

Alcohol exposure modulates endocannabinoid signaling and impairs fear extinction

Muhammad Farooq, PhD and S. June Liu, PhD

PTSD is a debilitating psychiatric disorder, and one underlying mechanism is enhanced consolidation and impaired extinction of fear memories. Epidemiological studies have revealed that more than 40% of PTSD patients meet criteria for alcohol use disorder (AUD).

Endocannabinoid signaling is important for emotional memory, and it is altered in PTSD and AUD. Clinical studies have shown that patients with PTSD exhibit reduction in circulating endocannabinoids and upregulation of central CB1 receptors (CB1R) and that cannabis and CB1R agonists alleviate symptoms of PTSD. Because the activity of monoacylglycerol lipase (MAGL), an enzyme degrading major endocannabinoid in brain, is also reduced in chronic alcoholics in a postmortem study, we propose that increased endocannabinoid signaling following chronic alcohol exposure would compensate for the decrease in endocannabinoid signaling as a mechanism for this comorbidity.

The cerebellum is involved in emotional and cognitive processes, as it is required for the formation of associative fear memories, involved in reward, drug addiction, and alcohol drinking behavior. Previous studies in our lab have shown that fear conditioning, which is an animal model to understand pneumatic aspects of PTSD, increases endocannabinoid degradation. Studies have also shown that alcohol exposure increases endocannabinoids in several brain regions. In this study, we determined the effect of acute and chronic alcohol exposure on fear conditioning and extinction and endocannabinoid signaling. Mice were either given two alcohol injections (2.5g/kg, i.p.) two hours apart or alcohol vapor for 16 hours immediately after fear conditioning. The animals were subjected to memory retention and extinction protocols the next day. Interestingly, alcohol exposure did not affect cued fear memory consolidation or extinction processes but did impair cued extinction memory retention tested on a later day. Alcohol exposure did not affect contextual memory. As fear conditioning increases endocannabinoid degradation, we next determined the effect alcohol exposure on MAGL activity. Chronic, but not acute alcohol exposure decreased MAGL activity in lobules 5/6 of cerebellum, a brain region involved in fear memory consolidation and alcohol drinking behavior. These data suggest that prolonged alcohol exposure mediated reduction in MAGL activity might be the underlying mechanism promoting development of alcohol use disorder.