Alzheimer's and diabetes

Several lines of evidence suggest that Alzheimer's disease has strong links with insulin action and that the condition could be described as 'diabetes of the brain'

Until recently, it was the view that insulin had little effect on the energy metabolism of the brain. It was thought illogical that something as important as the brain would be dependent in any way on when a person last ate a meal. This was because the brain is a particularly energy intensive organ, consuming approximately 25% of the body's total glucose.

However, it was first discovered that astrocytes and microglial cells, which are major communicating cells in the brain, are insulin sensitive and later that the insulin receptor had a wide distribution in the brain. Fluorodeoxy-glucose positron emission tomography studies demonstrated that insulin had a role in regulating global brain glucose utilisation in humans, most markedly in the cortical regions. Other studies have demonstrated that insulin plays a key role in neuroplasticity, neuromodulation and neurotrophism – the process of neuronal growth, stimulated by neuronal differentiation and survival.

Epidemiology studies demonstrate that the risk of developing Alzheimer's disease is increased by 50% in subjects with diabetes. Type 2 diabetes, which accounts for 90% of all diabetes, is due to both insulin resistance and decreased pancreatic β-cell function. In the early stages, insulin resistance results in the pancreatic islets secreting more insulin, in an attempt to overcome the resistance. Over time, this leads to an increasing failure of the islet to produce enough insulin and ultimately hypoinsulinaemia so that the patient requires insulin injections.

Insulin resistance

A key question is whether the brain develops insulin resistance. Recent studies using *postmortem* brains from patients with Alzheimer's, but without diabetes, showed markedly reduced responses to insulin in the insulin receptor → insulin receptor substrate -1 → phosphoinositol-3 kinase signalling pathway in the hippocampus and to a lesser degree in the cerebellar cortex.

In the hippocampus, the biomarkers of insulin resistance increased progressively from normal cases through mild cognitive impairment cases to Alzheimer's disease regardless of diabetes. However, there is no evidence that the brain in Alzheimer's disease is hyperglycaemic, unlike peripheral tissues in diabetes. Thus an appropriate term to describe the state of Alzheimer's disease brain is 'insulin-resistant brain'. This is analogous to insulin resistance syndrome, which is a feature of several peripheral tissue disorders. Insulin resistance in peripheral tissues could promote insulin resistance in the brain by reducing brain insulin uptake and by raising brain levels of Aβ.

A second reason why peripheral resistance to insulin may affect the brain has now been proposed. This is that toxic ceramides generated by the disturbed lipid metabolism in insulin-resistant liver pass into the circulation and transit across the blood brain barrier into the brain. There they induce inflammation leading to a second-pronged attack on central insulin action.

These studies lead to the view that drug treatments that improve either or both central and peripheral insulin resistance are potential treatments, or at least agents, to delay the progression of mild cognitive impairment to Alzheimer's disease. In fact two anti-diabetes drugs have already been shown to have some beneficial effects. They are metformin and the thiazolidinedione rosiglitazone and a third drug pioglitazone has been proposed for a large clinical trial.

Potential treatment

However, none of these drugs are a perfect treatment. Many patients do not easily tolerate metformin as a result of gastrointestinal side effects and the thiazolidinedione insulin sensitiser drugs produce weight gain and water retention. There is, therefore, a need for a concerted effort to discover drugs that act to cause insulin sensitisation in the brain and liver. Such drugs are a potential treatment for Alzheimer's patients possibly when coupled with nasal delivery of insulin, which has been shown to improve learning and memory in clinical trials. The greater need, however, is to develop strategies that will delay the onset and progression of mild cognitive impairment towards Alzheimer's.

For this, drugs are not the answer, unless one had diagnostic assays that were highly predictive, since it would be unethical to give drugs with inherent risks to people who might not develop the disease. However, if non-toxic plant extracts with similar insulin sensitiser action could be identified, these could be made available to the public.

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