Conditioned Stimulus Effects of Nicotine: The Role of Nicotine Dose during Extinction

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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 conditioned stimulus (CS) for an appetitive unconditioned stimulus (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).

Using the DGT, task Reichel et al. (2010) found that the conditioned responding evoked by the nicotine CS can be attenuated by repeated non-reinforced (i.e., extinction) presentations of ligands (e.g., varenicline and nornicotine) that shares interoceptive stimulus properties with nicotine. We refer to this attenuated conditioned responding as "transfer of extinction learning".

To understand the nature of the interoceptive stimulus effects of nicotine and related extinction processes, we examined the extent to which extinction learning with nicotine doses other than the training dose transferred back to the trained nicotine CS.

Method

- Rats (N=224) received sucrose (36 interspersed, 4-s access) reinforced nicotine (0.2 or 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 either 0.05, 0.075, 0.1, 0.2, 0.4, 0.6 mg/kg nicotine, or saline during repeated 20-min sessions (no sucrose was available); nicotine doses used have been shown to fully (0.1, 0.2, and 0.4) or partial substitute (0.05 and 0.075, and 0.6) for the CS effects of nicotine (0.2 and 0.4 mg/kg).
- The day after extinction, all rats underwent transfer testing in which they received their training dose of nicotine.
- Full transfer was declared if test doses differed significantly from saline (^), but not from the nicotine training dose.
- Partial transfer was declared if test doses differed significantly from saline (^) and the nicotine training dose (*).

Discrimination Training

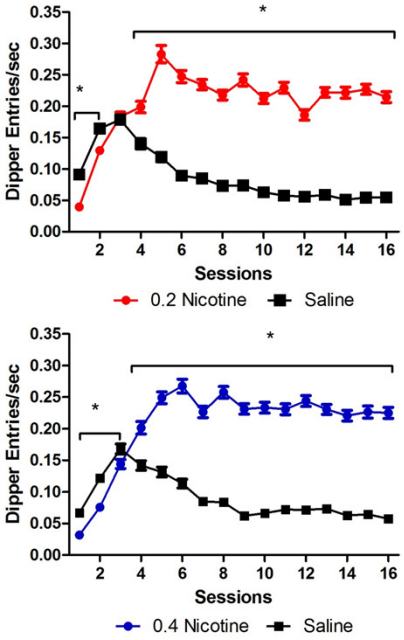

Figure 1: Rats show an increase in the rate of head entries in the receptacle on reinforced nicotine sessions compared to non-reinforced saline sessions (dipper entry measure comes from the start of the session before any sucrose delivery). *Significantly different.

Extinction Training

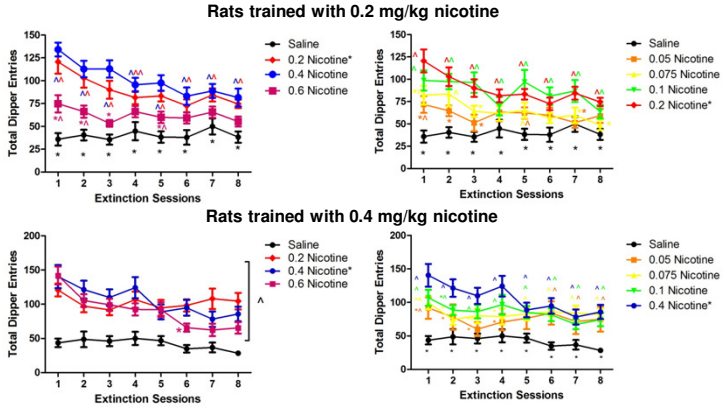

Figure 2: When sucrose was withheld, responding (total number of dipper entries) declined for all nicotine dose. This was the case whether rats were trained with 0.2 mg/kg (top panels) and 0.4 mg/kg (bottom panels) nicotine. Significantly different from nicotine(*); saline(^)

Transfer Test

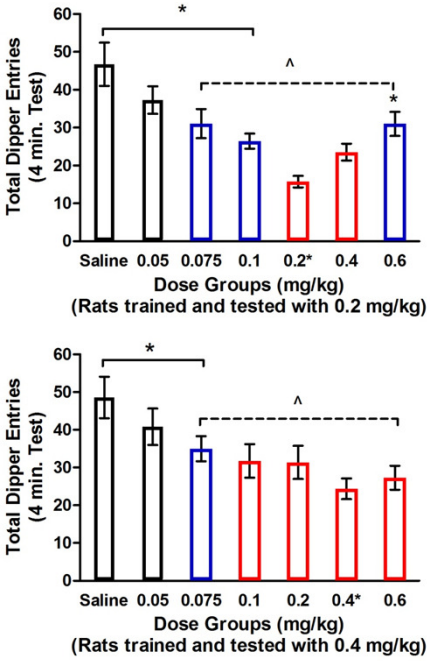

Figure 3: Greater transter ot extinction was observed in rats trained on the 0.4 nicotine CS than those trained on the 0.2 nicotine CS. Rats tested with 0.4 nicotine showed full transfer (red) on more doses from extinction, whereas rats trained on 0.2 nicotine showed more partial transfer (blue) on extinguished doses. Significantly different from nicotine(*); saline(^).

Conclusion

Rats trained with 0.4 mg/kg nicotine showed full transfer of extinction learning with doses known to substitute to that nicotine CS (0.1, 0.2, and 0.6 mg/kg), while partial transfer was observed for the dose known to partially substitute (0.075 mg/kg).

Conversely, rats trained with 0.2 mg/kg nicotine showed full transfer of extinction learning only with 0.4 mg/kg, whereas 0.075, 0.1, and 0.6 showed partial transfer.

Nicotine, when acting as an interoceptive CS, is a complex polymodal event and its elements may reflect the neurobiological process on which the drug acts directly or indirectly (Bevins & Murray, 2011).

The differences observed in the transfer of extinction tests between the two nicotine training doses (0.2 and 0.4 mg/kg) maybe due to different neurobiological elements that are activated when other nicotine doses are presented during extinction.

References

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