Endocannabinoid (eCB) Regulation of Escalated Alcohol Drinking after Stress & Withdrawal

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Humans with post-traumatic stress disorder (PTSD) are more likely to develop alcohol use disorder (AUD) than the general population, and AUD is the most commonly co-occurring mental health disorder in humans living with PTSD. PTSD and AUD diagnoses are each associated with escalated alcohol drinking. Pre-clinical models suggest that traumatic stress and alcohol dependence each produce alterations in brain endocannabinoid (eCB) signalling, and that administration of drugs that modulate eCB signalling alters normal and escalated alcohol drinking in rodents. Here, we will present data from two research groups (Gilpin and Parsons labs) that support the idea that escalated alcohol drinking produced by traumatic stress and alcohol dependence are attributable to changes in brain eCB signaling.

Methods: The first part of this talk will describe data collected using a predator odor model in which rats are tested for persistent avoidance of a predator odor-paired chamber, divided into Avoider and Non-Avoider groups, then tested for differences in post-stress neural and behavioral outcomes relative to each other and unstressed controls. The second part of this talk will describe data collected using two rat models of alcohol dependence: these include the alcohol vapor inhalation model in which rats are exposed to alcohol vapor for 14 hrs per day, and the alcohol-liquid diet procedure in which rats are exposed to alcohol in their sole source of nutrition. In both of these procedures, rats are tested for behavioral and neurochemical outcomes during alcohol withdrawal relative to their own baseline and also relative to non-dependent controls.

Results: Using the predator odor stress model described above, data from the Gilpin & Tasker labs show that avoidance is persistent in individual animals, resistant to extinction, and produces lasting and compulsive-like increases in operant alcohol self-administration in Avoider rats, relative to Non-Avoiders and unstressed Controls and their own baseline. Re-exposure to predator odor context elicits phosphorylation of extracellular signal-regulated kinase (pERK) in basolateral amygdala (BLA) that is negatively correlated with post-stress escalation of alcohol drinking in Avoiders but not Non-Avoiders. We will present data describing post-stress alterations in BLA levels of cannabinoid type-1 receptors (CB1R) as well as eCB synthetic and clearance enzymes. Finally, we report that systemic injection of a CB1R antagonist blocks post-stress escalation of operant alcohol responding. Ongoing work seeks to test the hypothesis that traumatic stress promotes escalation of alcohol drinking via BLA disinhibition that is mediated by persistent alterations in eCB signaling.

Using rodent models of alcohol dependence, work from the Parsons group shows that alcohol self-administration acutely mobilizes release of 2-arachidonoylglycerol (2-AG), but not n-arachidonoylethanolamine (AEA), in the central amygdala (CeA) of non-dependent rats, but not alcohol-dependent rats. Alcohol-dependent rats exhibit persistent 2-AG, but not AEA, deficits during withdrawal, and alcohol self-administration normalizes 2-AG levels in CeA only in scenarios where alcohol-withdrawn rats are allowed to consume high quantities of alcohol. Finally, systemic inhibition of the major 2-AG clearance enzyme monoacylglycerol lipase (MAGL), but not the AEA clearance enzyme fatty acid amide hydrolase (FAAH), reduces alcohol drinking in alcohol-dependent rats and mice, and this effect is mimicked by intra-CeA infusion of a CB1R agonist. These results suggest that alcohol withdrawal is associated with deficient 2-AG/CB1R signaling in the CeA that may underlie excessive alcohol drinking in alcohol-dependent individuals.

Discussion: Collectively, these data make the case that stress associated with trauma and alcohol withdrawal alters eCB signalling in the amygdala, and suggest that escalated alcohol drinking after traumatic stress and alcohol dependence may be mediated by brain eCB signalling. Interestingly, amygdala eCB signaling may be affected differently by predator odor stress and alcohol withdrawal, suggesting that effective eCB-based treatment strategies may differ for reducing escalated alcohol drinking in these two groups.

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