IS-026 Alterations in tight junction composition in brains of mice with fulminant hepatic failure

Department of Transplantation, Mayo Clinic College of Medicine, Jacksonville, USA¹, Department of Neuroscience, Mayo Clinic College of Medicine, Jacksonville, U.S.A.²

Shimojima Naoki¹, Justin H, Nguyen¹, Christopher B. Eckman²

Dysfunction of the blood-brain barrier (BBB) in fulminant hepatic failure (FHF) results in increased BBB permeability. Tight junction (TJ) is a cell-to-cell contact between endothelial cells in BBB. TJ regulates a permeability of small molecules and water. The role of TJ in FHF has not been explored. We hypothesized that alteration in TJ proteins results in altered BBB permeability in FHF. In this study, we examined the TJ composition in brain microvessels isolated from FHF mice. FHF was induced with azoxymethane in C57BL/6J mice. The animals were monitored through precoma and comatose stages of FHF. Control mice received saline alone. Brain microvessels were isolated using centrifugation and differential microfiltration. Liver injury was evaluated with serum ALT and histology of hepatocellular necrosis. BBB permeability was assessed with sodium fluorescein (NaF). TJ protein expression was determined using western blot. TJ protein cellular distribution was examined using immunofluorescent microscopy (IF). Cerebral NaF extravasation was significantly increased in comatose FHF mice, suggesting a marked increase in BBB permeability. Western blot analysis showed a significant decrease in expression of ZO-2, a cytosolic TJ protein, in precoma and comatose FHF animals. IF showed that the distribution of ZO-2 was markedly perturbed showing disrupted pattern in precoma and comatose FHF mice. We conclude that ZO-2 is significantly altered in cerebral microvessels of FHF animals. These results suggest that ZO-2 plays a critical role in the pathogenesis of brain edema in FHF.