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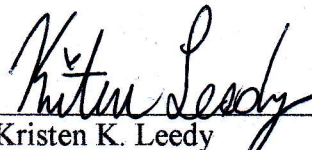
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The Synergistic Effects of Methylphenidate on the Behavioral Effects of Nicotine

By

Kristen Kaye Leedy

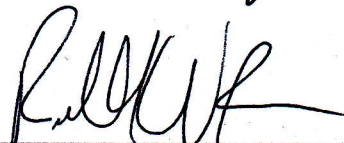
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Dr. Russell W. Brown, Thesis Mentor

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ABSTRACT

The Synergistic Effects of Methylphenidate on the Behavioral Effects of Nicotine

by

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One of the most common childhood disorders, attention-deficit hyperactivity disorder (ADHD) places individuals at a higher risk for nicotine (NIC) dependence. Approximately 37.2% of individuals with ADHD currently smoke compared to the 18.3% of individuals with no record of mental illness. Methylphenidate (MPH; Trade name Ritalin) is the most commonly prescribed treatment for ADHD. Research regarding the synergistic effects of MPH and NIC, however, is divided. Some research indicates that MPH may enhance susceptibility to NIC effects, whereas other studies report that MPH may inhibit sensitization to NIC. The present study examines the effects of pre-exposure to MPH (1.0 mg/kg) on the behavioral effects of NIC (0.5 mg/kg) in adolescent male and female Sprague-Dawley rats. We used behavioral sensitization and conditioned place preference (CPP) on animals postnatal day (P)28-50; this is defined as adolescence in rats. For behavioral sensitization, results revealed a significant interaction between day of testing, drug pre-exposure, and adolescent drug treatment ($p = .004$). On the other hand, CPP results revealed a significant interaction between adolescent drug treatment and drug pre-exposure ($p = .031$). Findings suggest that pre-exposure to MPH reduces behavioral sensitization to NIC during adolescence. In addition, results indicate that MPH enhances NIC CPP in adolescent male and female rats, suggesting that MPH may enhance the rewarding effect of NIC.

Keywords: Methylphenidate, Nicotine, Ritalin, Conditioned Place Preference, Adolescence, Sensitization

DEDICATION

I would like to dedicate this thesis to my mentor, Dr. Russell Brown, for his supervision and guidance throughout this project. I have to thank everyone over in the Brown lab for volunteering their time and efforts. Without your support I could not have accomplished this endeavor. Thank you so much for believing in me and helping me fulfill my dreams. In addition, this project would not have been possible without Elizabeth Cummins-Freeman, the light at the end of my undergraduate tunnel. I grew not just as a researcher, but as a person under your supervision.

This thesis is also dedicated to my boyfriend, Dakota. I could not have asked for more support and love than you have already shown me. Thank you for being there for me through all of the sleepless nights and fast-approaching deadlines. Finally, I would also like to dedicate this thesis to my family; thank you for always giving me a place to come home to.

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INTRODUCTION

Compared to those without psychiatric disorders, individuals with ADHD are at a higher risk for smoking (Lambert & Hartsough, 1998; Molina & Pelham, 2003; Milberger et al., 1997; McClave et al., 2010). About 2.5 - 4% of the adult population is affected by ADHD (Kessler et al., 2006; McClave et al., 2010; Simon et al., 2009). In an analysis of findings from the National Health Interview Survey, McClave et al. (2010) reported that 37.2% of individuals with ADHD currently smoke compared to the 18.3% of individuals with no record of mental illness. Previous research indicates that a greater proportion of individuals with ADHD start smoking at a younger age and experience greater difficulty quitting in comparison to individuals without ADHD (Humfleet et al., 2005; Lee, Humphreys, Flory, & Glass, 2011; McLernon & Kollins, 2008). The National Comorbidity Survey Replication study reported that ADHD, in regards to childhood externalizing disorders, was one of the strongest predictors of nicotine use/dependence in adulthood (Glantz et al., 2009). Although research has failed to determine why individuals with ADHD are more likely to smoke, some researchers posit that these individuals may be self-medicating their symptoms (Gehricke et al., 2007; Khantzian, 1997; Milberger et al., 1997). This supposition has been supported by research indicating that the nicotine patch and nicotinic agonists do alleviate certain ADHD symptoms (Gehricke et al., 2006, 2009; Levin et al., 1996; Wilens et al., 1999, 2006).

Methylphenidate (MPH) is the most widely prescribed treatment for cases of ADHD in children and adults (Findling & Dodgin, 1998; Goldman, Genel, Bezma, & Slanetz, 1998; Zito, Sater, dosReis, Gardner, Boles, & Lynch, 2000). However, despite its widespread use, Urban and Gao (2013) found that MPH may cause impairments in prefrontal functioning and neural plasticity. In addition, Maier et al. (2013) reported that ADHD medications are used by students

to enhance cognitive performance, with MPH being the most commonly used. Abusing stimulants such as MPH has serious implications; psychostimulants have been found to significantly alter neuron functioning and transmission, increasing extracellular levels of dopamine (DA), serotonin, and norepinephrine (Angelucci et al., 2009). Calipari and Jones (2014) reported that MPH abuse may cause changes in the DA system, eventually leading up to the abuse of other addictive substances.

Even though research indicates that children and adults respond differently to MPH (Torres-Reveron & Dow-Edwards, 2005), in recent years there has been a significant increase in MPH prescriptions for ADHD (Olfson, Gameroff, Marcus, & Jensen, 2003; Safer, Zito, & Fine, 1996; Zito et al., 2000). Acting as a stimulant, MPH increases pre-synaptic dopamine release while simultaneously blocking dopamine reuptake (Volkow, Fowler, Wang, Ding, & Gatley, 2002). Some research suggests that ADHD may result from problems with dopamine transporter (DAT) availability (Cheon et al., 2003; Dougherty et al., 1999; Krause, 2008; Krause et al., 2000). MPH blocks DAT, which is believed to be how MPH essentially treats ADHD symptoms (Krause et al., 2000). Our lab has shown that MPH upregulates the DAT (Cummins et al., 2013).

Reports have shown that MPH should cause a reduction in smoking behaviors if the medication (as opposed to nicotine) reduces ADHD symptomology (Winhusen et al., 2010). In support of these findings, some research has suggested that stimulants, such as MPH, may act as an aid to smoking cessation. Monuteaux et al. (2007) found promising results while examining the efficacy of bupropion as an adult smoking cessation aid in ADHD children. Although bupropion is already a smoking cessation aid, results did suggest that other stimulants may be effective as well. Additional support for this was found by Hammerness et al. (2013) in an open-label, long-term clinical trial of extended-release MPH in adolescents diagnosed with ADHD.

Results indicated that 10 months of treatment, on average, was correlated with a low rate of cigarette smoking. In fact, this rate was similar to individuals without ADHD as well as individuals under treatment for their ADHD (Hammerness et al., 2013).

However, some research has suggested that MPH increases smoking behaviors even in individuals without ADHD. Rush et al. (2005) and Vansickel et al. (2007, 2009) demonstrated that non-ADHD individuals saw an increase in smoking when treated with MPH. In these studies, individuals treated with at least one dose of MPH saw an increase in cigarette puffs in comparison to the placebo group (Rush et al., 2005; Vansickel et al., 2007, 2009). Other studies have demonstrated that MPH can elicit a change in preference for cigarettes over money (Stoops et al., 2011). Therefore, there appears to be some disagreement in the literature as to whether MPH actually blunts the rewarding effects of nicotine or changes the brain's reward system, making it vulnerable.

The present study examined the effect of pre-exposure to MPH on the behavioral effects of NIC. We focused our research on the vulnerable developmental period of adolescence; in rats this is defined in postnatal days (P) ranging from P28 to 50 (Spear, 2000; Laviola et al., 2003). We used two behavioral tests: behavioral sensitization and conditioned place preference (CPP). Behavioral sensitization is a behavioral test of the augmented motor response that occurs with repeated intermittent exposure to a drug. CPP is a behavioral test of the associative effects of drugs. The present experiment also utilized a clinically relevant dose of MPH (1.0 mg/kg; Devilbiss & Berridge, 2008) that results in brain plasma levels relevant to the MPH-medicated ADHD population. In addition, we employed a dose of nicotine (NIC; 0.5 mg/kg) that has been shown to produce both behavioral sensitization and CPP (Kelley & Rowan, 2004; Justo et al., 2010; Fanous, Lacagnina, Nikulina, & Hammer, 2011). Regarding sensitization, a significant

increase in dopamine release and activation of the mesolimbic dopamine projections occurs after chronic psychostimulant exposure (Boileau et al., 2006); the locomotor activity that results can be measured from horizontal and vertical movements, which indicate psychomotor sensitization (Tirelli, Laviola, & Adriani, 2003; Fanous et al., 2011). Unlike behavioral sensitization, CPP is a behavioral paradigm that allows researchers to test the rewarding effects of drugs in rodents.

METHODS

Subjects. Male and female adolescent Sprague-Dawley rats were used as subjects and raised in the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) accredited animal colony at East Tennessee State University. All animals were given food and water ad libitum and housed in a climate controlled vivarium on a 12 hour on/off light dark cycle. All behavioral testing was conducted during the light cycle. All procedures were approved by the ETSU Committee on Animal Care which is consistent with the NIH Guide on Care and Use of Animals.

Drug pre-exposure. On P28, drug pre-exposure began and continued throughout the remainder of the experiment. Animals were ip administered daily with either MPH (1.0 mg/kg) or SAL in the morning at approximately 8 am; animals were randomly assigned to each group. This dosing regimen was chosen because it mimics the average MPH prescription; there are five days “on,” two days “off,” designed to be consistent with school day dosing in humans. Behavioral testing began on P42 in two different sets of animals; one group was tested on behavioral sensitization and the other was assessed using the CPP paradigm.

Behavioral Sensitization. On P42, behavioral sensitization began with habituation. For three consecutive days, each animal was ip injected with SAL and placed into the locomotor arena after a 10 minute delay. The purpose of the delay was to allow for proper drug distribution

before testing. Activity counts were then recorded for 10 minutes using Any Maze behavioral scanning software (Stoelting Co., Wood Dale, IL). This software superimposes a virtual grid onto the locomotor arena, while keeping track of the number of “grid-breaks” the animal makes. Here our dependent measure was activity counts; essentially, the number of grid-breaks is analogous to level of activity. On P45, NIC (or SAL) treatment began. Animals were ip injected with either SAL or NIC (0.5 mg/kg). After a 10 minute delay, each animal’s activities were once again recorded for 10 minutes. All animals were behaviorally tested in a (72 cm/side) square locomotor arena and allowed to move around freely.

Conditioned Place Preference (CPP). For behavioral testing on the CPP paradigm, a different set of animals was used to examine the effects of pre-exposure to MPH on the reward-aspect of the drug. The CPP apparatus used was a three-chambered wooden box; the center compartment was painted solid gray, while the outer two compartments are distinct from one another. Each compartment was the same size (90 cm/side), but unique in tactile surface and visual appearance. In addition, the gray compartment had wooden flooring; the remaining two contexts had either wire mesh or metal dowel rod flooring with either black/white horizontal or vertical stripes on the walls. These three contexts were separated by removable dividers. The difference in environmental contexts allows the animal the ability to distinguish between contexts and associate one with the rewarding effect of a drug such as NIC. Again Any Maze behavioral scanning software was used to track animal movements, but here the main focus was how much time the animal spent in the context paired with NIC as compared to SAL controls on the post-conditioning test. The dependent measure was calculated by subtracting the percent of time spent in the paired context during pre-test from the percent of time spent in the paired

context during the post-test. Time spent in the middle compartment was not considered time spent outside the paired context.

Two initial preference tests were conducted P42-43 with the dividers removed. The average time spent in each compartment was recorded, revealing any natural preferences, and animals were conditioned against their natural preference. After determining initial preferences by averaging performance on these two initial preference tests, conditioning began on P44 and occurred every day; each animal received a session in the morning and one later in the afternoon. Animals were given either NIC or SAL ip and were placed into the locomotor arena after a 10-minute delay for a 10 minute test. For conditioning, dividers were inserted into the apparatus and each animal was assigned to their unpaired context in the morning session and administered SAL. During the afternoon sessions, animals were assigned to their paired context and administered NIC or SAL depending on group assignment. Conditioning occurred every consecutive day for eight days from P44-50. On P51, a post-conditioning preference test was conducted; this test was identical in procedure to the initial pre-conditioning preference tests. Dividers are once again removed and animals receive SAL ip 10 minutes before being tested for 10 minutes.

RESULTS

In regards to behavioral sensitization, we were unable to find any sex differences, so we collapsed across the factor of sex. A three-way ANOVA revealed a significant three-way interaction between drug pre-exposure x adolescent drug treatment x day of testing ($p = .004$). At day one of testing, no significant differences were found among treatment groups; therefore, acute NIC treatment did not change locomotor activity regardless of MPH pre-exposure (see Figure 1). However, at day 9 SAL-NIC animals displayed the highest activity counts in

comparison to all other groups besides MPH-SAL. These animals demonstrated behavioral sensitization to NIC. Compared to SAL-NIC animals, NIC animals pre-exposed to MPH actually showed a decrease in locomotor activity at day 9. These results suggest that pre-exposure to MPH reduces behavioral sensitization to NIC in male and female adolescent rats compared to controls. In other words, MPH appears to reduce the behavioral activating effects of NIC.

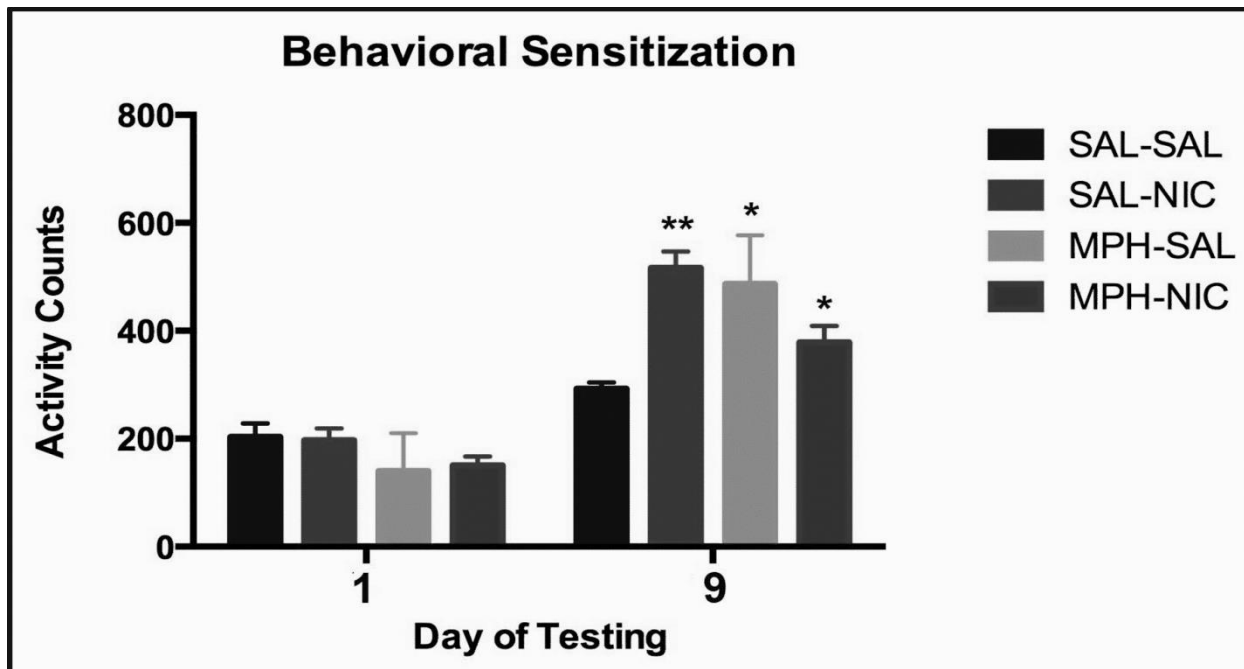


Figure 1. Activity counts are represented as a function of day of testing and drug condition (** indicates group is greater than MPH-NIC and SAL-SAL, $p < .05$; * indicates group is greater than SAL-SAL, $p < .05$).

For analysis of CPP, we again collapsed across the factor of sex after discovering no sex differences. A two-way ANOVA revealed a significant interaction between drug pre-exposure and adolescent drug treatment ($p = .031$). In comparison to other groups, animals pre-exposed to MPH and treated with NIC displayed the greatest preference for the context paired with NIC (see Figure 2). In addition, SAL pre-exposed animals displayed nicotine CPP in that this group displayed a significant preference as compared to SAL-treated controls. The results suggest that

pre-exposure to MPH may enhance NIC CPP in adolescent male and female rats compared to controls. Essentially, MPH appears to enhance the reward aspect of NIC.

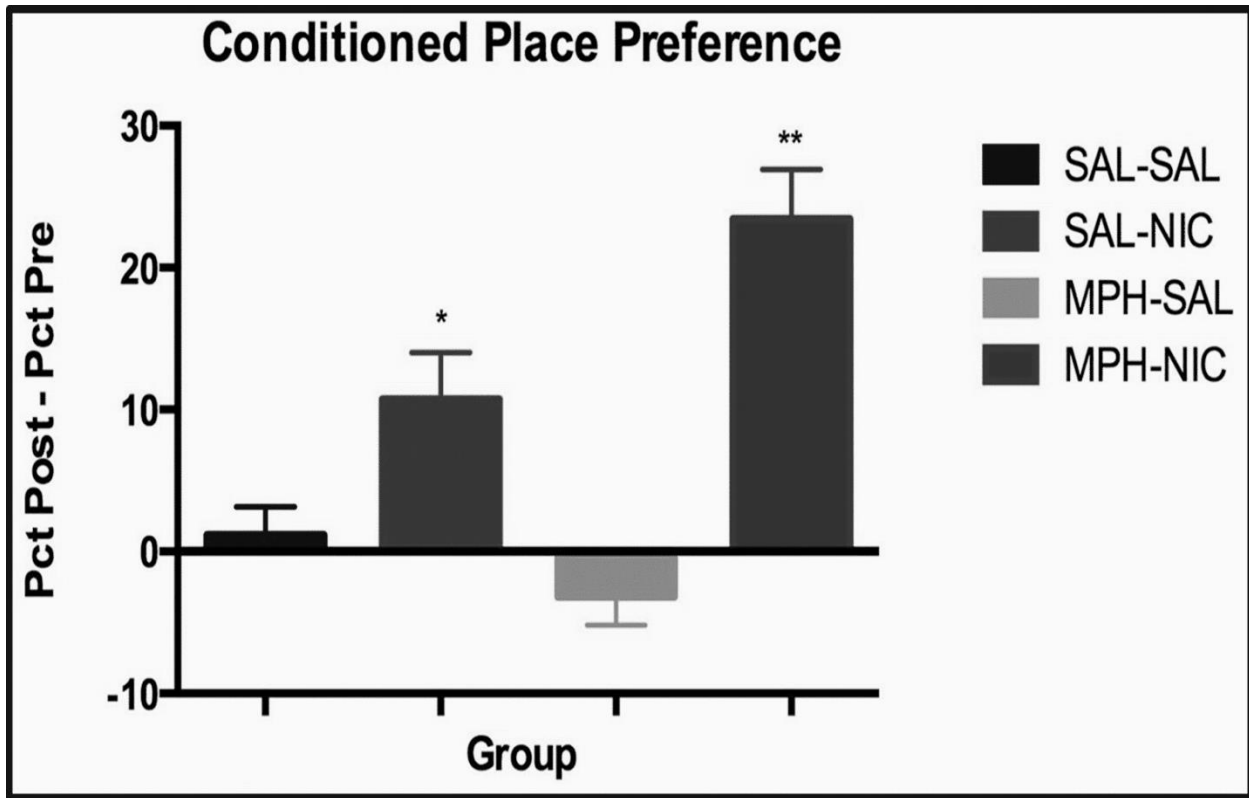


Figure 2. The percent time difference spent in the paired context on the pre and post-conditioning preference tests is presented as a function of condition (** indicates MPH-NIC group is significantly greater than all other groups, $p < .05$; * indicates SAL-NIC is greater than SAL-SAL and MPH-SAL, $p < .05$).

DISCUSSION

At a clinically relevant dose, MPH appears to reduce behavioral sensitization to NIC in adolescent male and female rats. Thus, we failed to support our original hypothesis that pre-exposure to MPH would enhance the behavioral effects of NIC. On the other hand, we also demonstrated that pre-exposure to MPH enhances NIC CPP in male and female adolescent rats. This supports our original hypothesis that MPH would enhance NIC CPP in adolescent male and

female rats. This finding suggests that MPH enhances the reward aspect of NIC. Unfortunately, due to a fairly low number of males, we were required to further generalize our findings and exclude sex differences from our final analyses. Preliminary data from our lab has suggested that females are affected more robustly by this synergistic relationship. Also of interest, we demonstrated NIC CPP in a non-biased CPP procedure, the first instance of NIC CPP outside a biased paradigm.

Future research should continue to tease apart these complex findings; although the research is divided, it is not necessarily inconsistent. The high count of locomotor activity in animals pre-exposed to MPH is likely a result of an increase in stereotypic behaviors. Stereotypies are inappropriate, repetitive behaviors that serve no real biological purpose or function (Garner, 2005; Turner, 1997); an increase in stereotypic behavior and hyperlocomotion is indicative of increased dopamine activity (Creese and Iversen, 1974; Kelley et al., 1975; Kelley & Iversen, 1976; Lucot et al., 1980). Wallace, Gudelsky, and Vorhees (1999) demonstrated that repeated high-dose administration of methamphetamine increased stereotypic behaviors and increased the release of DA. The animals in sensitization are likely displaying MPH-induced stereotypy as a response to increased DA activity in the brain.

Finally, MPH has been shown to affect neurotrophic factors, such as brain-derived neurotrophic factor (BDNF; Brown et al., 2012). BDNF is found throughout the brain and plays a direct role in neuronal growth, function, and development (Reichardt, 2006). MPH may increase levels of BDNF in the brain, affecting brain areas that mediate drug reinforcement. This in turn, could result in an increased DA response.

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