Ventral Pallidal Signaling During Alcohol Seeking Elicited by Pavlovian Cues

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A critical area of inquiry in the neurobiology of addiction is the neural mechanisms by which drug and alcohol-predictive cues gain the ability to elicit craving and relapse. The ventral pallidum (VP) has been suggested to act as part of a common pathway for relapse to drug and alcohol seeking. Recently we have shown that activity of VP neurons in response to a cue predicting reward availability encodes both the likelihood and latency of subsequent instrumental reward-seeking actions (Richard et al., 2016). Here, we assess VP encoding of Pavlovian cues predicting sucrose or alcohol, and test the functional contribution of VP activity to cue-elicited reward seeking.

Methods: Male and female Long Evans rats were trained to associate one auditory cue (CS+) with delivery of 20% alcohol or 10% liquid sucrose reward and an alternative auditory cue (CS-) with no delivery of reward. Rats were trained until they enter the reward port on >70% of CS+ trials and <30% of CS- trials, and then were implanted with drivable electrode arrays aimed at the VP. We then recorded single unit activity in VP during performance of Pavlovian-conditioned alcohol or sucrose seeking. We next probed the functional contribution of VP activity to Pavlovian responses to alcohol cues using optogenetics. Rats received infusions of virus for the expression of the inhibitory opsin, ArchT, and optical fiber implants aimed at the VP. Following Pavlovian training with alcohol, we photoinhibited VP with green light (532 nm) during 50% of cue presentations to assess the impact on cue-elicited behavior.

Results: We find that ~25% of VP neurons are excited by presentations of the CS+ for sucrose, and that in the majority of neurons these excitations are greater to the CS+ than the CS-, and greater on trials when the rats make a port entry during the cue presentation. An additional ~30% of neurons are inhibited by the CS+, but many of these neurons are also inhibited by the CS-. We observed similar patterns of responding to cues predicting alcohol, except that neurons excited by the CS+ made up a larger proportion of the population (~40%). We found that inhibition of VP during cue presentations reduces the number of port entries and time spent in the port during the cue period, and increases the latency to enter the port during the cue.

Discussion: Our results indicate that cue-related neural activity in VP encodes the likelihood of Pavlovian-conditioned reward seeking behaviors. Additionally, normal VP activity during the cue is critical for conditioned alcohol seeking, making this region a promising candidate for interactions between alcohol cues and other factors that enhance craving and relapse. Ongoing works is aimed at identifying the inputs to VP that drive cue-elicited activity, and whether the dominant inputs vary during reinforced alcohol seeking and models of relapse.

References: Richard J.M., Ambroggi F., Janak P.H. & Fields H.L. *Neuron, 90*(6): 1165-1173 (2016).

Funding was provided by NIH grants AA022290, AA014925 and a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation.