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CONTRIBUTION OF ENDOCANNABINOIDS TO ALCOHOL CONSUMPTION AND ANXIETY-LIKE BEHAVIOR FOLLOWING TRAUMATIC BRAIN INJURY

BACKGROUND: In the USA, approximately 1.7 million people suffer from traumatic brain injury (TBI) annually, and 80-90% of these injuries are classified as mild. TBI can lead to psychiatric disorders such as depression, anxiety, and substance use disorder (SUD). Comorbid SUD may affect recovery and rehabilitation and increases the risk for subsequent TBI. Endocannabinoids (EC) are released in response to injury and may have a protective role following TBI. ECs are rapidly degraded by monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH) soon after their release. Our previous studies show that inhibition of MAGL following TBI reduced motivation for alcohol consumption, decreased anxiety-like behavior, reduced neuroinflammation, and decreased glutamate toxicity. The purpose of this study was to test the prediction that JZL195 (a dual MAGL and FAAH inhibitor) reduces post-TBI alcohol consumption and anxiety-like behavior.

METHODS: Male Wistar (n=60) rats were trained to consume alcohol using operant self-administration 3 weeks before TBI. Rats underwent no surgery (naïve), a sham procedure, or TBI and were randomized to receive a single dose of JZL195 (16mg/kg, i.p.) or vehicle 30 minutes post-TBI. Apnea, righting reflex, and respiratory rate were measured immediately after TBI to evaluate injury severity. Animals resumed alcohol consumption two days after injury. Anxiety-like behavior was determined by open field test and elevated plus maze at 7 and 9 days post-TBI.

RESULTS: Neither escalation of alcohol consumption nor increased anxiety-like behavior was observed post-TBI. JZL195 administration did not alter post-TBI alcohol consumption. Regardless of the condition (naïve, sham or TBI), animals treated with JZL195 spent significantly more time exploring the center of the open field compared to animals in the vehicle group. No significant differences were observed for the elevated plus maze across experimental groups.

CONCLUSION: These results suggest a role for ECs in modulating anxiety-like behavior in conditions considered mildly aversive such as the open field test but not in more anxiogenic conditions such as the elevated plus maze. Ongoing studies will examine whether increased neuronal excitability is an underlying mechanism of post-TBI anxiety-like behavior and if this is attenuated by increasing EC tone.