The Effects of Multiple Exposure Ethanol on Barrier Tightness and Passive Permeability in a Human Stem Cell Derived Blood-Brain Barrier Model.

Ryan D. Stoffel[1], Kameron T. Bell[1], and Scott G. Canfield[1]

[1]Department of Anatomy, Cell Biology, and Physiology, Indiana University School of Medicine–Terre Haute

Background and Hypothesis:

Numerous animal studies have shown the negative aspects of ethanol at sustained concentrations as well as the intense depressive effects of multiple ethanol exposures on the central nervous system. Chronic ethanol use as a possible contributor to earlier onset neurocognitive decline has been indicated. A portion of these studies have implicated that ethanol exposure induces blood-brain barrier (BBB) impairment; however, these effects are not completely understood. In humans the BBB serves as a protective barrier that restricts the passage of nutrients, metabolites, and pathogens into the central nervous system from the blood and is essential in protecting the brain tissue from harmful substances. *We hypothesize that multiple doses of pathologically-relevant ethanol will cause decreased BBB tightness and increase passive permeability.*

Experimental Design:

In this study, we utilized brain microvascular endothelial cells (BMECs) derived from human induced pluripotent stem cells (iPSCs) to assess the effects ethanol has on barrier tightness and passive permeability through the BBB. BMECs were treated with multiple exposures of 50mM ethanol and transendothelial electrical resistance and sodium fluorescein permeabilities were measured. Trolox, a free radical scavenger, was used to identify if ethanol-induced barrier damage could be salvaged by reducing its oxidative impact.

Results:

Upon multiple exposure treatment with ethanol, iPSC-derived BMECs displayed diminished transendothelial electrical resistance and elevated sodium fluorescein permeability when compared to non-treated BMECs. Additionally, BMECs that were treated simultaneously with Trolox and ethanol had reduced barrier damage compared to ethanol treatment alone.

Conclusion and Potential Impact:

From these results, we conclude that multiple ethanol exposure-induced barrier damage in iPSC-derived BMECs, is in part due to elevated oxidative stress. Disruption of the BBB can potentiate a number of negative effects on the brain parenchyma and can lead to earlier onset neurocognitive decline. Alcohol’s impact on the BBB must be studied to ensure we limit these effects.