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Neuropathology of type 2 diabetes: a short review on insulin-related mechanisms

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Abstract

Postmortem studies have shown that cerebrovascular disease (CVD) neuropathology occurs frequently in type 2 diabetes (T2D) through mechanisms associated with chronic hyperglycemia such as advanced glycation end-products (AGEs). The involvement of T2D in Alzheimer's disease (AD)-type neuropathology has been more controversial. While postmortem data from animal studies have supported the involvement of T2D in AD-type neuropathology through insulin mechanism that may affect the development of neuritic plaques and neurofibrillary tangles (NFTs), findings from postmortem studies in humans, of the association of T2D with AD, have been mainly negative. To complicate matters, medications to treat T2D have been implicated in reduced AD-type neuropathology. In this review we summarize the literature on animal and human postmortem studies of T2D neuropathology, mainly the mechanisms involved in hyperglycemia-related CVD neuropathology and hyperinsulinemia-related AD-type neuropathology.

Keywords

Type 2 diabetes; Cerebrovascular Disease; Alzheimer's disease; Neuropathology; Review

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Elizabeth Guerrero-Berroa: conducted the literature search and wrote the manuscript. James Schmeidler: contributed to the writing and editing of the manuscript. Michal Schnaider Beeri: led discussion of the original idea of the review and its organization, provided supervision and guidance, and contributed to the writing and editing of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest
None

1. Introduction

There are two major types of diabetes. Type 1 (T1D), which affects primarily children results from dysfunction in insulin-producing pancreatic beta cells; and type 2 diabetes (T2D), which results from insulin resistance (reduced response to insulin), affects primarily adults, represents about 90% of all diabetes cases, and is the focus of this review. T2D causes micro-and macrovascular complications including peripheral neuropathy, nephropathy, retinopathy, cardiovascular disease (Cefalu, 2006; Wrighten, Piroli, Grillo, & Reagan, 2009), and cerebrovascular disease (CVD). Brain changes observed in T2D (white matter lesions, lacunar infarcts, and cortical atrophy) (Nelson et al., 2009; van Harten, 2006) are associated with cognitive dysfunction and worsened by vascular risk factors (hypertension and dyslipidemia) (Gold, 2007; van Harten, 2007). Alzheimer's disease (AD)-related neuropathology (neuritic plaques and neurofibrillary tangles [NFTs]) is also found in T2D. These brain abnormalities are also associated with the cognitive deficits and increased risk for dementia consistently observed in T2D, particularly in those carrying the apolipoprotein E-epsilon 4 (APOE ε4) allele (Peila, Rodriguez, & Launer, 2002). In view of the projected increase in percentage of the elderly population from 2015 to 2060—particularly those aged 65 and over (14.84% to 21.90%, respectively) and 85 and above (1.96% to 4.33%, respectively)— (US Census Bureau, 2012), and the projected prevalence of T2D (by 2030, 82 million of elderly over 64 years of age are projected to have T2D in developing countries and over 48 million in developed countries) (Wild, 2004), disentangling neuropathological complications deriving from T2D leading to cognitive impairment and disability is an intensifying public health and scientific concern.

This paper reviews the literature describing the neuropathology of T2D in brain tissue samples of animals and humans, with a focus on CVD and AD-type neuropathology. The contribution of insulin dysfunction and hyperglycemia in CVD and in AD-type neuropathology is discussed.

Considering the decades-long survival with T2D in humans, animal research is both time- and cost-effective. Although no animal models exhibit all T2D characteristics observed in humans—its pathophysiology, progression, and complications that lead to comorbidity and mortality—they provide a crucial window for understanding T2D pathophysiology (Cefalu, 2006), and will be included in this review. In this issue of European Neuropsychopharmacology, Brundel et al. reviews neuroimaging findings in T2D and thus those are excluded from this review.

2. Cerebrovascular Disease in T2D

2a. Overview

One of the largest neuropathological studies of CVD in T2D dates back to 1973 with 5,479 autopsies of which 677 were individuals with diabetes, primarily T2D. T2D cases presented with more infratentorial encephalomalacia (softening of brain tissue) as shown by at least three times as many infarctions in the pontine basis in various age groups (e.g., ages 56-65, 66-75, 76-85) (Aronson, 1973). That these infarcts were non-lethal and subclinical is supported by more recent postmortem T2D studies that also showed higher frequency of

severe cerebral atherosclerosis (Kameyamai, Fushmi, & Udaka, 1994). In the very elderly (those above the age of 85 who are survivors by nature of their age), autopsy findings have reported that those with T2D had more cerebral infarctions than those without T2D (Ahtiluoto, 2010).

The consequences of CVD can be more damaging for T2D patients than for or non-T2D individuals, since older adults with T2D very commonly have CVD and also vascular risks such as hypertension and dyslipidemia. In the context of T2D, research has focused on hyperglycemia-related mechanisms involved in CVD neuropathology which affect cells implicated in the formation of lipid masses in the arterial walls (atherogenesis), primarily endothelial cells (and also smooth muscle cells and macrophages) (Monnier, 2006; S Roriz-Filho, 2009).

Vascular damage could result from both chronic hyperglycemia and glucose fluctuations (Monnier, 2006). Animal models have shown reduction in brain weight and neorcortical volume, as well as neuronal loss and shortening of neocortical capillaries after one year of induced diabetes. Blood glucose daily fluctuations and hyperglycemia were suggested mechanisms involved in the loss of brain tissue (Jakobsen, 1987).

2b. Chronic hyperglycemia

Chronic hyperglycemia is linked with increased formation of advanced glycation end-products (AGEs), which increase oxidative stress and vascular damage (Münch, 1998; S Roriz-Filho, 2009). For these reasons, AGE formation/accumulation is hypothesized to be one of the mechanisms linking hyperglycemia to vascular disease in T2D. AGEs are produced by the reaction of reduced sugars, such as glucose, which interact with amino groups in a Maillard reaction (Heitner, 1997). AGE formation is part of the normal aging process, but increased in T2D due to its association with hyperglycemia (Furth, 1997). AGEs lead to microvascular complications and microinfarcts, and are found in greater quantities in brain lesions of both humans and animals with T2D or T1D than without them (van Deutekom, 2008). Increased levels of AGEs, such as Nepsilon-(carboxymethyl)-lysine (CML), have been associated with diabetes complication (McCance, 1993) and progression (Genuth, 2005). After controlling for furosine (glycated collagen) and CML, hemoglobin A1c (HbA1c; a measure of glycemic control) was no longer associated with the progression of retinopathy and nephropathy in patients with diabetes (Genuth, 2005), thus providing support for the involvement of AGEs in the association of hyperglycemia with risks for diabetes complications—which include CVD. In this vein, postmortem animal studies have demonstrated the effects of AGEs on CVD. For instance, one study found that levels of CML were significantly higher in cerebral vessels of hyperglycemic streptozotocin (STZ, a pancreatic beta cell toxin)-treated T2D adult male Wistar rats than in the non-T2D, normoglycemic rats (van Deutekom, 2008). This same study also found that CML was significantly greater in cerebral vessels of T2D and T1D compared to non-diabetic participants. High levels of AGEs in patients with CVD have also been associated with worse cognition (Southern, 2007), with the suggestion that AGE formation may be a biological mechanism involved in the cognitive deficits observed in dementia. Consistent

with that, we have shown that methylglyoxal, a precursor of AGEs, is associated with a faster rate of cognitive decline in initially non-demented individuals (M. S. Beeri, 2011).

3. T2D involvement in AD Neuropathology

3a. Overview

While AGEs may be important mechanisms involved in the association between hyperglycemia and CVD in T2D, disruption in insulin signaling appears to be implicated in the association of T2D with AD neuropathology. Peripheral insulin can cross the blood-brain barrier, thus increasing the amount of insulin and affecting its receptors in the brain. A small proportion of insulin is also synthesized in the brain, and its receptors are located in brain areas including the hippocampus and the cortex. Findings from both human and animal postmortem studies suggest that insulin regulates pathways that may accelerate AD-type pathology by affecting the metabolism of amyloid beta (Aβ) and the phosphorylation or hyperphosphorylation of tau (Gasparini, 2002; Grünblatt, 2007; Ho, 2004; L. Li, 2007; Umegaki, 2010).

Insulin promotes release of intracellular Aβ through the acceleration of its trafficking from the trans-golgi network to the plasma membrane, so decreased brain insulin may compromise the trafficking of Aβ from the intracellular to the extracellular areas (Cholerton, Baker, & Craft, 2013). Insulin can also stimulate clearance of Aβ through the insulin degrading enzyme [IDE], one of the proteases involved in Aβ degradation. Hyperinsulinemia in T2D sequesters IDE, which has higher binding affinity for insulin than for Aβ, thus reducing the clearance of Aβ from the extracellular space (S Roriz-Filho, 2009). Indeed, knockout animals lacking IDE have shown decreased brain degradation of Aβ and hyperinsulinemia (Farris, 2003), and decreased activity and levels of IDE in the hippocampus have been reported in human brains, particularly AD patients with the APOE ε4 allele (Cook, 2003; Pérez, 2000).

Insulin can inhibit phosphorylation of tau, the protein that forms NFTs. Hyperphosphorylation of tau leads to NFTs by preventing the affinity of the tau protein for microtubules. In human neuronal cultures, insulin and insulin-like growth factor 1 (IGF-1; an insulin-associated peptide) were found to reduce phosphorylation of tau and to promote the binding of tau to microtubules through the inhibition of glycogen synthase kinase-3β (GSK-3β), a protein kinase which is downstream of the insulin signaling pathway and whose activity is downregulated by insulin or IGF-1 (Hong, 1997).

Moreover, insulin treatment has demonstrated to regulate plasma Aβ, insulin levels in the central nervous system, and cognition (Reger, 2008), and its effectiveness appears to be dependent on APOE genotype status. For instance, among AD and mildly cognitively impaired (MCI) individuals, while intranasal insulin treatment improved performance on memory tasks in non-carriers of APOE ε4, no benefit or decline was observed in APOE ε4 carriers (Reger, 2008). The authors suggested several explanations for these differential effects that included insulin dose. In an earlier study, it was demonstrated that intravenous insulin infusion improved memory in APOE ε4 carriers at only very low doses (Craft, 2003).

These remarkable associations of insulin with AD and the biological mechanisms that connect insulin to AD neuropathology—through regulation of Aβ and tau protein—has led to the new terminology referring to AD as *type 3 diabetes* (de la Monte, 2008), reviewed in this issue of European Neuropsychopharmacology by de la Monte.

3b. Animal Studies

In the transgenic 2576 (Tg2576) mouse model of AD, a high fat diet that induced T2D-associated insulin resistance stimulated generation of amyloidonegic Aβ peptide that corresponded with reduced IR signaling, increased activation GSK-3α and GSK-3β associated with γ-secretase activity, decreased IDE activities, and reduced spatial cognition. (Ho, 2004). In contrast, attenuation of insulin resistance by high ω-3 fatty acid and ω-3 rich fish oil diets was found to reduce production and deposition of amyloid, and stimulated clearance of Aβ in the Tg2576 mice and Wistar rats (Cole & Frautschy, 2007; Delarue, LeFoll, Corporeau, & Lucas, 2004; Lim et al., 2005; Puskás, Kitajka, Nyakas, Barcelo-Coblijn, & Farkas, 2003).

Intracerebroventricular (icv) treatment of STZ administered to male Wistar rats led to dysfunction in the insulin system as shown by decreased insulin 1 and 2 mRNA expression and insulin receptor mRNA expression in the hippocampus and frontoparietal cortex, increased insulin receptor tyrosine residues and hippocampal protein tyrosine kinase activity, and decreased hypothalamic total insulin receptor beta-subunit, which may all lead to increased hyperphosphorylated tau protein (Grünblatt, 2007). Interestingly, this same study showed that the deficits in learning and memory abilities, also affected by STZ treatment, were not eliminated after pre administration of glucose transport inhibitors—systemic pre administration of these inhibitors are known to prevent STZ-induced beta cell toxicity and diabetes (Ganda, 1976; Wang, 1993)—thus suggesting different peripheral and central mechanisms by STZ damage. Consistent with these results, insulin-resistance brain state induced by icv injection of STZ in Tg2576 mice showed increased cerebral aggregated Aβ fragments, congophilic amyloid deposits, total tau protein, and a decrease in spatial cognitive ability (Plaschke, 2010). Impairment in learning and memory are also reported in the db/db mouse model of T2D, characterized by insulin resistance and obesity (Stranahan, 2008). Moreover, a novel therapeutic intervention using glucagon-like peptide-1 (GLP-1) receptor agonists that promotes insulin secretion, such as exendin-4 (Ex-4), has shown to counteract the effects of T2D (e.g., increasing insulin secretion and reducing hyperglycemia) in db/db T2D mice and in mice treated with repeated low doses of STZ (Greig, 1999; Y. Li et al., 2010). In Triple transgenic AD (3xTg-AD) mice who underwent repeated low doses systemic administration of STZ, Ex-4 treatment counteract T2D effects as shown by elevation in plasma insulin and decrease in both plasma glucose and HbA1c levels, as well as reduction of Aβ protein precursor, and Aβ protein in the brain (Y. Li et al., 2010). These results call for the need of clinical trials to investigate Ex-4 on AD in humans. This is crucial since peroxisome proliferator-activated receptor-*y* agonist therapies, which improve insulin sensitivity, reduce accumulation of Aβ, inflammation, and neurotoxicity in vitro and in animal models (Combs, 2000; Delerive, 2001; Pathan, 2006) are still questionable regarding efficacy and safety (Cholerton et al., 2013)

Overall, the above findings in animal studies demonstrate that insulin resistance—which characterizes T2D—is involved in AD-type neuropathology. Moroz and colleagues, using a mouse model of T2D induced by a high fat diet, demonstrated that although T2D brains showed insulin resistance and increased insulin gene expression, no development of Aβ and phosphorylated tau was observed (Moroz, 2008), suggesting that manipulation of insulin alone is not sufficient to cause AD.

3c. Human Studies

In humans, the nature of T2D involvement in AD remains controversial in autopsy studies. Reductions in both insulin and IGF-1 have been correlated with AD neuropathology (Rivera, 2005), and insulin resistance has been associated with cognitive decline prior to death (Talbot, 2012). However, these findings and those from animal studies are in contrast to other reports that have shown either lack of an association between T2D and AD pathology (Arvanitakis, 2006), or similar AD pathology severity in both T2D patients and age-matched controls (Heitner, 1997), or less AD pathology (neuritic plaques and NFTs) in T2D cases compared with controls (Ahtiluoto, 2010; Michal Schnaider Beeri, 2005; Nelson et al., 2009).

Thus, despite numerous epidemiological studies finding increased risk for AD in T2D patients, and despite the biological plausibility for such an association (Cholerton et al., 2013), most of the recent postmortem human studies do not find an association between T2D and AD neuropathology. One explanation is that although the vast majority of T2D patients are treated, medications for T2D were not accounted for in most postmortem studies. Indeed, brains of T2D patients who were treated with both insulin and a hypoglycemic medication, had 80% lower neuritic plaques in the hippocampus and several cortical regions, compared to non-T2D and to subjects who received either insulin or a hypoglycemic medication (M. S. Beeri, 2008). Another potential explanation for the discrepancy between the epidemiological and neuropathological studies is that only some subgroups of T2D participants might be at particularly high risk of developing AD neuropathology. For instance, the Honolulu Asia Aging Study found that having both T2D and the APOE ε4 allele led to an increased risk in the number of hippocampal neuritic plaques, hippocampal and cortical NFTs, and the risk of cerebral amyloid angiopathy. Consistent with that, co-localization of APOE and AGEs—which in addition to their atherogenic effect—have been found in amyloid deposits and NFTs (Dickson et al., 1996), and both co-localization and interaction between APOE ε4 and AGEs have been linked to plaques deposition and NFTs (Y. M. Li, 1997; Sasaki, 1998). Although the relationship between T2D and AD neuropathology has been found after taking into account dementia, including AD, taking account of vascular disease burden may diminish the relationship between T2D and AD neuropathology. More large scale and well-characterized post-mortem studies are warranted before a definite conclusion can be achieved regarding the association between T2D and AD neuropathology.

4. Conclusion

CVD is a well-established neuropathology associated with T2D. Mechanisms deriving from hyperglycemia (e.g., AGEs) underlie this increased prevalence of CVD in T2D. In contrast, a relationship of T2D to AD neuropathology has not been established despite substantial support for such a relationship from epidemiological studies, and from animal models. This discrepancy may depend on the fact that the vast majority of T2D patients are treated by T2D medications making it difficult to tease out the effects of the disease from its treatment. Insulin and other T2D medications seem to have beneficial effects on the brain.

Novel T2D medications (such as GLP-1 agonists) and new technologies (such as intranasal methods of administration that target more precisely the central nervous system) may further help prevent or treat T2D-related neuropathology. Since AGEs are involved in both atherogenesis and CVD, and in AD neuropathology, targeting inhibition of AGE accumulation may be an effective strategy. Finally, insulin treatment seems to ameliorate cognition especially in those who do not carry the APOE ε4 allele, which may reflect that more AD neuropathology is found in T2D patients who carry the APOE ε4 allele. This suggests that clinical trials can be designed to target those who may benefit the most from treatment.

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