# Role of TRPV6 in Mitigating Alcohol-Induced Disruption of Tight Junctions, Barrier Function, and Hepatic Injury

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**Background:** Persistent alcohol consumption is widely recognized as a precursor to alcoholic liver disease. However, the intriguing observation persists that only a minority, approximately 20%, of individuals with alcohol use disorder succumb to this liver ailment. The factors contributing to this variability remain elusive. Studies indicate that individuals with alcoholic liver disease exhibit endotoxemia, with endotoxins primarily originating from colonic microflora. Moreover, these patients manifest disruptions in epithelial tight junctions, leading to compromised barrier function in the gastrointestinal tract. In this context, the transient receptor vanilloid receptor 6 (TRPV6) emerges as a crucial regulator of calcium absorption and transport, particularly in epithelial cells within the gastrointestinal tract. Research strongly suggests that suppressing the TRPV6 channel in Caco-2 cells can alleviate alcohol-induced disruption of tight junctions and barrier function.

**Methods, Results, and Conclusions:** A scientific study subjected adult wild-type and Trpv6$^{-/-}$ mice to chronic alcohol feeding. Barrier function was assessed through *in vivo* measurement of inulin permeability, while tight junctions (TJ) and adherens junctions (AJ) integrity were evaluated using immunofluorescence microscopy. Systemic responses were analysed by assessing endotoxemia, systemic inflammation, and liver damage. Our findings highlight that alcohol induces the redistribution of tight junctions and adherens junctions, closely associated with the presence of TRPV6. Crucially, experiments with murine models reveal that the absence of TRPV6 mitigates alcohol-induced disruption of tight junctions, adherens junctions, gut barrier integrity, endotoxin absorption, and subsequent liver damage. Additionally, enteroids and colonoids generated from mice demonstrate that alcohol and its metabolite, acetaldehyde, increase the permeability of these organoids. Interestingly, organoids derived from TRPV6 knockout animals exhibit resistance to heightened permeability. Collectively, these findings suggest a pivotal role for the TRPV6 channel in mediating alcohol-induced damage to the gastrointestinal tract and liver. Our research provides valuable insights into potential mechanisms underlying alcohol-induced liver disease and emphasizes the significance of TRPV6 as a promising target for further exploration and potential therapeutic interventions.

**Keywords:** TRPV6