Brandon Farmer

APOE AS A METABOLIC REGULATOR IN HUMANS, MICE, AND ASTROCYTES

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Altered metabolic pathways appear to play central roles in the pathophysiology of late-onset Alzheimer’s disease (AD). Carrier status of the E4 allele of the APOE gene is the strongest genetic risk factor for late-onset AD, and increasing evidence suggests that E4 carriers may be at an increased risk for neurodegeneration based on inherent metabolic impairments. A new appreciation is forming for the role of APOE in cerebral metabolism, and how nutritional factors may impact this role. In chapter 1, the literature on nutritional interventions in E4 carriers aimed at mitigating disease risk is reviewed. Studies investigating the mechanism by which E4 increases disease risk have focused primarily on the association of E4 with the neuropathological hallmarks. While these studies have aided in our understanding of the role of E4 in late-disease pathology, investigating metabolic signatures of E4 carriers who have not yet developed neuropathology gives insight into the potential earlier mechanisms of E4 as a risk factor for AD. For example, an early and consistent biological hallmark of AD is cerebral glucose hypometabolism as observed by fluorodeoxyglucose positron emission tomography (FDG-PET). Interestingly, E4 carriers also display an AD-like pattern of decreased glucose metabolism by FDG-PET far before clinical symptomology. Since glucose hypometabolism occurs early in AD and early in E4 carriers, it may represent a critical prodromal phase of AD. Beyond this brain imaging finding, it is unclear if APOE has any other discernable metabolic effects in cognitively unimpaired young people. In chapter 2 we answer this gap in the field. We utilized indirect calorimetry (IC) as a method for assessing metabolism in young and middle aged volunteers with and without the E4 allele. While IC is commonly used in clinical settings to assess nutritional status, it has never been used to assess risk for cognitive decline. Thus, repurposing IC to study the metabolic effects of an AD risk factor such as E4 represents a simple, cost-effective, and innovative new approach. We found that young female E4 carriers show a lower resting energy expenditure compared to non-carriers. We also tested how E4 carriage affects response to a glucose challenge by administering a glucose rich beverage in conjunction with IC measurements and plasma metabolomics. We found that female E4 carriers were unable to increase oxygen consumption relative to non-carriers, reflecting an impairment in glucose oxidation. Additionally, the plasma metabolome of E4 carriers showed increased lactate and an overall metabolic profile consistent with aerobic glycolysis. We translated these findings to mice expressing the human alleles of APOE. We found that E4 mice on a normal chow diet have lower energy expenditure than E3 mice, a difference further exacerbated by high carbohydrate diet feeding. Stable isotope tracing in mice whole brains and astrocytes implicate increased utilization of aerobic glycolysis as a mechanism for altered glucose handling in E4 carriers. A pathological feature of the Alzheimer’s brain is glial lipid accumulation. The mechanism for this is largely unknown. In chapter 3, the literature pertaining to lipid droplets (LD) in the brain is reviewed. We show that LDs are much more than simple fat depots, playing critical roles in metabolism, inflammation, and various neurodegenerative diseases. In chapter 4, the effect of the E4 allele on astrocyte LD accumulation and turnover is assessed. Using an in vitro model of APOE we probed the storage and oxidation capacity of fatty acids in E3 and E4 astrocytes. We observed that E4 astrocytes exhibit greater storage of fatty acids as LDs under control and lipid loaded conditions compared to E3 astrocytes. Furthermore, we found that E4 astrocytes rely on these LDs as a source of fuel for oxidation. Therefore, APOE appears to regulate whole body energy expenditure, cerebral glucose oxidation, astrocyte LD metabolism, and risk for a host of metabolic diseases. In chapter 5, the evolutionary history of APOE is presented to posit a hypothesis for why E4 may be disadvantageous in modern times compared to its prior advantages in the pre-historic era. These results point toward a larger role for APOE in the regulation of metabolism than previously understood and advocates for alternative nutritional approaches including calorie reduction and intermittent fasting as plausible interventions to mitigate disease risk in E4 carriers.
MD/PhD training brings with it unique challenges that I do not possess the constitution to weather independently. These individuals formed my support structure and are due as much credit as I for this dissertation.

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