

DIABETES

Is altered dopamine turnover the missing link between insulin resistance and cognitive decline?

The mechanisms that underlie behavioural disorders, such as depression and accelerated cognitive decline, in patients with type 1 diabetes mellitus and type 2 diabetes mellitus (T2DM) have remained largely unknown. A new study in mice demonstrates that loss of insulin signalling in the brain leads to central mitochondrial dysfunction and altered expression of enzymes that regulate dopamine turnover. These findings suggest that insulin signalling is an important regulator of dopamine signalling and oxidative stress in the brain, with disruptions in this pathway leading to the development of symptoms associated with cognitive decline.

The team of researchers from Boston, MA, USA, found that mice with a brain-specific deletion of the insulin receptor (NIRKO mice) exhibited age-dependent depressive-like behaviours, as well as increased anxiety and stress responses. The mitochondria in the brains of NIRKO mice had altered morphology and function, which was associated with an increase in oxidative stress; an effect that was exacerbated as the mice aged. In addition, dopamine signalling was decreased in the NIRKO mice. Studies performed in cultured neurons demonstrated that the reduction in dopamine signalling was a result of increased dopamine turnover that was mediated by increased levels of monoamine oxidase (MAO) A and MAO B due to loss of insulin signalling.

Treatment of NIRKO mice with one of two antidepressants (imipramine or phenelzine, which are inhibitors of MAO activity) reversed the depressive-like behaviours in NIRKO mice to the extent

that these mice were indistinguishable from saline-treated control animals.

On the basis of these findings, the authors suggest that the increased incidence of depression in patients with diabetes mellitus could be a consequence of central insulin resistance. However, Geert Jan Biessels, an expert in the field who was not involved in the study, believes these results should be interpreted with caution. "We are not so well informed as to the degree of insulin resistance in the brain in humans with T2DM and given that many people with T2DM are also hyperinsulinaemic, it may even be that some brain areas could be exposed to excess insulin activity," he warns.

Jennifer Sargent

Original article Kleinridders, A. *et al.* Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. *Proc. Natl Acad. Sci. USA* doi:10.1073/1500877112



iStock/Thinkstock