ISSN 2639-8109 | Volume 14

Annals of Clinical and Medical Case Reports®

Review Open Access

Spotlight on the Pathophysiological Trajectories Linked toAlzheimer's Disease (AD): Blood-Brain Barrier (BBB);Neuroinflammation; APOE4 Allele and AD-Insulin Resistance (IR) Pathogenic Link

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Received: 30 Mar 2025
Accepted: 06 Apr 2025
Published: 10 Apr 2025
J Short Name: ACMCR

Keywords: Alzheimer's Disease; Blood-Brain Barrier; APOE4;Neuroinflammation; Metabolic Syndrome;Brain Insulin Resistance

Citation: B Abdalla. Spotlight on the Pathophysiological Trajectories Linked toAlzheimer's Disease (AD): Blood-Brain Barrier (BBB);Neuroinflammation; APOE4 Allele and AD-Insulin Resistance (IR) Pathogenic Link. Anna Clin Med Case Rep®. 2025; 14(11): 1-18

1. Abstract

Alzheimer's disease (AD) is a predominant and incurable chronic debilitating neuro-degenerative disorder occupying more than 60% of all types of dementias. It is inaugurating by a cascade of events initiating from amnesic-type memory impairment and by gradually loss of cognitive and executive capacities, which is an intolerable problem for the patients and their familiars. Pathologically, there is overwhelming evidence that clumps of misfolded amyloid-β (Aβ) and hyperphosphorylated Tau protein aggregate in the brain. These pathological processes leading to synapse loss, neuronal loss, brain atrophy and gliosis culminating in neurodegeneration and fuelling AD. Thus, at a basic level, abnormality in brain proteins function is observed, causing disruption in the brain network and loss of neural connectivity.Nevertheless, AD is a multifactorial disorder, caused by a combination of age-related changes, genetic, environmental and lifestyle factors that affect the brain over time, its mysterious pathology seems non limited to senile plaques (Aβ) and neurofibrillary tangles (tau), but plethora of substantial and biological processes have been also emerged in its pathogenesis such as - breakdown and/or dysfunction of the blood–brain barrier (BBB); patients' carriers of the gene variant APOE4; and the immunosenescence of the immune system. Furthermore, type 2 diabetes (T2DM) and metabolic syndrome (MS) whose have also observed as early markers that may provoke pathogenic pathways that lead or aggravate AD progression and pathology. Notwithstanding, of various pathological pathways, there are numerous substantial AD features that require shedding light on, such as chronic neuroinflammation, decrease glucose utilization and energy metabolism as well as brain insulin resistance (IR). Herein, we come to broadened our understanding & to connect the dots of the multiple comorbidities and their cumulative impact that may have synergistic effects on BBB dysfunction and AD pathology. We shed light on the path-physiological modifications in the cerebral vasculature that may contribute to AD pathology and cognitive decline prior to clinically detectable changes in amyloid beta (Aβ) and tau pathology, diagnostic biomarkers of AD, neuroimmune involvement and the role of APOE4 allele and AD-IR pathogenic link - the shared genetics and metabolomics biomarkers between AD and IR disorders. Investment in the future researches brings us closer to know the pathogenesis of AD, and paves the way to build preventive and treatment strategy.

2. Introduction

Alzheimer's disease (AD) is an aging complex neuro-degenerative brain pathology that has been described firstly by the German psychiatric and neuropathologist Alois Alzheimer [1, 2] on 1906 as a chronic multifaceted illness characterized by an episodic and amnesic type memory impairment, impoverishment of language and visuospatial deficits, loss of cognitive and executive abilities, attention and affect, mood changes, apathy and increased dependence on others, which is a brain problem affecting the elderly [3]. AD is a predominant and incurable chronic debilitating disorder occupying more than 60%-80% of all types of dementias [4]. The neuropathological hallmarks of the disease represented by overwhelming evidence of clumps of misfolded amyloid-β (Aβ - a 36-43 amino acid peptides), and hyperphosphorylated Tau protein aggregate in the brain. Leading to formation of extracellular amyloid-beta (Aβ) deposition that form neurotic plaques, and intracellular neurofibrillary tangles respectively. In prodromal stage of the disease the pathological process is characterized by abnormal protein processing, leading to the aggregation and accumulation of Aβ peptides, aberrant activation of the brain's innate immune system cells, and neurotoxicity [5-13].Nevertheless, AD pathology non limited to accumulation of the hallmark senile plaques (Aβ) and the aggregation of the hyperphosphorylated microtubule- associated protein tau into neurofibrillary tangles (NFTs) in the brain, but other plethora of fundamental and biological processes have been also involved in its pathogenesis such as - blood–brain barrier (BBB) neurovascular dysfunction which is one relevant pathophysiological domain to be consider in AD pathogenesis framework as potential player, which may play a vital role in the beginning and progression of AD [14-19].According the two-hit vascular hypothesis of AD [20], which suggests that cerebrovascular damage (BBB dysfunction) could leads to chain of events, represented by the accumulation of amyloid-β (Aβ), because BBB is the one thrown at it to clean out the Aβ across the barrier. Thus, decrease clearance abilities may therefore promotes the built-up of Aβ plaques which is an initial insult itself sufficient to initiate neuronal loss and neurodegeneration [21-24]. BBB damage may also induce neurodegenerative processes via the penetration of neurotoxic substances across it into the brain [25], lead to neuroinflammation [26], and provokes pericyte-mediated cerebral hypoperfusion [27].In addition, far from the prevailing line of thought, or almost accepted theories, such as cholinergic theory, the Aβ cascade hypothesis or the abnormally excessive phosphorylated tau protein, other opinions suspected to play a role in the etiology of AD, or as an alternative theory, that depends more on the central factors, that may underpin the pathogenesis of AD and other dementias. Herein we will discuss and to draw attention to various events that my have crucial role in the pathogenesis of AD: "Impairment of the immune system (immunosenescence) may be implicated deeply in the pathogenesis of AD"[28-32],environmental

factors especially, type 2 diabetes (T2DM) and metabolic syndrome (MS) whose have also emerged as early markers that may provoke to some pathogenic pathways that lead or aggravate AD progression and pathology. Additionally, numerous substantial AD features that require shedding light on such as the role of the gene variant APOE4, chronic neuroinflammation, decrease glucose utilization and energy metabolism as well as brain insulin resistance (IR) [33-36].Pathogenic link between Blood-Brain Barrier (BBB), APOE4 polymorphism and Alzheimer's Disease (AD).Blood–brain barrier (BBB) created during the early embryonic angiogenesis approximately at the second embryonic week (W2) by angioblasts forming a vascular plexus of immature blood vessels which progressively branches to produce a vascularised brain [37]. It is a widened continuous tightly sealed monolayer of brain, contains non-fenestrated endothelial cell membrane within brain microvessels. Brain circulation is sophisticated per se, for example, brain capillaries are a key site of the BBB, there length in human brain is 650 km, which accounts for >85% of total cerebral blood vessel length, providing the largest endothelial surface area for solute transport exchanges between blood and brain, and vice versa (e.g., ~120 cm2/g of brain [38, 39]. The mean distance between the BBB and neurons is ~8 μm, allowing rapid diffusion of molecules across the brain interstitial space from capillaries to neurons, and vice versa [39]. The multi-functionality of BBB stress its importance in healthy and diseased brain; physiologically it regulates the influx and efflux of biological substances essential for the brain's metabolic activity and for neuronal survival. Indeed [20, 40], BBB is a selective gatekeeper for the brain has semipermeable distinctive and chemical barrier which plays a meticulous physiological role in the regulation of paracellular permeability, ion balance, nutrient transport, and it performs a hemodynamic orchestration of the cerebral blood flow (CBF) to meet the metabolic demands of the neurons [37, 41, 42]. Thus, BBB ensures a stable brain internal milieu by maintaing homeostasis and adequate microenvironment which is essential for adequate synaptic and neural activity [43]. Moreover, BBB represents a biological barrier, through the interface between neural tissues of CNS and blood components including circulating cells of the immune system, it guarantees the export of potentially neurotoxic blood-derived debris from the brain to the bloodstream, remove microbial pathogens, expels red blood cells and leukocytes. additionally, due to its barrier's role, it protects the brain from exogenous components, xenobiotics and filtrating the blood flow [44, 45]. The particularity of BBB as a semipermeable barrier of the brain aroused interest of many researcher's; Paul Ehrlich (1885,1906) firstly examined this phenomenon, he noticed that a peripherally infused dye did not stain the brain tissue [46]. This finding was further supported by later observation turned 110 years ago by his associate Edwin E. Goldmann (1909, 1913) as he applied the same trypan dyes to the cerebrospinal fluid [47]. The dye stained only the brain tissue without extravasating in the periphery [48]. These illustrations support the role of BBB as an intricate barrier, that strictly regulates the passage of substances between blood and brain parenchyma selectively [47].Anatomically, BBB is a highly specialized, multicellular structure formed by brain microvascular endothelial cells (BMVECs), which are characterized by a lack of fenestrations, presence of sealed junctions and minimal pinocytotic activity, which, along with astrocyte end-feet unsheathing the capillary, and pericytes embedded in the capillary basement membrane (BM), forming a functional element: the neurovascular unit (NVU) [41, 38, 49, 50]. NVU are highly specialized cells and the major component of the barrier. They cover all brain microcapillaries with a total surface of between 12 and 18 m2 in an adult human [51]. The brain microvascular contains small blood vessel diameter < 20 μm, it maintains blood supply but also conveys signal and, transfer information between astrocytes, microglia and neurons [52]. Additionally, BMECs show an uninterrupted compact junction, exhibiting remarkably diminished pinocytotic activity relative to the microvascular endothelial cells found in peripheral organs. The complex tight junction inhibits the paracellular diffusion of water-soluble molecules into the CNS. In addition, it expresses important transporters and efflux pumps on their surface, such as ATP binding cassette (ABC) and synthesize relevant neurotransmitter molecules such as nitric oxide (NO) [37].Furthermore, the restricted expression levels of endothelial adhesion molecules on the surface of BMECs strictly control immune cell trafficking into the CNS [53].Due to its lipophilic nature, hydrophobic compounds and gases can diffuse across the BBB by passive diffusion, but larger and hydrophilic compounds require specific transporters located within the barrier. only solutes of a molecular weight below 400 Daltons (Da) are able to circulate freely through the BBB endothelium [54]. Typically, 98% of small-molecule drugs, and close to 100% of large-molecule drugs, fail to enter the central nervous system (CNS) through the tight barrier of endothelial cells [55].Since, its role as a unique physical and biochemical barrier that comprehend a combination of physical transporter and metabolic barrier, and its multifunctionality, BBB appears as a specific physiological compartment, that strictly regulates the passage of substances between blood and brain parenchyma. like further two membrane compartments in the brain that form a barrier between the blood and cerebrospinal fluid (CSF): the arachnoid epithelium forming the middle layer of the meninges, and the choroid plexus epithelium [56].Under pathological conditions, the level of expression of endothelial adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1(VCAM-1), is upregulated compared with that under physiological conditions and is crucial for immune cell infiltration into the CNS [53]. BBB dynamics and functional instability during neuroinflammation - which is the response of the CNS to endogenous and/or exogenous factors that disrupt normal cellular homeostasis, lead to severe consequences, involves both a loss of BBB selective transport mechanisms and a reduction in its structural integrity [57, 58]. It was shown that changes in the BBB's permeability is implicated in the pathophysiology of neurodegenerative diseases, including AD, by facilitating neuroinflammation through unregulated protein entry [20, 59]. Moreover, because AD is ageing-related disease characterised by systemic abnormalitiesin both intracellular and extracellular microenvironments for almost all organs [60], age-related decrease in pericyte cells further corrupt the BBB, impairing blood flow and neuronal function [61]. Undoubtedly, neuroinflammation, ischemic stroke and AD can lead to initial breakdown and/or destruction of the architectural integrity of the BBB, leading to subsequent leakage, and cerebral edema with concurrent neuronal atrophy, early miscommunication and deprivation of endothelial cell-t0-cell connections. Although these initial damages to the BBB may eventually be repaired with restoration of endothelial tight junctions (TJs) [62, 63], which is an essential molecular component of the BBB composed of claudins, occludins, zonula occludens-1 (ZO-1), ZO-2, ZO-3, and adhesion molecules [64, 65]. It seems that activation of inflammatory pathways as well as other toxic processes may be the primary malefactors that cause brain damage, shortly after BBB dysfunction. However, even low-degree of chronic BBB injury may lead to BBB breakdown and physiological changes including the opening of the tight junctions (TJs), differential expression of proteins transport, and loss of organization of the neurovascular unit (NVU) network leading to entry of cells and molecules not usually found in the brain [37]. These effects have been identified in neuroinflammatory conditions associated with neurodegenerative diseases and CNS infections, as well as with inflammation typical to healthy aging [17, 37]. The breakdown of the BBB in AD, involves both a loss of selective transport mechanisms and a reduction in structural integrity, that often precedes detectable AD symptomatology and neurophysiological changes [21, 66, 67]. Dysfunction of BBB is supported by the anatomical thickness and functional changes in the cerebral microvasculature, which it might be directly responsible for the pathogenesis of sporadic AD, or indirectly or at least, could be a consequence of the disease process itself that participate synergistically with other pathogenic mechanisms in the development of neurodegeneration [68].

This fact has been confirmed by more than 20 independent postmortem human studies, whose show increased brain capillary leakages and perivascular accumulation of blood-derived fibrinogen, thrombin, albumin, immunoglobulin G (IgG), loss of BBB tight junctions, and red blood cells (RBC) extravasation, impaired glucose transport, impaired P-glycoprotein-1 function, perivascular deposits of blood-derived products, cellular infiltration, microbial pathogens associated with degeneration of endothelial and pericytes - cells nestled in the wall of cerebral capillaries, and endothelial cells [69-71]. All these events create inflammation and activates the innate immune responses, which can initiate multiple pathways of neurodegeneration.

Apolipoproteins isoforms in AD, and their role in BBB breakdown:

Apolipoprotein E (ApoE) gene belongs to a family of fat-binding proteins (apolipoproteins), located on chromosome 19, encodes and binds to a specific liver and peripheral cell receptor. It is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. In the CNS, APOE is expressed mainly in astrocytes and microglia and in the peripheral tissues it primarily produced by the liver and macrophages [72, 73]. APOE encodes major lipid-carrier protein in the brain [74], but also vascular mural cells and choroid plexus cells. APOE modulates multiple pathways, its activities are associated with the endocytosis of lipoproteins, synaptic plasticity, membrane integrity, neurogenesis and neuronal degeneration, neuroinflammation, mitochondrial function, tau phosphorylation, and Aβ metabolism [75]. There are three isoforms of APOE in human: apoE2, apoE3, apoE4 and there are six different genotypes, i.e., three homozygous and three heterozygous [76]. These isoforms have functional and structural differences, inconsistencies, and discrepancies in their interaction with low-density lipoprotein (LDL) receptors [77].

As with almost all genes, individuals carry two allele copies of APOE, which can be either homozygous (APOE2/APOE2, APOE3/APOE3, APOE4/APOE4) or in heterozygous forms (ApoE genotypes series are involved in cholesterol metabolism and immune modulation) [78]. Within the cell, ApoE plays a role in cellular processes and play a prominent role in the overall health of neurons, involve in the maintenance of the cytoskeleton, mitochondria and dendrites [77]. In the circulation, ApoE present as part of several classes of lipoprotein particles, including chylomicron, very low density lipoprotein, low density lipoprotein, and some high density lipoprotein. Moreover, APOE has a crucial role in amyloid beta-protein (Aβ) clearance, aggregation and deposition [79, 80]. The main associated pathological isoform of APOE in AD, is the APOE-ε4 genotype, it is the highest risk factor for late-onset Alzheimer's disease (LOAD), with the underlying mechanism of this link being both presynaptic - and postsynaptic dysfunction [81]. APOE ε4 gene variant promotes Aβ plaque formation [82], which facilitates the loss of key presynaptic proteins [83] as well as disrupts long-term potentiation and plasticity [84] and leads to reduction in dendritic density [85] and has a role in the hereditary pathogenesis of AD — up to 4-fold in people in the heterozygous form (APOE3/APOE4 or APOE2/APOE4), and in the homozygous form (APOE4/APOE4) confers up to 15-fold [66, 74, 86]. It is worthily to mentioned, particularly in case of AD, that association alone not mean causation and not every individual who carry APOE ε4 should develop the disease. However, AD is a multifactorial disorder, that generally requires involvement of environmental risk factors accompanied with genetic factors to cause the disease [87, 88]. Destructive environmental factors should orchestrate together with genetic risk factors to stimulate and accelerate the emergence of the disease. Not every individual carrier two APOE4 copies are necessarily at risk, but their fate to develop AD is inevitable [88, 89]. The presence of APOE ε4 accelerates the age of onset of AD roughly 15 years in carriers compared to non-carriers (mean age of onset in those who are carriers being 68.4 years versus 84.3 years in non-carriers [34]. In this context, it was shown that individuals who were cognitively intact and carried either one or two copies of APOE4 had a leaky BBB, initially in the hippocampus and in the parahippocampal gyrus [90]. Remarkable atrophy in these two regions, due to BBB dysfunction was observed, leading to memory and cognitive impairment. Moreover, histological analysis of post-mortem brain tissue has reported that BBB breakdown in AD patients, reduced cerebral blood flow, neural loss, and behavioral deficits independent of Aβ, and it is more noticeable among APOE4 carriers compared to APOE3 or APOE2 [91 – 95].

To cast more light on APOE4 association with BBB Montagne et al, [90], described the relationship between BBB and ApoE4. The authors demonstrated that ApoE4 isoform is secreted by pericytes cells, located close to endothelial cells that line cerebral capillaries at the BBB. ApoE4 activates array of proteins, beginning with the protein cyclophilin A (CypA) in the pericytes, which in his turn stimulates a downstream signalling pathway involving activation of the inflammatory protein matrix metalloproteinase-9 (MMP9) in pericytes, and in endothelial cells. This activation by ApoE4 leads to MMP-9–mediated degradation of BBB tight junction and basement membrane proteins causing BBB breakdown [90, 96-98]. Controversially, APOE3 and APOE2, but not APOE4, act via low-density lipoprotein receptor–related protein-1 (LRP1) on pericytes to inhibit the proinflammatory cyclophilin A (CypA)–matrix metallopeptidase-9 (MMP-9) pathway. — on other hand, it well known, that pericytes are normally safeguard the BBB [99, 100] by preventing the breakdown of the tight junctions located between endothelial cells. In support of this idea, biomarker of pericyte injury — a soluble form of a protein known as platelet-derived growth factor-receptor-β (sPDGFRβ) — In addition, to cyclophilin A (CypA) and to matrix metalloproteinase-9 MMP9) proteins - which are part of inflammatory pathway- are implicated in APOE4-driven pericyte damage and BBB breakdown, and all are elevated in the CSF of APOE4 carriers [95, 101]. Thus, APOE4-status is a risk factor for BBB-breakdown via activation of the Cyp-A-MMP9 pathway [96, 102], and has been associated with increased hippocampal BBB leakiness and higher sPDGFRβ [90] the novel and sensitive biomarker of BBB disfunction [103, 104].

Because, pericytes is adjacent to the capillary endothelial cells and thereby part of the neurovascular unit, they can through constriction regulate capillary blood flow, clean Aβ out of the brain, thus they are crucial for maintaining overall BBB integrity. Sagare and colleagues [105] have shown that only pericytes shed sPDGFRβ into the CSF in response to noxious stimuli. sPDGFRβ may thereby serve as a biomarker of pericyte degeneration and a proxy for BBB integrity [106 – 110]. Consequently, sPDGFRβ, according to some studies was increased in AD [111] and linked to APOE4-status [90], other studies reported an association with cognitive dysfunction irrespective of AD-pathology [106]. On other hand, Cicognola and colleagues identified age-dependent effects on sPDGFRβ and associations with neuroinflammation but no association with AD-biomarkers APOE4 or cognitive decline [112]. Notwithstanding, a routinely method used in clinical practice to measure the integrity of the BBB was studied by Halliday et al., [102], who examine and demonstrates that the ratio of albumin in the cerebrospinal fluid (CSF)/plasma albumin quotient (QAlb), is an established marker of BBB breakdown [113].

However, the low molecular weight of albumin of 66.5 kDA [114], raise the question of appropriateness of this method to detect minor paracellular BBB leakage. Kurz et al., [115] limited the diagnostic sensitivity of CSF/QAlb, for thin BBB changes in the context of AD with some researches illustrating increased QAlb in patients with dementia [14, 116] but not in mild cognitive impairment (MCI) [116, 117].

It is well known that the liver is the single organ capable of synthetizing albumin and no active transport mechanisms across the BBB have been described. Nevertheless, of all these inconsistencies and reservations, it is still a suitable candidate to assess BBB integrity [23, 118].

However, Qalb index, which is a relation of CSF to blood albumin and is an indicator of how much serum Alb is leaking into the CNS, has been established as biomarker of BBB leakage [119]. It was shown that AD patients had increased Qalb [119], which correlates with the progression of cognitive impairment [14, 116]. Indeed, CSF/serum albumin (Qalb) index was introduced as a reliable measure, with values of >9 indicating BBB dysfunction [119]. Pathological Qalb was described ranging from 16% [119] to 22% in patients with mild to moderate AD dementia [14, 116, 120]. Importantly, increases in QAlb values correlated positively with both CypA and active MMP-9 CSF levels in all studied individuals ($r = 0.37$, $p < 0.01$; $r = 0.45$, $p < 0.01$) indicating the greater the increase in CypA and active MMP-9 levels the greater the magnitude of BBB breakdown assayed by QAlb. It was seen that ApoE4 transgenic model mice showed an increase in BBB vulnerability [121] and CSF concentration of CypA-MMP9 in APOE4 but not in APOE3 and APOE2 transgenic mice, this finding also occurs in humans [40, 97, 109].

Pathogenic link between Insulin Resistance (IR), Alzheimer's Disease (AD), and Blood-Brain Barrier (BBB) disorders.

Since the discovery and isolation of insulin hormone in 1921 by Drs. Frederik Banting & Charles Best (Toronto University), the hormone received great attention, initially, due to its role in regulating peripheral glucose levels. Later on, more efforts poured on the reciprocal relationship between brain and insulin signaling, followed by understanding the mechanism of transport of insulin into the brain from circulation, and how insulin enter the brain by binding brain micro-vessels via the blood-brain barrier (BBB) [122].

Insulin is a peptide hormone produced by the β-cells located in the pancreatic islets of Langerhans, which are of various size roughly from 50 to 300 micrometers in diameter and contain a few hundred to a few thousand endocrine cells. Islets of Langerhans (named endocrine pancreas), are separated anatomically and functionally from pancreatic exocrine tissue (which secretes pancreatic enzymes and fluid directly into ducts that drain into the duodenum). In healthy human the number of islets is about one million, weight 1-2 grams and represent 1 to 2 percent of the total mass of pancreas. At least 70 percent of islets of Langerhans are β-cells that secrete insulin, which are mostly localized in the core of the islet. β-cells are surrounded by other three major cell groups: alpha cells that secrete glucagon, delta cells that secrete somatostatin, and PP cells that secrete pancreatic polypeptide, and by other two minor cell types (D1 and enterochromaffin cells) produce hormones and synthesize serotonin, respectively [123].

Historically, the islets of Langerhans named for the German physician Paul Langerhans (1847-1888), who first discovered the islets in 1869.

Insulin protein is composed of two chains, an Alpha chain (with 21 amino acids) and a Beta chain (with 30 amino acids), linked together by sulfur atoms [123].

In 1921, two scientists Frederick Grant Banting (1891-1941) and Charles H. Best (1899-1978), who work hardly on pancreas, were the first pioneers who succeeded in isolating the insulin in pancreatic extracts, followed by Nicolas C. Paulescu (1869-1931), who firstly called the substance “pancrein.” The purified extract, was obtained and accomplished with the collaboration of Scottish physiologist J.J.R. Macleod (1876-1935). Only Banting and Macleod shared and awarded the 1923 Nobile Prize for physiology or medicine for their work.

Today, the role of insulin in the regulation, of glucose metabolism in peripheral tissues, lipid metabolism, vascular regulation, and cell growth is well known [124], but, the quandary of insulin’ multi-functionality in the brain still need more clarifications. Plethora of research studies in human and animal, shed lights on its various activities, and indicate that insulin motivates nutritional metabolism and cerebral bioenergetics, increases synaptic efficiency – by enhancing the capacity of a presynaptic input to influence postsynaptic output; increases the synaptic viability by strengthening and maintaining active synapses through increased expression of cytoskeletal and extracellular matrix elements and postsynaptic scaffold proteins; increases dendritic spine formation, and turnover of neurotransmitters, such as dopamine. Insulin also has a role in proteostasis process that regulates and stabilizes the proteins within the cell. In pathological state, it plays an important role in AD, by influencing clearance of the amyloid β peptide and enhance phosphorylation of tau, which are both hallmarks of AD [125, 126].

For optimal activity of the brain, insulin is wanted due to its sensitivity to maintain: nerve action potential, neuronal ion gradients; cell membrane lipid remodeling, signal conduction and other pleiotropic biological effects.

Indeed, brain requires a continuous flow and large quantity of energy to maintain proper activity. Taking in consideration that the brain mass only constitutes 2% of total body mass, brain requires around 25% of total body’s glucose and 20% of the body’s oxygen to meet metabolic demand [127-130].

Intriguingly, the importance of glucose as an obligate fuel in the CNS, responsible for cerebral energy metabolism, which utilized to foul neuronal activity via oxidative metabolism both in basal and activated state. This is illustrated by the disproportionate metabolic rate of the brain relative to most organs and tissues. In fact, the brain preferred glucose as source of energy (The brain requires 6–7 mg/100 gr. of glucose per minute, which is equivalent to 120–130 gr. per day) [131], and the alternative sources are (lactate, ketone bodies, proteins, and lipids). Because, glucose chemical properties as a polar substance, prohibits it to pass freely through the cell membrane. Entrance to cell requires a special transporter – the glucose transporters (GLUT) - In the Brain, the main glucose transporters are GLUT1 and GLUT3 and are not insulin dependent type transporters. In the peripheral circulation insulin acting via GLUT4 glucose transporter to lower blood glucose by transporting glucose into cells [132-134].

GLUT4 levels is relatively low in the brain comparing to GLUT1 and GLUT3, but the importance of GLUT4 still crucial, because it involved in glucose influx into synaptic areas, especially during high synaptic activity [135].

Anyway, the delivery of energy sources into the brain obtain through a sophisticate passage - the Blood Brain Barrier (BBB) -, which permits pass to lipid-soluble substances, but other substances need transporters including glucose [136]. After the entrance of glucose through the BBB, glucose links to neurons through two pathways: via the interstitial fluid, glucose connects to GLUT1 transporter, spreads into the interstitial fluid, and after enter neurons through GLUT3 [137]. While, the astrocytes pathway, after passing through GLUT1 transporter of vascular endothelial cells, and then enters astrocytes through GLUT1, in astrocytes glucose converted to glycogen for storage, or to lactic acid by glycolysis. Lactic acid leaves the astrocytes to the extracellular matrix by MCT1 (monocarboxylate transporter-1) or MCT4 (monocarboxylate transporter-4), and enter the neurons by MCT2 (monocarboxylate transporter-2). This mechanism called (Astrocyte-Neuron Lactate Shuttle Model) [138]. During the phenomenon of insulin resistance, the insulin pancreatic production increases, to meet the demand of chronically elevated levels of glucose in the circulation and/or increased amount of adipose tissue that requires insulin for its glucose metabolism [139]. The consequences of insulin resistance (IR), come from the fact that insulin binding to its receptors diminished dramatically, and the glucose transport into cells is affected remarkably, causing decrease bio-utility and bio-activity of insulin in the target organs [140, 141].

Thus, an inverse relationship happened in this case: when insulin resistance increases, the glycemic regulation of insulin decreases, leading to hyperglycemic state, and the intracellular insulin signal deteriorate [142].

Insulin resistance, underlies the pathophysiology mechanism of diabetes, and it is considered a cornerstone reason for obesity,

metabolic syndrome, and different cardiovascular diseases. Brain insulin resistance is the process in which the quantity of insulin in the brain diminished or the no response of brain cells to insulin [143, 144]. However, due to the fact that brain not act as a storehouse of glucose in hyperglycemic state, insulin resistance does not obligatorily provoke to a decrease in glucose concentration in the brain tissue, but it may affect synaptic activity [124].

The underpinning pathogenesis of insulin resistance and Alzheimer's disease (AD) still need more clarification. Notwithstanding, that both meet common pathologic exclusiveness encompass amyloidogenesis, bioenergetic dysfunction, inflammation and obesity, which all together strengthen the notion that insulin resistance may accelerate the appearance of AD [145, 146]. One of the mechanism by which insulin impact cognitive abilities is by affecting cerebral energy metabolism. Insulin resistance (IR) have catastrophic consequences on the brain function [145, 146].

For example, the role of insulin deficiency and insulin resistance (IR) in AD have emerged over the past three decades as potential candidates for the pathogenesis of AD [147-149].

In this concept, there are plethora of pathways that may explain the link between AD and IR [150, 151].

Initially, in case of insulin resistance state, three detrimental events happened, the IR, followed by the compensated peripheral hyperinsulinemia, and the resultant hyperglycemia or glucose intolerance. Definitively, IR is observed among individuals with impaired insulin-stimulated glucose output into adipocytes tissues and muscle, accompanied by impaired insulin suppression of hepatic glucose output [152]. This phenomenon of reduced cells response to insulin/insulin resistance that leads to hyperinsulinemia, can occur due to genetic polymorphisms of tyrosine phosphorylation of the insulin receptor, insulin receptor proteins, PIP-3 kinase, or abnormalities of GLUT 4 function and/or environmental factors [153-156].

Insulin resistance is a complicated pathophysiological disorder with impaired biologic response of target tissues to insulin stimulation, impaired ability to inhibit glucose production and stimulate peripheral glucose elimination, often come with hyperinsulinemia to maintain normoglycemia [157].

IR etiology depends on any factor causing disturbances in the insulin signaling pathway in the host, including decrease peripheral target tissue responsiveness to insulin, abnormalities in receptor binding, autophagy, intestinal microecology, in addition to metabolic dysfunction of the liver and other abnormalities in the host extracellular environment such as, lipo-toxicity, inflammation, hypoxia and immunity abnormalities that can trigger intracellular stress factors in key metabolic target tissues, which impairs the normal metabolic activity of insulin in these tissues thereby provoking the progression of whole-body IR [158, 159].

When IR developed a compensatory hyperinsulinaemia occurs due to increased secretion of insulin from the pancreatic β cell in order to achieve normoglycemia, this fact leads to inadequate or vicious cycle of IR ↔ hyperinsulinemia [150, 151, 154, 160-162].

This detrimental cycle of IR-hyperinsulinemia causes metabolic consequences include hyperglycemia, high blood pressure, hyperuricemia, dyslipidemia, high levels of elevated inflammatory markers, endothelial dysfunction, cardiovascular diseases, and may lead to metabolic syndrome, and type 2 diabetes. All together consequences mentioned up maybe implicated in AD pathogenesis in different degrees [161, 162, 154, 163].

Chronic elevation in peripheral insulin (peripheral hyperinsulinemia) levels impacts central insulin availability and function. Indeed, peripheral hyperinsulinemia leads to increase in insulin level in the brain, because the transport of molecules across the blood brain barrier (BBB) is highly affected by the variation in their peripheral levels, especially the high level of insulin [145, 163, 164].

Insulin is degraded into the brain by the insulin degrading enzyme (IDE), also named-insulysin), structurally, in human the gene encoding IDE is located on the long arm of chromosome 10 (q23-q25) and contain 24 exons and large sequence of introns [165].

It is presenting an atypical spiral shape structure, confirming unique enigmatic enzymological properties. IDE is a polypeptide with a molecular weight of 110-kDa, it is a neutral thiol-dependent metallopeptidase, bound to the metal Zn2+ [166]. Originally known as the main enzyme involved in the cleavage of insulin as well as other amyloidogenic peptides, such as the β-amyloid (Aβ) peptide and it eliminates Aβ's neurotoxic effects – one of the hallmarks of Alzheimer's disease (AD) – this stress the relationship between IDE, diabetes and AD [167, 168].

Thus, IDE has been long envisaged as a potential therapeutic option; i.e., metabolic and neurodegenerative diseases [169].

However, The IDE cleaves a numerous of peptides unevenly, including β-amyloid, demonstrating a critical role in pathophysiological processes regulated by these peptides [170-175]. It is well known, that insulin-degrading enzyme (IDE) represent the link and the key factor in the crosstalk between hyperinsulinemia and AD [176]. Uncountable epidemiological studies have demonstrated that hyperinsulinemia and type 2 diabetes (T2DM) increased dramatically the risk of developing AD in the elderly. Both, T2DM and AD share common characteristics, including inflammation, alteration of insulin signaling, insulin resistance and glucose metabolism. Furthermore, genetic studies have demonstrated that IDE gene variations share clinical symptoms of AD as well as the risk of T2DM. An optional consequence due to deficiency of IDE gene, may be caused by either genetic variation, or by the deviation of IDE from the degradation of amyloid-β peptide. Decrease catabolic regulation and degradation of amyloid-β peptide by IDE, in favor of insulin creates an extracellular deposit, and failure of clearance of amyloid-β peptide. Therefore, the deficiency of IDE favors extracellular deposits of amyloid-β neuritic plaques, which is one of the underlying neuropathological hallmarks of AD [177-180].

The dual role of insulin degrading enzyme (IDE), in degrading insulin along with amyloid-β peptide, creates a kind of considerable competition between insulin and Aβ protein for IDE receptors, the result is in favor insulin, thus, insulin cleavage mechanism prevails, because IDE is more specific to insulin, and has more affinity binding sites for its receptors comparing to Aβ protein. A cross- linking study carried out by Hari et al [181], has illustrated that insulin binds IDE specifically in the intact cells, other study carried out by Kuo et al [182], demonstrate that overexpression of IDE in cells in culture has been found to enhance the rate of insulin degradation [169, 182-184].

Thus, in addition to the already low amount of insulin that entered to the brain due to the downregulation of BBB transporters, and to the higher linkage of IDE to insulin, the free quantity of Aβ nonattached to IDE is more notable and led to Aβ accumulation in the brain, which is one of the important hallmarks of AD [185]. Moreover, insulin increases Aβ protein in the extracellular spaces [186]. Therefore, considering the pathogenic interaction between Aβ and impaired insulin signaling, it is not surprising that central metabolic dysfunction is a certain feature of AD, illustrated by brain glucose hypometabolic changes, in addition, to defects in insulin signaling, usually proceeds AD signs and symptoms by several years [187, 188]. Concerning insulin signaling consequences at the cellular level, insulin affects all the BBB network including vascular endothelial cells, neurons, glial cells and pericytes, by its involvement in the regulation of capillary vasodilatation (high concentration of insulin) and vasoconstriction (low concentration of insulin) [189-191]. Through this, the BBB structure and discharge of Aβ from the brain tissue into the blood vessels is maintained. However, insulin resistance provokes negatively the cerebral blood pressure regulation, incremented BBB permeability, and increased intracerebral Aβ accumulation [192]. In fact, IR as well as hyperglycemia affect memory performance and

neuronal growth which play role in cognitive dysfunction, a key clinical feature of AD [193].

In another way, IR has been linked to tau hyperphosphorylation tauopathy which is crucial pathogenic feature in AD [194]. In addition, IR affects and decreases neurotransmitters' levels [195]. For instance, impaired insulin signaling reduces acetylcholine level in the brain leading to crucial cholinergic perturbations which are largely implicated in AD progression [193]. In fact, the synthesis of acetylcholine from choline and acetyl-Coenzyme A (Acetyl-Co-A) is reduced significantly in AD patients [196].

CNS insulin deficiency is associated with AD pathogenesis and its progression as well [197]. In other words, AD represents a state of type 3 diabetes where combined effects of IR and insulin deficiency are implicated in its pathogenesis [160, 197].

Pathogenic link between Neuroinflammation, Immune system, BBB leakiness and Alzheimer's Disease

Neuroinflammation is defined as a reaction to inflammatory response within the CNS. This process of inflammation demands key pro-inflammatory mediators such as cytokines (IL-1β, IL-6, and TNFα), chemokines (CCL2, CCL5, CXCL1), secondary messengers (NO and prostaglandins) and reactive oxygen species (ROS) produced by brain glial cells (microglia and astrocytes), endothelial cells, and peripherally derived immune cells [198-200].

One of the cornerstone mechanism that underlie neurodegeneration process in AD patients are the massive neuroinflammations [200].

Neuroinflammation plays a dual role in the brain, firstly, it has advantageous effects and neuroprotective role in its normally innate response when the inflammatory activity is for a shorter period, by activation the immune system especially the phagocytic process that are presented by astrocytes and microglial cells in order to eliminate toxics cellular components, catabolites and microbial pathogens. Thus [201], the neuroinflammation supposed to be a primary mechanism to conserve the homeostasis of the brain and to save the microenvironment. Its critical role and function in protecting, saving and restoring synaptic functions against traumatic events or contagious harm is highly substantial.

Secondly, the aforementioned dual role of neuroinflammation turn into dangerous stage when a prolonged or maladaptive neuroinflammation occur, which represent a key pathological driver for many diseases including AD and it requires direct intervention to get rid of it due to it dis-advantageous effects and harmful pathological consequences for whole brain [202-204]. Cytokines are the messengers during inflammation and carry information between different cells, and are one of the substances showing pro-inflammatory activities [205]. Furthermore, they are important signaling molecules in health and disease, hence their role is critical, as neurotransmitters and hormones. Cytokines encompass; chemokines, interleukins, interferons, lymphokines and tumor necrosis factors [206].

Synthesized mainly by macrophages and lymphocytes, but also, by polymorphonuclear leukocytes, peripheral tissues, and by glial cells and other brain-resident cells in the CNS. Cytokines distinguished by their functional redundancy and pleiotropism; it influences various cells, and intervein in the regulation of systemic homeostatic functions especially the host responses to infection, regulate immune system signaling, and inflammation, cell growth, survival and differentiation.

Instantly, when there is an acute inflammation within the brain, to circumvent this event, and to tackle it before spreading throughout the brain, and convert to be chronic, aggressive and intolerable, cascade of events occurs, beginning initially with the secretion of pro-inflammatory cytokines, chemokines, small molecule messengers, tumor necrosis factors and reactive oxygen species produced by glial brain resident cells represented mainly by microglia. The widespread activation of this first line immune system (microglia & astrocyte) is essential for the beginning of the inflammatory process.

Indeed, discovery of several AD risk factor genes liked with immune response and microglia, such as CD33 and TREM2, through GWAS has increase our understanding on their part in the AD [207, 208]. It has been demonstrated that TREM2 is excessively expressed in microglial cells and has been shown to facilitate phagocytosis [209].

Transition to activated microglia states is generally associated with the upregulation of proteins like TREM2, apolipoprotein E (APOE) [36].

The outcomes of this process depend on the intensity and duration of the inflammation [199]. Infiltration of peripherical immune cells into the healthy brain isn't an easy task, compared to other tissues, because CNS is considered as an immune-privileged site and has its own immune cells that strictly regulate immune cell-BBB interaction. Indeed, glial cells represented by innate immune system, confront relentlessly to strange invaders, without the intervention of the peripheral immune systems. When the brain's innate immune system is in insolvency state or unable to combat the stubborn acute inflammation, for one reason or other, such as, in severe intensity of the pathological conditions and persistence inflammation, this led to an expansion of the acute inflammation region, and in this case, adaptive immune cells/peripheral immune cells and blood cells infiltrate into the brain parenchyma after the failure of the innate immune system, and compromised BBB to prevent the shedding of the acquired immune cells from entering the brain, along with the main inflammatory cytokines (IL-1β, TNF-α, and IL-6) through the compromised tight junctional system (TJs) of the blood-brain barrier (BBB), which further increases BBB leakage and escalate the neural loss. The dysfunction of the immune system has largely been painted as detrimental to the AD pathology [210, 211].

This process is considered progressively chronic with highly destructive or pathological consequences, which in turn induces neurodegeneration and cognitive impairment [212-214].

The inflammatory escalation and the chronic situation may occur also as a result of lack of balance between anti-inflammatory and proinflammatory response, as happened in Alzheimer's disease (AD), due to over-activation of microglia and cytokines [215, 216]. The association of AD with BBB come from the pathological event that strike the BBB. BBB normally acts as a gatekeeper of peripheral immune cells and actively contributes to immune cell trafficking into the brain. Dysfunction of BBB, causes it loses its validity and its unique semipermeable property, this permit trafficking of peripheral immune cells into the CNS. Isolated microvessels from AD patients highly expressed proinflammatory cytokines, indicating that BMECs contribute to neuroinflammation in AD [217]. Additionally, an increased number of macrophages, neutrophils, natural killer cells, T cells, and B cells who infiltrate the vessel wall or perivascular space in brain areas such as the hippocampus and frontal cortex are typically affected in AD [218-232]. Chronic immune response in the brain of patients with AD has been considered a substantial part of the central pathology of AD, which has been observed in AD brain autopsy and AD preclinical models. Chronic stimulation of brain resident microglia [233] and other immune cells has been observed, as a leading factor who triggers Aβ and Tau pathologies and could be linked to the pathogenesis of AD [232]. Therefore, the brain loses its property and no longer owns the title of immuno-privileged organ and NVU dysfunction loses its property too, due to the increase permeability and entrance of peripheral immune cells and various substances into the brain territory [36, 234, 235].

It is widely accepted that unappropriate activation of the innate immune system by accumulated neurotoxic material and decrease blood flow can trigger microglia and astrocytes, provoking an inflammatory response with secretion of neurotoxic cytokines and chemokines. Particularly activation of microglia, along with increased expression of markers associated with innate and adaptive immune system responses contribute to neuroinflammation, and

neuropathological changes in AD [236, 237]. GAWS studies have calibrated risk loci that are substantially involved with the pathogenesis of AD, almost all are located near or within genes that are predominantly expressed in microglia [238]. Additionally, chronic neuroinflammation and innate immune system activation including pro-inflammatory gene polymorphisms, such as CCL3/MIP-1α and IL-6, which are produced by activated microglia have been exhibited to be part of AD pathology and especially mediate Aβ plaques and neurofibrillary tangles (NFTs) [207]. In fact, the relationship between microglia activity and the Aβ load when it reaches a culmination point, is inversely proportional. Thus, increase Aβ load causes a decrease of the activity of microglia [239, 240]. Thus, the term "microgliopathy" as has been suggested, is a cogent term, recognizing that dysfunction of microglia represents a primary disease-causing mechanism [241].

Microglia and AD:

It is worthily to mention, that microglia continuously monitor the healthy CNS, commands the dynamic process of Immunosurveillance in CNS through its multiple functions such as eliminating foreign pathogens, including bacteria, viruses, or pre-cancerous and cancerous cells from the body, providing immune defense and maintaining homeostasis [242, 243]. A meticulous controlled microglia network throughout the CNS parenchyma facilitates efficient immunosurveillance, where each cell responsible on special tissue territory. Each cell is recognizing and surveilling its environment and knowing the surrounding cells, dislodging cell metabolites and has a tight communication with neighboring cells and facilitating cellular crosstalk.

The tissue surveillance is another central function of microglia during embryogenesis and adult CNS, it has an essential role to structure, wire, and maintenance of neural networks [244-246]. During healthy state, this "tissue surveillance" by microglia represents an essential process for CNS homeostasis and development [243]. The unique feature of microglia cells as housekeeper come from their possession of highly motile branching processes (amoeboid shape), and their plasticity highlights the transition between several activation states during the progression of AD pathology [247]. Initially, microglia function focuses on guarding, and in a protective role by contributing to tissue repair, such as Aβ clearance and combat inflammation [248, 249]. Additionally, intracerebral overproduction of Aβ and the enhance of inflammatory triggers lead to continuous chronic activation of microglia during severe stages of AD [36, 250, 251]. This hinders the process of dislodging of Aβ and increases the process of secretion of pro-inflammatory agents such as, cytokines, chemokines, reactive oxygen species (ROS) and other neurotoxic products, leading to the accumulation of Aβ and thereby amplifying the general inflammatory environment that increases neuronal atrophy and synaptic disfunction [36, 250-253]. Both brain resident cells, such as neuroglial cells, and peripheral immune cells contribute to neuroinflammation. Neuroglial cells as microglia, has a relatively late intervention in the neuroinflammation of AD, in contrary, peripheral inflammatory factors who play a crucial role in the early stages of AD progression [254, 255]. Indeed, plethora of blood samples collected from patients with mild cognitive impairment (MCI) and AD suggest that peripheral immune response is a very early feature of the disease [254]. The early intervention is in harmony with the activation of peripheral leukocytes and their insertion into the brain via the BBB [256-260]. Indeed, trafficking of immune system cells have recently been implicated in the pathogenesis of AD, based on studies showing that neutrophils invade the brain and contribute to the induction of cognitive dysfunction and promote the neuropathology of AD [235].

Shedding light on the innate immune system: Glial cells, mainly microglia and astrocyte:

Glial cells are brain resident cells, and the main two players in neuroprotection and neuroinflammation, depending on the circumstances: Through development, microglia are the brain's primary immune cells, responsible for the phagocytosis of cellular debris and participate to model the developing CNS, also to control of apoptosis mechanism, that occurs during the early postnatal development. furthermore, it is necessary for the dislodging the unnecessary synapses, and removal of apoptotic neurons [261, 262]. The doctrine and or the prevailing line of thought regarding microglia as a disease indicator, is now undoubted, since experimental evidence shows that either inactivity or excessive activity of microglia is critical and dangerous. The CNS environment must favor an appropriate and specific response of microglia, with the final goal of maintaining the CNS in health. Multifactorial risk factors (Epigenetic factors and genetic variations) stimulate microglia activation in individuals exposed to environment challenges which may provoke an aberrant microglial response that deviates the normal neural network development. Microglia diversity in humans has been entrapped by single cells transcriptomics and goes across the classic concept of M1/M2 phenotypes. The classic M1-M2 dichotomy has been used traditionally to describe the microglial activation states when purified microglial cells are exposed to stimuli provoked by pathogens. Microglia upon activation, depends on disturbances of brain homeostasis which can determine rapid and profound changes in microglial morphology, gene expression and function [263-266]. Changes in gene expression, reorganization of surface molecules for interaction with extracellular environment and neighboring cells, and release of soluble factors acting as pro- or anti-inflammatory factors causing microglia to polarized into pro-inflammatory or anti-inflammatory phenotype (M1 phenotype and M2 phenotype respectively), depending on the stimulus.

The M1 type is triggered via the classical pathway by pro-inflammatory stimuli, such as interferon-γ, the lipopolysaccharide (LPS) of gram-negative bacteria, or aggregated pathogenic proteins (Aβ, α-synuclein and others) [267, 268]. The outcome of M1 phenotype triggering is the demolition of surrounding glial and neural cells by secreting neurotoxic substances such as: pro-inflammatory cytokines and chemokines like interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), C-C motif ligand (CCL)-2, superoxide, and prostaglandin- 2 [269]. On other hand, the M2 phenotype functions are different and they comprehend tissue repair and wound healing by secreting anti-inflammatory mediators, such as: arginase-1 or chitinase-3. This phenotype can be induced by IL-4 or IL-13 in the alternative pathway, or via acquired deactivation by IL-10 or the transforming growth factor-beta (TGF-β). While both phenotypes are in homeostasis during acute stimulation, the M1 phenotype (pro-inflammatory phenotype) is predominant in chronic inflammation such AD neurodegeneration. Therefore, exaggerated microglia stimulation can lead to a potentiating of tissue destruction through a positive feedback loop as it happens in almost all neurodegenerative diseases [270].

Astrocytes play a wide role in CNS; their functions as a housekeeper support the BBB integrity, regulating neurotransmitters equilibrium and balance, and guarding existing and newly formed synapses [271]. Coincidentally, participate in removing catabolites of death cells, neurofibrillary tangles, amyloid plaques and respond to ischemia, infection, protein deposits, or other brain abnormalities via scar formation and reactive gliosis [271]. Astrocytes occupy a strategic position between capillaries and neurons. They are the most abundant cells in the brain. Astrocytic end-feet form a coating network around the brain vasculature, the glia limitans, and, together with endothelial cells and pericytes, they form the BBB, separating the bloodstream from the brain parenchyma. Astrocytes by secreting cytokines and exacerbating mechanisms contributing to neuroinflammation, a key player in both neurodevelopmental and neurodegenerative pathologies. Astrocytes are responsible for the maintenance of BBB integrity, also produce apolipoprotein E (ApoE). It was shown that ApoE knock-out mice present with a dysfunctional BBB develop psychotic behaviour, suggesting a relationship between impaired BBB function and neuropsychiatric diseases [272]. In accordance with the functions of microglia, stimulated astrocytes also display

neuroprotective and neurotoxic activities. According to Liddelow et al [271]. astrocyte shows different entities that are analogous to the M1/M2-type microglia, depending on the activation stimuli. A1 astrocyte phenotype rapidly develop after acute CNS injury, such as CNS neuroinflammation. It acts immediately in response to the proinflammatory mediators that are secreted by M1-type microglia, they create a secondary inflammatory response [273]. This A1-type astrocyte secretes neurotoxic factors that induce the rapid death of neurons and oligodendrocytes, thereby driving neurodegeneration and disease progression [271]. Although, it maintains a feedback loop that galvanizes further M1-type microglia, as well as leads to degradation of the extracellular matrix (ECM) and tight junction (TJ) of BBB via matrix metalloprotease (MMP) and vascular endothelial growth factor (VEGF)-A secretion [274, 275].

Pericytes role is maintenance of BBB permeability.

Pericytes located within the neurovascular unit (NVU) between endothelial cells, astrocytes, and neurons. The number of pericytes involved in the barrier inversely correlates with its permeability, thus a decrease in the number of pericytes correlates with an increase in the BBB permeability [276]. In addition, reduction in pericyte coverage across the BBB is inversely correlated with ageing [277] and neurodegeneration[276]. On the other hand, pericyte degeneration results in BBB breakdown with the accumulation of neurotoxic molecules leaking from the blood [278].

Conclusions

A plethora of hypothesis, ranging from the tauopathy, cholinergic hypothesis, neuroinflammation, amyloidogenic cascade, oxidative stress and disruption of BBB has been suggested to explain the pathogenesis of AD. Indeed, they are multiple hypothesis, but unfortunately, no conclusive one is adapted completely yet, and no convincing explanation for the dilemma of the underlying the pathogenesis of AD, that still looming on the horizon [82, 177, 279-282].

Notwithstanding, the mysterious etiology of AD that seems to be multifactorial, and multiple factors orchestrate together to cause this devastating illness, combination of age-related changes, genetic, environmental and lifestyle factors affect the brain over time may underpinning its complicated pathology, which non-limited to senile plaques (Aβ) and neurofibrillary tangles (tau) where accumulated intracellularly and extracellularly observed respectively. However, other substantial and biological processes have been also emerged in its pathogenesis in recent years, such as — breakdown and/or dysfunction of the blood–brain barrier (BBB); patients' carriers of the gene variant APOE4 and its link to BBB; and neuroinflammation option. Furthermore, type 2 diabetes (T2DM), metabolic syndrome (MS), brain insulin resistance (IR), whose have also observed as early markers that may provoke pathogenic consequences, that

Independently of whether BBB is the cause or consequence of AD, the involvement of BBB disruption in AD has been proven extensively [67, 283].

Strictly speaking BBB dysfunction has obtained recently a special gesture; plethora of studies have implied and illustrated that BBB dysfunction plays a crucial role in the initiation and development of AD. Furthermore, BBB damage promotes the buildup of Alzheimer's Aβ toxin in the brain [69, 284]. Thus, BBB breakdown, should be considered as one relevant pathophysiological domain in AD pathogenesis framework as potential player, which often precedes detectable AD symptomatology and neurophysiological changes [285].

Additionally, BBB dysfunction could lead to chain of events in neurodegenerative disorders, includes increased BBB permeability, microbleeds, impaired glucose transport, impaired P-glycoprotein function, perivascular deposits and accumulation of amyloid-β (Aβ) especially in AD pathology, because BBB is the one thrown at it to clean out the Aβ across the barrier. Thus, decrease clearance abilities may therefore promotes the built-up of Aβ plaques which is an initial insult itself sufficient to initiate neuronal loss and neurodegeneration [21-24, 286].

Although, BBB damage may also induce neurodegenerative processes via the activation of inflammatory pathways, via penetration of neurotoxic blood-derived products, pathogens, and cells across BBB into the brain [25], these primary malefactors that cause brain damage, shortly after BBB dysfunction, are associated with inflammatory and immune responses [26], and provokes pericyte-mediated cerebral hypoperfusion [27], which altogether can initiate multiple pathways of neurodegeneration. Undoubtfully, accumulation of neurotoxic material and hypoperfusion can activate glial cells (astrocytes and microglia within the brain), leading to inflammatory response with secretion of chemokines and cytokines [287].

It is well known, that innate immune system is a brain safeguard in health and disease, they constitute the first front in confronting any abnormal event in the brain, and they are primarily engaged in neuroinflammation in AD. Strikingly, activated astrocytes and microglias around plaques have shown by different studies, they release pro-inflammatory materials and trigger further inflammatory processes. Thus, glial cells-mediated inflammation holds two standards: advantageous and disadvantageous, or they have a "double-edged sword role", causing both beneficial and harmful effects in AD. Indeed, chronic activation of microglia in the brain beside other immune cells exacerbate Aβ and Tau pathologies and could be a link in the pathogenesis of AD [288-290].

In addition, leakage of the BBB tight junctions (TJs) increase permeability of BBB, this process paves the way for infiltration of peripheral macrophages and neutrophils into the brain and activate more the innate immune response. Besides entry of peripheral infiltration of circulating leukocytes into the brain and influx of T and B lymphocytes, this action indicate that both adaptive immune and the innate immune orchestrate together, which may cause catastrophic consequences and affect badly the integrity of the brain parenchyma, leading to more neural damage [21, 69, 291].

The importance of APOE in physiology and disease is well known. Its role is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. In the CNS, APOE is expressed mainly in astrocytes and microglia and in the peripheral tissues, it encodes major lipid-carrier protein in the brain [74], but also vascular mural cells and choroid plexus cells. APOE modulates multiple pathways, its activities are associated with the endocytosis of lipoproteins, synaptic plasticity, membrane integrity, neurogenesis and neuronal degeneration, neuroinflammation, mitochondrial function, tau phosphorylation, and Aβ metabolism [75].

Moreover, APOE has a crucial role in amyloid beta-protein (Aβ) clearance, aggregation and deposition [79, 80]. The main associated pathological isoform of APOE in AD, is the APOE-ε4 genotype, it is the highest risk category for late-onset Alzheimer's disease (LOAD), with the underlying mechanism of this link being both presynaptic - and postsynaptic dysfunction [81]. APOE ε4 gene variant promotes Aβ plaque formation [82], which facilitates the loss of key presynaptic proteins [83] as well as disrupts long-term potentiation and plasticity [84] and leads to reduction in dendritic density [85]

In this context, it was shown that individuals who were cognitively intact and carried either one or two copies of APOE4 had a leaky BBB, initially in the hippocampus and in the parahippocampal gyrus [90]. Remarkable atrophy in these two regions, due to BBB dysfunction was observed, leading to memory and cognitive impairment. Moreover, histological analysis of post-mortem brain tissue has reported that BBB breakdown in AD patients, reduced cerebral blood flow, neural loss, and behavioral deficits independent of Aβ, and it is more noticeable among APOE4 carriers compared to APOE3 or APOE2 [91 – 95].

ApoE4 activates array of proteins, beginning with the protein cyclophilin A (CypA) in the pericytes, which in his turn

stimulates a downstream signalling pathway involving activation of the inflammatory protein matrix metalloproteinase-9 (MMP9) in pericytes, and in endothelial cells. This activation by ApoE4 leads to MMP-9–mediated degradation of BBB tight junction and basement membrane proteins causing BBB breakdown [90, 96-98].

In addition, to cyclophilin A (CypA) and matrix metalloproteinase-9 MMP9) proteins which are part of inflammatory pathway are implicated in APOE4-driven pericyte damage and BBB breakdown were all are elevated in the CSF of APOE4 carriers [95, 101]. Thus, APOE4-status is a risk factor for BBB-breakdown via activation of the Cyp-A-MMP9 pathway [96, 102], and has been associated with increased hippocampal BBB leakiness and higher sPDGFRβ [90], the novel and sensitive biomarker of BBB disfunction [103, 104].

Other player is involved in the pathogenesis of AD is insulin resistance (IR), that still need more clarification. However, AD-IR meet common pathologic exclusiveness encompass amyloidogenesis, bioenergetic dysfunction, inflammation and obesity, which all together strengthen the notion that insulin resistance may accelerate the appearance of AD [145, 146]. One of the mechanism by which insulin impact cognitive abilities is by affecting cerebral energy metabolism. IR have catastrophic consequences on the brain function [145, 146]. Definitively, IR is observed among individuals with impaired insulin-stimulated glucose output into adipocytes tissues and muscle, accompanied by impaired insulin suppression of hepatic glucose output [152]. This phenomenon of reduced cells response to insulin leads to hyperinsulinemia, which occur due to genetic polymorphisms; of tyrosine phosphorylation of the insulin receptor, insulin receptor proteins, PIP-3 kinase, or abnormalities of GLUT 4 function and/or environmental factors [153-156].

Insulin resistance is a complicated pathophysiological disorder with impaired biologic response of target tissues to insulin stimulation, impaired ability to inhibit glucose production and stimulate peripheral glucose elimination, often come with hyperinsulinemia to maintain normoglycemia [157].

IR etiology depends on any factor causing disturbances in the insulin signaling pathway in the host, including decrease peripheral target tissue responsiveness to insulin, abnormalities in receptor binding, autophagy, intestinal microecology, in addition to metabolic dysfunction of the liver and other abnormalities in the host extracellular environment such as, lipo-toxicity, inflammation, hypoxia and immunity abnormalities that can trigger intracellular stress factors in key metabolic target tissues, which impairs the normal metabolic activity of insulin in these tissues thereby provoking the progression of whole-body IR [158, 159].

Plethora of pathways were suggested to explain the link between AD and IR [150, 151]. Initially, in case of insulin resistance state, several detrimental events happened, the IR, followed by the compensated peripheral hyperinsulinemia, and the resultant hyperglycemia or glucose intolerance. When IR developed a compensatory hyperinsulinaemia occurs due to increased secretion of insulin (extra-insulin) from the pancreatic β cell in order to achieve normoglycemia, this fact leads to inadequate or vicious cycle of IR ↔ hyperinsulinemia [150, 151, 154, 160-162].

This detrimental cycle of IR-hyperinsulinemia causes metabolic consequences include hyperglycemia, high blood pressure, hyperuricemia, dyslipidemia, high levels of elevated inflammatory markers, endothelial dysfunction, cardiovascular diseases, and may lead to metabolic syndrome, and type 2 diabetes. All together consequences mentioned up maybe implicated in AD pathogenesis in different degrees [161, 162, 154, 163].

Chronic elevation in peripheral insulin (peripheral hyperinsulinemia) levels impacts central insulin availability and function. Indeed, peripheral hyperinsulinemia leads to increase in insulin level in the brain, because the transport of molecules across the BBB is highly affected by the variation in their peripheral levels, especially the high level of insulin [145, 163, 164].

Insulin is degraded into the brain by the insulin degrading enzyme (IDE), also named-insulysin), structurally, in human the gene encoding IDE is located on the long arm of chromosome 10 (q23-q25) and contain 24 exons and large sequence of introns [165].

IDE originally known as the main enzyme involved in the cleavage of insulin as well as other amyloidogenic peptides, such as the β-amyloid (Aβ) peptide and it eliminates Aβ's neurotoxic effects – one of the hallmarks of Alzheimer's disease (AD) – this stress the relationship between IDE, diabetes and AD [167, 168].

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However, The IDE cleaves a numerous of peptides unevenly, including β-amyloid, demonstrating a critical role in pathophysiological processes regulated by these peptides [170-175]. It is well known, that IDE represent the link and the key factor in the crosstalk between hyperinsulinemia and AD [176]. Furthermore, genetic studies have demonstrated that IDE gene variations share clinical symptoms of AD as well as the risk of type 2 diabetes (T2DM). An optional explanation to the deficiency of IDE gene, may be caused by either genetic variation, or by the deviation of IDE from the degradation of amyloid-β peptide. indeed, decrease catabolic regulation and degradation of amyloid-β peptide by IDE, in favor of insulin creates an extracellular deposit and failure of clearance of amyloid-β. Therefore, the deficiency of IDE favors extracellular deposits of amyloid-β neuritic plaques, which is one of the underlying neuropathological hallmarks of AD [177-180].

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Thus, in addition to the already low amount of insulin that entered to the brain due to the downregulation of BBB transporters, and to the higher linkage of IDE to insulin, the free quantity of Aβ nonattached to IDE is more notable and led to Aβ accumulation in the brain, which is one of the important hallmarks of AD [185]. Therefore, considering the pathogenic interaction between Aβ and impaired insulin signaling, it is not surprising that central metabolic dysfunction is a certain feature of AD, illustrated by brain glucose hypometabolic changes, in addition, to defects in insulin signaling, usually proceeds AD signs and symptoms by several years [187, 188]. Concerning insulin signaling consequences at the cellular level, insulin affects all the BBB network including vascular endothelial cells, neurons, glial cells and pericytes, by its involvement in the regulation of capillary vasodilatation (high concentration of insulin) and vasoconstriction (low concentration of insulin) [189-191]. Through this, the BBB structure and discharge of Aβ from the brain tissue into the blood vessels is maintained. However, insulin resistance impacts negatively the cerebral blood pressure regulation, incremented BBB permeability, and increased intracerebral Aβ accumulation [192]. In fact, IR as well as hyperglycemia affect memory performance and neuronal growth which play role in cognitive dysfunction, a key clinical feature of AD [193].

In another way, IR has been linked to tau hyperphosphorylation tauopathy which is crucial pathogenic feature in AD [194]. In addition, IR affects and decreases neurotransmitters' levels [195]. For instance, impaired insulin signaling reduces acetylcholine level in the brain leading to crucial cholinergic perturbations which are largely implicated in AD progression [193]. In fact, the synthesis of acetylcholine from choline and acetyl-Coenzyme A (Acetyl-Co-A) is reduced significantly in AD patients [196].

Summary

Many hypotheses have investigated the conditions that undermine cognitive functioning. But the debate in full swing to

understand the basic pathogenesis of AD. Great efforts are still being made to comprehend better what allows, causes, or worsens AD. Many researchers put most attention to neuroinflammation, dysfunction of BBB, the link between AD-IR, and to apolipoprotein epsilon-4 allele to BBB and AD (Figure 1). Neuroinflammation is a two-edged sword-a well-intentioned but sometimes destructive helper, was studied extensively. Understanding in more depth how immune reactions interact with the various features of AD increases our efforts to find strategic prevention and appropriate treatment of chronic inflammatory conditions, by blocking the inflammatory proteins that microglia release when activated. Additionally, BBB is a highly selective semipermeable structural and biochemical barrier which ensures a stable internal environment of the brain and prevents foreign objects invading the brain tissue. BBB is critical for brain Aβ homeostasis and regulates Aβ transport. Faulty BBB clearance of Aβ through deregulated LRP1/RAGE-mediated transport, aberrant angiogenesis and arterial dysfunction may initiate neurovascular uncoupling, Aβ accumulation, cerebrovascular regression, brain hypoperfusion and neurovascular inflammation. Indeed, BBB breakdown has been suggested as an early marker for AD; yet the relationship between BBB breakdown and AD-specific biomarkers based on the amyloid/tau/neurodegeneration framework still need more clarification [286].

The importance of a healthy BBB for therapeutic drug delivery and the adverse effects of disease-initiated, pathological BBB breakdown in relation to brain delivery of neuropharmaceuticals are extremely important. The characterization of molecular mechanisms controlling vascular inflammation and leukocyte trafficking could therefore help to determine the basis of BBB dysfunction during AD and may lead to the development of new therapeutic approaches. In fact, the need for future directions, gaps in the field and opportunities to control the course of neurological diseases by targeting the BBB are warranted [292].

Furthermore, glial cells, which are normally responsible for maintaining the homeostasis of synaptic transmission and its remodeling by pruning, are the initiators of neuroinflammation and toxic tau and amyloid-β (Aβ) accumulation. Thus, they deliver the brain into a situation of sustained or even self-accelerated deterioration. We explain their function and their role in the neuroinflammation, the cell types and mediators involved in neuroinflammation and AD, the symptom manifestation in clinical settings, and potential candidates for improving diagnosis and treatment [293-295].

Insulin resistance (IR) is a complicated pathophysiological disorder with impaired biologic response of target tissues to insulin stimulation, impaired ability to inhibit glucose production and stimulate peripheral glucose elimination, often come with hyperinsulinemia to maintain normoglycemia [157].

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Plethora of pathways were suggested to explain the link between AD and IR [150, 151]. Initially, in case of insulin resistance state, several detrimental events happened, the IR, followed by the compensated peripheral hyperinsulinemia, and the resultant

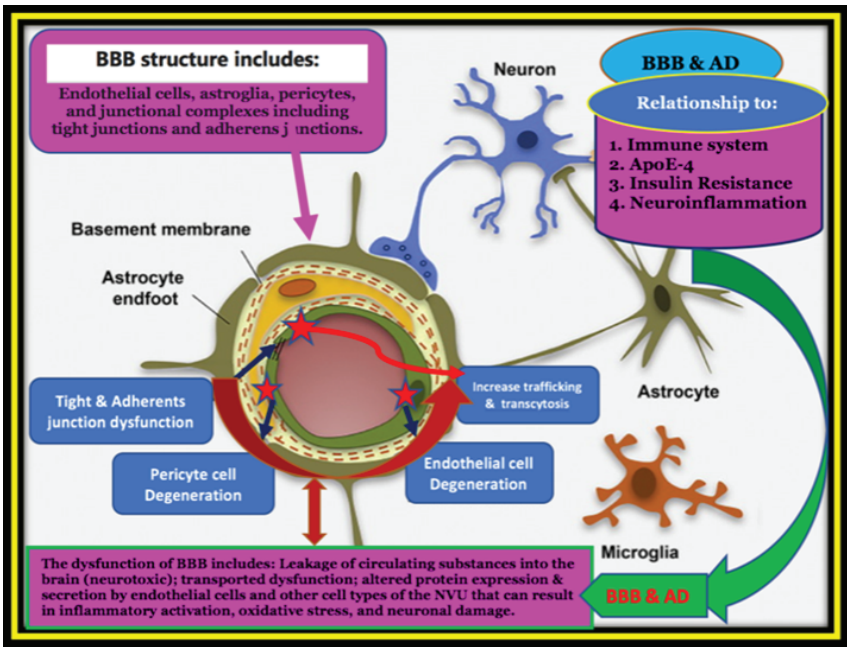

Figure 1. Alzheimer's Disease (AD) is a multifactorial disorder, caused by a combination of age-related changes, genetic, environmental and lifestyle factors that affect the brain over time. Plethora of substantial and biological processes have been also emerged in its pathogenesis such as-breakdown and/or dysfunction of the blood–brain barrier (BBB); patients' carriers of the gene variant APOE4; and the immunosenescence of the immune system. Furthermore, type 2 diabetes (T2DM) and metabolic syndrome (MS) whose have also observed as early markers that may provoke pathogenic pathways that lead or aggravate AD progression and pathology. There are numerous substantial AD features that require shedding light on, such as chronic neuroinflammation, decrease glucose utilization and energy metabolism as well as brain insulin resistance (IR). In this figure we describe the physiological and the pathological Blood Brain Barrier (BBB), and its relationship with AD. We tried to broadened our understanding &to connect the dots of the multiple comorbidities and their cumulative impact that may have synergistic effects on BBB dysfunction and AD pathology. We shed light on the path-physiological modifications in the cerebral vasculature that may contribute to AD pathology and cognitive decline prior to clinically detectable changes in amyloid beta (Aβ) and tau pathology, diagnostic biomarkers of AD, neuroimmune involvement and the role of APOE4 allele andAD-IR pathogenic link - the shared genetics and metabolomics biomarkers between AD and IR disorders.

hyperglycemia or glucose intolerance.

Chronic elevation in peripheral insulin (peripheral hyperinsulinemia) levels impacts central insulin availability and function. Indeed, peripheral hyperinsulinemia leads to increase in insulin level in the brain, because the transport of molecules across the BBB is highly affected by the variation in their peripheral levels, especially the high level of insulin [145, 163, 164].

Insulin is degraded into the brain by the insulin degrading enzyme (IDE),

originally known as the main enzyme involved in the cleavage of insulin as well as other amyloidogenic peptides, such as the β-amyloid (Aβ) peptide and it eliminates Aβ's neurotoxic effects – one of the hallmarks of Alzheimer's disease (AD) – this stress the relationship between IDE, diabetes and AD [167, 168].

It is well known, that IDE represent the link and the key factor in the crosstalk between hyperinsulinemia and AD [176]. Furthermore, genetic studies have demonstrated that IDE gene variations share clinical symptoms of AD as well as the risk of type 2 diabetes (T2DM). An optional explanation to the deficiency of IDE gene, may be caused by either genetic variation, or by the deviation of IDE from the degradation of amyloid-β peptide. indeed, decrease catabolic regulation and degradation of amyloid-β peptide by IDE, in favor of insulin creates an extracellular deposit and failure of clearance of amyloid-β. Therefore, the deficiency of IDE favors extracellular deposits of amyloid-β neuritic plaques, which is one of the underlying neuropathological hallmarks of AD [177-180].

The dual role of insulin degrading enzyme (IDE), in degrading insulin along with amyloid-β peptide, creates a kind of considerable competition between insulin and Aβ protein for IDE receptors, the result is in favor insulin, thus, insulin cleavage mechanism prevails, because IDE is more specific to insulin, and has more affinity binding sites for its receptors comparing to Aβ protein. Thus, IDE has been long envisaged as a potential therapeutic option; i.e., metabolic and neurodegenerative diseases [169].

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