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Attenuation of pharmacologically-induced attentional impairment by methylphenidate in rats

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ABSTRACT

Methylphenidate is widely used as a treatment option for attention deficit hyperactivity disorder. In animal models of attentional impairment, it is an important validation to determine whether this clinically effective treatment attenuates deficits. The purpose of the current study was to determine whether methylphenidate can diminish attentional impairment induced by three pharmacological agents with different mechanisms of action: scopolamine, mecamylamine, and dizocilpine. Female rats were trained on an operant visual signal detection task. Ten min before the test, the rats were injected subcutaneously with methylphenidate (0, 0.1, 0.3 mg/kg), scopolamine (0, 0.005, 0.01 mg/kg), mecamylamine (0, 2, 4 mg/kg), dizocilpine (0, 0.025, 0.05 mg/kg) or combinations of methylphenidate with these drugs. In each of the experiments, all rats received every treatment in a repeated measures counterbalanced order. Correction rejection accuracy was impaired by all three of the antagonists and these effects were attenuated by methylphenidate. Both scopolamine at 0.01 and dizocilpine at 0.05 mg/kg significantly impaired percent correct rejection choice accuracy, an effect that was ameliorated by methylphenidate. Mecamylamine (4 mg/kg) impaired attentional performance by reducing percent hit and percent correct rejection. Co-administration of methylphenidate failed to significantly affect the mecamylamine-induced attentional impairment. Methylphenidate alone at 0.3 mg/kg significantly improved percent hit choice accuracy only in low-performing rats in one experiment, an effect which was reversed by scopolamine. These data show that methylphenidate effectively reverses the attentional impairment caused by scopolamine and dizocilpine. These findings further validate the operant visual signal detection task for assessing attentional impairments and their reversal.

1. Introduction

Methylphenidate, a dopamine and norepinephrine transporter blocker is a central nervous system stimulant that has been widely used in the treatment of attention deficit hyperactivity disorder (ADHD) and attention deficiency (Greenhill et al., 2002; Volkow et al., 2002). Methylphenidate has been postulated to interact with monoaminergic systems in the brain by blocking dopamine and norepinephrine transporters or by stimulating the release of catecholamine from granular stores (Mcmillen, 1983). Methylphenidate has also been shown to facilitate attentional performance of rats in a modified five-choice serial reaction time task (5-CSRT) (Bizarro et al., 2004). Using this task as an instrument for assessing sustained attention, Puumala et al. (1996) demonstrated that methylphenidate at doses of 0.1 and 1 mg/kg slightly improved the attentional performance of poorly performing rats. However, interestingly methylphenidate did not affect the choice accuracy of intact normal animals tested at baseline conditions. Recently, Paine et al. (2007) demonstrated that out of 6 doses of methylphenidate (0.063–2.0 mg/kg) only one dose (0.5 mg/kg) improved accuracy suggesting a narrow therapeutic index for this drug. Methylphenidate, in addition to improving non-selective attention in spontaneously hyperactive rats (Aspide et al., 2000), has been shown to significantly reduce impulsivity in rats (Evenden and Ko, 2005). These works provide evidence for improving effects of methylphenidate on attention and impulsivity. However, it has been shown that methylphenidate did not affect attentional performance in intact rats (Mcgaughy et al., 1999). Thus, it has been argued that the lack of effect of methylphenidate on intact animals suggests that such normal animals are irrelevant as models for ADHD and for the purpose of screening and detecting compounds suitable for the treatment of ADHD in humans.

In the current study, the effects of methylphenidate on sustained attention in attentionally-compromised rats were assessed. We studied the acute effect of methylphenidate on choice accuracy using a visual signal detection task under normal circumstances and in the context of performance impaired by the muscarinic cholinergic receptor antagonist scopolamine, nicotinic antagonist mecamylamine, and NMDA antagonist dizocilpine (MK-801). The rationale for selecting scopolamine, dizocilpine and mecamylamine are based on

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the fact that these drugs have been shown to impair attention when given alone. For example, acute administration of dizocilpine reduces accuracy in 5-CSRT task (Paine et al., 2007) and visual signal detection task (Rezvani and Levin, 2003a) in rats. Mecamylamine has been shown to impair sustained attention in rats using visual signal detection task (Bushnell et al., 1997; Rezvani et al., 2002) and 5-CSRT task (Grottick and Higgins, 2000; Mirza and Stolerman, 1998). Anticholinergic agents, such as atropine and scopolamine, have been shown to impair attentive mechanism (Warburton and Brow, 1971; Bushnell et al., 1997).

An Operant visual signal detection task was used to assess the effect of methylphenidate on sustained attention. Following extensive training, animals are required to be attentive enough to discriminate between visual signals and non-signals in order to receive a food pellet (Bushnell et al., 1997; Bushnell, 1998; Mcgaughy et al., 1999; Rezvani et al., 2001, 2002, 2004, 2005, 2006; Rezvani and Levin, 2003a,b). The signal detection task has been found to be a sensitive and reliable assessment tool for evaluating the potential of novel compounds for the treatment of attentional impairment. Previously, we have demonstrated that a low dose of nicotine can improve performance and partially counteract dizocilpine-induced attentional impairment using this task (Rezvani and Levin, 2003a). In addition, we have shown that an acute dose of mecamylamine decreased choice accuracy using this task (Rezvani et al., 2002).

This study was conducted to help validate the signal detection operant task as a valuable forum in which to study not only attentional impairment but to also identify therapeutic treatments to reverse the impairment. In the present study, it was hypothesized that scopolamine, mecamylamine and dizocilpine would each impair attentional performance through their antagonistic actions on muscarinic, nicotinic and NMDA glutamatergic receptors and that the clinically effective ADHD medication methylphenidate would attenuate these impairments.

2. Materials and methods

2.1. Animals and housing

Adult female Sprague–Dawley rats (n=35) (Taconic Farms, Germantown, NY, USA) were housed in groups of three in plastic cages with wood shavings in a vivarium with 12L:12D reversed light schedule (light on at 7:00 PM). All training and testing sessions were performed between 9:00 A.M. and 5:00 P.M. during the dark phase of the circadian cycle. Room temperature was controlled at 21±1 °C and relative humidity at 50%±10%. Rats had *ad libitum* access to water in their home cage. Rats were fed daily after testing such that their weights were kept at 80–85% of free-feeding values. The rats weighed an average of 249± 4.65 (S.E.M.) on the first day of drug administration. The treatment and care of the animals was carried out under an approved protocol of the Animal Care and Use Committee of Duke University in an AAALAC-approved facility.

2.2. Experimental protocol

In these series of experiments, the acute effects of methylphenidate, scopolamine, mecamylamine, dizocilpine, and combinations of methylphenidate with these three drugs on sustained attention were examined. A total of 35 rats were trained for the sustained attention task.

In Exp. 1, 11 trained rats were injected acutely with a combination of methylphenidate (0, 0.1, and 0.3 mg/kg) and scopolamine (0, 0.01, and 0.05 mg/kg). All 11 rats received every treatment following a counter balance design with random assignment.

In Exp. 2, an additional 24 trained rats were injected acutely with a combination of methylphenidate (0, 0.1, and 0.3 mg/kg) and dizocilpine (0, 0.025, and 0.05 mg).

In Exp. 3, the same 24 rats from Exp.2 were used after three weeks of wash out. Rats were injected with a combination of methylphenidate (0, 0.1, and 0.3 mg/kg) and mecamylamine (0, 2, and 4 mg/kg). All rats in each group received every treatment following a counter balance design with random assignment. The interval between injections within each set of experiments was at least 48 h. Drugs were injected in a cocktail form 10 min before the test. To maintain their performance, rats were tested on the attention task every day except the weekends and holidays.

2.3. Drug preparation and administration

All drugs were prepared in saline solution. Scopolamine, mecamylamine, and dizocilpine were purchased from Sigma (St. Luis, MO, USA) and methylphenidate HCl was purchased from Research Biochemical International (Natick, MA, USA). Salt weights were used to calculate the doses of the compounds. Rats were injected with drugs and the control vehicle subcutaneously in a volume of 2 ml/kg body weight. Rats began testing 10 min after drug administration.

2.4. Visual signal detection task

Rats were trained to perform a visual signal detection task (Bushnell, 1998; Bushnell et al., 1997; Rezvani et al., 2004, 2005, 2006). Due to the sensitivity as well as complexity of the task, it required over 3 months to train these animals. Animals were trained once a day almost everyday except weekends and holidays until they reached a stable and reliable baseline. The task was conducted in daily 240-trial sessions approximately 45 min in duration. Two trial types, "signal" and "blank," were presented in equal number in each session in groups of 4 (2 signal and 2 blank, in random order) at each signal intensity. Each signal trial included a pre-signal interval, the signal (cue light), and a post-signal interval. The pre-signal intervals were selected randomly from 12 different values ranging from 0.3 to 24.4 s. Following the signal (0.5 s in duration), a post-signal interval of 2, 3, or 4 s (selected randomly) occurred. These temporal parameters yielded a trial presentation rate of 5 trials/min. A signal consisted of 500-ms increase in the brightness of the signal light to levels of 0.027, 0.269, and 1.22 lx above a background illumination of 1.2 lx. Blank trials were presented identically, except the signal light was not present.

A trial began with both levers retracted from the chamber; both levers were inserted into the chamber simultaneously at the end of the post-signal interval. The levers were both retracted when one was pressed or if 5 s passed without a press. If no press occurred, a response failure was recorded and the trial was not repeated. Every correct response (i.e. a press on the signal lever in a signal trial or a press on the blank lever in a blank trial) was followed by the illumination of the food cup and delivery of one 20-mg food pellet. After each incorrect response (i.e. a press on the signal lever in a blank trial or a press on the blank lever in a signal trial) or response failure, the rat received a 2 s period of darkness (time out). For half the rats, the left lever was defined as the signal lever and the right lever as the blank lever. The opposite assignment was made for the remaining rats.

2.5. Behavioral measures and statistical analysis

The effects of the drugs were measured by four dependent variables: percent hit, percent correct rejection, response latency, and response omissions. "Hits" were defined as correct responses on signal trials while "correct rejections" were counted as correct responses on blank trials. Percent hit = 100 × (number of hits / number of signal trials) and Percent correct rejection = 100 × (number of correct rejections / number of blank trials). Response latency was defined as the time elapsed between insertion of the levers and the first lever press by the rat. A response omission was recorded if the rat did not press a lever within 5 s after insertion of the levers. Increase in hit and/

or correct rejection was indicative of enhanced sustained attention and increase in response omission suggested the opposite. Percent correct performance refers to percent correct rejection plus percent hit. Each dependent variable was subjected to an analysis of variance for within subjects factors with each drug dose as a repeated measures factor (Superanova/Statview, SAS, Cary, NC, USA). The same statistical design was used for each experiment. The threshold for significance was set at $p<0.05$. Significant interactions were followed by tests of simple main effects.

2.6. Apparatus for signal detection task

Rats were tested in eight operant conditioning chambers with a working space of 29×25×29 cm (HWD). Each chamber was equipped with a signal light, a house light, two retractable levers, a food cup (Coulbourn Instruments, Lehigh Valley, PA), and a white noise amplifier (Med Associates Inc, Georgia, VT, USA). The food cup was located 2.2 cm above the floor in the center of the front panel of the chamber. The two retractable levers were located on both sides of the food cup 13 cm apart and 2.5 cm above the floor of the chamber. The levers were inserted horizontally 2.5 cm into the chamber. The white noise amplifier was mounted above the blank lever and generated a uniform background white noise of about 65 dB. The signal, or cue light, was located above the food cup at the center of the front panel 28 cm above the floor of the chamber. Signals were generated using Med Associates Inc. software running on a Pentium computer processor using the Windows operating system. The same software controlled all aspects of the behavioral testing.

3. Results

3.1. Methylphenidate scopolamine study

The overall analysis of percent correct response concerning methylphenidate and scopolamine effects showed a significant two-way interaction of methylphenidate and scopolamine [$F(4,40)=2.81$, $p<0.05$]. However, none of the comparisons of the individual dose combinations showed significant differences.

There was also a significant three-way interaction of methylphenidate×scopolamine×error type [$F(4,40)=2.68$, $p<0.05$]. Differential effects of methylphenidate and scopolamine were seen with hit and correct rejection performance. With percent hit (Fig. 1), an acute administration of 0.3 mg/kg methylphenidate by itself caused a significant [$F(1,40)=7.31$, $p<0.025$] improvement. Scopolamine co-administration at both the 0.005 mg/kg [$F(1,40)=19.08$, $p<0.0005$] and the 0.01 mg/kg doses [$F(1,40)=4.84$, $p<0.05$] significantly attenuated the methylphenidate-induced improvement in percent hit performance.

With percent correct rejection there was a different interaction of scopolamine and methylphenidate. Scopolamine (0.01 mg/kg) significantly [$F(1,40)=10.94$, $p<0.005$] impaired correct rejection relative to saline (Fig. 2). This scopolamine induced impairment in correct rejection was significantly attenuated by both 0.1 mg/kg [$F(1,40)=7.10$, $p<0.025$] and 0.3 mg/kg [$F(1,40)=6.62$, $p<0.025$] of methylphenidate.

In this study, methylphenidate doses of 0.1 or 0.3 mg/kg and scopolamine doses of 0.005 and 0.01 mg/kg did not significantly alter response latency or response omissions.

3.2. Methylphenidate dizocilpine study

In the methylphenidate–dizocilpine study, as shown in Fig. 3, the 50 µg/kg dizocilpine dose caused a significant [$F(1,88)=38.01$, $p<0.0001$] impairment in percent correct rejection. This impairment was significantly [$F(1,88)=7.60$, $p<0.01$] attenuated by the 0.3 mg/kg dose of methylphenidate. The lower methylphenidate dose (0.1 mg/kg) had a more modest effect and did not quite significantly ($p<0.07$) attenuate the dizocilpine-induced impairment. Neither the lower (0.025 mg/kg) dizocilpine dose nor either of the methylphenidate doses by themselves had significant effects on percent correct responding. No significant drug effects were seen with percent hit in this study (data not shown).

In this study, there was a significant dizocilpine×methylphenidate interaction [$F(4,88)=4.92$, $p<0.005$] for the latency. Tests of the individual drug effects showed that the lower dizocilpine dose (0.025 mg/kg) significantly [$F(1,88)=6.36$, $p<0.025$] reduced the latency from 132±13 ms with vehicle control to 112±12 ms with dizocilpine. The addition of 0.3 mg/kg of methylphenidate significantly [$F(1,88)=8.80$, $p<0.01$] further reduced the speed of responding to 89±8 ms from 132±13 ms with vehicle control. The higher dizocilpine dose did not have any significant effect on latency. In this experiment, dizocilpine (0.025 mg/kg) significantly [$F(1,92)=4.18$, $p<0.05$] decreased the number of response omissions compared to vehicle control (2.0±0.9 vs. 11.8±2.9), and methylphenidate at a higher dose (0.3 mg/kg) significantly [$F(1,92)=7.85$, $p<0.01$] increased the number of response omissions (25.2±6.4) compared to vehicle control. The higher dizocilpine dose did not have any significant effect on the number of response omissions.

3.3. Methylphenidate mecamylamine study

In the methylphenidate–mecamylamine study, as shown in Fig. 4, the 4 mg/kg mecamylamine caused a significant impairment in percent correct rejections [$F(1, 88)=20.62$, $p<0.0001$]. There was a trend for the 0.3 mg/kg methylphenidate dose to attenuate the mecamylamine-induced impairment but this rise was not quite significant ($p<0.10$). There was also a significant impairment in percent hit by the 4 mg/kg mecamylamine dose [$F(1,88)=5.58$, $p<0.025$]. Compared with control saline administration of 4 mg/kg mecamylamine significantly reduced the percent hit from 72.1±3.5 to 66.5±2.7. However, this effect was not significantly attenuated by methylphenidate co-administration. Also, in this study methylphenidate, by itself, did not have any significant effect on percent hit performance.

In this study, there was a significant [$F(1,92)=18.58$, $p<0.0001$] increase in response latency from 113±11 for vehicle control treatment to 146±12 for the 4 mg/kg mecamylamine dose. No significant effect of the lower mecamylamine dose or methylphenidate was observed. In this experiment, mecamylamine (4 mg/kg) significantly increased the number of response omissions compared with vehicle control treatment (40.4±6.5 vs. 12.5±4.5). The higher methylphenidate dose (0.3 mg/kg) showed a trend toward increasing response omissions (22.5±5.7) but this was not significantly higher than vehicle control ($p=0.09$).

4. Discussion

All three of the antagonists: scopolamine, mecamylamine and dizocilpine impaired percent correct rejection. In all three cases methylphenidate attenuated the percent correct rejection impairments. This test was sensitive not only to the impairments caused by muscarinic, nicotinic and NMDA glutamatergic antagonists but it was also sensitive to the therapeutic effects of the clinically effective ADHD medication methylphenidate.

Scopolamine at 0.01 mg/kg significantly impaired sustained attention by reducing percent correct rejection; an effect which was significantly reversed by both doses of methylphenidate (Fig. 2). The improving effect of methylphenidate in low-performing rats was significantly attenuated by concurrent scopolamine (0.005 and 0.01 mg/kg) administration (Fig. 1). These data suggest that improvement in sustained attention by catecholaminergic agonist such as methylphenidate can be reversed by muscarinic cholinergic blockade, and muscarinic blockade-induced impairment of attention can be

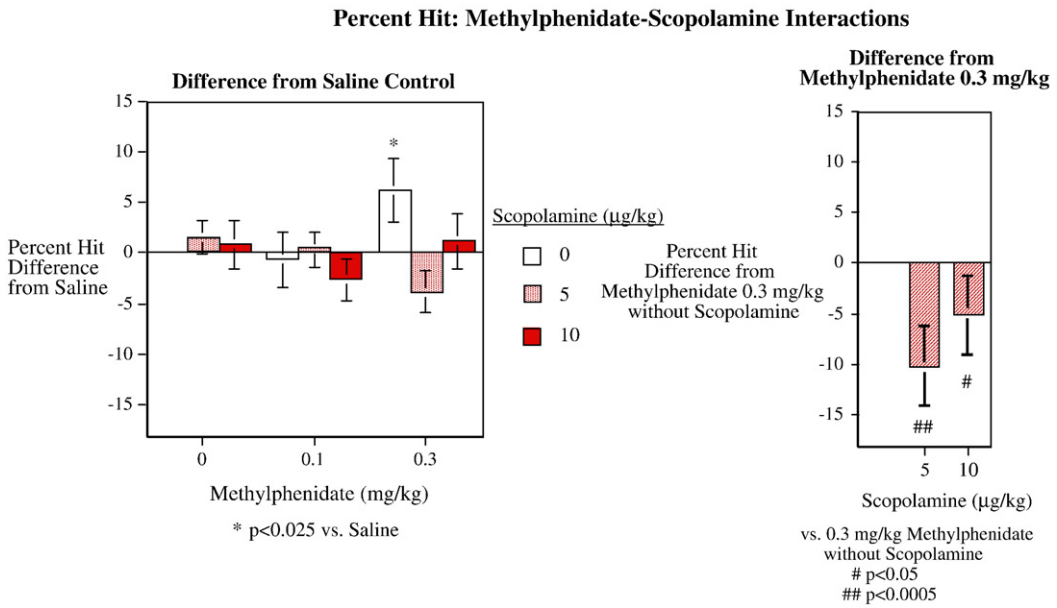

Fig. 1. Effects of methylphenidate and scopolamine alone and in combination on percent hit. The actual level of accuracy for percent hit for the saline control session was 68.4±4. 4. Data represent means±S.E.M. *N*=11.

reversed by catecholaminergic agonist treatment. These findings suggest the involvement of both cholinergic and catecholaminergic transmitter systems in sustained attention. These results fit in well with experience in humans in which methylphenidate has been demonstrated to improve attention (Volkow et al., 1998; Schiffer et al., 2006) whereas scopolamine has been shown to produce impairment (Ellis et al., 2006).

Our results are consistent with previous findings that muscarinic cholinergic receptor antagonist scopolamine impairs attention in both 5CSRTT attention task (Shannon and Eberle, 2006) and in a two-lever choice reaction time task in rats (Bushnell et al., 1997; Mishima et al., 2002). Furthermore, it has been demonstrated that scopolamine also impairs attention in marmoset monkeys (Spinelli et al., 2006) and healthy human volunteers (Ellis et al., 2006). Thus, with scopolamine being a classic amnestic drug, it is indeed possible that its impairing effect on cognition is the result of its general amnestic action (Bushnell et al., 1997). The lack of scopolamine on response latency suggests that the choice accuracy impairments were not merely due to an increased time over which memory processes were needed with scopolamine.

Methylphenidate, when given alone at a relatively low dose of 0.3 mg/kg, significantly improved attentional performance in intact rats which had a relatively low performance baseline in the attention task (i.e. Scopolamine Study) but not in rats with relatively higher performing baselines (i.e. Dizocilpine and Mecamylamine Studies). In the methylphenidate–scopolamine experiment, the average baseline for the percent hit, which was 68.4±4.4%, improved and reached to 75.2±4.4% following the 0.3 mg/kg methylphenidate treatment. However, percent

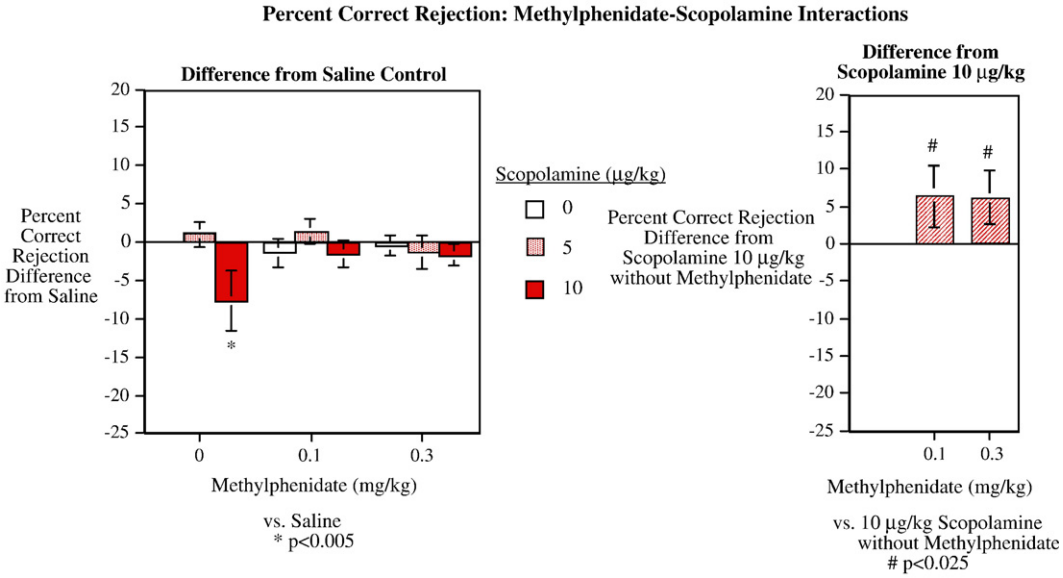

Fig. 2. Effects of methylphenidate and scopolamine alone and in combination on correct rejection. The actual level of accuracy for percent correct rejection for the saline control session was 75.5±4.6. Data represent means±S.E.M. *N*=11.

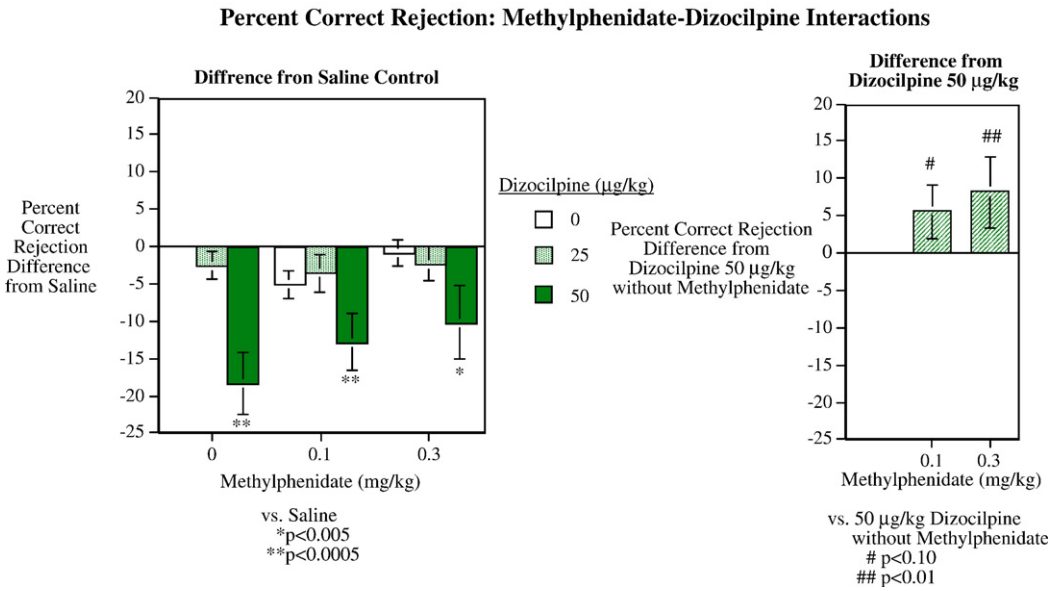

Fig. 3. Effects of methylphenidate and dizocilpine alone and in combination on correct rejection. The actual level of accuracy for percent correct rejection for the saline control session was 79.6±1.9. Data represent means±S.E.M. $N=24$.

correct rejection did not increase (Fig. 1), probably because it was already high. In other experiments, such as methylphenidate–mecamylamine and methylphenidate–dizocilpine, methylphenidate when given alone did not improve performance, probably because of higher level of baseline performance to begin with. Recently, it was found that methylphenidate increased accuracy in the 5CSRT task in rats with a relatively low baseline performance (about 60% correct response with less than 20% omissions) (Paine et al., 2007). Our results are consistent with the findings of Puumala et al. (1996) who demonstrated that methylphenidate did not affect the choice accuracy in normal animals using the same task. Similarly, using the same visual signal attention task, Mcgaughy et al. (1999) found that administration of methylphenidate in intact rats did not affect performance and Mirza and Bright (2001) have demonstrated that nicotine treatment improved attention only in rats which had lower baseline performance. Our findings, regarding the effects of methylphenidate on low performing rats in attention task, is consistent with these reports. Thus, it appears that the lack of methylphenidate effect in the second cohort experiments may be is attributed to higher performing baseline in that cohort. This is consistent with the suggestion that psychostimulants only improve impulse control under conditions in which baseline levels of impulsivity are high, as is seen in patients with ADHD (Paine et al., 2007).

The effects of methylphenidate on cognitive processes, like attention, have been attributed to both the dopamine and norepinephrine-enhancing properties of the drug (Arnsten, 2001; Volkow et al., 1998; Schiffer et al., 2006). Methylphenidate has been postulated to interact with monoaminergic systems in the brain by blocking dopamine and norepinephrine transporters or by stimulating the release of catecholamine from granular stores (Mcmillen, 1983). Methylphenidate, which enhances cognitive function in rats, preferentially increased catecholamine neurotransmission within the prefrontal cortex, suggesting that the improving effect of methylphenidate on attention may involve the preferential activation of catecholamine neurotransmission within the prefrontal cortex (Berridge et al., 2006).

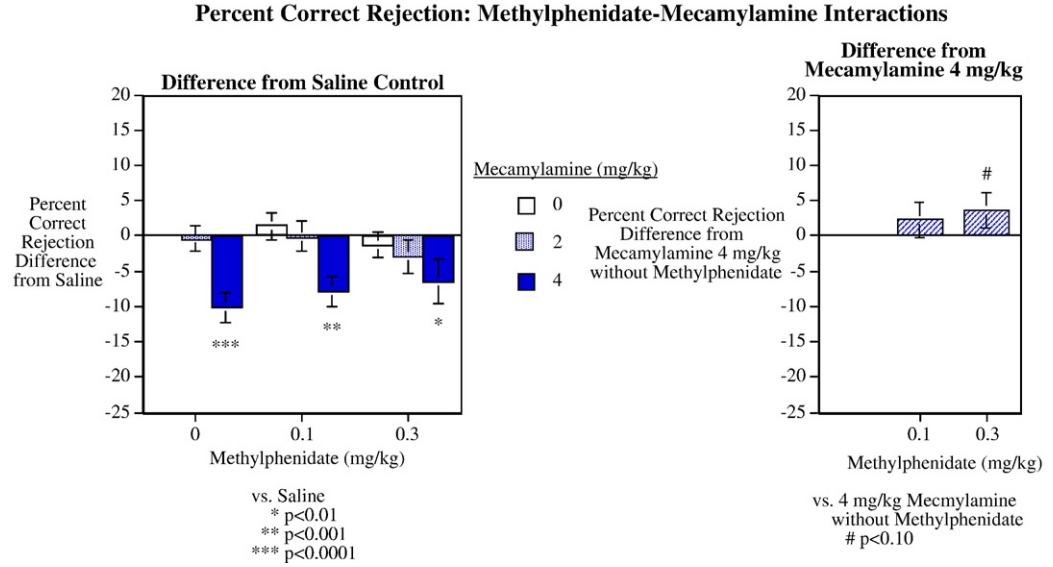

Fig. 4. Effects of methylphenidate and mecamylamine alone and in combination on percent correct rejection. The actual level of accuracy for percent correct rejection for the saline control session was 79.5±2.5. Data represent means±S.E.M. $N=24$.

As previously shown, dizocilpine at 50 μg/kg significantly impaired performance by reducing percent correct rejection; an effect that was reversed by 0.3 mg/kg methylphenidate. Dizocilpine did not have a significant effect on percent hit (Rezvani and Levin, 2003a). The current findings are consistent with our previous results which demonstrated that an acute administration of dizocilpine reduced sustained attention as measured by choice accuracy on a visual signal detection task (Rezvani and Levin, 2003a). Similar findings have been documented by other investigators suggesting that blockade of NMDA receptors impairs attentional performance in rats (Mirjana et al., 2004). Also, there is a large body of literature supporting a role for NMDA receptors in learning and memory (Castellano et al., 2001). It is conceivable that increase in locomotor activity induced by dizocilpine may contribute to its impairing effect on attention (Paine et al., 2007). The notion that methylphenidate at a higher dose when given alone did not have a significant effect on high performing rats but was able to reduce the impairing effects of dizocilpine may suggest a functional interaction between NMDA receptors and the central monoaminergic system. However, it is important to note that these drugs have different pharmacokinetic and pharmacodynamic profiles and their interaction with each other has not been studied.

Mecamylamine at the high dose of 4 mg/kg significantly impaired sustained attention by reducing both percent hit and percent correct rejection. This is consistent with our previous findings demonstrating that mecamylamine impairs sustained attention (Rezvani et al., 2002). However, contrary to our initial hypothesis, co-administration of methylphenidate failed to exert a significant effect on mecamylamine action on attention. It appears that the blockade of the nicotinic system by mecamylamine prevented methylphenidate from exerting its improving effects on sustained attention. A nicotinic function of methylphenidate has been suggested as mecamylamine blocks the effect of both nicotine and methylphenidate (Shih et al., 1976). These particular findings may suggest that an intact nicotinic system is required for methylphenidate to exert its effect on sustained attention. Alternatively, mecamylamine-induced side effects should be taken into consideration. Blurred vision; dizziness; and enlarged pupils have been reported as side effects of mecamylamine in humans. However, we are not sure if this was the case with the doses we used in theses studies. Increased in response latency and response omission by mecamylamine administration may have also contributed to the impairing effect of mecamylamine. Thus, although we do not know the side effects of this drug in rats, with the present data one cannot rule out the above mentioned side effects which might have a direct effect on visual detection. In addition, the effect of mecamylamine on motivation in rats in not known.

Overall, these findings suggest that scopolamine, mecamylamine, and dizocilpine when given systemically can impair sustained attention, and methylphenidate can reverse some aspects of these effects for scopolamine and dizocilpine but not for mecamylamine. These findings further validate the operant visual signal detection task for assessing drug effects on sustained attention and for developing novel treatment for attentional impairment. The successful detection of the beneficial therapeutic effects of methylphenidate in significantly attenuating scopolamine and dizocilpine-induced attentional impairments suggests that this task may be sensitive to the therapeutic effects of novel compounds under development.

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