JPn Neuroscience
The Journal of Physiology



PERSPECTIVES

# Does too much sugar make for lost memories?

**A. Stefanidis and M. J. Watt**
*Department of Physiology, Monash University, Clayton, Australia*

Email: aneta.stefanidis@monash.edu

Obesity and insulin resistance in peripheral tissues are the prominent drivers of the 'metabolic syndrome', a term coined to describe a clustering of metabolic abnormalities that include central obesity, raised triglycerides, reduced HDL cholesterol, raised blood pressure and increased fasting plasma glucose. The pathogenic outcomes associated with the metabolic syndrome have been extensively documented in peripheral tissues and include cardiovascular disease and type 2 diabetes. In contrast, the impact of the metabolic syndrome on the central nervous system is less clear. There is some evidence that an obesity-promoting diet alters the electrophysiological properties of neurons, reduces the density of synaptic inputs, induces gliosis and impairs insulin signalling in hypothalamic neurons controlling energy balance (Horvath *et al.* 2010). A growing literature suggests that individuals with the metabolic syndrome are more likely to develop cognitive impairments that are postulated to be mediated by insulin resistance, dyslipidaemia, inflammation, adiposity and micro/macrovascular changes (Yaffe, 2007). However, direct examination of whether the metabolic syndrome impacts higher order brain centres or deeper brain structures has been limited.

In a recent issue of *The Journal of Physiology*, Agrawal & Gomez-Pinilla (2012) investigated the impact of omega-3 fatty acid deficiency and the metabolic syndrome on cognition and synaptic plasticity, and explored the potential mechanisms mediating changes to these processes in the hippocampus, a region in the brain critical for learning and memory. The authors fed rats a diet deficient in omega-3 fatty acids to represent the 'normal' Western diet, which is particularly low in the omega-3 fatty acid, docosahexaenoic acid (DHA; C22:6*n*-3), compared with the diet on which humans evolved. Dietary omega-3 fatty acids are abundant in fish and are important for normal growth and development, while dietary omega-3 supplementation (including DHA) counteracts several metabolic dysfunctions. It is notable that most 'standard chow' diets provided in vivarium facilities contain <0.4% of total energy from omega-3 fatty acids (and ∼0.05% from DHA), below the recommended 0.5–2%, and thereby represents a state of omega-3 deficiency. Rats were also provided with fructose in their drinking water to induce several components of the metabolic syndrome, including insulin resistance and dyslipidaemia.

Dietary omega-3 deficiency impaired spatial learning and memory retention, which was further impaired by the intake of fructose. These changes in cognitive function were accompanied by reduced expression of the synaptic plasticity-associated proteins synaptophysin and synapsin I. The addition of omega-3 fatty acids to the diet improved memory and ameliorated the memory impairments induced by fructose consumption. Together, these observations support the requirement of omega-3 fatty acids above current consumption levels to maintain neural function and cognition under 'normal' conditions, and particularly, to protect against cognitive decline during metabolic stress.

The diet-induced impairments in cognition correlated with whole body insulin resistance and hypertriglyceridaemia, suggesting either factor could impact memory performance. Accordingly, Agrawal & Gomez-Pinilla (2012) assessed insulin signalling in the hippocampus. Phosphorylation of the insulin receptor and the distal signalling molecule Akt were reduced in rats fed the omega-3 deficient diet in combination with fructose, while insulin signalling was restored with the inclusion of omega-3 fatty acids in the diet. A role of insulin resistance in memory impairment is supported by the observation that acute administration of exogenous insulin enhances memory, even in individuals with Alzheimer's disease (Craft *et al.* 1999). However, a problem with this interpretation is that insulin signalling was assessed in the basal state, and conclusions regarding insulin action require assessment under insulin-stimulated conditions. In addition, the interpretation that insulin resistance is mediating memory impairments is at odds with the finding that insulin receptor knockout mice perform normally in spatial learning and memory tests (Schubert *et al.* 2004). Thus, these contrasting data suggest that it is premature to conclude that hippocampal insulin resistance contributes to impaired cognitive function (Reagan, 2007). Alternatively, omega-3 deficiency reduced DHA, one of the major *n*-3 polyunsaturated fatty acids in the brain, but increased docosapentaenoic acid (DPA; C22:5*n*-6). These fatty acids are key constituents of cell membranes and alter membrane fluidity, suggesting that a change in the *n*-6/*n*-3 fatty acid ratio could impact synaptic plasticity and neuronal function through undefined mechanisms.

The data presented by Agrawal & Gomez-Pinilla (2012) provide a platform for further experiments that should delineate the factors that alter cognitive function in obese, insulin resistant phenotypes. First, several experimental models that mimic the 'metabolic syndrome' should be employed (e.g. high-fat feeding) since obesity, or its associated pathologies, are not always driven by the overconsumption of a single sugar. Second, future experiments should provide detailed assessment of synaptic plasticity and determine the neurochemical/neuroanatomical substrate subserving cognitive dysfunction induced by the metabolic syndrome. For example, does omega-3 deficiency alter synaptic reorganisation, synaptic efficacy or the nature of postsynaptic elements to influence connectivity between neurons? Third, studies examining cellular signalling and lipid composition should be performed in isolated neurons, which will extend the existing data obtained in whole brain sections that contain an abundance of other cell types such as astrocytes/tanycytes. Next, it remains to be determined if pre-existing cognitive impairments can be 'reversed' by omega-3 supplementation, a simple nutritional intervention. And finally, does the dysfunction reported in the hippocampus extend to other brain regions controlling divergent physiological functions?


DOI: 10.1113/jphysiol.2012.235028

Agrawal & Gomez-Pinilla (2012) provide evidence that dietary omega-3 fatty acids are essential for normal cognition and that diets deficient in omega-3 fatty acids increase the brain's susceptibility to fructose-induced derangements. This is especially pertinent given the evidence that most Western diets are deficient in omega-3 fatty acids and the vigorous public health debate surrounding the use of fructose-containing sugars in foods and the putative links with obesity and the metabolic syndrome (Lustig *et al.* 2012).

## References


Agrawal R & Gomez-Pinilla F (2012). *J Physiol* **590**, 2485–2499.

Craft S, Asthana S, Newcomer JW, Wilkinson CW, Matos IT, Baker LD, Cherrier M, Lofgreen C, Latendresse S, Petrova A, Plymate S, Raskind M, Grimwood K & Veith RC (1999). *Arch Gen Psychiatry* **56**, 1135–1140.

Horvath TL, Sarman B, Garcia-Caceres C, Enriori PJ, Sotonyi P, Shanabrough M, Borok E, Argente J, Chowen JA, Perez-Tilve D, Pfluger PT, Bronneke HS, Levin BE, Diano S, Cowley MA & Tschop MH (2010). *Proc Natl Acad Sci U S A* **107**, 14875–14880.

Lustig RH, Schmidt LA & Brindis CD (2012). *Nature* **482**, 27–29.

Reagan LP (2007). *Curr Opin Pharmacol* **7**, 633–637.

Schubert M, Gautam D, Surjo D, Ueki K, Baudler S, Schubert D, Kondo T, Alber J, Galldiks N, Kustermann E, Arndt S, Jacobs AH, Krone W, Kahn CR & Bruning JC (2004). *Proc Natl Acad Sci U S A* **101**, 3100–3105.

Yaffe K (2007). *Curr Alzheimer Res* **4**, 123–126.