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RESEARCH HIGHLIGHT

A role for amygdala endocannabinoid signaling in reconsolidation of cocaine-associated memories

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The use of cocaine and other stimulants, as well as related overdose deaths, is on the rise, highlighting the urgency for further research into stimulant use disorders. Substance use disorders (SUDs) are characterized by compulsive seeking and chronic relapse despite negative consequences. Unfortunately, current treatment options are limited in scope and effectiveness, with as many as 30–60% of individuals relapsing within the 1st year of treatment [1]. Treating stimulant use disorders is particularly difficult, as there are no FDA-approved medications. SUDs are perpetuated, in part, by cues that become associated with the rewarding effects of the drug [2], including contextual cues (i.e., location wherein drugs were purchased or used). Encountering these cues can trigger retrieval of drug-associated memories, which can increase the motivation to drug seek and, ultimately, relapse. This suggests that protection against relapse may be conferred through a reduction in cue reactivity. One approach to the selective targeting of drug-associated memories is through the disruption of memory reconsolidation, a brief temporal window that exists after retrieval when a memory is labile and may be modified. For a memory to once again be stabilized for long-term storage, it must undergo reconsolidation through a series of neurobiological processes; many of which occur within ~6 h of retrieval [3]. Preclinical and clinical evidence suggests certain manipulations during reconsolidation may be capable of achieving complete, selective disruption of a specific memory [4].

Reconsolidation is critically mediated by the basolateral amygdala (BLA) [3] and requires new protein synthesis and synaptic plasticity [5], both of which can be modulated by cannabinoid type-1 receptor (CB1R) signaling [6]. Moreover, the endocannabinoid system can modulate many components of associative memory, including reconsolidation, reinstatement, and extinction [6]. Recently, the Fuchs' laboratory reported that systemic administration of a CB1R antagonist (AM251) following retrieval of a contextual cocaine-associated memory attenuate seeking during a subsequent memory retention test [7]. Furthermore, they found protein expression and electrophysiological differences in the BLA following retrieval and injections of AM251 [7]. However, the functional role of endocannabinoid signaling in BLA during reconsolidation remained unknown. Therefore, in this issue of *Neuropsychopharmacology*, Higginbotham et al. [8] aimed to determine the role of CB1R signaling in the BLA during reconsolidation. To test this, they used the same cocaine self-administration and context-induced reinstatement (i.e., renewal) approach as before. Briefly, rats underwent acquisition of cocaine self-administration in a unique context (Context A), extinction in a different context (Context B), and then were briefly placed back into Context A (15 min; retrieval test). This is often how context-induced reinstatement is assessed during full-length sessions of an hour or more. However, shorter sessions allow for the drug-associated memory to be briefly retrieved and thus made labile to modifications, without prolonged extinction occurring. Therefore, to examine the effect of CB1R inhibition on reconsolidation of a contextual drug-associated memory, Higginbotham et al. [8] administered the pharmacological manipulation following the retrieval test, then subjected rats to additional extinction sessions in Context B, before memory retention was tested again in Context A (2 h; retention test). Using these procedures, the authors first demonstrated that intra-BLA infusions of AM251 immediately after the retrieval test increased drug seeking during the subsequent retention test. These results were both time and region specific, as infusions of AM251 either into BLA 6 h after the retrieval test (thus, likely outside the reconsolidation window [3]) or into posterior caudate putamen immediately after the retrieval test did not affect drug seeking during the retention test. Interestingly, no differences were observed following post-retrieval test infusions of the CB1R agonist WIN55212-2.

Together, their results suggest that inhibiting CB1R activity in the BLA immediately following memory retrieval may allow the memory to be strengthened during reconsolidation, causing potentiated cocaine seeking during the retention test. Furthermore, as BLA CB1R activation does not suppress context-induced cocaine seeking, CB1R activation alone may not be sufficient to affect memory reconsolidation and, therefore, may not act in isolation. One potential co-factor is the stress hormone corticosterone. Corticosterone release upon exposure to stress does more than just mobilize energy stores for restoration of homeostasis, it can also enhance memory consolidation through actions in the BLA [9], initiate endocannabinoid signaling in many regions including the BLA [9], and promote drug seeking through endocannabinoid signaling [10]. To explore this potential relationship, Higginbotham et al. [8] examined changes in total serum corticosterone levels before and after the final extinction session, after a retrieval test, and following vehicle or AM251 BLA infusions. Corticosterone levels were increased following retrieval compared to extinction and homecage (no retrieval) levels, and intra-BLA infusions of AM251 increased corticosterone levels compared to vehicle-infused rats following retrieval for at least 90 min. As previous reports suggest such increases in BLA corticosterone may facilitate memory consolidation [9], this may be the mechanism through which CB1R inhibition strengthened reconsolidation to promote context-induced drug seeking during the retention test. However, intra-BLA corticosterone infusions following the retrieval test had no effect during the subsequent

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retention test. Notably, administration of corticosterone in the absence of stress can rapidly increase endocannabinoid levels in the BLA [9]. Therefore, it is possible that intra-BLA corticosterone infusions could mimic the null effects of CB1R agonists. Additionally, corticosterone exerts numerous effects throughout the brain and body, thus the elevations in corticosterone resulting from BLA CB1R inhibition may still act as a co-factor in strengthening drug-associated memories during reconsolidation in a different brain region. These results suggest that BLA CB1R inhibition may mimic the effects of systemic corticosterone elevations to strengthen drug-associated memory reconsolidation and promote context-induced cocaine seeking.

In summary, Higginbotham et al. [8] demonstrated that blocking CB1R in the BLA during reconsolidation potentiates context-induced cocaine seeking during the retention test, and increased corticosterone levels were observed after memory retrieval and intra-BLA CB1R inhibition. Together, these results suggest a potential mechanism wherein blocking intra-BLA CB1Rs allows for corticosterone levels to elevate and strengthen plasticity occurring during reconsolidation, which results in increased cocaine seeking during the retention test. The findings in this paper invite further investigations into the complicated relationship between stress, drug use, endocannabinoid signaling, and memory reconsolidation.

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ADDITIONAL INFORMATION

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