

'Type 3 diabetes': linking a brain insulin-resistant state with dementia and Alzheimer's disease

Ken Shaw

'We propose the term Type 3 Diabetes to reflect this newly identified pathogenic mechanism of neurodegeneration.' de la Monte, 2005.¹

At the 60th (June 2000) Annual Scientific Sessions of the American Diabetes Association, on an otherwise dismal afternoon in San Antonio, attending delegates were enthralled by a presentation from Trevor Orchard (University of Pittsburgh) asking them to contemplate a concept of 'Double Diabetes', a combination of type 1 diabetes and insulin resistance, so familiar with hindsight and even more so in this modern era. 'Double Diabetes' has since been described as type 3 diabetes (not to be confused with MODY3), and so the proposal of yet another different form of diabetes also labelled as type 3 does create some confusion while at the same time providing an intriguing insight into potential shared pathogenic mechanisms between type 2 diabetes and Alzheimer's disease.¹

Further publication from the Rhode Island team last year² reiterated that there is 'growing evidence supporting the concept that Alzheimer's disease is fundamentally a metabolic syndrome that leads to abnormalities linked to progressive brain insulin resistance' with consequent impairment of central insulin signalling processes, accumulation of neuro toxins, neuronal stress and in due course neurodegeneration. The medical implications of this proposal received rapid and prominent coverage in the popular media, including *New Scientist*: 'Food for thought: Eat your way to dementia'.³ Having already noted interest in the *New Scientist* article, this author was then further motivated with the topic following challenge, while captive in the dentist's chair, with: 'What is your opinion on the recent *Guardian* newspaper article – "Alzheimer's could be the most catastrophic impact of junk food"?'⁴ Clearly, an important issue has been identified. But within these somewhat sensational speculations, it would appear that insulin does play a significant role within the brain, and that abnormalities of allied insulin function may contribute to cognitive decline. Much still remains of a controversial nature and largely derived from experimental investigation, but the science so far does suggest that there is a syndrome of central insulin resistance, similar to that seen with type 2 diabetes, that may be associated with impaired cognitive function, including memory loss, learning difficulties and dementia.

Accelerated cognitive decline is sadly a recognised long-term complication of diabetes, with causation likely to be of multifactorial nature including circulatory and metabolic considerations as well as the uncertain consequences of exposure to recurrent hypoglycaemia. Examining a possible association between serum insulin levels and cognitive function, the Rotterdam Study,⁵ using mini-mental state scores in an elderly population,

observed that raised insulin levels, such as typically seen in response to insulin resistance, were associated with decreased cognitive function and dementia in women, independent of other cardiovascular risk factors.

Insulin-resistant brain state

A decade ago, challenging the then accepted view that human brain glucose was entirely insulin-independent, Stephanie Amiel's research group at King's College Hospital, London, were able to demonstrate, employing autoradiographic technology in human volunteers, that insulin derived from the systemic circulation does access cerebral insulin receptors and exert a significant effect on glucose metabolism within the brain cortex.⁶ This research work has continued, examining the relationship between brain glucose metabolism and cerebral function in various ways. In a recent review⁷ of current understanding of insulin resistance and brain activity, Amiel observes that not only are there implications in respect of appetite control and obesity, but with 'the epidemiological evidence linking insulin resistance and type 2 diabetes with dementia, the role of insulin in cognitive function offers an exciting opportunity for potential new preventative strategies'.

On the basis that Alzheimer's disease and type 2 diabetes 'share many age related pathophysiological features', researchers at the University of Pennsylvania⁸ have found evidence of brain insulin resistance associated with reduced central insulin and IGF-1 responsiveness as an early feature in Alzheimer's disease and cognitive decline, but expressed preference for the term 'insulin-resistant brain state' and not type 3 diabetes, as neither hyperglycaemia nor conventional diabetes are consistently found in Alzheimer's disease, although still recognising that features of metabolic syndrome may be observed in up to two-thirds of Alzheimer's disease cases. Communicating their findings with *Science News*,⁹ the Pennsylvania team extended their conclusions, commenting that their research studies of post-mortem brain tissue from Alzheimer patients without diabetes had identified 'extensive abnormalities in the [central] activity of two major signaling pathways for insulin and insulin-like growth factor'. They observed that these abnormalities showed significant correlation with episodic memory loss and a number of cognitive disabilities, and postulated that brain insulin resistance may directly contribute to cognitive decline in Alzheimer's disease, thereby opening a potential therapeutic role for the use of insulin-sensitising drugs in the treatment of Alzheimer's disease.

A toxic cycle

The Rhode Island proposal¹⁰ for the term type 3 diabetes derives from experimental studies in rats with streptozotocin-induced diabetes, demonstrating an association between impaired central insulin signalling

mechanisms and altered behaviour in the rats under observation. Other studies in alloxan-treated diabetic rabbits¹¹ have linked incremental hyperglycaemia with build up of beta amyloid proteins, characteristic of the neuropathology seen with Alzheimer's disease. Indeed, considerable basic science application is currently addressing these complex metabolic inter-relationships in this important clinical domain. Drawing from this complexity, and quoting a paper from research workers in Chicago,¹² Bijal Trivedi (*New Scientist*) describes the development of a 'toxic cycle' with the brain responding to undue insulin exposure by inducing neuronal insulin resistance and an accumulation of excess beta amyloid protein, which further increases central insulin resistance.³ Again further experimental work,¹³ observing that abnormal accumulation of beta amyloid is associated with impairment of neuronal insulin receptor function and central insulin responsiveness, provides added confirmation of a vicious cycle linking the key pathogenic processes of insulin resistance, neurodegeneration and dementia.

Therapeutic opportunities

So where are these experimental observations leading? It would seem that there is now an established body of reasonable evidence indicating a link between brain insulin resistance and the neurodegeneration that characterises Alzheimer's disease. Insulin would appear pivotal and of physiological importance in terms of brain function. Insulin does enter the brain and benefits both learning and memory, and probably a number of other important cerebral functions as well. Both insulin deficiency and excess insulin exposure are seemingly detrimental. Much further research work still needs to be done to extrapolate these implications to clinical practice. The similarities or association with type 2 diabetes are there to be elucidated, but potential therapeutic avenues, including treatment with insulin-sensitising agents and GLP-1 agonists, are being explored. The popular media placed their prime emphasis on the

modern diet with increased consumption of refined carbohydrate of high glycaemic index being particularly provocative of what they have termed 'insulin surges'. The science linking insulin resistance and dementia is still work in progress but as the media highlight, there is certainly 'Food for Thought'.

Professor Ken Shaw, MA, MD, FRCP, Emeritus
Professor of Medicine, University of Portsmouth, UK;
Editor-in-Chief, *Practical Diabetes*

Declaration of interests

There are no conflicts of interest declared.

References

1. Steen E, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – is this type 3 diabetes? *J Alzheimers Dis* 2005;7(1):63–80.
2. de la Monte SM, et al. Dysfunctional pro-ceramide, ER stress, and insulin/IGF signaling networks with progression of Alzheimer's disease. *J Alzheimers Dis* 2012; 30(Suppl 2):S217–29.
3. Trivedi B. Food for thought: Eat your way to dementia. *New Scientist* 3 Sept 2012; issue 2880.
4. Monbiot G. Alzheimer's could be the most catastrophic impact of junk food. *Guardian* 10 Sept 2012.
5. Stolk RP, et al. Insulin and cognitive function in an elderly population. The Rotterdam Study. *Diabetes Care* 1997;20(5):792–5.
6. Bingham EM, et al. The role of insulin in human brain glucose metabolism: an ¹⁸F-fluoro-deoxyglucose positron emission tomography study. *Diabetes* 2002;51(12): 3384–90.
7. Hunt KF, et al. Brain Insulin Resistance. In *The Metabolic Syndrome*, 2nd edn. Byrre CD, Wild SH (eds). Blackwell Publishing Ltd, 2011. Chapter 9.
8. Talbot K, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J Clin Invest* 2012;122(4):1316–38.
9. Brain insulin resistance contributes to cognitive decline in Alzheimer's disease. *Science News* 23 March 2012.
10. de la Monte SM, Wands RJ. Alzheimer's disease is type 3 diabetes – evidence reviewed. *J Diabetes Sci Technol* 2008;2(6):1101–13.
11. Bitel CL, et al. Amyloid- β and tau pathology of Alzheimer's disease induced by diabetes in a rabbit animal model. *J Alzheimers Dis* 2012;32(2): 291–305.
12. Farris W, et al. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proc Natl Acad Sci U S A* 2003;100(7):4162–7.
13. Chen Y-H, et al. Amyloid beta oligomers induce impairment of neuronal insulin receptors. *FASEB J* 2008;22(1):246–60.