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Cognitive Impairment and the Diabetic Brain

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Abstract

Alzheimer's disease (AD) and diabetes mellitus (DM) are the two most common and devastating health problems in the elderly. DM is a known risk factor for the development of cognitive dysfunction and dementia. Epidemiological and biological evidences support a link between type 2 DM (T2DM) and AD, but the precise mechanisms involved in the development of cognitive impairment in diabetics are not fully understood. Possible pathogenic pathways include genetic factors, ageing, ApoE status, hypo- and hyperglycaemia, cardiovascular risk factors, hypertension, obesity, multimorbidity and other factors the impact of which is in the focus of current research. Since disturbances of insulin signal transduction may be of pathogenic relevance in AD and related dementias, insulin and other antidiabetic drugs may be effective in slowing cognitive decline and may have neuroprotective effects in AD high-risk patients.

Keywords

Diabetes mellitus, Cognitive impairment, Pathogenesis, Multimorbidity, Vasculo-neural dysfunction, Anti-diabetic drugs in AD treatment

Introduction

An aging global population increases the incidence of Alzheimer disease (AD) and type 2 diabetes mellitus (T2DM). Both share a number of common factors causing an important impact on the quality of life and substantial health care costs. People with T2DM are at increased risk of cognitive dysfunction [1] and dementia [2-7], in particular diabetic patients with prior hypoglycaemia have a significantly increased risk of dementia [3,8-11]. The prevalence rates varied from 6 to 39% [12]. The relative risk of AD and T2DM ranges from none to over two-fold risk due to variations in the definition of AD and T2DM used for the selection of patients as well as their ages [13-16]. In a recent population-based study, newly diagnosed DM was associated with a 16% increase in the risk of dementia among seniors [3]. DM has been shown to influence the rate of functional decline among patients with mild cognitive impairment (MCI) and mild AD compared to those without DM [17]. The role of MCI attributable to DM was 8.8%, with higher risks for Afro-American and Hispanic persons (8.4 and 11.0%, respectively) [1]. Cognitive impairment with T2DM often presents as a decline in attention, psychomotor speed, executive function, and memory [2]. Undiagnosed cognitive impairment in T2DM-pateints is associated with reduced health status and more depressive symptoms. Detection of cognitive impairment in these patients may identify a vulnerable patient group that could benefit from tailored treatment and care [18].

The duration of DM, glycaemic fluctuations as well as hypoglycaemia are related to increased risk of developing cognitive decline and dementia [6,11]. However, cognitive impairment and dementia are associated with poorer DM management, indicating that the association between DM and dementia is bidirectional [19]. In contrast, good control of DM may improve cognitive decline and prevent AD [20]. The diabetic severity and progress frequently reflect the risk of dementia. The early change in the adapted Diabetes Complications Severity Index (aDCSI) may predict the risk of dementia in new-onset diabetic patients [21]. The aim of this article is to give a timely review of the neurobiology of cognitive impairment and the diabetic brain.

Impact of DM on Brain Structure and Function

Most of the insulin produced by pancreatic β-cells is transferred to the brain through the blood-brain barrier (BBB), while insulin production from cerebral neurons is still under debate [22]. DM alters cerebral metabolism, structure, and function, depending on the age of the individual and the type of DM (type 1 or 2). Both types induce regional abnormalities in both cortical and subcortical (hippocampus, amygdala) brain structures. The patterns of volumetric and neurocognitive deficits in diabetic populations are highly similar to that reported in individuals with major depressive disorder [23]. In T1DM, microstructural changes in white matter, reduced gray matter density, and reduced activation of the thalamus have been reported, while hypoglycaemia in T1DM and T2DM are associated with a reduction in neurocognitive function [7].

Epidemiological and biological evidence support a pathophysiological link between T2DM and cognitive impairment [6,8,20,24-36]. However, the precise mechanisms involved in the development of cognitive impairment and AD in diabetics are not fully understood. Several pathogenic pathways have been discussed [25,26]. Common pathogenic factors in both conditions include chronic hyperglycaemia per se, hyperinsulinaemia, insulin resistance, acute hypoglycemic episodes, especially in the elderly, microvascular disease, fibrillar deposits (in brain in AD and in pancreas in T2DM), altered insulin processing, inflammation, obesity, dyslipidemia, altered levels of insulin like growth factor and occurrence of variant forms of the protein butyrylcholinesterase [20]. Correction of these by lifestyle changes and pharmacological agents can be expected to prevent or retard the progression of both diseases.

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Brain insulin signaling plays an important role in learning and memory [37]. It declines with age [38]. Insulin receptors are widely distributed in the brain with variably high levels in different regions [39]. Insulin receptor substrates (IRS) are key moderators in insulin signaling and play a central role in maintaining basic cellular functions and metabolism [40]. The levels of IRS-1, 2, and IGF-R (insulin-like growth factor) are reduced in AD brain [41], which suggests that reduced insulin and IGF-1 signaling may result in hyperphosporylation of tau [42]. At least mice deficient with these substrates showed accelerated tau hyperphosphorylation [43-45]. Insulin resistance-induced hyperglycaemia decreases the activation of the Akt/CREB signalling pathway in hippocampal neurons that may suppress cognition [46]. Insulin resistance induces medial temporal hypermetabolism in MCI conversion to AD [47] and glucose uptake changes in medial temporal regions in AD are associated with worse memory performance [48].

Recent evidence has focused on T2DM as a potent risk factor of AD development which is likely to be mediated by insulin and insulin-like growth factors (IGF-1, IGF-2). The impairment of insulin/IGF signaling caused by insulin/IG resistance, characterized by reduced IR and IGF receptor binding causes oxidative stress (OS), mitochondrial dysfunction, and inflammation. In turn, reactive oxygen species (ROS) produced by OS and mitochondrial dysfunction as well as proinflammatory cytokines secreted during inflammation exacerbate insulin/IGF resistance, which is characteristic in both AD and DM 2 [49-51]. Increased levels of ROS are involved in insulin resistance and AD [52,53]. An excess of hyperglycaemia-driven OS increases the formation of advanced glycation end-products (AGE) [29,54], which overwhelm innate defences of enzymes and receptor-mediated endocytosis and promote cell damage via pro-inflammatory and pro-oxidant receptors for AGEs. OS may induce AGE formation which in turn induces OS [55]. OS further disturbs cell signal transduction, especially insulin-mediated metabolic responses and mediates insulin resistance [56]. Other common pathogenic factors include the protein butyrylcholinesterase (BChE), alterations of which occur in T2DM and may be related to amyloid pathology [20,57,58].

DM and Alzheimer Pathology

Autopsy studies stated that diabetic patients show significantly less AD pathology (senile plaques, neurofibrillary tangles, cerebral amyloid angiopathy, etc.) but more cerebrovascular lesions including microvascular lesions and white matter changes than subjects without DM [59-64], and increase of peripheral insulin was associated with reduced AD pathology and dementia severity [65,66].

Vasculo-neural dysfunction has been suggested to represent a potential etiological linkage between T2DM and AD [67,68], while others suggested an association between DM and dementia being only partially mediated through cerebrovascular disease (CVD). Furthermore, DM is associated independently with overall dementia among elderly, but not with AD or vascular dementia [69]. The increased risk of cognitive decline in elderly subjects with DM is due to dual pathology, involving both the CVD and cortical atrophy [70]. Two different patterns of cerebral injury were seen in patients with dementia depending on DM status: greater amyloid plaque load in untreated diabetic patients but more frequent deep microvascular infarcts in those with treated DM [71]. Central vascular disease and exacerbated pathology was seen in a mixed model of T2DM and AD by crossing APP/PS1 mice (AD model) with db/db mice (T2DM model) that show an age-dependent synergistic effect between T2DM and AD, including brain atrophy, senile plaques, tau pathology, hemorrhagic burden, and increase of microglia activation [31].

Positive T2DM status appears to exacerbate AD pathology in the presence of ApoE ε4 [72]. Although insulin mitigates Aβ deposition and hyperphosphorylation of tau [73,74], DM in combination with ApoE ε4 may lead to excessive phosphorylation of tau and accelerated formation of neuritic plaques [75], but only in subjects with late stage AD [59]. ApoE ε4 allele is believed to play an important role on insulin effects because AD patients without the ε4 allele showed beneficial effects of memory impairment compared to patients with the ε4 allele [76,77]. Furthermore, insulin-degrading enzyme (IDE) in the hippocampus is reduced by about 50% in AD patients with the ApoE ε4 allele compared to those without it [78]. These findings and recent genome wide association study (GWAS) data suggest that HHEX-23AA genotype enhances the effect of DM on dementia and AD [79]. Hence, gene expression backgrounds should be taken into account when evaluating the effects of insulin on patients and animal models of AD [26].

DM modifies metabolism of Aβ and tau causing Aβ/tau-dependent pathological changes [29], although there is evidence that suggests an interaction of Aβ/tau-dependent and -independent mechanisms [74] and underlines the role of insulin in cognition, synaptic remodeling and facilitation of memory [80]. AD pathophysiology might be in part referred to as intensive neuroendocrine disease caused by impairment in signaling in the brain that can be defined as type III DM [52,80]. On the other hand, insulin and IGF-1 have been shown to modulate the level of Aβ, to protect neurons against detrimental effects of Aβ on synapses [80]. Similarly, IDE also known as insulin protease, can degrade Aβ [81]. IDE is controlled via the insulin-P13K-akt signaling pathway, the impairment of which leads to a reduction of IDE [82], which also appears to be involved in Aβ accumulation. *In vivo* seeding and cross-seeding of local amyloid may represent another molecular link between AD and DMT2 [83]. Insulin further facilitates reduction of amyloid plaques, downregulation of Aβ-derived diffusible ligand-binding sites and also mitigates tau phosphorylation, which stabilizes microtubules. IRS-deficient AD mice delayed Aβ accumulation, while IGF-IR deficient AD mice reduced it [84,85]. This suggests a compensatory mechanism to reduce Aβ toxicity. Recent biomarker studies in elderly patients with T2DM showed that it may promote neurodegeneration independent of AD dementia diagnosis, and its effects may be driven by tau phosphorylation. However, the mechanism by which T2DM may promote tau phosphorylation deserves further studies [86-88]. DM and cholesterol dyshomeostasis involve abnormal α-synuclein and Aβ transport in neurodegenerative diseases and their understanding is important for the prevention and treatment of AD linked to DM and aberrant lipid metabolism [89]. Early intervention with glucagon-like peptide 1 analog liraglutide prevented tau hyperphosphorylation in diabetic db/db mice [90].

Pathogenic Pathway Complexity

Insulin resistance, hyperinsulinaemia and hyperglycaemia can affect the amyloid cascade by reducing Aβ clearance and promote the onset of AD [36,68,91]. Overlapping with AD pathology, they aggravate the progression of neurodegeneration due to OS, disordered control of protein translation, neurotoxicity by AGEs, mitochondrial dysfunction, neuroinflammation, and a variety of other mechanisms as common pathogenic background culminating in synaptic dysfunction and memory loss [8,50,51,64,92-95]. Hyperglycaemia modulates extracellular Aβ concentrations and neuronal activity in the hippocampus of aged mice with marked Aβ plaque pathology [34]. Recent research data indicate that there is a widespread conformational change in the protein control and other molecular mechanisms involved in both AD and T2DM that form β-sheet like motifs, interacting with other proteins and consequently catalyzing their translation into the toxic state. This may lead to neurodegeneration and also to cerebral hypoperfusion, which result in dysfunction and degeneration of neuroglial cells and myelin components. These and other results support the idea that alterations in mitochondrial function, biogenesis and autophagy cause synaptic damage in AD [30].

In conclusion, there is evidence for multiple mechanisms contributing to the pathological interaction between T2DM and dementia, the relationship of which is regulated by several modifiers, e.g. genetic risk, ageing, ApoE status, cardiovascular and general status of an individual [96] including hypertension and obesity [35,97]. Probably these factors form a complex vicious circle that underlies the interaction between AD and DM [88]. Recent population-based studies concluded that management of modifiable risk factors for cognitive decline and dementia, such as cardiovascular risk factors

(diabetes, obesity, smoking, and hypertension) may reduce the risk of cognitive decline [20,98,99]. Since a disturbance of insulin signal transduction may be of pathogenic relevance in AD and related dementias, and the observation that the combination of insulin and other anti-diabetic medications is associated with lower neuritic plaque density [61,66,80], antidiabetic drugs may have an important role in treating MCI and AD [35,100]. Intranasal administration of insulin successfully improved memory deficits without the risk of peripheral hypoglycaemia in AD patients [20,73,101,102]. Thus, insulin therapy could be effective in slowing cognitive decline in patients with AD [103]. A longitudinal pilot study showed that the cognitive impairment was significantly lower in AD patients with treated T2DM compared to AD patients without DM [104]. It should be emphasized that the therapeutic effects of those drugs are influenced by the ApoE ε4 genotype, since patients without this allele showed better treatment effects than those without this allele [77].

Given the epidemic of T2DM in the world, more information is needed about cerebral hypofunction and underlying pathologies in the context with DM. The way DM modifies the pathophysiological mechanisms leading to cognitive impairment by the modification of insulin signaling are required to develop potential preventive and therapeutic strategies [105,106].

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