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“5-HT2C receptor antagonism effects on stress-induced activation of specific central amygdala neuronal populations”

BACKGROUND: Post-traumatic stress disorder (PTSD) encompasses a range of symptoms that stem from a traumatic experience, including avoidance of reminders of the traumatic event and chronic physiological arousal. PTSD is highly comorbid with alcohol use disorder (AUD), the impaired ability to control alcohol use despite adverse consequences. The link between stress and alcohol use has previously been studied in rats using a predator odor exposure model. These studies reported that predator odor (i.e., bobcat urine) exposure increases in c-Fos (an immediate early gene often used as a proxy for neuronal activation) and corticotropin releasing factor (CRF) expression in the central nucleus of the amygdala (CeA) and leads to avoidance of a stress-paired context and increases alcohol self-administration. Given this connection, CRF type 1 receptor (CRF1) antagonists have been extensively tested in animal models, and these agents robustly reduce alcohol self-administration and consumption in rodents, but this drug class has not translated to the clinic. The Gilpin lab has recently identified an upregulation of the *5-hydroxytryptamine receptor 2C (Htr2c)* gene in CRF1 cells in the CeA of stressed rats. These findings suggest that 5-HT2C receptors may represent an alternative target for modulating stress-induced neural activity in CRF1 cells of the CeA. We hypothesize that the administration of a selective 5-HT2C receptor antagonist, SB 242084, will reduce *Fos* expression in CRF1 cells.

METHODS: Adult (≥ 8 weeks of age) male (N=7) and female (N=7) Wistar rats were given an intraperitoneal (i.p.) injection of either SB 242084 (1.0 mg/kg) or vehicle (DMSO + hydroxypropyl- β -cyclodextrin (HBC)) prior to either bobcat urine odor exposure (Stress group) or normal room air (Unstressed group). The rats were sacrificed 45 minutes after odor exposure, and brains were collected, fresh frozen, then sectioned at 10 μ M for *in situ* hybridization with *Crhr1* and *Fos* probes using RNAscope. Brain sections were imaged using a Zeiss Axioscan and quantified using QuPath.

RESULTS: Analysis of the RNAscope showed a significant increase ($p = 0.0321$) in the percentage of *Crhr1/Fos*⁺ cells in the medial CeA in rats that were treated with SB 242084, in both the stressed and unstressed groups. Additionally, there was an increase ($p = 0.0266$) in the number of *Crhr1/Fos*⁺ cells in the medial CeA. The percentage of *Crhr1*⁺ cells in the medial CeA was not affected by SB 242084 or stress. Similarly, the percentage of *Fos*⁺ cells in the medial CeA was not affected by SB 242084 or stress.

CONCLUSION: SB 242084 increases *Fos* expression in CRF1 cells in the medial CeA under both stressful and neutral conditions. This suggests that antagonism of the 5-HT2C receptor increases neuronal activation of the medial CeA CRF1 cells.