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Current Alzheimer Research, XXXX, *XX*, 1-31

REVIEW ARTICLE

Relationship between Alzheimer's Disease and Type 2 Diabetes: Critical Review On Cellular and Molecular Common Pathogenic Mechanisms

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Abstract: ***Objective/Background*:** Type 2 Diabetes Mellitus (T2D) and Alzheimer's disease (AD) are two diseases with a high prevalence today that share common pathophysiological mechanisms, suggesting a potential causal relationship between them. AD is also known as Type 3 Diabetes Mellitus (T3D). A complete understanding of this complex issue (T2D-AD) is necessary to develop fully effective and easily applicable therapies that do not yet exist. A critical update on the subject is presented, delving into the pathophysiological implications and defining new research for promoting new therapeutic interventions.

***Methods*:** Revision and critical analysis of the described and observed cellular and molecular common pathogenic T2D-AD mechanisms in human and model studies.

***Results*:** Both diseases exhibit common genetic, epigenetic, biochemical and physiological characteristics. Pathogenic mechanisms such as peripheral inflammation, mitochondrial dysfunction, oxidative stress, insulin resistance, hyperglycemia, formation of advanced glycation end products, neuroinflammation, neuroglial dysfunctions, and deposition of aberrant misfolded proteins are commonly displayed in dysmetabolic diseases and AD. The T2D, AD and T2D-AD pathogenic courses present several close key contacts (or identities). The clinical course of T2D has different incidence in the neurodegenerative course of AD (from its onset to its aggravation). There are theoretical, practical and interpretative problems in studies on human and experimental models, as well as in the clinical and pathological interpretation of T2D-AD dementia, which are of great importance in the development of knowledge of this subject and the therapeutic application of its results.

***Conclusion*:** In recent years, there has been a great advance in the study of the relationships between T2D (and related dysmetabolic diseases) and AD. There is no doubt about their close relationship and/or the inclusion of AD as a metabolic disease (T3D). Joint therapies seem to be absolutely necessary. Key pathogenic processes (insulin resistance, genetic and epigenetic regulation, peripheral inflammation and neuroinflammation) must be investigated to develop new and effective therapies.

ARTICLE HISTORY

Received: December 18, 2024
Revised: February 20, 2025
Accepted: February 20, 2025

DOI:
10.2174/0115672050375461250325074826

Keywords: Alzheimer's disease (AD), Type 3 diabetes (T3D), type 2 diabetes (T2D), pathogenic mechanisms, insulin resistance, hyperglycemia, peripheral inflammation, neuroinflammation, oxidative stress, mitochondrial dysfunction, neuronal degeneration, neuroglial dysfunction, genetic causes, epigenetic causes.

1. INTRODUCTION

For decades, it has been accepted that there is a strong relationship between Alzheimer's Disease (AD) and Type 2 Diabetes (T2D). T2D and AD metabolism relationships were first postulated by Hoyer *et al.* in 1989-2007 [1-4], Nicolls in 2004 [5] and de la Monte, in 2008 [6], as both diseases exhibit a decline in insulin levels, insulin altered binding and tyrosine kinase activity as well as diminishing glucose uptake, functioning of insulin-degrading enzyme and pyruvate dehydrogenase complex (yielding reduced levels of acetyl-coenzyme A and adenosine triphosphate). AD was postulated as a metabolic condition that augmented the amyloid cascade hypothesis of AD [7]. A large number of research articles and reviews (more than 3,500; Medline assessed) have been published on this topic. However, only a selection of important and recent references can be analyzed

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1567-2050/XX $65.00+.00

[8-32]. There is still no definitively accepted consensus on the key pathogenic mechanisms that link both pathologies or identify (or not) these two clinic-pathological processes as a single basic metabolic disease with different presentations in its clinical-pathological course in different individuals and/or different organs of an individual. The study of this very important theoretical and practical issue (remember that millions of people suffer these diseases [33-37] and T2D has become increasingly prevalent in young populations. People aged 20-39 years-IDF Diabetes Atlas 2021 [38]; The Lancet 2024 [39]) is very difficult due to three main problems: a) AD is not a clearly differentiated disease, but rather a very complex syndrome with a large but bad defined etiopathogenic causes [17, 40-47]; b) T2D is also a complex disease and a conspicuous part of a metabolic syndrome that is difficult to characterize, which affects different organs in different ways, including the CNS, and gives rise to very varied pathological manifestations in different patients [48-53]; c) The relationship between Type 2 Diabetes Mellitus (T2D) and Alzheimer's disease (AD) is complex and multifaceted [8-32].

Although the two conditions appear to be distinct over the years, there is more and more evidence suggesting connections between them, as mentioned above. The main reasons argued for this close relationships T2D-AD, mentioned in every all the studies and reviews, are: *(a)* both diseases share common risk factors such as genetic expressions, epigenetic modulations and clinical metabolic disturbances (obesity and other disorders coursing with chronic inflammation) [17, 27, 30, 54-60]; *(b)* both diseases present common pathogenic mechanisms such as insulin resistance, hyperinsulinemia, hyperglycemia, and mitochondrial dysfunctions [16, 19, 20, 26, 31, 61]; *(c)* vascular pathogenic factors are common to both diseases, but with different damage intensity on the blood brain barrier (BBB) [62]; *(d)* chronic inflammation is present in both conditions development [14, 15, 59, 63]; *(e)* chronic hyperglycemia conducts increased oxidative stress, which damages cells, including neurons and neuroglial cells leading to Alzheimer's development [9]; *(f)* T2D induces the formation of the characteristic deposits of misfolding proteins of AD (amyloid β-protein in plaques and phosphor-Tau protein in tangles) and interferes with removal of these aberrant proteins, thus contributing to AD development [8, 64-67]; *(g)* different pharmacological and non-pharmacological interventions can be beneficials for both diseases [68, 69].

Many authors consider that insulin resistance is the intersection link between T2D and AD pathways. But we must not forget that it has also been pointed out that mitochondrial dysfunction and inflammation are seminal causes that promote both diseases [59, 61, 63]. Moreover, peripheral inflammation induces neuroglial dysfunctions/neuroinflammation that are causes of AD [27, 63, 70]. A graphical summary of pathways involved in neurodegeneration in the diabetic brain and critical links between T2D and AD is presented in Fig. (**1**).

Four important considerations on the common T2D and AD mechanisms need to be retained:

1. The mechanisms proposed in the last years to explain the reasons T2D contributes to AD development and progression are very varied, as has been mentioned: genetic, epigenetic, glucose-lipid dysmetabolic alterations [71, 72], inflammatory/neuroinflammatory disordering, mitochondrial dysfunctions, vascular dysfunctions. For many authors, the T2D-AD relationship is so close that they consider AD to be a dysmetabolic clinic-pathological manifestation included in the complex T2D and have proposed the term type 3 diabetes (T3D) to refer to AD even when there are no apparent signs of peripheral disorders related to alterations in glucose metabolism [19, 73, 74].

2. The pathogenesis of AD and T2D involves complex interactions between genetic factors, environmental influences, and lifestyle choices. Genetics factors, increasingly studied in recent decades, with more and more precise techniques, have shown us in an unquestionable manner that both the genetic heritage of AD and T2D patients is one of the most important etiological causes of the conditions they suffer when developing one, the other pathology or both pathologies. In these many last cases, common genetic alterations are shared to develop a complex pathogenic course of both pathologies, even manifested in varied clinical-pathological phenotypes. Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA (ncRNA), play critical roles in regulating gene expression without altering the DNA sequence, bridging the gap between genetics, environment, and disease development. Early environmental exposures to risk factors can influence the likelihood of developing neurodegenerative diseases later in life, highlighting the significant contribution of environmental factors to AD onset. Common epigenetic modifications have been implicated in both AD and T2D, contributing to their pathogenesis. This highlights the connection of epigenetic regulation in complex diseases and underscores the importance of epigenetic-based interventions for prevention and treatment [75]. Associated comorbidities (systemic metabolic syndrome, cardiovascular diseases) are particularly important modifiers of the course of both T2D and AD diseases.

3. The pathogenic course from T2D to AD (considering the different existence of two different diseases) has been more or less described as follows (Fig. **1**). T2D leads to dysregulation of glucose and lipid metabolisms, resulting in hyperglycemia and insulin resistance. Chronic hyperglycemia contributes to oxidative stress, inflammation, and neuronal damage, all of them observed in AD. In parallel, through direct and indirect ways, T2D affects the blood vessels, leading to microvascular damage, dysfunctional blood-brain barrier (BBB) and impaired cerebral blood flow regulation. This disruption in cerebrovascular homeostasis may contribute to AD by compromising nutrient and oxygen delivery to the brain, as well as impairing the clearance of amyloid β-protein, a hallmark feature of AD [76]. T2D is associated with peripheral chronic low-grade inflammation, characterized by increased levels of pro-inflammatory cytokines.

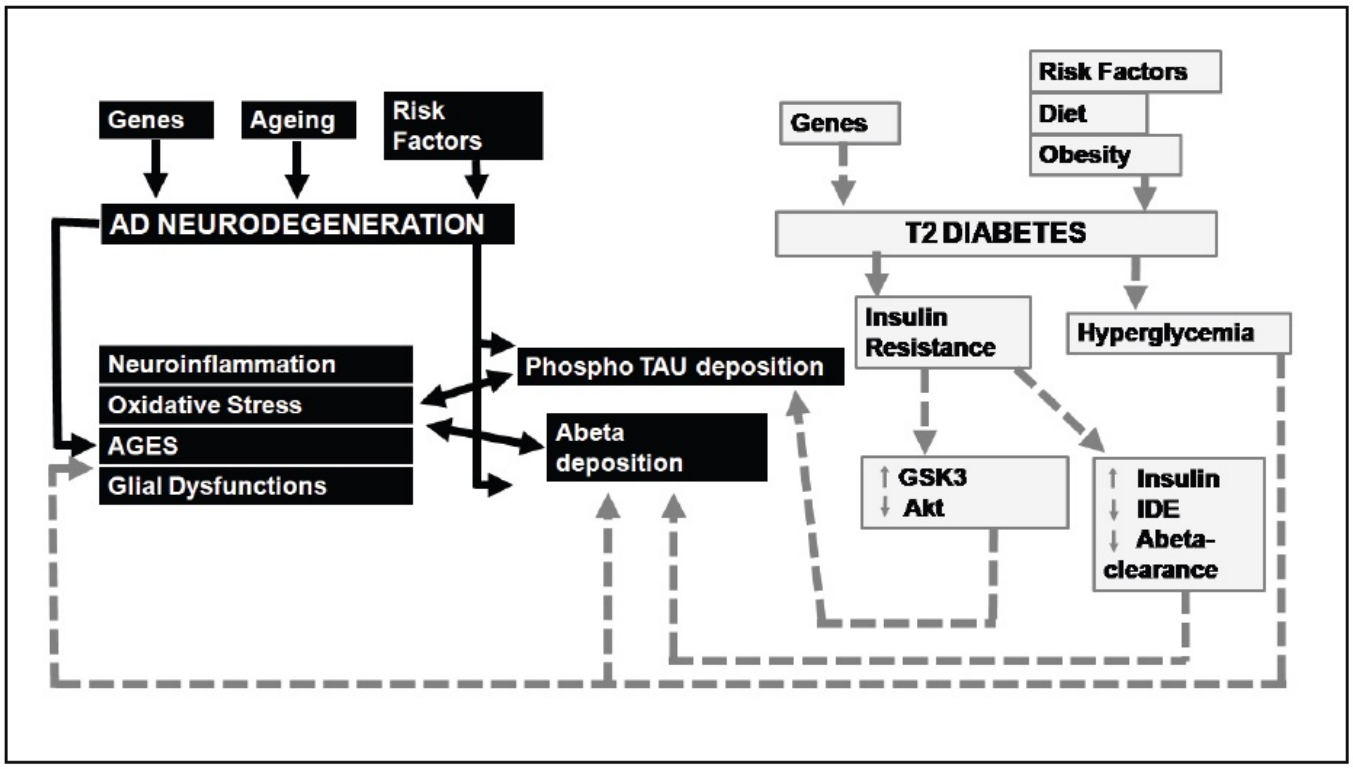

Fig. (1). Pathways of neurodegeneration in the diabetic brain. Critical links between Type 2 diabetes (T2D) and Alzheimer´Disease (AD). The two main neuropathological manifestations in AD are intracellular deposits of phosphorylated TAU protein (which give rise to dysfunctional dystrophic neurites and neurofibrillary tangles) and extracellular deposits of amyloid β-protein. Both pathways are facilitated by insulin resistance, the major cause of type 2 diabetes. Insulin resistance, through the activation of Akt and GSK3-beta, increases the phosphorylation of the Tau protein. Moreover, through increased insulinemia, the clearance of the beta-amyloid protein decreases by deactivating the insulin degrading enzyme (IDE). On the other hand, hyperglycemia induced by T2D leads to an overproduction of amyloid β-protein that is deposited as plaques and/or diffuse amyloid. The chronic hyperglycemia generates advanced glycation end products (AGEs), oxidative stress and neuroinflammation that causes neurodegeneration. Phospho-Tau andamyloid β-protein also activate these same neurodegenerative processes. (Based on reference 70). *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

This peripheral inflammation is associated with other pathological disorders (oxidative stress, mitochondrial dysfunctions). It induces neuroinflammation mediated by the activation and/or dysfunctions of neuroglial cells in the brain, which plays a key role in AD neurodegeneration induction and progression [71, 77-79].

4. An increasing number of preclinical and clinical studies are showing that it is possible to act therapeutically in the prevention and treatment of AD and the T2D-AD complex with specific interventions on the common T2D-AD pathogenic mechanisms. Not only are medications used in the treatment of T2D proven to be effective in AD, but many non-pharmacological interventions are equally beneficial in both pathologies. Programs or healthy lifestyle patterns, such as exercise, may prevent a sedentary lifestyle or dietary patterns, and supplementation targeting insulin resistance, hyperglycemia, and cognitive impairment associated with T2D and AD have shown promise in improving glycemic control and reducing cognitive decline.

Although the link between T2D and AD is increasingly recognized, much remains to be understood about the specific mechanisms linking these two pathologies. There are many aspects of this important relationship between T2D and AD where controversies are very important both in the theoretical aspect and in the practical aspect of therapeutic care. There is controversy over whether AD is a metabolic disease (Type 3 Diabetes - T3D) or whether cognitive impairment resulting from the progression of T2D causes AD or vascular dementia. Other controversies are related to the role of peripheral inflammation and the links to neuroglial dysfunctions and neuroinflammation, as well as the BBB dysfunctions.

Continuous research is crucial for better understanding this connection and developing effective prevention and treatment strategies for both diseases. The most recent studies, using the new advanced techniques (genetic, molecular, transcriptomic, and proteomic analysis; characterization of cellular subtypes or individualized cells involved in pathogenic mechanisms), increase the knowledge of these diseases. However, they have not yet been sufficiently developed to obtain therapeutic benefits in both diseases because well-defined etiopathogenic subgroups that can be diagnosed

and treated in a specific and effective manner have not been identified. Currently, it also seems especially important to clarify the intrinsic organization and function of the involved mechanisms and deepen the knowledge of these common pathogenic mechanisms both to better understand the pathogenic course of diseases and to define/characterize therapeutic targets that can prevent or positively modify the pathogenic function of these mechanisms.

In this review, we attempt to highlight, in a critical manner, both the most commonly accepted and the most discussed topics regarding the close pathogenetic relationship between AD and T2D, always thinking about the possibilities of an effective therapeutic intervention.

In the following sections, we will discuss the most important aspects of this topic: section 2: Difficulties in the study of the pathogenic mechanisms relating the T2D and AD diseases, section 3: Common internal and external risk factors for the development of T2D and AD, genes (section 3.1), epigenetic modifications (section 3.2); comorbidities (section 3,3) and other external risk factors such as diet and lifestyle (section 3.4), section 4: common molecular pathways and therapeutic targets, section 5: controversies in the AD and T2D close relationships, section 6: the metabolic theory of AD based on the close relation of T2D-AD, in front of other AD theories, section 7: discussion, conclusions and future research.

The pharmacological, non-pharmacological, cellular, and molecular therapies of the T2D, AD, and T2D-AD targeted to these common mechanisms described here are developed in the second part of this manuscript.

2. DIFFICULTIES IN THE STUDY OF THE PATHOGENIC MECHANISMS RELATING THE T2D AND AD DISEASES

Studies on this topic present various difficulties. Diverse types of important circumstances can be pointed out that are having a significant impact on the interpretation of the results.

First of all, it should be noted that both T2D and AD are complex syndromes rather than well-defined diseases. Their ambiguous etiologies and their unhidden relationships with other pathologies make it difficult to reach solid conclusions when they are studied and give rise to a lot of controversies.

T2D has been shown to have a great genetic diversity that reveals a great heterogeneity in its pathophysiology [51]. T2D is also related to many metabolic disorders. T2D and T1D are vastly different clinic-pathological diseases. However, T2D has complex relationships with T1D, as demonstrated by genetic analyses [80]. In a comparable way, there exist many pathogenic and pathological links with various pathological disorders linked to glucose and lipid dysmetabolism, such as obesity and other pathological problems that affect various peripheral organs in a more or less selective manner. T2D forms part of the generalized "metabolic syndrome" that is difficult to define [81, 82]. Some of these metabolic disorders may be the origin of T2D or consequences of this pathology in different peripheral organs or the brain. Likewise, within T2D (or closely related but not totally included because of its dual resemblance to T1D in pathogenesis and to T2D in clinical presentation [83] or the presentation of a mixed cellular immunological pattern with features overlapping T1D and T2D [84]) there is an autoimmune variant (Latent Autoimmune Diabetes in Adults- LADA [80, 83, 85-88]: or T1.5D [89]) that represents 7-15% of cases [90, 91], is difficult to diagnose/define and requires specific treatment [92]. Another type of TD is the adult-onset autoimmune (AOA) diabetes pathophysiology that starts with immune changes, followed by dysglycaemia and overt disease [93], and maturity-onset diabetes of the young (MODY) [94]. MODY is a dominantly inherited form of early-onset non-autoimmune diabetes and the most common and widely characterized presentation of monogenic diabetes. MODY has been estimated to account for two to five percent of young-onset diabetes and is commonly classified into T2D cases [92]. All these clinic pathogenic diabetic T2D variants or diabetic disorders misclassified as T2D must logically have different implications in the neuropathological response of the brain, producing a bias in the interpretation of the results of clinical and neuropathological studies. Moreover, there is a great diversity of pathogenic courses in T2D that condition both the pathogenic manifestations and the possible treatments. There are cases of early presentation in young individuals (aged <40 years) or advanced adulthood and in presenile/senile phases. The earliest presentations induce rapid pancreatic involution [95], and the senile presentations lead to a subclinical state of chronic inflammation of low intensity (inflammaging) and immune dysfunctions [96-99]. In the same way, there are very different pathogenic courses induced or modified by an early or late diagnosis and (adequate) treatment and/or by an adequate lifestyle. T2D is a disease highly dependent on epigenetic and environmental factors (exercise, diet) [80].

AD is a syndrome with a complex and varied etiopathogenesis (genetic changes [100], neurotransmitter dysfunctions [101-103], neuroglial dysfunctions/neuroinflammation [104-107], neuronal dysfunction [108-111] vascular disturbances [112], metabolic dysfunctions [104, 113], misfolding protein processes [114], aging/cellular senescence [115-117], mitochondrial dysfunction [118-120] *etc.*). The attempts to define a unified theory of the neurodegenerative process related to the "amyloid cascade" [2, 5, 121-125] have provided great advances in the knowledge of AD and its therapeutic approach. Still, they show that the causes that give rise to the syndrome are very diverse, which gives rise to variants in the clinical-pathogenic courses, and that preventive and disease-modifying treatments are difficult to specify [125, 126].

All this means that in human studies, there may be important unnoticed biases in the selection of study cases.

Another important aspect is the question of whether the study of T2D cases has been treated for many or only a few years (increasingly less nowadays) with effective treatments

against disease (this item is not the case in AD). This leads to comparing patients regulated in the pathogenic course of their metabolic disorder (T2D) with patients freely developing their AD neurodegenerative pathogenic course. Therefore, it is difficult to specify the neuropathological differences in both pathologies and the most important studies to establish the pathological differences in brains focus on T2D cases with little clinical and AD neuropathology. T2D patients are not routinely evaluated in terms of their cognitive status, and AD patients are not routinely evaluated for insulin resistance and related disorders [19]. Another significant difference is related to the life span of each disease, T2D and AD. Many authors consider that the brain deterioration induced by T2D does not clinically reach AD due to vascular problems incompatible with life. In section 5, the controversies that have arisen in the correlation between T2D and the development of AD or other forms of brain neurodegeneration (cerebrovascular disease or cognitive deficit different from AD) are discussed. Many authors point out that vascular alterations induced by T2D lead to systemic and cerebral vascular disorders, often causing death before AD pathology develops. However, in many cases, neuropathological signs of AD (such as amyloid plaques and neurofibrillary tangles), especially neuroglial dysfunctions, can still be observed. It is also important to highlight that one of the major sources of information on the pathogenic connection between T2D and AD (which can be considered the basis of our currently accepted theories) comes from the study of experimental models [127-129]. Neurotoxins (streptozotocin) or diet or genetic manipulation (ob/ob and NSY mice) produce animals with obesity and/or T2D. The insertion of human pathological genes provides AD models. Different types of joint interventions or manipulations (from the hypercaloric/diabetogenic diet applied to transgenic AD models [70] to the production of new mixed models by crossing obese mice with AD transgenic mice [130]) provide mixed T2D-AD models. These animal models show a strong connection between the pathogenic mechanisms that promote brain involution in T2D and AD. The concurrence of both pathologies significantly aggravates the deleterious effects on the neurons and neuroglial cells [131, 132]. However, several authors question the results obtained in these models either because they consider that the alterations do not correspond to what is observed in humans or because they interpret the results differently (see section 5).

3. COMMON INTERNAL AND EXTERNAL RISK FACTORS FOR THE DEVELOPMENT OF T2D AND AD

In both T2D and AD, epidemiological studies carried out for many years repeatedly insist on pointing out the existence of common cellular and molecular pathogenic pathways (section 4) always related or induced by intrinsic (genetic, comorbidities, age) and extrinsic causes (epigenetic modifications mainly induced by diet, lifestyle, physical activity, social conditions, environmental conditions). In this section, the following risk factors will be analyzed:

3.1. Genes

In recent years, considerable progress has been made in the characterization of the genes and their isoforms, which are in some way involved in the presentation and/or development of both pathologies. The isoforms confer different degrees of suffering from the pathologies, which explains the individual differences between patients as well as those existing in different subgroups of patients. Important genes are related to some of these pathologies more specifically (although they can cause alterations in related diseases such as metabolic diseases in the case of T2D or neurodegenerative diseases in the case of AD). There are also altered genes common to both pathologies, such as those that involve dysfunctions in lipid metabolism or mitochondrial function (see 3.1).

3.2. Comorbidities

Although there are other causes of AD-T2D comorbidity (extrinsic or intrinsic toxins, gut dysbiosis, infectious processes, *etc.*), most neuropathogenic processes are related to alterations that may be included in a generalized process of metabolic glycemic-lipidic alteration (Metabolic Syndrome). Increased adiposity, cardiovascular dysfunctions, hypertension, and diabetic-related disorders are important clinical manifestations of this broad and sometimes ill-defined syndrome (see 3.2).

3.3. Age

Many pathogenic metabolic processes related to T2D occur at early ages in an individual's life, but the specific clinical manifestations of T2D are more evident in adulthood or senility. In this last phase of life, it has been pointed out that there is “pre-diabetes” without clinical significance (see T3D). Similarly, the most significant implications for AD-related brain neurodegeneration arise in senility, when cognitive deficits, cerebrovascular alterations of varying severity, and intense neuroglial changes-closely linked to aging-occur. AD develops in the senile phase of the life course of individuals, with a greater epidemiological coincidence with T2D, regardless of whether the pathogenic processes have been developing during the previous years without clinical manifestations. Brain “senescence” is closely related to aging, T2D and AD (see 3.3).

3.4. Epigenetic Modifications

Epigenetic reprogramming of the gene expression is a dynamic process that predicts the long-term health outcomes of diseases. It involves shifts between healthy and diseased states governed by intricate epigenetic networks [133]. Three different epigenetic mechanisms have been described that we present in the next section. This genetic reprogramming is not yet well known. It is considered one of the most important ways to induce modifications of the abnormal genetic expression underlying AD and T2D for therapeutic purposes. At the moment, it has been demonstrated that certain non-pharmacological interventions can be the basis of effective preventive therapies in T2D and AD by acting on common epigenetic mechanisms [34].

3.5. Extrinsic Causes Induce T2D and AD by Direct Metabolic Interactions or Indirectly by Epigenetic Modifications

Diet and personal lifestyle are important determinants for the development of T2D and AD. These risk factors have an important and direct involvement in the presentation and development of the clinical course of both pathologies, as well as the characteristics of the clinical-pathological manifestations in each individual. These extrinsic causes modify epigenetic mechanisms that can regulate the expression of genes related to the pathogeny of T2D, AD, or T2D-AD (see 3.5).

3.5.1. Common Genes Involved in Both Diseases, T2D and AD

The differentially expressed genes between AD and T2D are not highly overlapped, but the functional similarity between them is significantly high when considering Gene Ontology semantic similarity and protein-protein interactions, indicating that AD and T2D share some common pathways in disease development.

Common genetic links between the two diseases involve genes related to insulin signaling and glucose metabolism. IDE (Insulin Degrading Enzyme) is responsible for degrading both insulin and Aß-peptides. Dysfunctional IDE activity leads to impaired insulin signaling in T2D and accumulation of Aß-peptides in AD [134-136]. Mitochondrial dysfunction presents another important link [137].

Certain APOE (apolipoprotein E) gene variants (APOE-4) have been linked to increased risk for both diseases [138]. APOE participates in lipid metabolism, insulin resistance pathway and β-cell dysfunction in T2D, as well as in Aß-peptides clearance in AD.

The SLC2A4 gene is a member of the solute carrier family 2 (facilitated glucose transporter) family and encodes a protein that functions as an insulin-regulated facilitative glucose transporter, among other pathways. It has the highest connectivity with GLUT4 and cerebellum, cortex, hippocampus, hypothalamus, pituitary, astrocytes, neurons and fueling of active synapses [139] as well as other differentially expressed genes (DEGs) for both AD and T2D. Therefore, it is suggested as a potential contributor to linking T2D and AD *via* glucose metabolism related pathways. Brain studies indicate that glucose transport is primarily regulated by GLUT1 and GLUT3, while GLUT2 increases the vulnerability of specific neuronal populations to the pathogenic mechanisms underlying AD [140].

An association between a variant of *HMOX1* and AD has been found [141]. Additionally, *HMOX1* upregulation has been shown to contribute to increased ferroptosis in the development of diabetic atherosclerosis [142], suggesting that HMOX1 may serve as a potential therapeutic or drug development target for diabetes and AD. A high correlation has been found between AD and diabetes based on the existence of 40 common genes [143]. Results of analyses revealed 14 genes in AD and 12 genes in diabetes as key genes that regulate many underlying brain mechanisms, 7 of which were common, including caspase 3 (CASP3), insulin--like growth factor 1 (IGF1), catalase (CAT), tumor necrosis factor (TNF), leptin (LEP), vascular endothelial growth factor A (VEGFA), and interleukin 6 (IL-6) [143].

It has been concluded that both diseases have the highest effect on NAFLD, which suggests that NAFLD is a key connector disease between these two diseases [143].

In addition, it has identified the following genes common to T2D and AD: APP (Amyloid Beta Precursor Protein), AMPK (AMP-activated protein kinase), FTO (fat mass and obesity), PPAR-γ (peroxisome proliferator-activated receptor), SORCS1 (sortilin-related VPS10, vacuolar protein sorting, domain containing receptor 1), ABCA1 (ATP-binding cassette sub-family A member 1), VEGF (vascular endothelial growth factor), and PCK1 (Phosphoenolpyruvate Carboxykinase 1) [144].

Most of these genes encode proteins involved in both the development of T2D and AD, but their role in the relationship between the two diseases has yet to be elucidated.

Other shared genetic factors between AD and T2D include genes related to inflammation, mitochondrial function, and lipid metabolism [57]. For instance, variants in genes encoding inflammatory cytokines such as IL-6 and TNF-α have been associated with increased risk for both diseases [145]. Additionally, genes involved in mitochondrial function and oxidative stress, such as PGC-1α and SIRT1, have been implicated in both pathologies [146]. Furthermore, genes related to lipid metabolism, such as PPAR-γ, have been linked to insulin resistance in T2MD and amyloid β-protein metabolism in AD [147].

In a recent study, a large number of alterations in the expression of genes, using transcriptomics/gene expression modification analysis, has been described in the temporal cortex of T2D patients who have manifested a low degree of cognitive deficit and present low grade of AD-like neuropathology. Changes have been found in neurons, astrocytes and endothelial cells [148]. The gene expression changes in neurons include pathogenic promoters for altered insulin signaling pathways, glucose/lipid metabolism, cell cycle cellular reentering, cellular senescence, pro-inflammatory molecule production and oxidative products, and mitochondrial dysfunctions. A larger number of genes (2,202 in astrocytes and 1,227 in endothelial cells) were significantly differentially expressed. Changes in cortical impaired insulin signaling were shared by these cells, and apoptotic pathway changes in astrocytes and dysregulation of advanced glycation end-product signaling in endothelial cells are important to note (see also neuroglial dysfunctions).

There is growing evidence suggesting a shared genetic basis between these two seemingly unrelated diseases. Several genes have been identified that play roles in both AD and T2D, suggesting common underlying mechanisms. Understanding these shared genetic factors is not only crucial for unraveling the pathophysiology of both diseases but also holds promise for drug repositioning, where drugs devel-

oped for one condition may be repurposed for the treatment of the other [57, 149, 150].

3.5.2. Common Comorbidities in T2D and AD

Different peripheral diseases have been proposed as inducers of T2D and AD pathologies. Most of them are related to metabolic dysfunctions that we can observe in pre-diabetic or T2D. We can highlight the role of obesity as the most important comorbidity of these two diseases.

Obesity (Fig. **2**) is the most important risk factor for explaining both the development of T2D and the relationship between T2D-AD in most clinical-pathological cases. Obesity is defined as a chronic disease characterized by an excessive accumulation of adipose tissue or a pathology where fat accumulates. Obesity occurs when adipocytes increase excessively in number (hyperplasia) and/or in size (hypertrophy) [151, 152]. Adipocyte hyperplasia leads to obese patients exhibiting normal levels of inflammatory markers in the microenvironment of adipose cells [153]. These patients are classified as having metabolically "healthy obesity," and they do not exhibit the typical indications of dyslipidemia or hypertension [154]. Conversely, hypertrophic adipocytes trigger immune system responses by secreting pro-inflammatory factors [155]. As a consequence, the microenvironment undergoes a substantial change to a pro-inflammatory state, characteristic of pathologic obesity [156], and patients are considered to suffer from unhealthy obesity. This differentiation regarding the "healthiness" of the patient with an obese morphological phenotype is not accepted by many authors who consider that inadequate intake before or after will lead to the presentation of inflammatory alterations and insulin resistance, which are the two basic manifestations of this disease. It must be remembered that there are also patients with obesity in whom the accumulation of fat is not so evident.

Moreover, hypertrophic adipocytes are susceptible to hypoxia [10, 152]. Long-term exposure of adipocytes to pro-inflammatory factors and hypoxia leads to endoplasmic reticulum stress and mitochondrial dysfunction, which we can consider the point of the main adipose tissue dysfunction [151, 152].

This condition promotes the recruitment of immune cells (eosinophils, macrophages) to the adipose tissue. The vicious cycle of inflammation results in local insulin resistance [151, 152]. Insulin-resistant adipocytes are overwhelmed, resulting in ectopic lipid excess translocation into the non-adipose organs like skeletal muscle, liver, pancreas, and heart, among other intermediaries of lipid metabolism such as ceramides, reactive oxygen species (ROS) and reactive nitrogen species (RNS) cause more inflammation, endoplasmic reticulum stress and systemic insulin resistance that led to oxidative stress and mitochondria dysfunction [151, 152]. Under these conditions, the antioxidant defense is altered, and the organs' storage capacity is saturated, resulting in lipotoxicity that induces peripheral insulin resistance, metabolic insults, and multi-organ dysfunction [10]. Insulin resistance produces glucose accumulation in the blood that stimulates the production of more insulin reaching hazardous levels that cause T2MD [10]. This condition induces BBB dysfunction, which decreases CNS protection and increases the permeability of neuroinflammatory and oxidative mediators along with cytotoxic ceramides from the periphery to the brain [10, 79, 157]. This triggers the activation of the resident immune system -microglia- promoting brain inflammatory response [10, 158, 159], that interferes with insulin and its receptor binding, interrupting later signaling events [10, 160, 161].

3.5.3. The Close Relationship between Age, T2D and AD

Both clinical practice and epidemiological studies have shown that T2D and AD are diseases closely related to aging. Cognitive decline induced by these diseases is manifested in old age, although all studies indicate that underlying neuropathological alterations develop in mild life without clinical symptoms. Risk factors are decisive in youth and adulthood to develop the pathological processes that lead to the diagnosis of T2D and AD. In the aging process of humans, many cellular and molecular involutive alterations have been described, both in peripheral organs and in the CNS. Paradoxically, the CNS, with almost no neuronal renewal, can better resist senile involution because of its high capacity for adaptation demonstrated by neurons and neuroglial cells in very different physiological and pathological scenarios [162-175]. The capacity to maintain cognitive functions in the elderly is well known, even in very advanced ages (very old individuals). However, the deterioration of other organs and functions could be very noticeable [176]. There is no single model of normal "physiological" aging in humans versus "pathological" aging. However, there is a tendency to focus the aging of the individual on the involution/degeneration of the cognitive functions of the brain. Dementia can be considered the maximum expression of pathological aging; there is a slowly progressive process of neurodegeneration behind it. The "normal", "healthy" or "physiological" senile brain has morphological and functional characteristics that make it different from the brain in adulthood. There are changes in the different neuronal and neuroglial cells, in their responses and their relationships [70, 106, 126, 177-180]. In physiological aging of the CNS, defined as a mild involution of cognitive functions without the presentation of AD or cerebrovascular neuropathology, reactive changes in neuroglial cells, BBB dysfunctions, alterations in synaptic connections, neuronal dysfunctions, neuronal and neuroglial metabolic alterations, apoptosis and decreases in neuronal density are observed. Oxidative stress and mitochondrial dysfunctions are always related to all these involutive/degenerative situations (Fig. **3**). There is a considerable increase in "senescent" cells that tend to dysfunction and/or cell death. It is in this new scenario that the pathogenic processes induced by diseases develop. In most cases, the induced alterations by other diseases will have an accelerating effect on senile degeneration (T2D case) or a clear shift towards neurodegeneration (T2D-AD case). One must also consider the decrease in the capacity of neuronal and neuroglial response and adaptation that favors neurodegeneration. In this situation, all the factors that promote neu-

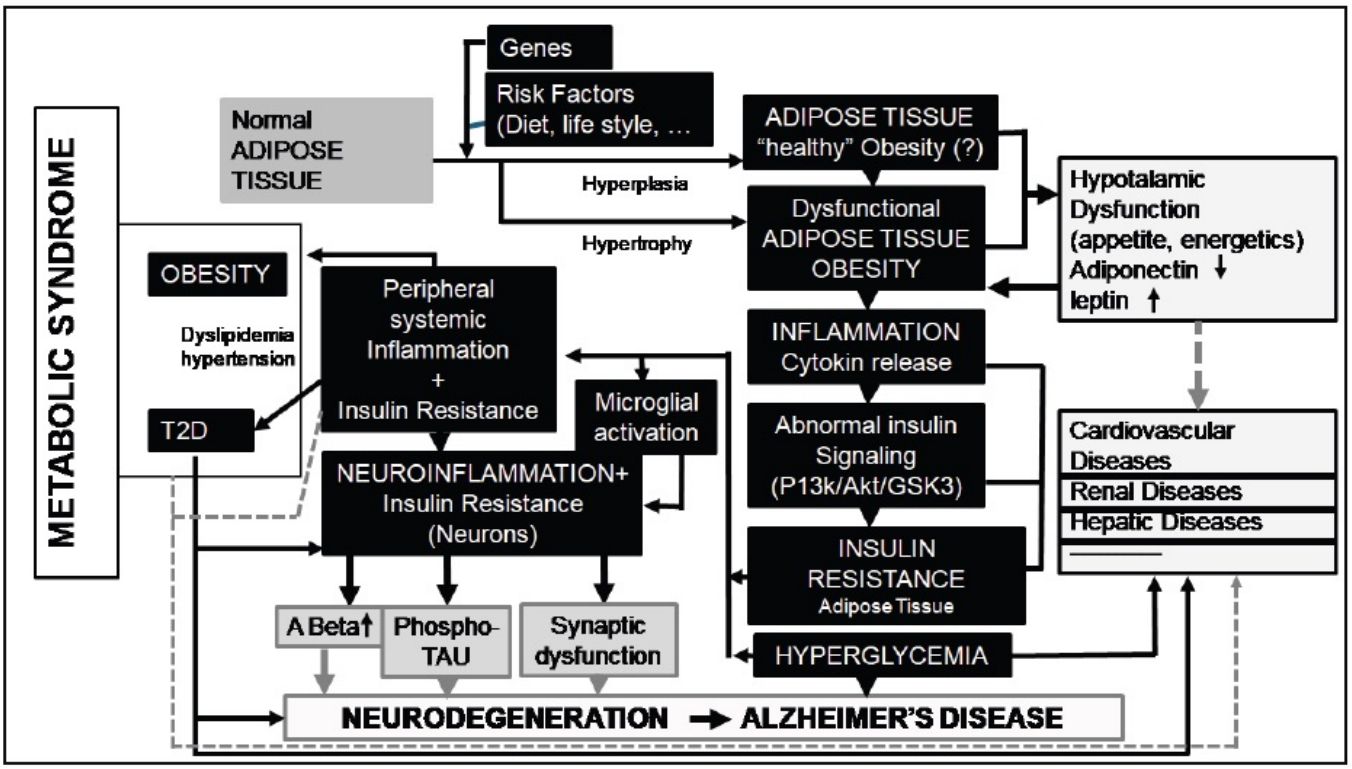

Fig. (2). Relationship of Obesity with Type 2 Diabetes and Alzheimer's disease. Possible association pathways and pathogenic mechanisms. Under normal conditions, each individual has specific peripheral areas of adipose tissue made up of adipocytes (cells responsible for accumulating fat and regulating blood glucose and lipids). The number of adipocytes is determined from the prenatal period until adolescence and subsequently stabilizes. Due to GENETIC FACTORS or the effect of RISK FACTORS (INADEQUATE DIET OR LIFESTYLE), NORMAL ADIPOSE TISSUE can increase in volume in its normal areas of location or appearing in other peripheral areas (ectopic adipose tissue -or fat). Adipocytes can increase in number (hyperplasia) or size (hypertrophy). This anomaly is called OBESITY. Some authors consider that "healthy obesity" can exist without inducing pathological changes in the body; most deny it. Highly hypertrophic adipocytes are generally dysfunctional. Obesity, as a pathological process (DYSFUNCTIONAL ADIPOSE TISSUE), is accompanied by low-grade chronic INFLAMMATION that causes abnormalities in the INSULIN SIGNALING PATHWAY and favors the appearance of a state of INSULIN RESISTANCE in the adipose tissue and HYPERGLYCEMIA in the body. In this pathological scenario, different processes of PERIPHERAL SYSTEMIC INFLAMMATION + INSULIN RESISTANCE (renal, liver, muscle) but also of the CNS can occur. In the first case, localized pathological disorders can be induced in certain organs or systems (cardiovascular, renal, hepatic, *etc.*) or generalized disorders such as the so-called Type 2 Diabetes (T2D) or the so-called METABOLIC SYNDROME (in which OBESITY, T2D, Dyslipidemia and Hypertension coexist). In the case of CNS involvement, after MICROGLIAL ACTIVATION, a process of NEUROINFLAMMATION AND NEURONAL CHANGES DUE TO INSULIN RESISTANCE are triggered that increase amyloid β-protein and phospho-Tau deposits along with synaptic dysfunction, all signs of neurodegeneration, typical of Alzheimer's disease (AD). Insulin Resistance is a metabolic disorder in which cells do not recognize insulin. An insulin-resistant cell does not admit glucose inside, so the blood glucose level increases (hyperglycemia), which in turn stimulates the overproduction of insulin (hyperinsulinemia) in the pancreas, which, over time, leads the body to develop a T2D. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

rodegeneration are key to explaining the final pathology we can observe, and to defining possible pathogenic mechanisms that can be regulated to prevent the advance of neurodegeneration. But always consider the altered morpho--functional situation of neurons, neuroglial cells and the homeostasis of the senile brain. Many pathogenic mechanisms of T2D are common to AD, and/or many alterations of T2D trigger or aggravate pathogenic mechanisms of AD. All these mechanisms are related to physiological processes of senile involution and will condition a change towards a neurodegenerative development that can lead to dementia: increase in pro-inflammatory factors, insulin resistance, hyperglycemia, oxidative stress, BBB dysfunction, neuronal functional impairment, neuroglial dysfunctions, *etc* [181].

Two aspects are separate issues to consider in this matter. First, the importance of chronic peripheral inflammation (which is often underestimated or minimized when trying to assess obesity, subclinical dysmetabolism, or unhealthy lifestyle habits - excessive consumption of sugars or fats, sedentary lifestyle) that can alter the CNS from youth to levels where it cannot remain resistant to neurodegeneration. Warnings are being issued because of the large increase in cases of T2D in young people, the pathogenic consequences of which are considered very worrying. Second, the importance

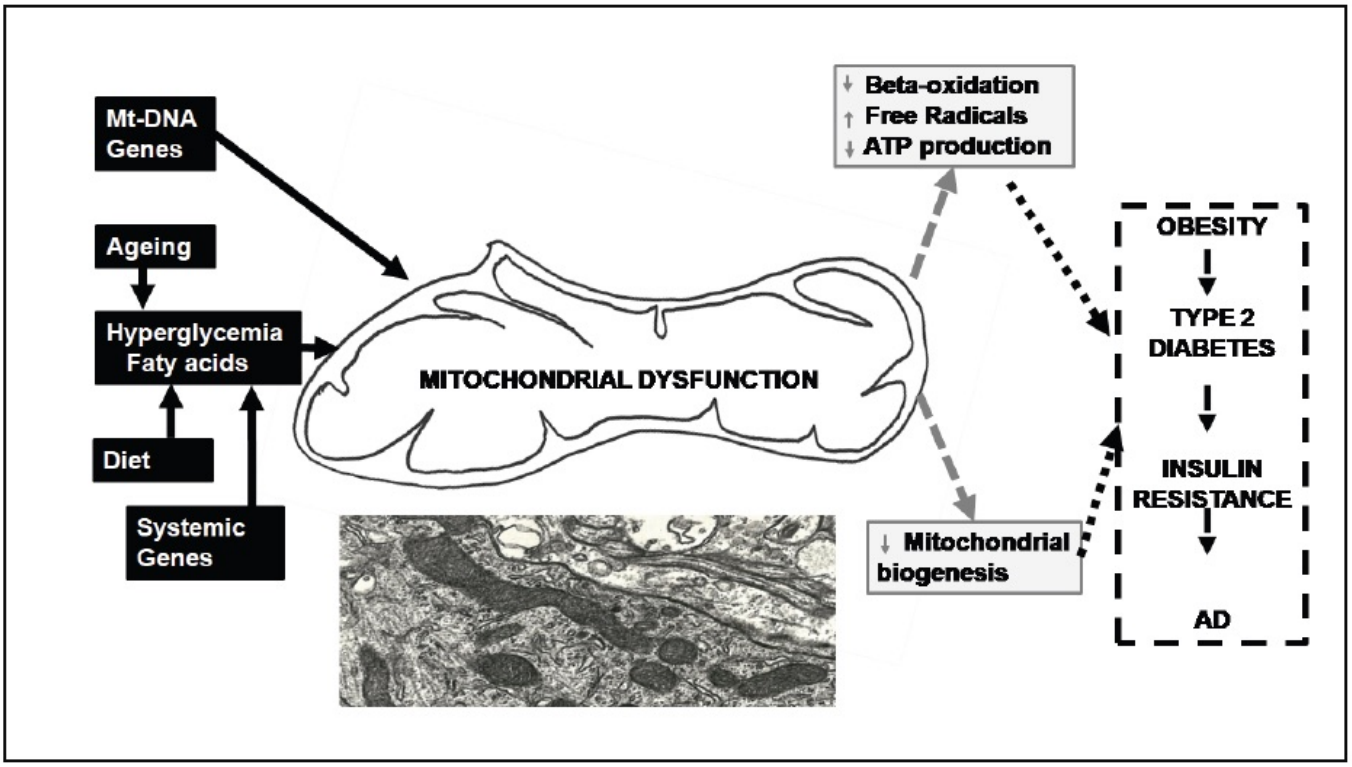

Fig. (3). Mitochondrial Dysfunction. Multiple factors are known to cause mitochondrial dysfunction. These factors include DNA mutations and polymorphisms in the mitochondrial genome as well as nuclear mutations in genes producing mitochondrial associated proteins, age involutive processes and increased free fatty acids and/or hyperglycemia (of different origin). Dysfunctional mitochondria produce impaired β-oxidation, reduced ATP, and increased Free Radicals (reactive oxygen and nitrogen species). Moreover, decreased mitochondrial biogenesis can be observed. These events may contribute to obesity, type 2 diabetes (T2D), insulin resistance and AD in elderly. [Image: cytoplasm of a pyramidal neuron from layer VI of the cerebral frontoparietal cortex (rat) where a high density of mitochondria is observed. 12,000 x]. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

of the subclinical, subtle, and unnoticed underlying metabolic dysfunction in cases of AD that do not appear to be related to diagnosed peripheral metabolic disorders but that present insulin resistance and related alterations when studied in depth postmortem. From these studies has emerged the concept that considers AD as a variant of diabetic metabolic disease (T3D) [181].

3.5.4. Common Epigenetic Modifications in T2D and AD

As was indicated, epigenetic reprogramming, a dynamic process, predicts the long-term health outcomes of diseases. It involves shifts between healthy and diseased states governed by intricate epigenetic networks [133]. Three different epigenetic mechanisms have been identified: DNA methylation, histone modification and RNA-associated silencing:

DNA Methylation participates in both AD and T2DM, highlighting their potential implications for disease pathogenesis and therapeutic strategies. Changes in DNA methylation levels at specific gene promoters influence key pathways such as insulin signaling, inflammation, and amyloid β-protein metabolism, all of which are involved in both diseases. Methylation analysis has shed light on genes potentially implicated in insulin resistance and AD [75]. Histone modifications such as histone acetylation, methylation, and phosphorylation have been implicated in AD and T2D. These alterations can affect chromatin structure and gene expression, influencing processes such as insulin sensitivity, ß--cell function, neuroinflammation, and synaptic plasticity [33, 182, 183]. Dysregulation of microRNAs (miRNAs) has been associated with both AD and diabetes [184]. The miRNAs, small non-coding RNAs that post-transcriptionally regulate gene expression, can target genes involved in insulin signaling, amyloid β-protein metabolism, inflammation, and other pathways relevant to both diseases [185, 186]. There is an increasing body of evidence demonstrating the role of diabetes-associated chromatin modifications in epigenetic mechanisms and their potential significance in the pathogenesis of diabetes. It suggests that individuals with diabetes may exhibit alterations in the expression of chromatin modification enzymes in the brain compared to those without diabetes. These changes coincide with altered expression of proteins involved in synaptic function, such as synaptophysin, which is indicative of potential synaptic dysfunction. Moreover, similar changes in chromatin modifications and synaptic protein expression are observed in mouse models of T2MD. Importantly, these changes are associated with increased suscepti-

bility to AD neurodegenerative insults, such as oligomeric amyloid β-protein and phosphor-Tau protein. This suggests a potential causal link between diabetes-induced epigenetic mechanisms and neuropathological mechanisms leading to increased susceptibility to insults associated with neurodegenerative or vascular impairments, providing an epigenetic explanation for the increased risk of people with diabetes developing dementia [187].

The expressions measurement of epigenetic chromatin modification enzymes in the brains of diabetic patients suggests that epigenetic alterations in histone deacetylases (HDACs) cause decreases in H3 and H4 acetylation at the proximal promoter of pancreatic and duodenal homeobox factor 1 (Pdx-1) in pancreatic β-cells, leading to defects in glucose homeostasis and insulin resistance and eventually to T2D. Similarly, histone modifications of glut4 mediated by DNA methyltransferase (Dnmt) and HDACs result in reduced transcription of GLUT4, contributing to insulin resistance and T2D development, particularly in intrauterine growth-restricted offspring. Epigenetic alterations in diabetic brains make the brain not only more susceptible to amyloid β-protein but also to aberrantly aggregated neurofibrillary tangles made of hyperphosphorylated Tau, the other pathological feature of AD. It is also possible that these changes make the brain vulnerable to infarction and small--vessel disease, which may lead to vascular dementia and other insults such as inflammation and AGE products that are prevalent in diabetes [187].

Another study concludes that diabetes alters acetylation homeostasis *via* upregulation of HDACs, decreasing memory and synaptic plasticity-related proteins like brain-derived neurotrophic factor (BDNF), synaptophysin (SYP), postsynaptic density-95 (PSD-95), causing diabetes-associated cognitive decline. Further, the histone deacetylases (HDAC) inhibitors attenuate diabetes-induced memory impairment in T1D and T2D mice. Also, HDAC modulators function as therapeutic targets to reprogram memory-associated impairment in diabetes [188].

Overall, this highlights the importance of epigenetic mechanisms, specifically, chromatin modifications mediated by HDACs and DNA methyltransferases, in the pathogenesis of diabetes. Understanding these epigenetic alterations may provide valuable insights into the molecular mechanisms underlying diabetes development and could lead to the identification of novel therapeutic targets for T2D. While these genes and epigenetic modifications are shared between AD and T2D, their specific roles and contributions to disease pathogenesis may vary. Further research is needed to fully elucidate the molecular mechanisms underlying the relationship between these conditions and to identify potential therapeutic targets for intervention.

Environmental factors like diet and exercise wield significant influence in shaping these epigenetic modifications, impacting developmental trajectories and lifelong health outcomes. Unlike changes in DNA sequence, epigenetics governs gene activity, thereby determining phenotype variations despite identical genomes across cells [189]. It is very important to highlight that metabolic and functional behavioral changes induced in cells by epigenetic mechanisms can operate over very long periods of time and outside the presence of the inducing causes. A recent article [190] showed that "adipose tissue retains an epigenetic memory of obesity after weight loss." This is of capital importance for understanding both the course of complex diseases such as T2D-AD and for establishing treatments. This aspect will be discussed in more detail in the second part of the monograph.

Depending on their quality and quantity, diet and exercise can either promote or hinder proper physiological functioning. Therefore, implementing tailored dietary and exercise regimens emerges as a novel approach to modulate epigenetic processes and mitigate the onset or progression of human diseases.

Phytochemical compounds found in plants, particularly fruits and vegetables, have garnered attention since some natural compounds have exhibited promising epigenetic effects. However, there has been limited research on the pleiotropic role of natural products in modifying epigenetic pathways related to brain disorders. Bioactive substances derived from food have the potential to influence both epigenetic processes and their associated targets.

3.5.5. Common External Causes of T2D and AD

Diet and personal lifestyle are important determinants for the development of T2D and AD. These risk factors have an important and direct involvement in the presentation of T2D and AD or an indirect implication through epigenetic modifications on the development of the clinical course of both pathologies, as well as the characteristics of the clinical-pathological manifestations in each individual. These extrinsic causes can modify epigenetic mechanisms that regulate the expression of genes related to the pathogeny of T2D, AD, or T2D-AD (section 3,2). Preventive medicine focuses largely on advising and designing a "healthy" living environment appropriate to each age and individual situation. This topic will be fully developed in the second part of the review. Inadequate diets and sectarianism have long been shown to induce T2D and AD. Excess intake, both in quantity and abuse of carbohydrates or lipids, leads to a significant alteration in the general metabolism, giving rise to pro-T2D or pro-neurodegenerative "induced metabolic diseases" (AD and AD-relative). In the field of metabolic diseases, one of the main pathologies induced by diet is Obesity, which is discussed below. It could be said that these two risk factors, inadequate diet and personal lifestyle, directly produce obesity and this, in turn, T2D. T2D indirectly leads to AD, a disease that can be directly accelerated by these aforementioned risk factors. Clinical evidence suggests that lifestyle factors, in particular nutrition, are decisive in AD control and prevention [191-193].

4. COMMON MOLECULAR PATHWAYS AND THERAPEUTIC TARGETS

Alzheimer's disease and Type 2 Diabetes Mellitus share common molecular pathways and therapeutic targets,

suggesting an interaction between the underlying pathological mechanisms of both diseases [194]. Some of these common molecular targets are included in (Fig. **1**) and described as follows.

4.1. Insulin Resistance and induced Pathogenic Mechanisms

Insulin and its signaling pathways regulate glucose metabolism in all cell types. In the brain, it maintains the life and physiological function of neurons, glial cells neuronal circuits, influencing cognitive function and synaptic plasticity. Dysfunction in insulin signaling contributes to the development of both T2D and AD [72, 195, 196] and is considered the molecular link between T2D and AD [31, 196]. It appears that most of the insulin used by the brain comes from pancreatic secretion. Still, it is also the main cause of T2D and AD by an important number of researchers [14, 16, 20, 26, 31, 61] and has been defined as the inability of brain cells, either neurons or glia cells, to respond to insulin action due to deficient insulin receptor signaling [197]. This definition and other similar ones from different authors are certainly ambiguous and do not define either the etiology(ies) of this pathogenic mechanism or the different implications in each cellular subtype (neuronal or glial in the case of the CNS). Brain insulin resistance was further characterized by reduced and altered expression/response not only by insulin but by other related IGF polypeptides [198, 199]. Also implicated in impaired brain insulin metabolism are reduced neuronal glucose uptake and reduced expression of glutamate transporters [197, 200]. Insulin resistance demonstrated in Alzheimer's brains in clinical cases that are somehow related to peripheral metabolic disorders (metabolic syndrome, T2D, obesity) can be explained by a generalized alteration that affects all insulin (and IGF) receptors. An "insulin-resistant brain state" [201, 202] has even been observed in cases of coexisting metabolic syndrome (MetS) and MCI, as well as a statistically significant correlation between plasma insulin level and plasma neurotoxic amyloid β-protein 1-42 (not displayed in healthy controls) [203]. The fact (which is absolutely unquestionable) that insulin resistance is observed in AD brains not related to peripheral glucose (and lipid) dysmetabolism is more difficult to explain. Insulin resistance has been demonstrated in astrocytes [204] and neurons. These findings are the fundamental basis for the definition of AD as type 3 diabetes, *i.e.,* diabetes mellitus specifically developed in the brain. In these brains, the insulin receptor and IGF-1 receptor were similar to those of controls; however, tyrosine kinase activity, a signal transduction mechanism common to both receptor systems and essential for the fulfillment of their physiological functions, was reduced [205]. Insulin resistance not only affects glucose metabolism but also causes other metabolic disorders and oxidative stress, which induce neurodegeneration. Insulin resistance also appears to be an essential pathogenic mechanism in AD but remains poorly understood. In animal models of T2D and AD, it has been more precisely demonstrated that insulin resistance develops during the pathogenic course [206]. Additionally, animal studies have shown that administering 7,8-dihydroxyflavone to AD models improved cognitive function by reversing insulin resistance [207].

Of the different intracellular insulin signaling pathways, the one most implicated in the development of insulin resistance is the so-called IP3/Akt signaling pathway [206, 208-212]. The decrease and/or dysfunction of Akt isoforms (see neuroglial dysfunctions) induces a great level of insulin resistance, and in animal models, its overexpression reverses the effects of insulin resistance. Another important insulin signaling pathway is the so-called mTOR, whose dysfunction has been highlighted in an important work by de la Monte, 2023 [181] as the most important pathway for the development of CNS dysmetabolic disorders leading to AD, especially when peripheral metabolic disorders are not manifested. mTOR dysfunction may be a fundamental basic component to define AD as T3D.

The major direct effects of insulin resistance in AD are hyperglycemia, which induces the production of AGEs (advanced glycation endproducts), oxidative stress, and neuroinflammation, as well as hyperinsulinemia [212] that produces Akt involution/dysfunction and activation of GSK3 (with increased hyperphosphorylation of TAU protein) and deactivation of IDE (which induces increased accumulation of beta protein in CNS due to lack of degradation of this protein) [10, 65, 67] (Fig. **1**).

Insulin resistance enhances the deposition and toxicity of Abeta protein by inducing pathogenic-related changes. The plasma β-site APP-cleaving enzyme 1 (BACE1) levels and APP levels of T2D patients, with or without cognitive impairment, are significantly higher than those of normal subjects. Moreover, the main degrading regulator of Aβ protein, insulin-degrading enzyme (IDE), is downregulated, and the MAPK pathway, involved in the transport of Abeta protein, becomes dysfunctional [213]. In parallel, insulin resistance promotes the development of Tau pathology. Tau can be phosphorylated by several kinds of protein kinases, including GSK-3β, one downstream component of the PI3K/AKT insulin signaling pathway. This kinase stays inactive under normal conditions. However, when insulin resistance is developed in T2D, GSK-3β becomes active and then phosphorylates Tau [214].

4.2. Disruption of Glucose and Energy Metabolism

Dysfunction in glucose and energy metabolism is a common feature of both T2D and AD. Alterations in glucose utilization and the ability to obtain energy from cells may contribute to neurodegeneration and cognitive dysfunction in both diseases [215, 216]. Impaired cerebral glucose metabolism is reported in T2D, and its consequences account for most of the structural and functional anomalies of AD [217].

4.3. Inflammation and Neuroinflammation

Both T2D and AD are associated with chronic inflammation (Fig. **4**). This chronic inflammation could be said to comprise two subprocesses, the peripheral one that affects various organs to varying degrees (which is usually initial in

the most frequently observed and studied pathogenic course of obesity - T2D-AD - see obesity) and the central one that affects the brain and is the most frequently studied in the course of AD and T2D-AD cases leading to cognitive deficit/dementia. The chronic peripheral process induces two theoretical but practically interrelated pathogenic processes: first, a morphofunctional disruption of the BBB, and second, a dysfunction of neuroglial cells. The first subprocess causes the fall of brain protection against peripheral neurotoxic agents, and the second subprocess, the onset and/or acceleration of AD originated by other cause(s). In a scenario where the neuropathological alterations of T2D (and related metabolic problems) and AD are manifested, it can be said that the BBB will suffer greater damage, induced "from both sides" (extravascular and intravascular) with the consequent reflection in the cerebrovascular pathology of T2D-AD, which is repeatedly discussed in this review. The neuroinflammatory process is closely linked to neuroglial dysfunction, which is analyzed below. Brain inflammation (or neuroinflammation), characterized by the activation of glial cells and the release of pro-inflammatory cytokines, contributes to the development and progression of AD. The overexpression of proinflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukins such as interleukin 6 (IL-6), and acute phase proteins are present in AD brain [107]. These proinflammatory mediators increase the neurological damage to the brain, and a synergistic pattern between AD senile plaques and proinflammatory is observed. Moreover, systemic inflammation and immune response activation significantly influence brain diabetes pathogenesis. Hyperglycemia, insulin resistance, and dyslipidemia trigger a cascade of detrimental processes, including oxidative/nitrosative stress, endoplasmic, and mitochondrial stress, amplifying cellular damage (Fig. **3**). These interconnected factors create vicious cycles, perpetuating diabetes progression. Glucotoxicity, insulinopenia, and lipotoxicity induce oxidative/nitrosative stress in neurons, activating various kinases such as protein kinase C (PKC), mitogen-activated protein kinase (MAPK), and Jun N-terminal kinase (JNK), as well as redox-sensitive transcriptional factors, including NF-κB. These, in turn, catalyze the production of pro-inflammatory cytokines and chemokines, including proinflammatory interleukins (IL-1β, IL-2, IL-6, IL-8), tumor necrosis factor-α (TNF-α), and chemokine ligands, fueling inflammation and exacerbating neuronal damage [71, 218, 219].

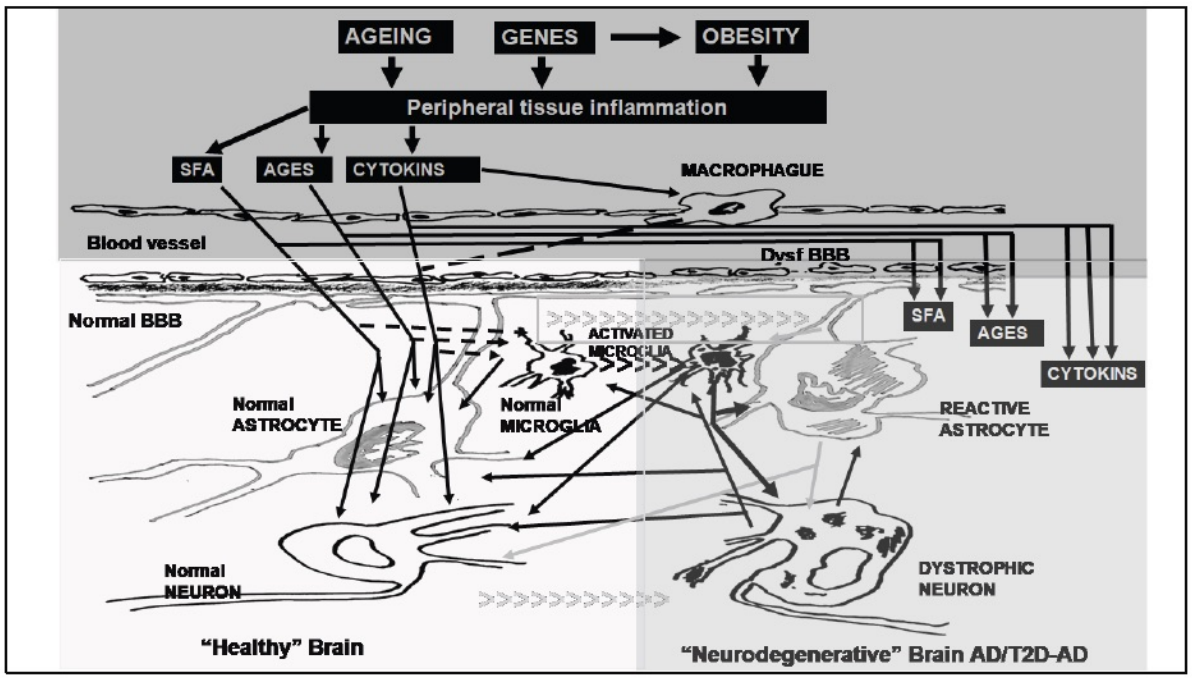

Fig. (4). The T2D brain: peripheral inflammation, neuroinflammation and neurodegeneration. The brain in T2D undergoes a neurodegenerative process similar to that observed in AD. The neuroinflammation that it manifests is considered a result of the inflammation suffered by peripheral tissues that gives rise to T2D. In the first phase, cytokines (CYTOKINS) from activated macrophages, as well as cytokines, saturated fatty acids (SFA) and advanced glycation endproducts (AGEs) produced in pathological peripheral tissues, cross the blood-brain barrier (normal BBB) initiating the neuroinflammatory process (left panel) by activating microglia cells and modifying functions of astroglia and neurons. The local inflammatory response may initially be protective, but if it persists it becomes neurotoxic. In a second phase (right panel), the integrity of the blood-brain barrier is lost (dysfunc BBB), making the brain highly vulnerable to imbalances in the peripheral inflammatory system. SFA, AGEs and Cytokines such as tumor necrosis factor alpha (TNF-α) and interleukins (IL-1β, IL-6) cross in a very high concentration the dysfunctional BBB (dysfunc BBB) activating microglia and causing neuroglial and neuronal dysfunctions typical of AD. [small arrows = [transition from normal cells to reactive cells (astroglia and microglia) and from normal neurons to dystrophic neurons]. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

4.4. Oxidative Stress

Oxidative Stress is implicated in both T2D and AD development and plays a crucial role in the development of insulin resistance and pancreatic β-cell dysfunction [220]. Oxidative stress occurs due to an excess of ROS produced by an imbalance between ROS production and antioxidant defense, which damages cells and tissues, contributing to cellular dysfunction and the neurodegenerative process [221, 222]. Hyperglycemia induces the production of free radicals or oxidative/nitrosative toxic radicals or ROS through several pathways, including the mitochondrial electron transport chain (see later) and PKC activation [223] (Fig. **3**). ROS impairs insulin signaling pathways, leading to insulin resistance and pancreatic β-cell dysfunction [224] as well as endothelial dysfunction, inflammation, and diabetic complications development [225]. The brain is vulnerable to oxidative damage due to its high metabolic rate, high levels of polyunsaturated fatty acids, and relatively low levels of antioxidant defenses [226]. Another source of ROS production directly mediated by amyloid β-protein involves microglia activated in the brain during an inflammatory response to the deposition of extracellular amyloid plaques [227, 228]. Simultaneously, ROS excess enhances Aβ accumulation, inducing oxidative damage to proteins, lipids, neuronal membranes, and nucleic acids [229], contributing to neuronal dysfunction, synaptic loss, and neurodegeneration characteristic of AD [212, 230, 231].

4.5. Mitochondrial Dysfunction

An increasing amount of research shows that mitochondrial dysfunction presents the link between T2D and AD [26, 232-234] (Fig. **3**). Mitochondria are responsible for adenosine triphosphate (ATP) production, β-oxidation of fatty acids, modification of phospholipids, biosynthesis of metabolites, intracellular calcium buffering and signaling, ROS generation, immune responses, apoptosis, and stem cell reprogramming. Moreover, mitochondria play a critical role in neuronal membrane excitability, neurotransmission, and plasticity [196]. Altered mitochondrial morphology, distribution and movement contribute to oxidative stress and synaptic dysfunction [235-237] and impairs brain metabolism as well as mitochondrial biogenesis in AD subjects [238]. Calcium dyshomeostasis and dysregulation of MAPK signaling pathways are also important players in AD and T2D [239]. In summary, studies suggest that altered mitochondrial quality control contributes to the pathogenesis of T2D and AD, highlighting the role of mitochondrial dysfunction in diabetes-related cognitive impairment [240]. Mitochondrial dysfunction acts as a trigger for AD pathology, contributing to neuronal dysfunction and neurodegeneration [241]. The mitochondrial pathological changes in both diseases (or the different forms of one basic but complex metabolic disease) in different periods of the clinic-pathological courses are very similar [239, 242]. Otherwise, mitochondrial dysfunction may be a consequence of insulin resistance and/or the accumulation of misfolded proteins, such as amyloid plaques, in AD. The Aβ-plaques and phosphorylated Tau contribute to defective autophagy and mitophagy, leading to mitochondrial dysfunction in AD [243].

4.6. Neuroglial Dysfunctions

Neuroglial cell dysfunction is a key factor in the development of morphofunctional alterations (neurodegeneration and subsequent cognitive decline/dementia) in both T2D and AD (or T2D-AD). This dysfunction has been shown to present practically identical characteristics, except for some nuances, and has been mostly studied in animal models of T2D, AD and T2D-AD [70]. The literature on neuroglial changes in human AD has been enormously abundant in recent decades since neuroinflammation has been included in all pathogenic cascades leading to AD. On the contrary, in humans, T2D or T2D-AD is not very abundant. However, important studies on models of these disorders have led to the recognition in almost all studies on T2D of the seminal importance of alterations of the neuroglial cells underlying neuroinflammatory phenomena (rodents [244-251]; monkeys [252-254].

As is well-known, neuroglial cells constantly accompany neurons throughout their life [106, 107]. They are not only their morphological and metabolic supports, but they are also co-participants in all neuronal responses, in the maintenance of neuronal circuits and synaptic connections, and in maintaining the optimal environment for the correct functioning of the nervous system [106, 180]. In the face of potential neurotoxic situations or substances, neuroglial cells react to return the nervous system to normal [106, 107, 172, 173, 180, 255-257], including an inflammatory process of a neuroreparative nature. If this fails, the glial cells continue to react but in a neurotoxic manner, favoring the development of different pathologies [258-262]. This is the case with T2D, AD and T2D-AD. Astroglia and microglia alterations and their toxic responses (to a large extent mediated by proinflammatory molecules such as cytokines, chemokines, glycated end products and free radicals) are the main inducers in the genesis and development of CNS neurodegeneration in metabolic pathologies (obesity, metabolic syndrome, and T2D). On the other hand, the alterations induced by insulin resistance and hyperglycemia, typical of T2D, have a pathological response in the glial cells. It should be noted that several studies have pointed out significant differences between the sexes in T2D and its transition to T2D-AD [263].

Common pathological alterations of astrocytes in the T2D-AD complex correspond to aberrant responses that induce neurotoxic changes and significant BBB alterations. Astroglial cells suffer from insulin resistance and are sensitive to hyperglycemia [204, 264]. Some morphological alterations (astrogliosis) and truly relevant phenotypic changes have been described in T2D. Various intracellular signaling systems are modified [204, 265], and an increased release of cytokines and chemokines, NO, and oxidative/nitrosative reactive products are noted. The PI3K-Akt insulin signaling pathway is the most important in regulating glucose homeostasis in the CNS [206, 210, 211]. The down-expression or dysfunction of this pathway is a main pathogenic factor in both T2D and AD that causes the development of insulin resistance and the alteration of other insulin signaling-dependent cellular functions in neurons and neuroglial cells of the

CNS [206, 210, 211]. It has been shown that astrocytes specifically express one isoform, Akt2, overexpressed in reactive astrocytes [208, 209], but that its deficiency or dysfunction causes astrocytic dysfunction and the consequent alteration of brain nervous tissue [266]. In several experimental models, insulin resistance has been reversed by activating or overexpressing Akt2 [212]. A relevant study by Bury *et al.*, 2021 [148] has shown new gene expression in astrocytes closely related to blood vessels and endothelial cells in T2D cases with low cognitive deficits.

Common alterations in oligodendroglia cells have also been described in T2D and AD. Oligodendrocytes are well known for myelin sheath formation and delivering energy-rich metabolites to axons [267]. Oligodendrocyte degeneration and myelin deterioration are noteworthy features of both AD and T2D [268, 269]. It has also been found that in these scenarios, an oligodendroglial cyclin-dependent Kinase 5 (Cdk5) is related to neuroinflammation and neurodegeneration. The close relationship between T2D and AD in oligodendroglia behavior suggests that Cdk5-mediated oligodendrocyte myelin breakdown and the associated neuroinflammation are important links between Type 2 Diabetes and Alzheimer's disease [270]. Theoretically, in these pathologies, the oligodendrocyte precursors should have the ability to prevent neuropathological development, but it has been proven that they collaborate in the pathogenesis [271, 272]. It has been shown that acting against their proliferation (genetically or pharmacologically eliminating these cells) results in an improvement in cognitive deterioration in experimental models [271, 272].

Common reactive responses in microglial cells have been observed in T2D and AD, but specific differences are also observed. Human studies on alterations of microglia in the T2D and T2D-AD situations are scarce but essential information has been obtained in the study of the experimental models. The phenotypic changes of microglial cells in the T2D-AD complex are especially related to dysfunctions of neuronal connections, with the maintenance of a pro-inflammatory toxic environment and with the disruption of the elimination systems of toxic products such as amyloid and cellular debris. In diet- or genetic-induced obesity or T2D models, activation and/or dysfunction of astroglial and microglial cells are always present. In an obesity model, it has been demonstrated that IL-1β originating from microglia promotes neuroinflammation and impairs the cephalic phase of insulin release [127]. In some obese models, changes in brain insulin resistance and microglial responses can be obtained by phenolic substances [128] or by blocking selected microglial receptors [129]. A lower capacity of reactive microglia to phagocytose, the amyloid protein deposited in plaques, has been observed in several models [70, 264]. In dietary obesity, single-nuclei transcriptomics of the mouse cortex reveals the existence of dysregulations of microglia, more intense than of other cell types (neurons and other neuroglial cells). Most relevant, these phenotypic changes are like those observed in AD (humans and models) [273].

It is important to note that in various models of T2D and T2D-AD, neuroglial dysfunctions, especially microglial dysfunctions, manifest before other neuropathological manifestations appear, especially alterations related to disturbances in amyloid and Tau protein formation and processing [70]. This could indicate that genetic or epigenetic factors involved in the T2D-AD complex may function as triggers of AD before other neuropathological mechanisms more related to metabolic dysfunction operate. Moreover, as a general rule, the gene expression changes in microglia and astroglia from high-fat diet/obesity and T2D animal models are similar to those observed in humans.

5. CONTROVERSIES IN THE AD AND T2D CLOSE RELATIONSHIPS

In the previous sections, it has been presented that T2D and related metabolic disorders such as obesity, prediabetes, or the "Metabolic Syndrome" induce cognitive decline and AD in humans. This has been confirmed by studies on T2D, AD, and T2D-AD models, which have manifested common pathogenic mechanisms to develop a neurodegeneration quite similar to human AD. But other studies conducted to clarify the T2D, and AD relationships seem to indicate that the greatest damage to the T2D brains is due to the direct interaction on the structure and function of the vascular-CNS connection [148, 274-277]. That is, T2D would induce cerebrovascular dementia, although the neurodegenerative process could later manifest pathological features of AD [274-277]. This would go against the concept that AD is a type 3 diabetes. Authors who support the cerebrovascular theory consider alterations in small cerebral vessels, in the BBB (astroglia and endothelial cell damage and dysfunction) and the presence of brain infarcts and hemorrhages of varying intensity to be more important than neuronal and neuroglial dysfunctions and the neuroinflammatory process common to T2D and AD. An important proportion of these authors do not deny the close connection between both pathologies, but they do not consider the diagnosis of AD to be well-founded in many cases of T2D [278]. It has even been proposed that in T2D, there is a new type of cognitive deficit/dementia that is different from AD [278]. Some molecular alterations have been considered relevant for a clear difference between T2D and AD, but all of them are questionable. The deposition of pancreatic amylin, typical of T2D, is added to amyloid β-protein deposits, increasing the amyloid burden and their deleterious effects: neuronal degeneration, apoptosis and neuroinflammation [279-283]. This molecule also interacts with the metabolism of the Tau protein and its phosphorylation. Moreover, it has been observed in AD cases that are not well related to peripheral dysmetabolic diseases. The problem may lie more in the interpretation of the observed neuropathological alterations than in the actual existence of radically different morphological and functional changes between T2D and AD. There are also problems (as pointed out in section 2) that come from the selection of T2D and AD cases analyzed in the studies where the clinical history is not usually considered. The clinical history of T2D patients can be very heterogeneous in its

clinical course (pre-diabetes, obesity, MetS, *etc.*; duration of each dysmetabolic phase; lipid dysmetabolism; antidiabetic treatment, non-compliance with treatment, *etc.*) must condition many alterations that can lead to incorrect conclusions. Long treatments with antidiabetic drugs can induce alterations in the pathogenic course of AD or modify the presentation of the characteristic signs of AD [278]. Most of the studied T2D cases with cognitive deficit or AD present a low-degree image of AD-like neurodegeneration associated with cerebrovascular disturbances. The coincidence of these two/three pathologies could lead to death before reaching the most florid development of AD. More complete and in-depth studies should be carried out on this subject to clarify the basis of dementia in T2D-AD. Transcriptomic and gene expression analysis have shown neuronal, glial, and vascular mixed alterations in T2D patients with few cognitive deficits related to AD. For example, a study on six cases of T2D with minimal AD neuropathology (Braak 0-II) demonstrated significant dysregulation of key signaling pathways associated with T2D and AD. The alterations involve neurodegenerative processes in neurons, astrocytes and endothelial cells and are compatible with cellular and molecular mechanisms present in T2D and AD. Mitochondrial involution and cellular senescence are also observed.

Most authors believe that the experimental results obtained in the study of normal or transgenic rodent models seem to confirm the identity of the main mechanisms leading to the development of T2D and AD. Indeed, many of the pathogenic mechanisms common to T2D and AD have been known from studies performed in these models. However, the results obtained with the T2D, AD and T2D-AD models are also questioned by different authors because they do not fully represent the reality of the pathology in humans or because some of their results seem to contradict the views on the intrinsic correlation between T2D and AD. The most controversial issues in these studies have been those related to cerebrovascular alterations and the similarities and differences in cognitive deficits and neuropathological responses. Cerebrovascular neuropathological differences have been assessed between pre-diabetes and diabetes situations, as well as an increase in AD neuropathological manifestations when pre-diabetes has induced vascular alterations [284]. Cognitive dysfunctions not related to AD-like neuropathology are attributed to vascular deterioration in some of these studies. The induction of diabetes in some AD models worsened cognitive deficits without an increase or acceleration in parenchymatous amyloid deposits but showed intense cerebrovascular alterations and severe amyloid angiopathy [130, 285]. In all these models, it is considered that diabetes and/or obesity lead to a deleterious morphofunctional dysfunction of the vasculature, leading to a sequence of strokes and a more and more significant cognitive impairment that is unlikely directly dependent on amyloid β-protein deposition. In other contradictory studies, the development of cognitive impairment has been clearly associated with induced and/or accelerated amyloid and or Tau pathology [286, 287].

6. THE METABOLIC THEORY OF AD (T3D), BASED ON THE CLOSE RELATION OF T2D-AD, IN FRONT OF OTHER AD THEORIES

It is very pertinent to ask whether the dysmetabolic theory of AD (T3D type of diabetes) or the conjunction of T2D and AD based on common cellular and molecular pathogenic mechanisms is against or in favor of other theories on AD. It must be considered that AD is a syndrome of varied and complex etiopathogenesis and that it is difficult, if not impossible, to define a unitary theory on the origin of AD. The authors of this review do not believe that there are very significant differences with other theories on AD, but that there are many points of agreement with them and that they reinforce other descriptions of the "pathogenic cascades" (mainly based on the theories of Hardy and Higgins, 1992 [121], that lead to AD, as stated by Hoyer in 2002-2004 [2, 3]. Moreover, the following concordances can be noted:

Many studies on different pathogenic mechanisms taking place in the pathological course of T2D or AD have been considered as an "important link" between T2D and AD. We can point out the coincidences with the most important theories:

- Genetic studies on late-onset AD show that there are genetic alterations or altered gene expressions common with T2D, especially related to disorders in mitochondrial or microglial cells or metabolic dysfunctions [148]. This also occurs in epigenetic changes [288] and in the risk factors inducing them [251, 289, 290].

- The theories that have been unified in the various interpretations of the "amyloid cascade" of AD, such as the aberrant production and catabolization of the amyloid β-protein, the proteinopathy caused by the hyperphosphorylation of the Tau protein, oxidative stress, and neuroinflammation (a consequence of the dysfunction of astroglial and microglial cells), are completely consistent with the changes and pathogenic mechanisms described in T2D.

- Alterations in neurotransmitter systems (aminoacidic, cholinergic, dopaminergic, *etc.*) are always dependent on proper energy metabolism [291-294].

- Mitochondrial dysfunctions that have been described in T2D and AD are common and have been described as "links" in various studies [26, 232-234, 239].

- Senescence of neuroglial and neuronal cells (analyzed in previous sections) shows a strong relationship with preexisting metabolic problems or those that occur in the advanced stages of the life of individuals [291, 295, 296].

7. DISCUSSION

This first part of the monograph "Relationships between Type 2 Diabetes Mellitus and Alzheimer's Disease," has been dedicated to analyzing the common mechanisms that these two pathologies share. Likewise, special attention was paid to studying the relationships they have both at the onset and in the clinical course of each of them, as well as in the T2D-AD complex. This issue is of worldwide relevance

since the number of patients suffering from both pathologies has increased enormously and continues to increase in societies that are more and more aged and where diets and lifestyles are frequently inadequate. The risk factors described clearly lead to a real pathology that, in many cases, is not perceived as extremely dangerous for the development of obesity, metabolic diseases, T2D, and closely related cognitive deficits and AD.

Comparative studies between T2D and AD conducted at very different cellular and molecular levels show, in general, that there are not only many points of contact in their pathogenic courses but also the identity of common pathogenic mechanisms set in motion towards neurodegeneration and subsequent dementia (Fig. **5**).

Firstly, we can point out the coincidences in common genetic and epigenetic markers. T2D and AD are two complex disorders with varied etiopathogenesis in which more and more gene isoforms or altered expressions involved in their pathogenic courses are being discovered. In this genetic context, coincidences have been found between both processes, as indicated in section 3.1. Transcriptomic studies also indicate that there are expression changes in a remarkably high number of genes involved in neurodegeneration in neurons, astrocytes and endothelial cells in cases of T2D with a low level of cognitive deterioration that coincide with those observed in AD [148, 239]. For the purposes of this review, it is important to note that many of these genes are involved in glucose metabolism, the functional architecture of insulin signaling pathways, the development of insulin resistance, oxidative stress production, and mitochondrial dysfunction. All these genetic alterations induce molecular pathological changes observable in T2D and AD.

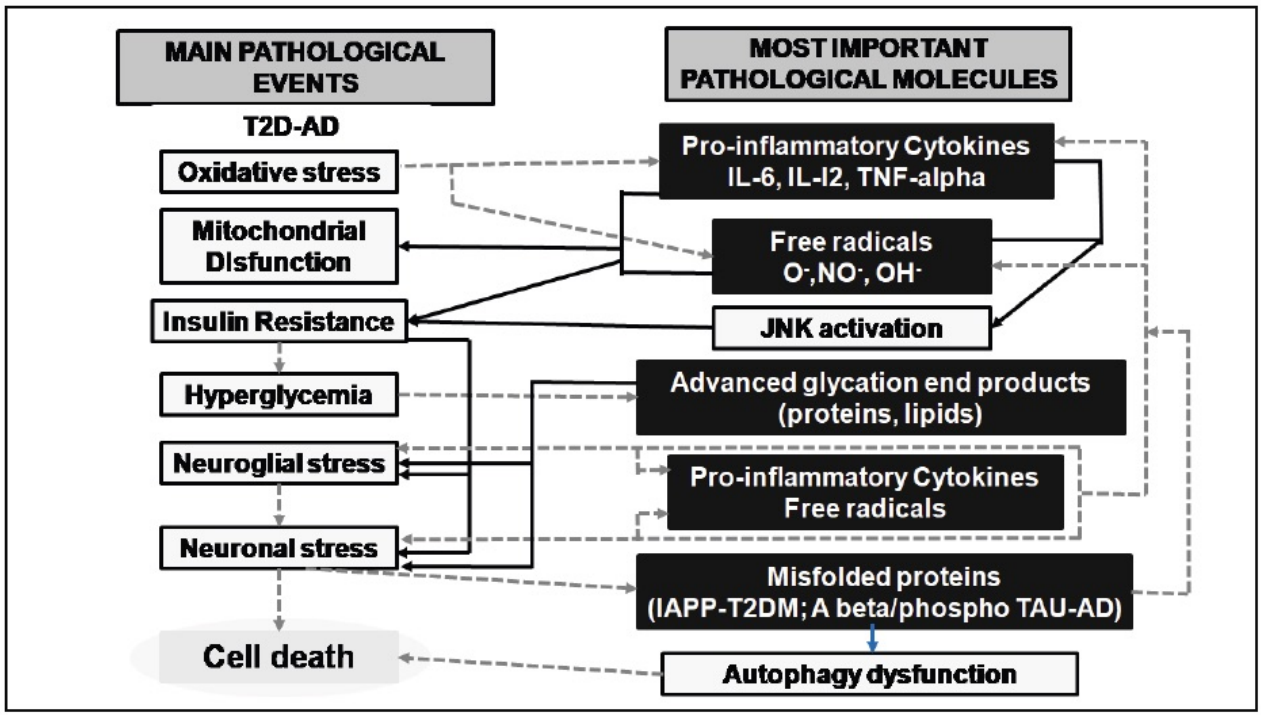

Fig. (5). Collaborative effects between T2D and AD pathological processes in the brain. Main pathological events and most important pathological molecules that are interrelated in the brain of patients with both clinical processes. We have considered six main pathological events ordered according to the most common pathological process in T2DM (oxidative stress, mitochondrial dysfunction, insulin resistance, hyperglycemia, neuroglia stress, neuronal stress), in the complex T2D-AD. Peripheral metabolic inflammatory products induce oxidative stress and mitochondrial dysfunction that triggers neuroinflammation (a complex neuropathological mechanism that involves abnormal neuroglial but also neuronal responses, producing neurotoxins, free radicals, and pro-inflammatory cytokines (blue arrows). Mitochondrial free radical overproduction impairs functions by changing the redox balance. Increased levels of pro-inflammatory cytokines promote insulin resistance *via* JNK (c-Jun terminal kinase) activation. Hyperglycemia (consequence of insulin resistance) favors the formation of toxic non enzymatically glycated proteins and lipids (advanced glycation end-products). Accumulation of misfolded proteins (IAPP in diabetes; amyloid β-protein and phosphor-Tau in Alzheimer's disease) affects autophagy pathways. Oxidative stress, with the correlation of the production of free radicals and proinflammatory cytokines, is in the first phases of the two pathological processes (T2D and AD) and in the most advanced phases of the same, perhaps becoming more acute in the association of both. Neuroglial stress is the main event in the neuroinflammatory process. Neuronal stress reduces cell survival and promotes apoptosis. **Abbreviations:** O2• = superoxide radical; HO• = hydroxyl radical; NO• = nitric oxide radical; IL-6 = interleukin 6; IL-12 = interleukin 12; TNF-α = tumor necrosis factor alpha; JNK = c-Jun N-terminal kinase; AGEs = advanced glycation end products; Aβ = amyloid β-protein; IAPP = islet amyloid polypeptide. (Based on reference 70). *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Similarly, epigenetic studies have shown a remarkably close coincidence between T2D and AD. The most important risk factors, unhealthy lifestyle habits - diet, sedentary lifestyle - seem to act jointly on epigenetic factors inducing T2D, AD and T2D-AD (see sections 3.4 and 3.5).

The most important aspect of the close pathogenic correlation between T2D and AD is the existence of common pathogenic mechanisms (which have been analyzed in section 3.5). These common mechanisms can be interpreted in different ways by different authors: from the simple concurrence of pathogenic links/mechanisms in the pathological course of a disease (as is often the case with the "oxidative stress" in the explanation of any pathology), to the assumption of an absolute coincidence in pathogenic mechanisms between T2D and AD, which may even support the hypothesis that AD can be considered a supertype of cerebral metabolic disease/diabetes (T3D). In our review, we have pointed out five basic pathogenic mechanisms that are included with greater or lesser intensity in the descriptions of the "pathogenic cascades" that individually or jointly lead to T2D, AD or T2D-AD: insulin resistance, disruption of glucose and energy metabolism, oxidative stress, mitochondrial dysfunction, and neuroglial dysfunction and neuroinflammation. To these basic mechanisms, another mechanism could be added, such as the genesis and deposition of misfolded proteins (amyloid protein, hyperphosphorylated Tau protein and amylin). The initial molecules in the formation of the deposits are toxic for neurons and other cells of different tissues, and the deposits themselves may also be toxic. However, there are controversies of interpretation that consider the appearance of deposits as a consequence of the inability to eliminate neurotoxic molecules. Although there are differences in the intensity of these pathogenic mechanisms in T2D, AD and T2D-AD, which will be analyzed later, the authors of this critical review, after working on this topic for years with human material and T2D-AD models, as well as having reviewed the scientific literature for years, consider that the conception of AD as a cerebral metabolic disease is increasingly stronger.

It is also worth highlighting the coincidence in many cases of associated dysmetabolic disorders of greater or lesser relevance and occurring throughout the life of each individual (obesity, metabolic syndrome, metabolic diseases in different peripheral organs, vasculopathies). In advanced stages of adult life and senility, there is also a broader concurrence of involutive/degenerative phenomena such as stress and cellular senescence (which affects both neurons and neuroglial cells) and an altered reactivity of neuroglia. T2D triggers AD-type degeneration in the brain or collaborates and/or aggravates the development of AD originating from other causes (Fig. **6**).

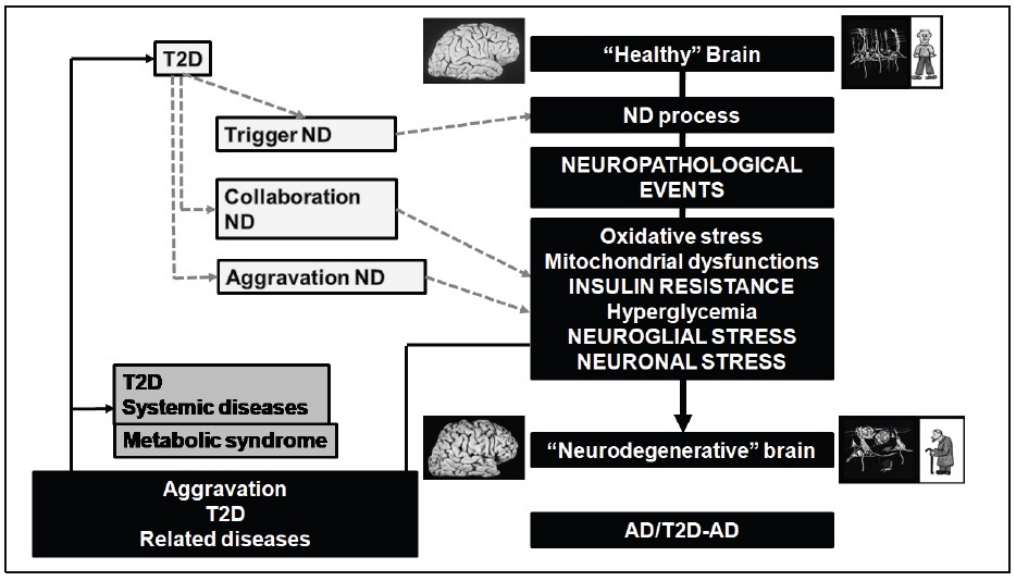

Fig. (6). Pathophysiological relations of T2D and AD may reciprocally influence and reinforce the progression of both diseases. T2D and AD are closely related from their initiation in an individual's life to its end. Each disease has its characteristic symptoms and signs in the different organs and systems, but in the brain, the deterioration induced by its coexistence (T2D-AD) manifests as AD with greater neuropathological degeneration and dementia with an earlier presentation and a longer course. fast in many cases. If we consider that in AD there is a Neuro degenerative process (ND process) that leads from a "healthy" brain to a "Neurodegenerative" brain, through a "cascade" of neuropathological events where INSULIN RESISTANCE is crucial, T2D influences several ways the course of this process. It may be a trigger for ND, a contributor to the development of the cascade of neuropathological events (collaboration ND) or an aggravating factor in the final phase of the ND process (aggravation ND). In turn, the neurodegenerative process produces an aggravation of both T2D, and the diseases of various organs and systems associated with T2D, including metabolic syndrome. This pathological influence is exerted both by brain dysfunction in the regulation of organs and tissues, and by the diffusion of toxic products from the brain in neurodegeneration. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Perhaps one of the most important problems in resolving the identity or divergence of the pathological courses of T2D and AD lies in the poor definition of neuropathology and the type/subtype of dementia in cases of T2D and T2D-AD (or cognitive deficit). This has been pointed out in sections 2 (Difficulties in the study of the pathogenic mechanisms relating the T2D and AD diseases) and 5 (Controversies in the AD and T2D close relationships). It should be noted that studies in human cases of T2D indicate the existence of important cerebrovascular alterations that may lead to classifying dementia as "cerebrovascular type" rather than AD. This has already been indicated in many studies for decades, also including a new category of dementia [297]. However, in most AD cases (if not all), there are signs of more or less intense alterations of the cerebral blood vessels, striking alterations of the BBB, infarcts, and hemorrhages. An important number of cases are classified as "mixed AD-cerebrovascular dementia". In this regard, genetic expression studies are important, as they indicate the similarity of molecular alterations as well as the identity of existing pathogenic mechanisms in order to correctly interpret the results of the studies. As has been pointed out, there may be causes related to other factors that modify the course of T2D and that damage the cerebral vascular system, leading to death before the full development of AD neuropathology. In any case, the characteristic signs of amyloid (including amylin in close deposition with amyloid protein) and alterations due to the formation of phospho-Tau have always been recognized in the cases of T2D studied, as well as insulin resistance and glucose dysmetabolism in AD. The relationship between T2D and AD is independent of vascular involvement [144].

The pathological events we have described that underlie the development of these complex T2D-AD disease(s) (oxidative stress, mitochondrial dysfunction, insulin resistance, peripheral inflammation, neuroinflammation, neuroglial dysfunction, neuronal dysfunction) can define therapeutic targets to prevent or slow the course of these pathologies. This item will be treated in the second part of this review.

CONCLUSION AND FUTURE RESEARCH AREAS

In this review, sufficient arguments have been presented to affirm that there is a strong relationship or coincidence between T2D and AD. However, it is still necessary to continue investigating distinct aspects both to gain a deeper understanding of these pathologies and to find specific therapeutic targets in each case and phase of the pathogenic course. In recent years, much progress has been made in the knowledge of these complex and intrinsically related pathologies (Obesity, T2D, AD, T2D-AD) in humans and animal models. However, we wish to highlight that the cellular and molecular common pathological mechanisms relationships need to be more clarified mainly in humans, because the underlying pathogenic problems have been only studied in-depth using animal models. This means that an important number of conclusions may be biased due to the lack of complete coincidence between the pathologies induced in experimental animals (sometimes more related to the inducing toxins or genes) and those that actually occur in humans. There are still many unclear points in the common pathogenic mechanisms of T2D-AD that need to be clarified. We know the importance and repercussions of insulin resistance, but the causes of insulin receptor desensitization, their key alterations and regulation in the various insulin signaling pathways, are not clear. Similarly, it is necessary to precisely define the underlying genetic and epigenetic causes and the response of cells in the pathogenic course, specifically, which neuroglial reactions must be counteracted or favored in each phase of the pathological processes in T2D-AD, as well as which inflammatory and immune phenomena must be regulated in the initial phases of chronic peripheral inflammation.

In this scenario, we propose that it is necessary to intensify parallel research in humans and experimental models in the different scientific fields directly involved, as well as dedicate special interest in selected topics:

- In human research, it is mandatory to conduct studies on well-defined population groups and/or those at risk of suffering from T2D, AD, or T2d-AD to define characteristic phenotypes for diagnosis, prevention, treatment research and application of effective treatments. It is necessary to implement study protocols for the diagnosis and monitoring of preclinical and clinical cases with determinations of insulinemia, glycemia, HbA1c and cognitive and behavioral analysis in obesity, T2D and risk of AD [298]. Although already indicated years ago, these protocols are not applied regularly in studies of populations, groups of well-studied individuals, or a significant number of individuals in trials. We consider that there are different pathological forms of dysmetabolic disease with different presentations of different degrees in different organs throughout life. AD is a syndrome and T2D-AD, with many variants, is a way of presenting itself. The challenge is to diagnose and prevent these different clinical-pathological forms and treat them in a specific way.

- In experimental research, new models must be sought to reach irrefutable conclusions. It is necessary to develop new models for the study of these complex pathologies, both new animal models (AD and T2D) and *in vitro* cellular models.

- In the same sense of seeking conclusive results, novel studies must be encouraged with the most current and profitable techniques (genomics, epigenomics, proteomics, metabolomics, *etc.*) in human beings and models. Studies aimed at clarifying the phenotype of individuals suffering from these diseases, as well as the altered cells they exhibit-whether involved in adaptive/reparative changes or pathological/toxic changes-must be properly designed to understand the pathogenic course and identify potential targeted therapies.

There is no doubt that the genetic and epigenetic components inherited by each individual condition the pathogenic development of his or her life course, modified by external risk factors directly or through modifications of epigenetic mechanisms. However, many pathogenic courses in these

pathologies do not manifest at early ages (obesity in the first years, T2D in middle age, AD in advanced age, although there is a wide degree of clinical manifestation). This supposes that there are adaptive mechanisms that maintain a status of clinical normality for years that should be studied in depth to obtain a clear benefit from them in the prevention and control of these pathologies/disorders.

Further research is needed to find more genes involved in the development of the T2D-AD complex. For greater accuracy, we should say which gene isoforms are more susceptible to developing these dysmetabolic diseases and which genes can be modified in their expression to condition the development of these pathologies - at different times in the life course of each individual. The results will help to better understand the underlying common pathogenic mechanisms and the relationship or identity of AD and T2D, especially when new methods of studying correlations and dependencies in gene expressions are applied. This will lead to better diagnosis, definition of subtypes/phenotypes of T2D-AD cases and, ultimately, more effective and personalized treatment. Several gene expressions are correlational and identify therapeutic hypotheses tailored to the T2D-AD axis. In fact, six T2D and two treatments against dementia induced gene expression profiles associated with a non-T2D or non-AD state. They also assessed blood-based T2DxAD biomarker signatures in post-mortem human AD and control brain gene expression data from the hippocampus, entorhinal cortex, superior frontal gyrus, and postcentral gyrus. Using partial least squares discriminant analysis, they identified a subset of genes from our cross-disease blood-based biomarker panel that significantly separated AD and control brain samples, which may predict the future onset of AD in this population [299].

Epigenetic mechanisms need to be studied to control these diseases and reverse insulin resistance. Some works indicate these possibilities. For example, KAT7, a histone acetyltransferase that participates in the modulation of various genes, seems to be suppressed in APP/PS1-dE9 and db/db mice that mimic AD and diabetes, respectively. KAT7 overexpression decreased ROS and MDA levels, elevated SOD activity in the brain, suppressed neuronal apoptosis and alleviated insulin resistance [300].

In cellular and molecular studies (both peripheral or CNS tissues), it is necessary to delve deeper into pathogenic mechanisms and cellular responses. We have repeated that this is an important key to elucidating the genesis of insulin resistance and how cell behavior is modified (and what its responses are) in the face of a scenario of altered response of insulin receptors and hyperinsulinemia, and/or changes in the normal function of affected cells. In the brain, different subpopulations of neuroglial cells (astroglial and microglial cells, the basis of the neuroinflammatory responses and which are mentioned below) are present with very different sets of genetic expressions of neuroactive substances that induce very diverse changes that are beneficial or toxic depending on the place and time (destruction of damaged neurons, synaptic reconstruction and control, phagocytosis, *etc.*).

Various factors predispose dysmetabolic processes, such as obesity or metabolic syndrome, to modify gene expression to favor the accumulation of fat, promoting insulin resistance and hyperinsulinemia. With appropriate treatments (GLP-1 analogues) a reduction in body weight is achieved, but abandoning the therapy causes the pathology to flare up again and the initial situation quickly returns [190]. This is because the cells "retain the memory" of the epigenetic changes that were induced when the pathological process originated and the pathogenetic pattern that was configured manifests itself again even when these risk factors no longer exist. For all these reasons, it is of utmost importance to increase and advance research into variations in epigenetic induction and gene expression in order to carry out therapies at the highest level of cellular function control so that these remain within the normal range in terms of metabolism and prevention of senescence.

A major problem in AD and T2D-AD is the dysfunction of neuroglial cells. The generic characterization of pro-inflammatory astroglial and microglial cells (A1 and M1) or anti-inflammatory cells (A2 and M2) is no longer supported by the wide variety of phenotypes that are present and the different overall effects on the pathogenic course that they can produce. It is now recommended that studies on glial cells define phenotypes by characterizing the analyzed markers (upregulated, downregulated, or newly expressed) in specific regions or subregions (layers) of the CNS [70, 106, 107, 301, 302]. While some studies have already implemented this approach, it is essential to extend these analyses across different stages of the pathogenetic course. This is a slow and expensive process, but undoubtedly, an effective neuroglial treatment will be achieved through it. It would be very necessary to know whether there are specific neuroglial phenotypes for certain phases of the T2D-AD pathogenic course in order to develop specific treatments.

The cellular alterations that can characterize the metabolic disorder in each organ (not only in the brain) in each phase of the different subtypes of the pathogenic dysmetabolic course T2D-AD should be defined at a genetic and molecular level and analyzed to propose specific therapies.

In the coming years, we will have a better understanding of these pathologies and will be able to develop new (personalized) therapies.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: study conception and design were contributed by A.T., draft manuscript was provided by A.R-C., J-J.M. and A.T-D. and visualization was presented by M.I.A. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

BBB	=	Blood-brain Barrier

ncRNA	=	Non-coding RNA
T3D	=	Type 3 Diabetes Mellitus
T2D	=	Type 2 Diabetes Mellitus
AD	=	Alzheimer's Disease

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

José Julio Rodriguez-Arellano (Iberbaske and UPV, Bilbao, Spain) and María Eugenia Cabaña-Muñoz (CIROM Clinic, Murcia, Spain).

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