Neurobiology of Disease 84 (2015) 22–38

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

The role of type 2 diabetes in neurodegeneration

Giuseppe Verdile [a,b,c], Stephanie J. Fuller [c], Ralph N. Martins [a,b,c,*]

[a] School of Biomedical Sciences, CHIRI Biosciences, Curtin University, Bentley, Western Australia 6102, Australia
[b] Centre of Excellence for Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, Joondalup, Western Australia 6027, Australia
[c] Sir James McCusker Alzheimer's Disease Research Unit, School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, Western Australia 6009, Australia

ARTICLE INFO

Article history:
Received 6 February 2015
Revised 18 April 2015
Accepted 21 April 2015
Available online 26 April 2015

Keywords:
Diabetes
Alzheimer's disease
Beta amyloid
Amylin
Tau
Neurodegeneration

ABSTRACT

A growing body of evidence links type-2 diabetes (T2D) with dementia and neurodegenerative diseases such as Alzheimer's disease (AD). AD is the most common form of dementia and is characterised neuropathologically by the accumulation of extracellular beta amyloid (Aβ) peptide aggregates and intracellular hyper-phosphorylated tau protein, which are thought to drive and/or accelerate inflammatory and oxidative stress processes leading to neurodegeneration. Although the precise mechanism remains unclear, T2D can exacerbate these neurodegenerative processes. Brain atrophy, reduced cerebral glucose metabolism and CNS insulin resistance are features of both AD and T2D. Cell culture and animal studies have indicated that the early accumulation of Aβ may play a role in CNS insulin resistance and impaired insulin signalling. From the viewpoint of insulin resistance and impaired insulin signalling in the brain, these are also believed to initiate other aspects of brain injury, including inflammatory and oxidative stress processes. Here we review the clinical and experimental pieces of evidence that link these two chronic diseases of ageing, and discuss underlying mechanisms. The evaluation of treatments for the management of diabetes in preclinical, and clinical studies and trials for AD will also be discussed.

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* Corresponding author at: Edith Cowan University, 270 Joondalup Drive, Joondalup, Australia. Fax: +61 6304 5851.
E-mail address: r.martins@ecu.edu.au (R.N. Martins).
Available online on ScienceDirect (www.sciencedirect.com).

http://dx.doi.org/10.1016/j.nbd.2015.04.008
0969-9961/

1. Introduction

Dementia is highly prevalent in the elderly, and accounts for a significant proportion of age-related disability. With the proportion of people aged >65 years expected to increase to above 20% by the year 2050, the incidence of dementia is expected to rise dramatically. Indeed, it is estimated that there are currently 35.6 million people world-wide with dementia, which will double to 65.7 million by 2030 and more than triple to 115 million by 2050 (World Health Organization report, 2012). The ageing brain accrues pathological changes attributable to multiple risk factors, and these can alter the clinical threshold for dementia in an individual. T2D is becoming increasingly recognised as a major contributor to the risk of developing dementia (Ninomiya, 2014).

Type 2 diabetes itself is a complex, age-related chronic disease and the increasing prevalence is also of great public concern. Currently, 366 million people have diabetes mellitus world-wide, and this number is expected to reach 552 million by 2030 (IDF, Diabetes atlas). T2D occurs more commonly in older age with a prevalence of 12–25% in people > 65 years, and is characterised by cellular insulin resistance, several metabolic abnormalities and chronic inflammation. T2D causes accelerated ageing in most organ systems (Morley, 2008) leading to premature morbidity and mortality. For example, serious complications of T2D include kidney damage, neuropathy, blindness and coronary artery disease. The effects of T2D on the brain are now well recognised: it is known to be a major risk factor for cognitive decline and dementia. In fact, T2D increases the long-term risk of dementia by nearly 2-fold (Biessels et al., 2014), and one in ten cases of dementia in the world population may be attributable to the effects of T2D (Biessels et al., 2014). Models of disease projection suggest that attention to modifiable risk factors (such as diabetes) may delay the onset of dementia, and doing so by even 1 year may reduce the world-wide burden of cases in people over 60 years by ~10% (Johnson et al., 2007).

Of all the sub-types of dementia, AD is the most common. This progressive neurodegenerative disease is characterised by the accumulation in the brain of extracellular neuritic plaques and fibrils (primarily consisting of aggregated Aβ peptides), intracellular neurofibrillary tangles (accumulation of hyperphosphorylated tau), microglial infiltration, brain atrophy and widespread synaptic and neuronal loss. In contrast to a small subset of AD cases (~3%) attributable to inherited genetic causes, the pathogenesis and aetiology of sporadic, late onset AD (LOAD) are multifactorial, involving genetic and life-style risk factors. The recognition of T2D as a major risk factor for dementia, particularly AD, has driven research to understand the underlying mechanisms linking these two age-related chronic disorders. Metabolic disturbances associated with the diabetic phenotype (ie hyperglycaemia, hyperinsulinaemia, hypercholesterolaemia) are known to be associated with brain atrophy and the pathological hallmarks of AD. Here we review clinical evidence of the impact of T2D on changes in the brain that contribute to cognitive decline and dementia, and discuss potential underlying mechanisms linking T2D with neurodegeneration promotion. We also discuss the targeting of insulin resistance and signalling impairments (systemically and/or in the brain) as a therapeutic approach for slowing down or preventing the neurodegenerative process.

2. The impact of T2D on the brain — evidence from imaging studies

It is well known that T2D is associated with poorer cognitive function and greater cognitive decline compared to non-T2D controls (Biessels et al., 2014). However, the longitudinal impact of T2D on cognitive functioning and neurodegeneration remains poorly understood. Cerebral infarcts (Saczynski et al., 2009) and markers of microvascular disease [e.g. lacunes (Moran et al., 2013); diabetic retinopathy (Bruce et al., 2014; Exalto et al., 2014); microalbuminuria (Saczynski et al., 2009)] are predictors of an increased risk of future dementia in T2D, suggesting that vascular pathways are involved. However, this relationship is not clearcut and may not be specific to diabetes, as there are conflicting findings amongst studies: some studies have found cognitive decline to be independent of microvascular disease burden (van Elderen et al., 2010), whereas others have observed small or moderate associations (Espeland et al., 2013; Qiu et al., 2014).

2.1. Imaging studies of structural changes

More consistently, studies have shown that T2D is associated with brain atrophy. For example, structural MRI studies have shown that T2D is strongly associated with brain atrophy in regions that are severely affected in AD, including the hippocampus (Moran et al., 2013). However, more recent studies have suggested that the atrophy observed in specific regions simply reflects the degree of total brain loss (Biessels and Reijmer, 2014). Nevertheless, longitudinal case control studies have suggested that the rate of global brain atrophy in T2D is up to 3 times faster than in normal ageing (Kooistra et al., 2013; van Elderen et al., 2010), suggesting that T2D accelerates neurodegeneration. Both grey and white matter losses have been observed in T2D, indicating loss of brain connectivity (Biessels et al., 2014), most likely contributing to associated cognitive impairment. Grey matter volume changes have also been shown to correlate with insulin resistance in healthy controls as well as AD cases, yet in Parkinson's disease, there is a positive relationship between brain volume and insulin resistance, suggesting that the effect of insulin resistance is disease-specific (Morris et al., 2014). Another recent study of whole-brain connectivity patterns using diffusion tensor imaging, has shown reductions in type-2 diabetics compared to age-matched controls, and this was associated with slower processing speeds (Reijmer et al., 2013). The duration of T2D may also be particularly harmful to the brain, as a study showed that individuals that have had insulin resistance and diabetes longer exhibited smaller brain volumes compared to controls and those at earlier stages of insulin resistance (Saczynski et al., 2009). Although cerebrovascular lesions and brain atrophy are both thought to mediate the relationship between T2D and cognitive impairment, a cross-sectional study of individuals with or without T2D revealed that although infarcts were by themselves associated with poorer cognition, brain atrophy was the predominant change linked to cognition at earlier stages of the disease (Moran et al., 2013). Whether the combination of vascular and neurodegenerative processes accelerate dementia remains to be determined.

2.2. Imaging studies of brain amyloid load and glucose metabolism

Imaging studies of cerebral glucose metabolism (^{18}F-deoxyglucose-positron emission tomography: FDG-PET) and amyloid deposition (eg ^{11}C-Pittsburg compound B-PET: PIB-PET) have revealed that impaired neuronal glucose metabolism and neocortical amyloid accumulation are early pathological features of the AD brain (for recent review see Cohen and Klunk, 2014). However, few imaging studies have investigated these hallmarks in the brains of type 2 diabetics or have investigated the relationship between insulin resistance and amyloid load. One recent cross-sectional study examined this association using PIB-PET and FDG-PET imaging in the population-based Mayo Clinic Study of Aging