Capturing cognitive deficits associated with nicotine withdrawal in rats.

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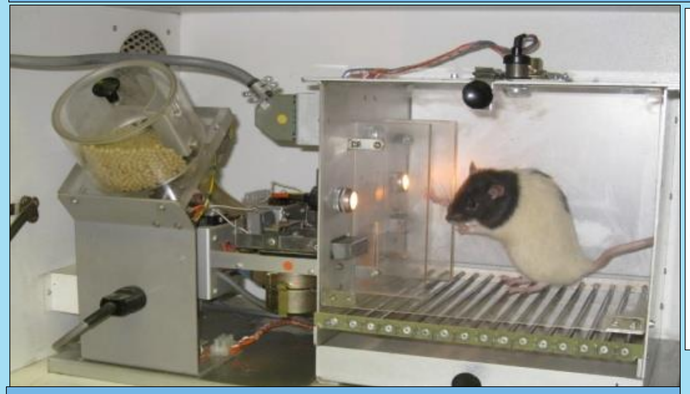
Introduction:

- Nicotine is the active compound in tobacco that leads to dependence (1).
- Nicotine and varenicline, a nicotinic partial agonist, target the cholinergic system in the brain. Activation of nicotinic receptors are linked to cognitive flexibility, attention and higher executive functions (2).
- Cognitive flexibility can be measured using a probabilistic reversal learning (PRL) task in rodents (3).
- Reduction in cognitive flexibility from nicotine withdrawal may account for difficulty in quitting tobacco smoking which may result in high relapse rates (4).

Aim: To examine clinically effective smoking cessation aids, nicotine replacement therapy or varenacline.

Results:

- Nicotine, in a dose of 0.2mg/kg, delayed the onset of cognitive deficits associated with nicotine withdrawal, as seen by maintenance of correct responses, reversals and decreased increase of latency and omissions, as illustrated in Figures 1-4.
- Varenicline produced a dose-related restoration of the deficits, which mitigated cognitive deficits associated with nicotine withdrawal. This was observed on the correct responses, reversals and decreased increase of latency and omissions, as illustrated on Figures 1-4.
- Rats showed decreased performance across all measures of the PRL task which were time dependent when withdrawn from nicotine.



Apparatus used in experiment

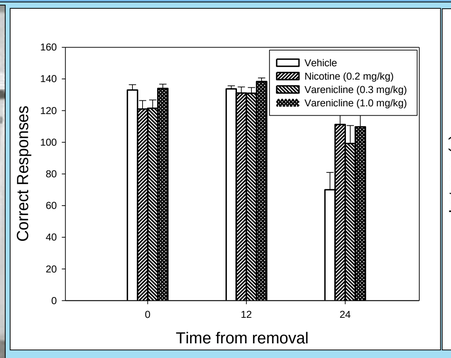


Figure 1: Effects on correct responses during nicotine withdrawal following administration of vehicle, nicotine and varenicline at 0.3 & 1.0 mg/kg at times 0, 12 and 24 hours abstinence.

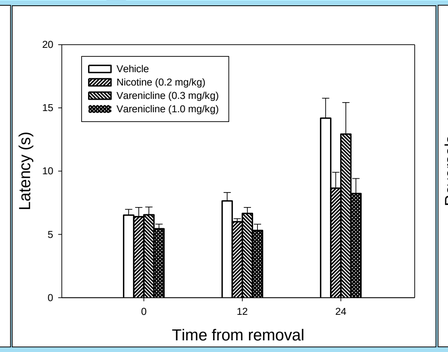


Figure 2: Effects on latency to perform trials during nicotine withdrawal following administration of vehicle, nicotine and varenicline at 0.3 & 1.0 mg/kg at times 0, 12 and 24 hours abstinence.

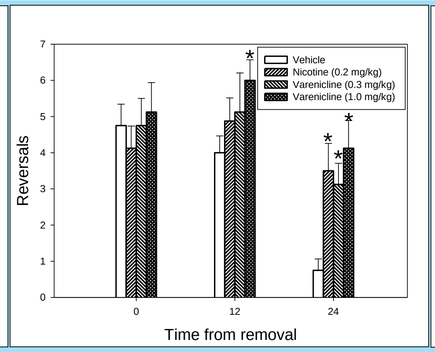


Figure 3: Effects on reversals during nicotine withdrawal following administration of vehicle, nicotine and varenicline at 0.3 & 1.0 mg/kg at times 0, 12 and 24 hours abstinence.

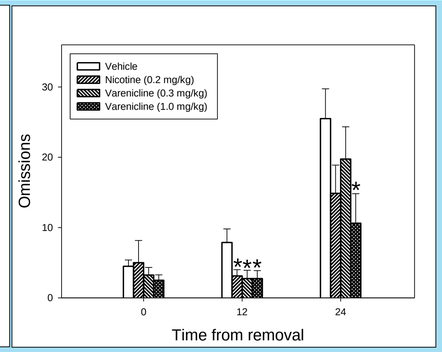


Figure 4: Effects on omissions of trials during nicotine withdrawal following administration of vehicle, nicotine and varenicline at 0.3 & 1.0 mg/kg at times 0, 12 and 24 hours abstinence.

Methods:

PRL task:

Subjects: 32 male Lister hooded rats maintained at 90% free feeding weight.

Two lights were presented on each trial and the correct hole reversed after eight correct trials.

A nose poke in the correct hole resulted in a food pellet reward on 70% of the trials.

Retrieval of the food pellet initiated the next trial until 40 minutes or 199 trials were complete.

Conclusion:

- The results highlight the sensitivity of the PRL task in providing a translational model of deficits in cognition reported by tobacco smokers.

Withdrawal from nicotine demonstrated impairment in the PRL task. Such deficits on cognitive flexibility could be restored by pre-treating the rats with a dose of nicotine or varenicline.

Thus, varenicline may be an effective cessation aid by targeting cognitive deficits rather than alleviating the physical aspects withdrawal.

References: (1) Mansvelder H.D., Mertz M., Role L.W. (2009) Seminars in Cell & Developmental Biology, 432-440. (2) Zhang H, Kranzler HR, Poling J, Gelernter J. (2010) Neuropsychopharmacology, 2211-24. (3) Gottfried JA. (2011) Neurobiology of Sensation and Reward, Chapter 16.4. (4) Miyata H. (2013) Japanese Journal of psychopharmacology, 191-197.