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17alpha-estradiol improves systemic and neural outcomes in middle-aged APOE4 mice

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Abstract

Background: In this study, we investigate the hypothesis that recently identified longevity-promoting intervention 17α-estradiol (17αE2) will protect against senescent changes in brain and throughout the body that are associated with *APOE4* and heightened AD risk. The most significant genetic factor for late-onset Alzheimer's disease (AD) is the apolipoprotein E gene (*APOE*): AD risk is reduced by the *APOE2* variant and increased by the *APOE4* variant. *APOE* genotype is associated with longevity in the same pattern, with *APOE2* linked with increased and *APOE4* with decreased lifespan. This is of particular interest as advanced age is the single greatest risk factor for AD. Indeed, *APOE* genotype may regulate AD vulnerability in part by affecting aging processes. Thus, compounds that increase health and longevity may be particularly relevant to *APOE4*-associated AD risk.

Method: Male mice homozygous for human *APOE3* or *APOE4* were maintained on normal chow in the absence or presence of 14.4 ppm 17αE2 for 20 weeks, starting at age 10 months. Animals were assessed on a range of systemic metabolic, inflammatory, and frailty outcomes as well as on established areas of *APOE4*-associated neural impairment, including neuroinflammation, neurogenesis, and cognition.

Result: In middle-aged male mice, *APOE4* genotype was associated with significantly poorer systemic and neural phenotypes relative to *APOE3* genotype. In general, treatment with 17αE2 yielded improvements in both *APOE3* and *APOE4* mice across multiple measures, though the benefits were typically much stronger in *APOE4* mice. For example, 17αE2 reduced body weight, plasma leptin, hepatic steatosis, and frailty index more strongly in *APOE4* than *APOE3* mice. Neural results are pending.

Conclusion: These data confirm and extend prior findings that *APOE4* is associated with senescent effects both peripherally and neurally, outcomes linked with AD risk. Importantly, 17αE2 significantly improved a range of measures. This study will establish proof-of-principle for 17αE2 as an AD therapeutic with efficacy predicted to be strongest in *APOE4* genotype. Given that the majority of AD cases in the U.S. are *APOE4* carriers, mitigating the effects of *APOE4* would have significant therapeutic potential.

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