NEURODEGENERATIVE DISEASE

Putting the brakes on cognitive decline

Central to the amyloid hypothesis of Alzheimer's disease is the primary role of aggregated β-amyloid (Aβ) peptide in causing the pathogenesis and loss of cognitive function characteristic of the disease. But the fashionability of Aβ as a potential therapeutic target suffered a setback last year when Elan/Wyeth-Ayerst's much heralded clinical trial of passive immunization against Aβ as a treatment for Alzheimer's disease was halted owing to the development of adverse reactions in a subset of patients. At the time, the paucity of information surrounding the reasons for interrupting the trial only increased concern about the validity of the approach, and it was subsequently revealed that 6% of patients had developed a potentially life-threatening asepticmeningoencephalitis. Although the trial remains suspended, a paper in the 22 May issue of *Neuron* now reports reduced cognitive decline in a small cohort of enrolled patients that developed a high titre of antibodies to Aβ.

The study by Hock *et al.* describes results obtained from the Zurich cohort of the Phase IIa multicentre trial, which represents just 30 patients out of a total of 300. Of these, 24 had received an intramuscular injection of pre-aggregated synthetic $A\beta_{42}$, together with adjuvant to stimulate an immune response, followed by a booster injection one month later. Placebo had been given to the remaining six patients, and investigators were not informed of the drug/placebo status of any of the trial group. The cognitive abilities of this patient population were followed over the course of the year following immunization, with neuropsychological assessment being carried out at baseline and after eight and twelve months. Measures of cognitive status were then correlated with the development of antibodies to Aβ plaques, quantitatively assessed using a specially designed tissue amyloid plaque immunoreactivity assay, which measures the immunoreactivity of human sera for Aβ plaques in fixed tissue sections taken from the brains of a mouse model of Alzheimer's disease.

Of the twenty-eight patients still enrolled after a year (there were two dropouts), the nineteen who generated antibodies against Aβ were found to perform significantly better in neuropsychological tests after eight and twelve months than the nine patients that did not show immunoreactivity. Overall, Mini Mental State Examination (MMSE) scores in the antibody-producing patients remained unchanged during the course of the year, indicating no significant cognitive decline by this measure. Cognitive status reported by the patients' caregivers, measured by the Disability Assessment for Dementia rating scale, also showed significantly less decline in the immunoreactive population. However, the MMSE scores for the group that did not produce antibodies declined significantly more than would be expected for an untreated population, an observation which emphasizes the risks of over interpreting data gleaned from such a small sample of patients.

The finding that sustained production of serum antibodies generated against Aβ plaques can slow cognitive deterioration is key evidence for the involvement of Aβ in Alzheimer's disease progression. This good news is somewhat tempered by the reported development of aseptic meningoencephalitis in three of the Zurich patients, although two of these patients did exhibit serum immunoreactivity and improved cognitive function.

Adam Smith, Editor,
Nature Reviews Drug Discovery

References and links

ORIGINAL RESEARCH PAPER Hock, C *et al.* Antibodies against β-amyloid slow cognitive decline in Alzheimer's disease. *Neuron* **38**, 547–554 (2003)

SYSTEMS NEUROSCIENCE

Buffet belly

We all know how it feels to have overindulged at dinner. That bloated feeling is the result of ignoring signals from a complex pathway that has the hypothalamus — which senses the availability of circulating nutrients — at its centre. By focusing on the lipid metabolism branch of this regulatory network, Silvana Obici and colleagues have shown that carnitine palmitoyltransferase-1 (CPT1) has a crucial role in the control of food intake and endogenous glucose production.

In a study published in *Nature Medicine*, Obici *et al.* selectively reduced lipid oxidation in the hypothalamus by decreasing the activity of CPT1, an enzyme that regulates the entry of long-chain fatty acids (LCFAs) into mitochondria. The authors used intracerebroventricular infusion of a CPT1-specific ribozyme or pharmacological inhibitors to reduce CPT1 activity — and consequently increase the hypothalamic concentration of LCFAs — in the arcuate nuclei of rats. The result was a 50% reduction in voluntary food intake, an effect that lasted at least 48 hours after a single dose of ribozyme or inhibitor.

To assess the impact of CPT1 inhibition on glucose homeostasis, the rate of glucose infusion required to prevent hypoglycaemia in CPT1-inhibited rats was measured while maintaining the peripheral insulin concentration at a fixed basal level. Inhibition of CPT1 necessitated a rate of glucose administration that was up to fivefold greater than in untreated controls. The authors showed that suppression of endogenous glucose production — not stimulation of glucose uptake — accounted for this excessive requirement for exogenous glucose.

These data show that the build-up of LCFAs in a population of hypothalamic neurons due to the inhibition of CPT1 represents a central signal of 'nutrient abundance' that feeds back to limit glucose production. Manipulation of fatty acid oxidation therefore warrants further investigation as a potential target for the treatment of metabolic disorders such as obesity and type 2 diabetes.

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References and links

ORIGINAL RESEARCH PAPER Obici, S. *et al.* Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. *Nature Med.* **9**, 756–761 (2003)