The diabetic brain and cognition: neuropathological view

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A causative association between diabetes mellitus (DM) and cognitive impairment has been suggested based on clinical, epidemiological, and experimental studies [1-6]; however, the precise mechanisms involved in the development of Alzheimer disease (AD) in diabetic patients are not yet fully understood [1, 2]. Some autopsy studies stated that diabetics have significantly less AD pathology but more frequent cerebrovascular lesions including microvascular changes [1, 7-9] or both types of cerebral pathology [1, 3, 9-12], and white matter lesions [4]. Positive DM2 status appears to exacerbate AD pathology in the presence of APOE ε4 [13]. Insulin resistance, hyperinsulinemia and hyperglycemia can affect the amyloid cascade and promote the onset of AD [14, 15] by accelerating tau phosphorylation and neuritic plaque formation [5, 16] and, overlapping with AD pathology, aggravate the progression of neurodegeneration due to oxidative stress, mitochondrial dysfunction, neuroinflammation, etc as a common background [4, 6, 11, 17]. Thus, impaired insulin signaling may be a possible link between AD and DM [12]. Although insulin mitigates Aβ deposition and phosphorylation of tau [18], DM in combination with APOE ε4 may lead to excessive hyperphosphorylation of tau [16], but only in subjects with late stage of AD [1]. More information should be available on cerebral pathologies in the context with DM2 in order to better elucidate the molecular mechanisms of increased dementia risk in diabetic patients that may have preventive and therapeutic implications.

References


