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Interaction Between Nicotinic and Dopaminergic Therapies on Cognition in a Chronic Parkinson Model

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Abstract

While levodopa therapy for PD may effectively relieve motor symptoms, many of the cognitive deficits experienced by PD patients (and in animal models of PD) are not effectively managed by this treatment. In contrast, previous work has shown positive effects of nicotinic therapies on cognition in PD models. The present study evaluated the effects of levodopa, nicotine and the nicotinic acetylcholine receptor agonist SIB-1553A alone and in combination on cognition in a non-human primate model of early PD. Three adult male Rhesus monkeys, previously administered low doses of the neurotoxin MPTP over several months to produce cognitive deficits, were trained to perform a modified spatial delayed response task in which the attentional demands of the task were manipulated by varying the duration of the cue presentation while keeping the memory demands of the task low and constant. Task performance was assessed after administration of levodopa, nicotine ditartrate, or SIB-1553A and after administration of drug combinations. Animals performed normally when task attentional load was low (i.e., with long cue durations) but performance was significantly impaired on short cue duration trials. Levodopa further impaired performance on short cue duration trials and induced a deficit on long cue duration trials. Nicotine and SIB-1553A improved performance on short cue trials and when co-administered with levodopa, counteracted levodopa-induced deficits. These results confirm that nicotinic therapies may be useful for treating cognitive deficits associated with PD and suggest that negative effects of levodopa on cognition may be amenable to correction with adjunctive nicotinic therapies.

Keywords

Parkinson; Monkey; Cognition; Levodopa; Nicotine

1. Introduction

In addition to the characteristic motor deficits observed in Parkinson's disease (PD) patients, cognitive deficits also appear, even at the early stages of the disease (Brown and Marsden, 1988; Dubois and Pillon, 1997; Johnson et al., 2004; Lees and Smith, 1983; Taylor et al., 1986). The cognitive deficits seen in early PD are primarily frontal in nature and involve aspects of attention, executive functioning and working memory (Cooper et al., 1991; Downes et al.,

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1989; Flowers and Robertson, 1985; Owen et al., 1992; Sharpe, 1990; Sharpe, 1992). In particular, the deficits in attention and executive functioning include impaired performance on sustained attention and attention shifting tasks, increased distractibility and impaired cognitive flexibility (Downes *et al.*, 1989; Lange *et al.*, 1992; Sharpe, 1992).

In order to study non-motor aspects of parkinsonism experimentally, our laboratory has developed a model of early parkinsonism in non-human primates in which low doses of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are administered over an extended period of time to produce animals with cognitive deficits characteristic of early PD but without the potentially confounding effect of significant motor impairment (Schneider and Kovelowski, 1990; Schneider and Pope-Coleman, 1995). These animals develop deficits in performing an attention set shifting tasks, discrimination reversals, and sustained/focused attention tasks (Decamp and Schneider, 2004). The animals also develop deficits in performing delayed response and delayed matching to sample tasks (Schneider and Kovelowski, 1990; Schneider and Roeltgen, 1993), although deficits on these tasks are more attentional-related than memory-related per se (Decamp *et al.*, 2004). Although dopaminergic therapies have had little or no positive effect on performance of these tasks in these animals (Schneider *et al.*, 1994; Schneider *et al.*, 1998), nicotine and nicotinic receptor subtype selective agonists have shown efficacy in ameliorating many of the cognitive deficits in chronic low dose MPTP-treated animals (Decamp and Schneider, 2006; Schneider *et al.*, 1998; Schneider *et al.*, 1999; Schneider *et al.*, 2003b). However, since nicotinic therapies would be used clinically as adjuncts to levodopa administration it is important to know how these two therapies interact.

In the present study, animals with prior MPTP exposure and with attentional and central executive deficits were trained to perform a modified delayed response task in which the attentional demands of the task were manipulated to allow good performance on trials with low attentional load and impaired performance on trials with higher attentional load. The effects of levodopa, nicotine, and the nicotinic acetylcholine receptor (nAChR) subtype selective agonist SIB-1553A on task performance were assessed. Nicotine and SIB-1553A improved task performance while levodopa administration impaired task performance. The co-administration of nicotine or SIB-1553A with levodopa counteracted the negative effect of levodopa on task performance.

2. Results

2.1 Learning and task performance

The animals used in this study, previously exposed to the neurotoxin MPTP and with attentional and other central executive deficits (Decamp and Schneider, 2004), had difficulty learning the modified delayed response task when a cue duration of 2 seconds was employed. Increasing the length of time of cue presentation resulted in improved learning and eventually, nearly flawless performance with cue durations of 6 to 8 seconds. The longest cue duration used for each individual was selected in order to obtain a performance level of at least 85% correct responses per session.

After asymptotic levels of performance were reached (approximately 4–6 months of training), the animals were presented with sessions consisting of 20 trials each with short, medium and long cue durations (2, 4 and 6 to 8 seconds). Using this modified delayed response protocol, animals performed the task at a level of 65.0 % (± 3.23) correct, 81.11% (± 2.9) correct and 88.33 % (± 1.8 %) correct at 2, 4 and 6–8 sec. cue durations respectively ($F(18,2) = 31.08$, $p < 0.001$) (Fig. 1). Performance on 2 sec. cue duration trials was significantly different from performance at 4 and 6–8 sec. cue duration trials ($p < 0.001$); performance on 4 sec. cue duration trials was significantly different from performance at 6–8 sec. cue duration trials ($p = 0.024$). Animals made mostly commission errors on this task, with rare omission errors.

2.2 Effects of nicotine and SIB-1553A on task performance

Nicotine administration resulted in an overall improvement in task performance ($78.2\% \pm 3.5$ total correct responses vs. $86.3\% \pm 3.9$, $p < 0.01$). This improvement was mainly due to enhanced performance at trials with the shortest cue duration (65.0% correct responses ± 3.2 at baseline vs. 84.0% correct responses ± 4.6 following nicotine administration, $p < 0.01$). Nicotine administration did not significantly improve task performance at medium and long cue duration trials (Fig. 2).

Administration of SIB-1553A also resulted in an overall improvement in task performance ($78.2\% \pm 3.5$ total correct responses at baseline vs. $90.0\% \pm 4.1$ correct responses following SIB-1553A). As with nicotine, this improvement was due primarily to enhanced performance on 2 sec. cue duration trials (65.0% correct ± 3.23 at baseline vs. $86.7\% \pm 4.4$ post SIB-1553A, $p < 0.01$). SIB-1553A did not significantly improve performance on either the 4 or 6–8 sec. cue duration trials. Nonetheless, in contrast to baseline performance, following SIB-1553A administration, animals performed similarly at 2, 4 and 6–8 sec. cue duration trials (Fig. 2).

2.3 Effects of levodopa on task performance

Administration of levodopa (20mg/kg) resulted in an overall decrease in task performance ($78.2\% \pm 3.5$ correct responses at baseline vs. $54.8\% \pm 5.7$ post levodopa, $p < 0.001$). In particular, animals performed significantly worse on 4 sec. and 6–8 sec. cue duration trials ($p < 0.05$ for each) following levodopa administration. Following levodopa administration, animals performed at almost chance levels on all trials ($50.7\% \pm 5.6$, $60\% \pm 3.1$, and $53.6\% \pm 7.7$ correct responses on 2, 4 and 6–8 sec. cue duration trials, respectively). No animals showed any signs of hyperactivity or stereotypies following levodopa administration.

2.4 Effect of nicotine and SIB-1553A on cognitive deficits induced by levodopa

There was a significant effect of the administration of nicotine + levodopa compared to levodopa alone ($p < 0.05$). Co-administration of nicotine and levodopa improved overall task performance compared to levodopa alone ($54.8\% \pm 5.68$ correct responses following levodopa alone vs. $78.9\% \pm 6.1$ correct responses following levodopa + nicotine). Following nicotine + levodopa administration animals performed significantly better than following levodopa administration alone at all cue duration trials ($p < 0.05$ at each cue duration). Nicotine + levodopa administration resulted in levels of performance not significantly different from those obtained from vehicle control sessions. (Fig 4).

Administration of SIB-1553A together with levodopa also improved overall task performance ($54.8\% \pm 5.68$ correct responses following levodopa alone vs. $82.2\% \pm 4.36$ correct responses following levodopa + SIB-1553A administration, $p < 0.05$) (Fig 4). As with nicotine, improved performance was observed on all cue duration trials ($p < 0.05$ at each cue duration). As seen with the co-administration of nicotine with levodopa, trials performed following SIB-1553A + levodopa administration resulted in task performance not significantly different from that observed following vehicle administration.

3. Discussion

The present study demonstrates that animals with pre-existing attentional and executive functioning deficits consequent to chronic low dose MPTP exposure, are capable of learning a new task as long as the attentional demands of the task are sufficiently low.

In previous studies (Schneider and Pope-Coleman, 1995; Schneider et al., 2000; Schneider et al., 2002), animals were trained to perform a variable delayed response task with a 2 sec cue duration identical to the shortest cue duration used in the present study and delay intervals

ranging from 2 to 60 secs. Following chronic low dose MPTP exposure, these animals performed poorly on trials with 2 or 5 sec. delays, i.e., trials with high attentional and low working memory demands. The low level of performance of these animals on these trials allowed evaluation of potential cognition enhancing therapies but did not allow assessment of potential negative effects of various agents on task performance. In the present study, using a modified delayed response task in which we manipulated the attentional demands of the task while keeping the memory demands consistently low, animals could perform very well on long cue duration trials (low attentional demand) but poorly on short cue duration trials (high attentional demand), allowing positive or negative effects of therapeutic interventions to be evaluated.

We have previously observed that nicotine and putative $\alpha 4\beta 4$ and $\alpha 4\beta 2$ subtype selective nAChR agonists improved performance of a variable delayed response task with both attentional and memory components in chronic low dose (CLD) MPTP-exposed monkeys. In one study (Schneider *et al.*, 1999), administration of the $\alpha 4\beta 2$ subtype selective nAChR agonist SIB-1508Y significantly improved performance of CLD MPTP-treated monkeys on short and medium delay duration trials but failed to improve performance on trials with the longest delays. In a subsequent study (Schneider *et al.*, 2003b), administration of the putative $\alpha 4\beta 4$ subtype selective nAChR agonist SIB-1553A, improved performance of CLD MPTP-treated animals on both short and long delay duration trials, suggesting efficacy in both attentional and memory components of the task. More recently, in a study that utilized the same animals as in the present research, the effect of nicotine and SIB-1553A on attention set shifting, focused attention and impulse control was examined (Decamp and Schneider, 2006). Both nicotine and SIB-1553A produced a dose dependent enhancement of performance on a focused attention task and decreased response time in an impulse control task while only SIB-1553A improved performance on discrimination reversal and compound discrimination components of a set shifting task. The dose of nicotine and SIB-1553A used in the present study, the same as that used in the above-mentioned study, presently produced a significant improvement in the modified delayed response task, suggesting a general ability of these drugs to improve attention.

In the current study, levodopa administration to CLD-MPTP exposed monkeys resulted in a worsening of task performance on trials with short and long cue durations. These animals received a dose of levodopa previously shown to improve motor symptoms in MPTP-exposed monkeys (Schneider *et al.*, 2003a). Although the animals used in this study have not yet been characterized for individual neurochemical deficits, we have previously shown (Schneider, 1990) that CLD MPTP-treated monkeys have a severe decrease of dopamine (DA) in the striatum, with the dorsal caudate being more significantly affected than the putamen and DA levels in the nucleus accumbens being relatively preserved. At the cortical level, DA concentrations were not different from those in normal animals in the areas surveyed but norepinephrine levels were decreased in some frontal regions. Thus in this model, there is much greater DAergic depletion in the striatum than in frontal cortex. Thus, we hypothesize that the amount of DA produced from levodopa administration led to sufficiently high DA levels in the frontal cortex (and perhaps other cortical regions) that have a relatively preserved DAergic innervation (compared to the striatum) so as to disrupt attention and task performance. This idea is consistent with reports of medicated, mild PD patients performing worse than unmedicated mild PD patient on a task dependent on striatal-orbitofrontal circuits (Swainson *et al.*, 2000). Similarly, Cools *et al.* (2001) showed that levodopa administration improved performance on a task believed to be dependent on the integrity of frontal-dorsal caudate circuits that are more severely dopamine depleted in PD patients while the same dose of levodopa impaired performance on a task that is believed to be more dependent on the functioning of orbitofrontal cortex, an area with relatively less DA denervation in the PD brain (Kish *et al.*, 1988).

Both nicotine and SIB-1553A, given as adjunctive therapy with levodopa, reversed levodopa-induced cognitive deficits in CLD-MPTP exposed monkeys. Although the specific mechanisms underlying this effect are unclear at present, it is possible that by stimulating release of multiple neurotransmitters (i.e., norepinephrine, serotonin, acetylcholine) at cortical and subcortical levels, these drugs were able to overcome or counterbalance the negative effect of levodopa. Alternatively, the beneficial effect of these nicotinic agents may be related to the DA system itself. As mentioned above, the deficits induced by levodopa could have resulted from excess DA overflow in the prefrontal cortex. Nicotine may alter the rate of clearance of DA in the frontal cortex by influencing the activity of the dopamine transporter. In one study (Middleton *et al.*, 2007), nicotine increased DA reuptake in rat striatal synaptosomes. Other work showed that nicotine increased DA clearance by enhancing dopamine transporter function in the nucleus accumbens of anesthetized rats (Hart and Ksir, 1996). Using *in vivo* voltammetry, Middleton and colleagues (Middleton *et al.*, 2004) showed that nicotine, in a dose dependent fashion, decreased DA signal amplitude from exogenous DA application in both the striatum and the medial prefrontal cortex (mPFC). The dose response curve for the nicotine effect on DA reuptake was different for the mPFC and striatum, with mPFC showing greater sensitivity to nicotine. Mecamylamine completely inhibited the nicotine-induced decrease in signal amplitude, suggesting the effect was mediated by nAChRs. Thus, it is possible that nicotine was able to reverse the cognitive deficit induced by levodopa in CLD-MPTP-treated monkeys by modulating a potential overflow of DA in the frontal cortex by enhancing DA clearance.

In conclusion, the present data suggest that cognitive deficits in CLD-MPTP-treated monkeys induced by levodopa may be reversible through nicotinic mechanisms. Further research is needed to understand the mechanisms underlying these effects and to examine the extent to which nicotinic/levodopa interactions remain functional in animals with an even greater severity of parkinsonism.

4. Experimental Procedures

4.1 General methods

Three adult male Maccaca mulatta monkeys (8 – 9 years of age, weight 8.3 to 10.4 kg.) were used in this study. These animals were previously trained to perform attention and executive function tasks and were chronically administered low doses of MPTP (MPTP-HCl, Sigma/RBI, St Louis, MO, USA, 0.025 to 0.10 mg/kg) two to three times per week by intravenous injection over a period ranging from 98 to 158 days. The nature of their MPTP-induced attentional and central executive deficits have been described in detail previously (Decamp and Schneider, 2004). These animals had also previously participated in a behavioral pharmacology study and had received acute administration of nicotine and the nAChR subtype selective agonist SIB-1553A (Decamp and Schneider, 2006). All procedures were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by the Thomas Jefferson University Institutional Animal Care and Use Committee.

4.2 Apparatus and general behavioral procedures

Animals were maintained on a food restriction schedule and received water ad libitum. For training and testing, an animal was transferred (using a specially designed transport cage) from its home cage to a testing cage located in a quiet room away from the main colony. A test panel consisting of a touch sensitive computer display and a reward delivery system was attached to the testing cage. House lights were dimmed, white noise provided, and the animal interacted with the system.

The task used was a modified delayed response task. Upon initiation of the task, a cue (filled white circle) appeared on the right or left side of the screen for two, four or eight seconds in blocks of twenty trials presented randomly. On short cue duration trials (two seconds), the attentional demand is higher than at four or eight second cue duration trials. The cue was then extinguished for a fixed delay period of two seconds (to minimize the working memory component of the task) and then identical left and right choice stimuli (red circles) were presented until a choice touch was made by the monkey. The monkey was rewarded with a sugar pellet if it touched the response circle located in the same spatial position as the cue. If no response was made in 30 sec., the task timed out and a “no response” error was recorded. Side of cue presentation was distributed quasi-randomly over the 60 trials that made up a daily testing session.

4.3 Drug administration

Drug treatments were counterbalanced across monkeys. Levodopa (20 mg/kg, i.m.) was dissolved in sterile saline and injected 20 minutes after injection of benserazide (7 mg/kg, i.m.; Sigma/RBI, St Louis, MO, USA). The dose of levodopa chosen was based on previous work done in this laboratory (Schneider *et al.*, 2003a) in which this dose optimally alleviates sensorimotor deficits resulting from MPTP exposure. Nicotine ditartrate (0.5 mg/kg, Sigma/RBI, St Louis, MO, USA) and SIB-1553A (0.5 mg/kg, synthesized by RTI International, Research Triangle Park, NC, USA) were dissolved in sterile saline immediately before use, pH adjusted to 7.0 and administered intramuscularly. The dose used for both nicotine and SIB-1553A was selected based on the best effect of these drugs on cognitive task performance obtained with the same animals in a previous study (Decamp and Schneider, 2006).

Levodopa was administered 60 minutes prior to testing; nicotine and SIB-1553A were administered 20 minutes prior to testing. For drug combination trials, on the same day, levodopa was administered 60 minutes prior to testing and nicotine or SIB-1553A 20 minutes prior to onset of testing.

Each drug alone and in combination was administered at least twice and a minimum of 4 days washout was maintained between drug-testing sessions. Control testing sessions (no injection or saline injection) were performed on days in between drug testing trials to insure that level of performance was at baseline level prior to the next drug administration.

4.4 Data analysis

The results from individual animals were pooled for statistical analysis. As baseline performance prior to treatment sessions did not significantly differ from performance on days between drug session (saline control or no administration), data were pooled and used as comparison for drug administration sessions. Animals served as their own controls and data were analyzed using repeated-measures ANOVA and post hoc t-test comparison using Newman-Keuls test.

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Figure 1.

Performance of animals on the modified delayed response task with cue durations of 2, 4 and 6–8 seconds. Results are expressed as mean percent correct performance ($\pm$ SEM). CLD MPTP-treated animals performed at approximately chance level on trials with a 2 sec. cue duration. When the cue duration was increased to 4 sec. or 6–8 sec., performance improved significantly. (^ $p < 0.05$ and * $p < 0.01$).

Figure 2.

Effect of nicotine ditartrate (filled bars) and SIB-1553A (dashed bars) on performance of the modified delayed response task with cue durations of 2, 4 and 6–8 seconds. Results are expressed as mean percent correct performance ($\pm$ SEM). Baseline performance is shown by unfilled bars. Both nicotine and SIB-1553A significantly improved performance on 2 sec. cue duration trials (* $p < 0.01$ compared to baseline).

Figure 3.

Effect of levodopa (filled bars) on performance of the modified delayed response task. Baseline performance is shown by unfilled bars. Results are expressed as mean percent correct performance ($\pm$ SEM). Levodopa significantly impaired performance of trials with short or long cue durations (* $p < 0.01$ compared to baseline).

Figure 4.

Effect of nicotine and SIB-1553A on levodopa-induced deficits on the modified delayed response task. Results are expressed as mean percent correct performance ($\pm$ SEM). Nicotine or SIB-1553A, administered together with levodopa, reversed levodopa-induced performance deficits on trials with 2, 4 or 6–8 cue durations. Baseline = unfilled bars; levodopa alone = filled bars; levodopa + nicotine = vertical lined bars; levodopa + SIB-1553A = cross-hatched bars. * $p < 0.01$ compared to baseline; + $p < 0.05$ vs. levodopa alone.