Pharmacological Evaluation of Potential Therapeutics on Smoking Cessation: Behavioral and Computational Analyses

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Qing Chang, Wenzhong Min, Adrian C. Hackett, Michael T. Lang, Mukesh Bansal and Taleen Hanania*

PsychoGenics Inc., Paramus, NJ, USA

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Introduction

Tobacco use causes serious health problems and huge economic cost. Pharmacological intervention is an important employment to quit smoking. Varenicline (Chantix) is currently approved as a smoking cessation treatment, but more effective smoking cessation treatments with a superior profile to the current standard are needed.

In this project we sought to establish rodent models of smoking cessation and tested 18 compounds and / or compound combinations with diverse mechanisms of action to determine their efficacy as treatment for smoking cessation. Based on the results of the behavioral studies and biological informatics, we ranked each compound's effectiveness. Here we report some important findings using two most important models in studies of drug abuse liability: nicotine self-administration (SA) and intravenous drug discrimination (DD).

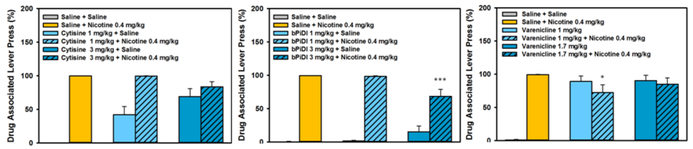
Methods

Drug discrimination assesses the degree of overlap of interoceptive stimulus effects with relevant comparison drugs. Self-administration determines a compound's reinforcing properties.

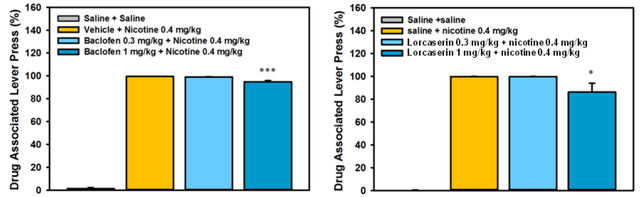
Young adult, male Sprague-Dawley rats from Envigo were used. Training and test took place in operant chambers within sound-attenuating cubicles equipped with an exhaust fan (Med Associates, VT). Each chamber contained two levers situated on one wall of the chamber. The detailed methods of DD and SA can be found in publications including ours.

A within-subject design in which each rat received all treatments was applied with a Latin square test schedule. All rats demonstrated stable baseline behavior prior to drug testing.

1. Effects of Compounds in Nicotine Discrimination

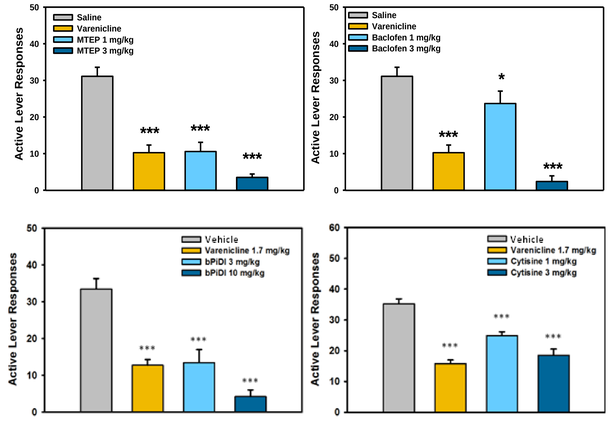


❖ Effects of the nicotinic receptor ligands Varenicline, Cytisine and bPiDI on both substitution and disruption of nicotine discrimination. Asterisks in the figures show comparisons with saline-nicotine 0.4 mg/kg treatment in disruption studies (bars with stripe vs. original bar). Data are presented as mean + SEM. *: P<0.05; ***: P<0.001).



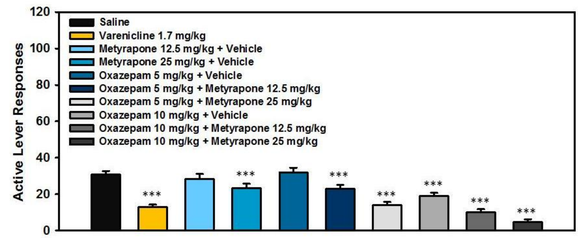
❖ Non-nicotinic compounds Baclofen (a $GABA_B$ receptor agonist) and Lorcaserin (a 5-HT_{2C} receptor agonist) also showed effectiveness in disrupting nicotine discrimination. (*: P<0.05; ***: P<0.001 compared with nicotine 0.4 mg/kg treatment).

2. Effects of Compounds on Nicotine Self-administration



❖ Compounds bPiDI , Cytisine, Lorcaserin and Baclofen showed efficacy in reducing nicotine self-administration. Varenicline 1.7 mg/kg was used as positive control in the SA studies. Data are presented as mean + SEM. *: P<0.05; ***: P<0.001 as compared with saline-treated rats.

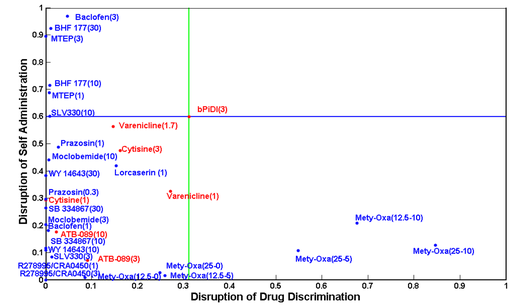
3. Drug Combinations on Nicotine Self-administration



❖ The combination of Metyrapone (a corticosteroid synthesis blocker) x Oxazepam (a benzodiazepine) showed obvious effects in inhibiting nicotine self-administration in multiple doses. Data are presented as mean + SEM. *: P<0.05; ***: P<0.001 as compared with saline-treated rats. Varenicline 1.7 mg/kg was used as positive control.

4. Efficacy Scores of the Compounds

Besides behavioral tests, we also used bio-informatics tools to develop a system which derive smoking cessation scores of the tested compounds and compound combinations. All tested compounds at various doses (compound/dose pair) are plotted in two-dimensional phase space where two dimensions represent efficacies from self-administration and drug discrimination assay (SA-DD). The raw data of SA efficacies are the indexes of blocking of self-administration, and the raw data of DD efficacies are the indexes of disruption of nicotine discrimination.



❖ Relative potency of each compound are plotted on the two-dimensional phase space. In each dimension, 0 means no effects on nicotine self-administration or no effects on nicotine discrimination (disruption approach); 1 means entire blocking of self-administration or entire blocking of nicotine discrimination . Compounds in red represent their properties of nicotinic receptor ligands.

Summary

➢ Among the compounds we have studied, Cytisine and bPiDI seems to be the best candidates for smoking cessation. Both compounds displayed efficacy in substituting for nicotine in DD model, caused disruption of nicotine DD as well showed efficacy in suppressing nicotine SA. In addition Baclofen and MTEP also showed efficacy in suppressing nicotine DD and/or SA

➢ Efficacy of combinations of Metyrapone x Oxazepam in inhibiting nicotine SA is very obvious. This is especially encouraging because the two compounds are clinically used drugs.

➢The approach to use bioinfomatics tools to obtain efficacy scores is important. This method evaluates the relative position with respect to the best possible achievable efficacy and also to compare the efficacy with other compounds. Although it is still in its prototype, we are hopeful it can be a validated evaluation system for drug screening in the future.

Acknowledgement

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