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The NK1 antagonist L822429 inhibits stress-induced reinstatement of alcohol seeking behavior in rats

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ABSTRACT

Substance P (SP) and its preferred neurokinin-1 (NK1) receptor play a significant role in stress and anxiety-related behaviors. While the influence of the NK1 receptor on stress responses is well documented, less is known about its role in reward and addiction. Recent studies have suggested a critical role of the SP/NK1 system in the rewarding properties of morphine, but not that of cocaine. Furthermore, our lab was the first to demonstrate that alcohol consumption is decreased by a genetic deletion of the NK1 gene in mice, and that administration of NK1 antagonists to human alcoholics can alleviate craving. In the studies presented here, we utilize the well-validated models of rat self-administration and reinstatement to assess the effects of a specific NK1 antagonist, L822429. This antagonist has anxiolytic properties in rodent models when administered systemically, and therefore represents an intriguing agent for altering alcohol-related behaviors. NK1 antagonism has presented a rather complicated target thus far, as receptor affinity shows significant interspecies variation and many antagonists that are effective in humans are inactive in rat. We found that while L822429 had little effect on baseline alcohol self-administration or cue-induced reinstatement of alcohol seeking behavior, it dose-dependently blocked the expression of stress-induced reinstatement. Importantly, this drug had no effect on locomotor activity or self-administration of sucrose solution. To our knowledge, this is the first exploration of the effects of NK1 receptor antagonists on alcohol-related behaviors in rats. Taken together, these results indicate NK1 antagonists generally, and L822429 specifically, as promising candidates for pharmacotherapy for alcoholism.

INTRODUCTION

-Substance P (SP) is a neuropeptide that signals primarily through the neurokinin-1 (NK1) receptor and is highly involved in stress, anxiety, and addiction¹⁻².

-Manipulations of the SP/NK1 system have been shown to impact rewarding and reinforcing properties of morphine, but not cocaine³⁻⁵.

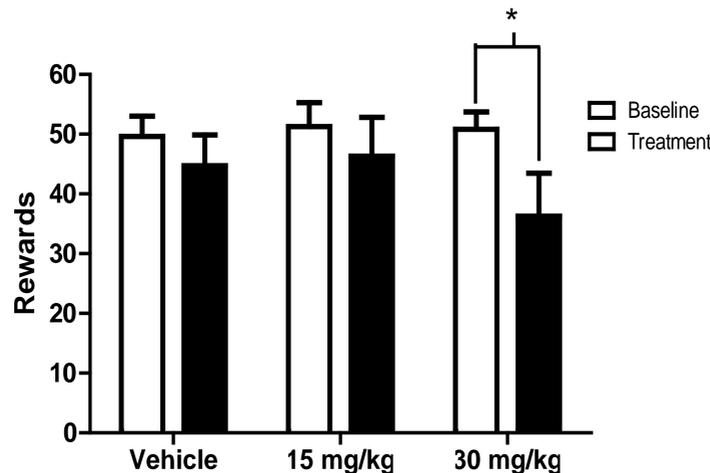
-NK1 -/- mice drink less alcohol, show blunted alcohol associated reward, and do not escalate alcohol consumption following intermittent access⁶⁻⁷.

-NK1 antagonists decrease alcohol consumption in wildtype mice and attenuate craving in alcoholics⁶⁻⁷.

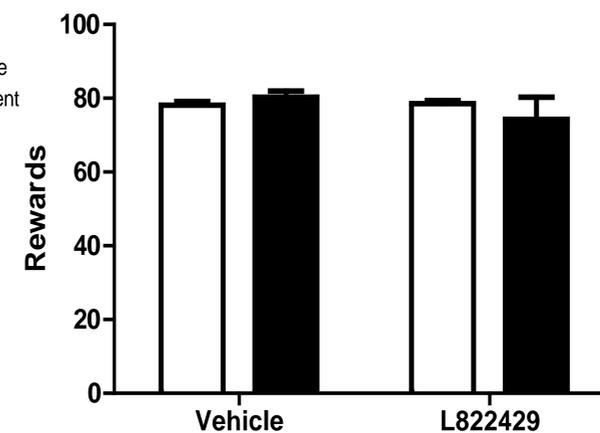
-L822429 is a highly specific NK1 antagonist that has central activity when delivered systemically and has anxiolytic properties⁸⁻⁹.

-The studies outlined here attempt to assess the effect of L822429 on alcohol self-administration and reinstatement.

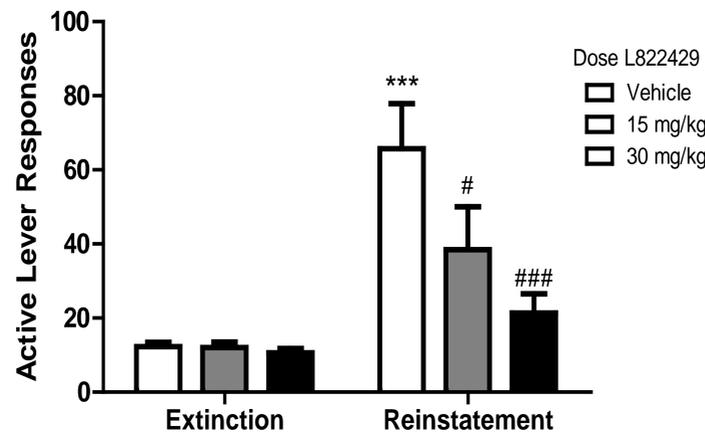
RESULTS



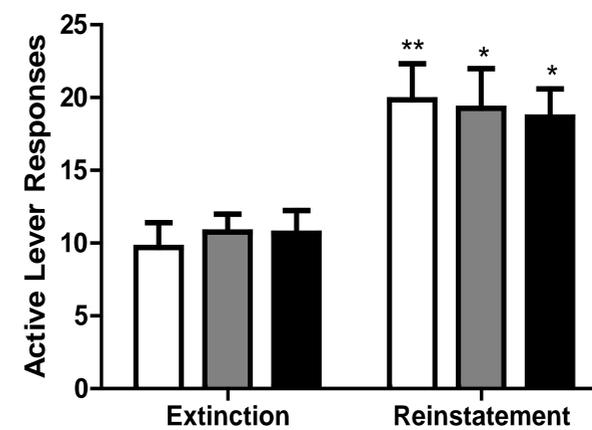
Alcohol self administration. Two way ANOVA revealed a main effect of session only ($p < 0.01$, $n = 11-12/\text{group}$). Post-hoc tests indicated a significant decrease from baseline in the number of rewards obtained on treatment day for the 30 mg/kg L822429 treated group only ($*p < 0.05$).



Sucrose self administration. L822429 (30 mg/kg) had no effect of sucrose self-administration ($n = 7/\text{group}$). These results indicate that L822429 did not effect natural reward.



Stress-induced reinstatement. Two way ANOVA revealed main effects of session ($p < 0.001$, $n = 13-14/\text{group}$) and drug treatment ($p < 0.05$), as well as an interaction ($p < 0.05$). Post-hoc tests indicated a significant reinstatement in the vehicle group only. There was a decrease from vehicle reinstatement responding for both the 15 mg/kg and 30 mg/kg L822429 treated groups. # $p < 0.05$, ### $p < 0.001$ compared to vehicle responding; *** $p < 0.001$ compared to extinction responding.



Cue-induced reinstatement. Two way ANOVA revealed a main effect of session only ($p < 0.001$, $n = 12-13/\text{group}$). Post-hoc analysis indicated a significant increase from extinction responding during the reinstatement test for all treatment groups. * $p < 0.05$, ** $p < 0.01$ compared to extinction responding.

METHODS

Animals: Male Wistar rats weighing approximately 400 to 500 grams at the time of experimentation were used in these studies. Rats were housed in a reversed light cycle (lights on 20:30, lights off 08:30), and all testing took place during the dark phase.

Alcohol Self-Administration: 10% ethanol (v/v) was available during self-administration sessions on an FR1 schedule. Alcohol was dissolved in tap water and delivered in a 0.1 ml volume onto a tray within the self-administration chamber, from which the rat consumed the alcohol solution. A 5 second time out was initiated following alcohol delivery during which a house light was illuminated. During time out, alcohol delivery was not activated following active lever press, but these responses were recorded. Following the timeout, the session returned to the FR1 schedule of reinforcement. For cue-induced reinstatement experiments, orange scent was also present in the self-administration chambers during alcohol sessions.

Self-Administration Experiments: After a stable level of responding was reached for at least three consecutive days, rats were injected with L822429 (0, 15, or 30 mg/kg) 60 minutes before the next self-administration session.

Extinction & Reinstatement: After 14-16 days of self-administration, extinction sessions were begun where responding on the active lever did not result in a delivery of alcohol. In the stress-induced reinstatement experiment, the time out light cue remained in place during the extinction sessions. For the cue-induced reinstatement experiment, the light cue and orange scent were removed during extinction sessions. Extinction conditions were in place for 15-19 sessions. To reinstate responding, specific stimuli were delivered to induce active lever pressing behavior. In the stress-induced reinstatement experiment, 15 minutes of intermittent footshock (0.5 sec shock, 0.6 mA) was delivered immediately before the reinstatement session. In cue-induced reinstatement experiments, presentation of orange scent and contingent house light illumination served as the reinstatement stimuli. In both experiments L822429 was injected 60 minutes prior to reinstatement testing.

Drugs: L822429 was synthesized from the literature by K. Rice and K. Cheng. L822429 was dissolved in 45% (w/v) 2-hydroxypropyl β -cyclodextrin and pH was adjusted with 1 N NaOH. L822429 was injected i.p. at a volume of 2 ml/kg.

CONCLUSIONS

-L822429 induces a small, but statistically significant, reduction in alcohol self administration.

-L822429 induced a potent, dose dependent suppression of alcohol seeking behavior during footshock-induced reinstatement testing. However, this drug does not affect cue-induced reinstatement of alcohol seeking behavior.

-L822429 does not effect self-administration of 10% sucrose or general locomotor activity (data not shown).

-The experiments outlined above indicate an important role of the NK1 receptor in alcohol-induced behaviors.

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