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Review

A close connection: Alzheimer's disease and type 2 diabetes

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ABSTRACT

In the recent years a growing body of evidence links insulin resistance and insulin action to neurodegenerative diseases, especially Alzheimer's disease (AD). The importance of insulin in ageing as well as its role in cognition and other aspects of normal brain functions are well established. The hippocampus and cerebral cortex-distributed insulin and insulin receptor (IR) have been shown to be involved in brain cognitive functions. Conversely, deterioration of IR signaling is involved in aging-related brain degeneration such as in AD and cognitive impairment in type 2 diabetes patients. Insulin administration, while maintaining euglycemia, improves memory in both healthy adults and Alzheimer's disease patients. In the present review, some common links between AD and type 2 diabetes are presented. Furthermore, several biochemical aspects existing in both pathologies are highlighted.

KEYWORDS: insulin, Alzheimer's disease, protein aggregation, amyloid, oxidative stress

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in the elderly and covers more than 50% of all cases of dementia worldwide [1]. It is a neurodegenerative cognitive disorder with the typical features characterized by the impairment of memory, language, attention, executive functioning, apraxia, agnosia, and aphasia. Cognitive and also behavioral symptoms cause a reduction of functional activities compared to a previous level of functioning. At cellular level, AD is characterized by neuronal cell loss and increasing accumulation of neurofibrillary tangles (NFT) in neurons and amyloid fibers, due to the ordered aggregation of amyloid-beta peptide, in neuritic plaques and in the walls of blood vessels [2]. These structures progressively accumulate in the brain starting from the hippocampus and then spreading to the cerebral cortex where neurons are lost causing memory, language and in general cognitive impairment [3]. Amyloid beta-peptides of varying lengths (39-43 residues) are produced by cleavage of a large transmembrane protein, the amyloid beta-protein precursor (APP) [4]. The 42 residue beta-peptide (Aβ-42) is the predominant form found in plaques and, under physiological conditions, the ratio between Aβ-42 and Aβ-40 is about 1:10 [5]. Aβ-42 has a neurotoxicity greater than Aβ-40 and its aggregation kinetics is faster than other beta-peptides [6]. A recent and now convincing belief is that small diffusible oligomers of Aβ-42, called ADDLs, are the determining pathogenic species causing synaptic dysfunction and eventually neuronal degeneration [7, 8].

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Familial AD is a rare form of dementia and is caused by autosomal dominant mutations in one or more of the genes encoding the APP, presenilin 1 or presenilin 2 (the latter two proteins form the catalytic core of γ-secretase) [9]. By contrast, late-onset AD might be caused by environmental and/or lifestyle factors [10]. 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 [11]. Numerous studies report that patients with diabetes have an increased risk of developing AD if compared with healthy individuals [12-14] and some studies revealed that 80% of patients with AD exhibited impairments either in glucose tolerance or diabetes [15]. In particular, similarities between type 2 diabetes (T2D) and AD include age-related processes, degeneration, high cholesterol levels, peripheral and CNS insulin resistance, dysfunctional insulin receptor (IR) and IR-mediated signaling pathways, decreased glucose transport and metabolism, despite the higher non-metabolized glucose levels in cerebral blood [16-18]. The unbalance between low and high glucose levels in T2D patients may be responsible for brain vascular damage and neurodegeneration thus facilitating the AD onset. Most recently, metabolic syndrome (MetS), which represents a cluster of metabolic factors such as insulin resistance, abdominal obesity, glucose intolerance, hypertension, hyperinsulinemia and raised fasting plasma glucose has also been described in association with an increased risk of AD [19, 20]. Interestingly, strong evidences suggest that systemic inflammation and central adiposity contribute to and perpetuate MetS [21, 22]. All these alterations predispose individuals to type 2 diabetes and cardiovascular disease [21-24].

Genetic background, age, sex, diet, physical activity, and habits in general all influence the prevalence of the MetS and its components. In the Mediterranean area, already 20 years ago, it was assessed that 70% of adults have at least one of the disorders characterizing MetS. However, in European population the rate of MetS is 7-30% [25].

Worldwide there are 1.1 billion overweight people with a body mass index (BMI) between 25 kg/m^2 and 30 kg/m^2 and 312 million with a BMI > 30 kg/m [26]. In the last forty years the rate of obesity in the US has increased and nowadays 66% of adults have a BMI > 25 kg/m^2 and half of those have a BMI > 30 kg/m [27].

Another link between obesity, inflammation, insulin signaling and dementia is the amyloid precursor protein (APP) [28]. APP is considered an adipokyne, produced and processed in $A\beta_{40-42}$ by adipose tissue. This fragment is expressed in fat tissues and overexpressed in abdominal adipocytes of obese patients [28].

Recent data support an increased susceptibility to AD in patients with MetS [29], although from the age of 85 and older the association between MetS and accelerated cognitive decline vanished [30]. On the other hand, some American scientists hypothesize that AD is a third form of diabetes [31]. This hypothesis was formulated in 2005 when they analyzed 45 AD patients post-mortem, showing lower levels of insulin in the brain. In particular, the authors analyzed the frontal cortex of AD individuals, calculating the concentration of insulin, insulin-like growth factor 1 and insulin receptor. Data showed that later stages of disease were associated with decrease of these parameters up to 80% compared to healthy brain [31]. According to the latter association, some authors proposed the concept of "metabolic cognitive syndrome" when describing co-occurrence of AD and MetS. Indeed, dementia and MetS present some overlap both in predisposition factors and in altered signaling cascade. Environmental elements like diet, lifestyle, smoke and socio-economic status give a critical contribute to these disorders. Altered insulin signaling pathway has a key role in their pathogenesis. In particular insulin resistance might be the first step towards both disorders, constituting a bridge between AD and MetS [32].

It was previously thought that insulin did not play any significant regulatory role in the brain. However, many studies have demonstrated that insulin not only controls glucose and lipid metabolism in the brain, but also regulates neural development and neuronal activities and plays an important role in learning and memory [33, 34]. Furthermore, insulin has a crucial role in the neuroplasticity, that is the ability of the CNS to react to the environment. Both insulin and insulin receptor (IR) are found in the brain, and IR is highly expressed in brain neurons [35, 36].

Data discussed below are consistent with the view that diabetes-related dysfunction is exacerbated by aging and/or by the presence of neurotoxic agents, such as Aβ, suggesting that diabetes and aging are risk factors for the neurodegeneration induced by these peptides. An association between diabetes and AD has long been recognized. Here we presented evidence that the association between diabetes and AD signifies a common underlying pathology.

Metabolism of glucose and insulin resistance in AD

Glucose is, by far, the major brain energy substrate, and it maintains cerebral metabolism due to the combination of relatively high plasma glucose concentration and the presence of powerful transporters (GLUT1-5, 7 and 8), responsible for facilitated diffusion of glucose across the blood-brain barrier (BBB), the plasma membrane of neurons and glial cells [37, 38]. Glucose uptake and metabolism are impaired in AD brain, and this impairment appears to be a cause, rather than a consequence, of neurodegeneration [39]. A reduction in the cerebral metabolic rate of glucose utilization is one of the most predominant abnormalities generally found in AD brain. PET with fluorodeoxyglucose (FDG) has been approved in the USA for diagnostic purposes and it is sensitive and specific in detecting AD in its early stages [40]. Impaired glucose uptake is found in transgenic mouse models of AD [41, 42]. During early stages of AD, glucose utilization deficit (50%) is greater than blood flow/oxygen deficits (20%), and only in the later stages of AD do the changes in these factors become similar [43]. This suggests that the glucose utilization deficit may be more important in the genesis of pathology than blood flow and oxygen utilization. Moreover, recently, it has been shown that the levels of the two major brain glucose transporters (GLUT1 and GLUT3), responsible for glucose uptake into neurons, are decreased in AD brain [44]. This decrease is correlated with the decrease in O-GlcNAcylation, hyperphosphorylation of tau protein, and density of NFT in human brain [44]. Taken together, these findings suggest a contribution of glucose metabolism in the early pathophysiology of AD. Although brain glucose metabolism is of pivotal significance for the maintenance of CNS structure and function [45], its regulation by insulin remains controversial. More recently, it has been suggested that cerebral glucose metabolism is controlled by neuronal insulin/IR signaling pathways [38, 46, 47]. Thus, brain can be regarded both as an insulin- and glucose-sensitive tissue [48].

Insulin resistance is a central feature of type 2 diabetes and increasing evidence supports that insulin resistance is present in AD, contributing to neurodegeneration processes [49, 50]. Overexpression of Aβ in transgenic mice results in reduced glucose utilization [41], thus causing the typical effects of insulin resistance. Different mechanisms have been proposed to explain the insulin resistance in AD. Lee and coworkers [51] showed that in cell culture, Aβ expression inhibited both insulin-induced Akt phosphorylation and activity. Aβ oligomers, more than large structured aggregates, specifically interrupted the PDK-dependent activation of Akt. Aβ also blocked the association between PDK and Akt in cell-based and *in vitro* experiments**.** Furthermore, Aβ oligomers reduced both activation of insulin receptors and the levels of phospho-Akt [52] (Figure 1). In mature cultures of hippocampal neurons, ADDLs linked to dendrites cause a rapid and substantial loss of neuronal surface insulin receptors (IRs) [53]. Removal of dendritic IRs is associated with increased receptor immunoreactivity, indicating its redistribution in the cell body. The neuronal response to insulin, measured by evoked IR tyrosine autophosphorylation, is greatly inhibited by ADDLs [53, 54]. Moreover, decreased IR expression, its desensitization, and/or tyrosine kinase inactivity are reported in AD brain [31, 39]. Defects in IGF-I receptor and increase in the phospho-inactive form of IRS-1 and IRS-2 in AD have recently been found, further indicating resistance to insulin-like growth factor-1, IGF-1, signaling [55]. Insulin, IR, IGF-1 receptor (IGF-1R), insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2) mRNA and protein levels decrease in age- and AD-related diseases [31, 55-58]. Interestingly, persistent and pathological hyperactivation of Akt-mTOR-S6K signaling pathways within AD neurons may increase IRS-1 phosphorylation at Ser312 or 616,

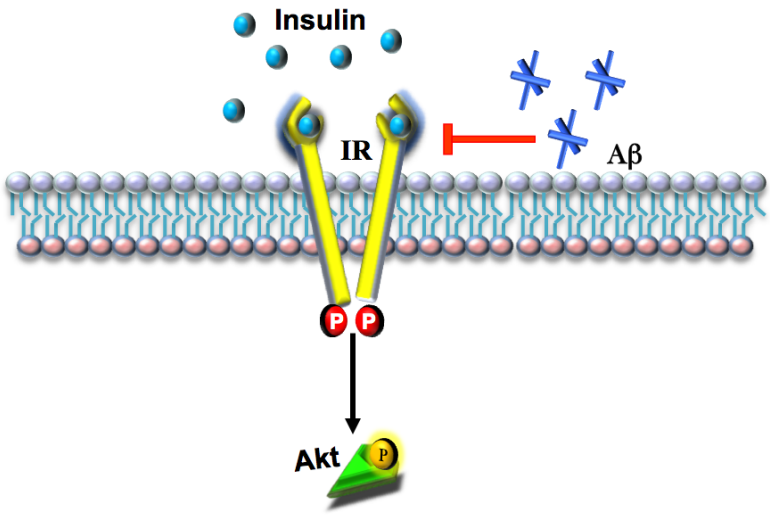

Figure 1. Insulin, by binding to its own receptor (IR), activates the signaling pathway via Akt phosphorylation. The presence of Aβ oligomers inhibit IR activation and the correlated signaling.

resulting in IRS-1/2 degradation, thus impairing IR-associated neurotrophic and metabolic brain functions [55]. Taken together, these findings confirm that AD can be considered an "insulin-resistant brain state" or even a "type 3 diabetes". Chronic peripheral hyperinsulinemia typical of type II diabetes is associated with insulin resistance in the brain, because initially high brain insulin levels tend to decrease, due to a downregulation of its supposed brain synthesis and/or transport [59]. The abnormalities in the insulin signal transduction cascade have an impact on APP trafficking causing an intracellular accumulation of Aβ. Furthermore, the hyperphosphorylation of tau protein and the consequent formation of neurofibrillary tangles (NFT) are enhanced by insulin signal transduction abnormalities and low levels of ATP. Thus, it is not surprising that insulin resistance increases Aβ levels and inhibits insulin signaling in the AD transgenic mice Tg2576 [60]. Another potential mechanism could be the interference of insulin with extracellular proteolytic Aβ degradation by the insulin-degrading enzyme (IDE), a metalloprotease involved in the insulin and IGF-1 metabolism. Under this perspective, insulin resistance may competitively inhibit IDE, thus impairing Aβ degradation, increasing its neurotoxicity and promoting AD [47, 59, 61-66]. This suggestion is supported by: i) a decrease in IDE activity and mRNA and protein levels in AD brain; ii) impaired brain Aβ and insulin degradation in IDE knockout mice [67-69]; iii) increased IDE immunoreactivity around senile plaques and iv) enhanced IDE activity in IDE and APP double transgenic mice associated with a decrease in Aβ [70].

Metabolic-cognitive syndrome: Insulin and central nervous system (CNS)

Insulin is known as a peripheral regulator of nutrient storage but it is also essential for the control of energy balance in the CNS. Neuronal insulin signaling pathway has an important function in mammals fat storage, and in *C. elegans* and *Drosophila* the cellular signaling systems mediating these effects bear remarkable homology to those described in mammals [71].

There are many evidences that demonstrate the insulin action in the control of neuronal function in cortical and hippocampal areas, involved in memory process and cognitive functioning [59, 72]. Insulin directly influences neurons by processes not linked to modulation of glucose uptake. Neurotransmitters release, neuronal-outgrowth, tubulin activity, neuronal survival and synaptic plasticity are all directly modulated by insulin [73-76]. Insulin signaling pathway modulates synaptic plasticity by: i) promoting the recruitment of GABA receptors (gamma-aminobutyric acid receptor) on post-synaptic membranes; ii) influencing

NMDA receptor (N-methyl D-aspartate receptor) conductance (neuronal Ca^{2+} influx) and iii) regulating AMPA receptor (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) cycling.

The Metabolic-Cognitive Syndrome (MCS) was elaborated on 2010 by Frisardi and his colleagues. It is based on the co-existence, in patients, of MetS and cognitive impairment of degenerative or vascular origin [32]. Insulin resistance can be manifested in peripheral tissues or directly in the brain as insulin-resistant brain state, thus contributing to cognitive impairment and neurodegeneration for the reason described above [32].

Many molecules participate in the regulation of insulin signaling pathway, therefore an alteration in the function or expression of some of these proteins causes a reduction in glucose uptake. Consequently glucose is accumulated in the blood determining hyperglycemia and hyperinsulinemia. Hyperglycemia induces an increase of peripheral utilization of insulin which results in a reduction of insulin disposable for the brain. As insulin is essential for memory, learning, neuronal survivor and longevity processes, the alteration of its concentration might cause important consequences on tau and Aβ processing [59, 72]. For example, an impairment of insulin signaling pathway causes a reduction of the activity of phosphatidylinositol 3-kinase (PI3K) and consequently a reduction in AKT/PKB pathway. This leads to an increase of glycogen synthase kinase 3 α/β (GSK-3 a/b) activity that phosphorylates tau protein and causes intraneuronal Aβ accumulation [31]. Moreover, glucose metabolism plays a role in the protein post-translational modification involving the hexosamine biosynthetic pathway, which leads to the generation of O-N-acetylglycosamine (O-Glc-NAc). If insulin resistance is established, intraneuronal glucose metabolism is impaired. Consequently, the amount of O-Glc-NAcylation is reduced. This post-translational modification competes with phosporylation process, thus more phosphate groups are added, with an increase of the amount of phosphorylated tau protein [77].

Insulin is also involved in the metabolism of APP [78] and the latter, in turn, competes with insulin receptor, thus its inefficient degradation might play a key role in AD brain insulin resistance [54].

Mitochondrial dysfunction and oxidative stress: A further link between diabetes and AD

Diabetes and AD are associated with deficits in mitochondrial activity, metabolic dysfunction and oxidative stress [79-83]. Increasing data support the idea that mitochondrial function declines with aging and in age-related diseases, such as diabetes and AD [80, 84]. Mitochondria are the subcellular organelles, essential for generating the energy that fuels normal cellular function and, at the same time, they monitor cellular health in order to make a rapid decision (if necessary) to initiate a programmed cell death. Accumulating evidence suggests that mitochondrial dysfunction is intimately associated with AD pathophysiology. Aβ interacts with Aβ-binding dehydrogenase (ABAD) in mitochondria of AD patients and in transgenic mouse brains, suggesting that ABAD is a direct molecular link between Aβ and mitochondrion [85]. Moreover, it has been reported that ABAD enhances Aβ-induced cell stress via mitochondrial dysfunction [86]. It has, also, demonstrated that the Aβ is imported into mitochondria via the translocase of the outer membrane (TOM) machinery, independently of the mitochondrial membrane potential [87]. In 2004, Swerdlow and Khan [88] proposed the "mitochondrial cascade hypothesis". It postulates that mitochondrial dysfunction represents a primary pathology in sporadic/late-onset AD. The most consistent defects in mitochondria in AD, are deficiencies in several key enzymes responsible for oxidative metabolism including α-ketoglutarate dehydrogenase complex (KGDHC) and pyruvate dehydrogenase complex (PDHC), two enzymes involved in the rate-limiting step of tricarboxylic acid cycle, and cytochrome c oxidase (COX), the terminal enzyme in the mitochondrial respiratory chain [89-95]. These functional abnormalities in mitochondria favor the production of ROS and, consequently, electron transport, ATP production, and mitochondrial membrane potential all become impaired. In conclusions, mitochondrion can be considered both the source and the target of oxidative stress induced by Aβ. Moreover, increased production of reactive oxygen and nitrogen

species, coinciding with a depletion of antioxidant defenses is observed in neuronal systems after Aβ treatment [96] and the assumption of natural antioxidants, such as vitamins C and E, promises to be a powerful preventive treatment against AD occurrence [97-100]. Recently, it has been shown [101] that AD patients present a significantly lower expression of 70% of the nuclear genes encoding subunits of the mitochondrial electron transport chain in posterior cingulate cortex, 65% of those in the middle temporal gyrus, 61% of those in hippocampal CA1, 23% of those in entorhinal cortex, 16% of those in visual cortex, and 5% of those in the superior frontal gyrus, if compared with healthy individuals. Mitochondria are also important cytoplasmic calcium ion buffers since they avoid the increase of Ca^{2+} above a critical value termed "set-point". In oxidative stress conditions, a sustained increase in intracellular Ca^{2+} concentration occurs (Figure 2) [102] and the cytosolic calcium levels play a role in the modulation of several intracellular signaling pathways, including protein kinase C-α and calmodulin-dependent signaling [103] which have also been implicated in apoptotic processes. It has been observed that Aβ exacerbates Ca^{2+}-induced opening of mitochondrial permeability transition pores (MPT) without inducing the permeability per se [104, 105]. Brain mitochondria isolated from streptozotocin (STZ) diabetic rats, a model of type 1 diabetes, possess a lower content of coenzyme Q9 (CoQ9) indicating a deficit in antioxidant defenses in diabetic animals and, consequently, an increased probability of oxidative stress occurrence [106]. In addition, the decrement in oxidative phosphorylation (OXPHOS) efficiency is related to a loss in the control of glucose homeostasis as evidenced by the increase in tissue and blood lactate levels, as well as by the change in glucose tolerance. Cytoplasmic hybridor "cybrid" (eukaryotic cell produced by the fusion of a whole cell with a cytoplasm) cells constructed from individuals with maternally inherited diabetes exhibited lactic acidosis, poor respiration and marked defects in mitochondrial morphology and respiratory chain complex I and IV activities [107]. Data show the existence of an age-related impairment of the respiratory chain and an uncoupling of OXPHOS in brain mitochondria isolated from Goto-Kakizaki (GK) rats, a model of type 2 diabetes. Furthermore, aging exacerbates the decrease in the energetic levels promoted by diabetes [108]. The maintenance of OXPHOS capacity is extremely important in the brain since about 90% of the ATP required for the normal functioning of neurons is provided by mitochondria. Diabetes decreases the capacity of mitochondria to accumulate Ca^{2+}, a favorable intracellular environment for MPT opening [108, 109].

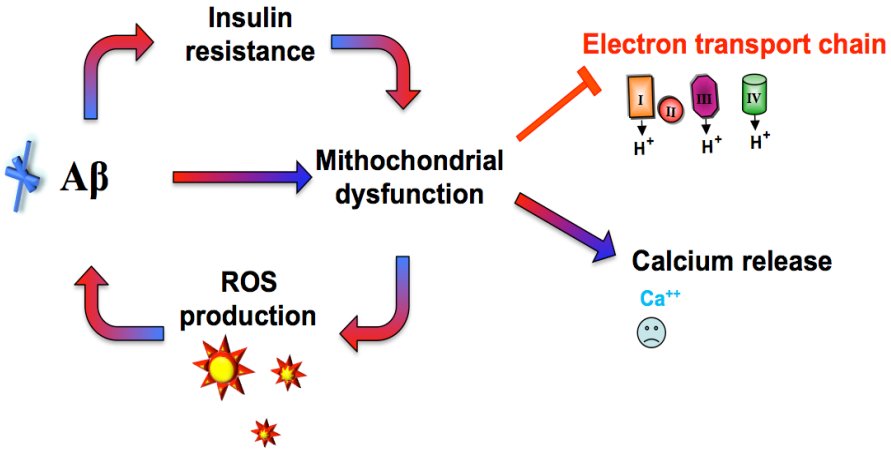

Figure 2. A vicious circle triggered by insulin resistance. Insulin resistance induces mitochondrial dysfunction generating ROS production that, in turn, increases Aβ oligomers formation, thus stimulating AD progression. The effects of mitochondrial dysfunction are the inhibition of the electron transport chain and the increase of Ca^{++} release.

Advanced glycation end products (AGE)

Abnormal glucose metabolism and oxidative stress contribute to the formation of advanced glycation end products (AGE). These molecular species are formed 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. The first step of the process leads to the rather labile Schiff bases which as a rule rearrange to the more stable Amadori products. These are slowly degraded, in complex reaction pathways via dicarbonyl intermediates, to a plethora of compounds [110] designated summarily as "advanced glycation end products" (AGEs). The 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 [111].

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 the protein conformations leading to protein inactivation. Numerous AGEs have been isolated and characterized after cleavage from the protein backbones, by spectroscopic analysis. AGEs involving protein cross-links include pentosidine (a dimer of arginine and lysine), methylglyoxal-lysine dimer (MOLD, a dimer of two lysine residues), 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 arg-pyrimidine, 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 [112].

The formation and accumulation of AGEs occurs 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 [113]. AGE immunoreactivity is present in both Aβ plaques and NFTs in patients with AD. Furthermore, hippocampal neurons from patients with this neurodegenerative disease contain Aβ-positive, AGE-positive and RAGE positive granules. [114]. Whether the modifications of Aβ 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 [115]. Moreover, diabetic mice with cognitive impairments exhibit increased RAGE expression in neurons and glia compared with wild-type control mice [116], 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 [117].

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 the 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.

Inflammation in Alzheimer's disease and diabetes

Inflammation is a teleonomic response to eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult. If tissue health is not restored in response to stable low grade irritation, inflammation becomes a chronic condition that continuously erodes the surrounding tissues. In fact, in chronic inflammation immune responses, tissue injury and healing proceed simultaneously. The lateral damage caused

by this type of inflammation usually accumulates slowly, sometimes asymptomatically for years and can lead to severe tissue deterioration. A characteristic feature of chronic inflamed tissues is the presence of an increased number of monocytes, as well as monocyte derived tissue macrophages, i.e. microglia cells in the central nervous system [118].

Inflammation clearly occurs in pathologically vulnerable regions of the AD brain, with increased expression of acute phase proteins and pro-inflammatory cytokines which are hardly evident in normal brain [119].

Since amyloid fibrils represents a chronic stimulus, the innate immune systems clearly makes an initial attempt to clear these potentially toxic products. The hypothesis is that the intractable nature of the plaques and tangles stimulates a chronic inflammatory reaction to clear this debris. Activated cells strongly produce inflammatory mediators as pro-inflammatory cytokines interleukin-1β (IL-1β), IL-6, and TNF-α as well as the chemokine IL-8,macrophage inflammatory protein-1α, and monocyte chemo-attractant protein-1, prostaglandins, leukotrienes, thromboxanes, coagulation factors, ROS and other radical molecules, nitric oxide, complement factors, proteases, and protease inhibitors and pentraxins, such as C-reactive protein and serum amyloid Pcomponent [120].

The genes involved in the inflammation process are numerous and the role of an individual genetic background might show a predisposition to inflammation and its healthy or chronic resolution. Research in AD patients have found some functional polymorphisms, mostly single nucleotide polymorphisms (SNPs), in the promoter region or other untranslated regions of genes encoding inflammatory mediators or their enzymes. Actually, Primary responses are mediated by pathogen recognition receptors such as Toll-like receptor (TLR), pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6, anti-inflammatory cytokines such as IL-10 and eicosanoids [3].

Aggregated amyloid fibrils and inflammatory mediators secreted by microglial and astrocytic cells equally contribute to neuronal dystrophy. The microglia activation can be due to local or systemic inflammation. In fact a strong local inflammatory stimulus such as a previous head trauma is a risk factor for AD and several epidemiological studies clearly show that blood elevations of acute phase proteins, markers of systemic inflammatory stimuli, may be risk factors for cognitive decline and dementia. Furthermore, in experimental animals, chronic systemic inflammatory response induced by lipopolysaccharide administration also induces glial activation [121].

The basic function of astrocytes is to protect neurons. In the early phase of AD there is an astrogliosis that represent a response to the accumulation of the amyloid beta in the brain parenchyma and in the cerebral microvasculature [122].

Migration of astrocytes to amyloid beta plaques is promoted by the chemochines CCL2 and CCL3 released by activated microglial cells that surround the plaques [123].

There is the evidence that indicates an involvement of the immune system, other than neuroinflammatory processes in CNS, accompanied by changes or defects in immune responses in the blood of AD subjects [124].

The molecular and cellular components that mediate the communication between peripheral inflammation and the brain, have been studied in experimental models, and major routes of communication are known. All of them lead to the synthesis of cytokines and inflammatory mediators in the brain parenchyma, phenomena typically associated with tissue injury [125].

In recent years, much has been learned about the intracellular signaling pathways activated by inflammatory and stress responses and how these pathways intersect with and inhibit insulin signaling. Insulin affects cells through binding to its receptor on the surface of insulin-responsive cells. The stimulated insulin receptor phosphorylates itself and several substrates, including members of the insulin receptor substrate (IRS) family, thus initiating downstream signaling events [126, 127].

The inhibition of signaling downstream of the insulin receptor is a primary mechanism through which inflammatory signaling leads to insulin

resistance. Exposure of cells to TNF-α or elevated levels of free fatty acids stimulates inhibitory phosphorylation of serine residues of IRS-1 [128, 129]. This phosphorylation reduces both tyrosine phosphorylation of IRS-1 in response to insulin and the ability of IRS-1 to associate with the insulin receptor and thereby inhibits downstream signaling and insulin action [130].

Several serine/threonine kinases are activated by inflammatory or stressful stimuli and contribute to inhibition of insulin signaling, including JNK and inhibitor of NF-KB kinase (IKK) [131]. The activation of these kinases highlights the overlap of metabolic and immune pathways; these are the same kinases, particularly IKK and JNK, that are activated in the innate immune response by Toll-like receptor (TLR) signaling in response to LPS, peptidoglycan, double-stranded RNA, and other microbial products [132]. Hence it is likely that components of TLR signaling pathways will also exhibit strong metabolic activities.

Inflammatory cytokine stimulation can also lead to induction of inducible nitric oxide synthase (iNOS), an enzyme expressed only after cell activation and nitric oxide for rather long periods of time (hours to days). Overproduction of nitric oxide also appears to contribute to impairment of both muscle cell insulin action and β cell function [133]. Thus, induction of SOCS proteins and iNOS represent 2 additional and potentially important mechanisms that contribute to cytokine-mediated insulin resistance, nevertheless, there are additional mechanisms linking inflammation with insulin resistance which remain to be uncovered.

However, it is noteworthy that inflammation is involved in ROS production and in turn ROS and AGEs stimulate inflammation [3, 134].

CONCLUSIONS

The increased lifespan of the human population is coupled to the progression of neurodegenerative diseases. The effort of the scientific research in the field of neurodegeneration is focused on improving the quality of life of people affected by these diseases. New insights into basic neurodegeneration and cell death programs will offer new ways for future prevention and treatment strategies.

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ABBREVIATIONS

ABAD (Aβ-binding dehydrogenase); AD (Alzheimer's disease); ADDLs (Small diffusible oligomers); AGE (Advanced glycation end product); AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid); APP (Amyloid Precursor Protein); Aβ (Amyloid Beta Peptide); GABA (Amino-butyric acid); IDE (Insulin degrading enzyme); IGF-1 (Insulin-like growth factor); iNOS (Inducible nitric oxide sinthase); IR (Insulin receptor); IRS (Insulin receptor substrate); MCS (Metabolic cognitive syndrome); MetS (Metabolic syndrome); MPT (Mitochondrial permeability transition pore); NMDA (N-methyl D-aspartate); NFT (Neurofibrillary tangles); RAGE (Receptor for advanced glycation end products); ROS (Reactive oxygen species); T2D (Type 2 diabetes); TOM (Translocase of the outer membrane).

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