

HUNTER L. ALIFF, Dept. of Chemistry, West Virginia State University, Institute, WV 25112, MATTHEW L. ECKARD, KRISTEN R. TREXLER, STEVEN G. KINSEY, Dept. of Psychology, West Virginia University, Morgantown, WV 26506, and EMILY SILVESTRI, Dept. of Biological Sciences, University of New Hampshire, Durham, NH 03824. Differential effects of endocannabinoid modulation of gastric inflammation following exposure to ethanol or nonsteroidal anti-inflammatory drugs.

The endogenous cannabinoid system possesses several potential targets to reduce gastric inflammatory states, including gastric hemorrhages (i.e., gastric ulcers), which can pose serious health risks in certain populations (e.g., elderly or chronically ill). Of particular interest is the endocannabinoid ligand, 2-arachidonoylglycerol (2-AG) arachidonoylglycerol, which has shown some promise as a potential therapeutic target in reducing gastric hemorrhages through cannabinoid receptor 1 (CB₁) activation. While effective, increases in endogenous 2-AG are only possible through the use of monoacylglycerol lipase (MAGL) inhibitors, which carry a host of side effects that have hindered their use in human populations. Positive allosteric modulators (PAMs) offer an alternative approach to enhance CB₁ receptor function for therapeutic gain. In the present study, both a MAGL inhibitors, JZL184, and a PAM, ZCZ011, were used to attempt to attenuate gastric hemorrhage formation in two models of hemorrhage induction. On the morning of the assay, mice were administered either Vehicle (1:1:18; ethanol:Cremophor:saline), JZL184 (40 mg/kg), or ZCZ (10, 20 or 40 mg/kg) followed two hours later by hemorrhage induction using ethanol or Diclofenac. Either 1 h (ethanol) or 6 h (Diclofenac) later, stomachs were harvested and hemorrhage size was quantified. Finally, stomachs were evaluated for myeloperoxidase (MPO), a byproduct of neutrophils used as a proxy measure of inflammation, via ELISA. These data suggest that ethanol or diclofenac can induce gastric hemorrhage, in accordance with previous literature, and that CB₁ activation may alter hemorrhage induction. (Supported by NIH Grant P20GM103434 to the West Virginia IDeA Network for Biomedical Research Excellence)