The Diabetic Brain and Dementia

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Abbreviations: AD: Alzheimer’s Disease; DM: Diabetes Mellitus; DMT2: Type 2 Diabetes Mellitus; MCI: Mild Cognitive Impairment

Alzheimer’s Disease (AD) and Diabetes Mellitus (DM) are the two most common and devastating health problems in the elderly. They share a number of common features among which are important impact on quality of life and substantial health care costs. Epidemiological and biological evidence support a pathophysiological link between Type 2 Diabetes Mellitus (DMT2) and cognitive impairment [1-3]. A causative association between DM and Alzheimer’s disease has been suggested on the basis of clinical, epidemiological, genetic and experimental studies [2,4-9]. Persons with DM have a higher incidence of cognitive decline and an increased risk of developing AD and other types of dementia, and comorbidity increases the risk [10,11]. Insulin resistance predicts medial temporal hypermetabolism in Mild Cognitive Impairment (MCI) conversion to AD [12] and glucose uptake changes in AD in medial temporal regions predicting worse memory performance [13]. DM has been shown to influence the rate of functional decline among patients with mild AD dementia than in those without comorbid DM [14]. However, the precise mechanisms involved in the development of AD in diabetics are not yet fully understood, and several pathogenic pathways have been discussed [3,4,15-20].

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 [5,21-27]. Vasculo-neural dysfunction has been suggested to represent a potential etiological linkage between DMT2 and AD [6,28], while others suggested that the association between DM and dementia is only partially mediated through cerebrovascular disease and that DM is associated independently with overall dementia among elderly, but not with AD or vascular dementia [29].

Positive DMT2 status appears to exacerbate AD pathology in the presence of ApoE ε4 [30]. Although insulin mitigates Aβ deposition and hyperphosphorylation of tau [17,31], DM in combination with ApoE ε4 may lead to excessive phosphorylation of tau [32], but only in subjects with late stage AD [21]. DM modifies metabolism of Aβ and tau causing Aβ/tau-dependent pathological changes, although there is evidence that suggests an interaction of Aβ/tau-dependent and -independent mechanisms [31]. Evidence supports insulin’s role in cognition, synaptic remodelling and facilitation of memory [33]. On the other hand, insulin has been shown to modulate the level of Aβ, to protect neurons against detrimental effects of Aβ on synapses [33]. It further facilitates reduction of amyloid plaques, downregulation of Aβ-derived diffusible ligand-binding sites and also to promote tau hypophosphorylation, which stabilizes microtubules. These data and the observation that the combination of insulin and other antidiabetic medication is associated with lower neurotic plaque density [33,34] are providing a rationale for using insulin to treat AD high-risk patients [35-37].

Insulin resistance, hyperinsulinemia and hyperglycemia can affect the amyloid cascade by reducing Aβ clearance and promote the onset of AD [9,28,38]. Overlapping with AD pathology, they aggravate the progression of neurodegeneration due to oxidative stress, disordered control of protein translation, neurotoxicity by Advanced Glycation End-Products (AGE), mitochondrial dysfunction, neuroinflammation, and a variety of other mechanisms as common pathogenic background culminating in synaptic dysfunction and memory loss [16,26,39-44]. Recent research data indicate that there is a widespread conformational change in the protein control and other molecular mechanisms involved in both AD and DMT2 that form β-sheet like motifs, interacting with other proteins and consequently catalyzing their translation into the toxic state may lead to neurodegeneration and also to cerebral hypoperfusion, which result in dysfunction and degeneration of neural cells and myelin components [45,46]. In vivo seeding and cross-seeding of local amyloid may represent another molecular link between AD and DMT2 [47].

In conclusion, there is evidence for multiple mechanisms contributing to the pathological interaction between DMT2 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 [48] including hypertension and obesity [49], thus forming a complex vicious circle that underlies the interaction between AD and DM [46]. 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 [50,51]. Since a disturbance of insulin signal transduction may be of pathogenetic relevance in AD and related dementias, antidiabetic drugs may have an important role in treating MCI and AD [52,53] and insulin therapy could be effective in slowing cognitive decline in patients with AD [54]. More information is needed about cerebral hypofunction and underlying pathologies in the context with DM, and better identification of the mechanisms whereby DM modifies the pathophysiological mechanisms leading to cognitive impairment through the modification of insulin signaling are required to develop potential preventive and therapeutic strategies.

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References


