“CSF Cortisol and APOE Genotype” (NACC Project #2001-04)

Principal Investigator
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Collaborating Centers
Indiana University, Oregon Health and Science University, University of California Davis, University of California San Diego, University of Pennsylvania

Project Dates
2001-current

Project Description
Hypothalamic-pituitary-adrenal (HPA) axis activity is increased in Alzheimer’s disease (AD) as manifested by increased concentrations of cortisol in plasma, urine and cerebrospinal fluid (CSF). Because cortisol elevations induced by exogenous cortisol administration or by stress produce hippocampal dendritic atrophy and may contribute to aging-associated hippocampal neuronal loss in several mammalian species, exposure of the brain to elevated concentrations of cortisol in AD may lower the threshold for neuronal degeneration in this disorder. In our preliminary data, presence of the apolipoprotein E (APOE)-ε4 allele, which is the chief known genetic risk factor for AD, increases cortisol in CSF in both AD subjects and nondemented older subjects in a dose-dependent manner. In addition, the ε2 allele, which reduces AD risk, reduces CSF cortisol. These preliminary data raise the possibility that increased brain exposure to cortisol is a mechanism by which APOE-ε4 increases risk for expression of AD in later life. If one assumes that the human APOE-ε4 allele produces at least partial aging-dependent loss of normal APOE function, then recent studies in transgenic mice also support this possibility. ApoE-deficient (APOE-/-) knockout mice have aging-related increases in corticosterone (the rodent glucocorticoid equivalent of cortisol) accompanied by brain neurodegenerative changes in the hippocampus and neocortex. The goals of this multi-Center ADC project are to confirm and extend our preliminary finding that APOE-ε4 increases CSF cortisol in an aging-dependent manner. Cortisol will be measured in CSF because of our preliminary findings demonstrating that CSF cortisol provides a more integrated measure of cortisol release over time than does plasma or saliva cortisol, and because CSF cortisol provides a likely estimate of brain neuron exposure to biologically-active free cortisol. We are pursuing the specific aim of determining the effect of APOE genotype on CSF cortisol concentrations in persons with AD, nondemented older persons, and normal young and middle-aged persons. CSF samples are being collected in a standardized manner in 120 AD, 120 older normal, 60 middle-aged normal, and 60 young normal subjects. CSF cortisol concentration, cognitive and functional measures, a quantified measure of stressful life events, and APOE genotypes will be determined. Timely replication of our initial findings is essential to establish the rationale for long-term evaluation of the interaction between CSF cortisol and APOE genotype on cognitive decline in later life. In addition, confirmation of these findings is necessary to provide rationale for mechanistic studies in animal models.

Publications to Date
Contact Information
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