APOE, Metabolism and Cognitive Function: An Assessment via Indirect Calorimetry

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Both genetic factors and metabolic disturbances are associated with declines in cognitive performance and increased risk of dementia. The gene Apolipoprotein E (APOE) encodes for three isoforms in the human population (E2, E3, and E4), and the E4 isoform – carried by approximately 1/5 of the population – is associated with up to a 15-fold increased risk of late onset Alzheimer's Disease (AD). Both AD and E4 have been associated with inefficient brain glucose uptake and impaired metabolism. Interestingly, our preliminary data show that aged mice expressing human E4 demonstrate a metabolic "shift" compared to those expressing human E3. This is reflected as a preference of E4 mice for lipids vs carbohydrates as a fuel source. As the brain relies primarily on glucose as an energy source, these data suggest that E4 may negatively influence metabolic pathways which are critical for cognitive function. We hypothesize that similar apoE differences are present in cognitively normal individuals, and therefore aim to translate these exciting findings to human subjects. We believe an E4-directed shift away from glucose utilization may represent a critical step in the progression of cognitive decline, and thus a potential novel biomarker for AD risk. To test our hypotheses, we aim to measure metabolic rate and respiratory quotient (RQ) – a reflection of substrate preference – using indirect calorimetry (IC). Metabolic analyses employing IC are commonly used in clinical settings and exercise studies. However, while technically feasible, to our knowledge, IC has never been applied to investigate biomarkers of cognitive impairment. Thus, repurposing IC to study the metabolic effects of an AD risk factor such as E4 represents a simple and cost-effective new approach. In the current study, real-time metabolic measures will be assessed in individuals with various APOE genotypes – both at rest and during a cognitive and dietary challenge. Accuracy and interpretation of RQ will be aided by measuring adiposity, blood glucose, and urinary urea nitrogen (for estimation of protein oxidation). Our initial feasibility studies show measurable increases in RQ during a cognitive challenge (novel object, novel location test), as well as a trend toward increased resting energy expenditure (REE). Additionally, an acute dietary challenge (sugar water drink) resulted in a steady increase in RQ following ingestion. Recruitment of ~75 young, cognitively normal subjects is scheduled to begin in October 2017. We hope to expand our methods in future studies to measure elderly subjects (cognitively normal, mild cognitive impairment and AD), as well as potential collaborative efforts in other areas of neuroscience.

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