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Dextromethorphan interactions with histaminergic and serotonergic treatments to reduce nicotine self-administration in rats

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ABSTRACT

Combining effective treatments with diverse mechanisms of action for smoking cessation may provide better therapy by targeting multiple points of control in the neural circuits underlying addiction. Previous research in a rat model has shown that dextromethorphan, which has α3β4 nicotinic and NMDA glutamatergic antagonist actions, significantly decreases nicotine self-administration. We have found in the rat model that the H1 histamine antagonist pyrilamine and the serotonin $5HT_{2C}$ agonist lorcaserin also significantly reduce nicotine self-administration. The current studies were conducted to determine the interactive effects of dextromethorphan with pyrilamine and lorcaserin on nicotine self-administration in rats. Young adult female rats were fitted with jugular IV catheters and trained to self-administer a nicotine infusion dose of 0.03-mg/kg/infusion. In an initial dose–effect function study of dextromethorphan, we found a monotonic decrease in nicotine self-administration over a dose range of 1 to 30-mg/kg with the lowest effective dose of 3-mg/kg. Then, with two separate cohorts of rats, dextromethorphan (0, 3.3, and 10-mg/kg) interactions with pyrilamine (0, 4.43, and 13.3-mg/kg) were investigated as well as interactions with lorcaserin (0, 0.3125 and 0.625-mg/kg). In the pyrilamine–dextromethorphan interaction study, an acute dose of pyrilamine (13.3-mg/kg) as well as an acute dose of dextromethorphan caused a significant decrease in nicotine self-administration. There were mutually augmenting effects of these two drugs. The combination of dextromethorphan (10-mg/kg) and pyrilamine (13.3-mg/kg) significantly lowered nicotine self-administration relative to either 10-mg/kg of dextromethorphan alone ($p < 0.05$) or 13.3-mg/kg of pyrilamine alone ($p < 0.0005$). In the lorcaserin–dextromethorphan study, an acute dose of lorcaserin (0.312-mg/kg) as well as an acute dose of dextromethorphan (10-mg/kg) caused a significant decrease in nicotine self-administration replicating previous findings. Augmenting interactions were observed with dextromethorphan and pyrilamine as well as lorcaserin. These findings suggest that combination therapy may be more effective smoking cessation treatments than monotherapy.

1. Introduction

Tobacco addiction is estimated to cause over 540,000 premature deaths per year in the United States and millions more worldwide (Carter et al., 2015). It is estimated that tobacco use is responsible for almost 20% of all deaths in developed countries, making it the single largest cause of premature death worldwide (Dani and Heinemann, 1996). Although American tobacco consumption has declined significantly since the 1950s, a half century later still one in five Americans classified themselves as smokers (Giovino, 2007). Only 3 to 5% of cigarette smokers who attempt to quit without assistance are able to remain abstinent for six to twelve months (Hughes et al., 2004). Despite a wide variety of current treatments available for smoking cessation including nicotine replacement, bupropion and varenicline, relapse rates remain high, often >80%. Smokers who quit successfully usually only do so after numerous attempts. Clearly, more effective treatments are needed to help tobacco cessation. Recently, there has been an increased interest in the use of combination therapy with pharmacological agents as a potential option for smoking cessation treatment. The results of both clinical and preclinical studies investigating this potential treatment mechanism have been promising. Studies in humans have shown that combining FDA-approved smoking cessation aids results in significantly improved outcomes, with combinations of bupropion with either the nicotine patch or nicotine replacement therapy (NRT) (Jorenby et al., 1999; Rose and Behm, 2013), and combinations of varenicline with NRT or bupropion (Ebbert et al., 2009, 2014; Koegelenberg et al., 2014; Rose and Behm, 2014) having improved efficacy to monotherapy with these treatments. We have previously shown that combining varenicline and bupropion reduces nicotine self-administration in rats more effectively than either treatment

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alone (Hall et al., 2015). This study was designed to explore the effects of combination therapy with other currently available pharmacological agents that have been shown to reduce nicotine self-administration in the rat model when given alone.

Dextromethorphan is an over-the-counter antitussive agent with multiple mechanisms of action on neurotransmitter systems in the brain. It acts as an NMDA glutamate receptor antagonist, a nonselective serotonin reuptake inhibitor, and sigma-1 receptor agonist (Henderson and Fuller, 1992; Maurice et al., 2001; Netzer et al., 1993). Dextromethorphan also been shown to act as a noncompetitive antagonist at α3β4, α4β2, and α7 nicotinic receptors (Damaj et al., 2005; Hernandez et al., 2000). The compound has received attention as a potential smoking cessation agent due to its ability to reduce nicotine self-administration in rats (Glick et al., 2001) as well as block nicotine's anti-nociceptive effects in thermal pain assays (Damaj et al., 2005).

Pyrilamine is an H1 histamine antagonist that is often used as an antihistaminergic agent in over-the-counter cold medications. We have previously shown that pyrilamine decreases nicotine self-administration in rats (Cousins et al., 2014; Levin et al., 2011b). Although pyrilamine significantly reduces nicotine self-administration independently, combining this histamine antagonist with other drugs may result in neurotransmitter system interactions that reduce nicotine self-administration more significantly. A close relationship is known to exist between the histaminergic and cholinergic systems, and pyrilamine has been shown to interact with nicotinic receptors whereby the compound appears to inhibit catecholamine secretion (Chen et al., 2001; Kim et al., 2014). These qualities make pyrilamine a promising potential agent for combination therapy.

Lorcaserin is a serotonin $5HT_{2C}$ agonist. The compound has been shown to be effective in the treatment of weight gain and is currently FDA-approved for the treatment of obesity (Higgins et al., 2015; Johnson and Oliver, 2014). Lorcaserin has also been shown to interact with nicotinic systems. We and others have shown that lorcaserin significantly reduces nicotine self-administration as well as alcohol intake in rats (Higgins et al., 2012; Levin et al., 2011a; Rezvani and Levin, 2014). A recent Phase 2 trial showed the efficacy of lorcaserin in smoking cessation treatment (Shanahan et al., 2015). Lorcaserin also blocks intracranial self-stimulation and nicotine-enhanced responding for a conditioned reinforcer (Guy et al., 2014; Zeeb et al., 2015). Taken together, these findings suggest a role for $5HT_{2C}$ receptors in the reinforcement and reward-related learning processes in the brain.

The current studies investigated combinations of dextromethorphan and pyrilamine as well as dextromethorphan and lorcaserin in a rat model of nicotine self-administration to determine if the combined effects of these drug actions on different receptor types exceed that of each alone. It was hypothesized that treatment with these combinations would result in greater reductions in nicotine self-administration than would be observed with mono-treatment with any of these drugs, that therapy acting of more than one part of the addiction circuitry would have better effects.

2. Methods

2.1. Subjects

Young adult female Sprague–Dawley rats (Charles River, Raleigh, NC, USA) used in these studies were housed singly in colony rooms close to the self-administration facility so that they could be moved with minimal stress. Females were used to be congruent with our previous studies. The housing room was kept on a reverse 12:12 h (lights on 7:00 AM) day/night cycle to ensure that rats were in an active phase during the self-administration sessions. Rats were fed daily after behavioral testing with an amount of chow to keep them at a lean health weight approximately 85% of ad lib weight, and were given constant access to water through standard cage bottles or through automatic delivery lines in housing room racks. The procedures of this study were approved by the Duke University Institutional Animal Care and Use Committee in accordance with state and federal regulations.

2.2. Experimental design

All of the studies tested acute drug treatment effects on nicotine self-administration using a repeated measures counterbalanced design. Each subject received each of the doses in an order of dose combinations that was counterbalanced across subjects, avoiding possible confounding of dose effect with the order of dose administration. The full range of dose conditions and vehicle control were administered to each subject twice. All doses of drugs and drug combinations used in each study were initially assessed for adverse effects on locomotor activity and food-motivated responding.

2.2.1. Study 1

Doses of 1, 3, 10 and 30-mg/kg of dextromethorphan and saline vehicle were injected (sc) 10-min prior to the onset of the test sessions. The acute dose–effect function of dextromethorphan on locomotor activity, food motivated responding and nicotine self-administration was evaluated. The doses were given in a repeated measures counterbalanced design, twice for the nicotine self-administration study and once each for the food motivated responding and locomotor activity studies.

2.2.2. Study 2

Interactions of dextromethorphan (0, 3.3, and 10-mg/kg) and pyrilamine (0, 4.43 and 13.3-mg/kg) was studied via s.c. injection 10 min prior to sessions using a repeated measures counterbalanced design. Following the results of the locomotor activity and food motivated responding sessions, the dose ranges of dextromethorphan and pyrilamine for the nicotine self-administration trials were tested.

2.2.3. Study 3

Combinations of dextromethorphan (0, 3.3, 10-mg/kg) and lorcaserin (0, 0.625 and 1.25-mg/kg) were administered via s.c. injection 10 min prior to sessions using a repeated measures counterbalanced design. Following the results of the locomotor activity and pellet sessions, the dose ranges of dextromethorphan and lorcaserin for the nicotine self-administration trials were conducted.

2.3. Preparation of drug solutions

Solutions of 0.03-mg/kg nicotine ditartrate were prepared according to the nicotine base weight. Using sterile glassware, the nicotine salt was dissolved in sterile saline and adjusted to a standard pH between 7.0 and 7.2. After being adjusted to a pH appropriate for intravenous infusion, the nicotine solution was filtered through a 0.22-μ Nalgene filter for sterilization. These solutions were stored in conical tubes wrapped with aluminum foil to prevent exposure to light. Between sessions nicotine solutions were refrigerated for no longer than two weeks before replacement. Pyrilamine, lorcaserin and dextromethorphan were dissolved in saline solution and were injected s.c. in a volume of 1 ml/kg.

2.4. Nicotine self-administration procedure

Rats were trained to self-administer nicotine in a manner described previously (Hall et al., 2014, 2015). Briefly, animals were trained to press a lever to receive a 45 mg food pellet reward (FR1), and subsequently underwent jugular catheterization surgery. The rats then began nicotine self-administration sessions. Responses on the active lever (signaled via illuminated cue-light) delivered a 0.03-mg/kg/infusion dose of nicotine via the delivery line and catheter (FR1). Responses on the opposite (inactive) lever had no effect. Following each lever press and nicotine delivery, the cue light extinguished for a one-minute time out, the house light was illuminated, and the responses on the active lever were recorded but were without consequence. Prior to the start of the