RESEARCH HIGHLIGHT

Stimulation of muscarinic acetylcholine M₁ receptors reallocates choice between cocaine and an alternative reinforcer

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Cocaine use in the United States has remained relatively steady over the past decade and continues to pose a substantial public health threat. There are currently no approved medications for the treatment of cocaine use disorder (CUD). Thus, the need for effective pharmacotherapies and treatment strategies is becoming increasingly important. One defining characteristic of CUD is the repeated choice of taking cocaine in the context of an environment that contains alternatives that may be rewarding, or at least objectively lead to a higher probability of increased health and security in the future. Choice procedures, as a preclinical model in rodents and primates, attempt to model this dynamic environment by pitting a drug of interest against an alternative reinforcer such as food [1], a palatable treat [2], or social interactions [3]. Thus, choice procedures as a preclinical model are increasingly used and appreciated for determining reinforcing efficacy of multiple, concomitantly presented reinforcers at baseline and in the presence of therapeutic interventions [4].

In this issue of *Neuropsychopharmacology*, Weikop et al. [5] test whether the highly-selective muscarinic acetylcholine M₁ receptor agonist, VU0364572 [6], alters the reinforcing efficacy of cocaine using a cocaine-food choice task in male rats. A strength of the choice task used in this study is that a full range of cocaine unit doses (0.06–1.0 mg/kg/infusion) is tested within each session in each rat; from small unit doses that engender little to no choice for cocaine to high-unit doses that engenders 100% choice for cocaine. The resulting choice curve provides an orderly metric for reinforcing efficacy of cocaine against a “dose” of an alternative reinforcer (in this case a 32% dilution of Vanilla flavored liquid Ensure). This choice procedure is well validated, orderly, and prior work has shown the resulting choice curve to be stable across sessions [1]. The authors show that VU0364572 reallocated choice away from cocaine and toward an alternative food reinforcer across the full range of cocaine doses, effectively flattening the choice curve. The reallocation of choice away from cocaine was present for both 0.1 mg/kg and 1.0 mg/kg doses of VU0364572, with the effect appearing by Day 2 for the lower dose and dissipating by Day 14. Remarkably, the effects of a single administration of high dose VU0364572 on cocaine choice developed gradually over weeks, reached maximal effects 28 days post administration, and persisted for the entirety of the four-week study.

Given the behavioral complexity and difficulty in executing choice procedures, there are few studies that measure

neurotransmitter levels or seek to elucidate neural mechanisms in the reallocation of choice for cocaine (however, see ref. [7]). Thus, another strength of the current manuscript was the use of dual-probe microdialysis to record dopamine and glutamate in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) in cocaine naïve and experienced rats. Although this was not performed in rats undergoing choice, it did show that administration of VU0364572 in combination with cocaine had long-term effects on neurotransmitter response to cocaine challenge. Perhaps most notably, VU0364572 blocked cocaine-induced increases in mPFC dopamine and NAc glutamate in cocaine-experienced rats nearly 4 weeks after treatment. Both of these effects have been associated with reductions in cocaine self-administration. The authors suggest that VU0364572 could be blocking corticostriatal plasticity caused by cocaine experience and perhaps restoring the balance on AMPA/NMDA ratios that are altered following a history of cocaine self-administration. Future experimentation could extend these findings in rats undergoing choice to examine whether VU0364572-induced changes in glutamate and dopamine are specific to conditions in which rats choose cocaine, or whether they extend to trials in which the food reinforcer is chosen. Indeed, prior work has shown differences in orbitofrontal activation in choice for food vs. cocaine [7].

These compelling effects naturally beg the question of behavioral mechanisms that might underlie such a dramatic reallocation of choice so long after treatment cessation. For example, reallocation of choice in this study could be a result of, but not limited to, (1) decreased reinforcing efficacy of cocaine, (2) increased reinforcing efficacy of the alternative reinforcer, or (3) alteration in the subject's learning or understanding of discriminative stimuli for each unit dose of cocaine. For example, it is notable that although not significant, a trend toward increasing food consumption across each choice session was present, suggesting a possible shift in the reinforcing efficacy of the alternative food reinforcer. However, the authors provide additional experimentation in mice demonstrating that VU0364572 reduced cocaine intake under a fixed-ratio (FR) 1 schedule of reinforcement, which is consistent with prior work from this group using combination M1/M4 receptor agonists [8]. While low FR schedules in this study do not necessarily measure reinforcing efficacy per se, it is notable that cocaine intake was reduced in these mice to levels observed with saline self-administration. This suggests that cocaine may not be serving as a reinforcer in the VU0364572 treated mice. Therefore, a strong candidate

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Received: 18 May 2020 Accepted: 25 May 2020

Published online: 15 June 2020

mechanism for VU0364572-induced reallocation of choice is a reduction of cocaine's reinforcing efficacy.

With respect to possible learning mechanisms, these authors previously showed that M1/M4 agonists decrease the discriminative stimulus effects of cocaine in an M1-dependent manner [9]. In this choice design, a noncontingent priming dose of cocaine is injected prior to each component within a session and likely serves, in combination with distinct light stimuli, as a discriminative stimulus (S^D) to differentiate unit doses of cocaine within each session and signal the beginning of a new component. If VU0364572 is decreasing the subjective (or other interoceptive) effects of cocaine it might not only decrease cocaine's reinforcing efficacy, but might serve to disrupt interoceptive cues that serve as an S^D for any particular unit dose of cocaine. Indeed, contextual effects provided by a drug when under the influence is an important determinant of choice [10]. A mechanism of reduced reinforcing efficacy and a mechanism of disrupting cocaine-environment associations can be teased apart with future experimentation and are both promising with respect to treatment of CUD if either were to be translated into the clinic.

FUNDING AND DISCLOSURE

MJF and ACL are supported by the National Institutes of Health grants R00 DA031791, P50 DA006634, P50 AA026117, T32 DA041349, and support from the Peter McManus Charitable Trust. The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

ACL and MJF equally contributed to conceptualizing, drafting, editing, revising, and finalizing this manuscript. ACL and MJF approve the final version of this manuscript for publication. ACL and MJF agree to be accountable for all aspects of this work.

ADDITIONAL INFORMATION

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