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Orexin/Hypocretin, Central Amygdala, and Escalation of Cocaine Intake

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Cocaine addiction is characterized by a transition from controlled and episodic drug use to a state of compulsive drug taking. This transition often involves a process of escalated cocaine intake that is associated with repeated and chronic exposure to the drug (1). Nearly 20 years ago, Ahmed and Koob (1) reported that the phenomenon of exaggerated drug use could be recapitulated in laboratory animals by giving rats extended (6-hour) access to cocaine in daily self-administration sessions. This long access (LgA) paradigm results in escalation of drug intake over self-administration days, which is in contrast to animals with restricted access (1 hour/day; short access [ShA]) to cocaine that exhibit relatively stable levels of cocaine consumption. Since this original demonstration, the LgA model has been widely adopted as the gold standard approach to modeling drug abuse in rats (2). Despite this, the brain circuitry underlying escalated drug use remains poorly understood.

One hypothesis is that addiction is associated with the recruitment of brain stress circuitry, which in turn drives excessive cocaine intake through negative reinforcement mechanisms (3). The central nucleus of the amygdala (CeA) has been highlighted as a key structure in this process, with withdrawal from various drugs of abuse being associated with increased transmission at gamma-aminobutyric acidergic (GABAergic) synapses in this region (3,4). Currently, however, it is unclear what systems influence GABAergic transmission within the CeA following drug exposure. The hypothalamic orexin/hypocretin system is a strong candidate, with orexin/hypocretin neurons providing direct and reciprocal connections with the CeA, and strong evidence now implicates the orexin/hypocretin system in the expression of stress behaviors and pathologies (5). In addition, the orexin/hypocretin system mediates a large range of addiction behaviors, especially when high effort is required or in animals that display a high addiction propensity (5,6). In this issue of *Biological Psychiatry*, Schmeichel *et al*. (7) tested the hypothesis that GABA transmission in the CeA following LgA is enhanced by orexin/hypocretin signaling, and that this is associated with escalation of drug taking.

To examine the role of the orexin/hypocretin system in excessive drug intake, Schmeichel *et al*. (7) trained rats to self-administer cocaine on either an LgA (6 hours/day) or ShA (1 hour/

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day) paradigm for 14 days before assessing the effects of systemic injections of the orexin receptor-1 antagonist SB-334867 (SB) on self-administration behavior. LgA rats escalated their intake of cocaine over self-administration days, and this was attenuated by SB, whereas intake in ShA rats remained stable and was not affected by SB. Although a role for the orexin/hypocretin system in regulating the motivational properties of cocaine is well established (5,6), this is the first demonstration that blocking orexin/hypocretin signaling can reduce the hedonic value of cocaine. The authors also report that SB reduced break points for cocaine on a progressive ratio task (a common measure of motivation for a drug reward) in both LgA and ShA rats.

Might the orexin/hypocretin system mediate the hedonic value of cocaine via actions in the CeA? To test this, Schmeichel *et al.* (7) asked whether the effects of systemic SB treatment on cocaine intake could be recapitulated by infusing SB directly into the CeA. Indeed, intra-CeA SB reduced the total number of infusions earned during the first hour of self-administration sessions following 14 days of LgA intake. Because the CeA is a major component of the extended amygdala circuitry that mediates anxiety associated with drug dependence (3), intra-CeA SB infusions may have alleviated a negative emotional state that increased cocaine intake in these animals. Although this was not tested directly, Schmeichel *et al.* showed that infusions of SB into the CeA significantly reduced reinstatement of extinguished cocaine seeking elicited by the pharmacological stressor yohimbine, indicating that orexin signaling in the CeA may play a role in the modulation of stress associated with cocaine abuse.

To understand how LgA to cocaine affects GABAergic neurotransmission in the CeA, and how orexin/hypocretin may influence this transmission, Schmeichel *et al.* (7) carried out electrophysiological recordings on CeA brain slices. They recorded spontaneous inhibitory postsynaptic current (sIPSC) responses as an index of action potential–dependent GABAergic transmission in the CeA. CeA neurons from LgA animals exhibited significantly increased sIPSC frequencies compared with cells from both cocaine-naïve and ShA animals, indicating that extended access to cocaine results in enhanced activity-dependent GABAergic tone in the CeA. To assess action potential–independent vesicular GABA release, tetrodotoxin was bath applied to CeA slices, and miniature IPSCs (mIPSCs) were recorded. The authors report a strong, but not significant, trend toward increased frequency of mIPSCs in CeA neurons from LgA animals relative to naïve and ShA animals, possibly reflecting increased vesicular GABA release following extended access. No changes in amplitude were observed for either sIPSCs or mIPSCs, indicating that enhancement of GABAergic tone in the CeA following extended access may result from changes at the presynaptic or network level.

To test whether changes in CeA GABA release were orexin dependent, Schmeichel *et al.* (7) carried out similar recordings during SB bath application. SB had no effect on the frequency of sIPSCs in CeA neurons from either naïve or ShA animals but significantly reduced sIPSC frequencies in cells from LgA animals, indicating that signaling at the orexin/hypocretin receptor-1 regulates action potential–dependent GABA release in CeA following extended access to cocaine. Similarly, SB application significantly reduced the frequency of mIPSCs in CeA neurons from LgA rats, but not from naïve or ShA rats, indicating that SB also

reduces vesicular GABA release in these animals. In the case of both sIPSCs and mIPSCs, no changes were observed in IPSC amplitudes, again indicating that these effects are likely mediated by presynaptic mechanisms. Taken together, these electrophysiological data support the findings of the aforementioned behavioral studies by implicating the CeA as a site for neuroadaptations following LgA and by demonstrating that these effects are mediated, at least in part, by the orexin/ hypocretin system.

In sum, Schmeichel *et al.* (7) provide compelling evidence that escalated cocaine intake following extended access to cocaine is associated with orexin/hypocretin-dependent enhancement of GABAergic signaling in the CeA. These findings are noteworthy because the orexin system has previously been thought to have limited influence over the hedonic properties of cocaine. This is likely due, at least in part, to the fact that our understanding of the orexin/hypocretin system in addiction comes overwhelmingly from studies using restricted access paradigms. Although these paradigms offer a powerful approach to studying specific addiction-like endophenotypes, they might not fully recapitulate the neurological sequelae that result from uncontrolled drug use in human addicts. In this respect, the current study provides a strong starting point for understanding the role of orexin/hypocretin in pathological drug seeking but at the same time highlights a number of key questions that must be addressed by future studies. For example, the authors have elegantly implicated the orexin/hypocretin system as a key modulator of escalation of drug intake, but it remains to be demonstrated whether this mechanism is also involved in the regulation of other key addiction behaviors known to be enhanced by LgA such as compulsive (punished) responding and economic demand (8). Given the persistent nature of addiction, it is also important that future studies seek to determine whether the electrophysiological changes observed here immediately following cocaine self-administration persist into withdrawal and to what extent they contribute to relapse-like behavior. Moreover, recent evidence indicates that giving animals intermittent, rather than constant, access to cocaine in daily 6-hour sessions promotes motivated drug seeking beyond that induced by the LgA model (9). Thus, it is important that future studies examine the involvement of the orexin/hypocretin system in the development and expression of pathological drug seeking in this novel model of addiction.

Future studies should also seek to provide a more direct link between perturbations in orexin/hypocretin function and the development of negative emotional states, both during self-administration training and during withdrawal. For example, is LgA training associated with a gradual increase in negative symptomology, and is the emergence of these states correlated with changes in orexin/hypocretin-mediated GABA release in the CeA? How does increased GABA signaling in the CeA lead to negative states, and how do drugs such as cocaine produce negative reinforcing effects with such states? Is the SB-mediated reduction in cocaine intake associated with a concurrent alleviation of anxiety and/or depression-like symptoms? Is it still possible to block CeA GABA release with SB after protracted withdrawal when negative emotional states remain strong (10)? In addition, what role does orexin/ hypocretin play in other brain areas that have important roles in stress, anxiety, and addiction (e.g., bed nucleus of the stria terminalis)? Finally, as Schmeichel *et al.* (7) note, the role of orexin receptor-2 in these processes should be explored, especially given the emerging role for this receptor type in mediating stress behaviors. Regardless, data presented

by the authors provide novel and important insight into the role of the orexin/hypocretin system in the regulation of pathological drug seeking. These findings are particularly timely given ongoing clinical trials investigating the effectiveness of the recently Food and Drug Administration–approved dual orexin/hypocretin receptor antagonist suvorexant (Belsomra) for the treatment of cocaine addiction (6).

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