Title: Molecular and cellular mechanisms underlying the relationship between metabolic alterations and cognitive decline

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Abstract
Increasing evidence suggests an association between metabolic disorders, notably insulin-resistance and type 2 diabetes, with cognitive decline and Alzheimer's Disease. Recent studies have shown that diet-induced changes in peripheral insulin sensitivity contribute to alterations in brain insulin signaling and cognitive functions. Deranged glucose metabolism in the brain accompanied by elevated levels of fatty acids and chronic low-grade inflammation has been postulated as the pathogenic mechanism associating type 2 diabetes with Alzheimer's Disease.

We set up a preclinical animal model of diet induced-glucose intolerance: young mice were fed with 45% and 60% high fat diets for several weeks. These diets induced a significantly increase in body weight, already after one week of diet, glucose intolerance after 3 weeks and insulin intolerance after 5 weeks of diet. To assess the presence of cognitive impairments behavioral tests were performed. We investigated the effects of the high fat diet on neurotransmission, neuroinflammation, myelination, endoplasmic reticulum stress and DNA damage by western blot analyses in hippocampus and prefrontal cortex of mice. To investigate more in depth the molecular mechanism underlying glucose-intolerance in the brain, palmitic acid treatments were used in vitro on primary neuronal cell cultures to mimic the metabolic condition determined by high fat diet. Hippocampal neurons treated in vitro with palmitate recapitulate salient features observed in ex vivo tissue. Our results suggest that high fat diet, even for a short period of exposure, can alter relevant brain functions, including neurotransmitter receptors and myelination. The precise molecular mechanisms underlying these effects are still under investigation.

By this work we want to identify novel pathways affected by high fat diet and eventually translate this knowledge into a clinical setting for identifying subjects at risk for cognitive decline and possibly intervene with life style changes preventing the decline.

References:

Keywords: dietary interventions, cognitive decline, metabolism

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