

'Type 3' diabetes: a brain insulin-resistant state linked to Alzheimer's disease

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Over the years, identifying novel sub-type variants of diabetes has always provided a measure of academic interest as well as an engaging area for debate and discussion. Having established the relatively clear-cut classification of type 1 and type 2 diabetes, it was perhaps inevitable that a further category of type 3 diabetes would in due course emerge. Indeed, a number of putative candidates has been put forward, including 'Double Diabetes' (a combination of type 1 diabetes and insulin resistance), MODY3 and more recently type 3c (pancreatogenic) diabetes. But the most intriguing remains the proposal by Suzanne de la Monte and colleagues¹ that the term type 3 diabetes could be appropriately applied to an association between a state of brain insulin resistance and dementia, including Alzheimer's disease.

Diabetes itself transcends into every aspect of clinical medicine, with familiar consequences to a legion of other specialist disorders. For good reason, a major focus of diabetes in recent years has been directed towards its long-term adverse cardiovascular effects, with clinical trials of new therapeutic interventions designed to evaluate potential benefits, or otherwise, in respect of reducing the substantial risk to the heart, the circulation and to overall mortality. In the same context, the effects of diabetes on the brain should now be considered with comparable concern. Although it may still seem difficult to justify the precise terminology of 'type 3' diabetes, given that hyperglycaemia itself is not an absolute prerequisite, the concept, nonetheless, of a brain insulin-resistant state, associated with increased risk of developing dementia, has not been unduly challenged. Certainly, it has engendered a stimulating two-way perspective on underlying pathogenic mechanisms shared between type 2 diabetes and Alzheimer's disease.

This fascinating notion of a new sub-type of diabetes prompted an editorial review in *Practical Diabetes* some four years ago,² outlining the emerging evidence of cerebral metabolic dysfunction, characteristic of a central insulin resistance, linked to a process of progressive neuronal stress, neurodegeneration, cognitive decline and eventual dementia. Although acknowledging the proposal was somewhat speculative at the time, the possibility of such pathogenic mechanisms contributing to the process of dementia, with or without underlying diabetes, seemed sufficiently plausible to warrant further studies and potential therapeutic opportunities.

Cascade of neurodegeneration

The underlying nature of Alzheimer's disease is not straightforward. Even the current focus on amyloid accumulation may not necessarily provide the definitive explanation. Some patients with clinically typical Alzheimer's disease may show no amyloid deposition, while others with 'extraordinary' intellect have been

found with 'enormous' plaque build-up.³ These exceptions apart, it is possible that some brain amyloid protein may be important for healthy brain function, rather similar to the cholesterol story – too much associates with increased cardiovascular risk, while some cholesterol requirement remains as an integral component of basic cellular structure and molecular function.

However, while recognising its complex and heterogeneous nature, de la Monte and Tong⁴ have continued to argue that Alzheimer's disease is 'fundamentally a metabolic disease with molecular and biochemical features that correspond with diabetes mellitus and other peripheral resistance disorders'. Although conceding some uncertainty as to whether of primary or secondary in origin, they propose that brain insulin/insulin-like growth factor (IGF) resistance initiates a cascade of events of metabolic dysfunction with increased oxidative stress, neuroinflammation, and an accumulation of toxic amyloid beta protein aggregates. Insulin and IGF serve important roles in maintaining neuronal and neurotransmitter integrity, which become progressively compromised as reduced levels of insulin/IGF receptor binding and responsiveness develop and a central brain insulin-resistant state ensues.

As stated, to complicate understanding even further, neither hyperglycaemia nor peripheral insulin resistance need necessarily be present, despite their known separate association with increased risk of cognitive impairment and dementia. But, as with conventional type 2 diabetes, de la Monte and Tong suggest that causation is likely to be a multifactorial combination of genetic susceptibility, predisposing lifestyle factors and chronic low-grade inflammation. Of particular interest, they postulate that a 'low-level nitrosamine exposure through diet, smoking, and agriculture, plus excessive caloric intake of fats and sugars, is responsible for the insulin resistance diseases epidemic'. For more detailed discussion concerning the nature of brain insulin/IGF resistance and its proposed consequences in terms of the neurodegeneration and neuropathology as seen in Alzheimer's disease, this review paper is well worth reading.

Dietary sugar and dementia risk

Despite hyperglycaemia *per se* not being determined as an essential pathogenic prerequisite for 'type 3' diabetes, a recent report from the University of Bath⁵ along with colleagues at King's College, London, has indicated that a high dietary consumption of sugar in people, not necessarily with diagnosed diabetes, significantly increases the risk of developing Alzheimer's disease. It is suggested that an excess of glucose intake can lead to glycation and oxidation of an enzyme called macrophage migration inhibitory factor (MIF),

an immune regulator, damage to which by these processes may be linked to Alzheimer's disease.

From these observations concerning the multifaceted nature of Alzheimer's disease, several diverse therapeutic approaches have been derived with the dual aims of ameliorating symptoms (boosting memory and cognitive fluency) as well as minimising disease progression. Sadly, recent clinical trials of a class of drugs known as BACE inhibitors (beta-site amyloid precursor protein cleaving enzyme 1 [1]), which modify the accumulation of amyloid proteins, have been disappointing. It may be that treatment intervention has been started too late in the disease process, and that therapy commenced at an earlier stage would be more likely to succeed. This may be the way forward, as new sophisticated technology is developed, enabling detection of abnormal, early-onset brain amyloid accumulation and offering opportunity for intervention before irreversible cognitive impairment becomes established.

Drugs for diabetes: shared dividend for dementia

With increasing evidence of an association between brain insulin resistance and Alzheimer's disease, the role of drugs normally used for the treatment of diabetes has been brought into focus⁶ as conceivably useful for Alzheimer's disease, where current therapies are very limited. All existing diabetes drugs have the potential to modify Alzheimer's disease, but those capable of penetrating the brain and improving insulin receptor sensitivity have particular appeal. Perhaps somewhat counter-intuitively, trials of intranasal insulin, which directly enters the cerebrospinal fluid circulation, have shown an early indication of benefit in mild cognitive impairment and Alzheimer's disease.⁷

However, trials with insulin sensitisers (thiazolidinediones,) have so far been disappointing, probably because of poor penetration across the blood-brain barrier. Nor has any clinically significant benefit yet been observed with metformin, the most commonly prescribed drug for type 2 diabetes.

In contrast, incretin-based agents (GLP-1 analogues and DPP4 inhibitors) are considered promising candidates for the treatment of neurodegenerative diseases.⁸ Research work by Holscher and colleagues (University of Lancaster) with various incretin-based therapies has demonstrated what are described as positive cytoprotective effects, with promise for the treatment of neurodegenerative diseases such as Alzheimer's disease, and interestingly Parkinson's disease as well. A beneficial,

protective effect of lixisenatide, a GLP-1 analogue, on memory function in rats has also been reported,⁹ possibly due to alleviation of the adverse effects of amyloid beta protein. Whether incretin-based peptide therapies can prevent or reverse cognitive decline associated with brain insulin resistance is still to be determined, but the outcome of clinical trials presently being undertaken is awaited with considerable interest.

Phase 3 clinical trials of new drugs for the treatment of diabetes are now expected to address either efficacy or risk in terms of cardiovascular complication. Equally, a similar understanding could reasonably be made in respect of novel antidiabetic agents and their potential effects on the brain, with observations on the neuropharmacology of central insulin signalling processes and, in particular, the consequences of such on cognitive function. The common pathways between type 2 diabetes and Alzheimer's disease suggest a shared therapeutic dividend may well be achieved from these clinical trials. But, it is salutary to remember that reducing risk of Alzheimer's dementia, be it with or without overt diabetes, is still a multifaceted approach where lifestyle considerations such as exercise, smoking, alcohol, diet and mental challenge can all contribute in different ways. As recently reported in the *New Scientist*:³ 'What's good for the heart, is good for the brain'.

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Declaration of interests

There are no conflicts of interest declared.

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