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Cocaine-Paired Cues Activate Aversive Representations in Accumbens Neurons

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Abstract

Aversive states are proposed to drive addiction. Here, Wheeler and colleagues show that drug-associated cues come to activate neural representations of aversive information in nucleus accumbens and that this activation predicts subsequent drug use. These remarkable data identify a potential neural substrate through which aversive affective representations may motivate drug use.

An important challenge faced by addiction researchers today is to create animal models that more closely approximate the human condition of addiction. Many currently popular models do not represent very well the role played by aversive affective states, which may come to be triggered by drug-associated cues. Such aversive states are proposed to incline the addict toward further drug use (Koob and Le Moal, 2001; Solomon and Corbit, 1974).

In this issue of *Neuron*, Wheeler and colleagues (Wheeler et al., 2008) identify a potential neural substrate for this effect. The authors took advantage of the observation that animals learn to avoid taste cues that are predictive of addictive drugs (Grigson and Twining, 2002; Wise et al., 1976). The authors measured the development of the conditioned taste aversion for a drug-paired taste by tracking the stereotyped orofacial movements that are known to reflect the hedonic valence of taste stimuli (Grill and Norgren, 1978). Two differently flavored saccharine solutions were infused intraorally during a 30 min period. The rats were then allowed to self-administer either saline or cocaine. On initial exposure, the rats responded to both solutions with stereotypical appetitive orofacial movements, and these movements were correlated with suppression of neural spiking activity in accumbens. After development of stable cocaine self-administration, the solution paired with saline continued to evoke appetitive responses and suppress activity in nucleus accumbens neurons. By contrast, the solution paired with cocaine had become aversive, evoking orofacial movements, termed gapes, which are associated with rejection and causing a phasic *increase* in neural activity in the accumbens. These behavioral and neural features are *identical* to those previously reported by the same authors after infusion of quinine, an innately aversive taste (Roitman et al., 2005).

Two points here are particularly noteworthy. First, the similarity between the orofacial movements and neural responses to the drug cue and to tastes hardwired to be aversive, such as quinine, suggests that the drug-paired cue actually comes to evoke representations in the brain that are normally linked to aversive outcomes. Second, the neurophysiological changes observed in the accumbens provide a candidate neural substrate for such learning in a region that is closely related both to processing of positive and negative emotions (Balleine, 2005;

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Corbit et al., 2001; Schoenbaum and Setlow, 2003) and also to the development of addiction (Kalivas et al., 2005). Indeed, the general procedure used here bears certain similarities to Pavlovian-to-instrumental transfer, in which affective representations evoked by a Pavlovian cue are proposed to motivate instrumental responding (Cardinal et al., 2002). The accumbens is heavily implicated in this transfer phenomenon (B.W. Balleine and L.H. Corbit, 2005, Soc. Neurosci., abstract).

Thus, the negative affective information triggered by the taste cue in the accumbens would be well positioned to influence accumbens-dependent drug seeking. Consistent with such conjecture, the authors found that the strength of the taste aversion was *predictive* of subsequent cocaine self-administration. The more aversive the rats found the taste paired with cocaine, the more rapidly they loaded up on the drug when it was made available. This result lends strong support to the proposal that triggering of aversive affective states by drug-associated cues plays a role in drug-seeking behavior and provides a novel behavioral model in which to investigate the circuit basis of this phenomenon.

References

Balleine BW. Physiol Behav 2005;86:717–730. [PubMed: 16257019]

Cardinal RN, Parkinson JA, Hall G, Everitt BJ. Neurosci Biobehav Rev 2002;26:321–352. [PubMed: 12034134]

Corbit LH, Muir JL, Balleine BW. J Neurosci 2001;21:3251–3260. [PubMed: 11312310]

Grigson PS, Twining RC. Behav Neurosci 2002;116:321–333. [PubMed: 11996317]

Grill HJ, Norgren R. Brain Res 1978;143:263–279. [PubMed: 630409]

Kalivas PW, Volkow ND, Seamans JK. Neuron 2005;45:647–650. [PubMed: 15748840]

Koob GF, Le Moal M. Neuropsychopharmacology 2001;24:97–121. [PubMed: 11120394]

Roitman MF, Wheeler RA, Carelli RM. Neuron 2005;45:587–597. [PubMed: 15721244]

Schoenbaum G, Setlow B. J Neurosci 2003;23:9833–9841. [PubMed: 14586012]

Solomon RL, Corbit JD. Psychol Rev 1974;2:119–145. [PubMed: 4817611]

Wheeler RA, Twining RC, Jones JL, Slater JM, Grigson PS, Carelli RM. Neuroz 2008;57:774–785.this issue

Wise RA, Yokel RA, DeWit H. Science 1976;191:1273–1275. [PubMed: 1257748]