CHAPTER 19

NEURODEGENERATION IN DIABETES MELLITUS

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Abstract: Diabetes mellitus is recognized as a group of heterogeneous disorders with the common elements of hyperglycaemia and glucose intolerance due to insulin deficiency, impaired effectiveness of insulin action, or both. The prevalence of Type 2 diabetes mellitus (T2DM) increases with age and dementia also increases its incidence in later life. Recent studies have revealed that T2DM is a risk factor for cognitive dysfunction or dementia, especially those related to Alzheimer's disease (AD). Insulin resistance, which is often associated with T2DM, may induce a deficiency of insulin effects in the central nervous system (CNS). Insulin may have a neuroprotective role and may have some impact on acetylcholine (ACh) synthesis. Hyperinsulinemia, induced by insulin resistance occurring in T2DM, may be associated with insulin deficiency caused by reduced insulin transport via the blood brain barrier (BBB). Insulin has multiple important functions in the brain. Some basic research, however, suggests that insulin accelerates Alzheimer-related pathology through its effects on the amyloid beta (Aβ) metabolism and tau phosphorylation.

Asymptomatic ischemic lesions in T2DM subjects may lower the threshold for the development of dementia and this may explain the inconsistency between the basic research and clinicopathological studies.

More research to elucidate the mechanism of neurodegeneration associated with T2DM is warranted.

INTRODUCTION

Diabetes mellitus is recognized as a group of heterogeneous disorders with the common elements of hyperglycaemia and glucose intolerance due to insulin deficiency, impaired effectiveness of insulin action, or both. Diabetes mellitus is classified on the basis of

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etiology and the clinical presentation of the disorder into mainly two types; Type 1 diabetes and Type 2 diabetes (T2DM). Type 1 diabetes is sometimes called insulin-dependent, immune-mediated or juvenile-onset diabetes. It is caused by destruction of the insulin-producing cells of the pancreas, typically due to an auto-immune reaction, in which they are attacked by the body's defense system. The disease can affect people of any age, but usually occurs in children or young adults. On the other hand, T2DM is characterized by insulin resistance and partial insulin deficiency, either of which may be present at the time that diabetes becomes clinically manifested. Insulin resistance is defined as an inadequate response by insulin target tissues, such as skeletal muscle, liver and adipose tissue, to the physiological effects of circulating insulin and often is accompanied by raised insulin levels. T2DM is often, but not always, associated with obesity, which itself can cause insulin resistance and lead to elevated blood glucose levels.

The prevalence of T2DM increases with age and dementia also increases its incidence in later life. Therefore, the coincidence of T2DM and dementia increases with ageing. Moreover, recent studies have indicated that older people with T2DM have a higher risk of cognitive dysfunction or dementia.[1] There is ample evidence that T2DM is related not only to vascular dementia but also to the clinical diagnosis of Alzheimer's disease (AD)-type dementia.[2]

In a large epidemiological study, The Rotterdam Study,[3] T2DM patients showed an increased risk for developing dementia. Patients treated with insulin were at an even higher relative risk, as high as 4.3-fold. In another study,[4] which examined some 800 nuns and priests longitudinally over 9 years, 15% of the cohort had or developed T2DM and showed a 65% increased risk for developing AD. A cohort of Japanese-Americans in Hawaii[5,6] showed a 1.8-fold higher risk for developing AD and a 2.3-fold higher risk for vascular dementia.

BRAIN IMAGING STUDIES IN TYPE 2 DIABETES

In T2DM patients the incidence of small vessel disease including lacunae infarcts and white matter lesions increased.[7,8] Some studies have shown that Type 2 diabetic patients compared to nondiabetic individuals show reduced volumes of the hippocampus and amygdala[9,10] and a threefold increased risk for medial temporal lobe atrophy.[11]

UNDERLYING MECHANISM OF COGNITIVE DYSFUNCTION IN T2DM

The precise mechanisms underlying T2DM-related cognitive dysfunction or the development of dementia, especially AD-type dementia, remain to be elucidated; however, several hypothetical mechanisms have been proposed.

High glucose concentration, a major pathological characteristic of diabetes, may have toxic effects on neurons in the brain through osmotic insults and oxidative stress and the maintenance of chronic high glucose also leads to the enhanced formation of advanced glycation endoproducts (AGEs), which have potentially toxic effects on neurons. AGEs are formed as the end-products of the Maillard reaction,[12] during which reducing sugars can react with the amino groups of proteins to produce cross-linked complexes and unstable compounds. AGEs have been found in the central nervous system (CNS) of diabetics. AGEs couple with free radicals and create oxidative damage, which in turn leads to neuronal

injury.[13] Other than their direct toxicity, AGEs also reactivate microglia in the CNS. There is a wealth of evidence demonstrating that microglia, the resident innate immune cells in the brain, can become deleterious and damage neurons.[14] This process is implicated as an underlying mechanism in diverse neurodegenerative diseases, including AD. While microglial function is beneficial and mandatory for normal CNS functioning, microglia become toxic to neurons when they are over-activated and unregulated. In diabetes, oxidative stress also increases because of reduced antioxidant capacity.[15] It has been suggested that oxidative stress leads to neuronal injury through mitochondrial dysfunction.[16]

T2DM, especially in conjunction with obesity, is characterized by insulin resistance and/or hyperinsulinemia. The insulin molecule consists of two peptidic chains joined by two disulfide bonds. It is primarily secreted by the beta cells of the pancreas and is normally released into the circulation through the portal vein in response to a rise in blood glucose. Insulin degrading enzyme (IDE) catabolizes insulin in the liver, kidneys and muscles.[17,18] It is generally agreed that insulin located within the brain is mostly of pancreatic origin, having passed through the blood-brain barrier, although there is debate about the amount of insulin that is produced de novo within the CNS.[19] Major known actions of insulin in the brain include control of food intake (via insulin receptors located in the olfactory bulb and thalamus) and effects on cognitive functions, including memory.[20,21]

Blood glucose abnormalities and insulin resistance may also have some impact on acetylcholine (ACh) synthesis. Acetylcholine transferase (ChAT), which is an enzyme responsible for ACh synthesis, is expressed in insulin receptor-positive cortical neurons and insulin regulates the ChAT expression. Because ACh is a critical neurotransmitter in cognitive function, it may be relevant to neurocognitive disorders in diabetics.[22]

Recent basic research demonstrated that insulin signaling in the CNS prevents the pathologic binding of amyloid beta (Aβ) oligomers. Aβ oligomers are soluble molecules that attach with specificity to particular synapses, acting as pathogenic ligands.[23] The attack on synapses inhibits long-term potentiation (LTP).[24] Insulin and PPAR-gamma agonist, an insulin sensitizer, may have some protective effects on the toxic effects of Aβ oligomer.[25]

Insulin has multiple important functions in the brain, as mentioned above. These functions are disrupted in insulin-resistant states. The transport of insulin into the brain across the BBB is reduced in insulin-resistance-associated hyperinsulinemia and insulin levels in the brain are subsequently lowered.[26,27] A small pilot study demonstrated that intranasal insulin had some benefits in early AD patients.[28] With intranasal administration, insulin bypasses the periphery and the blood-brain barrier, reaching the brain and cerebrospinal fluid (CSF) within minutes via extracellular bulk flow transport along olfactory and trigeminal perivascular channels, as well as through more traditional axonal transport pathways.[29,30] Intranasal administration of insulin improved memory and attention in humans without affecting plasma glucose levels.

Some basic research, however, suggests that insulin accelerates AD-related pathology through its effects on the Aβ metabolism and tau phosphorylation.[2] Insulin reportedly raises Aβ concentrations in plasma in AD subjects and these effects may contribute to the risk of AD in T2DM. The desensitization of insulin receptors, i.e., insulin resistance, reduces the synthesis of several proteins, including insulin-degrading enzyme (IDE). IDE degrades Aβ as well as insulin and reduced amounts of IDE may result in greater amyloid deposition. Less insulin signaling may also induce increased activity of glycogen synthase kinase-3β (GSK-3β), which leads to the enhanced phosphorylation of tau protein and the formation of neurofibrillary tangles (NFTs). The results of pathological assessments in AD with or without DM are highly controversial. Several pathological studies using

autopsy samples have demonstrated, however, that dementia subjects with diabetes have less AD-related neuropathology than subjects without diabetes. One study demonstrated that diabetics show significantly less AD-associated neuropathology,[31] while another failed to show any relationship between diabetes and AD-associated neuropathology.[32]

VASCULAR CONTRIBUTION TO T2DM-ASSOCIATED COGNITIVE DYSFUNCTION

AD has been thought to be a neurodegenerative disorder which can be sharply distinguished from vascular dementia. Recent studies, however, suggest that the distinction between AD and vascular dementia may not be tenable. There is now substantial and growing evidence that vascular disorders and/or impaired cerebral perfusion contribute to the development of sporadic AD. For example, cerebrovascular pathology including stroke seems to play an important role in the eventual development of the clinical symptoms of AD.[33]

On cerebral MRI, white matter hyperintensities and lacunae, both of which are frequently observed in the elderly, are generally viewed as evidence of small vessel disease in the brain (white matter lesions and lacunae). These lesions are frequently concomitant with Alzheimer-related neuropathology (senile plaques and NFTs) and contribute to cognitive impairment in AD subjects.[34] We previously reported that small vessel diseases affect cognitive function in older diabetics who have not developed either overt dementia or symptomatic stroke.[35,36] The number of asymptomatic infarcts and the extent of white matter lesions in the brain detected with magnetic resonance imaging (MRI) were found to be associated with the scores on several cognitive functional tests, especially the digit symbol substitution test, a neurocognitive test that primarily reflects declines in perceptual speed. We also reported that an inflammatory cytokine, tumor necrosis factor-α (TNF-α), which is a risk factor for atherosclerosis, is related to cognitive dysfunction in older nondemented diabetics.[37] A recent study demonstrated that T2DM subjects with a clinical diagnosis of dementia have less Alzheimer-related pathology but more ischemic lesions.[38] This finding supports the hypothesis that small vessel disease lowers the threshold for the development of dementia. That is, if subjects have the same level of cognitive dysfunction, those with a combination of two types of pathologies have fewer pathological changes in each of their pathologies than those with a single pathology that is severe enough to cause the cognitive dysfunction. Therefore, these pathological reports do not necessarily eliminate the possibility that DM accelerates the development of Alzheimer-related neuropathology in patients with a clinical diagnosis of dementia. Arvanitakis et al demonstrated in 2004 that T2DM increases the incidence of AD as determined by clinical dignosis,[39] but T2DM ameliorated perceptual speed but not global cognition. A previous study[40] and our own studies[35,36] showed that cerebral ischemic lesions are preferentially associated with a lower measure of perceptual speed. These results also suggest that small vessel disease contributes to cognitive decline in these populations.

Hypertension is often accompanied by diabetes and several longitudinal studies appear to support the notion that hypertension predisposes individuals to cognitive decline and the development of dementia.[41] Vascular alterations induced by high blood pressure may contribute to cognitive dysfunction. Hypertension is also associated with cerebrovascular disease including lacunar brain infarcts and white matter lesions, which may contribute to cognitive impairment in diabetics.

THE EFFECTS OF BLOOD GLUCOSE CONTROL

A large cohort study, the ACCORD-MIND trail, showed that HbA1c levels were cross-sectionally associated with worse performance on several cognitive functional tests that were very similar to the ones that we used in the current study.[42] Maggi et al[43] reported that higher HbA1c levels at baseline were prospectively associated with delayed verbal memory decline.[41] We also reported that higher HbA1c levels at baseline correlated with a greater decrease in scores on the DSS and Stroop tests after three years. These results suggest that diabetic disease control is important for the preservation of cognitive function in elderly diabetic patients. A recent prospective study however, reported that HbA1c levels at baseline had no effect in 5 cognitive domains.[44] Large prospective studies are warranted regarding this issue.

Another recent report suggested that a history of severe hypoglycemic episodes was associated with a greater risk of dementia.[45] Diabetic control should be balanced the merit of the treatment with the risk of hypoglycemia.

FUTURE DIRECTION

Recently, amyloid imaging technology with positron emission tomography (PET), which visualizes Aβ depositions in the human brain, has been developed and is now widely available,[44] although some limitations in resolution and specificity still exist. This technology can be used to investigate the relative contributions of ischemic and neurodegenerative changes to the increased development of dementia in T2DM subjects. Longitudinal follow-up of T2DM subjects without overt dementia using both amyloid imaging and MRI may help to elucidate these issues, especially with higher field MRI with some potential for the imaging of small vessel diseases,[46] also diffusion tensor imaging method may also provide useful data.[47] Furthermore, the CSF biomarkers total tau, hyperphosphorylated tau and the 42 amino acid form of Aβ (Aβ-42) are now established markers for AD[48] and can be used to identify AD in the early, MCI stage of the disease with high accuracy.[49] The CSF of AD and MCI patients shows decreased values of Aβ-42 and increased total tau or phosphorylated tau.[50] Following up until the development of overt dementia would make it possible to compare both the amyloid load and ischemic lesions before and after the development of dementia with these technologies. Moreover, amyloid imaging and measuring CSF biomarkers in nondemented older people with or without insulin resistance could verify the hypothesis that insulin plays a role in the processing and deposition of Aβ. These investigations are important considering the future availability of disease-modifying therapeutics such as Aβ vaccination and inhibitors for Aβ secretions.

At present, vascular risk factors may represent a therapeutic target, while neurodegenerative pathologies have not yet been amenable to treatment. Vascular risk factors including diabetes and hypertension are reportedly associated with the progression of lacunae and white matter lesions;[51] however, the beneficial effects on cognitive function of pharmaceutical interventions with antidiabetics and antihypertensives are less clear in terms of the inhibition of the progress of lacunae and white matter lesions. It remains to be investigated whether medical interventions that mitigate vascular risk factors have protective effects against the development and progress of dementia. If such protective effects do exist, the underlying mechanism of the therapeutic effects should

be interesting, whether it relies on the inhibition of the development of vascular lesions or on the inhibition of the neurodegenerative process.

With the ongoing increase in the size of the older population, T2DM-associated cognitive dysfunction and dementia are becoming increasingly larger problems. A greater understanding of the relevant pathophysiology and the establishment of better therapeutic interventions are urgent needs.

CONCLUSION

T2DM is associated with cognitive dysfunction and the incidence of dementia including AD. The underlying mechanism of this association should be elucidated. This could lead to clarification of the pathogenesis of AD and to the development of a treatment or preventive method.

REFERENCES

1. Stewart R, Liolitsa D. Type 2 diabetes mellitus, cognitive impairment and dementia. Diabetic Medicine 1999; 16:93-112.
2. Li L, Hölscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. Brain Res Rev 2007; 56:384-402.
3. Ott A, Stolk RP, van Harskamp F et al. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology 1999; 58:1937-1941.
4. Arvanitakis Z, Wilson RS, Bienias JL et al. Diabetes mellitus and risk of Alzheimer's disease and decline in cognitive function. Arch Neurol 2004; 61:661-666.
5. Peila R, Rodriguez BL, Launer LJ. Honolulu-Asia Aging Study. Type 2 diabetes, APOE gene and the risk for dementia and related pathologies. Diabetes 2002; 51:1256-1262.
6. Peila R, Rodriguez BL, White LR et al. Fasting insulin and incident dementia in an elderly population of Japanese-American men. Neurology 2004; 63:228-233.
7. Vermeer SE, Koudstaal PJ, Oudkerk M et al. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2002; 33:21-25.
8. de Leeuw FE, de Groot JC, Achten E et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001; 70:9-14.
9. den Heijer T, Vermeer SE, van Dijk EJ et al. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia 2003; 46:1604-1610.
10. Korf ES, White LR, Scheltens P et al. Brain aging in very old men with type 2 diabetes: the Honolulu-Asia Aging Study. Diabetes Care 2006; 29:2268-2274.
11. Korf ES, van Straaten EC, de Leeuw FE et al. LADIS Study Group. Diabetes mellitus, hypertension and medial temporal lobe atrophy: the LADIS study. Diabet Med 2007; 24:166-171.
12. Yamagishi S, Ueda S, Okuda S. Food-derived advanced glycation end products (AGEs): a novel therapeutic target for various disorders. Curr Pharm Des 2007; 13:2832-2836.
13. Valente T, Gella A, Fernàndez-Busquets X et al. Immunohistochemical analysis of human brain suggests pathological synergism of Alzheimer's disease and diabetes mellitus. Neurobiol Dis 2010; 37:67-76.
14. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci 2007; 8:57-69.
15. Evans JL, Goldfine ID, Maddux BA et al. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocr Rev 2002; 23:599-622.
16. Moreira PI, Santos MS, Seiça R et al. Brain mitochondrial dysfunction as a link between Alzheimer's disease and diabetes. J Neurol Sci 2007; 257:206-214.
17. Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. CNS Drugs 2003; 17:27-45.
18. Davis SN, Granner DK. Insulin, oral hypoglycemic agents and the pharmacology of the endocrine pancreas. In: Hardman JG, Gilman AG, Limbird LE, eds. Gilman and Goodman's the Pharmacological Basis of Ttherapeutics, 9th. New York: McGraw-Hill, 1996:1487-1517.

19. Woods SC, Seeley RJ, Baskin DG et al. Insulin and the blood-brain barrier (BBB). Curr Pharm Des 2003; 9:795-800.
20. Havrankova J, Roth J, Brownstein M. Insulin receptors are widely distributed in the central nervous system of the rat. Nature 1978; 272:827-829.
21. Freychet P. Insulin receptors and insulin action in the nervous system. Diab Metab Res Rev 2000; 16:390-392.
22. Rivera EJ, Goldin A, Fulmer N et al. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J Alzheimers Dis 2005; 8:247-268.
23. Lacor PN, Buniel MC,Chang L et al. Synaptic targeting by Alzheimer's-related amyloid beta oligomers. J Neurosci 2004; 24:10191-10200.
24. Walsh DM, Klyubin I, Fadeeva JV et al. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature 2002; 416:535-539.
25. Sato T, Hanyu H, Hirao K et al. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. Neurobiol Aging 2009. [Epub ahead of print]
26. Zhao WQ, Townsend M. Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. Biochim Biophys Acta 2009; 1792:482-496.
27. Craft S, Peskind E, Schwartz MW et al. Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and apolipoprotein E genotype. Neurology 1998; 50:164-168.
28. Reger MA, Watson GS, Green PS et al. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology 2008; 70:440-448.
29. Thorne RG, Pronk GJ, Padmanabhan V et al. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. Neuroscience 2004; 127:481-496.
30. Benedict C, Hallschmid M, Hatke A et al. Intranasal insulin reportedly improves memory and attention in humans. Psychoneuroendocrinology 2004; 29:1326-1334.
31. Beeri MS, Silverman JM, Davis KL et al. Type 2 diabetes is negatively associated with Alzheimer's disease neuropathology. J Gerontol A Biol Sci Med Sci 2005; 60:471-475.
32. Arvanitakis Z, Schneider JA, Wilson RS et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Neurology 2006; 7:960-1965.
33. de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma and dialectics. Lancet Neurol 2004; 3:184-190.
34. Riekse RG, Leverenz JB, McCormick W et al. Effect of vascular lesions on cognition in Alzheimer's disease: a community-based study. J Am Geriatr Soc 2004; 52:1442-1448.
35. Akisaki T, Sakurai T, Takata T et al. Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus. Japanese elderly diabetes intervention trial (J-EDIT). Diabetes Metab Res Rev 2006; 22:376-384.
36. Umegaki H, Kawamura T, Mogi N et al. Glucose control levels, ischaemic brain lesions and hyperinsulinaemia were associated with cognitive dysfunction in diabetic elderly. Age Ageing 2008; 37:458-461.
37. Suzuki M, Umegaki H, Ieda S et al. Factors associated with cognitive impairment in elderly patients with diabetes mellitus. J Am Geriatr Soc 2006; 54:558-559.
38. Sonnen JA, Larson EB, Brickell K et al. Different patterns of cerebral injury in dementia with or without diabetes. Arch Neurol 2009; 66:315-322.
39. Arvanitakis Z, Wilson RS, Bienias JL et al. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Arch Neurol 2004; 61:661-666.
40. Schneider JA, Wilson RS, Cochran EJ et al. Relation of cerebral infarctions to dementia and cognitive function in older persons. Neurology 2003; 60:1082-1088.
41. Peters R, Beckett N, Forette F et al. Incident dementia and blood pressure lowering in the hypertension in the very elderly trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 2008; 7:683-689.
42. Cukierman-Yaffe T, Gerstein HC, Williamson JD et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial; Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) Investigators. Diabetes Care 2009; 32:221-226.
43. Maggi S, Limongi F, Noale M et al. LSA Study Group. Diabetes as a risk factor for cognitive decline in older patients. Dement Geriatr Cogn Disord 2009; 27:24-33.
44. Ikonomovic MD, Klunk WE, Abrahamson EE et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain 2008; 131:1630-1645.

45. Whitmer RA, Karter AJ, Yaffe K et al. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 15; 301:1565-1572.
46. Novak V, Abduljalil AM, Novak P et al. High-resolution ultrahigh-field MRI of stroke. Magn Reson Imaging 2005; 23:539-548.
47. Kodl CT, Franc DT, Rao JP et al. Diffusion tensor imaging identifies deficits in white matter microstructure in subjects with type 1 diabetes that correlate with reduced neurocognitive function. Diabetes 2008; 57:3083-3089.
48. Zetterberg LO,Wahlund K, Blennow. Cerebrospinal fluid markers for prediction of Alzheimer's disease. Neurosci Lett 2003; 352:67-69.
49. Hansson H, Zetterberg P, Buchhave E et al. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol 2006; 5:228-234.
50. Ewers M, Buerger K, Teipel SJ et al. Multicenter assessment of CSF-phosphorylated tau for the prediction of conversion of MCI. Neurology 2007; 69:2205-2212.
51. Gouw AA, van der Flier WM, Fazekas F et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. Stroke 2008; 39:1414-1420.