Review

Gut dysbiosis, insulin resistance and Alzheimer's disease: review of a novel approach to neurodegeneration

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TABLE OF CONTENTS

1. Abstract

Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) share many common features including inflammation, oxidative stress and neuronal degeneration. Insulin resistance (IR) appears to be a common path in these pathological processes. IR is an early pathogenic event in AD, which leads to augmentation of hyperphosphorylated tau and Amyloid beta (Aβ).

The reviewed studies related to AD have revealed a positive association between T2DM and AD. This association was maintained in peripheral hyperinsulinemia cases without the presence of T2DM, which might be due to decreased insulin transport to the brain or the inadequate cerebral insulin production. Gut dysbiosis induces inflammation and consequently provokes both peripheral and cerebral IR and can amplify processes promoting AD.

Additionally, the risk of increased progression of AD was revealed due to pre-diabetes, T2DM and gut dysbiosis. The pro-inflammatory changes might affect progression of AD pathology by inhibition of the autophagolysosomal pathway and cerebral insulin signaling pathway. This review elaborates the role that cerebral IR might play in the underlying pathological events in AD.

2. Introduction

Alzheimer's disease (AD) is a neurodegenerative brain disorder and the most common cause of dementia [1].

According to an estimation of the 2010 US Census Bureau and the Chicago Health and Aging Project (CHAP) 5.8 million Americans age 65 and older are living with Alzheimer's disease in 2020. The population with AD increases with age, and the estimated growth of the population of age 65 and older is from 56 million in 2020 to 88 million by 2050. If there are no preventative measures instituted, the number of those suffering from AD is expected to grow to 13.8 million by 2050 [2, 3].

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association revised the diagnostic guidelines of AD, determining the stages of the disease based on clinical symptoms and biomarkers [4, 5]. Their recent studies have examined the brain processes underlying cogni-

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tive impairment by using post-mortem samples and *in vivo* biomarkers. In AD, slowly progressive cognitive decline is associated with characteristic pathological changes such as accumulation of beta-amyloid plaques outside neurons, and tau-protein tangles inside neurons [4, 5]. Inflammatory processes and enhanced amyloid aggregation consequently increase tau-protein accumulation, which exacerbate the progression of cognitive decline [6, 7].

Alzheimer's disease is a multifactorial disease associated with both genetic and modifiable factors. Early-onset AD has been linked with genetic mutations of presenilin 1 and 2, as well as of the encoding gene of APP (amyloid precursor protein) [8]. Late-onset AD has been associated with factors such as older age, especially above 75 years, family history of AD, and being a carrier of the APOE (apo-lipoprotein E) ε4 gene [9–12].

Multidomain lifestyle prevention trials have shown a significant effect on maintaining cognitive decline or improving cognitive performance among elderly who had increased risk of dementia. The interventions included dietary counseling, exercise, cognitive training, and management of vascular and metabolic risk factors [13–15]. The latest World Health Organization report highlighted diabetes, obesity, smoking and hypertension as leading risk factors contributing to increased risk of dementia and cognitive decline [16].

T2DM predisposes to the development of dementia in the elderly population and increases the risk of AD by two-to three-fold compared with subjects without T2DM [17–19]. Type 2 diabetes (T2DM) and AD share common pathological features including inflammation, oxidative stress, which contribute to insulin resistance and neuronal degeneration in both disorders [20–24]. Moreover, metabolic disturbances such as peripheral hyperglycemia and hyperinsulinemia before the T2DM stage have a negative impact on the pathophysiological processes and progression of AD [25–27]. A positive correlation was revealed between brain insulin signaling desensitization, brain insulin resistance and AD progression during the early stage of the disease regardless of the presence of T2DM [28, 29]. Dysbiosis due to the increased level of pro-inflammatory bacteria of the gut caused by a long-term high-fat diet can lead to systemic oxidative stress, inflammation and thus metabolic disturbance [30, 31]. This systemic inflammatory state might explain the increased risk of development of T2DM and AD with a high-fat diet [32–34].

Overall, prevention strategies that focus on improvement of metabolic impairment, such as lifestyle modification, may have a protective effect against cognitive decline in AD [13, 35, 36]. Our review aims to discuss the role that insulin resistance plays in Alzheimer's disease as well as the effect of Type 2 diabetes and gut dysbiosis in the progression of cognitive decline in AD.

3. Methods

We searched PubMed for articles, clinical studies and human experimental studies published during 2015–2020, with search terms including Alzheimer's disease, peripheral and brain insulin resistance, type 2 diabetes mellitus, gut microbiome and gut dysbiosis. The search yielded publications which covered human cell culture and brain tissue experiments, clinical trials, and population based studies, and excluded all animal related studies.

4. Impact of peripheral insulin resistance and presence of brain insulin resistance in Alzheimer's disease

4.1 Population studies regarding the association between AD and T2DM

T2DM-associated decreased in cognitive function, memory impairment, and increased risk of AD have previously been shown by preliminary epidemiological studies [18, 37, 38]. Subsequent studies discussed below have focused on the correlation between AD progression and the level of peripheral insulin as well as the role that insulin plays in the brain.

Among numerous clinical trials which have demonstrated an association between DM and cognitive decline was a prospective cohort study, which showed a 19% greater cognitive decline over 20 years-in participants with diabetes than in participants without diabetes [39]. Decreased cognitive performance was found in the pre-diabetic group (HbA1c 5.7–6.4%), the poorly controlled diabetic group (HbA1c $\geq$ 7.0%), and in the group of participants who had longer standing diabetes. Moreover, a higher baseline insulin resistance, calculated using the homeostatic model assessment (HOMA), was related with a greater impairment of overall cognition, especially of memory. This association is independent of other vascular risk factors and hyperglycemic status [40, 41]. According to another prospective population-based study with an average 10-year follow up, insulin resistance and a higher level of plasma insulin increased the risk of AD within a short period [42]. However, the risk of AD was no longer evident after 3 years, which might indicate that insulin level is more an accelerator of neuropathological changes in AD rather than the causative factor (Table 1).

4.2 Association between CSF insulin level and insulin resistance and AD

It is known that peripheral insulin levels correspond with insulin levels in the cerebrospinal fluid (CSF), as human studies have shown an increase in CSF insulin after injection of insulin peripherally in normal individuals [43]. Recent studies showed that individuals with peripheral insulin resistance have reduced CSF insulin levels. A study by Heni *et al*. showed a positive correlation between

Table 1. Relationship between Alzheimer's disease, cognitive performance, and insulin resistance.

Study design and objectives	Sample Size	Results		Conclusions	References
		Statistical Analysis	*P*-value		
• Prospective study (1993–2004). To determine relation between insulin resistance and the risk of AD	• N = 3139	Insulin resistance and AD: 1.39 (95% CI 1.04, 1.86)	< 0.05	• Higher plasma insulin level and insulin resistance were associated a higher short-term risk of AD with an increase in risk of approximately 40%.	[43]
• Prospective study (1987–2013). To determine if diabetes in mid-life is associated with a 20-year cognitive decline	• N = 13351	20 years decline, No diabetes: -0.78 (95% CI: -0.80, -0.75) 20 years decline, Diabetes: -0.92 (95% CI: -1.00, -0.85) Difference: -0.15 (95% CI: -0.22, -0.08)	0.071	• Diabetes in midlife was associated with significantly greater cognitive decline over 20 years. Subjects with poorly controlled diabetes (HbA1c ≥ 7.0%) had a larger decline compared to persons whose diabetes was controlled (HbA1c < 7.0%).	[40]
• Prospective study (1990–2013). To determine the association between HOMA- IR and cognitive performance in individuals with cardiovascular disease, with and without diabetes	• N = 1232 1. follow-up between 2004–2009 (N = 489) 2. follow-up between 2011–2013 (N = 347)	1/a. β = -3.66 ± 1.24 1/b. exclusion of DM cases: β = -4.45 ± 1.54 2/a. β = -0.16 ± 0.06 2/b. exclusion of DM cases: β = -0.17 ± 0.06	1/a. 0.003 1/b. 0.004 2/a. 0.006 2/b. 0.008	• Higher baseline HOMA-IR levels were associated with poorer cognitive performance after 15 years. The observed relationships were independent of vascular risk factors and diabetic status.	[41]
• Cross-sectional study (2014). To determine the association between HOMA-IR and cognitive performance	• N = 444 1. With diabetes (N = 61) 2. Without diabetes (N = 383)	1. MMSE score: β = -0.105 HOMA-IR 2. Logical memory II score: β = -0.091	1. 0.022 2. 0.047	• Hyperglycemia was associated with cognitive dysfunction, mainly in the executive function domain. IR was associated with memory impairment.	[42]

AD: Alzheimer's disease; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; DM: diabetes mellitus; IR: insulin resistance.

Table 2. Relationship between Insulin Resistance and Alzheimer's disease biomarkers and pathology.

Study designs and objectives	Sample Size	Results		Conclusions	References
		Statistical Analysis	*P*-value		
• Cross-sectional study. To evaluate whether a higher HOMA-IR may predict greater amyloid burden using [C-11]-Pittsburgh compound (PiB) and PET scanning in asymptomatic, late middle-aged adults.	• N = 186	1. HOMA-IR frontal: F (1, 135) = 5.429 2. HOMA-IR temporal: F (1,135) = 4.751 3. PiB uptake frontal: R^2 = 0.071 4. PiB uptake temporal: R^2 = 0.036	1. 0.021 2. 0.031 3. < 0.05 4. < 0.05	• Normoglycemia with higher insulin resistance corresponded to higher PiB uptake in frontal and temporal areas, reflecting increased amyloid deposition.	[58]
• Cross-sectional study. To evaluate whether higher HOMA-IR and APOE-ε4 levels would be associated with greater AD pathology in the CSF and worse memory performance.	• N = 70 middle-aged cognitively asymptomatic adults with a parenteral history of AD	1. CSF sAPP-β (HOMA-IR): F (1 ,63) = 4.21 2. Aβ42 (HOMA-IR): F (1, 63) = 4.26 3. CSF sAPP-α (APOE ε4): F (1, 63) = 8.65 4. sAPP-β (APOE ε4): F(1,63) = 7.74 5. P-tau181/Aβ42: F (1,63) = 5.21 6. memory performance: F (1,60) = 6.14	1. 0.044 2. 0.043 3. 0.005 4. 0.007 5. 0.026 6. 0.016	• Higher HOMA-IR was associated with higher sAPP-β and Aβ42 levels. APOE-ε4 carriers had significantly higher levels of sAPP-α, sAPP-β and P-tau181/ Aβ42 ratios compared to noncarriers. Higher HOMA-IR and greater P-tau181/ Aβ42 ratios predicted lower memory performance.	[55]
• Cross-sectional study. To examine the influence of IR on AD using plasma and CSF biomarkers related to IR and AD in cognitively healthy men (age and APOE-ε4- matched).	• N = 58 cognitively asymptomatic men 1. IR (N = 28) 2. non-IR (N = 30) 3. compare IR (N = 28) and non-IR (N = 30)	1. P-insulin and CSF T-tau: r = 0.310 2. P-insulin and CSF T-tau: r = 0.299 3. FCN2 β = -0.57	1. 0.018 2. 0.023 3. 0.014	• Significant correlation between plasma insulin and CSF Aβ/tau ratio. CSF and serum proteins significantly correlated with CSF AD biomarkers (Aβ, T-tau and P-tau).	[53]

Aβ, amyloid beta; AD, Alzheimer's disease; APOE, apolipoprotein E; CSF, cerebrospinal fluid; FCN2, Ficolin-2; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; IR, insulin resistance; PET, Positron emission tomography; P-insulin, peripheral insulin; sAPP-α, soluble amyloid beta precursor protein alfa; sAPP-β, soluble amyloid beta precursor protein beta.

CSF insulin level and serum insulin level in insulin sensitive individuals, and a negative correlation between the two factors in insulin-resistant participants [44]. Another study by Kern *et al.*, obese human subjects showed, independently from other variables, that insulin resistance negatively correlated with the CSF: plasma insulin ratio [45]. Reduced CSF insulin levels might be a consequence of impaired insulin transport through the blood-brain barrier (BBB) by receptor mediated transcytosis [46, 47]. According to an experimental model, reduced insulin receptor density on microvascular endothelial cell cultures of T2DM subjects can support this theory [48].

Reduced insulin levels were found in the CSF of participants with mild cognitive impairment (MCI) and early stage AD without the presence of an increased level in peripheral insulin [49]. On one hand, this could potentially be explained by the reduced brain insulin production in AD [29]. The insulin gene and insulin receptor expression was found to be at a higher distribution in the hypothalamus and the hippocampus in postmortem brain tissue and its reduction corresponded with the progression of AD [50, 51]. On the other hand, transcytosis of insulin may also be affected in AD and have an impact on the CSF insulin level. An experimental model of the BBB consisting of human cerebral microvascular endothelial cells (hCMEC/D3) showed decreased insulin transcytosis in the presence of Aβ40 and Aβ42 [52].

4.3 Association between CSF biomarkers, insulin resistance and AD

Although an inverse correlation was found between peripheral insulin levels and CSF insulin levels in AD, but a positive association was found between peripheral insulin levels and levels of AD biomarkers. This is supported by the study performed by Westwood *et al.*, whereby a significant association was found between plasma insulin levels and CSF Aβ/tau ratio and tau levels [53]. In this study, the CSF and serum levels of molecules involved in the pathogenesis of AD and insulin resistance were also measured. One of the highlighted proteins was FCN2 (Ficolin-2), previously associated with brain atrophy, which is reduced in insulin resistance and its level showed a negative correlation with CSF Aβ levels in the insulin-resistant group [54, 55]. This can be support the idea that AD and insulin resistance, and thus T2DM, share common pathological pathways. Another study showed that even in cognitively asymptomatic individuals, the higher the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) value, the higher the level of soluble beta-amyloid precursor protein (sAPP-β) and Aβ42 markers in the CSF and the worse the memory performance [55]. sAPP-β is a product of cleavage of amyloid precursor protein (APP) by the enzyme β-secretase (BACE1), which is part of the amyloidogenic pathway and contributes to the formation of amyloid plaques [56]. An experiment model showed decreased cleavage at the β-secretase sites of APP in the presence of insulin [57]. The influence of insulin resistance on the accumulation of amyloid plaques examined with Pittsburgh compound B (PiB) PET scan and increased HOMA-IR value was associated with a higher amyloid burden in the frontal and temporal lobes in cognitively normal individuals [58]. Further investigation via follow-up of individuals with higher HOMA-IR should be performed in order to observe changes in cognitive function and amyloid deposition (Table 2).

4.4 Association between brain glucose metabolism, insulin resistance and AD

Cerebral glucose uptake through the BBB and metabolism in the brain are mainly insulin-independent and peripheral hyperinsulinemia does not have a strong effect on this process [59, 60]. However, some studies have found insulin resistance to alter brain glucose metabolism.

Insulin-independent glucose transporters are glucose transporter (GLUT) 1 in the astrocytes, GLUT3 in the neurons, and GLUT5 in the microglia [61–63]. The insulin-dependent, GLUT4 has limited expression in the brain and is found mainly in astrocytes [64]. A study examining the effects of insulin on human SH-SY5Y neuroblastoma cells revealed increased GLUT4 transporter translocation to the plasma membrane, as well as increased glucose uptake in the presence of insulin [65]. However, the role of insulin is mainly of regulatory nature within the brain. Insulin plays an important role in memory and learning processes, which was demonstrated in the medial-temporal lobe where it enhanced neuronal activity [66].

Insulin has been shown to directly stimulate neurite outgrowth by regulation of tau phosphorylation, which likely contributes to neuronal cytoskeleton dynamics and neural plasticity [67, 68]. Additionally, insulin enhances the proliferation and glycogen storage of astrocytes [69], which is supported by the fact that abundant insulin-dependent glucose transporters (GLUT4) can be found in astrocytes [64]. Thus, astrocytes can contribute to the metabolic changes in the brain during disease processes by effect on the metabolic demand of neurons [24].

Older adults with prediabetes or diabetes were shown to have greater insulin resistance associated with decreased cerebral glucose metabolism observed on fluorodeoxyglucose (FDG)-positron emission tomography (PET) [70]. The brain regions with reduced glucose metabolism were found in the posterior cingulate cortex, the precuneus region, the parietal cortices (Brodmann areas (BA) 7 and 40, the temporal/angular gyri (BA 39)), and the anterior and inferior prefrontal cortices, which are all affected in AD as well. Although the participants were not diagnosed with MCI, a reduced ability to recall words was recorded during an activation scan compared to the healthy adult group of similar age and level of education [70].

Table 3. Relationship between Alzheimer's disease, insulin resistance, and cerebral glucose metabolism.

Study designs and objectives	Sample Size	Results		Conclusions	References
		Statistical Analysis	*P*-value		
• Cross-sectional study. To examine cognitively normal individual with higher HOMA-IR value and diagnosed prediabetes and diabetes were associated with reduced cerebral glucose metabolic rate in AD related brain areas.	• N = 23 with pre-diabetes or diabetes	1. Right frontal glucose metabolic rate uptake (HOMA-IR): r = -0.63 2. Posterior cingulate cortex glucose metabolic rate uptake (HOMA-IR): r = -0.58	1. < 0.05 2. < 0.05	• Higher HOMA-IR associated with reduced glucose metabolic rate at areas affected by AD, including posterior cingulate cortex, the precuneus region, parietal cortices, the temporal/angular gyri, and the anterior and inferior prefrontal cortices.	[25]
• Cross-sectional study. To determine the association between IR, deficits in brain glucose metabolism, and cognitive performance in those at risk for AD.	• N = 150 middle-aged adults with normal cognition and parental history of AD	1. global glucose metabolism (HOMA-IR): β = -0.29 2. medial temporal lobe glucose metabolism (HOMA-IR): R^2 = 0.178 3. immediate memory (Lower glucose metabolism): β = 0.317 4. delayed memory (Lower glucose metabolism): β = 0.305	1. < 0.01 2. < 0.001 3. < 0.001 4. < 0.001	• Insulin resistance is associated with significantly lower regional cerebral glucose metabolism, especially the medial temporal lobe, which in turn may predict poorer memory performance.	[71]
• Cross-sectional study. To determine the association between FDG metabolism and HOMA-IR in MCI and AD.	• N = 280 1. Control (N = 26) 2. MCI (N = 194) 3. Stable (N = 148) 4. MCI progressed to AD (N = 39) 5. AD (N = 60)	FDG metabolism in hippocampus (MCI progressed): F = 0.098 ± 0.029 FDG metabolism in medial temporal lobe (MCI progressed): F = 0.099 ± 0.020 R^2 = 0.211 5. /a FDG metabolism in hippocampus (AD): F= -0.076 ± 0.032 5. /b FDG metabolism in medial temporal lobe: F = -0.074 ± 0.034 R^2 = 0.096	4. /a < 0.01 4. /b < 0.001 5. /a < 0.05 5. /b < 0.05	• Higher HOMA-IR predicted lower FDG metabolism in the medial temporal lobe and hippocampus among participants with AD, and higher FDG for MCI participants who progressed to AD by 24 months.	[72]
• Prospective study (24-month follow-up). To evaluate relationships between cerebrospinal fluid (CSF) analyses include hyperphosphorylated tau (p-Tau181p), β-amyloid 1-42 (Aβ1-42) and total tau (t-Tau). To evaluate change in cognitive function. To assess change in FDG uptake using PET scanning.	• N = 412 1. Normal cognition (N = 82) 2. MCI (N = 241) 3. AD (N = 89)	t-Tau (FDG-PET 24 months): r = -0.17 p-Tau181p (FDG-PET 24 months): r = -0.27 p-Tau181p/Aβ1-42 (FDG-PET 24 months): r = 0.25 t-Tau/Aβ1-42 ADAS-Cog (24 months): r = 0.37 t-Tau (ADAS-Cog 24 months): r = 0.28 FDG-PET M24 (ADAS-Cog 24 months): r = -0.66 3. FDG-PET M24 (ADAS-Cog 24 months): r = -0.40	< 0.00047 3. < 0.00047	• Higher baseline concentrations of t-Tau, and p-Tau181p were associated with a decline in cerebral glucose metabolism. FDG-PET changes appeared to mediate t-Tau or t-Tau/Aβ1-42-associated cognitive change across all brain regions. Significant direct effects of alterations in Aβ1-42 levels on hypometabolism were observed in a single brain region: middle/inferior temporal gyrus.	[74]

Aβ, amyloid beta; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale-13 items; FDG, [18F]-fluorodeoxyglucose; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; MCI, mild cognitive impairment; PET, Positron emission tomography.

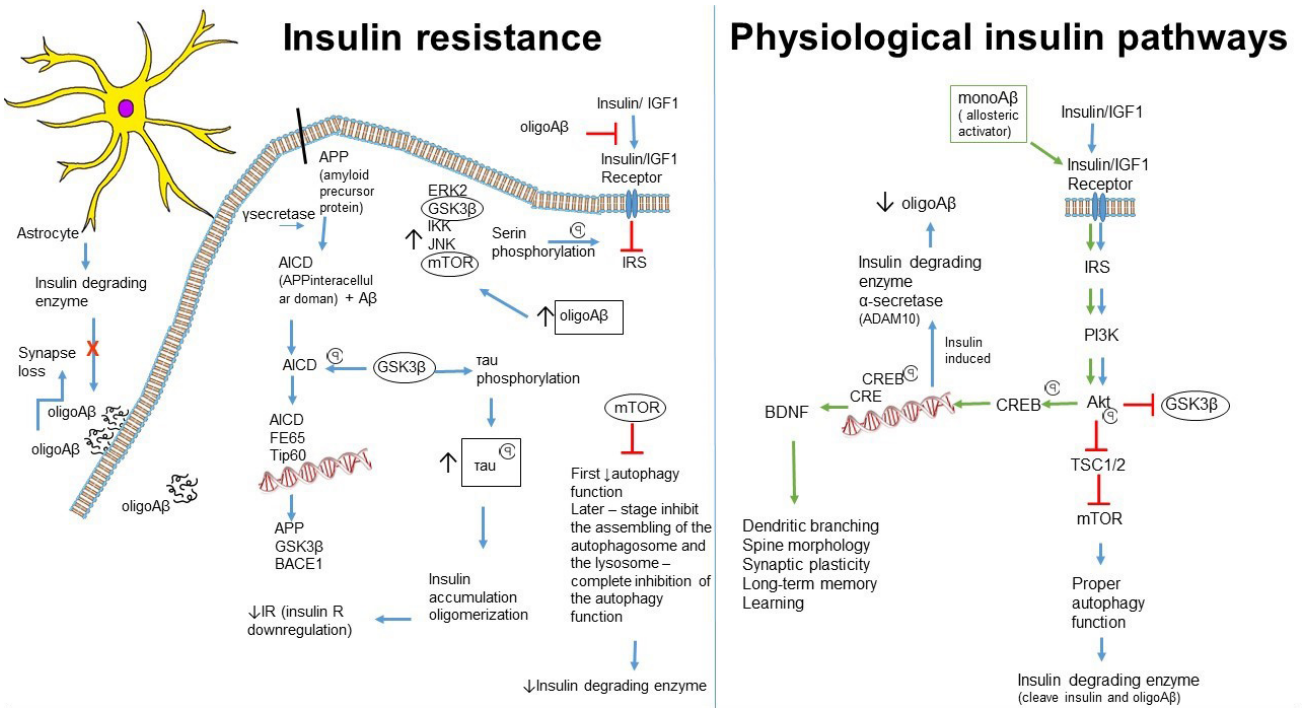

Fig. 1. Connection between neuronal insulin resistance and progression of Alzheimer's Disease.

Other studies have found similar results, whereby a higher HOMA-IR value and decreased glucose metabolism in the medial temporal lobe were associated with worse immediate and delayed memory performance on neuropsychological testing [71]. Further examinations of the medial temporal lobe and hippocampus of individuals with MCI and higher HOMA-IR values showed hypo- or hypermetabolism in these areas, depending on the rate of progression of the disease [72]. Namely, active progression of the MCI stage is related with hypermetabolism, and AD with hypometabolism, as detected by FDG-PET scanning [72]. This phenomenon might be explained by metabolic compensation against the incremental amount of the amyloid deposition [73]. In addition to using FDG-PET scanning to map cognitive performance, Dowling *et al.* also measured CSF biomarkers in subjects during a 24-month period [74]. This study found that towards the later stages of AD, there is an inverse correlation between baseline CSF biomarkers of intra-neuronal neurofibrillary degeneration, t-Tau and p-Tau181p, and the progression of hypometabolism and cognitive decline [74]. Tau hyperphosphorylation can be stimulated by amyloid beta oligomers and it was revealed that insulin is able to inhibit Aβ-induced neuronal cell death and prevent Aβ fibrillarization in AD [75, 76].

Reduced brain insulin signaling, and thus brain insulin resistance, which was observed in AD and T2DM cases, can promote neurodegeneration by decreasing brain glucose metabolism and hyperphosphorylation of tau [76]. These pathological changes and the previously mentioned regulatory role of insulin points toward the direction that insulin resistance has an indirect effect on metabolic disturbance of the brain by contribution to neuronal cell death (Table 3) (Fig. 1).

5. Brain insulin pathway and mechanism

The presence of insulin resistance and the detailed steps of the insulin pathway were examined on post-mortem brain tissues from non-diabetic subjects with AD and MCI and control subjects [77, 78]. The examined areas were the hippocampus, the dentate gyrus and subiculum, the prefrontal cortex and the cerebellar cortex. The insulin biological pathway under normal conditions is Insulin $\rightarrow$ Insulin receptor (IR) $\rightarrow$ insulin receptor substrate-1 (IRS1) $\rightarrow$ phosphoinositide 3-kinase (PI3K) $\rightarrow$ Akt, which inhibits several intracellular regulatory molecules, including apoptosis- inducing molecules such as, glycogen synthase kinase 3 (GSK-3) and the mammalian target of rapamycin (mTOR) complex. The central molecule in insulin signaling is IRS1, which is inhibited by serine kinases such as GSK-3 and mTOR via feedback inhibition, and extracellular signal-regulated kinase 2 (ERK2), inhibitor of kappa B kinase (IKK), and c-Jun N-terminal kinase (JNK) via feed-forward inhibition. Phosphorylation of the serine residue instead of the tyrosine residue on IRS1 leads to the disruption of the insulin signal, and therefore towards insulin resistance.

The levels of all the aforementioned kinases were elevated in brain tissue samples of subjects with AD, and elements of the amyloid plaques (Aβ oligomers) were shown to activate some of these kinases as well [77, 78]. Gradually increased levels of serine phosphorylated IRS1 (pSer-IRS1), from MCI to AD, were measured in post mortem brain tissue without diabetes and independently of APOE ϵ4 status, which found that elevated levels of serine kinases correlated with an increased accumulation of amyloid plaques [79]. Another complex study further provided evidence of the role of IRS1 in AD, which focused on the association between the neuronal phosphorylated IRS1 and brain atrophy in AD [80]. In this study, brain volume was positively associated with p-panTyr-IRS-1 (insulin signaling pathway) and negatively associated with pSer312-IRS-1 (insulin inhibition pathway) in the parietal-occipital junction and middle temporal gyrus bilaterally [80]. The volumetric variations were spatially correlated with IRS1 expression in normal brains [81]. Briefly, a likely cause of atrophy could be the impaired inhibitory effect of the insulin signal against apoptosis and oxidative stress [80]. All of these steps are directly affected by Aβ oligomers and lead to insulin signal inhibition [82].

Insulin has a role in impeding amyloid beta accumulation by promoting APP cleavage into the non-amyloidogenic, soluble sAPPalfa and stimulating the degradation of Aβ and proper functioning of the autophago-lysosomal pathway [56, 57, 77, 83]. Insulin enhances the transcription of α-secretase (ADAM10), which cleaves the APP in normal conditions [56, 57]. However, APP cleaved by beta-secretase (BACE1) and y-secretase lead to the amyloidogenic sAPP-β and AICG production [56, 57]. GSK3 phosphorylates APP intracellular domain (AICD), which is then able to translocate into the nucleus and form a complex with nuclear proteins, thereby activating transcription of amyloid production proteins such BACE1, APP, GSK3. Insulin inhibits AICD translocation by inhibition of GSK3 activity [83, 84]. Insulin also stimulates insulin-degrading enzyme (IDE) transcription, which promote Aβ degradation. Astrocytes are the main source of IDE and Aβ can be degraded by stimulating IDE secretion of astrocytes via the autophagy-based secretory pathway in AD [85]. Increased IDE activity was found in postmortem brain tissue in AD and its reduced activity towards the later stage of the disease is explained by increased neurodegeneration [86].

Aβ and tau are removed by autophago-lysosomal pathway and mTOR is one of the regulatory molecules of autophagy induction. However, the increasing level of Aβ leads to mTOR hyperactivity, which in turn inhibits autophagosome and lysosome fusion in neurons [87]. The increased level of Aβ further activates mTOR, which as a vicious cycle leads to a higher level of Aβ. Insulin can contribute the proper autophagy function by induction of mTOR through the PI3K/akt pathway [77, 83].

The Aβ monomer, in contrast to the Aβ oligomer, is the physiologic form of Aβ. It activates the PI3K/Akt pathway, leading to the phosphorylation of cAMP response element binding (CREB) protein, which binds to the cAMP response element (CRE) and mediates brain-derived neurotrophic factor (BDNF) transcription [88]. Aβ oligomers inhibit BDNF transcription by decreasing the level of the phosphorylated active form of CREB [88]. BDNF has a crucial role in human hippocampal synaptic plasticity via increasing the expression of synaptic proteins involved in the learning and memory processes, and the absence of it can therefore lead to neurodegeneration [89, 90].

6. Gut dysbiosis- inflammatory pathway—neurodegeneration

The microglia is the main phagocyte in the central nervous system (CNS), and provides a surveillance mechanism against pathogens via toll-like receptors (TLR), antigen presentation and cytotoxicity activity, such as the production of reactive oxygen species and cytokines [91]. Microglia shows pro-inflammatory hyperactivation in AD, which is induced by interferon gamma (INFγ), tumor necrosis factor alpha (TNFα), interleukins (IL) 4 and 13 and TLR ligand. The cytokines produced by microglia are TNFα, IL1-β and α, and IL6 [92, 93]. One of the several effects of the pro-inflammatory signal is insulin signal inhibition via augmentation of JNK activity, which in turn leads to the inhibition of IRS1 as was detected in post-mortem AD brain tissues [94].

Furthermore, the transcription of certain microRNAs (miRNA), such as miRNA-125b, is upregulated in AD, and has a higher concentration in the CSF [95]. This is thought to be a consequence of activated nuclear factor kappa B (NF-κB) via the inflammatory pathway. The upregulated miRNA-125b has been shown to downregulate several essential brain genes that have a critical role in neuroprotection via neuroprotectin D1, anti-inflammation via NF-kB regulation, and immuno-regulation via vitamin D3 receptor (VDR) [96]. The overexpression of miRNA-125b was also associated with tau hyperphosphorylation due to the downregulation of phosphatases and the neuroprotective Bcl-2-like protein 2 (Bcl2L2, Bcl-w) [97].

Peripheral proinflammatory cytokines may be able to activate the microglia, as the integrity of the BBB decreases with age. BBB degradation, which begins in the hippocampus, was observed to be more prominent in MCI and in early-onset AD than in normal aging brains [98, 99]. Moreover, hyperglycemia and hyperinsulinemia, as seen in T2DM, synergistically impair the permeability of the BBB [100]. Additionally, T2DM enhances the pro-inflammatory signals due to the increase the oxidative stress and NF-κB - mediated inflammation [101].

The enhanced pro-inflammatory signals in the brain due to the increased cytokines and reactive oxygen species (ROS) leads to initiation of autophagy. Accumula-

tion of Aβ increases the production of ROS and blocks the aforementioned lysosomal degradation. A study by Lipinski *et al*. revealed that besides the ROS- dependent activation, autophagy is up-regulated at the transcriptional level as well in AD. Although increased autophagic activity can be preventive in normal aging brain it is counterproductive in AD due to the failure of autophagolysosome formation [102, 103].

Production of pro-inflammatory cytokines (IL-1, IL-6, TNFα) can be triggered by bacterial lipopolysaccharides (LPS), and as the integrity of the human intestinal barrier decreases with age, the cytokines and LPS can further cause systemic and cerebral inflammation [104, 105]. Furthermore, these pathological connections correspond to the detected LPS and *Escherichia coli* fragments in amyloid plaques of post-mortem AD brain tissues [105].

Several bacteria have the ability to cause inflammation, such as *Bacteriodes*, *Alistipes*, *Gemella*, and *Blautia*, which are more abundantly found in AD cases, whereas the anti-inflammatory bacteria, including *Firmicutes*, *Actinobacteria*, *Dialister*, and *Bifidobacterium* are less abundant in AD [106]. An increased number of AD-related bacteria was associated with a greater level of CSF AD biomarkers (p-tau and p-tau/Aβ42), while presence of the less abundant AD-related bacteria were associated with a lower level of AD biomarkers in the CSF [106].

An investigation by Cattaneo *et al*. showed a greater number of pro-inflammatory bacteria, such as *Escherichia* and */Shigella* species, and a lower number of anti-inflammatory, *Eubacterium rectale* species in the gut of cognitively impaired individuals [107]. Furthermore, an increased level of pro-inflammatory bacteria was found in cognitively impaired subjects with detectable amyloid plaques by PET scan, but not in subjects with undetectable amyloid plaques [107].

The abundant pro-inflammatory bacteria already predominate in the pre-diabetic state, and the increased ratio of *Bacteroidetes* to *Firmicutes* is accompanied by reduced glucose tolerance in diabetes [108, 109]. This indicates that systemic inflammation, influenced by the composition of the gut microbiome, may have a significant role in the progression of pre-diabetes and that of AD.

Dietary habits influence the composition of the microbiome; an animal-based diet, including meat, eggs, and cheeses increased the abundance of *Bacteriodes* and decreased the abundance of *Firmicutes* [110]. In contrast, the plant-based diet, rich in grains, legumes, fruits, and vegetables increased the abundance of fiber-fermenting *Firmicutes*, such as *Eubacteria* and *Roseburia*, which leads to an increased level of short-chain fatty acids [110].

SCFAs, particularly butyrate, have several protective features such as maintenance of the integrity of the intestinal wall, tight junction amplification and maintaining the balance of the inflammatory pathways [111]. Butyrate suppresses production of the bacterial LPS-induced pro-inflammatory cytokines, IL-1, IL2, IL6, IL8, IL12, and TNFα by blocking the NF-κB transcription factor [112]. Moreover, it can promote the differentiation of anti-

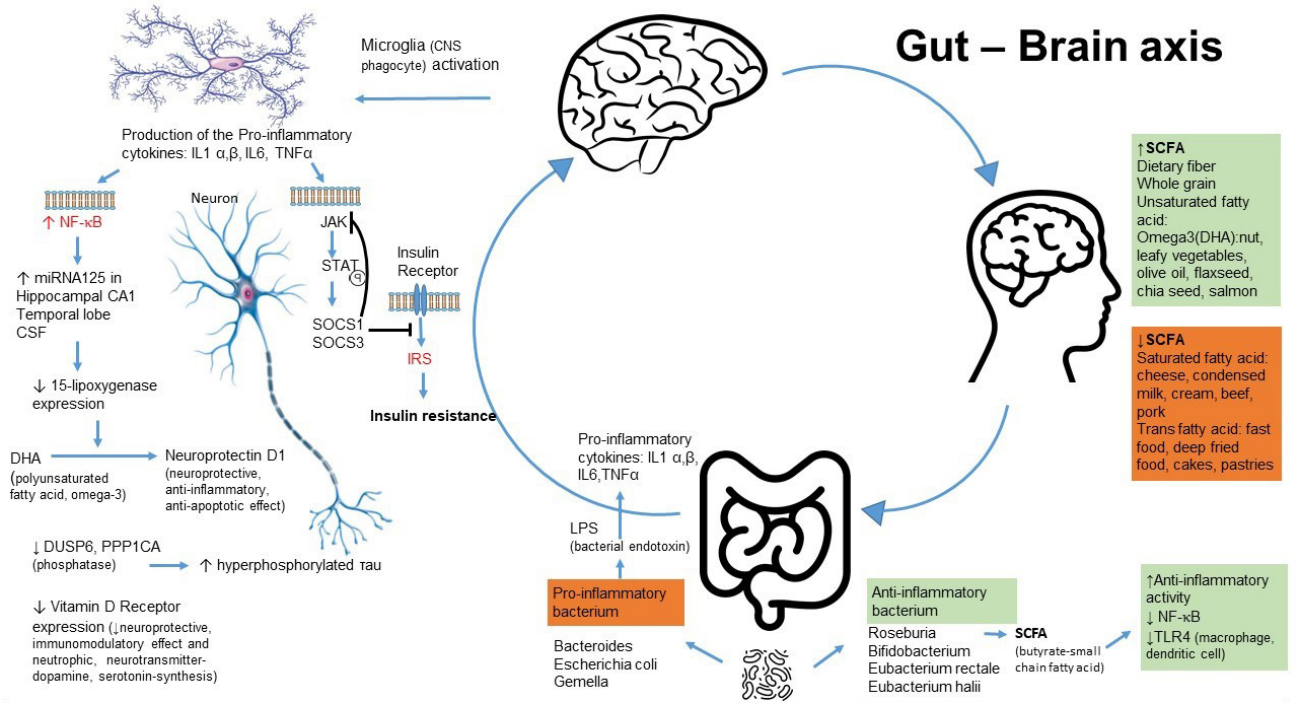

Fig. 2. Dietary effect on the gut microbiome. The gut microbiome plays an important role in insulin resistance in Alzheimer's Disease and in Type 2 Diabetes.

inflammatory IL-10-producing type 1 regulatory T cell by inhibiting histone deacetylases [113]. In addition to the immunomodulatory features, SCFAs have been shown to regulate the protein-protein interactions between Aβ1-40 and Aβ1-42 peptides, thus impeding the assembly of neurotoxic Aβ aggregates [114] (Fig. 2).

7. Conclusions

The pathological processes of AD and T2DM share many common features such as inflammation. Moreover, the peripheral insulin resistance without the development of T2DM can further exacerbate the pathological processes in the progression of AD. The pathological changes of AD may also be involved in causing insulin resistance in neurons. It is important to note that the function of the insulin in the central nervous system is primarily neuroregulatory, and has less of a role in the metabolism of glucose in the brain, in contrast to its function in peripheral organ systems.

Numerous factors play a role in the development of AD, and each enhancing the other can cause a vicious cycle in its progression. The discussed experimental models, clinical trials and population-based studies indicate that brain insulin resistance can be present independently of peripheral insulin resistance, which itself leads to amyloid plaque and tau neurofibrillary tangle formation and consequently neuronal cell death.

The presented studies indicate that gut dysbiosis might be one of the causative factors of brain insulin resistance, independently of peripheral insulin resistance. This theory is supported by the previously revealed pathological inflammatory pathways stimulated by gut dysbiosis. Peripheral insulin resistance can also develop or become further accelerated by the stimulated pro-inflammatory pathways in gut dysbiosis. Therefore, evidence suggests that gut dysbiosis may have a crucial role in the progression of AD by promoting insulin resistance in the periphery and in the brain. There is a negative association between a reduced anti-inflammatory bacterial load and AD pathology. On the other hand, an abundantly anti-inflammatory gut microbiome presumably decreases the risk and progression of AD by production of protective factors, such as SCFA. Consequently, lifestyle modification, which a properly composed healthy diet is a pivotal part of, has proved its efficient protective role in deceleration of cognitive decline in AD.

Both AD and T2DM are considered chronic diseases, which constantly develop from the asymptomatic to the symptomatic forms. The progression of AD can be mitigating by alleviation of aggravating factors, such as systemic inflammation and diabetes. The presence of brain IR in AD, elaborated in this review, needs further clarification by possible postmortem brain tissue evaluation and clinical trials. Increasing evidence shows the determinative role of inflammation in the progression of AD that might attain its effect through the brain insulin pathway and the defective autophagic function. Moreover, it was revealed that insulin can affect autophagy via regulatory molecules. These associations point towards new therapeutic targets.

In conclusion, we propose the importance of implementing adequate lifestyle changes and initiating timely treatment of chronic inflammatory conditions and metabolic dysfunction in order to decrease the risk of and prevent progression of AD. Further research is warranted in the investigation of these associations.

8. Author contributions

EL conceived and designed the research project and interpreted the data. She was a major contributor in writing the manuscript. AS, DS and JA contributed writing and editing the manuscript. AS and DS revised manuscript. All authors read and approved the final manuscript.

9. Ethics approval and consent to participate

Not applicable.

10. Acknowledgment

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11. Funding

Not applicable.

12. Conflict of interest

The author declares no conflict of interest.

13. References

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