PHARMACOLOGY

Exploring the *APOE*-specific effects of VEGF family expression and signaling in cognitive aging and Alzheimer's disease

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No current pharmacologic treatments stop the progression of Alzheimer's disease (AD), the most common major neurocognitive disorder. High levels of cerebrospinal fluid (CSF) vascular endothelial growth factor (VEGFA) are associated with less hippocampal atrophy and cognitive decline in AD biomarker-positive subjects, suggesting VEGFA is especially protective among those at highest risk for AD. *APOE*-ε4 carriers represent a highly susceptible population for AD and cognitive decline. Thus, we hypothesized that high VEGFA gene and protein expression, and potentially other members of the VEGF family associated with angiogenic signaling, would confer distinct protection among *APOE*-ε4 carriers. We evaluated interactions between cortical expression of *VEGF* genes and *APOE*-ε4 genotype to clarify which *VEGF* components modify the association between ε4 and cognitive decline. *NRP1* and *VEGFA* expression interacted with *APOE*-ε4 on cognitive performance, whereby higher expression was correlated with worse outcomes among ε4 carriers but better outcomes among ε4 non-carriers. These differential *NRP1* expression associations based on *APOE*-ε4 allele status were validated at the protein level. VEGF is involved in diverse signaling cascades, spanning angiogenesis, neurotrophic signaling, and microglial proliferation. To determine which biological pathway is driving the differential VEGF effects based on *APOE*-ε4 genotype, we performed isoform-specific and gene set enrichment analyses. Results indicated that *VEGF* isoforms that positively modulate

angiogenesis drive the interaction with *APOE*-ε4 on cognition and supported a role for angiogenesis in the differential VEGF associations in *APOE*-ε4 carriers and noncarriers. Additional gene set enrichment results using predicted gene expression suggested that an angiogenic contribution to cognition may reflect a repair process in response to disease. Blood brain barrier leaking is associated with the *APOE*-ε4 allele, perhaps placing young vessels formed during angiogenesis at risk for ischemia. Therapeutics aimed at increasing brain angiogenesis may only be beneficial among non-carriers of the ε4 allele. Future work will seek replication and test our hypothesis using *in vitro* models of the blood brain barrier to better understand how VEGF signaling may be modulated for the treatment of AD, with respect to *APOE*-ε4 genetic background.

Approved  Date 6/4/2020

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