

Dopamine Reuptake Inhibitors Partially Substitute for Nicotine as a Conditioned Stimulus



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Introduction

Recent research has shown that nicotine can function as a conditioned stimulus in a Pavlovian goal-tracking task (Besheer et al., 2004; Bevins & Palmatier, 2004). Typically, rats are trained to discriminate nicotine from saline. That is, on nicotine sessions rats receive intermittent access to sucrose, whereas on saline sessions no sucrose is delivered. Rats show increased goal tracking (dipper entries) on nicotine sessions in comparison to saline sessions. Further, bupropion (20 mg/kg, IP) substitutes for the nicotine cue in rats trained to discriminate 0.4 mg/kg nicotine (SC) from saline (Besheer et al., 2004; Wilkinson et al., 2005). This substitution may result from bupropion's inhibition of dopamine and norepinephrine reuptake. It has yet to be determined whether bupropion will substitute when a lower dose of nicotine is used as a conditioned stimulus. Therefore, the purpose of this study was to determine whether bupropion would substitute for 0.2 mg/kg nicotine cue and to examine the importance of dopamine and norepinephrine transporters in the conditioned stimulus effects of nicotine.

Methods



Subjects: 16 male Sprague-Dawley Rats from Harlan (Indianapolis, IN) were individually housed on a 12 hr light/dark cycle. Water was provided continuously. Bodyweights were maintained at 85% of their free-feeding weight.



Apparatus: All sessions were conducted in standard conditioning chambers (Med PC, VT). An emitter/detector unit located within the receptacle was used to record head entries. A second emitter/detector unit that bisected the chamber was used to record chamber activity.



Drugs: Nicotine (pH of 7.0 ± 0.2), bupropion, cocaine, and GBR 12909 were purchased from Sigma. Atomoxetine was purchased from Tocris Cookson. Nicotine, cocaine and bupropion were dissolved in 0.9% saline. GBR 12909 and atomoxetine were dissolved in sterile water.

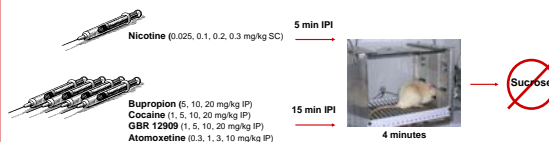
Procedures

Acquisition & Discrimination



*PreInjection to Placement Interval

Test Day



Dependent measure: dipper entries and activity counts before the first sucrose delivery or equivalent time on saline and test sessions (about 2 min)

Results

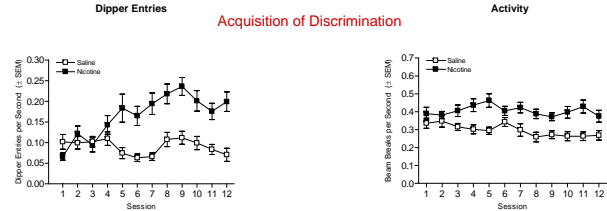


Figure 1. Dipper entries for rats (n=16) trained with 0.2 mg/kg nicotine. Rats readily acquired the discrimination between nicotine and saline over the 24 training sessions.

Figure 2. General chamber activity for rats (n=16) during acquisition. Rats were more active on nicotine sessions than on saline sessions.

Nicotine Dose Effect

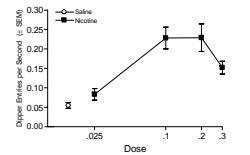


Figure 3. Dipper entries for generalization testing (i.e., nicotine dose effect). Responding was dose dependent. Conditioned responses were similar to saline at 0.025 nicotine and generalized to the training dose of 0.2 mg/kg nicotine at 0.1 mg/kg nicotine, but not at 0.3 mg/kg nicotine.

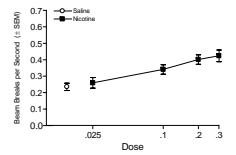


Figure 4. General chamber activity during generalization testing increased dose dependently.

Bupropion Substitution

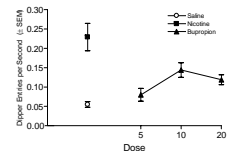


Figure 5. Dipper entries for substitution testing with bupropion. Bupropion (10 and 20 mg/kg) partially substituted for 0.2 mg/kg nicotine.

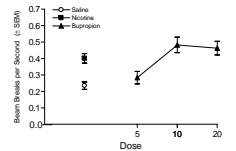


Figure 6. During substitution testing with bupropion, activity increased with 10 and 20 mg/kg bupropion increasing activity to levels consistent with the training dose of nicotine.

Cocaine, GBR 12909, and Atomoxetine Substitution

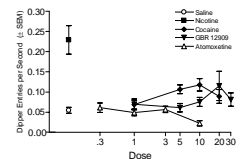


Figure 7. Dipper entries for substitution testing with cocaine, GBR 12909, and Atomoxetine. Cocaine (5 and 10 mg/kg) and GBR 12909 (20 mg/kg) partially substituted for 0.2 mg/kg nicotine. Atomoxetine did not substitute at any dose.

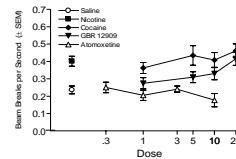


Figure 8. During substitution testing with cocaine and GBR 12909 activity increased dose dependently. Atomoxetine did not change activity regardless of dose.

Summary

•Acquisition

- Rats readily acquired the discrimination between 0.2 mg/kg nicotine and saline.
- When rats were given nicotine, they were more active than on saline.

•Nicotine Dose Effect

- Nicotine generalization was dose dependent.
- Additionally, activity counts increased as the dose of nicotine increased.

•Bupropion Substitution

- Bupropion partially substituted for the nicotine cue at doses that also increase motor activity (i.e., 10 and 20 mg/kg).

•Cocaine, GBR 12909, and Atomoxetine Substitution

- Dopamine reuptake inhibitors
 - Cocaine partially substituted for nicotine at 5 and 10 mg/kg, whereas activity was increased at 5, 10, and 20 mg/kg.
 - GBR 12909 partially substituted for nicotine at 20 mg/kg and increased motor activity at 5, 10, 20, and 30 mg/kg.

•Norepinephrine reuptake inhibitor

- Atomoxetine did not substitute for the nicotine cue, nor did it alter motor activity.

•Conclusion

- These substitution patterns suggest that the dopamine transporter contributes in part to nicotine's ability to function as a conditioned stimulus.

References

Besheer J, Palmatier MI, Metschke DM, & Bevins RA (2004) Nicotine as a signal for the presence or absence of sucrose reward: A Pavlovian drug appetitive conditioning preparation in rats. *Psychopharmacology*, 172, 108-117.

Bevins RA & Palmatier MI (2004) Extending the role of associative learning processes in nicotine addiction. *Behavioral and Cognitive Neuroscience Reviews*, 3, 143-158.

Wilkinson JI, Penrod RD, Murray JE, Bevins RA (2005) Conditioned stimulus effects of nicotine: bupropion substitution and the effects of sucrose concentration. Program No. 685.6 *Abstract Viewer/Itinerary Planner*, 35th Annual Society for Neuroscience Conference, DC.

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