Lateral Habenula neurons expressing the serotonin receptor 5HT2c drive sex-specific social and arousal disturbances induced by binge alcohol consumption

Meghan Flanigan, Olivia Hon, Kristen Boyt, and Thomas Kash

University of North Carolina School of Medicine, Bowles Center for Alcohol Studies

Binge alcohol drinking is a serious public health issue that is associated with increased risk of developing alcohol use disorder (AUD) and is on the rise following the COVID-19 pandemic. Recent research suggests that chronic binge alcohol consumption leads to AUD, at least in part, by inducing negative social and emotional symptoms that promote escalated alcohol use in attempts to seek relief. The lateral habenula has recently emerged as a potential driver of negative social and emotional states following chronic alcohol consumption, but remains highly understudied, especially in female subjects. Here, we first identified sex-specific social and arousal disturbances induced by chronic binge alcohol consumption in mice. While Drinking in the Dark (DiD) induced deficits in social recognition in females during abstinence, it potentiated acoustic startle behavior in males. These sex-specific behavioral changes were associated with distinct adaptations in physiology and gene expression in LHb neurons expressing the serotonin receptor 5HT2c (LHb5HT2c). Following DiD, males displayed increased in-vivo LHb5HT2c activation in response to acoustic startle stimuli, increased excitability of LHb5HT2c, increased spontaneous activity of LHb5HT2c, and increased expression of 5HT2c in the LHb. While females also displayed increased spontaneous activity of LHb5HT2c following DiD, their DiD-induced changes in gene expression and in-vivo patterns of neuronal activation differed from males significantly. Specifically, DiD induced a trend for increased activation of and serotonin release onto LHb5HT2c in females upon interaction with a novel social target. Changes in excitability in females following DiD were also modest and highly specific to the LHb5HT2c cells located in the medial aspect of the LHb. In addition, while 5HT2c expression was not altered by DiD in females, 5HT1a and 5HT1b expression in LHb neurons (which are co-expressed on LHb5HT2c) was markedly decreased. This suggests that DiD influences the physiological effects of serotonin on LHb neurons in males and females via different underlying molecular mechanisms, both of which would shift the effects of serotonin on LHb neurons to greater excitation. Chemogenetic inhibition of LHb5HT2c following DiD normalized social recognition behavior in females and acoustic startle behavior in males, indicating that enhanced activity of these neurons is critical for the expression of social and arousal disturbances following chronic binge alcohol consumption. This work may have important implications for the development of sex-specific treatments for AUD.