Nicotinic Acetylcholine Receptor Agonist SIB-1508Y Improves Cognitive Functioning in Chronic Low-Dose MPTP-Treated Monkeys

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ABSTRACT

Monkeys that receive chronic low-dose 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration have difficulty performing numerous cognitive tasks. This study further examines the extent to which chronic low-dose MPTP exposure affects performance of a visual memory task [variable delayed response (VDR)] with both attentional and short-term memory components and assesses the effects of the novel neuronal nicotinic acetylcholine receptor agonist SIB-1508Y and levodopa on cognitive task performance. Before MPTP treatment, these monkeys displayed a delay-dependent decrement in performance on the VDR task and performed well on delayed matching-to-sample and visual pattern discrimination tasks. Chronic low-dose MPTP treatment caused a shift to a delay-independent pattern of responding on the VDR task, such that short-delay trials were performed as poorly as long-delay trials. There were also deficits in performing the delayed matching-to-sample task, whereas visual discrimination performance remained intact. SIB-1508Y normalized the pattern of response on the VDR task by significantly improving performance on short-delay trials and on the delayed matching-to-sample task. These effects lasted up to 24 to 48 h after SIB-1508Y administration. Neither levodopa nor nicotine significantly improved task performance. These results suggest that chronic low-dose MPTP exposure results in a cognitive disturbance that can be corrected by the nicotinic acetylcholine receptor agonist SIB-1508Y but not by levodopa. Thus, SIB-1508Y may be useful in the treatment of the cognitive deficits in Parkinson’s disease.

Numerous cognitive deficits have been described in monkeys after chronic administration of low doses of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; Schneider et al., 1988; Schneider and Kovelowski, 1990; Schneider and Roeltgen, 1993). In particular, deficits were observed in performance of delayed response (DR), delayed alternation, delayed matching-to-sample (DMS), visual discrimination reversal, and object-retrieval tasks. Correct performance of all of these tasks is believed to be dependent on the integrity of frontostriatal circuits (Battig et al., 1960; Divac et al., 1967; Brozoski et al., 1979). These monkeys had virtually normal motor functioning and retained the ability to perform a visual pattern-discrimination task, performance of which is most likely dependent on the integrity of the inferotemporal cortex (Divac et al., 1967).

Nondemented Parkinson’s disease (PD) patients also show several neuropsychological deficits that are present at all stages of the disease (Lees and Smith, 1983; Levin et al., 1989; Owen et al., 1993a). Many of these deficits are “frontal” in nature and consist of problems in attentional set shifting (Owen et al., 1993b), distractibility (Sharpe, 1990), and planning and “executive functions” (Moris et al., 1988). In contrast to Alzheimer’s disease patients (Sahakian et al., 1988), PD patients are characterized more by apparent attentional impairments than by memory impairments.

Although many of the motor symptoms of PD can often be controlled successfully with levodopa (L-dopa) therapy, the same cannot be said for many of the cognitive deficits of PD. Some parkinsonian cognitive deficits may be dopa-responsive, but others are not (Cooper et al., 1992; Lange et al., 1992). Furthermore, L-dopa therapy, at doses optimal for controlling motor symptoms, may exacerbate some cognitive problems (Gotham et al., 1988). Whereas the effects of L-dopa on cognitive disturbances in PD remain controversial, it is apparent that cognitive dysfunction in PD remains poorly understood, and treatment of cognitive dysfunction represents a major, unmet therapeutic need of PD patients.

Several lines of evidence suggest that nicotine may have
protective (Baron, 1986; Morens et al., 1995) and ameliorative (Moll, 1926; Ishikawa and Miyake, 1993; Fagerstrom et al., 1994) effects on PD. Although controlled clinical studies have not directly examined nicotine effects on cognition in PD patients, nicotine has improved attention in adults with attention deficit/hyperactivity disorder (Levin et al., 1995) and has improved perceptual and visual attentional (but not visual short-term memory) deficits in Alzheimer’s disease patients (Jones et al., 1992). Despite the potential therapeutic effects of nicotine, dose-limiting side effects on the gastrointestinal and cardiovascular systems, most likely relating to lack of specificity of nicotine for central versus peripheral nicotinic acetylcholine receptors (nAChRs), limit its use for treating chronic disorders such as PD. Compounds that selectively activate central nAChR subtypes, stimulating release of dopamine, acetylcholine, and norepinephrine from presynaptic terminals, might be more effective therapeutic agents. The nAChR agonist (S)-(−)-5-ethyl-3-(1-methyl-2-pyrrolidinyl)pyridine (SIB-1508Y) may be such a compound, because it has been reported to enhance striatal dopamine and hippocampal acetylcholine release in vivo (Menzaghi et al., 1996; Sacan et al., 1997a,b), to stimulate locomotor activity in rats (Menzaghi et al., 1997a,b), and to improve motor function in monkeys with MPTP-induced parkinsonism (Schneider et al., 1998a).

These studies were conducted to 1) assess the extent to which chronic low-dose MPTP-treated monkeys, with cognitive deficits but not a coexisting parkinsonian motor disorder, exhibit performance deficits on visual memory tasks with both attentional and short-term memory components and 2) assess the effects of SIB-1508Y on the frontal-like cognitive dysfunction in these animals.

Materials and Methods

Four adult male Macaca fascicularis monkeys (5.4–6.9 kg b.wt. at the start of the study) and one adult female M. nemestrina monkey (5.3 kg b.wt. at the start of the study) were trained to perform DR tasks, and two of these monkeys were also trained to perform a DMS task. Two monkeys performed computer-automated DR tasks while seated in front of a touch-sensitive computer monitor, whereas the other two monkeys performed similar tasks while seated inside a modified Wisconsin General Test Apparatus (Schneider and Kovelowski, 1990). Before the start of training, all monkeys were adapted to chair restraint and the experimental setup. Monkeys performing automated and nonautomated tasks were water and food deprived, respectively, overnight before testing.

Automated Testing

Spatial DR. During the test session, the monkey 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. Each daily session consisted of 30 trials. Animals were trained until performance with a 2-s cue and 5-s delay was 90% correct or better on 5 consecutive days.

For VDR testing, five different delay lengths were randomly distributed in blocks of trials over the 40 trials that made up a daily testing session. In two of the animals, the delays were 2, 5, 10, 20, and 30 s. In a third animal, the delays were 2, 5, 10, 20, and 60 s. These delay conditions yielded performance of approximately 60% at the longest delays.

Drug Administration

Once animals achieved stable baseline task performance, MPTP administration began. MPTP-HCl was administered i.v. two or three times per week while animals were seated in a restraining chair, as described previously (Schneider and Kovelowski, 1990). Adequate precautions were taken to protect personnel from exposure to MPTP during injections and from any possible unmetabolized MPTP in
animal excreta (Schneider and Roeltgen, 1993). MPTP was adminis-
tered to each animal in doses ranging from 0.075 mg/kg at the start of the study to 0.20 mg/kg. By the time drug testing commenced, animals had received cumulative MPTP doses of 8.2, 11.6, 14.4, 16.0, and 36.1 mg over periods of 38, 84, 99, 83, and 178 days, respectively. The different total amounts of MPTP administered reflect individual animal variability in response to the toxin. Although somewhat different amounts of MPTP were administered to different animals for different periods, the nature of the cognitive deficits were similar in all animals. Pharmacological testing commenced after animals consistently showed at least a 15% performance deficit on the standard DR task for at least 1 week. On average, pharmacological testing began 16 ± 6 days after the last injection of MPTP. SIB-1508Y (synthesized by SIBIA Neurosciences, Inc., La Jolla, CA) was diluted in sterile saline immediately before each drug-
testing session and pH adjusted to approximately 7.0 by the addition of 1 N NaOH, when necessary. The range of drug doses used was 0.5 to 2.5 mg/kg i.m. administered approximately 20 min before testing. The 20-min injection/test interval was based on the onset of SIB-
1508Ys motor effects in parkinsonian MPTP-treated monkeys (Schneider et al., 1998a). Different doses of SIB-1508Y were adminis-
tered in quasi-random order (Arndt et al., 1988) and not more than once or twice per week in any individual monkey. In some cases, extended washout periods were necessary because of long-lasting effects of some doses in some animals. Noninjection control sessions were performed on days between SIB-1508Y testing, and saline vehicle control sessions were randomly interspersed between SIB-
1508Y sessions. Each dose of SIB-1508Y was assessed in comparison to nondrug performance during the days immediately preceding the SIB-1508Y testing. During some of these sessions, saline injections were administered before testing.

The effects of L-dopa treatment on cognitive deficits were also assessed in three of the monkeys. L-Dopa methyl ester (2.5, 5.0, 10.0, 15.0, or 20.0 mg/kg; Sigma Chemical Co., St. Louis, MO) was dissolved in sterile saline and injected i.m. 30 min after injection of benserazide (10 mg/kg i.m.; Hoffman LaRoche, Nutley, NJ). Behavioral testing began 20 to 30 min after l-dopa administration. Doses of 15.0 and 20.0 mg/kg i.m. of l-dopa methyl ester in combination with benserazide are known to markedly ameliorate the motor deficits observed in parkinsonian MPTP-treated monkeys (Schneider et al., 1998a).

Two of the monkeys were also tested for effects of nicotine on cognitive performance. Nicotine bitartrate (Sigma) was dissolved in sterile saline and administered i.m. in doses of 0.10, 0.25, and 0.50 mg/kg. Behavioral testing began approximately 20 min after nicotine administration. As with SIB-1508Y testing, each dose of L-dopa and nicotine was assessed in comparison to nondrug performance during the days immediately before drug testing.

**Data Analysis**

Each dose of each drug was replicated at least twice, and the data were pooled for statistical analysis. Task performance on drug was compared with matched control performance (nondrug) within the same week. Animals served as their own controls, and statistical analyses used repeated-measures designs: one-way ANOVA on all drug doses, with pairwise post hoc comparisons (paired t-test, Bonferroni correction) of baseline (nondrug) and drug performance.

**Results**

Animals learned the automated and nonautomated tasks to similar criterion levels, and the tasks were disrupted to a similar degree by MPTP exposure and responded similarly to drug treatments (Fig. 1C). This suggested that, although technically different, the tasks were assessing the same cogni-

tive domains. Thus, the data from automated and nonauto-
mated testing have been combined for analysis.

**Effects of Chronic Low-Dose MPTP Exposure on Spatial DR, VDR, DMS, and Visual Pattern Discrimination Performance.** Before initiation of MPTP exposure, the animals had a mean baseline performance of 91.5% correct responses (±4.8) on the standard 5-s DR task. All mon-
keys developed significant difficulties in performing this task after chronic low-dose MPTP exposure. Post-MPTP DR per-
fomance, before starting SIB-1508Y testing, was 63.3% correct responses (±5.7; t = 19.55, p < .0001; Fig. 1B).

Before MPTP exposure, all monkeys performed well on short-delay trials on the VDR task. Performance of this task deteriorated in a delay-dependent manner, with almost chance performance at the longest delay (Fig. 2A). That is, in normal animals, there was a significant effect of delay, where performance at short delays (i.e., 2 or 5 s) differed significantly from performance at longer delays (10, 20, or 30 s, F(4,120) = 43.39, p < .0001]. Short-delay trials (2 and 5 s) were performed almost flawlessly (98.1 ± 0.9 and 96.1 ± 1.6% correct responses, respectively), whereas performance declined with increasingly long delays (10-s delay, 88.1 ± 2.6%; 20-s delay, 75.4 ± 3.2%; 30-s delay, 60.4 ± 2.9%). In one monkey, a 60-s delay was necessary before performance approached the chance level. Overall, monkeys performed the task at an 83.6 ± 7.0% correct level during the pre-MPTP baseline period.

After chronic MPTP exposure, overall performance on the VDR task deteriorated to 66.0 ± 3.1%. In contrast to the normal performance of this task, monkeys exhibited a delay-
dependent performance deficit after chronic exposure to MPTP. That is, monkeys were now almost as likely to perform poorly on 2- and 5-s delay trials (66.7 ± 3.1 and 68.3 ± 4.8% correct responses, respectively) as on 10- (59.6 ± 4.3%), 20- (64.3 ± 3.3%), and 30-s (or 60-s; 51.2 ± 4.5%) delay trials (Fig. 2B). The effect of MPTP exposure on performance at different delays was significant [F(9, 240) = 25.09, p < .0001] when performance at each delay was compared with performance at the same delay before MPTP exposure. Pairwise post hoc comparisons showed that performance at 2-, 5-, and 10-s delays changed significantly after MPTP exposure (t = 6.89, p < .001; t = 6.10, p < .001; t = 6.26, p < .001, respectively), whereas performance at 20- and 30-s delays (t = 2.43, p > .05; t = 2.00, p > .05, respectively) was unaffected by the MPTP exposure.

In the normal state before MPTP administration, the DMS task was performed at a level of 86.9 ± 4.1% correct responses at a 0-s delay and 82.5 ± 4.8% correct responses at a 3-s delay. After chronic MPTP exposure, performance on 0-s delay trials deteriorated to 66.3 ± 7.6% correct responses (t = 8.58, p < .0001), whereas performance on 3-s delay trials declined to 65.8 ± 3.9% correct responses (t = 10.04, p < .0001; Fig. 3).

Before receiving any MPTP, visual pattern discrimination was performed at a 97.5 ± 3.2% correct level, and task performance remained intact after chronic MPTP exposure (93.9 ± 5.4% correct responses; raw data not shown).

**Effects of SIB-1508Y on DR, VDR, DMS, and Visual Pattern Discrimination Performance.** There was no signif-
ificant difference in DR task performance in sessions after saline injection (66.5 ± 1.9% correct) or when there were no treatments at all (68.3% correct ± 1.6; t = 2.00, p > .05). This was true for performance on other tasks as well (data not shown). Thus, both saline and noninjection control sessions
were used for baseline comparisons. SIB-1508Y caused a dose-dependent improvement in performance of the standard 5-s DR task in the MPTP-treated monkeys ($F(8,72) = 5.616, p < .0001$; Fig. 1A). There were individual differences in the dose response to SIB-1508Y such that animals had a “best-dose” effect at different doses. We thus selected the best dose (the most facilitating dose of SIB-1508Y for each animal) and averaged these responses, as shown in Fig. 1B. Data from individual animals show that there are no differences between the results obtained from animals performing automated and nonautomated DR tasks. The same best-dose method of analysis was also used to show drug effects on the other behavioral tasks described below. As for the DR task, there were no differences in performance on automated versus nonautomated tasks (Fig. 1C). The average best dose for improvement on the DR task was 1.8 mg/kg (range, 1.0–2.5 mg/kg). When the best-dose effects from each animal were analyzed together, SIB-1508Y significantly improved spatial DR performance assessed 20 min after drug administration (88.7 ± 2.2% correct, $t = 10.05$, $p < .0001$, versus nondrug post-MPTP baseline) and 24 to 48 h after drug administration (91.4 ± 3.3% correct, $t = 9.13$, $p < .0001$, versus nondrug post-MPTP baseline; Fig. 1B). The best dose for cognitive effects was below the emetic dose (i.e., did not stimulate vomiting) and was not associated with any obvious distress or deleterious effects.

In addition to the immediate effects of SIB-1508Y on spatial DR performance, cognitive effects were also observed that lasted for days and, in the case of one monkey, weeks...
after SIB-1508Y administration. When tested 24 to 48 h after receiving SIB-1508Y, monkeys continued to show improved DR performance, often equal to or better than that observed 20 min after drug administration (Fig. 1). In some animals, the best response occurred 24 h after SIB-1508Y administration, whereas in other animals, it occurred 48 h after drug administration. Thus, long-response data are presented as data obtained at 24 to 48 h. In one monkey, spatial DR performance remained at an almost normal level for almost 1 month after administration of a single dose of 1.0 mg/kg SIB-1508Y (data not shown). Additional MPTP had to be administered to this monkey to reinstate its deficits. A second treatment with SIB-1508Y again reversed the cognitive deficit (data not shown).

Administration of SIB-1508Y also improved VDR performance in all monkeys (Fig. 4 and Table 1). Overall performance on the task increased in a dose-dependent fashion with administration of SIB-1508Y, and performance tended to revert back to a normal delay-dependent pattern of responding (Fig. 4). The average best dose for improvement on the VDR task was 1.7 mg/kg (range, 1.0–2.5 mg/kg). Both immediate [@F(5,40) = 7.59, p < .0001; Fig. 4A] and long-lasting [@F(5,90) = 7.87, p < .0001; Fig. 4B] effects (at least 24–48 h after drug administration) were observed. Twenty minutes after administration of SIB-1508Y, performance improved on short-delay trials (2, 5, and 10 s: t = 4.37, p < .001; t = 4.35, p < .001; t = 3.13, p < .05, respectively) but not on long-delay trials (20 or 30 s: t = 1.10, p > .05; t = 1.30, p > .05, respectively). Twenty-four to 48 h after SIB-1508Y, performance was still improved at 2-, 5-, and 10-s delays (t = 4.50, p < .001; t = 3.93, p < .001; t = 2.93, p < .05, respectively) but not at 20- or 30-s delays (t = 1.78, p > .05; t = 0.47, p > .05, respectively).

Improvements in DMS performance were also observed after SIB-1508Y administration. Although the dose-response curves were different for the two animals tested, best-dose analysis again revealed significant improvements in performance of both 0- and 3-s delay trials [@F(5,18) = 21.78, p < .0001; Fig. 3]. SIB-1508Y-induced improvements in task performance were observed 20 min after drug administration and were still apparent 24 to 48 h later. The average best dose for improvement on the DMS task was 1.8 mg/kg (range, 1.0–2.5 mg/kg).

SIB-1508Y had no effects on visual pattern discrimination performance (data not shown), which remained unimpaired throughout the study.

**Effects of L-Dopa and Nicotine on DR, VDR, DMS, and Visual Pattern Discrimination Performance.** Neither L-dopa (2.5–20.0 mg/kg, @F(5,55) = 0.95, p > .05) nor nicotine (0.10–0.50 mg/kg, @F(5,6) = 0.12, p < .05) had any significant effects on DR performance (Table 2). L-Dopa had no effect on DMS performance in two monkeys at either 0-s delay (@F(9,38) = 0.92, p > .05) or 3-s delay (@F(9,34) = 1.17, p > .05). Likewise, nicotine (0.10–0.50 mg/kg i.m., tested in two monkeys) did not improve performance on the DMS task.

**Discussion**

The results of this study confirm and extend our previous reports of cognitive deficits in chronic low-dose MPTP-treated monkeys. Although we have previously described deficits in DR and DMS performance (Schneider and Kovelowski, 1990; Schneider and Roelting, 1993), the results herein suggest that task performance deficits in these animals may be related to an attentional disturbance either independent of or in addition to a possible working memory deficit. On the DR and VDR tasks, the ability of the animals to maintain information about the location of the reward during the delay until retrieval is permitted (whether this is called working memory or sustained attention) depends on
monkeys may have developed attentional problems as a result of chronic MPTP exposure. The existence of a working memory deficit cannot be completely excluded, considering the nature of the tasks and the difficulty in completely separating attentional from memory components of performance. However, our interpretation is consistent with the human PD literature, in which PD patients have been shown to be impaired in performance of tests sensitive to frontal lobe dysfunction (Gotham et al., 1988; Lange et al., 1992; Owen et al., 1992) and tests of attentional abilities (Flowers and Robertson, 1985; Downes et al., 1989; Owen et al., 1992; Sharpe, 1990, 1992). PD patients also show delay-independent deficits in performance of a variable DMS task (Sahakian et al., 1988) similar in nature to the VDR task used in this study. This pattern of responding, where errors are made on trials with little or no demand on working memory, is suggestive of attentional difficulties and contrasts with delay-dependent deficits seen in Alzheimer disease patients, which are indicative of visual memory deficits (Sahakian et al., 1988). If the VDR performance deficit in chronic MPTP-treated monkeys was entirely due to a working memory problem, we would have seen performance consistently worsen as the working memory demands of the task increased. Such a response pattern was not observed.

These data also extend our knowledge of the cognitive effects of SIB-1508Y and nAChR agonists in general in nonhuman primates and in models of PD. The improvement in performance of the shortest-delay trials in the VDR task suggest that SIB-1508Y may enhance attentional abilities. From this study, it is uncertain as to the extent to which SIB-1508Y may enhance short-term working memory. SIB-1508Y did not improve performance on long-delay trials that were performed poorly even when the animals were normal but did improve performance on intermediate-duration trials (i.e., 10-s delay). The beneficial effect of SIB-1508Y is not paradigm specific, because marked amelioration was also observed in performance of 0- and 3-s delay trials on the DMS task. The use of these relatively short delays in the DMS task puts little demand on short-term memory, and correct task performance more likely depends on intact attentional processes. The possibility that SIB-1508Y may enhance attention is further supported by the observation of increased arousal and alertness in MPTP-treated common marmosets administered SIB-1508Y (P. Jenner, personal communication).

In contrast to the effects of SIB-1508Y, neither l-dopa nor nicotine, at the doses used, produced significant improvements in task performance. The lack of effect of nicotine might be related to more nonselective effects of nicotine compared with the selective nAChR agonist SIB-1508Y or to the doses of nicotine used (higher doses provoked emesis, and behavioral effects could not be evaluated). SIB-1508Y (or its racemate SIB-1765F) is highly selective for \( \alpha_4\beta_2 \) neuronal nAChRs and is more effective than nicotine in stimulating dopamine release from striatum, limbic areas, and frontal cortex (Cosford et al., 1996; Sacaan et al., 1997b). In studies of DMS performance in young and aged monkeys, nicotine improved performance on long-delay trials, suggesting an effect on working memory (Elrod et al., 1988; Buccafusco and Jackson, 1991). nAChR agonists have also been shown to decrease distractibility in monkeys (Jackson et al., 1997).

The effects of nicotine in normal animals relates to our

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Fig. 4. Best-dose data for SIB-1508Y effects on VDR performance assessed at 20 min (A) and 24 to 48 h (B) after drug administration. Best-dose responses (i.e., the most facilitating dose of SIB-1508Y for each animal) to SIB-1508Y and corresponding nondrug baseline responses (baseline) were averaged for the five animals tested on this task. At 20 min and 24 to 48 h after drug administration, SIB-1508Y caused significant improvements in performance at short delays (2–10 s) compared with the corresponding nondrug baseline. In contrast, SIB-1508Y had no effect on performance of long-delay trials (20 and 30 s). SIB-1508Y effects were both immediate and long lasting. A, \( *p < .01 \) for 2-s delay trials versus corresponding baseline; \( *p < .05 \) for 5- and 10-s delay trials versus corresponding baselines. B, \( *p < .001 \) for 2-s delay trials versus baseline; \( *p < .01 \) for 5- and 10-s delay trials versus corresponding baselines. Columns denote means ± S.E.
study is unclear, because the neurochemical substrates of the cognitive deficits in normal aged monkeys are probably different from the neurochemical substrates of cognitive deficits in MPTP-treated monkeys.

L-Dopa treatment also did not significantly improve cognitive performance in chronic low-dose MPTP-treated monkeys. Although the animals used in this study have not been sacrificed, we previously examined the neurochemical deficits in the brains of chronic MPTP-treated monkeys (Schneider, 1990). Although cortical dopamine levels were intact in regions sampled, norepinephrine levels were decreased. Dopamine levels were decreased in the striatum, with the most significant decrease in the dorsal caudate. Norepinephrine levels were also significantly decreased in the caudate. Because the greatest deficit was in striatal dopamine in these animals, we suggested at the time that this striatal dopaminergic deficit might underlie the cognitive disturbances in these animals (Schneider, 1990). However, decreased norepinephrine levels in the frontal cortex and striatum could contribute to the attentional problems observed in our monkeys. It is also possible that nAChR stimulation in these areas increased norepinephrine release, which may have contributed to improved attention after SIB-1508Y (Sacan et al., 1997b).

Previously, the dopamine D1-receptor agonist dihydroxylend (Schneider et al., 1994a) but not methylphenidate, amphetamine, the dopamine D2-receptor agonist LY-171555, or the partial D1-receptor agonist SKF-38393 reduced the number of incorrect responses made by motor asymptomatic chronic low-dose MPTP-treated monkeys performing a DR task (Schneider et al., 1994b). Whereas the latter agents may improve motor function in parkinsonian monkeys, stimulating dopamine release or activating subtypes of dopamine receptors with these agents did not improve cognitive performance, at least on the tasks examined. The lack of effect of these dopaminergic agents argues against a simple role of striatal dopamine in the cognitive deficits of parkinsonism. There probably needs to be a balance in functional levels of dopamine in various areas of cortex (particularly frontal cortex) and striatum, as well as in other neurochemical systems, to maintain normal cognitive functioning, particularly in PD. Murphy et al. (1996a,b) have suggested that there is a critical range of dopamine turnover for optimal prefrontal cortical cognitive functioning, with excessive dopamine turnover leading to cognitive impairment. Studies have also suggested that the regulation of prefrontal cortical dopamine turnover and cognition is regulated by multiple neurotransmitter systems and that the ventral tegmental area may be an important regulatory site for these effects (Murphy et al., 1996b).

In human clinical studies, there has been little consensus

## Table 1

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<td>80.5±6.1</td>
<td>76.2±6.7</td>
<td>53.5±7.2</td>
</tr>
</tbody>
</table>

*p < .05 compared with the corresponding baseline assessments, post hoc paired t test, Bonferroni correction.

## Table 2

### L-Dopa Effects on Variable Delayed Response Performance in MPTP-Treated Monkeys

L-Dopa testing was performed twice at each dose in three monkeys. Values are means ± S.E. Baseline measures are those taken from nondrug testing sessions immediately before drug testing days.

<table>
<thead>
<tr>
<th>Dosage Condition</th>
<th>L-Dopa Condition</th>
<th>2 s</th>
<th>5 s</th>
<th>10 s</th>
<th>20 s</th>
<th>30 s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>69.9±5.9</td>
<td>68.0±6.6</td>
<td>69.9±7.1</td>
<td>64.4±5.8</td>
<td>62.7±10.2</td>
<td></td>
</tr>
<tr>
<td>2.5 mg/kg</td>
<td>77.0±7.4</td>
<td>80.6±4.6*</td>
<td>69.7±3.7</td>
<td>64.6±3.2</td>
<td>68.1±6.1</td>
<td></td>
</tr>
<tr>
<td>5.0 mg/kg</td>
<td>72.1±3.1</td>
<td>72.1±6.5</td>
<td>73.6±2.8</td>
<td>73.6±7.3</td>
<td>59.5±10.2</td>
<td></td>
</tr>
<tr>
<td>10.0 mg/kg</td>
<td>68.1±4.6</td>
<td>70.0±9.4</td>
<td>66.3±6.5</td>
<td>66.3±7.6</td>
<td>61.0±7.5</td>
<td></td>
</tr>
<tr>
<td>15.0 mg/kg</td>
<td>72.6±6.9</td>
<td>69.9±4.6</td>
<td>69.9±6.9</td>
<td>62.9±4.8</td>
<td>55.6±2.6</td>
<td></td>
</tr>
<tr>
<td>20.0 mg/kg</td>
<td>75.2±8.6</td>
<td>79.5±6.1</td>
<td>64.7±5.0</td>
<td>50.2±5.5</td>
<td>60.7±10.9</td>
<td></td>
</tr>
</tbody>
</table>

*a F (9,60) = 0.90, p > .05; b F (9,60) = 0.79, p > .05; c F (9,60) = 0.84, p > .05; d F (9,60) = 1.79, p > .05; e F (9,60) = 3.66, p < .05, f p < .05 versus the corresponding baseline.
as to the effects of L-dopa on cognitive functions in PD. In one study, PD patients performing frontal lobe tasks both on and off L-dopa were found to have greater cognitive impairments when receiving optimal L-dopa therapy for control of motor symptoms (Gotham et al., 1988). In another study (Lange et al., 1992), advanced PD patients performed worse on some cognitive tasks, including attention and executive function tasks, off L-dopa, whereas performance of other tasks were not influenced by L-dopa. Cooper et al. (1992) showed that L-dopa therapy improved working memory and cognitive sequencing but not other aspects of memory or executive functioning. Kulisevsky et al. (1996) recently showed that, in both stable L-dopa responders and patients with motor fluctuations, L-dopa improved response initiation times but not accuracy in performing memory or executive function tests. Patients generally made a similar number of cognitive errors on or off L-dopa. Thus, the lack of L-dopa response in our is not inconsistent with the human clinical literature.

The cognitive deficits in chronic low-dose MPTP-treated monkeys and most likely in PD patients probably arise from dysfunction of several cortical and subcortical neurotransmitter systems and functional circuits that L-dopa treatment alone cannot sufficiently normalize. SIB-1508Y, by virtue of its ability to release dopamine from striatal, limbic, and frontal cortical sites; norepinephrine from hippocampal, thalamic, and frontal cortical sites; and acetylcholine from various cortical and subcortical sites (Menzaghi et al., 1996; Sacaan et al., 1997b) may underlie this compound’s effect on cognition in chronic MPTP-treated monkeys. However, note that the effects of SIB-1508Y were not challenged with a nicotine antagonist; thus, we presume, based on other information (Menzaghi et al., 1996; Sacaan et al., 1997b), that the drug was acting through nAChRs. SIB-1508Y and perhaps other subtype-selective nAChR agonists may represent a broader approach to treating the complex neurochemical and behavioral pathology of PD. In monkeys with motor deficits of parkinsonism superimposed on preexisting cognitive deficits, L-dopa improved motor functioning but not cognitive functioning (Schneider et al., 1988b). The combination of subthreshold doses of SIB-1508Y and L-dopa significantly improved both cognitive performance and motor functioning and did so at one-third to one-sixth the L-dopa dose necessary to improve only motor functioning (Schneider et al., 1988b).

The combination of these drugs may address the dopamine deficiency underlying the motor (and perhaps some of the cognitive) deficits of PD while also addressing the noradrenergic and cholinergic deficits in this disorder, which may relate to the affective and cognitive dysfunction.

The long-lasting cognitive effect of SIB-1508Y in chronic low-dose MPTP-treated monkeys is unprecedented in this laboratory, and it is highly unlikely to be related to a spontaneous recovery because 1) the reversal of these cognitive deficits is rapid (often within 20 min postdose), 2) the cognitive deficits were stable for up to 2 to 3 months before long-lasting effects of SIB-1508Y treatment were observed and 3) a rapid spontaneous recovery has never been previously observed, whereas 100% of the animals in our study exhibited a behavioral recovery lasting 24 to 48 h, with a subsequent regression to pre-SIB-1508Y levels of performance. In aged rhesus monkeys, enhanced performance in a DMS task has also been observed 24 h after SIB-1508Y administration (J. Buccafusco, personal communication). Whereas the mecha-

nism of this long-lasting therapeutic effect of SIB-1508Y on cognition is not clear, a plausible hypothesis is that SIB-1508Y caused elevated levels of neurotrophic factors and receptors at various central nervous system sites. Such effects of nicotine and nAChR agonists on nerve growth factor, brain-derived neurotrophic factor, and their receptors have been described previously (Lapchak et al., 1993; Knipper et al., 1994; Terry and Clarke, 1994).

In conclusion, these data suggest that SIB-1508Y, and perhaps other nAChR agonists, may improve at least some of the cognitive deficits associated with PD.

References


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