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Investigating the importance of acylcarnitines in Alzheimer's disease

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Abstract

Background: L-carnitine is present in the mammalian cells as free carnitine (FC) and acylcarnitine and the adult human brain contains almost 10% of long chain acylcarnitine. Acylcarnitines are functionally involved in β-oxidation of fatty acids and are also known for their role in neuroprotection. Levels of plasma acylcarnitines are known to decreased on aging. It is important to understand the association of acylcarnitines with cognitive impairment in Alzheimer's disease (AD).

Method: We integrated the transcriptome data from 1000 post-mortem brain samples from ROS/MAP, Mayo clinic and Mount Sinai Brain bank cohort with the brain region-specific metabolic networks. We calculated the metabolic fluxes for the reactions in the model and identified those that showed differential fluxes in AD samples. We filtered the reactions that are involved in acylcarnitine synthesis and transport namely carnitine transport, fatty acid oxidation, citric acid cycle, and glutathione metabolism.

Result: We found differences in metabolic fluxes for reactions involved in the acetylcarnitine transport to mitochondria (ACRNtm), carnitine palmitoyl transferase 1 and 2 (CPT1 and CPT2) as well as acyl-CoA dehydrogenase short and medium chain (ACADS, ACADM) located in mitochondria in AD samples. Using gene-based association analysis in participants of the AD Neuroimaging Initiative (ADNI) phases 1, GO and 2, we identified genetic variants linked to CPT1, CPT2, ACADM and ACADS genes suggested from the metabolic flux analysis.

Conclusion: Our findings suggest that acylcarnitine synthesis and transport is altered in AD. Altered metabolism of short and medium chain acylcarnitines can be used as metabolic features of AD.