the samples, which was slightly increased by prolonging the delay in processing.

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**IDENTIFICATION OF ALTERED METABOLIC PATHWAYS IN PLASMA AND CSF IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER’S DISEASE USING METABOLOMICS**

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**Background:** Research evidence suggests that pathophysiological changes associated with Alzheimer’s Disease (AD) begin at least 10 to 25 years before the dementia onset. Compelling data demonstrate that increased levels of amyloid beta (Aβ) compromise multiple cellular mechanisms. The ability to monitor changes in a variety of pathways including non-amyloid pathways is essential to advance our understanding of the early disease mechanisms and to identify novel therapeutic targets to treat and modify the disease progression. Application of metabolomics, a powerful tool that allows detecting perturbations in the metabolome and represents an accurate biochemical profile of the organism in health and disease, offers new opportunities in biomedical research. **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. **Results:** Metabolic profiling detected a total of 342 plasma and 351 (P ≤ 0.05) CSF metabolites, of which 22% were identified. Based on the changes of >150 metabolites, we found 23 altered canonical pathways (P ≤ 0.05) in plasma and 20 in CSF (P ≤ 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 ≤ 10^{-5}) in plasma and the TCA cycle (P ≤ 10^{-5}) in CSF were significantly affected in MCI vs. CN. Cholesterol and sphingolipids transport (P ≤ 10^{-8}) was altered in both CSF and plasma of AD vs. CN. Other 30 canonical pathways significantly affected in MCI and AD patients included 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. **Conclusions:** Our data suggest AD pathogenesis involves early changes in multiple functionally connected networks shared in progression from MCI to AD. Our data validate plasma as reliable source for metabolomic profiling and suggest that metabolomics is a valuable tool for the identification of molecular mechanisms involved in the etiology of AD.

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**KIF6 719ARG CARRIER STATUS ASSOCIATION WITH HOMOCYSTEINE AND C-REACTIVE PROTEIN IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER’S DISEASE**

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**Background:** Recent research has demonstrated associations between statin use, KIF6 719Arg carrier status, and cholesterol levels and mild cognitive impairment (MCI) and Alzheimer’s disease (AD) patients. The association between 719Arg carrier status with homocysteine (tHcy) and c-reactive protein (CRP) levels in MCI and AD has not been previously investigated. This relationship is of interest given the established associations between MCI/AD, tHcy, and CRP levels. **Methods:** Data from 160 MCI and AD patients with an average age of 77.76 ± 8.15 years were used for the analysis. The sample was comprised of 78 females and 82 males. The Mann-Whitney U test was used to assess group differences for 719Arg carrier status on tHcy and CRP levels. The association between 719Arg carrier status with tHcy and CRP was analyzed using logistic regression, which adjusted for ApoE ε4 carrier status. For these analyses, tHcy and CRP levels for the study sample were dichotomized into elevated and non-elevated groups using recommended clinical guidelines. **Results:** 719 Arg carriers (13.72 ± 14.70 μ mol/L) had significantly lower levels of tHcy than non-carriers (15.12 ± 3.96 μ mol/L, p = 0.008). No difference in CRP levels between 719 Arg carriers (4.92 ± 8.93 mg/L) and non-carriers (4.24 ± 9.31 mg/L) was found (p = 0.38). Logistic regression yielded no significant effect for 719 Arg status on CRP [OR = 1.30 (0.64, 2.67), p = 0.47], but did demonstrate a significant effect for tHcy [OR = 0.43 (0.17, 0.65), p = 0.001]. Additional analysis of 719 Arg and ApoE ε4 carrier status interaction also yielded a significant effect for tHcy [OR = 0.44 (0.23, 0.87), p = 0.02]. tHcy was not significantly associated with ApoE ε4 carrier status [OR = 0.59 (0.52, 1.80), p = 0.92] **Conclusions:** This study is the first to explore the relationship between KIF6 719 Arg carrier status and tHcy and CRP levels. 719 Arg carriers were more likely to have normal tHcy levels after adjusting for ApoE ε4 status. Individuals who were carriers of both the 719 Arg and ApoE ε4 alleles were more likely to have normal tHcy levels. These results suggest that the KIF6 719 Arg allele might influence cardiovascular pathways that are involved in AD pathogenesis.