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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 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. While the influence of the NK1 receptor on stress responses is well documented, less is known about its role in stress and anxiety-related behaviors. Furthermore, our lab was the first to demonstrate that NK1 antagonists play a significant role in stress and anxiety-related behaviors. Furthermore, our lab was the first to demonstrate that NK1 antagonists play a significant role in stress and anxiety-related behaviors.

RESULTS

Alcohol self-administration. Two way ANOVA revealed a main effect of session only (p<0.01, n=11-12/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).

Stress-induced reinstatement. Two way ANOVA revealed main effects of session (p<0.001, n=13-14/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/group). Post-hoc analysis indicated a significant increase from extinction responding during the cue-induced reinstatement test for all treatment groups. *p<0.05, **p<0.01 compared to extinction responding.

METHODS

- 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.

- Extinction & Reinstatement: 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 alcohol seeking behavior. In the stress-induced reinstatement experiment, 15 minutes of intermittent footshock (0.5 sec, 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 stimulus. 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.

REFERENCES