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MODULATORY ROLE OF APREMILAST ON BINGE-LIKE DRINKING AND BRAIN CYTOKINE LEVELS

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Abstract

Our understanding of the neuroimmune response to alcohol exposure and its role in the development and maintenance of Alcohol Use Disorder (AUD) has provided an avenue for discovering potential pharmacotherapies. We tested 28 compounds (many of which target inflammatory processes) for their ability to reduce drinking in High Drinking in the Dark mice (HDID), a unique genetic model of drinking to intoxication. Many (11 out of 14) compounds that reduced binge-like drinking in HDID mice had one thing in common; they increased anti-inflammatory signaling in the periphery. We found that apremilast, an FDA approved phosphodiesterase type 4 (PDE4) and tumor necrosis factor alpha (TNFa) inhibitor used for the treatment of psoriasis, significantly reduced binge-like drinking and blood alcohol levels in both HDID-1 and HDID-2 mice (0, 20, 40mg/kg; n=11-13/sex/line/dose; p's < 0.05 for all). Apremilast is our most promising translational compound for reducing harmful drinking. Although we have previously shown that intracranial administration of apremilast reduces binge-like drinking, and thus inhibition of PDE4 and TNFa in the brain, the role of peripheral administration of apremilast altering pro- or anti-inflammatory cytokine levels in the brain has yet to be determined. Therefore, we hypothesize that anti-inflammatory signaling could be a mechanism by which apremilast reduced excessive drinking. Ongoing studies are testing whether apremilast increases levels of anti-inflammatory cytokines in brain regions important for AUD in inbred HDID-1 female and male mice. To test this hypothesis, we carried out a 4-day ethanol drinking in the dark assay, where on the 4th day, mice received apremilast or vehicle (n=8-11/sex/treatment group), and then we collected brain tissue. We are currently carrying out assays to quantify cytokine levels using a BioPlex200 multiplex assay. Our findings show that apremilast robustly decreased binge-like drinking in both sexes of two genetically unique animal models for excessive drinking (HDID-1 and -2). Moving forward, our work seeks to better understand the role of brain anti-inflammatory signaling in regulation of binge-like alcohol drinking. Supported by grants from the OHSU, NIH (U01 AA013519, P60 AA010760), and Department of Veterans Affairs (IK2 BX004699).