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A spectrum of contributions of type 2 diabetes and related metabolic characteristics to dementia

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Findings from epidemiological, clinical and preclinical studies in recent years point to the role of metabolic factors in brain disease in general (De Felice and Ferreira, 2014; Gorelick et al., 2011), and particularly in Alzheimer's disease (AD) (De Felice and Ferreira, 2014; de la Monte and Tong, 2014). Type 2 diabetes (T2D) and pre-diabetic states—such as insulin resistance (Craft et al., 2013), poor glycemic control (Ma et al., 2014; Ravona-Springer et al., 2014) in non-diabetic subjects (Enzinger et al., 2005), and obesity (Emmerzaal et al., 2014)—affect brain structure and function and are involved in the neuropathological pathways leading to neurodegeneration. In light of the borderline efficacy of currently approved medications for the treatment of AD (Tan et al., 2014), the failure of numerous clinical trials to prove efficacy of other medications developed for treatment of the disease, and the relatively good efficacy of medical (American Diabetes, 2010) and life-style (Hays et al., 2008) interventions in ameliorating or preventing other, non-brain-related complications of T2D, these findings raise the possibility that such interventions may have a beneficial effect on the brain.

In this issue of European Neuropsychopharmacology, several articles review the literature on the relationship of T2D and related conditions with brain structure, function, and neurodegeneration from different viewpoints.

Werner et al. provide evidence for the expression and function of insulin, the insulin-like growth factors (IGF1, IGF2), and their receptors in the brain. Their roles in the development and function of the central nervous system (CNS) include, among others, neuronal survival, neurogenesis, angiogenesis, neurotransmission, regulation of food intake, and cognition. Interestingly, these factors are shown to be involved in the clearance of amyloid-beta—the hallmark neuropathological feature of AD—from the brain, and its degradation through insulin degrading enzyme (IDE).

De la Monte further reviews the evidence pointing towards the metabolic nature of AD based on the impairment of brain responsiveness to insulin, utilization of glucose, and

energy metabolism. All these lead to increased oxidative stress, inflammation, and worsening of insulin resistance. De la Monte points to the involvement of metabolic derangements in the formation of the neuropathologic hallmarks of AD—neuronal loss, synaptic disconnection, amyloid plaques and neurofibrillary tangles—and suggests the conceptualization of AD as type 3 diabetes.

In these two reviews, the evidence for the role of insulin and related factors in AD-specific neuropathology is mainly based on animal studies. In contrast, Guerrero-Berroa et al. discuss findings from human post mortem studies, which do support the harmful role of T2D in the brain, but not specifically via effect on amyloid plaques and neurofibrillary tangles. This is apparently in contradiction with the epidemiological studies showing a consistent association of T2D with AD. The authors point to the effect of anti-diabetes treatments—both insulin and oral antidiabetic medications—in AD neuropathology, as a potential explanation for this discrepancy. The role of T2D and related characteristics (e.g. degree of glycemic control) in brain vascular pathology and the role of the latter in cognition is also discussed, emphasizing the multifactorial nature of T2D, and the biologically plausible different pathways underlying its relationship with AD and dementia.

The effect of diabetes on brain volume, function and vasculature as demonstrated by various brain imaging techniques is further reviewed by Brundel et al. They discuss brain characteristics that have been demonstrated to be associated with T2D, i.e. brain atrophy, white matter changes, and infarcts. They stress inconsistencies between studies, which, at least partly, may be explained by different populations (age, type of diabetes, population based or clinic based, etc.), imaging methods used, and the techniques applied for measurement of outcomes. It is also important to note that rather than T2D, per se, pathological brain imaging findings may be associated with T2D-related characteristics (poor glycemic control, comorbidities, hypertension, etc.). Since not all T2D subjects develop cognitive decline and/or dementia, understanding the characteristics of those who are at particularly high risk for cognitive deterioration, will enable development of specific, personally-tailored preventive treatments without endangering those who are not at risk with unnecessary treatment—as discussed below, hypoglycemia increases the risk for dementia.

Even in the absence of frank diabetes, obesity, considered to be a pre-diabetic state, has been shown to be associated with cognitive outcomes and dementia. This subject is discussed by Arnoldussen et al. Interestingly, the role of adiposity may change with age, with midlife obesity being a risk factor for late life cognitive decline and dementia, while decrease in body weight may be a risk factor or result from neurodegeneration at old age. The authors discuss the mechanisms of action of six adiponectins, secretory products of adipose tissue, in the periphery and in the brain. Adiponectins play a role in neurogenesis, neuroprotection, blood brain barrier (BBB) integrity, memory and in central mechanisms of satiety and energy expenditure. Challenges in further understanding the role of adiponectins and applying treatment strategies are the difference between the function of adiponectins in obese versus non-obese individuals, and the fact that some do not cross the BBB.

Good glycemic control has been shown to ameliorate/prevent some—mainly microvascular (American Diabetes, 2010)—complications of T2D. Even in non-T2D subjects, higher levels

of HbA1c, the gold standard indicator of glycemic control, have also been shown to be associated with brain volume and cognitive outcomes (Enzinger et al., 2005). Thus, good glycemic control, could, potentially, prevent or postpone dementia in T2D. Nevertheless, strict diabetes control cannot be universally implemented due to the increased morbidity and mortality associated with such an approach. One contributor to these adverse outcomes is increased risk for hypoglycemia, primarily caused by use of insulin or insulin secretagogues. Moreover, hypoglycemia, at least in its severe forms, is associated by itself with brain pathology. This subject is discussed by Whitmer, pointing to brain lesions and atrophy in the cortex, hippocampus, basal ganglia and other brain regions in subjects who experienced severe hypoglycemia. Remarkably, animal models of hypoglycemia have shown that hypoglycemic coma is associated with more brain damage in T2D compared to non-T2D animals. Most studies have reported on the effect of hypoglycemia in T1D rather than the more prevalent form—T2D. Also, there are methodological difficulties in assessing the role of hypoglycemic episodes with mild to moderate severity, which are the majority. Most studies rely on self-reports, but patients are often not aware of them.

These reviews clearly support the role of T2D and related conditions in brain pathology, cognition and dementia. However, there are inconsistencies between studies, which may result from the complexity and dynamics over time of these conditions, potentially acting through different mechanisms at different stages of diabetes. Additionally, studies of brain related outcomes of T2D are typically based on T2D diagnosis or poor glycemic control at a certain point in time rather than on the chronicity, duration, and dynamics of the disease. Further understanding of the relationships discussed may be achieved by consolidation of cohorts and harmonization of measurement methodologies. This will enable deeper understanding of the mechanisms associated with neuropathology and cognition in specific diabetic subpopulations (by age of onset of diabetes, diabetes duration, glycemic control patterns over time, comorbidities, genetics, medications, etc.), effect of which may be diluted when investigating the effects of T2D in general on the brain.

References

- American Diabetes A. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2010; 33(Suppl 1):S62–S69. [PubMed: 20042775]
- Craft S, Cholerton B, Baker LD. Insulin and Alzheimer's disease: untangling the web. *J Alzheimers Dis*. 2013; 33(Suppl 1):S263–S275. [PubMed: 22936011]
- De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. *Diabetes*. 2014; 63:2262–2272. [PubMed: 24931033]
- de la Monte SM, Tong M. Brain metabolic dysfunction at the core of Alzheimer's disease. *Biochem Pharmacol*. 2014; 88:548–559. [PubMed: 24380887]
- Emmerzaal TL, Kiliaan AJ, Gustafson DR. 2003–2013: a decade of body mass index, Alzheimer's disease, and dementia. *J Alzheimers Dis*. 2014
- Enzinger C, Fazekas F, Matthews PM, Ropele S, Schmidt H, Smith S, Schmidt R. Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. *Neurology*. 2005; 64:1704–1711. [PubMed: 15911795]
- Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Selkoe FW, Seshadri S. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American

Heart Association/American Stroke Association. Stroke. 2011; 42:2672–2713. [PubMed: 21778438]

Hays NP, Galassetti PR, Coker RH. Prevention and treatment of type 2 diabetes: current role of lifestyle, natural product, and pharmacological interventions. Pharmacol Ther. 2008; 118:181–191. [PubMed: 18423879]

Ma F, Wu T, Miao R, Xiao YY, Zhang W, Huang G. Conversion of mild cognitive impairment to dementia among subjects with diabetes: a population-based study of incidence and risk factors with five years of follow-up. J Alzheimers Dis. 2014

Ravona-Springer R, Heymann A, Schmeidler J, Moshier E, God-bold J, Sano M, Leroith D, Johnson S, Preiss R, Koifman K, Hoffman H, Silverman JM, Beeri MS. Trajectories in glycemic control over time are associated with cognitive performance in elderly subjects with type 2 diabetes. PLoS One. 2014; 9:e97384. [PubMed: 24887092]

Tan CC, Yu JT, Wang HF, Tan MS, Meng XF, Wang C, Jiang T, Zhu XC, Tan L. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014; 41:615–631. [PubMed: 24662102]