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Bupropion–varenicline interactions and nicotine self-administration behavior in rats

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ABSTRACT

Varenicline and bupropion each have been shown to significantly improve cessation of tobacco addiction in humans. They act through different mechanisms and the question about the potential added efficacy with their combined used has arisen. Preclinical animal models of nicotine addiction can help with the evaluation of this combined approach and what dose combinations of varenicline and bupropion may be useful for enhancing tobacco cessation. In this study, we investigated the interacting dose–effect functions of varenicline and bupropion in a rat model of nicotine self-administration. Young adult female Sprague–Dawley rats were allowed to self-administer nicotine in 1-h sessions under an FR1 reinforcement schedule. Varenicline (0.3, 1. 3 mg/kg) and bupropion (8.33, 25, 75 mg/kg) were administered alone or together 15 min before each session. The vehicle saline was the control. Higher doses of each drug alone reduced nicotine self-administration compared to control with reductions of 62% and 75% with 3 mg/kg varenicline and 75 mg/kg bupropion respectively. Lower dose varenicline which does not by itself reduce nicotine self-administration, significantly augmented bupropion effects. The 0.3 mg/kg varenicline dose combined with the 25 and 75 mg/kg bupropion doses caused greater reductions of nicotine self-administration than either dose of bupropion given alone. However, higher dose varenicline did not have this effect. Lower dose bupropion did not augment varenicline effects. Only the high bupropion dose significantly enhanced the varenicline effect. Likewise, combining 1 mg/kg varenicline with 75 mg/kg bupropion reduced self-administration to a greater extent than either dose alone. These results demonstrate that combination therapy with varenicline and bupropion may be more beneficial than monotherapy with either drug alone.
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1. Introduction

Tobacco use remains the single largest preventable cause of disease and premature death worldwide (CDC, 2014). Current treatments to promote tobacco cessation are only modestly effective. There is much room for improvement. There are currently two pharmacological therapies approved by the Food and Drug Administration (FDA) for tobacco addiction that do not contain nicotine: bupropion and varenicline (FDA, 2012). Bupropion, a norepinephrine/dopamine reuptake inhibitor (NDRI) with nicotinic acetylcholine receptor (nAChR) inhibitory activity (Lukas et al., 2010), was originally developed as an atypical antidepressant medication, but was later approved by the FDA for use as a smoking cessation aid in 1997. Varenicline is a partial agonist at α4β2*, α6β2* and α3β4 nAChRs, and a full agonist at α7 nAChRs (Bordia et al., 2012; Mihalak et al., 2006; Rollema et al., 2007); in 2006, varenicline became the first non-nicotine therapeutic to be approved by the FDA specifically to treat tobacco addiction. Both of these drug treatments have been shown to reduce cravings and tobacco use in human subjects, and both also reduce nicotine self-administration in rodent models of nicotine addiction (Le Foll et al., 2012; O'Connor et al., 2010; Rauhut et al., 2003, 2005; Reus et al., 2007). However, although the initial abstinence rates for each treatment are high, the rates of abstinence after one year of treatment were found to be only around 15% for bupropion and 23% for varenicline (Jorenby et al., 2006). While these numbers were shown to be significantly better than placebo treatment, there is a clear need to develop better treatment strategies for tobacco addiction.

There has recently been increased interest in the idea of employing varenicline and bupropion as a combination therapy for smoking cessation. It has previously been shown that combination therapy with bupropion and the nicotine patch produces more favorable outcomes than the nicotine patch alone (Jorenby et al., 1999), and that augmenting nicotine replacement therapy (NRT) with bupropion reduces failure rates for smokers who do not decrease smoking by more than 50% in the two weeks preceding their target quit date (Rose and Behm, 2013). Similar results have been found regarding varenicline and NRT (Koegelenberg et al., 2014). The initial efficacy results for varenicline/bupropion combination therapy in humans have been promising for shorter-term abstinence rates, if somewhat mixed for prolonged abstinence at 52 weeks (Ebbert et al., 2009, 2014; Rose and Behm, 2014).

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In addition, these studies have shown that combination therapy with varenicline and bupropion resulted in a reduction in post-cessation weight gain among study participants; weight gain being a commonly reported reason for the continuance of tobacco use (Veldheer et al., 2014).

To date, combination treatment with varenicline and bupropion has not been evaluated in preclinical animal models of nicotine addiction. Animal models can be helpful in clearly determining optimal dose combinations in a relatively economical way. The different mechanisms of action of each drug make them ideal candidates for use as a combination therapy for tobacco addiction, both to reduce craving for nicotine as well as to alleviate the somatic and affective symptoms of tobacco withdrawal. Indeed, both drugs have previously been shown, when administered individually, to reduce nicotine self-administration in rats and reduce withdrawal symptoms associated with nicotine (Cryan et al., 2003; Igari et al., 2014; Malin et al., 2006; Paterson et al., 2007). It is currently unknown whether the effects of a combination of varenicline and bupropion would be additive, synergistic, or time-course dependent and what the optimal dose combinations of these drugs would be. Previously we found that the nicotinic partial agonist sazetidine-A has a more prominent effect reducing nicotine self-administration later in the session {Johnson et al., 2012). In contrast, we found that the monoamine uptake inhibitor amitifadine had greater efficacy during the beginning of the test session (Levin et al., 2012). Therefore, we hypothesized that the nicotinic partial agonist varenicline would decrease nicotine self-administration preferentially during the later part of the session while the monoaminergic reuptake inhibitor bupripion would preferentially decrease nicotine self-administration during the initial part of the session. Nonetheless, it is a possibility that, given in combination, each drug may produce efficacious results at lower doses than would be needed if each drug were given individually. It remains to be seen whether this is indeed the case the rodent model.

This study was conducted to determine the interactive effects of combination treatment with varenicline and bupropion on nicotine self-administration behavior in rats. Each drug was administered both individually and in a series of combinations before self-administration sessions began to evaluate these effects. It was hypothesized that administration of higher doses of each compound would reduce nicotine self-administration in the rats, while lower doses given in combination would augment this reduction. It was also hypothesized that the effects of each drug would be time-course dependent throughout each session. The doses chosen for each drug were determined based on the extant literature and include doses that have been reported to have no undesirable off-target effects, such as suppression of food self-administration (George et al., 2011; Liu et al., 2008; O'Connor et al., 2010; Rauhut et al., 2003, 2005; Rollema et al., 2007). Also included in the study were sub-threshold doses that fall below those which have typically been observed to reduce nicotine self-administration. The results of this study could inform further research into the viability of combination therapy with varenicline and bupropion for smoking cessation treatments.

2. Materials and methods

2.1. Subjects

Young-adult female Sprague–Dawley rats (Charles River Labs, Raleigh, NC, USA) were used in the study. At the time of catherization surgery, the rats were 60 days old and had an average weight of 173 g. The rats were singly housed at Duke University in a vivarium adjacent to the testing facility. Rats were housed singly to prevent catheter harness damage occurring by cage-mates. The animals were housed in standard laboratory conditions and kept on a reverse 12:12 h light/dark cycle. A total of 13 animals were used in the study. All testing was performed during the animals' "active" (dark) phase of the cycle. While in their homecage environment rats were allowed unlimited access to fresh water and once behavioral testing began were kept on a restricted diet of standard rat chow so that each rat's body weight was approximately 85% of ad libitum feeding levels. All testing procedures in this study were conducted according to AAALAC guidelines and approved by the Duke University Animal Care and Use Committee.

2.2. Drugs

Nicotine hydrogen tartrate was purchased from Sigma-Aldrich (St. Louis, MO, USA). Varenicline tartrate was purchased from Abcam Inc. (Cambridge, MA, USA), and bupropion HCl was purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). All compounds were dissolved in 0.9% sterile saline (Hospira Inc, Lake Forest, IL, USA). For combined drug treatments of varenicline and bupropion, both compounds were dissolved together in the same sterile saline solution. Doses for each solution were injected subcutaneously (s.c.) in a volume of 1 ml/kg of body weight.

2.3. Surgical procedures

Catheters were surgically implanted into the right jugular veins of each animal in the manner as previously described (Hall et al., 2014). Briefly, animals were anesthetized with a combination of ketamine (60 mg/kg i.p.) and dexmedetomidine (0.15 mg/kg i.p.) and the jugular vein was exposed via blunt dissection using aseptic technique. The catheters (SAI Infusion Technologies, Libertyville, IL, USA) were then implanted in the vein and the opposing end routed subcutaneously around the animal's back to emerge between the scapulae where they were attached to an infusion harness. Surgical wounds were treated with the topical anesthetic bupivacaine, and each animal was administered ketoprofen (5.0 mg/kg, s.c.) for postoperative pain. Catheters were flushed daily after each self-administration session with a lock solution that contained heparinized saline, and the antibiotic gentamicin (8 mg/ml, Butler Schein Animal Health, Dublin, OH, USA).

2.4. Behavioral procedures

All behavioral procedures were conducted in operant chambers (Med Associates, St. Albans, VT, USA) that measured $30.5 \times 24.1 \times 21.0$ cm. Each operant chamber contained two response levers, two cue-lights (one placed above each response lever), a single house light, a tone generator, and a food trough. Animals were initially trained to press a lever to receive a 45 mg food pellet reward via FR1 response. The FR1 schedule was used to facilitate direct comparison to our previous studies with a wide variety of drug treatment some of which increase and others of which decrease nicotine self-administration. This schedule provides ample opportunity to see effects in both directions. An illuminated cue-light above one of the two levers in the operant chamber indicated the "active" lever. Criteria for completing the operant response training were defined as three consecutive 30 min sessions earning ≥ 50 pellets. Once the training criteria were met, rats underwent catheterization surgery (see above). After recovery from surgery, nicotine self-administration sessions were begun. Each self-administration session lasted 60 min. During self-administration sessions, a response on an active lever resulted in the delivery of a 50 μl infusion of nicotine (0.03 mg/kg, based on freebase weight) and the activation of the tone generator for 0.5 s. Responses on the inactive lever had no consequence in the operant program to deliver nicotine and proceed through the session. Each infusion of nicotine was followed by a 20 s timeout period wherein the cue-light above the active lever was extinguished and lever responses were recorded but no nicotine infusion was delivered. All behavioral sessions were programmed and recorded using MED-PC software (Med Associates, St. Albans, VT, USA).

After 10 baseline sessions of nicotine self-administration, sessions preceded by acute treatment with doses of varenicline and bupropion were begun. Drug solutions were injected (s.c.) 15 min before the

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