In Vivo Imaging of Brain Cortisol Regulation in Alcohol Use Disorder

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Stress dysregulation is associated with risky drinking (Koob, 2009). Stress is also a potent activator of the hypothalamic-pituitary-adrenal (HPA) axis, initiating the release of glucocorticoid hormones. Levels of glucocorticoids (e.g., cortisol, cortisone) present in the brain are dependent on the enzyme 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1), which catalyzes the conversion of cortisone to cortisol (Chapman et al., 2013). 11β-HSD1 is in brain regions critical to alcohol addiction, including the prefrontal-limbic circuit. Thus, high brain glucocorticoid levels, driven by 11β-HSD1 and induced by stress, may contribute to risky drinking. We used positron emission tomography (PET) imaging with the novel 11β-HSD1 specific radioligand [^{18}F]AS2471907 to assess 11β-HSD1 levels in individuals alcohol use disorder (AUD) vs. healthy controls. We also examined relationships between 11β-HSD1 levels and drinking behavior in a novel human laboratory alcohol self-administration model in AUD.

Methods: We imaged 10 individuals with AUD (n=6 men, n=4 women; mean age=38 years) and 12 healthy controls (n=8 men, n=4 women; mean age=29 years). Participants received 93.5±15.6 MBq [^{18}F]AS2471907 as a bolus injection at high specific activity and were imaged for 150-180 minutes on the High-Resolution Research Tomograph (HRRT; 2-3 mm resolution). 11β-HSD1 availability was quantified by [^{18}F]AS2471907 volume of distribution (V_T; mL/cm^3), the ratio at equilibrium of [^{18}F]AS2471907 in tissue to un-metabolized [^{18}F]AS2471907 in arterial plasma. *A priori* regions of interest included amygdala, anterior cingulate cortex (ACC), hippocampus, ventromedial PFC (vmPFC) and caudate. Individuals were required to be overnight abstinent from drinking. Levels of 11β-HSD1 were correlated with alcohol self-administration following stress (vs. neutral) imagery. Potential mechanisms underlying associations between 11β-HSD1 levels and drinking were examined (e.g., mood, anxiety, early life stress) in those with AUD.

Results: Individuals with AUD consumed 50.9 drinks/week and had 5.7 drinking days/week. Healthy controls consumed 2.8 drinks/week and had 1.30 drinking days/week. Pilot data suggest that 11β-HSD1 levels was higher in amygdala, ACC, hippocampus, vmPFC, and caudate in those with AUD compared to healthy controls (ps<0.03). Our human laboratory model was sensitive to the effects of stress on drinking (ps=0.01-0.05). Greater % alcohol consumed following stress was positively related to 11β-HSD1 levels (r=0.69) and with more severe childhood trauma (r=0.50).

Discussion: This is the first in vivo examination of 11β-HSD1 levels in individuals with AUD. Pilot data suggest higher brain cortisol-producing 11β-HSD1 in AUD compared to healthy individuals, and a possible relationship between [^{18}F]AS2471907 V_T and drinking behavior. Early life stress may also moderate stress-related alcohol use. Future studies will further investigate [^{18}F]AS2471907 as a marker of brain cortisol regulation.

References: Koob G. *Brain Res* 1293:61-75 (2009); Chapman K., Holmes M., and Seckl J. *Physiol Rev* 93(3):1139-206 (2013).

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