

Nicotine-like discriminative stimulus effects of e-liquids in a vaping model in male and female mice

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Conflict of Interest?



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Tobacco Addiction: A Preclinical Perspective

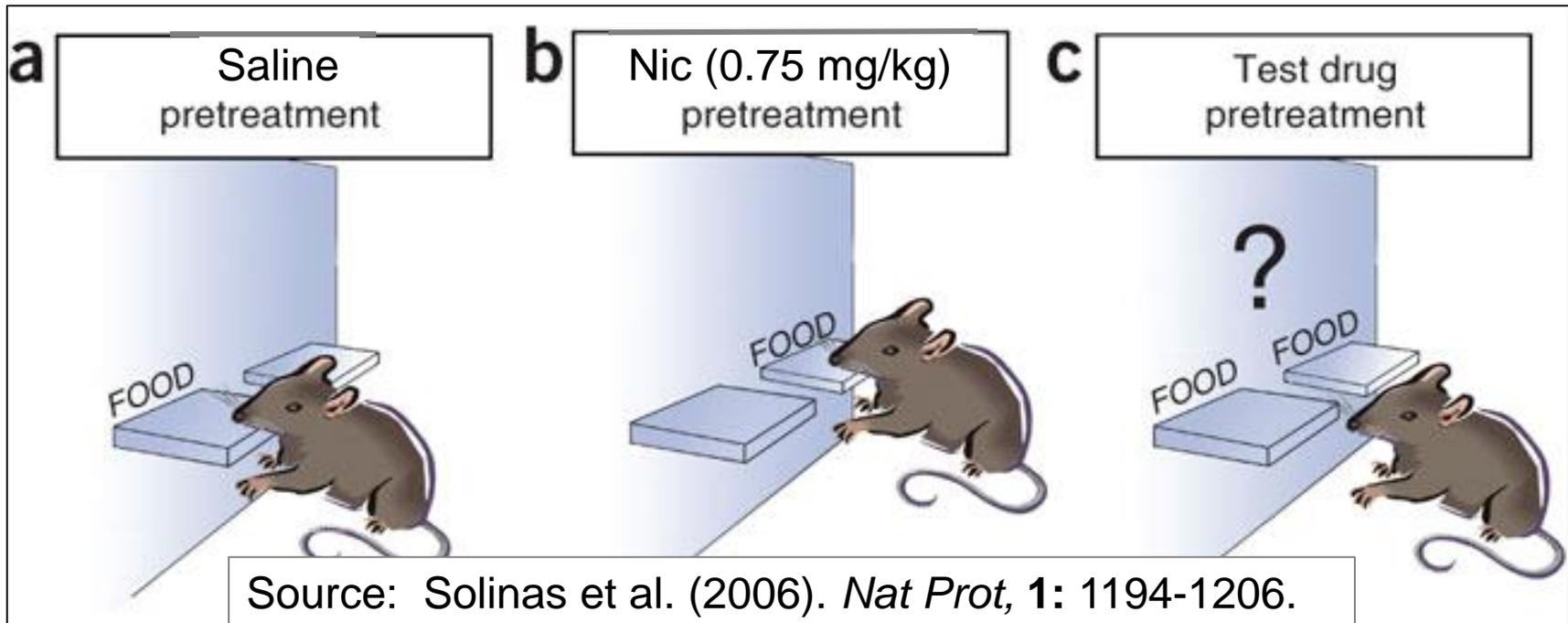
- **Nicotine is the primary driver of tobacco addiction.**
 - Basis for FDA's emphasis on nicotine in regulatory efforts.
 - Foundational principle of most preclinical research on tobacco addiction.

- **Tobacco / nicotine routes of administration.**
 - In humans, smoking and vaping are most common.
 - In preclinical research, injection (s.c., i.v.) is most common.

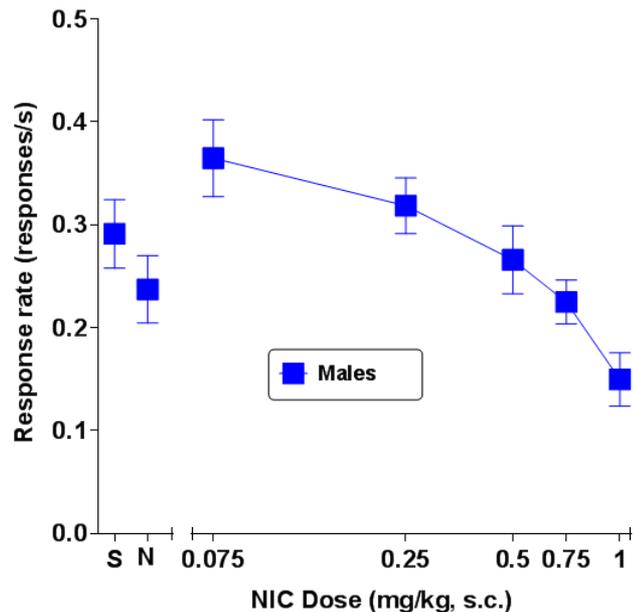
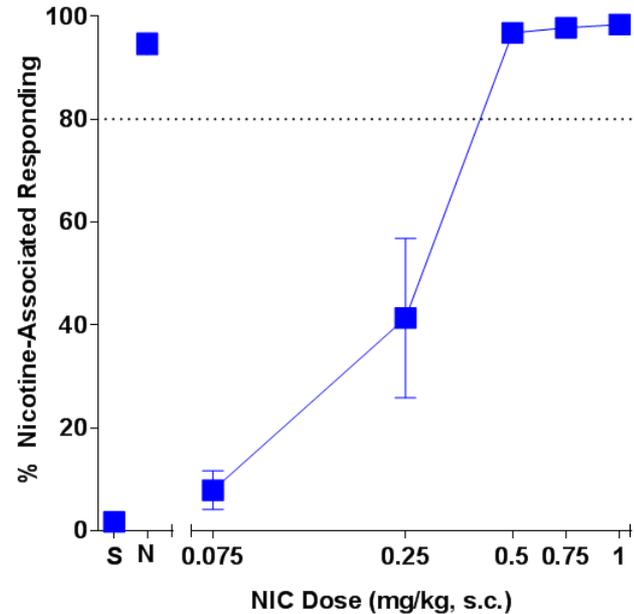
- **Animal models of nicotine's abuse-related effects.**
 - Self-Administration - Reinforcing effects.
 - Drug Discrimination - Subjective effects.

Nicotine Discrimination

- Adult male and female C57/Bl6 mice
- Nicotine (0.75 mg/kg) vs. Saline
- Subcutaneous (s.c.) injection; 10 min pre-session
- FR-10 for food reinforcer
- 15-min sessions

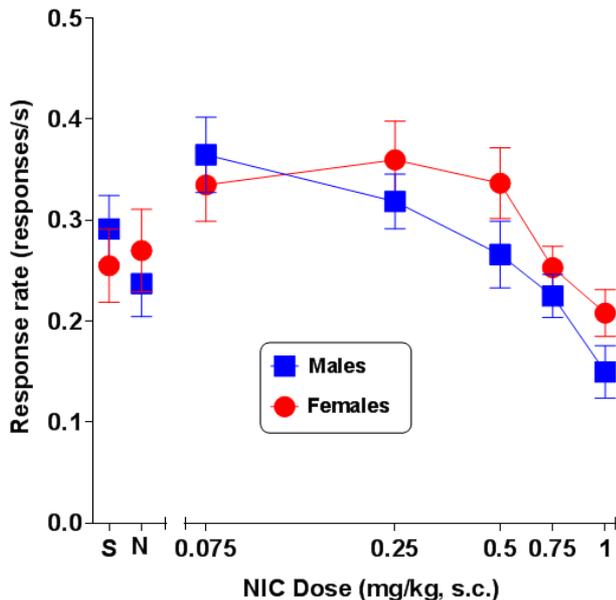
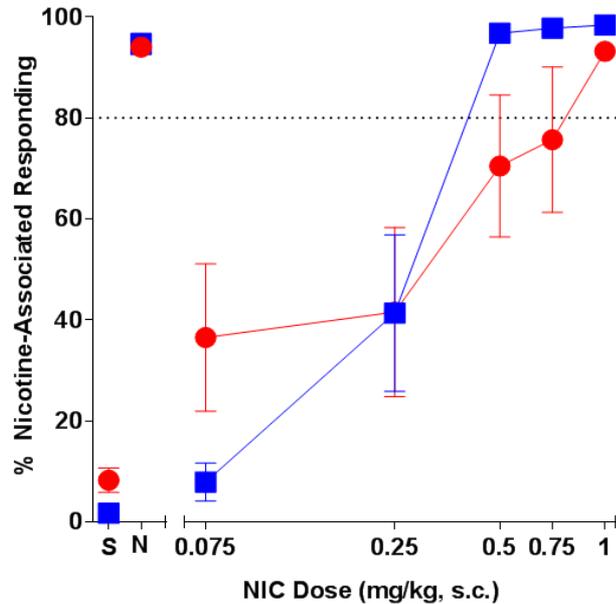


Effects of Injected (s.c.) Nicotine in Male Mice



- Male mice exhibit dose-dependent substitution for the 0.75 mg/kg nicotine training dose.
- Lowest dose at which full substitution ($\geq 80\%$ nicotine-appropriate responding) is observed is 0.5 mg/kg.
- ED50 (male) = 0.28 mg/kg (95% CI: 0.20-0.30)

Assessment of Sex Differences in S.C. Nicotine in Mice

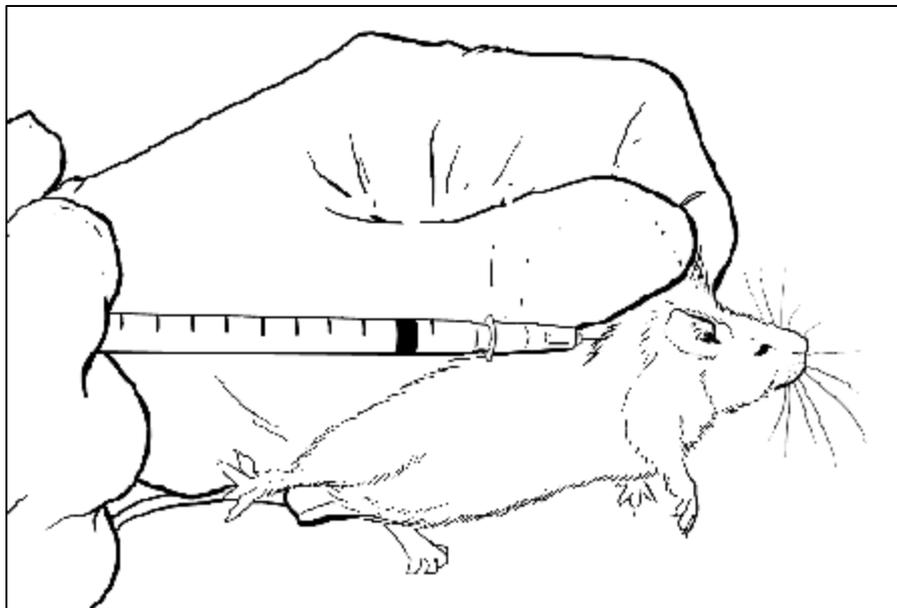


- Females also show dose-dependent substitution for the 0.75 mg/kg nicotine training dose.
- Lowest dose at which full substitution ($\geq 80\%$ nicotine-appropriate responding) is observed is 1 mg/kg.
- Females exhibit greater variability in nicotine-appropriate responding.
- ED50 (female) = 0.29 mg/kg (95% CI: 0.22 -0.40)

Improvement of Translation

- Investigation of injected nicotine's effects in animals has provided valuable data on brain mechanisms involved in tobacco addiction

HOWEVER

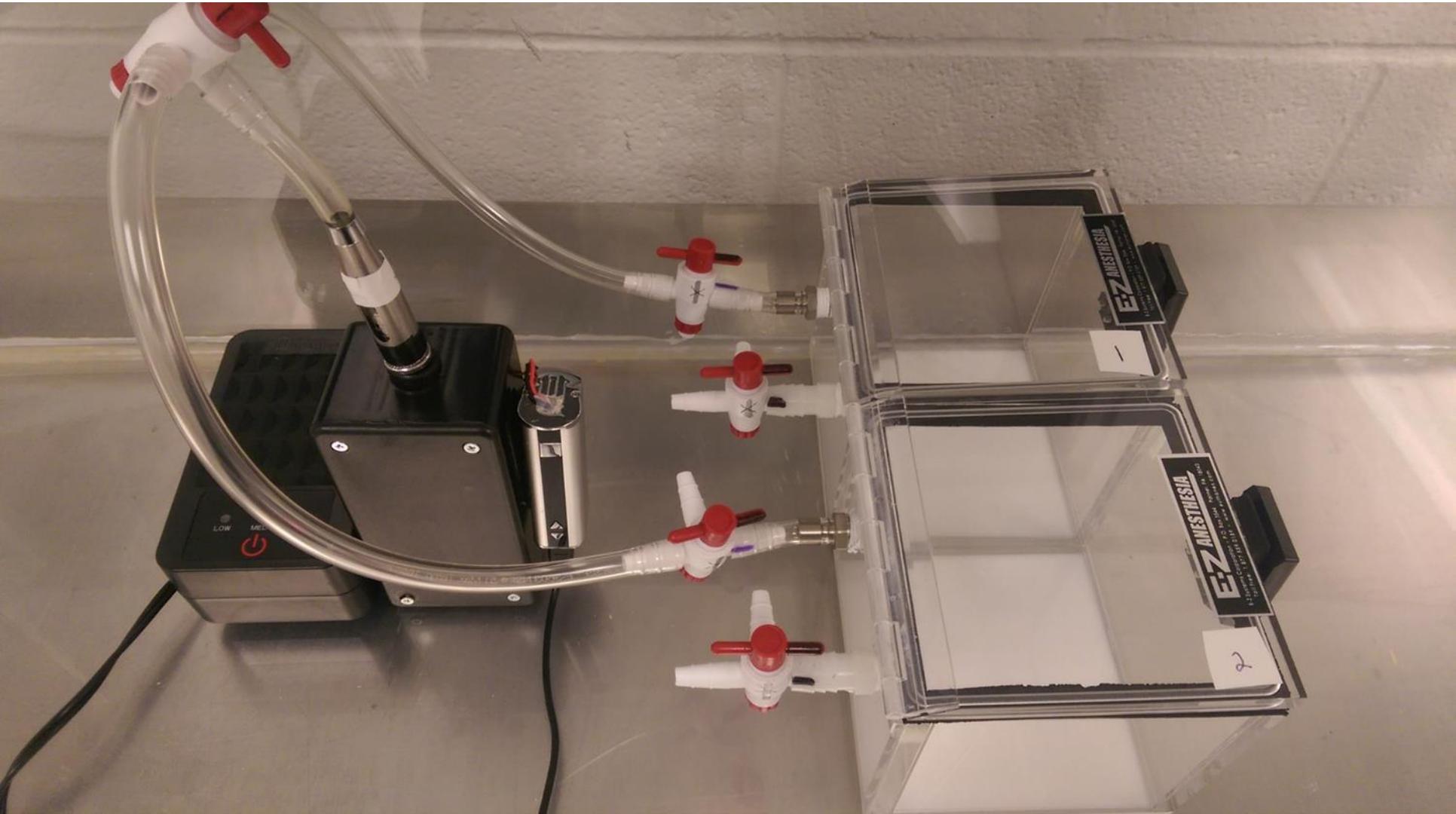


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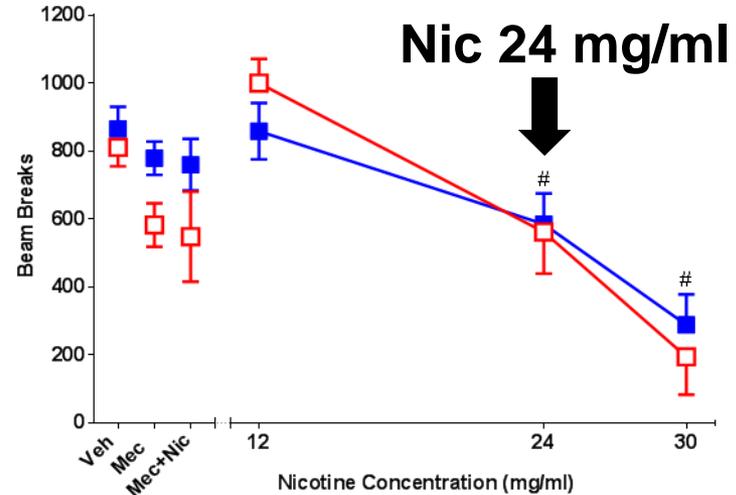
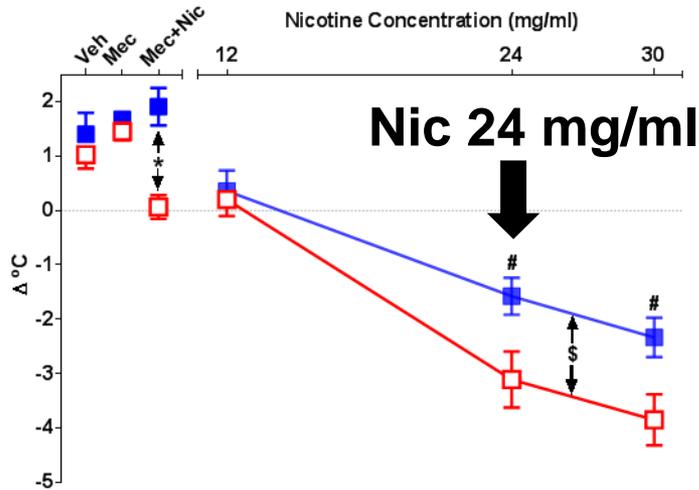
- Translational aspects of aerosol exposure:
 - Presence of chemosensory stimuli that is also associated with vaping in humans.
 - Improved ability to investigate flavors.
 - Heating may alter chemical composition of compounds.

E-Cigarette Aerosol Mouse Exposure Chambers

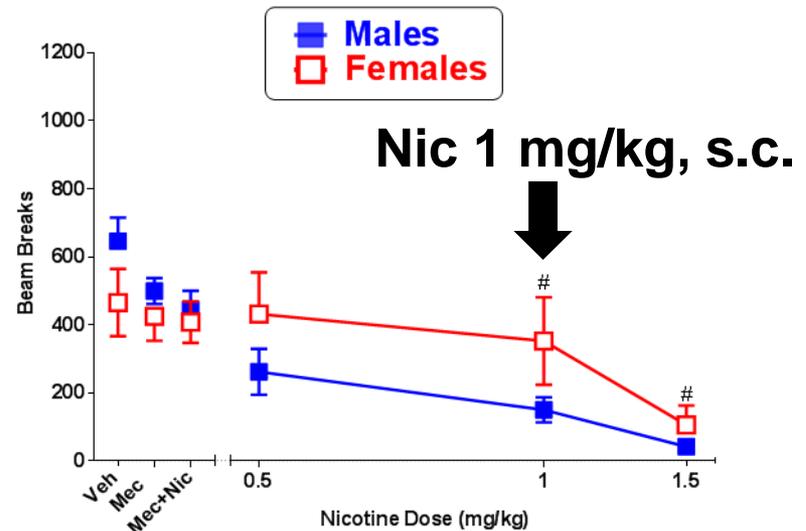
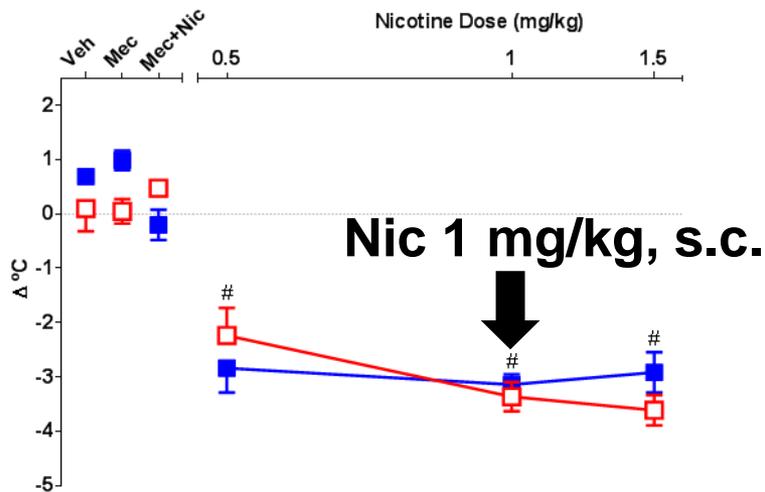


Nicotine's Effects: Aerosol vs. Injected

Aerosol Exposure

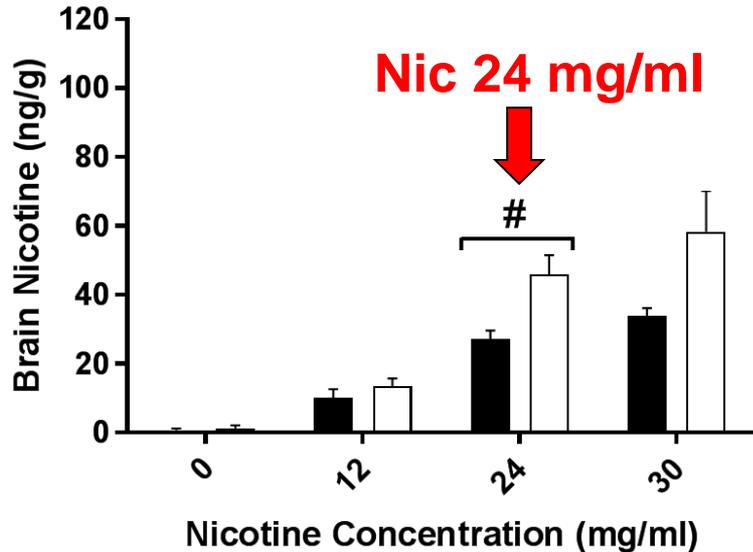


S.C. Injection



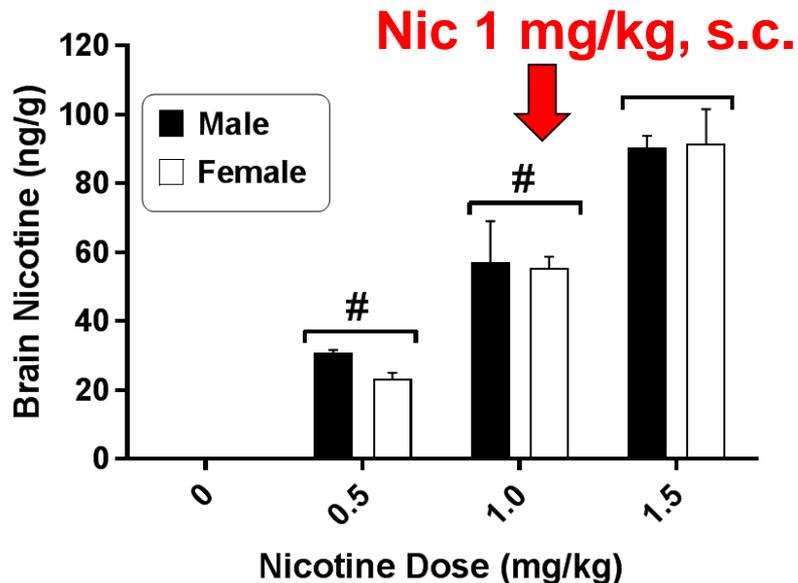
Adapted from: Lefever et al. (2017). *Drug Alcohol Depend*, **172**: 80-87.

Nicotine in Brain



➤ Aerosolized nicotine reaches the brain.

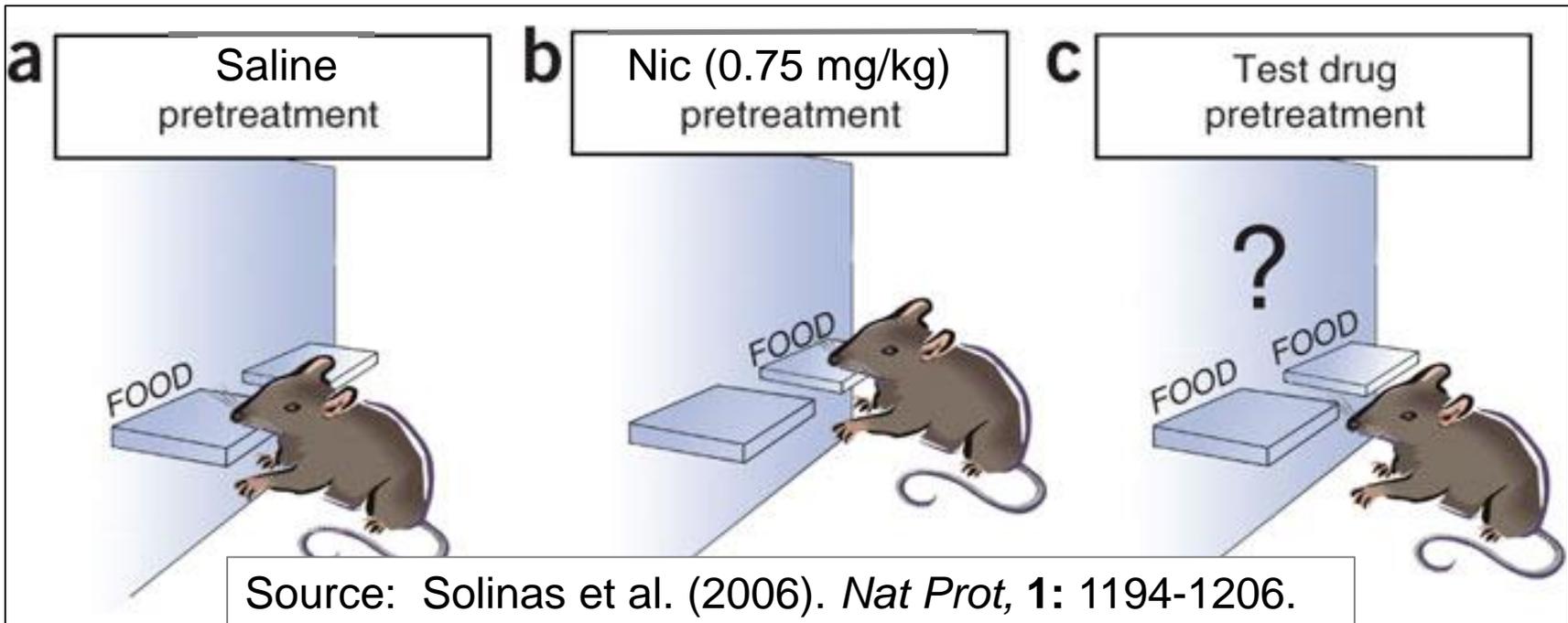
➤ Concentrations of nicotine in the brain after aerosol exposure are comparable to concentrations observed following behaviorally active s.c. doses.



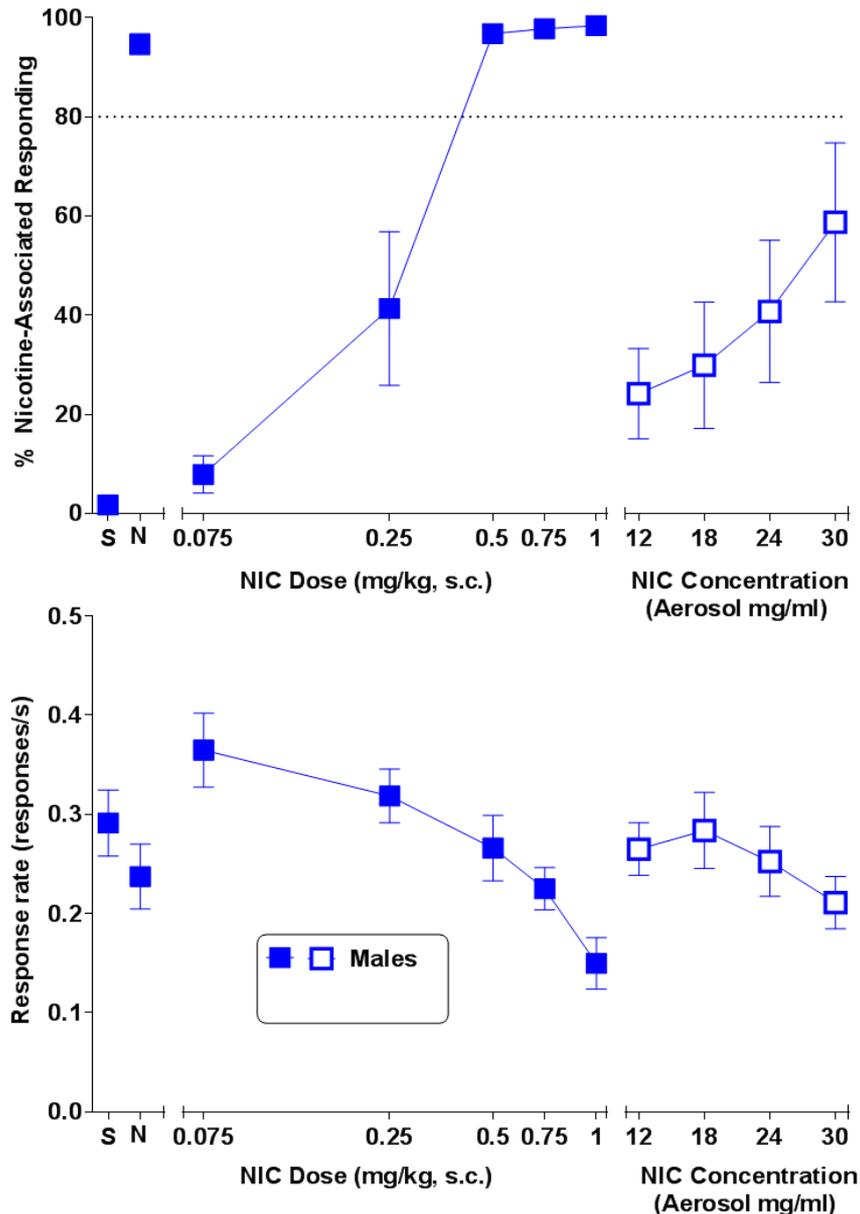
Adapted from: Lefever et al. (2017). *Drug Alcohol Depend*, **172**: 80-87.

Substitution of Aerosolized Nicotine in Discrimination

- Adult male and female C57/Bl6 mice
- Nicotine (0.75 mg/kg) vs. Saline
- Commercially available, non-flavored nicotine-containing e-liquid (purchased from Avail, Richmond, VA)
- FR-10 for food reinforcer
- 15-min sessions

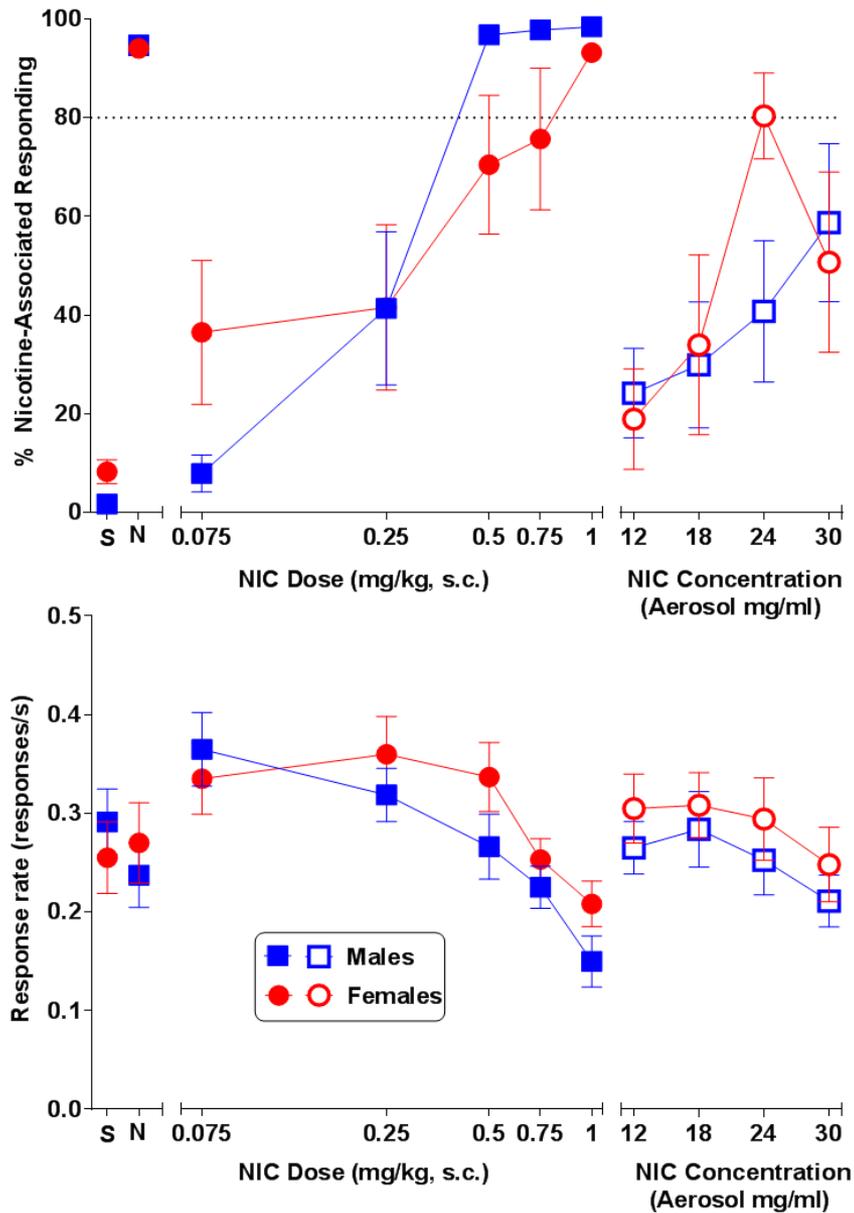


Nicotine Substitution (Injected vs. Aerosol) in Male Mice



- Aerosolized nicotine dose-dependently increased responding on the nicotine-associated aperture in male mice.
- At concentrations of nicotine up to 30 mg/ml/tank, full substitution was not observed.

Sex Differences in Effects of Aerosolized Nicotine in Mice



- Aerosolized nicotine also increased responding on the nicotine-associated aperture in female mice up to a concentration of 24 mg/ml/tank.
- Full substitution was observed at the 24 mg/ml/tank concentration in females.
- At a higher nicotine concentration (30 mg/ml/tank), responding on the nicotine-associated aperture decreased in females.

Summary / Conclusions

- These experiments represent the first examination of sex differences in nicotine's discriminative stimulus effects in mice.
- The finding that s.c. nicotine fully substitutes in male mice at lower doses than in female mice is consistent with previous work in humans showing that men are more sensitive to nicotine's discriminative stimulus effects than women (Perkins, 1999).
- Initial results of tests with exposure to aerosol nicotine in "vaping" model are promising, in that aerosol nicotine has been shown to reach the brain and to produce pharmacological and behavioral effects that have been observed following injection.
- Further development of the model is needed, particularly with respect to dose estimation, albeit inability to determine definitive dose is an issue that this model shares with human research.

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