Pharmacology, Biochemistry and Behavior 166 (2018) 42–47

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Mutually augmenting interactions of dextromethorphan and sazetidine-A for reducing nicotine self-administration in rats

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ARTICLE INFO

Keywords:
Sazetidine-A
Dextromethorphan
Mecamylamine
Treatment
Addiction

ABSTRACT

A variety of nicotinic drug treatments have been found to decrease nicotine self-administration. However, interactions of drugs affecting different nicotinic receptor subtypes have not been much investigated. This study investigated the interactions between dextromethorphan, which blocks nicotinic α3β2 receptors as well as a variety of other receptors with sazetidine-A which is a potent and selective α4β2 nicotinic receptor partial agonist with desensitizing properties. This interaction was compared with dextromethorphan combination treatment with mecamylamine, which is a nonspecific nicotinic channel blocker. Co-administration of dextromethorphan (either 0.5 or 5 mg/kg) and lower dose of sazetidine-A (0.3 mg/kg) caused a significant reduction in nicotine SA. With regard to food-motivated responding, 3 mg/kg of sazetidine-A given alone caused a significant decrease in food intake. However, the lower 0.3 mg/kg sazetidine-A dose did not significantly affect food-motivated responding even when given in combination with the higher 5 mg/kg dextromethorphan dose which itself caused a significant decrease in food motivated responding. Interestingly, this higher dextromethorphan dose significantly attenuated the decrease in food motivated responding caused by 3 mg/kg of sazetidine-A. Locomotor activity was increased by the lower 0.3 mg/kg sazetidine-A dose and decreased by the 5 mg/kg dextromethorphan dose. Mecamylamine at the doses (0.1 and 1 mg/kg) did not affect nicotine SA, but at 1 mg/kg significantly decreased food-motivated responding. None of the mecamylamine doses augmented the effect of dextromethorphan in reducing nicotine self-administration. These studies showed that the combination of dextromethorphan and sazetidine-A had mutually potentiating effects, which could provide a better efficacy for promoting smoking cessation, however the strength of the interactions was fairly modest.

1. Introduction

Several drug treatments have been developed to help people overcome tobacco addiction, including nicotine replacement of various sorts, varenicline and bupropion. Each of these treatments has been shown to improve tobacco smoking cessation to some extent, but the efficacy of each is relatively small and relapse rate is high. It is possible that combinations of effective treatments could provide greater efficacy. We and others have found that dextromethorphan, which among other actions blocks nicotinic α3β2 receptors, significantly reduced nicotine self-administration in rats (Glick et al., 2001, Briggs et al., 2016). Sazetidine-A is a selective ligand for nicotinic α4β2 receptors (Xiao et al., 2006) with agonist effects at one subtype and desensitizes at another subtype of α4β2 receptors. We have repeatedly shown that sazetidine-A significantly reduces nicotine self-administration in rats (Levin et al., 2010, Rezvani et al., 2010, Johnson et al., 2012). Mecamylamine, a non-specific nicotinic channel blocker, has also been shown to reduce nicotine self-administration in rats (Corrigall and Coen, 1989; Shoaib et al., 1997; DeNoble and Mele, 2006) and to have mixed effects on tobacco smoking in people (Pomerleau et al., 1987; Rose et al., 1989).

All three drugs tested in this set of studies, dextromethorphan, sazetidine-A and mecamylamine, have effects on nicotinic receptors with different specificities. Dextromethorphan has noncompetitive antagonist effects at α3β4, α4β2 and α7 nicotinic receptors (Hernandez et al., 2000, Damaj et al., 2005). Dextromethorphan also interacts with the glutamatergic receptors and similar to ketamine, it acts as an NMDA glutamate receptor antagonist (Netzer et al., 1993). Sazetidine-A is a desensitizing agent at nicotinic α4β2 receptors and an agonist at the high affinity concatemer of nicotinic α4β2 receptors and mecamylamine is a non-specific channel blocker at all nicotinic receptors.

The α4β2* nicotinic receptors play key roles in the modulation of dopamine innervation from the ventral tegmental area (VTA) to the nucleus accumbens (Zhao-Shea et al., 2011), a pathway involved in motivation and the action of addictive drugs such as nicotine. The hypothesized pathway for sazetidine-A effects on nicotine self-

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https://doi.org/10.1016/j.pbb.2018.01.005
Received 25 July 2017; Received in revised form 28 January 2018; Accepted 29 January 2018
Available online 31 January 2018
0091-3057/

administration is that it is a selective partial agonist at α4β2* receptors and desensitizes them in the VTA rendering them resistant to subsequent stimulation by nicotine. This would then decrease nicotine-induced dopamine release in the nucleus accumbens, leading to less motivation to take nicotine (Levin et al., 2010; Rezvani et al., 2010).

In the current studies, we evaluated the combination of relatively low doses of dextromethorphan with sazetidine-A and mecamylamine. It was hypothesized that the combination of these drugs at subthreshold doses would be more effective than individual drugs and will significantly reduce nicotine self-administration without significantly affecting food motivation responding.

2. Methods

2.1. Subjects

Adult female Sprague-Dawley rats (Charles River Labs, Raleigh, NC, USA) were used for the current studies. At the start of the study the rats were 60–70 days old and were naïve to nicotine. They were housed in a vivarium facility next to the testing rooms on a 12:12 h reverse day night cycle with lights off at 7:00 AM so that they were in their active phase during behavioral testing. All rats had ad lib access to water and were fed rodent chow once daily 30 min after their testing to keep them at approximately 85% of their ad lib body weight. All procedures used in this study were approved by the Duke University Animal Care and Use Committee. Each of the two studies used separate sets of rats. The rats were singly housed after catheter implant surgery to prevent cage mates from gnawing on the rats' catheters.

2.2. Behavioral training

The rats were trained to lever press for food reinforcement using a standard chamber with two levers (Med Associates, St. Albans, VT, USA). The chambers were equipped with two levers (one active, one inactive), a house light, two cue lights located directly above each lever, and a white noise generator. Following lever pressing training, animals experienced three consecutive 45-min sessions of lever pressing for food under a fixed ratio (FR) 1 schedule of reinforcement. After reaching criterion of 50 pellets/session for three consecutive days, rats underwent surgery for implantation of a catheter into their jugular vein for nicotine self-administration.

2.3. Surgery

After training to lever press for food and before the initiation of nicotine self-administration sessions, rats were anesthetized by IP injection of ketamine (60 mg/kg) and dexdormitor (15 mg/kg). After establishment of total anesthesia, a catheter (Strategic Application Inc., Libertyville, IL, USA) was implanted into their jugular vein. The jugular catheter was attached to a harness that could be tethered to the infusion pump during the experimental sessions. Nicotine self-administration sessions were started the day after the surgery after full recovery (Levin et al., 2010; Rezvani et al., 2010; Rezvani et al., 2013).

2.4. Nicotine self-administration

Following full recovery from the surgery, rats were trained to self-administer nicotine (0.03 mg/kg/infusion, IV) via operant lever response with a visual secondary reinforcer. Two levers were available to be pressed but only pressing the lever on the active side resulted in the immediate delivery of one 50-μl infusion of nicotine in < 1 s into the jugular vein. Each infusion was immediately followed by a one-minute period of timeout and presses on levers were recorded but not reinforced (Rezvani et al., 2010; Rezvani et al., 2013).

2.5. Locomotor activity

Since changes in motor activity may interfere with nicotine self-administration, the effects of the drug treatment on motor activity were measured using a Figure-8 Apparatus (Levin et al., 2010). Animals were allowed to roam in the Figure-8 maze during a one-hour session and photo beam breaks were recorded in 12 five-minute blocks to measure their activity. The mazes had continuous enclosed alleys 10 × 10 cm in the shape of a Figure-8. Eight infrared photobeams, which crossed the alleys, indexed locomotion of the rat. One photobeam was located on each of the two blind alleys and three were located on each of two loops of the Figure-8 maze. The number of photo beam breaks was recorded and tallied during the one-hour session. The linear and quadratic trends across twelve five-min blocks in each session were calculated to determine locomotor activity over the course of one-hour session.

2.6. Food-motivated responding

Subsequent to the nicotine SA sessions, the rats were tested to assess drug effects on responding for food reinforcement. The drug treatments as well as the saline control were administered in a repeated measures counterbalanced order. The behavioral paradigm used FR1, with activation of a feedback tone for 0.5 s after reinforcement. Cue lights were on throughout the session with no house light illumination and no time out after reinforcement. The rewards were 45-mg food pellets. As with nicotine SA, the sessions for food SA were 45-min long.

2.7. Preparation of drugs

Using pyrogen-free glassware, all drugs were dissolved in saline and were injected sc in a volume of 1 mg//kg 10 min before nicotine SA session. The pH of the nicotine solution for SA was adjusted to 7.0 using NaOH solution and then the solution was filtered through a 0.22 μm Nalgene filter (Nalgene Nunc International, Rochester, NY, USA) to ensure sterilization. Between sessions nicotine solutions were refrigerated for no longer than two weeks before replacement. The dose of nicotine used for each rat was calculated as a function of the nicotine base weight.

2.8. Drug treatment

Acute drug treatments were administered sc in a volume of 1 ml/kg. The same volume of saline was used as the control vehicle. Each study evaluated the interaction of two drug treatments using a 3 × 3 design with control, lower and higher doses of each drug. The dose combinations were given in a counterbalanced order to avoid confounding dose effects with dose order. There were three tests, for drug effects of nicotine self-administration, locomotor activity and food self-administration with nine dose combinations each. So, there were 27 total injections. The doses of sazetidine-A were 0, 0.3 and 3 mg/kg and the doses for dextromethorphan were 0, 0.5 and 5 mg/kg (N = 13). In a separate set of rats, the doses of mecamylamine were 0.1 and 1 mg/kg. Each dose was given in a counterbalanced order with at least a day between consecutive doses (N = 14). Then, the complete set of the nine doses and combinations was given again for a second phase. These dose ranges of dextromethorphan, sazetidine-A and mecamylamine has been shown in previous studies to span the behaviorally active doses for effects in rats on drug self-administration and cognitive function (Briggs et al., 2016, Levin et al., 2010, Rezvani et al., 2010, Rezvani et al., 2012, Glick et al., 2002, Levin et al., 1987, Levin et al., 1989, Levin et al., 2000 #12367, Glick et al., 2001, Pulvirenti et al., 1997).

2.9. Statistical analysis

Analysis of variance was used to assess the data. A three factor within subjects design was used with sazetidine-A, dextromethorphan,