SENSITIVITY TO NICOTINE + ALCOHOL COMPOUND INTEROCEPTIVE CUES: MECHANISM AND BRAIN REGIONAL INVOLVEMENT

J. Besheer
Bowles Center for Alcohol Studies, Department of Psychiatry, University of North Carolina-Chapel Hill, United States

Smoking and drinking behaviors commonly co-occur and consequently individuals experience the interoceptive effects of both together. Further, such interoceptive cues can play a fundamental role in incentive motivational processing, as a consequence of being associated with other reinforcing events. To this end, we sought to establish nicotine + alcohol (N + A) interoceptive conditioning and to begin to characterize brain regional involvement. Long Evans rats were trained to discriminate a nicotine (0.4 mg/kg) + alcohol (1 g/kg) drug state vs. vehicle. On N + A sessions, light presentations were followed by sucrose reward and goal-tracking behavior (head entries into sucrose receptacle) during light presentations was measured. Therefore, with training, goal-tracking comes under the control of the interoceptive effects of N + A. Rats acquired the N + A discrimination as confirmed by dose-dependent substitution of the N + A stimulus, and when tested on each component separately, nicotine was found to drive the goal-tracking behavior to a greater degree than the alcohol component. Interestingly, we found increased neuronal response (c-Fos immunoreactivity) in the medial prefrontal cortex (mPFC) following N + A. Next, we utilized a chemogenetic approach in which hM4D(Gi) designer receptors exclusively activated by designer drugs (DREADDs) were activated to silence the mPFC. Blunted sensitivity to the N + A drug state was evident following DREADD activation by clozapine-N-oxide, demonstrating functional involvement of the mPFC in modulating the N + A drug state. Together these data suggest that the N + A stimulus is distinct from each component alone, and that the mPFC is important for the expression of sensitivity to the interoceptive effects of this compound drug state.