Increased risk of Alzheimer's disease in Type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology?

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Abstract

Type II diabetes mellitus (DM2) is associated with an increased risk of cognitive dysfunction and dementia. The increased risk of dementia concerns both Alzheimer's disease and vascular dementia. Although some uncertainty remains into the exact pathogenesis, several mechanisms through which DM2 may affect the brain have now been identified. First, factors related to the 'metabolic syndrome', a cluster of metabolic and vascular risk factors (e.g. dyslipidaemia and hypertension) that is closely linked to DM2, may be involved. A number of these risk factors are predictors of cerebrovascular disease, accelerated cognitive decline and dementia. Secondly, hyperglycaemia may be involved, through adverse effects of potentially 'toxic' glucose metabolites on the brain and its vasculature. Thirdly, insulin itself may be involved. Insulin can directly modulate synaptic plasticity and learning and memory, and disturbances in insulin signalling pathways in the periphery and in the brain have recently been implicated in Alzheimer's disease and brain aging. Insulin also regulates the metabolism of β-amyloid and tau, the building blocks of amyloid plaques and neurofibrillary tangles, the neuropathological hallmarks of Alzheimer's disease. In this paper, the evidence for the association between DM2 and dementia and for each of these underlying mechanisms will be reviewed, with emphasis on the role of insulin itself.

DM (diabetes mellitus) is associated with slowly progressive end-organ damage in the brain [1]. Mild to moderate impairments of cognitive functioning has been reported both in patients with DM1 (Type I DM) [2], and in patients with DM2 (Type II DM) [3,4]. Clinically relevant deficits, however, mainly occur in elderly patients with DM2 [5], who may experience problems with day-to-day functioning due to their cognitive impairments [6]. The potential impact of DM on cognition in the elderly is further emphasized by several large epidemiological surveys that report an increased incidence of dementia among DM patients, apparently concerning both Alzheimer's disease and vascular dementia [3,7–9]. The observation that the effects of DM on the brain are most pronounced in the elderly has been attributed to an interaction between DM and the normal aging process of the brain [10,11]. Differences between the pathophysiology of DM1 and DM2 are also likely to play a role [11], as the latter is by far the most common form among the elderly. In DM1, the principal defect is an autoimmune-mediated destruction of pancreatic β-cells, leading to insulin deficiency, whereas in DM2 the principal defect is insulin resistance, leading to a relative insulin deficiency. Moreover, DM2 occurs in the context of a cluster of metabolic and vascular risk factors, which is referred to as the so-called 'metabolic syndrome' [12]. The metabolic syndrome itself, with or without hyperglycaemia, is associated with atherosclerotic cardiovascular disease, ischaemic stroke and with cognitive decline and dementia [13]. A key question is therefore whether disturbances in insulin and glucose metabolism or other factors from the metabolic syndrome lead to impaired cognition in DM2. The present work aims to provide an overview on the ways in which disturbances in glucose and insulin metabolism and other factors related to the metabolic syndrome may be implicated in the accelerated cognitive decline and the increased risk of dementia in patients with DM2 (Figure 1).

Key words: Alzheimer's disease, brain aging, cognitive dysfunction, insulin-induced amyloid, metabolic syndrome, Type II diabetes mellitus.

Abbreviations used: Aβ, β-amyloid; APOE, apolipoprotein E; DM, diabetes mellitus; DM1, Type I DM; DM2, Type II DM; IDE, insulin-degrading enzyme; LDL, low-density lipoprotein; MRI, magnetic resonance imaging.

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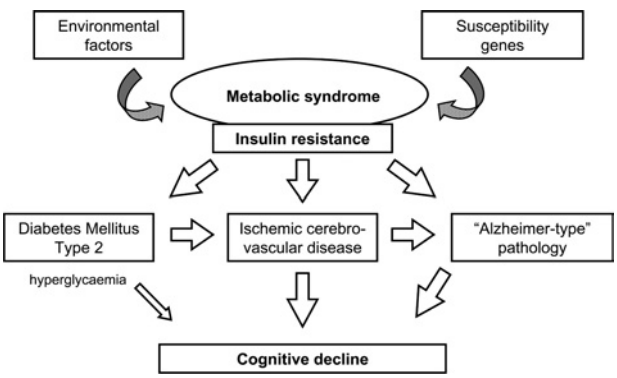
Cognitive dysfunction and dementia in DM2: underlying mechanisms

A role for hyperglycaemia?

Several lines of evidence suggest that 'toxic' effects of hyperglycaemia are involved in the development of diabetic end-organ damage to the brain [14]. Hyperglycaemic rodents, for example, express cognitive impairments and functional and structural alterations in the brain [14]. Toxic effects of high glucose levels are mediated through an enhanced flux of glucose through the so-called polyol and hexosamine pathways, disturbances of intracellular second messenger pathways, an imbalance in the generation and scavenging

Figure 1 | Suggested pathogenesis of cognitive decline in DM2
Insulin resistance and risk factors related to the metabolic syndrome lead to DM2. The adverse effects of the metabolic syndrome and DM2 on the brain are mediated through ischaemic cerebrovascular disease, in concert with other factors from the metabolic syndrome. Hyperglycaemia plays an additional role through 'toxic' effects on brain tissue and the development of cerebral microangiopathy. Alterations in insulin metabolism can also directly affect the brain, through involvement in synaptic plasticity and amyloid and tau metabolism. Ischaemic cerebrovascular disease plays a modulating role in these latter processes.



of reactive oxygen species, and by advanced glycation of important functional and structural proteins [15]. These processes directly affect brain tissue and lead to microvascular changes in the brain [11,14].

Still, hyperglycaemia is unlikely to be the only factor in the development of cognitive impairments in DM2: previous studies in DM2 patients do not invariably show an association between chronic hyperglycaemia, as assessed by HbA1 levels, and the severity of cognitive impairments [3,10]. Moreover, changes in cognition may already develop in 'pre-diabetic stages', such as impaired glucose tolerance, or in newly diagnosed DM2 patients that have not yet been exposed to long-term hyperglycaemia [16,17].

A role for the metabolic syndrome?

DM2 and insulin resistance are closely associated with factors such as obesity, atherogenic dyslipidaemia [elevated triacylglycerol level, small LDL (low-density lipoprotein) particles, low HDL (high-density lipoprotein) cholesterol], raised blood pressure, and pro-thrombotic and pro-inflammatory states. Together these factors constitute the metabolic syndrome, or insulin resistance syndrome [12,18]. A number of factors from this syndrome have been identified as independent predictors of cerebrovascular disease, ischaemic stroke and accelerated cognitive decline and dementia (e.g. [13,16,19–21]). The combined occurrence of these risk factors in the metabolic syndrome might reinforce these effects [19,22–24]. Given the clustering of insulin resistance, hypertension and dyslipidaemia in DM2 it may be difficult to determine which factor is the prime determinant in the development of cognitive dysfunction. The main question, however, is to determine if the metabolic syndrome is indeed a strong predictor of cognitive dysfunction in DM2, and if this effect is (partially) independent of disturbances in glucose and insulin metabolism.

Involvement of ischaemic cerebrovascular disease?

DM2 and the metabolic syndrome are risk factors for atherosclerosis of the carotid and intracranial arteries [22,25], thus increasing the risk of stroke, and of cognitive decline and dementia [26]. In the long term, exposure to hyperglycaemia in DM may lead to abnormalities in cerebral capillaries, such as basement membrane thickening [27]. These microvascular changes may also lead to chronic and insidious ischaemia of the brain, thus contributing, for example, to the development of subcortical white-matter lesions. On a population level these lesions are associated with cognitive impairments, particularly related to frontal lobe functions [28]. Although white-matter lesions are also common among healthy elderly subjects, their prevalence and severity is increased in patients with vascular risk factors or ischaemic vascular disease, and in demented patients [28]. MRI (magnetic resonance imaging) studies in DM2 patients indeed show an increased severity of white-matter lesions {[29], and S.M. Manschot et al., Utrecht Diabetic Encephalopathy Study Group (see Acknowledgements), unpublished work}, and an increased incidence of (silent) brain infarcts [30].

An interaction with aging?

As the effects of DM on the brain are most pronounced in the elderly, one may suggest that the aging brain is more susceptible to the effects of DM or that the effects of DM and aging interact. In fact, several of the mechanisms that are assumed to mediate the toxic effects of hyperglycaemia on the brain, such as oxidative stress, the accumulation of advanced glycation end-products and microangiopathy, are also involved in brain aging [11]. Moreover, experimental studies indicate that the behavioural and neurophysiological consequences of DM are accentuated by aging [31]. We are currently addressing this issue by comparing cognitive functioning and brain MRI in aged DM1 and DM2 patients with controls [32]. Our results suggest that the cognitive impairments and MR changes are less marked in the aged DM1 patients (average duration of DM ±35 years), than in DM2 (average known duration of DM 9 years) patients of similar age (A.M.A. Brands et al., Utrecht Diabetic Encephalopathy Study Group, unpublished work). This suggests that, in addition to age, differences in the pathophysiology of DM1 and DM2 are likely to be important determinants of the effects of DM2 on the brain.

Direct effects of insulin on the brain?

An increasing amount of evidence links insulin itself to cognitive decline and dementia in DM2 [33–35]. First, alterations in cerebral insulin receptor signalling may be involved, as a cerebral equivalent of peripheral insulin resistance. Secondly, insulin may affect the metabolism of Aβ (β-amyloid) and tau, two proteins that represent the building

blocks of amyloid plaques and neurofibrillary tangles, the neuropathological hallmarks of Alzheimer's disease.

Insulin is not a major regulator of glucose use in the brain, in contrast with its prominent action in peripheral tissues such as liver, muscle and fat [36]. Still, insulin and its receptor are widely distributed throughout the brain, with particular abundance in defined areas, such as the hypothalamus and the hippocampus [37], and play a role in the regulation of food intake and body weight [36]. In addition, insulin appears to act as a 'neuromodulator'. It influences the release and re-uptake of neurotransmitters, and also appears to improve learning and memory [37]. The initial components of the insulin receptor signalling cascade in the brain are largely similar to those of the periphery [37,38], but the downstream targets of the cascade are quite different, probably involving, among others, neuronal glutamate receptors [37].

Disturbances in cerebral insulin signalling pathways may be involved in Alzheimer's disease and brain aging [33–35]. Aging is associated with reductions in the level of insulin and the number of its receptors in the brain [39]. In Alzheimer's disease this age-related reduction in cerebral insulin levels appears to be accompanied by disturbances of the insulin receptor signalling [39], leading to the qualification of Alzheimer's disease as 'an insulin-resistant brain state' [40].

The relation between insulin and the metabolism of Aβ and tau is also receiving increasing attention [33,35]. Aβ is derived from the so-called amyloid precursor protein. After secretion into the extracellular space Aβ can aggregate with other proteins, to form senile plaques. Alternatively, excessive Aβ can be cleared through LDL-receptor-related protein mediated endocytosis, or through direct extracellular proteolytic degradation [41]. This latter process involves IDE (insulin-degrading enzyme) [42]. Insulin appears to stimulate Aβ secretion, and inhibits the extracellular degradation of Aβ by competition from IDE [33]. A recent histopathological study of the hippocampus in patients with Alzheimer's disease reported marked reductions in IDE expression, and IDE mRNA levels, relative to controls [43]. Interestingly, this reduced expression only occurred in patients with the APOE (apolipoprotein E) ε4 allele. An interaction with the APOE ε4 genotype has also been demonstrated for the risk of Alzheimer's disease in DM patients [8], an observation that was supported by neuropathological results [8].

Although the concepts of 'cerebral insulin resistance', and 'insulin-induced amyloid pathology' are an attractive explanation for some of the effects of DM2 on the brain, there are still many loose ends. In contrast with the increasing body of knowledge on the mechanisms of insulin resistance in peripheral tissues [44], we know relatively little on how DM2 and its treatment affect cerebral insulin and its receptor. Moreover, the knowledge on the role of insulin in brain physiology is far from complete. For example, in apparent contrast with previous observations that hippocampal insulin receptor expression and signalling in rats are up-regulated following a spatial learning task in a water maze [45], mice with a targeted knockout of insulin receptors in the brain readily learn this same task [46]. Hopefully, ongoing research in this rapidly evolving field of research will clarify these issues.

Conclusion

Several mechanisms may be involved in accelerated cognitive decline and the increase of dementia in patients with DM2 (Figure 1). Because these different mechanisms interact at several levels, it is unlikely that future studies will detect a single factor that link DM to impaired cognition. It may be possible, however, to identify processes, or clusters of risk factors, that explain at least part of the association, and can be targeted by preventive measures. These preventive measures may not only include improvement of glycaemic control [47], but could also be directed at vascular risk factors and insulin metabolism. In fact, there is already some evidence from studies in non-DM patients that these latter approaches may be successful. For example, treatment of vascular risk factors, such as hypertension, may decrease the incidence of dementia in the context of ischaemic cerebrovascular disease [48]. Moreover, a recent exploratory randomized placebo-controlled trial with the insulin-sensitizing compound rosiglitazone showed an amelioration of both cognitive decline and abnormalities in cerebrospinal fluid Aβ in non-DM patients with early Alzheimer's disease [49]. The challenge for future studies will be to determine what preventive strategy should be applied in which DM2 patient, at what stage of the disease.

The Utrecht Diabetic Encephalopathy Study Group consists of (in alphabetical order): Department of Clinical Neurophysiology: A.C. van Huffelen; Department of Internal Medicine: H.W. de Valk; Julius Center for Health Sciences and Primary Care: A. Algra, G.E.H.M. Rutten; Department of Medical Pharmacology: W.H. Gispen; Department of Neurology: A. Algra, G.J. Biessels, L.J. Kappelle, S.M. Manschot, J. van Gijn; Department of Neuropsychology and Helmholtz Research Institute: A.M.A. Brands, E.H.F. de Haan, R.P.C. Kessels, E. van den Berg; Department of Radiology: J. van der Grond, all part of the University Medical Center, Utrecht, The Netherlands. The research of the Study Group is supported by the Dutch Diabetes Research Foundation (grants 2001.00.023 and 2003.01.004).

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