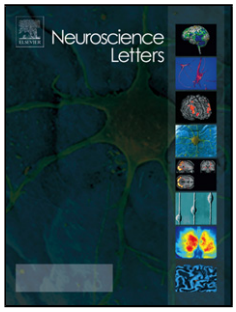

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Dose-dependent reduction in cocaine-induced locomotion by Clozapine-N-Oxide in rats with a history of cocaine self-administration

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Highlights:

- Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) are utilized to probe neurocircuitry of behavior and are activated by the ligand clozapine-N-oxide (CNO).
- Here we found that CNO itself, in the absence of DREADD expression, attenuated locomotor behavior induced by cocaine
- Only a higher dose (5 mg/kg) of CNO suppressed cocaine-induced locomotion and not a lower dose (3 mg/kg)

Abstract

Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) are novel tools for the dissection of circuitry mediating behavior and neural function. Designer receptors based on the muscarinic M3 and M4 subtypes were designed to be activated by clozapine-N-oxide (CNO), a ligand previously shown to be an inert metabolite of clozapine. However, recent work in rats has shown that CNO is reverse metabolized to its parent compound. Furthermore, CNO administration (5 mg/kg IP) attenuates amphetamine-induced locomotion and the evoked dopamine response that accompanies it. As these systems are routinely used to probe the neurocircuitry underlying cocaine-seeking behavior, here we sought to determine whether CNO would have similar effects on cocaine-induced locomotion in rats with a history of cocaine self-administration. In order for muscarinic-based DREADDs to be utilized for the dissection of circuitry underlying behavioral responses to cocaine, the doses of CNO administered to induce DREADD signaling must themselves have no effect on cocaine-induced behavior. Male Sprague-Dawley rats self-administered cocaine (0.35 mg/infusion) for 12 days, followed by 14-21 days of instrumental extinction training. Rats then underwent locomotor testing. CNO (0, 3, or 5 mg/kg) was injected (utilizing a within-subjects design), followed 20 minutes later by cocaine (10 mg/kg IP). Locomotion was monitored for the following 120 minutes. We found that the 5, but not the 3 mg/kg,