Conditioned Stimulus Effects of Nicotine and Varenicline Substitution in Female Rats

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Introduction

Smoking is a worldwide health problem. Associative learning processes involving nicotine, the major addictive component of tobacco, likely contributes to the tenacity of the addiction and the high relapse rates (Bevins & Palmatier, 2004). Recent research in our lab has examined nicotine as an interoceptive CS for an appetitive US using a discriminated goal-tracking (DGT) task (Besheer et al., 2004). In this task, the conditioned response (CR) is approach directed at the location of previous reinforcement (i.e., termed goal-tracking).

The most recent non-nicotine pharmacotherapy approved by the FDA for smoking cessation is varenicline (Chantix®), a partial agonist for α4β2* nicotinic acetylcholine receptor (nAChR) and an agonist at α7* nAChRs (Mihalak et al., 2006). Varenicline has 'nicotine-like' stimulus effects. It partially substitutes for nicotine in the two-lever drug discrimination task in male rats (LaSage et al., 2007), and this substitution in male rats is complete in the DGT task (Reichel et al., 2010).

The present investigation extended research on the nicotine stimulus to female rats by studying the CS effects on nicotine and varenicline substitution for the nicotine CS using a DGT task.

Methods

- Female rats (N = 8) received sucrose (36 interspersed 4-s access) reinforced nicotine (0.4 mg base/kg) sessions intermixed with non-reinforced saline sessions.
- Once discrimination criteria were met, rats advanced to the extinction phase where they received repeated nicotine sessions without sucrose.
- Following extinction was reacquisition on the DGT task.
- After the discrimination was reestablished, we repeatedly assessed substitution of four doses of varenicline (0.1, 0.3, 1.0, and 3.0 mg/kg) for the nicotine CS.
- To assess whether estrous cycle affected extinction or varenicline substitution, repeated vaginal smears were taken and classified as proestrus, estrus, metestrus, and diestrus.

Results

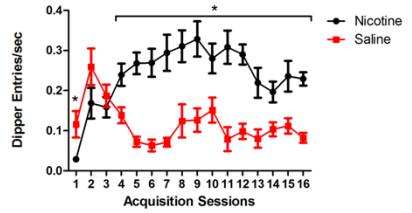

Figure 1: Female rats show an increase in the rate of head entries in the receptacle on reinforced nicotine sessions compared to non-reinforced saline sessions (dipper entry measure comes from the start of the session before any sucrose delivery).

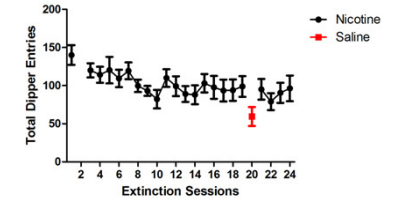

Figure 2: When sucrose was later withheld, responding decreased to saline levels (see Extinction Session 20).

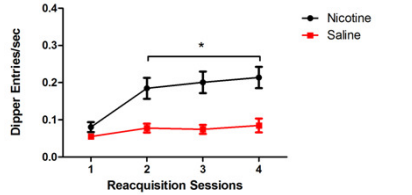

Figure 3: Reacquisition on the DGT task.

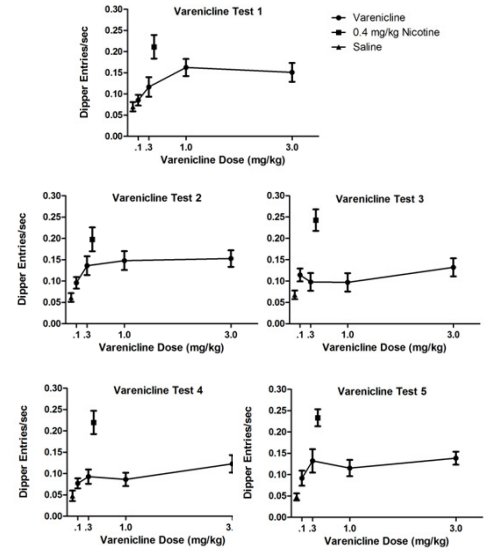

Figure 4: Female rats received five sets of varenicline tests in order to obtain data from each stage of estrous for each varenicline dose for each rat. At all doses, varenicline evoked higher responding compared to saline. Data were analyzed using advanced multilevel longitudinal models to access estrous effects on responding over repeated test sets.

Figure 5: A female rat goal-tracking. The rat is entering her head into the dipper receptacle were the sucrose had previously been presented.

Conclusions

- Nicotine acquired the ability to evoke a goal-tracking CR in females
- The CR (rate of head entries) decreased across extinction sessions when sucrose was no longer available.
- In substitution tests, varenicline evoked conditioned responding, indicating shared stimulus effects with the nicotine CS.
- Multilevel analyses in which day was modeled as nested within rat showed that estrous cycle had no effect on the progression of extinction or CR magnitude in varenicline testing.
- The present study is the first demonstration of nicotine's ability to serve as a CS in female rats, and that varenicline shares stimulus effects with the nicotine CS.

References

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