Effects of Amygdalar CaMKII Activity on Extinction and Reconsolidation of a Cocaine-Associated Memory

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INTRODUCTION

- Memories of environmental cues associated with drug use contribute to relapse-to-drug-taking, which is prevalent in addiction.1,2
- The amygdala is involved in the formation of memories associated with drug use.3
- Manipulating protein kinase activity within the amygdala regulates both the reconsolidation and extinction of drug-induced memories and may serve as a potential treatment for addictive disorders.4,5
- Proteomic approaches may be beneficial for identifying proteins that are differentially expressed following extinction and reconsolidation of a drug-cue associated memory.6
- Calcium/calmodulin-dependent protein kinase II (CaMKII), has been shown to modulate synaptic activity, contributing to memory storage, and may be involved in the formation of drug-associated memories.7,8
- The involvement of CaMKII in drug-cue memory formation in the basolateral amygdala (BLA) was investigated via phospho-proteomic analysis and a drug reinstatement paradigm

METHODS

Subjects: Male Sprague-Dawley rats (275-325 g) were maintained on a regular light/dark cycle, and given ad libitum access to water. Rats were maintained at 90% of their free-feeding weight throughout behavioral experiments.

Surgery: All rats were implanted with a chronic indwelling catheter into the right jugular vein for cocaine self-administration. In experiment 2, rats also received bilateral guide cannulae targeting the BLA.

Behavioral Procedures: Rats were trained to self-administer cocaine (1 mg/kg) accompanied by a 10 s light-tone cue (CS) on an FR1 schedule of reinforcement on an active lever. Rats underwent 10-14 daily 1 h sessions until reaching acquisition of self-administration (28 infusions for each of the last 3 consecutive SA sessions). Reconsolidation was then performed during S5-16 daily 1 h sessions, in which both levers were available but had no programmed consequences. After meeting extinction criteria (>25 active lever presses over 2 consecutive days) rats underwent a bilateral infusion of the CaMKII inhibitor KN62 (340 or 680 ng/side) or its vehicle in the BLA. 24 hours later, rats were subjected to a cue-induced reinstatement session.

Experiments 1: Proteomic Analysis of BLA Following Drug-Memory Manipulations. 15 min after memory test sessions, brains were dissected and BLA tissue was subjected to proteomic analysis. (a) Schematic of experimental timeline

2.) Intra-BLA infusion of KN-62, a specific CaMKII inhibitor, resulted in decreased expression of pSer331-CaMKII4 after memory reactivation and an increased expression following extinction relative to controls. (b) CaMKII phosphorylation at Ser331 was significantly upregulated following extinction and significantly downregulated in response to memory reconsolidation (n = 8 per group, * p < 0.001).

CONCLUSIONS & DISCUSSION

1.) Proteomic analysis of tissue from the basolateral amygdala (BLA) revealed decreased expression of pSer331-CaMKII after memory reactivation and an increased expression after cue extinction.

2.) Intra-BLA infusion of KN-62, a specific CaMKII inhibitor, resulted in decreased responding on a cue-induced reinstatement test both in rats that had undergone cue reactivation and cue extinction.

3.) Inhibition of CaMKII may interfere with the reconsolidation of drug-cue associated memories, thus impacting its stability.

4.) Blocking activity of CaMKII may facilitate extinction of drug-seeking behavior.

5.) Inhibitors of CaMKII might be useful adjuncts to extinction training in the treatment of addiction.

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