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The Subtype Selective Nicotinic Acetylcholine Receptor Agonist SIB-1553A Improves Both Attention and Memory Components of A Spatial Working Memory Task in Chronic Low Dose MPTP-Treated Monkeys

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chronic low dose (CLD); 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); novel neuronal nicotinic acetylcholine receptor (nAChR); variable delayed response task (VDR); Wisconsin General Test Apparatus (WGTA).

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Abstract

Monkeys that receive chronic low dose (CLD) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration develop deficits in spatial delayed response task performance. The present study examined the extent to which SIB-1553A ((±)-4-{[2-(1-methyl-2-pyrrolidinyl)ethyl]thio}phenol hydrochloride), a novel neuronal nicotinic acetylcholine receptor (nAChR) agonist with selectivity for β4 subunit-containing nAChRs, could counteract this cognitive deficit produced by CLD MPTP exposure. Prior to MPTP treatment, monkeys displayed a delay-dependent decrement in performance on a variable delayed response (VDR) task. CLD MPTP treatment caused a shift to a delay-independent pattern of responding on this task, such that short delay trials were performed as poorly as long delay trials. At lower doses (e.g., 0.025 mg/kg), SIB-1553A significantly improved performance on short delay trials but only at 24 hrs. after drug administration. At higher doses (e.g., 0.50 mg/kg) SIB-1553A significantly improved performance on both short and long delay trials, at both 20 min. and 24 hr. after drug administration. When tested 24 hr. after drug administration, monkeys performed long delay trials with greater accuracy than they did under normal (pre-MPTP) conditions. These results suggest that at lower doses, SIB-1553A may be more effective in improving attentional deficits while at higher doses, SIB-1553A may effectively improve both attentional and memory performance deficits associated with CLD MPTP exposure.

The cognitive deficits associated with Parkinson's disease continue to be among the least understood symptoms of this disease, as well as the least responsive to current pharmacological treatments. Non-demented Parkinson's disease (PD) patients display a number of neuropsychological deficits that are present at all stages of the disease (Lees and Smith, 1983; Boller, et al., 1984; Taylor and Saint-Cyr, 1986; Brown and Marsden, 1988). These deficits are mostly 'frontal-like' in nature and consist of problems of attention (Flowers and Roberston, 1985; Downes et al., 1989; Sharpe, 1990; Sharpe, 1992) and 'executive functions' (e.g., planning and cognitive flexibility) (Cooper et al., 1991; Owen et al., 1992). Other cognitive functions such as working memory have been found to be relatively unimpaired in PD patients (Taylor and Saint-Cyr, 1986; Freedman and Oscar-Berman, 1986) but when present may be related to attentional processes involved in task-related learning strategies (Pillon, et. al, 1998; Nieoullon, 2002) .

A number of cognitive deficits have also been described in monkeys following chronic administration of low doses of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Schneider and Kovelowski, 1990; Schneider and Roeltgen, 1993; Roeltgen and Schneider, 1994). Chronic low dose MPTP (CLD MPTP)-treated monkeys display deficits in performance of delayed response, delayed alternation, delayed matching-to-sample, visual discrimination reversal, and object retrieval tasks, while motor functioning and the ability to perform a reference memory task (e.g., visual pattern discrimination) remains intact.

Cognitive deficits in Parkinson's disease patients are often not significantly improved by dopamine replacement therapy (Cooper et al., 1992; Lange et al. 1992) and in some instances may even be exacerbated by this treatment (Gotham et al., 1988). Likewise, cognitive deficits in CLD MPTP-treated monkeys have been mostly unresponsive to levodopa administration (Schneider et al., 1999). On the other hand, the β2 subtype selective nAChR agonist (S)-(-)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine (SIB-1508Y), but not nicotine, significantly improved attentional aspects of cognitive performance in these monkeys (Schneider et al., 1999). The failure of nicotine to improve task performance in these animals was believed to be related to the low doses of nicotine used (the dose range was limited due to nicotine-induced emesis) and the nonselective effects of nicotine at nicotinic acetylcholine receptors (Schneider et al., 1999).

Subtype selective nAChR agonists are attractive candidates for cognition-enhancing agents due to their general ability to stimulate release of a variety of neurotransmitters, neuropeptides and amino acids from numerous brain regions (Decker and Brioni, 1997; MacDermott et al., 1999). While SIB-1508Y is primarily a β2 selective agonist, SIB-1553A ((±)-4-{[2-(1-methyl-2-pyrrolidinyl)ethyl]thio}phenol hydrochloride) is a novel nAChR agonist with selectivity for β4 subunit-containing receptors (Reid et al., 1997; Vernier et al., 1999). The different nAChR subtype selectivity for SIB-1553A compared to SIB-1508Y and nicotine may result in different pharmacological profiles. While both drugs stimulate the release of dopamine and norepinephrine at cortical and subcortical sites (Reid et al., 1997; Vernier et al., 1999), SIB-1553A appears to be a more potent releaser of hippocampal and prefrontal cortical

acetylcholine than either nicotine or SIB-1508Y (Reid et al., 1997; Vernier et al., 1999; Menzaghi et al., 1999).

In view of the above-described properties of SIB-1553A and our previous study of the effects of another nAChR agonist, SIB-1508Y, on delayed response performance in CLD MPTP-treated monkeys, the present study was conducted to evaluate the potential cognition enhancing properties of SIB-1553A in the same non-human primate model of early parkinsonism.

Materials and Methods

Three adult male Macaca fascicularis monkeys (5.4 to 6.9 kg body weight at the start of the study) were previously trained to perform a variable delayed response (VDR) task while seated inside a modified Wisconsin General Test Apparatus (WGTA) (Schneider and Kovelowski, 1990). These animals also previously received chronic low dose MPTP administration (0.075 to 0.20 mg/kg) over periods ranging from 38 to 178 days in order to produce stable cognitive deficits. The details of chronic low dose MPTP administration have been described previously (Schneider et al., 1999). All procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee.

Variable Delayed Response Task

The monkeys sat in a restraining chair situated in a sound-attenuating chamber with background masking noise, behind an opaque screen that when raised, allowed access to a sliding tray. The tray contained recessed food wells and identical sliding red Plexiglas covers that served as stimulus plaques that could be displaced by the animal to obtain rewards (raisins, dried fruit). The monkeys were trained to retrieve food from one of the wells after observing the experimenter bait a well. Right and left wells were baited in a balanced order. Five different delay lengths were randomly distributed in blocks of trials over the 30 trials that made up a daily testing session. The delays used were 2, 5, 10, 20, and 30 secs. These delay conditions yielded performance of approximately 60% correct at the longest delays. Animals were food deprived overnight prior to testing.

Drug Administration

These animals were previously used to assess the effects of SIB-1508Y, nicotine and levodopa on cognitive deficits produced by chronic low dose MPTP administration (Schneider et al., 1999). Testing with SIB-1553A commenced at least 4 months after the last administration of any other drug. SIB-1553A (synthesized by SIBIA Neurosciences, Inc.,) was diluted in sterile saline immediately prior to each drug testing session. The range of drug doses used was 0.00625 to 0.5 mg/kg, administered intramuscularly, 20 minutes prior to testing. SIB-1553A was administered in ascending doses and there was a minimum 4 day washout period between administration of drug. Control testing sessions (no injection or saline injection) were performed on days between SIB-1553A testing to assess any residual or long-lasting effects from SIB-1553A administration and to insure that baseline performance levels were stable and maintained prior to the next drug testing session. A subsequent dose of SIB-1553A was administered only if task performance was at baseline levels. Each dose of SIB-1553A was assessed in comparison to baseline (e.g., nondrug) performance during the days immediately preceding the SIB-1553A testing. During some of these sessions, saline injections were administered before testing.

Data Analysis

Each dose of SIB-1553A was administered at least twice and the data from individual animals were pooled for statistical analysis. The most efficacious dose of SIB-1553A for each animal was determined from the ascending dose-response data and was averaged and analyzed as 'best dose' effects. Task performance on drug was compared

with matched control (nondrug) performance for each animal. Thus, animals served as their own controls and statistical analyses used repeated measures designs: one way ANOVA followed by post hoc comparisons using Newman-Keuls test. Values of $p < 0.05$ were considered significant.

Results

Before MPTP exposure, all monkeys performed well on the VDR task (88.4% correct ± 1.5) and showed a delay-dependent decrement in performance. That is, performance at short to intermediate duration delays was almost flawless (2 sec. = 98.3% correct responses ± 1.2 , 5 sec. = 96.2% ± 1.9, and 10 sec. = 93.1% ± 2.5) and performance declined with increasingly long delay durations (20 sec. delay = 78.2% ± 3.2; 30 sec. delay = 67.5% ± 3.0) (Figure 1A). Pre-MPTP data reflect mean performance during the five testing sessions immediately prior to the start of MPTP exposure.

The performance of these same monkeys after CLD MPTP exposure declined to an overall performance level of 70.6% correct (± 1.6) ($p < 0.001$ vs. performance prior to MPTP). In addition, the delay-dependent performance profile shifted to a delay-independent profile. That is, monkeys were as likely to perform poorly on short delay trials (e.g., 2 and 5 sec. delay trials = 70.2% correct responses ± 2.0, 69.0% ± 2.0, respectively) as on long delay trials (e.g., 10 sec. (71.8% ± 2.3), 20 sec. (72.2% ± 2.2) and 30 sec. (60.9% ± 2.3) delay trials (Figure 1B). The effect of MPTP exposure on performance at different delays was significant [$F(9, 513) = 82.6$, $p < 0.001$]. Pairwise post-hoc comparisons showed that performance at 2, 5 and 10 s delays were changed significantly after MPTP exposure ($p < 0.01$ for each) whereas performance at 20 and 30 s delays was not significantly affected by the MPTP exposure (Figure 1B). Post-MPTP data reflect mean performance during the five testing sessions immediately prior to the start of SIB-1553A testing.

SIB-1553A improved VDR performance in a dose-dependent manner (Table 1). SIB-1553A at the best (e.g., most efficacious) dose used (0.50 mg/kg for 2 animals. 0.10 mg/kg for 1 animal) improved overall VDR performance in all monkeys when tested at both 20 min. (85.0% correct ± 2.2) and 24 hrs. after drug administration (91.2% correct ± 1.8). At this dose, both immediate [$F(9, 57) = 369.1$, $p < 0.0001$) and long-lasting effects [$F(9, 57) = 609.0$, $p < 0.0001$) were observed (Figure 2). At lower doses, SIB-1553A improved performance only at short duration delays (e.g, 2 or 5 s, Table 1). In contrast, twenty minutes after administration of the best dose of SIB-1553A, performance improved on short delay trials (2 and 5 s, $p < 0.01$ vs. baseline) as well as on long delay trials (10 s, $p < 0.01$, 20 s, $p < 0.05$, 30 s, $p < 0.01$) (Table 1, Figure 2). Twenty-four hrs. after drug administration, performance was still improved on both short delay trials (2 and 5 s, $p < 0.01$ vs. baseline) as well as on long delay trials (10, 20 and 30 s, $p < 0.01$ vs. baseline) (Table 1, Figure 2). In addition, when tested 24hrs. after SIB-1553A administration, animals performed 20 and 30 s delay trials significantly better ($p < 0.05$) than they did during normal, pre-MPTP testing ([$F(14, 210) = 16.5$, $p < 0.001$], Figure 3).

Discussion

The results of this study support a cognition enhancing effect of SIB-1553A, a β4-selective nAChR agonist, in chronic low dose MPTP-treated monkeys. As we have reported previously, monkeys developed deficits in performance of a spatial working memory task (e.g., variable delayed response task) after chronic exposure to low doses of MPTP (Schneider et al., 1999; Schneider et al., 2002). Normally, monkeys perform this task almost flawlessly on shorter delay trials and produce an increased number of errors at longer delay trials. As previously suggested, attentional processes play a greater role in performance of short delay trials (where load on working memory is minimal) whereas performance on longer delay trials reflects the limits of normal working memory in these animals (Schneider et al., 1999). After CLD MPTP exposure, VDR task performance was impaired, primarily because animals made approximately the same number of errors on short delay trials as on long delay trials. In the present study, SIB-1553A not only enhanced attentional processes (e.g., improved performance on short delay trials) but also improved spatial working memory functioning (e.g., improved performance on long delay trials). Interestingly, SIB-1553A did not produce a classical dose-response curve in that the quantitative aspect (magnitude) of the effect (mean percent correct responses) did not increase with dose but there was a qualitative enhancement of effect with increased dose.

The present findings are consistent with other reports of beneficial effects of SIB-1553A on attention (Terry et al., 2002) and non-spatial working memory (Bontempi et

al., 2001) in monkeys. SIB-1553A shared the property of enhancing attention with other nAChR agonists, such as SIB-1508Y (Schneider et al., 1999), ABT-418 and ABT-089 (Prendergast et al., 1998). However, in contrast to other drugs tested in our model system, including the β2-selective nAChR agonist SIB-1508Y (Schneider et al., 1999), SIB-1553A significantly improved performance on long delay trials as well as on short delay trials. In addition, after SIB-1553A administration, animals performed long-duration delay trials more accurately than when they were normal (i.e., pre-MPTP).

At this point, it is premature to ascribe these unique behavioral effects of SIB-1553A solely to its selectivity for β4 nAChR subtype receptors. The different behavioral effects of SIB-1553A vs. SIB-1508Y may be explained, at least in part, by the different pharmacological profiles of the two drugs. Both SIB-1553A and SIB-1508Y are more effective than nicotine itself in stimulating dopamine and norepinephrine release from striatum, limbic areas and frontal cortex (Vernier et al., 1999; Menzaghi et al, 1999). Since striatal and prefrontal noradrenergic and dopaminergic mechanisms have been implicated in attentional functioning in non-human primates (Goldman-Rakic, 1981; Arnsten et al., 1984; Nieoullon, 2002), and these transmitters are decreased in these brain regions in CLD MPTP-treated monkeys (Schneider, 1990), it is possible that nAChR agonist-induced improvements in attention were related to the ability of SIB-1553A (as well as SIB-1508Y (Schneider et al., 1999) to stimulate release of cortical and subcortical catecholamines. The different effects of SIB-1553A and SIB-1508Y on spatial working memory may be related to the different effects of these drugs on acetylcholine release. SIB-1553A is much more effective than either nicotine or SIB-1508Y in stimulating the

release of acetylcholine from the hippocampus and frontal cortex (Menzaghi et al., 1999; Vernier et al., 1999). Additionally, SIB-1553A has weak agonist activity at histaminergic H_3, serotonergic $_{1A}$ and sigma receptor sites (Terry et al., 2002). Thus, due to the complex pharmacological profile of SIB-1553A, behavioral effects of this drug cannot at this time be ascribed to any particular neurochemical function. They are likely due to a complex interaction of all of the above-mentioned nicotinic and non-nicotinic mechanisms. Although it is enticing to ascribe the unique behavioral effects of SIB-1553A to activation of the β4 nAChR subtype, more work is needed to define the nAChR subtype changes that may occur in CLD MPTP-treated monkeys before the role of the β4 receptors in attention and working memory can be defined.

The sustained behavioral effects of SIB-1553A, observed 24 hrs. after administration are of considerable interest. A trend towards improved levels of working memory performance the day after i.m. administration of SIB-1553A has also been described in monkeys (Bontempi et al., 2001), although this effect was thought not be as robust as that seen with nicotine itself (Buccafusco and Jackson, 1991). The mechanisms contributing to the long-lasting behavioral effects observed in the present study are unclear, particularly since these effects outlast the biological half-life of SIB-1553A, but may be related to the interaction of SIB-1553A with potentially up-regulated nAChRs in CLD MPTP-treated monkeys (Kulak et al., 2002].

In conclusion, the β4 selective nAChR ligand SIB-1553A improved attention and spatial working memory in a non-human primate model of early Parkinson's disease.

These cognition enhancing effects of this drug suggest that it may improve not only some of the cognitive deficits associated with Parkinson's disease but may have more general beneficial effects as a cognition enhancing agent. The improved behavioral profile for this drug, compared to other nAChR agonists, may be due to its unique pharmacological profile. The possibility that the β4 selectivity of this drug underlies its effects on attention and memory deserves further scrutiny.

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Figure Legends

Figure 1. Variable delayed response performance prior to (A) and following chronic low dose MPTP administration (B). In intact monkeys (A), there was a delay-dependent decrease in correct performance. Performance at 20 and 30 sec delays was significantly worse than at 2, 5 and 10 sec delays. After MPTP exposure (B), performance at the short duration delays deteriorated compared to normal ($p < 0.01$, 2, 5, and 10 sec delays) while performance at the longest delays was not significantly different from normal. Data shown are mean ± SEM for 3 animals. *$p < 0.01$ vs 2, 5 and 10 sec delay performance.

Figure 2. Best dose data for SIB-1553A effects on variable delayed response (VDR) performance, assessed at 20 min (A) and 24 hrs (B) after drug administration. Responses to the most efficacious dose of SIB-1553A and responses during corresponding non-drug baseline were averaged (mean ± SEM) for three animals tested on this task. At both 20 min. and 24 hrs. after drug administration, SIB-1553A caused significant improvements in performance at both short and long duration delays (2 to 30 sec.), compared to the corresponding non-drug baseline. *$p < 0.01$ vs. corresponding baseline. Black bars = post-MPTP, non-drug baseline; white bars = best dose SIB-1553A performance.

Figure 3. Cognition enhancing effects of the best dose of SIB-1553A compared to normal (pre-MPTP) baseline performance. When tested 24 hr. after drug administration, monkeys performed long delay trials of the variable delayed response task with significantly greater accuracy than they did under normal (pre-MPTP, non-drug)

conditions. * $p < 0.05$ vs. corresponding pre-MPTP performance. Black bars = normal, pre-MPTP performance; white bars = best dose SIB-1553A performance. Data were averaged (mean ± SEM) for 3 animals.

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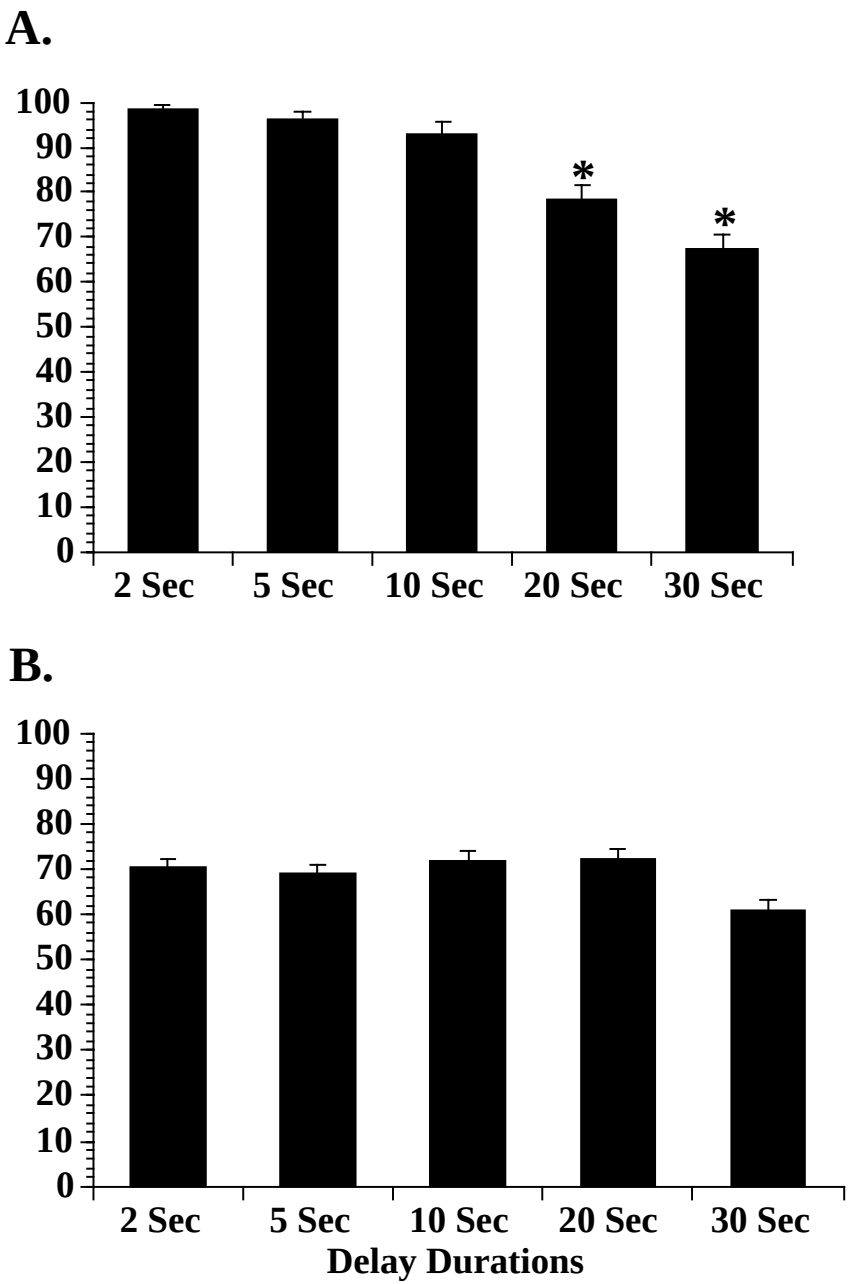
Table 1. SIB-1553A Effects on Variable Delayed Response Performance in MPTP-Treated Monkeys

Condition	**Delay Duration (Seconds)**				
	2	**5**	**10**	**20**	**30**
Baseline[1]	75.1 (4.9)	74.3 (4.5)	70.3 (7.0)	66.4 (5.0)	59.8 (5.0)
0.0062 mg/kg (20 min.)	73.2 (6.0)	77.5 (5.0)	81.5 (5.3)	75.2 (8.5)	69.0 (7.1)
0.0062 mg/kg (24 hrs.)	85.6 (7.4)	80.5 (4.1)	78.1 (7.7)	66.7 (5.3)	67.0 (6.9)
Baseline	71.0 (6.2)	69.0 (4.6)	73.8 (5.1)	69.7(5.6)	61.3 (6.7)
0.0125 mg/kg (20 min.)	82.1 (5.1)	82.1 (7.2)	84.8 (5.4)	79.4 (4.2)	68.2 (6.6)
0.0125 mg/kg (24 hrs.)	**87.7 (6.7)***	81.4 (6.7)	81.5 (5.3)	72.1 (5.6)	70.4 (5.7)
Baseline	73.4 (9.9)	71.7 (3.5)	71.7 (8.5)	69.0 (7.0)	62.0 (7.5)
0.025 mg/kg (20 min.)	78.1 (10.6)	79.8 (7.1)	84.6 (4.6)	80.0 (5.8)	73.5 (7.6)
0.025 mg/kg (24 hrs.)	**95.5 (2.2)****	**90.9 (4.5)***	86.2 (4.9)	81.5 (6.2)	68.9 (8.8)
Baseline	72.4 (2.7)	69.8 (5.9)	71.1 (7.2)	68.3 (4.7)	66.8 (6.2)
0.05 mg/kg (20 min.)	78.0 (5.0)	**86.7 (4.6)***	73.9 (5.3)	73.9 (5.3)	65.6 (7.7)
0.05 mg/kg (24 hrs.)	**87.7 (3.6)***	77.9 (6.7)	82.1 (5.1)	79.3 (4.7)	76.6 (3.8)
Baseline	64.1 (5.3)	76.6 (3.8)	63.8 (4.7)	66.4 (6.5)	62.7 (6.9)
0.10 mg/kg (20 min.)	**87.6 (6.3)****	**86.0 (6.6)***	**81.5 (4.1)***	70.4 (3.3)	75.3 (6.7)
0.10 mg/kg (24 hrs.)	**98.5 (1.5)****	**93.9 (3.3)***	**94.0 (2.3)****	**86.1 (3.7)***	76.9 (4.9)
Baseline	70.0 (5.0)	70.1 (3.8)	71.5 (5.3)	65.2 (5.5)	57.6 (3.4)
0.50 mg/kg (20 min.)	**98.9 (1.1)****	**92.1 (3.5)****	**88.9 (2.6)***	**79.7 (6.1)***	**77.5 (5.7)****
0.50 mg/kg (24 hrs.)	**92.3 (3.4)****	**89.0 (2.0)****	**93.4 (3.5)****	**87.6 (3.4)****	**84.4 (3.4)****

* $p<0.05$; ** $p < 0.01$, compared to corresponding baseline (bold). Values presented are mean percent correct performance ± SEM

[1] Baseline values obtained from non-drug or saline injection sessions performed immediately prior to drug testing sessions



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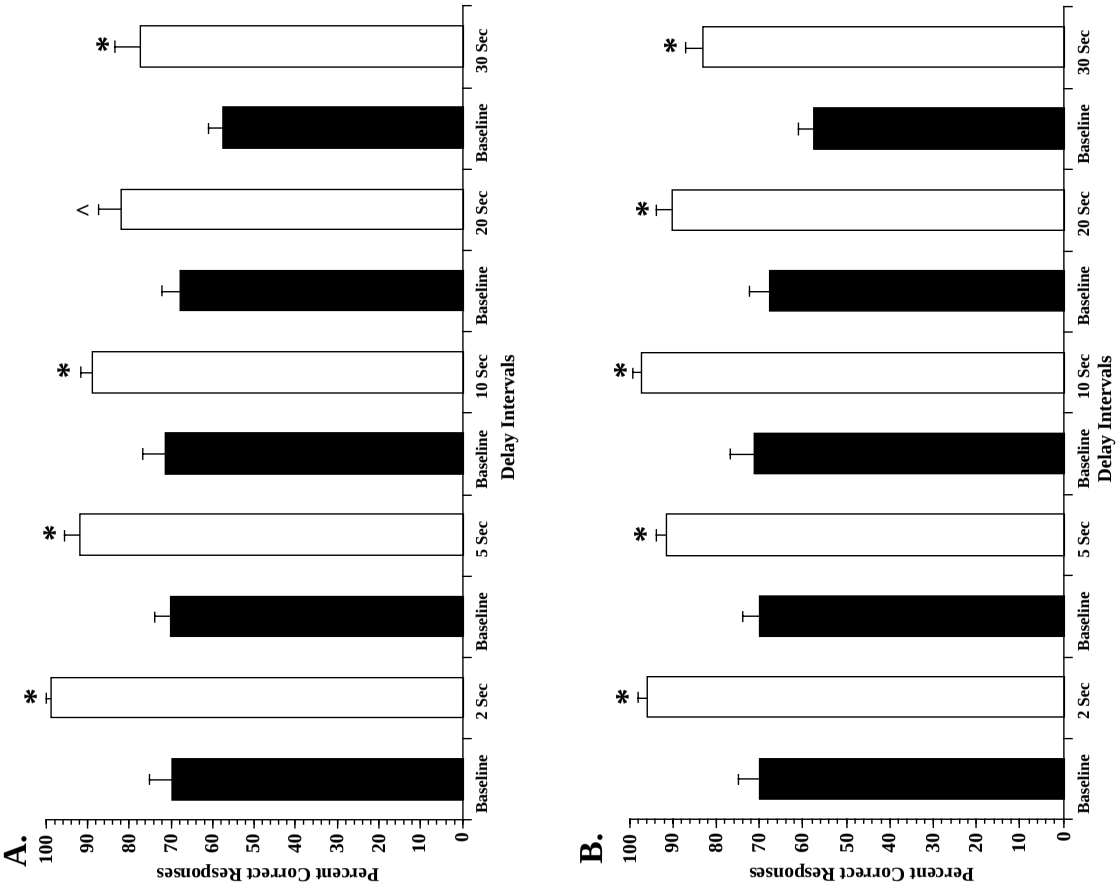

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