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Acute and chronic interactive treatments of serotonin $5HT_{2C}$ and dopamine D_1 receptor systems for decreasing nicotine self-administration in female rats

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ABSTRACT

A variety of neural systems are involved in the brain bases of tobacco addiction. Animal models of nicotine addiction have helped identify a variety of interacting neural systems involved in the pathophysiology of tobacco addiction. We and others have found that drug treatments affecting many of those neurotransmitter systems significantly decrease nicotine self-administration. These treatments include dopamine D_1 receptor antagonist, histamine H1 antagonist, serotonin $5HT_{2C}$ agonist, glutamate NMDA antagonist, nicotinic cholinergic α4β2 partial agonist and nicotinic cholinergic α3β4 antagonist acting drugs. It may be the case that combining treatments that affect different neural systems underlying addiction may be more efficacious than single drug treatment. In the current study, we tested the interactions of the D_1 antagonist SCH-23390 and the serotonin $5HT_{2c}$ agonist lorcaserin, both of which we have previously shown to significantly reduce nicotine self-administration. In the acute interactions study, both SCH-23390 and lorcaserin significantly reduced nicotine self-administration when given alone and had additive effects when given in combination. In the chronic study, each drug alone caused a significant decrease in nicotine self-administration. No additive effect was seen in combination because SCH-23390 given alone chronically was already highly effective. Chronic administration of the combination was not seen to significantly prolong reduced nicotine self-administration into the post-treatment period. This research shows that unlike lorcaserin and SCH-23390 interactions when given acutely, when given chronically in combination they do not potentiate or prolong each other's effects in reducing nicotine self-administration.

1. Introduction

Tobacco use is the leading cause of preventable death in the United States (U. S. Department of Health and Human Services, 2014). Smoking cigarettes, which contain tobacco, considerably increases the chances of cardiovascular disease, lung disease, and various types of cancer. The health complications from smoking have also created a substantial economic burden, with medical costs and productivity loss reaching approximately $300 billion per year in the U.S alone (U. S. Department of Health and Human Services, 2014). The gain in popularity of electronic cigarettes, or e-cigarettes, has also led to a trend in smoking under the ages of 18, with over 3 million middle school and high school aged youth reported smoking in the last month (U. S. Department of Health and Human Services, 2016). With the rise of tobacco use in youth, coupled with the continued impact on adults, effective aids to help people quit smoking are crucial.

The most common treatments for combating nicotine addiction and aiding smoking cessation are nicotine replacement therapies (NRTs): including nicotine patches, chewing gum, and nasal sprays. The purpose of NRTs is to supply a low, consistent dose of nicotine to alleviate withdrawal symptoms and to reduce the temptation to smoke (Gourlay and McNeil, 1990). This lower dose of nicotine has fewer negative health side effects compared to cigarette smoking, but with 85% of those using NRTs relapsing (Tang et al., 1994), more effective treatments for permanent cessation are needed.

Despite the need for new therapies to fight nicotine addiction, there has been little progress in finding adequate medications. The two main non-nicotine treatments approved by the FDA are bupropion (Zyban®)

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and varenicline (Chantix®). Bupropion, an atypical antidepressant, inhibits dopamine and norepinephrine reuptake and acts as a non-competitive antagonist of nicotine at α4β2-nicotine acetylcholine receptors (nAChR) (Damaj et al., 2004; Lukas et al., 2010). Varenicline acts as both a partial agonist of α4β2, α3β4, α3β2, and α6-subtypes of nAChRs and a full agonist at α7 nAChRs (Mihalak et al., 2006; Rollema et al., 2007). The use of a partial agonist to aid cessation is beneficial because it alleviates some of the negative symptoms of withdrawal while antagonizing the reward of nicotine (Gonzales et al., 2006). Bupropion and varenicline both improve smoking cessation, but there still remains a high percentage of smokers who relapse. In a randomized controlled trial, 77%, 85.4%, and 89.7% of people relapsed after forty weeks post-treatment with varenicline, bupropion, and placebo, respectively (Jorenby et al., 2006). These relapse rates demonstrate the continued need for the development of more effective treatment options.

The neural pathways of nicotine addiction involve a variety of targetable receptors in addition to nAChRs. Dopamine receptors are integral players in mediating addiction-associated behaviors, such as reward-seeking, reinforcement (Woolverton and Johnson, 1992), learning (Di Chiara, 1998), and memory (White, 1996). Important drug-dependent increases of dopamine signaling occur in the mesolimbic pathway in the brain, which projects from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and extends to prefrontal cortex (PFC) (D'Souza and Markou, 2011; Di Chiara, 2000; Fiorino et al., 1993). Heightened signaling of this pathway has been associated with addiction-like behaviors (Balfour, 2009; Corrigall et al., 1994). Therefore, limiting dopaminergic signaling in the mesolimbic pathway is a potential therapeutic strategy. Studies have shown that inhibiting dopamine signaling by blocking dopamine D_1 receptors using SCH-23390, a potent D_1 antagonist (Bourne, 2001), reduces nicotine self-administration in rats (Corrigall and Coen, 1991; DiPalma et al., 2019; Hall et al., 2015a, 2015b). Additionally, serotonin (5HT) also plays an important role in the neural systems involved with addiction in the mesolimbic pathway. Specifically, the $5HT_{2C}$ receptor has been implicated in mediating addiction-like behaviors (Liu et al., 2007). 5-HT_{2C} receptors are expressed in the VTA, NAc, and PFC. In the VTA, 5-HT_{2C} receptors are located on inhibitory γ-aminobutyric acid (GABA) neurons (Bubar and Cunningham, 2007; Zeeb et al., 2015). Activation of 5-HT_{2C} receptors on GABA neurons stimulates the release of GABA, which decreases the firing of post-synaptic dopaminergic neurons. This inhibition reduces the amount of dopamine released in the mesolimbic pathway, the NAc, and PFC and results in a lower reward response (De Deurwaerdere et al., 2004; Van Bockstaele and Pickel, 1995; Zeeb et al., 2015). Lorcaserin, a 5-HT_{2C} agonist, is an FDA-approved drug that decreases appetite in the treatment of obesity. Its effectiveness as a 5-HT_{2C} agonist has been repurposed to study its effect on reducing the reinforcing effects of drugs of abuse (Zeeb et al., 2015). Studies have shown that treatment with lorcaserin reduces nicotine (Briggs et al., 2016; Higgins et al., 2012; Levin et al., 2011a, 2011b), cocaine (Harvey-Lewis et al., 2016), and opioid (Neelakantan et al., 2017) self-administration in rat models, and reduces alcohol intake in alcohol-preferring rats (Rezvani et al., 2014). Some of these studies have progressed to work in Rhesus monkeys, where lorcaserin has shown promise in reducing cocaine and methamphetamine self-administration (Collins et al., 2016; Gerak et al., 2016). These treatments demonstrate the importance of understanding how neurotransmitter receptors orchestrate signaling in the reward pathway and utilizing that knowledge to find effective non-nicotinic pharmacological therapies.

While SCH-23390 and lorcaserin have shown promise as therapeutic drugs to aid nicotine cessation, possible combinations could exploit the distinct mechanisms to amplify their effects on the reward pathway. Our lab recently published that combining lorcaserin with NRT potentiated each's ability to reduce nicotine self-administration in rats (DiPalma et al., 2019). Other groups have also confirmed the benefits of combining NRTs with non-nicotinic treatments in patients (Ebbert et al., 2009; Sweeney et al., 2001). However, combining non-nicotinic treatments has been vastly understudied.

In this study, we present the acute and chronic combinations of SCH-23390 and lorcaserin treatments in models of nicotine self-administration in rats and compare results to respective monotherapies. The purpose of this study is to gain a better understanding about how nAChRs, D1Rs, and 5-HT_{2C}Rs interact in the mesolimbic pathway and their combined effects on drug seeking behavior.

2. Methods

2.1. Subjects

Young adult female Sprague-Dawley rats were used. They were housed singly in climate controlled conditions with a 12:12 h reverse light:dark cycle with lights on at 7:00 PM. The rats had *ad lib* access to water and were fed (5001 Rodent Chow, Lab Diet, Brentwood, MO, USA) daily 20–30 min after testing with sufficient food to keep their body weight at a healthy lean weight approximately 85% of *ad lib* levels. Maintaining 85% of *ad lib* levels is healthy for rats and is a common practice for self-administration studies. In addition, this is consistent with previously published studies. All nicotine self-administration sessions were conducted between 9 a.m. and 4 p.m., when rats were on their active phase of their diurnal cycle. All studies performed in accordance with the rules and regulations outlined by the Animal Care and Use Committee of Duke University.

2.2. Drug treatment

2.2.1. Acute interactions

The D_1 antagonist SCH 23390 (0.01 and 0.03 -mg/kg) and the $5HT_{2c}$ agonist lorcaserin (0.2 and 0.6 -mg/kg) were injected acutely (sc) 20-min before testing in a repeated measures counterbalanced order twice. Both drugs were dissolved in saline solution and injected in a volume of 1 ml/kg. The saline vehicle served as the control.

2.2.2. Chronic interactions

The D_1 antagonist SCH 23390 (0 and 0.02- mg/kg) and the $5HT_{2c}$ agonist lorcaserin (0 and 0.6 mg/kg) were injected 20-min before testing following a between-subjects design. These concentrations were chosen because 0.6- mg/kg of lorcaserin exhibited an effect in the acute study and 0.02 -mg/kg of SCH-23390 was in the middle of the concentrations tested in order to find a sub-saturating dose. There were four groups: control (saline, saline; s.c), SCH-23390 alone (0.02- mg/kg, saline; s.c.), lorcaserin alone (0.6 mg/kg, saline; s.c.), and combination of SCH-23390 and lorcaserin (0.02- mg/kg, 0.6- mg/kg; s.c.). All groups received two weeks of nicotine self-administration (5 days per week). Then, there was a one-week period of enforced abstinence with no treatment modeling a cessation attempt. This was followed by 5-days of resumed access to nicotine SA and continued treatment to determine the drug effects on relapse. Finally, there was a 5-day of continued access to nicotine SA after the treatments were halted to determine the possible persistence effect of treatment after the end of therapy.

2.2.3. Nicotine preparation

Nicotine bitartrate was dissolved in sterilized isotonic saline based on the base weight of nicotine and prepared in contaminant-free glassware bimonthly. For each solution, the pH was adjusted to 7.0–7.20 using NaOH, then was vacuum filtrated using a Nalgene filter (Nalgene Nunc International, Rochester, NY, USA) for sterilization. When not in use, solutions were refrigerated and stored in the dark to prevent decomposition of nicotine. For self-administration sessions, the dose of nicotine infused was 0.03 mg/kg/infusion.

2.3. Behavioral training and nicotine self-administration

Rats were trained to use the lever-press in self-administration

chambers. Each operant chamber contained two levers, a cue light over each lever, a house light, and a tone generator. The experimental data was collected by MED-PC computer software. Each rat was assigned an operant chamber with a selected activated lever; half of the subjects were trained to press the right lever and the other half were trained for the left lever. A cue light would be lit over the activated lever during the sessions. The first session consisted of an overnight (15-hour) session, in which the rat was aided by reinforcement pellets and needed one hundred responses to pass. Water was provided in the chambers throughout the overnight session. After successfully passing, the rats did three separate one-hour pellet sessions. Fifty correct lever presses in each session were needed to pass to the following sessions.

After passing all pellet training sessions and undergoing jugular catheterization and a full recovery from the surgery, the IV nicotine SA sessions started. The same delivery operant chamber was used, and the lever that previously administered a food pellet when pressed now delivered a 0.03-mg/kg/infusion dose of nicotine solution *via* the delivery line and catheter. As before, the inactive lever had no effect. Following each lever press and nicotine delivery, the cue light turned off for 1 min, the house light turned on, and the lever was inactivated until the cue light illuminated again. Prior to the start of the experiment, the rats were given five baseline training nicotine self-administration sessions in the absence of SCH-23390 or lorcaserin treatment. Before each session, catheters were flushed with 0.3-ml of a 100 units/ml heparinized saline solution. Sessions lasted for 1-hour, and responses were measured using MED-PC software. The software measured correct and incorrect lever presses, total nicotine infusion, and 15-min interval counts for nicotine infusion. Following each daily session, nicotine was drawn out of the delivery port and replaced with 0.3- ml of a saline solution containing 8-mg/ml of the antibiotic gentamicin and 500-units/ml of heparin.

2.4. Jugular catheterization surgery

Upon completion of preliminary behavioral training with pellet sessions, animals underwent jugular vein catheterization surgery to facilitate nicotine infusions during self-administration sessions. They were anesthetized with i.p. injections of ketamine (Fort Dodge Animal Health, Fort Dodge, IA, USA; 0.6- mg/kg) and dexdomitor (Pfizer, New York, NY, USA; 0.15 mg/kg). These anesthetics are consistent with prior experiments, as well as being standard practices. The rat was then shaved and prepared for surgery. Following incision and separation of tissue, the jugular vein was tied off at the distal end of the cannula insertion area. The catheter (Strategic Application Inc., Libertyville, IL, USA) was inserted into the jugular vein just distal to the heart and secured using cyanoacrylate adhesive. The external section of the catheter was sutured to the deep muscle and exited the body on the dorsal side of the rat just posterior to the scapulae. The catheter was held in place by a plastic delivery port and rubber underarm bands (SAI Infusion Technologies, Libertyville, IL, USA). After completion of the surgery, ketoprofen (5- mg/kg, s.c.) was administered to reduce post-operative pain and inflammation. Bupivacaine and a generic topical antibiotic were also applied. There was a 24-hour recovery time for animals before beginning their nicotine self-administration sessions.

2.5. Data analysis

The nicotine self-administration data were assessed for statistical significance by analysis of variance. For the acute study, treatment dose and repeated phases were within-subjects factors. For the chronic study treatment was a between-subjects factor and weeks of testing was the repeated measure. For interactions at $p < 0.10$, we examined whether lower-order main effects were detectable after subdivision of the interactive variables (Snedecor and Cochran, 1967). The $p < 0.10$ criterion for interaction terms was not used to assign significance to the effects, but rather to identify interactive variables requiring subdivision for lower-order tests of the main effects of nicotine, the variable of chief interest. A cut-off of $p < 0.05$ (two-tailed) was used as the threshold for statistical significance.

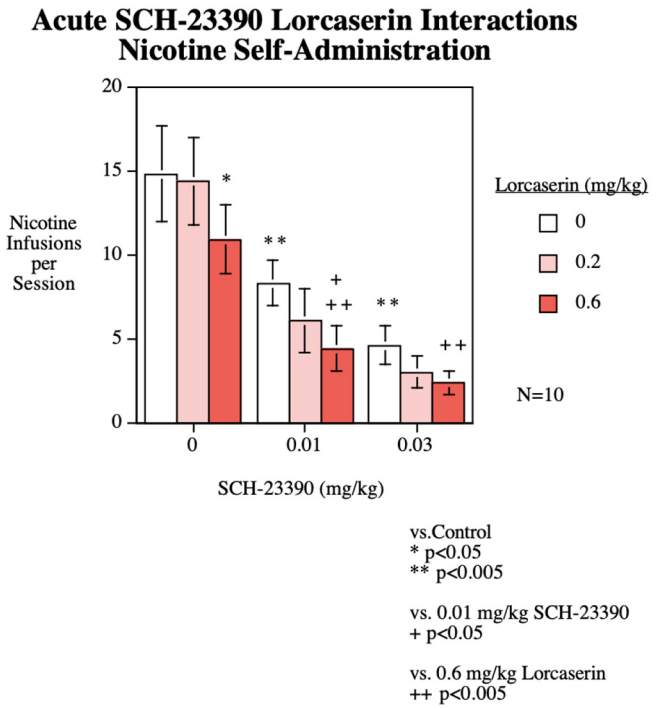

Fig. 1. Acute dose-effects of SCH-23390 and lorcaserin on nicotine self-administration (mean ± sem). Each drug significantly lowered nicotine self-administration and enhanced each other's effects in lowering nicotine self-administration. $N = 11$.

3. Results

3.1. Acute Interactions of SCH-23390 and Lorcaserin

Both the main effects of SCH-23390 ($F(2,18) = 24.70$, $p < 0.005$) and lorcaserin ($F(2,18) = 13.30$, $p < 0.005$) were significant. Lorcaserin alone at the higher but not the lower dose significantly ($p < 0.05$) reduced nicotine self-administration relative to levels with vehicle control treatment. SCH-23390 at both doses significantly ($p < 0.005$) reduced nicotine SA relative to levels with vehicle control treatment (Fig. 1). These treatments significantly enhanced each other's effects of reducing nicotine self-administration, with the combination of 0.-6 mg/kg of lorcaserin and 0.01- mg/kg of SCH-23390 significantly ($p < 0.05$) enhancing the decrease in nicotine self-administration caused by 0.01 -mg/kg of SCH-23390 alone. The addition of 0.6 -mg/kg of lorcaserin to the higher SCH-23390 dose also significantly ($p < 0.005$) enhanced the reduction of nicotine self-administration caused by 0.03 -mg/kg of SCH-23390. All of the drug treatments and control injections were given in a repeated measures counterbalanced order one time and then again in another phase of testing. There was a significant three-way interaction of lorcaserin x SCH-23390 x test phase ($4,36 = 3.32$, $p < 0.025$). Follow-up tests of the drug effects in the first and second phases showed that during the first phase both 0.01 ($p < 0.001$) and 0.03 -mg/kg ($p < 0.001$) of SCH-23390 caused significant reductions in nicotine SA relative to control as did the higher 0.6- mg/kg dose of lorcaserin ($p < 0.005$). The higher 0.6 -mg/kg dose of lorcaserin also significantly potentiated the effect of the lower 0.01-mg/kg dose of SCH-23390 ($p < 0.05$). In the second phase of drug testing in a similar fashion as the first, both the 0.01 ($p < 0.001$) and the 0.03- mg/kg ($p < 0.001$) doses of SCH-23390 significantly reduced nicotine SA relative to control. During the second treatment phase it

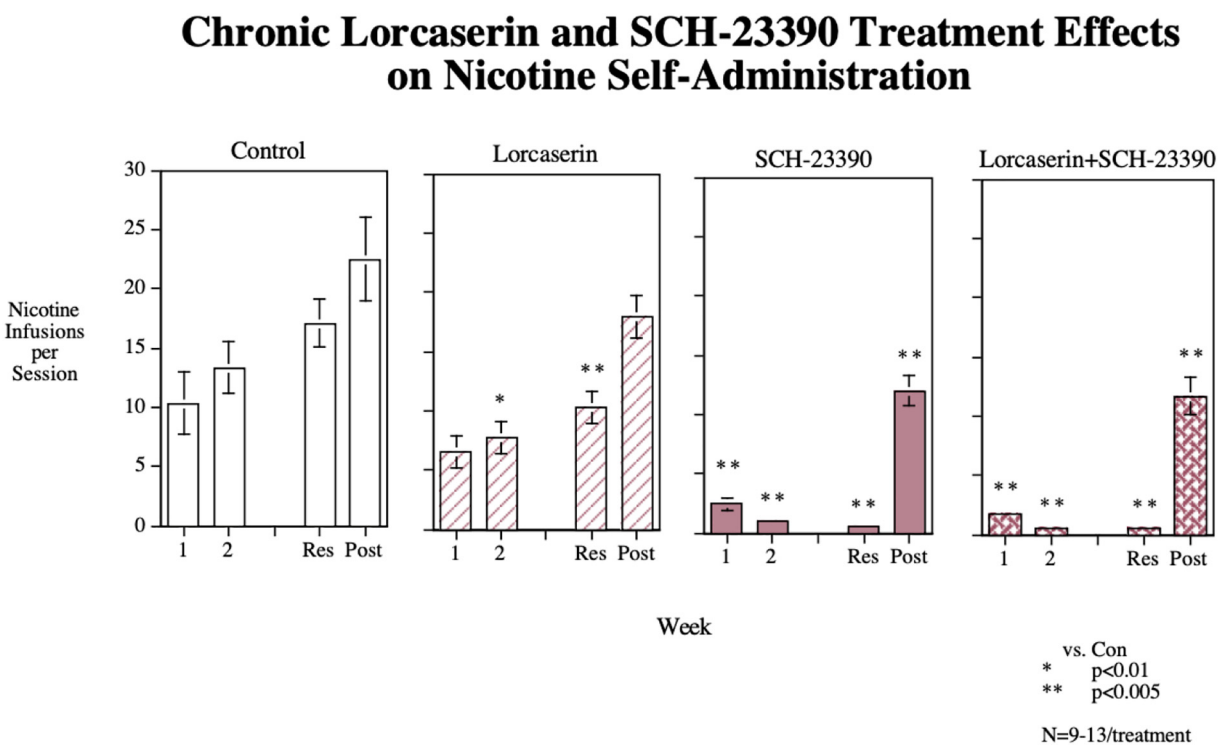

Fig. 2. Chronic time-effect interactions of 0.02- mg/kg of SCH-23390 and 0.6 mg/kg of lorcaserin on nicotine self-administration (mean ± sem). Sections 1 and 2 reference the two weeks of continued nicotine access during self-administrations sessions while receiving drug treatment (control, 0.02 -mg/kg SCH-23390, 0.6- mg/kg lorcaserin, or 0.02- mg/kg SCH-23390 + 0.6 -mg/kg lorcaserin) before the sessions. This was followed by a week of enforced nicotine abstinence while maintaining drug treatment, then resumed accessed and continued treatment (Res). Finally, during the last week, rats had continued access to nicotine in self-administration sessions without any drug treatments (Post). Each drug significantly lowered nicotine self-administration but were not found to enhance each other's effects in lowering nicotine self-administration. N = 9–13/treatment group.

was the lower 0.2- mg/kg lorcaserin dose that caused a significant reduction in nicotine SA relative to control. The mean value of infusions with the higher 0.6 mg/kg lorcaserin dose was lower than the control value but not significantly so. The 0.6- mg/kg of lorcaserin did significantly ($p < 0.025$) potentiate the effect of lower 0.01-mg/kg SCH-23390 dose in lowering nicotine SA during second phase of testing.

3.2. Chronic interactions of SCH-23390 and lorcaserin

Chronic SCH-23390 treatment, as we have seen with acute administration, had a dramatic effect of reducing nicotine self-administration (Fig. 2). There were significant main effects of both 0.02- mg/kg SCH-23390 ($F(1,38) = 49.72$, $p < 0.001$) and 0.6- mg/kg lorcaserin ($F(1,38) = 4.44$, $p < 0.05$). There was an interaction of 0.02 -mg/kg SCH-23390 × 0.6- mg/kg lorcaserin ($F(1,38) = 3.70$, $p = 0.083$) that prompted tests of the simple main effects. There was also a significant ($F(3,114) = 5.73$, $p < 0.01$) interaction 0.02- mg/kg SCH-23390 x week of testing. Right from the first week of treatment 0.02 -mg/kg SCH-23390 significantly ($p < 0.01$) reduced nicotine self-administration relative to the control group. This significant effect continued during the second week of treatment ($p < 0.001$) and during the resumption period after enforced abstinence ($p < 0.001$). Even though there was a jump in nicotine self-administration in the 0.02 -mg/kg SCH-23390 group after the end of treatment the level of nicotine self-administration remained significantly below that of control group during the same period ($p < 0.05$).

Chronic administration of 0.6 -mg/kg lorcaserin as with acute lorcaserin had a more modest effect of reducing nicotine self-administration. Significant reductions in nicotine self-administration relative to controls were seen during the second week of therapy ($p < 0.05$) and during the week after enforced abstinence ($p < 0.01$). This was a result of a 0.6 -mg/kg lorcaserin-induced reduction in nicotine SA and the continued increase in nicotine SA seen in the control group. After the end of lorcaserin treatment, nicotine self-administration jumped to the degree that it did not significantly differ from controls during the same period. The combination of 0.02- mg/kg SCH-23390 and 0.6- mg/kg lorcaserin, like 0.02- mg/kg SCH-23390 alone, dropped nicotine self-administration to nearly zero. There was no sign of additive effect because of this floor effect. After withdrawal of the drug treatment, nicotine self-administration rose in the group previously treated with 0.02 -mg/kg SCH-23390, and there was no longer a floor effect. But even without the floor effect there was no sign of additive effects of 0.02 -mg/kg SCH-23390 and 0.6 -mg/kg lorcaserin when given together.

4. Discussion

The reinforcing effects of nicotine are influenced by a variety of neural systems. In an attempt to reduce the reinforcing effects, we utilized a combination therapy that targeted the dopaminergic and serotonergic systems by treating with the D_1 antagonist SCH-23390 or the $5HT_{2c}$ agonist lorcaserin. This study examined the acute and chronic interactions of lorcaserin and SCH-23390 on reducing nicotine self-administration in a rat model. These data replicated the findings that acute and chronic treatments of lorcaserin or SCH-23390 alone significantly reduces nicotine self-administration in rats (Corrigall and Coen, 1991; DiPalma et al., 2019; Hall et al., 2015a, 2015b; Levin et al., 2011a, 2011b; Zeeb et al., 2015). In addition, we found that acute interactions of lorcaserin and SCH-23390 potentiated their respective effects on nicotine cessation in a dose-dependent manner. When the combination therapy was administered chronically, additive effects were not observed over the treatment period. However, the ability to detect mutually potentiating effects was limited by the substantial effect of SCH-23390 producing low levels of nicotine infusion during

treatment weeks such that a floor effect was established. This prevented analysis of whether lorcaserin had an additive effect in reducing nicotine self-administration during treatment sessions.

However, in the post-treatment nicotine self-administration sessions, a floor effect was not a problem. During this phase of the study, all treatment groups increased nicotine intake. The group that had received SCH-23390 alone rose in nicotine self-administration well above the floor but still significantly less than controls. The group which had received the combination treatment also rose well above the floor but stayed significantly below controls. There was no differential effect seen between the SCH-23390 alone and SCH-23390 + lorcaserin group, providing no evidence that combining lorcaserin and SCH-23390 might have an additive effect on reducing nicotine cessation upon removing treatment. Continuous treatment as monotherapies or a combination therapy are both effective treatment strategies. Once treatment is removed, reduction in nicotine self-administration is lessened but still present with SCH-23390, but not with lorcaserin.

While the combination therapy in this study did not have an additive effect in the chronic model, other combination treatments have shown successful potentiation in reducing nicotine self-administration. We previously showed that combining lorcaserin or SCH-23390 with nicotine replacement therapy were additive in reducing nicotine self-administration in rats (DiPalma et al., 2019). In those studies, the combinations of either lorcaserin + chronic nicotine or SCH-23390 + chronic nicotine did potentiate each other's effects both during treatment and after withdrawal of treatment.

By examining the acute and chronic interactions of combination therapies, we can provide comprehensive information on potential treatments for people wanting to quit smoking. In the counter-balanced acute interaction study, we are able to limit variability by having each rat serve as its internal control. It also demonstrates optimal doses of different drugs when given in combination. The chronic interaction study examines this combination therapy in a model that resembles human behavior of smoking: developing the habit, taking treatment to stop smoking, quitting, and usually followed by relapsing. Therefore, we are able to measure how these treatments could impact various stages of nicotine use and correlate to human behavior.

While combination therapy of chronic SCH-23390 + lorcaserin in this study was not optimal in maintaining nicotine cessation upon removal of treatment, this interaction should be further investigated. It may be the case that lower doses could be used in a combination treatment or that sequential treatments may show more effective combinations. A benefit of combining treatments is being able to use low or sub-threshold doses, which could result in fewer side effects. Combination treatments targeted at different parts of the interacting neural systems underlying the reinforcing effects of nicotine may be more beneficial for smoking cessation.

Addiction is a chronic disease that profoundly alters the normal functioning of the central organ of the nervous system and the seat of human behavior, the brain. As a delicate network of neurons interwoven and synapsing upon each other, it forms the neural bases of behavioral function and dysfunction. Recreational drugs disturb this balance in a multitude of ways, affecting numerous pathways, which we are beginning to understand. Uncovering the diverse sets of neurotransmitters and interacting brain regions that underlie motivational functions and dysfunctions, such as addiction, provides the potential for developing effective new therapeutic treatment. We have found that drugs affecting diverse neural systems including dopamine, serotonin, histamine and glutamate receptors impact nicotine self-administration (Briggs et al., 2016; DiPalma et al., 2019; Hall et al., 2015a, 2015b; Johnson et al., 2012; Kutlu et al., 2013; Levin et al., 2016; Levin et al., 2011a, 2011b; Levin et al., 2010; Levin et al., 2008). Accordingly, we have shown that combination treatments affecting different neurotransmitter systems may improve tobacco smoking cessation success.

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