Ethanol Induces Blood-Brain Barrier Dysfunction in a Familial Alzheimer's Human Stem Cell-Derived Model

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Background: Alcohol consumption has been directly linked to neurodegenerative diseases, including Alzheimer's disease (AD). Additionally, heavy consumption of alcohol has been shown to cause a faster cognitive decline in AD patients. A subset of studies demonstrated that alcohol can diminish BBB integrity and independently AD patients have suppressed barrier properties, but the direct effect of alcohol on barrier integrity in AD patients remains unclear. In this study, we utilize a human stem cell-derived AD BBB model with near *in vivo* properties to investigate the effects of alcohol on critical barrier properties.

Methods: Brain microvascular endothelial cells (BMECs) were derived from healthy (IMR90) and AD (*PSEN 1, PSEN 2*, and *APP*) human induced pluripotent stem cells (iPSCs). Healthy and AD cell lines were treated with physiologically relevant concentrations of alcohol (5, 25, and 50 mM). Following exposure, several critical barrier properties were monitored for up to 5 days post-exposure, including trans-endothelial electrical resistance (TEER), sodium fluorescein permeability, and tight junction localization.

Results: Moderate to severe alcohol exposure (25mM and 50mM) decreased barrier integrity in both healthy and AD-derived BMECs, as observed by an increase in sodium fluorescein permeability and a reduction in TEER. Furthermore, alcohol increased the number of discontinuous tight junctions directly contributing to the diminished barrier integrity. Interestingly, our preliminary results demonstrate that AD-derived BMECs are more susceptible to ethanol-induced barrier injury at lower concentrations of ethanol (5mM) compared to healthy-derived BMECs.

Conclusion and Potential Impact: Our results indicate that alcohol can diminish critical barrier properties in healthy-derived BMECs similarly to other non-human established BBB models. For the first time, we observed an increase sensitivity to alcohol-induced BBB dysfunction in a familial AD-derived BBB model. These data suggest that mild alcohol consumption could significantly alter the BBB and contribute to the development or exacerbation of AD-induced barrier dysfunction.