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RESEARCH HIGHLIGHT

The BNST balances alcohol's aversive and rewarding properties

Tiffany A. Wills[1]

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Alcohol is a complex substance that has both rewarding and aversive properties. The pleasurable or rewarding properties of alcohol (e.g. reduced anxiety, social facilitation) can facilitate initiation and maintenance of alcohol drinking, while the aversive properties of alcohol (e.g. sedation, motor incoordination, and nausea) can limit its use. These rewarding and aversive properties of alcohol not only regulate alcohol drinking, but also the propensity to abuse alcohol and therefore the likelihood of developing an alcohol use disorder (AUD). Furthermore, the rewarding and aversive properties of alcohol can support learned associations between external cues and drug properties. These cues can become powerful triggers for relapse to alcohol drinking. One animal model that is widely used to study the learned associations between internal drug effects and external cues is called place conditioning, a test based on the classical form of Pavlovian learning.

The place conditioning test is divided into three stages: pre-test, training, and post-test. It allows for the examination of neurobiological processes that support the acquisition and expression of a conditioned place preference (CPP) or conditioned place aversion (CPA). During the pre-test, the animal is able to freely explore an apparatus with multiple chambers that differ on specific visual and/or tactile stimuli, and time spent on each side is measured. In the training phase, the animal is given a drug that is paired with a specific side of the apparatus with discrete environmental cues (context, CS+) one or more times, depending on the drug. During the post-test, the animal is once again allowed to freely explore all chambers of the apparatus and time spent on each side is measured, allowing for calculation of preference or aversion for the drug-paired side. If an animal spends more time in the drug-paired side, this is interpreted as CPP (i.e., reward). Conversely, if an animal spends less time in the drug-paired side, this is interpreted as CPA (i.e., aversion). These tests allow insight into whether an animal interprets a drug to be rewarding or aversive. Place conditioning training allows animals to associate drug effects with discrete environmental cues and thereby provides a valuable model for understanding the neuroadaptations and circuitry contributing to drug-cue associations, which promote drug seeking and relapse.

In their recent manuscript in *Neuropsychopharmacology*, Pati et al. used a unique strategy to investigate the neuroadaptations that underlie alcohol CPP and CPA [1]. The authors utilized a conditioning paradigm originally described in Cunningham et al. [2], whereby the same dose of alcohol (2 g/kg) can produce either CPP or CPA depending on the timing of the injection [2]. If the alcohol injection is given immediately before being placed in the apparatus, then it produces CPP, but if the injection is given after removal from the chamber, then it produces CPA. The advantage of this paradigm is that it utilizes an equivalent alcohol dose and similar exposure to the conditioning apparatus. Differences in CPP & CPA neuroadaptations are therefore not attributable to alcohol dose, but to the learned associations between external cues and the rewarding and aversive properties of alcohol. The authors then evaluated the effects of CPP and CPA on physiology in the ventral bed nucleus of the stria terminalis (vBNST).

The BNST is a component of the extended amygdala that serves as a point of convergence for inputs throughout the brain (e.g. prefrontal cortex, amygdala, and ventral tegmental area [VTA]) and targets hypothalamic and limbic targets (e.g. amygdala, paraventricular nucleus of the hypothalamus, and VTA) [reviewed in refs. [3, 4]]. Behaviorally, the BNST is critical for modulating anxiety, fear, and social behavior, but the valence of these behaviors can be bidirectional depending on the BNST subnuclei involved or cell type. Lebow and Chen [3] used the term "valence surveillance" to describe these diverse roles of the BNST, citing that the BNST integrates sensory information with homeostatic, emotional, and motivational information to coordinate an appropriate action (with either a positive or negative valence) [4]. In addition to these behaviors, the BNST also plays a role in addiction. Alcohol impacts BNST physiology by altering inhibitory and excitatory neurotransmission, as well as the modulation of this transmission by various neuropeptides. After chronic alcohol use, the BNST contributes to negative affect (anxiety/depression) in the absence of the drug (i.e., withdrawal and abstinence), and also relapse to drug-seeking and -taking produced by stress. The BNST is also involved in place conditioning and has specifically been implicated in alcohol CPP, making it an intriguing candidate brain region for mediating alcohol reward and aversion.

In the current work by Pati et al., ex vivo slice electrophysiology was performed to assess neuroadaptations in inhibitory and excitatory transmission in the vBNST of animals that displayed CPP or CPA in vivo [1]. These findings show that CPP increases intrinsic excitability of vBNST neurons; while no change was seen following CPA or when comparable alcohol was given in the home cage. The CPP enhancement of intrinsic excitability was mimiced by blocking inward-rectifying potassium channels in saline treated mice and had no effect in alcohol-injected mice. This finding was interpreted to reflect CPP-induced increases in intrinsic excitability

[1]Department of Cell Biology and Anatomy, LSU Health Sciences Center New Orleans, 1901 Perdido Street, New Orleans, LA 70112, USA
Correspondence: Tiffany A. Wills (twills@lsuhsc.edu)

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through downregulation of inward-rectifying potassium channels. On the other hand, CPA led to a reduction in glutamate release (decrease sEPSC frequency and increased PPR), no change in GABAergic transmission, and a net result of reduced excitatory/inhibitory balance. This study did not investigate the specific source of this reduced glutamatergic tone or the mechanism for this change, but the authors suggest endocannabinoid signaling as one potential mechanism for reduced glutamate release in the vBNST of animals exhibiting a CPA. Because it is highly interconnected with numerous brain regions, these changes in BNST physiology could have wide ranging effects. One BNST output region highlighted by the authors is the VTA, another brain region that modulates both aversive and rewarding drug effects. In previous work by Pina and Cunningham [5], inactivation of BNST-VTA neurons using DREADDs reduced the expression of alcohol CPP, but the role of this projection in alcohol CPA has not been explored [5].

These results identify distinct BNST neuroadaptations linked with conditioned alcohol reward and aversion using the same behavioral paradigm and alcohol dose; thereby highlighting the complexity of learned alcohol-cue associations. Future studies that interrogate the circuitry and mechanisms behind these neuroadaptations in the BNST could provide critical evidence for how to switch the valence of alcohol in the addicted brain.

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ADDITIONAL INFORMATION

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