ACTIVATION OF $GABA_A$ RECEPTORS AND INHIBITION OF NEUROSTEROID SYNTHESIS HAVE SEPARABLE ESTROUS-DEPENDENT EFFECTS ON BINGE DRINKING IN FEMALE MICE

Laverne C Melón and Zachary T Nolan (Stephen L. Boehm, II), Department of Psychology, Program in Psychobiology of Addictions, Purdue School of Science, Indiana University–Purdue University Indianapolis, Indianapolis, Indiana 46202

Alcohol concentrations relevant to the beginning stages of binge intoxication may selectively activate $GABA_A$ receptor subtypes expressing δ-subunit proteins (δ-$GABA_A$R). Indeed, administration of agonists that interact with these δ-$GABA_A$R prior to alcohol access, can abolish binge drinking behavior (Melon and Boehm, 2011). Unfortunately, our ability to manipulate binge drinking in females is dependent upon estrous phase. The present experiments were designed to clarify the estrous-dependent effects of activation of δ-$GABA_A$R on binge drinking. Specifically, we were interested in demonstrating whether females display more persistent binge drinking as a function of cycle-dependent changes in the synthesis of endogenous neurosteroids that modulate δ-$GABA_A$R. Using the Drinking-in-the-Dark binge-drinking model, regularly cycling female mice were given 2 hours of daily access to alcohol (20%v/v). Vaginal cytology was assessed after each drinking session to track estrous status. In experiment 1, animals were administered gaboxadol (an agonist with high affinity for δ-$GABA_A$R) prior to their 8^{th} day of access. In experiment 2, these methods were repeated, but mice received vehicle or finasteride (a neurosteroid synthesis inhibitor) 22hr prior to their 8^{th} day of access. Results from experiment 1 demonstrated that diestrus females were insensitive to the significant gaboxadol-induced decrease in binge drinking observed for proestrus, estrus and metestrus females. In experiment 2, vehicle and finasteride treated diestrus females exhibited gaboxadol-induced reduction of their binge drinking. Surprisingly, finasteride pretreatment significantly reduced binge drinking for estrus females. These studies suggest that ovarian-linked changes to extrasynaptic $GABA_A$ R and to neurosteroid activity may be important factors in the binge consumption of alcohol for females. Future studies will further explore the role that acute stress during diestrus may play in inhibiting the effects of δ-$GABA_A$ R activation on binge drinking.

This work was supported by NIH grants AA016789 (SLB), AA07462 (LCM), an IUPUI UROP grant (ZTN) and the Indiana Alcohol Research Center.