, bind transition metals involved in some reactions in lipid peroxidation.

Vitamins A, C, and E are interesting antioxidant molecules because are diet-derived and directly detoxify free radicals. They also interact in recycling processes to generate reduced forms of the vitamins. Tocopherol is reconstituted when ascorbic acid recycles the tocopherol radical; dihydroascorbic acid, which is generated, is recycled by glutathione. Under some conditions, these vitamins also foster toxicity by producing pro-oxidants. Vitamin E, a component of the total peroxyl radical-trapping antioxidant system, reacts directly with peroxyl and superoxide radicals and singlet oxygen and protects membranes from lipid peroxidation (Weber et al., 1997). A deficiency of vitamin E is concurrent with increased peroxides and aldehydes in many tissues. There have been conflicting reports about vitamin E levels in diabetic animals and human subjects. Plasma and/or tissue levels of vitamin E are reported to be unaltered, increased, or even decreased by diabetes (Asayama et al., 1994).

Some AGE inhibitors and AGE crosslink breakers have been utilized as potential therapies. Some attention to AGE inhibitors was focused on aminoguanidine, which blocks electrophilically activated 1,3-dicarbonyl compounds, the precursors of AGEs (Thomas et al. 2005; Webster et al., 2005). This compound was not approved by the US Food and Drug Administration due to adverse side effects in diabetic patients during Phase III clinical trials, and the search to find alternatives continues. Pyridoxamine (vitamin B6, pyridorin) and thiamin pyrophosphate have been proposed as potential alternatives to aminoguanidine (Ahmed et al., 2007; Androver at al., 2008). Furthermore, these compounds are also good metal ion chelators and attenuate oxidative stress. N-acetylcysteine and lipoic acid act as inhibitors through attenuation of oxidative stress. While the AGE-inhibitory effect of these compounds is not clearly understood, a similar mechanism may operate in the case of AGEs. Carnosine, homocarnosine, and related compounds are potentially suitable as AGE inhibitors although further studies are needed to prove their efficacy in diabetes and AD (Reddy et al., 2005). Carnosine protects superoxide dismutase, catalase, and α-crystallin from non-enzymatic glycation and protein crosslinking (Hipkiss, 2007). OPB-9195 inhibits AGE formation, especially pentosidine and NΣ-(carboxymethyl)lysine (CML), apparently through carbonyl trapping and metal ion chelation (Wada et al., 2001). Thiazolium-based compounds such as alagebrium chloride (ALT-711) and N-phenyacyl-1,3-thiazolium bromide (PTB) are effective AGE crosslink breakers, and are potentially useful drugs for diabetes and AD (Susic, 2007). It should, however, be pointed out that the mechanisms of the action of the latter compounds are not clearly understood. In addition to their action as crosslink breakers of AGEs derived from 1,2-dicarbonyl compounds, they may also act as antioxidants through chelation of transition metal ions. The development of these drugs as therapeutics thus depends on the detailed understanding of their mechanisms of action. An alternative strategy involves removal of AGEs through the soluble receptors for AGEs (sRAGEs). Poor glycemic control in diabetes results in decreased concentrations of sRAGES, and upon insulin treatment, significant improvements in the levels of sRAGEs were observed, with concomitant decrease in AGEs (Devangelio et al., 2007). Treatment of diabetic patients with rosiglitazone, a 2,4-thiazolidine dione derivative, results in increase of plasma sRAGEs, comparable to controls (Tan et al., 2007). Significant amounts of plasma sRAGEs are also produced when angiotensin converting enzyme inhibitors (ACEi; e.g., perindopril) were used for the treatment of diabetes (Tan et al., 2006). However, the protective effect of sRAGEs has been questioned recently as their level are much higher in experimental animal models than those found in vivo, suggesting they may be only markers of inflammation (Humpert et al., 2007). Following the trend in using natural antioxidants, a recent paper has examined the effects of banana (Musa sp. var. elakki bale) flower and

pseudostem on hyperglycemia and AGEs in streptozotocin-induced diabetic rats. The results indicate that fructosamine and AGEs formed during diabetes were inhibited in treated groups when compared with the diabetic group (Bhaskar et al., 2011).
However, the results of clinical trials of antioxidant therapy are not clear because of duration of treatment as well as recruitment of patients at different stages of the diseases. In spite of inconsistency in the conclusions of clinical trials on the beneficial effects of antioxidants on these pathologies, epidemiological studies indicate that antioxidants may reduce the risk of their insurgence. It is suggested that a combination of antioxidants might be of greater potential benefit, especially if these agents work in different cellular compartments or have complementary activity (e.g. Vitamins E, C, and ubiquinone). If oxidative stress plays as important a role in AD and diabetes pathologies as the literature suggests, regular intake of antioxidants may be beneficial much before any sign or symptoms of the disease are visible.

7. Insulin resistance, Tau hyperphosphorylation and the amyloid cascade

In addition to being a modulator of food intake and energy homoeostasis, insulin is also an important neurothrophic factor. It modulates brain activity, particularly for such high glucose demanding functions such as memory. As mentioned above, T2D is associated with cognitive impairment. This form of diabetes is characterized by insulin resistance, hyperinsulinemia and impaired insulin signaling. Insulin resistance is the common link of the components of the much invoked metabolic syndrome (a cluster of high adiposity, abnormal glucose level, dyslipidemia, hypertension and high inflammation) and it is known to cause common diseases such as stroke, heart disease, and cancer. Given the aging of the population and the epidemic of elevated insulin resistance, evidenced by the rise in elevated adiposity, prediabetes, and diabetes, it is alarming that insulin resistance could contribute to AD. Many epidemiologic studies have found an association of elevated adiposity, insulin resistance, and T2D with cognitive impairment and dementia (Baker et al., 2011). However, there are several important questions to be addressed for investigators studying the relation of insulin resistance and AD. For example is not clear if the association between insulin resistance and AD is causal. However, one of the links found is that defects in brain insulin signaling have been reported in AD and it has been proposed that insulin resistance could be an early marker of AD (Baker et al., 2011) (Figure 2).

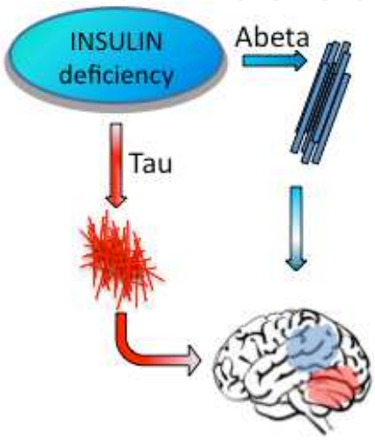


Fig. 2. Insulin deficency can lead to Abeta plaques formation and Tau hyperphos-phorylation

Insulin crosses the blood-brain barrier, and might even be produced locally in the brain, exerting its effects on cells by binding to a specific cell surface receptor. Insulin receptors are expressed throughout the CNS, expecially in the hippocampus and cortex, even if their function in the brain is not fully understood. Binding of insulin to its receptor activates the intrinsic tyrosine kinase activity of the cytoplasmic domain of the insulin receptor. This leads to autophosphorylation of tyrosine residues, which initiates several intracellular signaling cascades. In the brain, insulin influences the release and reuptake of neurotransmitters, and also appears to improve learning and memory (Zhao et al., 2004). The initial components of the insulin receptor signaling cascade in the brain are largely similar to those of the periphery. The downstream targets of the cascade are quite different, however, probably involving, among others, neuronal glutamate receptors (Zhao et al., 2004). Neurodegeneration and cognitive impairment in T2D and AD could be caused, in part, by damage to insulin receptor signaling (de la Monte & Wands, 2005). In fact, decreases in the sensitivity of such receptors are known to affect the expression and metabolism of Abeta and tau and impaired insulin receptor activity and hyperinsulinemia are observed in patients with AD and in animal models of this disease (Frolic et al., 1998). In addition, dysfunction of insulin receptor signaling is associated with impairments in Abeta oligomer clearance (Zhao, 2009) and increases the rate of NFT development (Lesort & Johnson, 2000). In fact, insulin transiently increases tau phosphorylation in primary cortical neurons, and hyperinsulinemia results in tau hyperphosphorylation in rat brains. Furthermore, insulin receptor substrate 2 knockout mice demonstrate typical pathological signs of T2D and have an increased number of NFTs in hippocampal neurons compared with control wild-type mice (Schubert, 2003). Thus, impaired insulin signaling could increase tau phosphorylation and cleavage. Insulin receptor signaling leads to the activation of two major signaling pathways, the mitogen-activated protein kinase (MAPK) pathway and the Akt signaling pathway. MAPK signaling is a required component of cell differentiation, cell proliferation and cell death, whereas Akt signaling is involved in the regulation of cell growth, cell proliferation, protein synthesis (via the mammalian target of rapamycin signaling pathway) and cell survival (through the inhibition of several proapoptotic agents).

Akt signaling induces the inhibition of glycogen synthase kinase-3β (GSK-3β) phosphorylates and, hence, inactivates glycogen synthase, a key enzyme in glycogenesis (Balaraman et al., 2006). Thus, under normal conditions, insulin signaling via the insulin receptor leads to GSK-3β inactivation, whereas insulin resistance leads to GSK-3β dephosphorylation and activation (Balaraman et al., 2006). The regulation of GSK-3β in the hippocampus and cortex changes in response to changes in glucose and insulin concentrations and in T2D an increase in GSK-3β activity might lead to insulin resistance by reducing glucose clearance (Lee & Kim, 2007). Increased GSK-3β activation might also lead to an elevation in Abeta production (resulting from a GSK-3β-mediated increase in presenilin 1 activity) and an increase in tau phosphorylation associated with NFT formation (Balaraman et al., 2006; Phiel et al., 2003). In contrast, inhibition of GSK-3β attenuates APP processing and inhibits hyperphosphorylated tau-associated neurodegeneration in cell-culture and animal models of AD (Phiel et al., 2003).

Another important link between insulin resistance and the amyloid cascade may be related to the insulin degrading enzyme (IDE). This enzyme is a metalloprotease responsible for insulin degradation and is also the main enzyme responsible for Abeta degradation (Farris et al., 2003). IDE is secreted to the extracellular space by microglial cells in the brain, where

it degrades Abeta peptide, thus reducing the rate of aggregation and the plaque formation (Qiu et al., 1998). IDE levels have been reported to be decreased in the brains of AD patients (Cook et al., 2003). It has also been hypothesized that hyperinsulinemia in people with pre-diabetes and T2D effectively sequesters IDE, reducing Abeta peptide degradation. This would increase levels of Abeta, and promote many of the pathological features associated with Alzheimer's disease. Supporting this model, the affinity for the binding of insulin to IDE is much greater than that for the Abeta (Qiuet al., 1997). In patients with Alzheimer's disease, IDE expression in the hippocampus is substantially reduced, with regards to controls, in particular among patients with the APOEvar epsilon4 genotype. This latter observation could explain the potential interaction between diabetes and the APOEvar epsilon4 genotype in multiplying the risk of dementia (Cook et al., 2003). Curiously, although the presence of the APOEvar epsilon4 is associated with an increased incidence of Alzheimer's disease, it seems that insulin resistance is only a significant risk factor for AD in those patients without APOEvar epsilon4 (Craft et al., 1998). Subjects with AD without the APOEvar epsilon4 also had improved memory scores when they had hyperinsulinemia, which was not the case for people with at least one APOEvar epsilon4 allele (Craft et al., 1999).

However, unexpectedly, recent clinicopathological studies have shown no evidence that the pathological hallmarks of AD, including amyloid plaque, were increased in the brains of diabetic patients. This suggests that T2D could affect the pathogenesis of AD through mechanisms other than modulation of Abeta metabolism even if the underlying mechanisms for this association remain largely unknown (Takeda et al., 2011).

8. FOXO: A common biomarker for AD and T2D

There is ongoing interest in defining mechanisms that govern insulin resistance and AD. The O subfamily of Forkhead/winged helix transcription factors (FOXO) plays important roles in regulating key physiological functions, including cell proliferation, cell differentiation, and survival together to cell cycle arrest and apoptosis. (Accili et al., 2004; Huang et al., 2007: van der Horst & Tindall, 2007). Thus, FOXO transcription factors are key players in cell death/life pathways. In addition, FOXO works in a complex way to regulate insulin signaling and glucose and lipid metabolism (Accili et al., 20004; Barthel et al., 2005). An additional layer of complexity exists in the transciptional activity of FOXO that is regulated by insulin through the phosphatidyl inositol 3 kinase (PI3K)/Akt signaling pathway. Both insulin and insulin-like growth factor-1 (IGF-1), through activation of their receptors, induce PI3K/Akt-dependent phosphorylation of FOXO, which facilitates its interaction with 14-3-3 protein, leading to nuclear exclusion and eventual ubiquitylation-dependent proteasomal degradation (Matzusaki et al., 2006). In particular, in presence of insulin, activated Akt translocates to the nucleus where directly phosphorylates FOXO at distinct sites stimulating interaction with 14-3-3 protein (Greer and Brunet, 2005). This chaperone protein promotes the nuclear export and inhibits the nuclear import of FOXO proteins, driving the cells towards cell survival (van der Heide et al., 2004). In contrast, FOXO proteins, under conditions of oxidative stress, are phosphorylated by other protein kinases, including Mst1 and JNK, able to disrupt its interaction with 14-3-3, promoting FOXO nuclear translocation and thereby inducing cell death in neurons, thus opposing Akt's action (Sunayama et al., 2005). Thus, it is well established that Akt plays a key role in repressing FOXO transcriptional activity. Immediately upstream from FOXO, the activity of

Akt itself is governed by several protein kinases and phosphatases. Akt is activated by phosphorylation at Thr-308 within its catalytic domain by 3-phosphoinositide-dependent protein kinase-1 (PDK1) and by phosphorylation at Ser-473 within a C-terminal hydrophobic motif by mammalian target of rapamycin (mTOR) (Stokoe et al., 1997; Sarbassov et al., 2005). Some studies show that phospho-Thr-308 and phospho-Ser-273 are dephosphorylated by protein phosphatase 1 (PP1), protein phosphatase 2A (PP2A), and pleckstrin homology (PH) domain leucine rich repeat protein phosphatase (PHLPP), a member of the protein phosphatase 2C family (Gao et al., 2005). Akt regulates a variety of key physiological functions, and there is strong evidence suggesting that defective Akt signaling contributes to development of insulin resistance (Zdychova & Komers, 2005).
However, although it is clear that FOXO governs multiple events in the insulin signaling cascade, mediating both positive and negative effects, the underlying molecular mechanisms are unknown. Some evidence has been reported that FOXO3 activation is also able to increase basal levels of Akt phosphorylation and kinase activity thus it is capable to activating its own inhibitor, providing a feedback regulation (Ni et al., 2007) . Moreover, FOXO transcription factors are involved in both the insulin action and the cellular response to oxidative stress, thereby providing a potential integrative link between AD and insulin resistence (Manolopoulos et al., 2010). Both insulin resistence and oxidative stress due to Abeta stimulus, may promote the transcriptional activity of FOXO proteins, resulting in hyperglycaemia and a further increased production of ROS.
The consecutive activation of c-Jun N-terminal kinases and inhibition of Wingless (Wnt) signalling may result in the formation of Abeta plaques and tau protein phosphorylation. Wnt inhibition may also result in a sustained activation of FOXO proteins with induction of apoptosis and neuronal loss, thereby completing a vicious circle from oxidative stress, insulin resistence and hyperglycaemia back to the formation of ROS and consecutive neurodegeneration. Thus, it has been proposed that FOXO proteins may provide a potential molecular target for the treatment of both insulin resistence and AD (Manolopoulos et al., 2010). Recently it has been demostrated that insulin plays a protective role by inhibiting mithocondrial dysfunction and apoptosis activation triggered by Abeta oligomers (Di Carlo et al., 2010) (Figure 3).

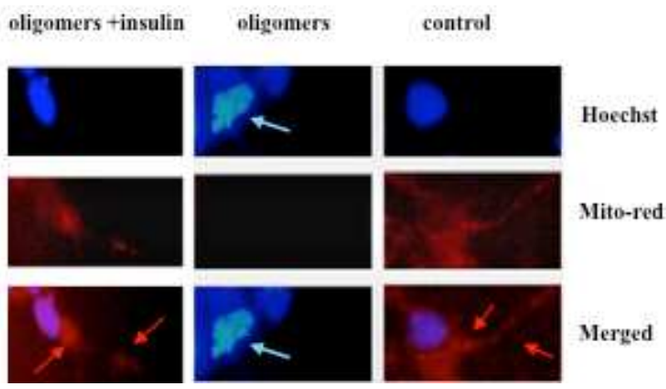


Fig. 3. *Insulin recovers mitochondrial respiratory activity reduced by rAb42 oligomers.* LAN5 untreated (control), treated with rAb42 oligomers oligomers), and rAb42 oligomers and insulin (oligomers+insulin) were incubated with Mito Red and Hoechst 33258. The images of each sample were merged. Mitochondrial activity is indicated by red arrows, fragmentation of nuclei is indcate by blu arrows.

Moreover, unpublished results indicate that insulin counteracts oxidative stress induced by amyloid beta by activation of Akt survival pathway. Akt traslocates from the cytoplasm to nucleus where phophorylates FOXO3a that, in turn, moves from the nucleus to the cytoplasm inhibiting, in this way the transcription of the FOXO-dependent genes. Since after Abeta-induced oxidative stress are usually activated pro-apoptotic genes, their trascriptional inhibition helps the survival program (Picone et al., 2011). Moreover, it has been suggested that since insulin signalling in the brain is known to decline with age, the outcome of the balance of different molecules, as Akt and FOXO, represents a risk factor for AD that is well suited for therapeutic intervention. By restoring the balance of molecules to favour neuron survival, new drugs, designed to specifically enhance CNS insulin signalling, would provide a new and potentially significant class of AD therapeutics.

9. Conclusions

The present chapter highlights the overlap and the many points of intersection existing between T2D and AD. Insulin resistence in the CNS results in the dysregulation of multiple extracellular and intracellular signaling cascades and molecular mechanisms, which in turn could lead to decrease in neuronal and synaptic functions up to neurodegeneration. An understanding of how each molecular pathway intersects and affects the others is essential for the development of future drug intervention strategies for these pathologies.

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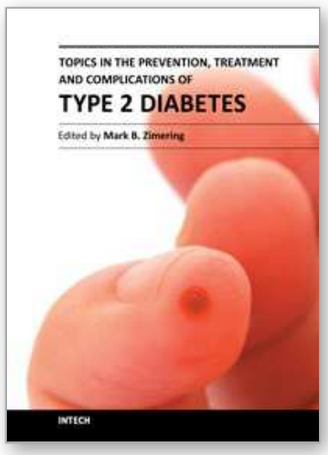
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Type 2 diabetes is estimated to affect 120 million people worldwide- and according to projections from the World Health Organization this number is expected to double over the next two decades. Novel, cost-effective strategies are needed to reverse the global epidemic of obesity which is driving the increased occurrence of type 2 diabetes and to less the burden of diabetic vascular complications. In the current volume, Topics in the Prevention, Treatment and Complications of Type 2 Diabetes, experts in biology and medicine from four different continents contribute important information and cutting-edge scientific knowledge on a variety of topics relevant to the management and prevention of diabetes and related illnesses.

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