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Chapter

Alzheimer's Disease and Type 2 Diabetes Mellitus: Molecular Mechanisms and Similarities

Karla Isabel Lira-De León, Alma Delia Bertadillo-Jilote, David Gustavo García-Gutiérrez and Marco Antonio Meraz-Ríos

Abstract

Alzheimer's disease (AD) has become one of the most threatening diseases in the elderly, and type 2 diabetes mellitus (T2DM) is a major health problem in the world, representing 7.4% of the population. Several studies have produced epidemiological, clinical, and pathological evidence of the relationship between AD and T2DM. Laboratory research using animal models has identified mechanisms shared by both T2DM and AD. Particularly, there is an increase of tau phosphorylation and cleavage, which is known to be particularly toxic to neurons and to form a nucleation for neurofibrillary tangles. Also, alterations in synaptic plasticity are associated to tau pathology through the direct abnormal interaction of pathological tau with synaptic proteins and indirectly through Tau-activated neuroinflammatory processes. Many T2DM complications are potentiated or initiated by the accumulation of specific forms of advanced glycation end products (AGEs) and their interaction with its receptors (RAGE). AGEs promote β-amyloid aggregation and cytotoxicity, while glycation of tau may enhance their aggregation. Therefore, this review addresses the analysis of the common mechanisms where the major molecular players of these two diseases participate and contribute to a better understanding of these diseases in their pathogenic relationship.

Keywords: Alzheimer's disease, type 2 diabetes mellitus, metabolic syndrome, β-Amyloid, tau

1. Introduction

Demographic trends show a dramatic increase in the elderly population; unfortunately this group showed a higher prevalence of chronic diseases worldwide, becoming a serious public health problem in both developed and developing countries [1, 2]. The increasing aging population phenomenon in association with chronic diseases has several repercussions: economic, social, and medical. Among these chronic diseases, the most prominent for occupying the first places in epidemiological studies are: cardiovascular, cerebrovascular, diabetes, cancer, and dementias [2, 3].

Diabetes mellitus (DM) is a complex and heterogeneous group characterized by hyperglycemia. In 2015, there were 415 million people with diabetes worldwide and this number is expected to increase to 642 million by 2040 [4, 5]. The major risk factors in DM are eating a diet high in fats and simple sugars coupled with sedentary lifestyle [3]. On the other hand, Alzheimer's disease (AD) is the most common dementia worldwide [6].

Several studies have produced epidemiological, clinical, and pathological evidence of the relationship between AD and DM [7, 8]. It has been reported that patients with diabetes have a 50–75% increased risk of developing AD compared with age- and gender-matched patients without diabetes [9]. In fact, both entities share metabolic dysfunctions associated with different pathological developments [10].

DM is a chronic disease characterized by the absolute or relative shortage of insulin, leading to chronic hyperglycemia, which results either in the progressive failure of pancreatic β-cell function and consequently a lack of insulin production (type 1 diabetes, T1DM) or in the development of insulin resistance and subsequently the loss in β-cell function (type 2 diabetes, T2DM) [4, 11]. Examination of diagnoses reveals that AD is by far the most common cause of dementia among people with T2DM (e.g., 91%) [12]; the insulin resistance in this metabolic disease is not yet clear, but obesity and age are the major risk factors [13, 14].

AD is the most common dementing disorder of late life, characterized by progressive loss of cholinergic neurons and a devastating cognitive decline [10]. The two major histopathological features of AD are: (1) amyloid plaques and (2) neurofibrillary tangles (NFTs). Amyloid plaques are composed of β-amyloid (Aβ) peptide, produced by the proteolytic cleavage of the amyloid precursor protein (APP) [9]. On the other hand, truncated and phosphorylated tau protein is the main component in the NFT and the amount of these aggregates correlates with cognitive impairment [15]. In AD, abnormal tau aggregates are present in the cell body and proximal dendrites [16].

Research studies, using animal models have identified mechanisms that are shared by T2DM and AD [7]. AD pathology has been evaluated extensively in two widely available T2DM spontaneous models: Bio-Breeding Zucker diabetic rat/Wor rats and db/db mice. They observed an increase in tau phosphorylation and cleavage, which is known to be particularly toxic to neurons and forms the nucleation for NFT [9]. The hyperglycemia in T2DM induces an increase in advanced glycation end products (AGEs), and these molecules also accumulate with aging and dementia [17, 18]. AGEs promote Aβ aggregation and cytotoxicity [19], while glycation of tau promotes their aggregation [20].

A fat and simple sugars-rich diet, coupled with sedentary lifestyle, is also a strong risk factor associated with another disorder known as metabolic syndrome (MS), characterized by abdominal obesity, dyslipidemias, high blood pressure, hyperglycemia, insulin resistance, and high body mass index [21–23]. Since many of the characteristic features of MS, including insulin resistance, obesity, dyslipidemia, and high blood pressure, are risk factors not only for DM and cardiovascular disease but also for AD [24], this review will focus on the common mechanisms involved in the development of these diseases.

2. Metabolic syndrome

Metabolic syndrome is a complex disorder defined by a cluster of interconnected factors that increase the risk of cardiovascular atherosclerotic diseases and T2DM [25]. MS is also associated with various cardiometabolic risk factors modulated by

several environmental conditions, mainly an inadequate diet and physical inactivity [26]. The syndrome presents simultaneously with insulin resistance, alterations in blood glucose levels, hypertension, triglycerides above normal, levels below recommended of high density lipoprotein (cHDL), and visceral obesity [22]. The process starts with an inadequate diet as well as a sedentary life, which induce the development of obesity, usually with episodes of hyperinsulinemia, which in turn can produce insulin resistance due to the blockade of insulin receptors and glucose transporters, with the presence of high levels of fatty acids and glucose in the extracellular space (associated with DM), associated with hypertension and low synthesis and increased triglyceride catabolism. There are also dyslipidemias due to the inability to inhibit lipolysis in fatty tissues, with an increase in low-density lipoprotein (cLDL) and a decrease in cHDL. Finally, obesity develops due to the continuous increase in visceral fat, a permanent pro-inflammatory state, and endothelial dysfunction [27].

2.1 Etiology

The etiology of MS is attributed to the combination of genetic and environmental factors associated with lifestyles.

Obesity is "a chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences." Includes the increase and accumulation of fat at the visceral level (fatty tissue deposit mainly in the liver, intestine and pancreas), the tissue is rich in macrophages; adipocytes produce a variety of biologically active molecules, known together as adipokines [28].

Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, the "bad" cLDL cholesterol and the triglyceride concentrations, and a decrease in the "good" cHDL cholesterol concentration in the blood. Dyslipidemia has been attributed to the inability of insulin to inhibit lipolysis at the level of adipose tissue, which leads to an increase in the release of free fatty acids and a greater contribution of these to the liver, inducing increased apolipoprotein B secretion [29].

Hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels have persistently raised pressure. Hypertension is produced as a consequence of the effects of the hyperinsulinemia. The blood pressure rises, due to an increase in the reabsorption of sodium and water in the renal proximal tubule. Hyperinsulinemia also increases peripheral vascular resistance and increases the activation of the sympathetic system with the consequent increase in circulating catecholamines and stimulation of the renin angiotensin-aldosterone system [30].

Hyperglycemia is the technical term for high blood glucose blood sugar. High blood sugar happens when the body has too little insulin or when the body cannot use insulin properly. This poor insulin secretion or action is due to lipotoxicity of the pancreatic β cells, since the excessive accumulation of triglycerides in pancreatic islets increases the expression of the inducible nitric oxide synthase (iNOS) enzyme, increasing nitric oxide levels and producing impaired function and finally apoptosis. The β cells, progressively losing its ability to compensate the insulin resistance with more insulin secretion, and finally increasing blood glucose levels [31].

Insulin resistance is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population. Insulin action is the consequence of insulin binding to its plasma membrane receptor and the signal is transmitted through the cell by a series of protein–protein interactions. Classically, this

refers to impaired sensitivity to insulin-mediated glucose disposal. Compensatory hyperinsulinemia occurs when pancreatic β cell secretion increases to maintain normal blood glucose levels in the setting of peripheral insulin resistance in muscle and adipose tissue [32].

Pro-inflammatory states acute and chronic hyperglycemias are pro-inflammatory states, central obesity and insulin resistance being implicated in its etiology. Adipose tissue is biologically active as an endocrine and paracrine organ. Adipocytes undergo hypertrophy and hyperplasia in response to nutritional excess that can lead the cells to outgrow their blood supply with induction of a hypoxic state. Hypoxia can lead to cell necrosis with macrophage infiltration and the production of adipokines, which include the pro-inflammatory mediators interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), as well as the prothrombotic mediator plasminogen activator inhibitor-1 (PAI-1, [33]). These mediators induce an oxidative stress and endothelial dysfunction, and nitric oxide (NO) regulates the vascular tone by activating guanylate cyclase and increasing the 3′5′-guanosine monophosphate and inhibits platelet activity. When there is an excessive production of superoxide anion, the bioavailability of NO decreases due to their oxidative inactivation in the vascular wall [34].

2.2 Diagnosis of metabolic syndrome

The diagnostic criteria of the MS have been subject to many definitions, such as those of World Health Organization (WHO), Adult Treatment Panel III of the National Cholesterol Education Program (ATP III), International Diabetes Federation (IDF), American Heart Association (AHA) and others. However, a new global definition of the metabolic syndrome was proposed by the IDF where obesity represents a necessary requirement for the diagnosis of MS. Once the obesity is confirmed, the diagnosis continues with the presence of two or more parameters such as decrease in cHDL and increase in triglyceride, blood pressure and blood glucose [35–37]. However, even with a good diagnosis for MS, in most cases the treatment is inadequate [38].

Several MS components are present in AD and T2DM, including insulin resistance, obesity, dyslipidemia, and high blood pressure [24]. These common mechanisms are required to be analyzed deeper, and how each one of them contributes in all these pathologies should be described.

3. Amyloid forming diseases

AD and T2DM are amyloid forming diseases characterized by the presence of insoluble protein aggregates with a fibrillary conformation in brain and pancreas, respectively [39].

The presence of proteinaceous plaques that primarily comprise islet amyloid polypeptide (IAPP, one of the major secretory products of the pancreatic β-cells) is found in the majority of patients (approximately 90%) with T2DM [40]. Although it is not clear why normally soluble IAPP can form toxic aggregates, the evidence suggests that the presence of an amyloidogenic sequence in the IAPP molecule could increase the IAPP production/secretion from β-cells associated with elevated insulin demand and abnormalities in trafficking/processing of pro-IAPP contribute to aggregation in T2DM, causing cellular dysfunction and consequent membrane disruption, channel formation and toxicity [41]. Further, several groups have found that Aβ1–42 and IAPP forms form early intermediate assemblies as spherical oligomers, implicating a common folding pattern (**Figure 1**, [42]).
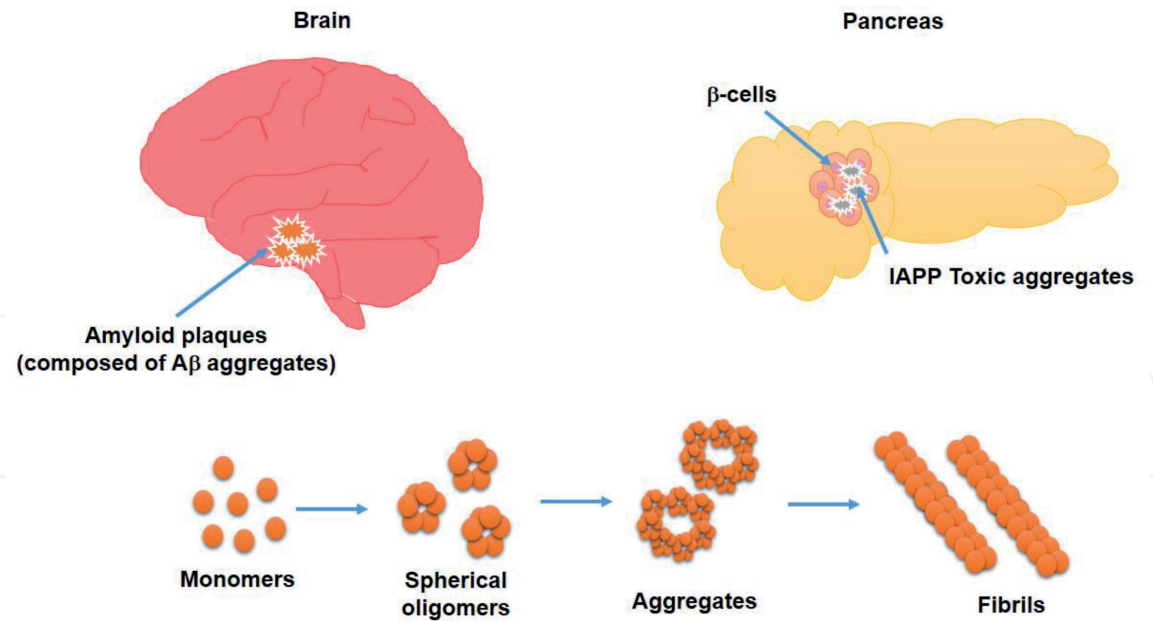
Figure 1.
Common ways of amyloid toxicity in Alzheimer's disease and type 2 diabetes mellitus. Insoluble protein aggregates with a fibrillary conformation are present in both entities, causing cell death in neurons and β-cells of brain and pancreas, respectively.

4. Insulin alterations

In addition to T2DM (insulin resistance), T1DM (insulin deficiency) shares mechanisms with AD, and researchers have called the set of these characteristics type 3 diabetes. Defects in insulin signaling causes alterations in glucose metabolism and leads to an energy imbalance causing the production of reactive oxygen species (ROS), DNA damage, and mitochondrial dysfunction; all these cascades lead to pro-apoptosis, pro-inflammatory and production of toxic peptides (tau and Aβ) [43].
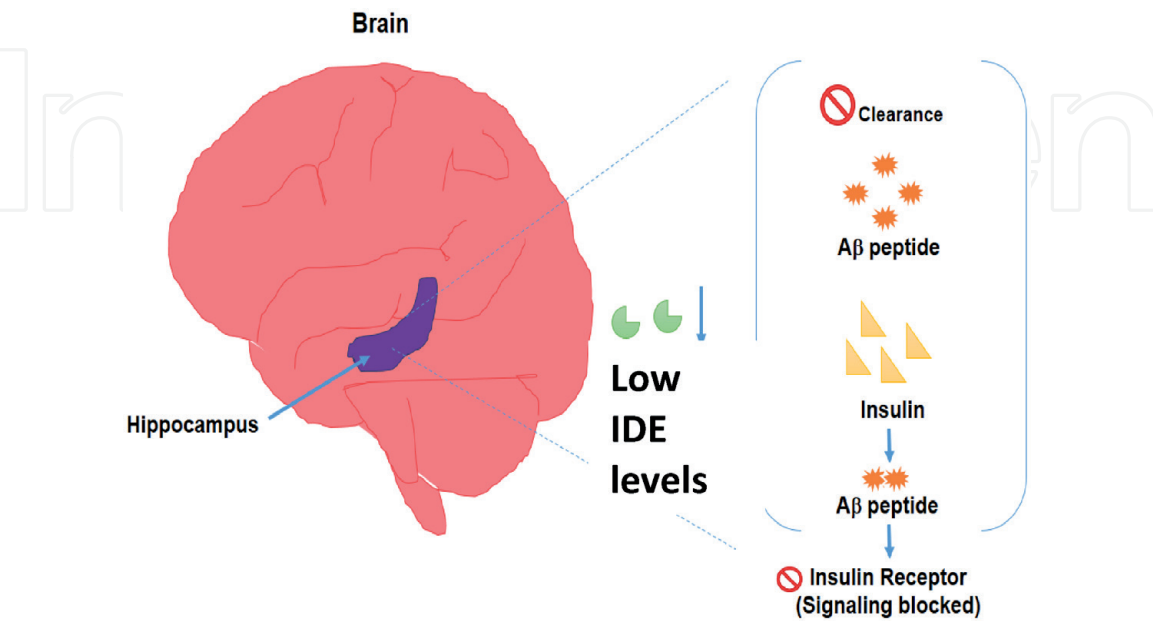

Figure 2.
Abnormal clearance of toxic species of β-amyloid by insulin degrading enzyme. Hippocampus with decreased levels of insulin degrading enzyme (IDE) leads to Aβ accumulation, which blocks the insulin receptor signaling, altering synaptic plasticity and architecture of dendritic spines.

Insulin regulates glucose metabolism in peripheral tissues and also affects brain functions including cognition, memory, and synaptic plasticity through complex insulin/insulin receptor (IR) signaling pathways [44]. Insulin resistance in the brain is presented by reduced levels of insulin and insulin growth factor (IGF) receptors. Insulin and IGF deficiency are associated with an altered expression of insulin and IGF polypeptides in the brain and cerebrospinal fluid (CSF), which causes accumulation of Aβ [45]. On the other hand, chronic peripheral hyperinsulinemia and central insulin resistance can modulate tau phosphorylation, and with the loss of insulin-like growth factor 1 (IGF-1) signaling, an increase in tau hyperphosphorylation and NFT formation has been observed [46]. Through the inhibition of insulin signaling, Akt kinase is also inhibited, which in turn activates the glycogen synthase kinase 3β (GSK3ß), probably causing an increase of tau phosphorylation and altering its binding to microtubules [9].

Insulin degrading enzyme (IDE) is a major factor responsible for insulin degradation. However, IDE degrades other targets like glucagon, atrial natriuretic peptide, and Aβ, and this could be another connection between T2DM and AD. The decrease of IDE in the hippocampus has been associated with a greater susceptibility of this region to the accumulation of Aβ (**Figure 2**, [47]).

5. Hyperglycemia

The T2DM patients have chronic hyperglycemia with an impaired glucose metabolism (poor glucose transport), altering neuronal cell and their metabolism contribute to AD. In patients with AD, a decrease in glucose metabolism has been observed, typically identified with fluorodeoxyglucose positron emission tomography (PET), even before clinical symptoms of dementia were present [48].

Deficits in glucose metabolism might also potentiate the neuronal cell death produced by other pathological processes (such as abnormal cholesterol metabolism or high levels of Aβ), which in turn might be influenced by genetic predisposition such as possession of Apolipoprotein E ε4 (APOE ε4) alleles [49].

It is generally accepted that many DM complications are potentiated or initiated by the accumulation of specific forms of AGEs and their interaction with its receptors (RAGE). The AGEs are molecules (including peptides and proteins) formed as a result of the Maillard reaction. In T2DM, periods of hyperglycemia induce an increase in AGEs formation, although these molecules also accumulate with aging accelerated formation [17, 18]. AGEs promote Aβ aggregation and cytotoxicity [19] and glycation of tau may enhance their aggregation as well [20].

6. Dyslipidemia

Cholesterol may be directly involved in Aβ aggregation, by abnormal oxidative metabolites such as cholesterol-derived aldehydes, which can promote the amyloidogenesis process. Also, it was observed that APOE ε4, cholesterol, and Aβ are components of the amyloid plaques both in humans and animal models of AD. Further, low levels of cholesterol affect APP metabolism, with an increase in the secretion of soluble APP, a non-amyloidogenic soluble N-terminal derivative, also found in human CSF [50].

7. Obesity

The mechanism for the association between obesity and dementia is still far from being understood. Whitmer et al. alluded to the involvement of adiposity with

inflammation and its markers [51] while Liu et al. report that obesity also has been related with defective brain insulin signaling in experimental models and postmortem brains [52]. This is important because there have been several reports where insulin regulates synaptic plasticity through altering internalization of neurotransmitter receptors, in the cortex and hippocampus, which are regions of the brain generally associated with learning and memory, respectively [14, 53]. Therefore, alterations in synaptic plasticity may be associated to tau pathology, through a direct abnormal interaction of pathological tau species with synaptic proteins but also indirectly through tau-activated neuroinflammatory processes [54].

Another possible mechanism linking obesity with dementia is the oxidative stress, resulting from an increased intake of sugars and fats, which is the hallmark of the modern diet [55, 56]. Rats maintained on a diet high in refined sugar and rich in fat generated higher concentrations of free radicals [51]. Inflammatory processes promote vascular complications in obesity, T2DM, and AD. The primary regulator of this response is NF-κB, and in these pathologies there is an increase of the NF-κB family of transcription factors. In AD, the reactive astrocytes in close proximity to the Aβ plaques produce inflammatory cytokines, including IL-1β and TNF-α, and inducible iNOS, which generate free radicals such as NO, that can be neurotoxic [38].

8. Hypertension

Mice that have been chronically subjected to high blood pressure show deposition of amyloid aggregates and loss of memory when they are examined in specific tasks. Besides this, the hypertensive challenge increases the expression of RAGE, leading to Aβ deposition and learning impairment [57, 58].

A few autopsy studies have showed that the severity of AD pathology is increased by the presence of cerebrovascular damage, which is strongly linked to hypertension [58, 59].

Chronic hypertension induced vascular abnormalities in the brain, such as increased vascular stiffness, and decreased vessel wall plasticity; this alters arterial pulsations, disturbing the glymphatic system and leading to a significant increase of Aβ deposition in the brain parenchyma [60]. The glymphatic system is a macroscopic waste clearance system that utilizes a unique system of perivascular tunnels, formed by astroglial cells, to promote efficient elimination of soluble proteins and metabolites from the central nervous system [61].

Cerebral amyloid angiopathy has been shown to interact with amyloid plaques and NFT and to increase the severity of cognitive impairment beyond that seen in people with each histopathological feature separately [62].

9. Conclusion

There are several mechanisms in common between AD and T2DM, and a better understanding of their interrelation would contribute to upgrade the control of these diseases. Working in this direction will be important in order to identify new therapeutic or common targets, especially before the most severe symptoms of both pathologies occur. In addition to better management of the patients, this will improve the patient's quality of life.

Conflict of interest

The authors declare no conflict of interest.

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