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Understanding Alzheimer's disease mechanism using metabolomics

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AD affects more than 5 million Americans and over 35 million people worldwide with numbers expected to grow dramatically as the population ages. The pathophysiological changes in Alzheimer's disease (AD) patients begin decades before the onset of dementia, highlighting the urgent need for the development of early diagnostic methods. We applied a liquid chromatography/mass spectrometry-based non-targeted metabolomics approach to determine metabolic changes in plasma and cerebrospinal fluid (CSF) from the same individuals with different AD severity. Metabolic profiling detected a total of 342 plasma and 351 ($P \leq 0.05$) CSF metabolites, of which 22% were identified. Based on the changes of >150 metabolites, we found 23 altered canonical pathways ($P \leq 0.05$) in plasma and 20 in CSF ($P \leq 0.05$) in mild cognitive impairment (MCI) vs. cognitively normal (CN) individuals with a false discovery rate (FDR) <0.05. The number of affected pathways increased with disease severity in both fluids. Lysine metabolism ($P \leq 10\text{-}5$) in plasma and the TCA cycle ($P \leq 10^{-5}$) in CSF were significantly affected in MCI vs. CN. Cholesterol and sphingolipids transport ($P \leq 10^{-8}$) were altered in both CSF and plasma of AD vs. CN. Other 30 canonical pathways significantly affected in MCI and AD patients were related to energy metabolism, Krebs cycle, mitochondrial function, neurotransmitter and amino acid metabolism, and lipid biosynthesis. Pathways in plasma that discriminated between all groups included polyamine, lysine, tryptophan metabolism, and aminoacyl-tRNA biosynthesis; and in CSF included cortisone and prostaglandin 2 biosynthesis and metabolism. These data correlate with our studies conducted in three transgenic mouse models of familial AD using targeted metabolomics. In these mice, metabolic signatures in the brain tissue revealed changes in the levels of metabolites reflecting altered energy metabolism and mitochondrial dysfunction similar to what we have found in MCI and AD patients. These changes in animals preceded the onset of amyloid deposits and memory deficit. Our data suggest AD pathogenesis involves early changes in multiple functionally connected networks that start early in disease and are shared in progression from MCI to AD. Thus, metabolomics could help to identify early mechanisms involved in disease pathogenesis and specific biomarkers associated with disease progression.

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