

Ethanol Induces Blood Brain Barrier Dysfunction in Healthy and Familial Alzheimer's Blood Brain Barrier Models

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Background/Objective:

The blood brain barrier (BBB) is a highly selective semipermeable membrane between the blood and brain. Active efflux transporters such as PGP, MRP-1, and BCRP and localized tight junction proteins ensure barrier integrity. Interestingly, both alcohol consumption and Alzheimer's disease (AD) suppress barrier functions independently. Furthermore, alcohol use can lead to or worsened neurodegenerative disorders, including AD. In this study, human stem-cell derived healthy and AD BBB models with near *in vivo* properties are used to investigate the effects of alcohol on critical BBB properties such as barrier tightness and efflux transporter activity.

Methods:

Induced pluripotent stem cells (iPSCs) from healthy (IMR90) and Familial Alzheimer's (APP, PSEN1, PSEN2) cell lines were differentiated into brain microvascular endothelial cells (BMECs). BMECs were treated with varying ethanol concentrations (5, 25, 50, and 100 mM) for one hour. Following ethanol treatment several barrier properties were assessed: trans-endothelial electrical resistance (TEER), sodium fluorescein permeability, tight junction localization, and efflux transporter activity.

Results:

Moderate to severe ethanol concentrations (25 mM and 50 mM) reduced TEER and delocalized tight junctions in healthy and AD-derived BMECs, indicating a disruption in barrier integrity. AD-derived BMEC cell lines also show an increased susceptibility to ethanol-induced barrier dysregulation at lower concentrations of ethanol (5 mM). Interestingly, our preliminary data shows that ethanol exposure seems to reduce BCRP efflux transporter activity in APP and PSEN1 AD cell lines.

Conclusion and Scientific Impact and Implications:

This study is novel in elucidating the enhanced disruption of BBB properties in familial AD-derived BMEC cell lines following ethanol exposure and provides insight into the potential harm of alcohol consumption in the development and/or exacerbation of BBB dysfunction in Alzheimer's disease. Further studies will also unveil the possibility of ethanol-induced reduction of BCRP efflux transporter activity in APP and PSEN1 AD.