Stressing the potential of guanfacine as a treatment for cocaine use disorder

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Cocaine use disorder (CUD) affects millions of people in the U.S. and represents a persistent public health challenge due to high rates of relapse and the lack of FDA-approved drugs for its treatment [1]. Chronic cocaine use is associated with lasting adaptations in the neural circuitry underlying stress responses and motivated behavior that are hypothesized to make abstinence from cocaine aversive and difficult for patients [1, 2]. Preclinical and clinical studies support a role for the central noradrenaline (NE) system in initiating cocaine craving and relapse behavior, and there is some evidence that drugs that suppress NE signaling reduce craving in patients with CUD [1, 3]. However, these therapies have yet to demonstrate clinically meaningful efficacy for preventing relapse to cocaine use. Candidate anti-adrenergic drugs for CUD have included agents like lodoxidine and guanfacine, which reduce NE transmission by activating inhibitory autoreceptors on adrenergic somatodendritic elements and terminals [1, 3].

Although α2-adrenergic receptors (α2-ARs), particularly the α2a subtype, are classically considered as inhibitory autoreceptors that suppress NE release, the pharmacology and function of α2-ARs has proven rather complex [4]. In fact, α2a-ARs are expressed by both adrenergic and non-adrenergic cells. While α2a-ARs expressed on noradrenergic elements indeed function as inhibitory autoreceptors that decrease neuron firing and NE release, the effects of systemic α2a-AR agonists are mediated to a surprisingly large extent by α2a heteroreceptors on non-adrenergic neurons [4]. Moreover, although stimulation of α2a autoreceptors promotes canonical inhibitory Gi-mediated signaling, activation of α2a heteroreceptors on non-adrenergic cells can be either inhibitory or excitatory [4, 5]. Thus, pharmacological activation of α2a heteroreceptors by guanfacine can elicit diverse responses in non-adrenergic cells in regions like the bed nucleus of the stria terminalis (BNST) that may contribute to side-effects and limit efficacy for the treatment of CUD.

The BNST is a common node in the circuitry underlying stress-induced and anxiety-like behavior [6]. Noradrenergic neurons in the locus coeruleus and A1/A2 nucleus of the medulla innervate the BNST via the dorsal and ventral noradrenergic bundles, respectively, although the ventral bundle is the dominant source of NE within the region [3, 7]. Pharmacological disruption of NE signaling in the BNST prevents stress-induced reinstatement of cocaine-seeking behavior, an animal model of relapse [2, 3, 6]. Previous research showed that β-adrenergic receptors (β-ARs) in the BNST are critical for stress-induced reinstatement of drug seeking [2], but the role of α2a heteroreceptors had not been investigated. Harris et al. [5] recently demonstrated that pharmacological activation of α2a heteroreceptors in the dorsal BNST (dBNST) increases, rather than decreases, neuronal excitability through non-canonical Gi-coupling to hyperpolarization-activated cyclic nucleotide–gated (HCN) channels. The authors found that a high dose of guanfacine (1 mg/kg) robustly induces c-fos within the dBNST and showed that this effect could be recapitulated by chemogenetic activation of Gi-coupled DREADDs (traditionally described as inhibitory). Since BNST activity is implicated in stress responses and relapse, unwanted activation of excitatory BNST α2a heteroreceptors by agonists like guanfacine could occlude beneficial drug effects in patients with CUD. In the current study [8], the authors extend these findings by demonstrating that a low dose of guanfacine (0.15 mg/kg) prevents forced swim-induced reinstatement of cocaine conditioned place preference (CPP) in mice, consistent with previous reports that reducing NE release suppresses stress-induced reinstatement of drug seeking [3, 9]. Unlike the high dose of guanfacine, the low dose did not induce c-fos in the dBNST, suggesting that stimulation of excitatory heteroreceptors only occurs at a higher dose of agonist. Chemogenetic activation of Gi-DREADDs within the dBNST elicited reinstatement of cocaine CPP even in the absence of a stressor, demonstrating that engagement of Gi-mediated signaling in the dBNST is sufficient to mimic the effect of swim stress on reinstatement.

Interestingly, mice lacking either all α2a-ARs or α2a heteroreceptors failed to express stress-induced reinstatement of cocaine CPP, indicating that α2a heteroreceptors on non-adrenergic cells are required for this behavior. Although assessing the consequences of intra-BNST infusions of guanfacine and selective ablation of BNST α2a heteroreceptors on relapse-like behavior will be critical tests of the hypothesis, these converging lines of evidence suggest that dBNST α2a heteroreceptors are essential for stress-induced reinstatement of cocaine CPP. Extrapolating to clinical applications, the dose of guanfacine and related compounds may need to be titrated for patients with CUD to preferentially target α2a autoreceptors and avoid activation of non-canonical excitatory Gi-mediated signaling.

The findings presented by Perez et al. [8] also raise new and interesting questions. For instance, the dissociable effects of low and high dose guanfacine on dBNST activity implies the existence of different α2a-AR affinity states, with autoreceptors having a
higher affinity for agonists than heteroreceptors. Although there is some evidence to support the idea that drugs can have different affinities for the same receptor depending on whether it is located pre- or post-synaptically [10], this phenomenon has not been well characterized. Electrophysiological experiments assessing the effects of different concentrations of guanfacine on dBNST excitability would be useful in this regard. Further studies investigating the efficacy of low dose guanfacine in other models of relapse such as reinstatement of operant cocaine self-administration and incubation of cocaine craving will also be illuminating [2, 9]. Moreover, the finding that $\alpha_2$-AR heteroreceptors in the dBNST are required for stress-induced reinstatement of cocaine CPP suggests complex and potentially synergistic signaling actions with dBNST $\beta$-ARs, which are also required for this behavior [3]. Another possibility is that stress-induced reinstatement depends on the participation of two distinct dBNST cell types that express either one receptor or the other.

Finally, the fact that high doses of guanfacine and Gi-DREADDs increase neuronal excitability within the dBNST should remind investigators that GPCR signaling is complex; validation that drugs or DREADDs are behaving as expected within the system or cell type targeted for manipulation should be a top priority before beginning further circuit-based experiments. Overall, this elegant neuroanatomical, genetic, and pharmacological investigation of $\alpha_2$-AR function on stress-induced cocaine-seeking behavior is of immediate translational value to clinicians, and a review of standard guanfacine dosing parameters for clinical trials and off-label use in CUD patients seems warranted. A more mechanism-guided dose titration may enhance the efficacy of guanfacine and related compounds for prevention of relapse in CUD and other substance abuse disorders.

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AUTHOR CONTRIBUTIONS
Respective Contributions DL conceived of the work and drafted the manuscript. DW conceived of the work and critically revised the manuscript.

ADDITIONAL INFORMATION

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