

Neurosciences

Role of Cingulate Cortex Glucocorticoid Signaling in Alcohol Dependence

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Introduction: Alcohol Use Disorder (AUD) is a chronic, relapsing disorder characterized by the development of negative motivational symptoms and emotional states, including escalation of alcohol intake, dysphoria, anxiety, and pain. We propose that the progression from recreational, limited alcohol consumption to uncontrolled, escalated intake involves a transition from positive to negative reinforcement mechanisms that drive excessive alcohol use and maintain AUD. Our lab models AUD in rats by utilizing a chronic intermittent ethanol vapor exposure (CIEV) procedure that produces both somatic and motivational symptoms of alcohol dependence.

Objective: To look for the role of cingulate cortex glucocorticoid signaling in alcohol dependence.

Material and Methods/Results: Using this model, we and others have shown that alcohol dependence is associated with dysregulated glucocorticoid signaling in brain regions that mediate stress and nociception, e.g., the central amygdala and anterior cingulate cortex (ACC). Specifically, we identified an increase in glucocorticoid receptor (GR) activation in the ACC of alcohol-dependent male rats. We tested the functional significance of this neuroadaptation on alcohol drinking. Alcohol-dependent and non-dependent male rats were trained to self-administer 10% alcohol and H₂O in 30 minute operant sessions. Rats were then surgically implanted with guide cannulas aimed at the ACC. The GR antagonist mifepristone (MIF) was microinjected into the ACC 90 minutes prior to the drinking sessions. MIF decreased levels of alcohol-dependent drinking to that of the non-dependent rats. Given that GR is a transcription factor, we then sought to determine how potentiated GR activity in the ACC of alcohol-dependent animals alters gene expression, and if MIF prevents these changes. Male rats received a subcutaneous implant of either chronic release MIF or placebo pellet and half of each group underwent

the CIEV alcohol dependence induction procedure. We then utilized a fluorescent bead-based multiplex assay to determine changes in mRNA levels of GR-regulated genes in the ACC.

Conclusions: Alcohol dependence increased mRNA of circadian regulatory genes *Per1* and *Per2*, while MIF treatment attenuated this elevation. Circadian and glucocorticoid signaling directly regulate one another and both systems are known to be dysregulated in humans with AUD. The efficacy of MIF for the treatment of AUD may therefore involve a normalization of the ACC circadian rhythm.

Keywords: alcohol dependence, mRNA, circadian regulatory genes, animal models