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Dopamine D_4 receptor antagonist reversal of subchronic phencyclidine-induced object retrieval/detour deficits in monkeys

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Abstract D_4 dopamine receptors (DRs) are enriched in the primate prefrontal cortex, a brain region implicated in cognitive processes, and mesoprefrontal dopaminergic systems appear to be involved in modulating some cognitive functions of the prefrontal cortex. Despite anatomical localization of D_4 DRs within the frontal cortex, the role of these receptors, specifically, in the regulation of cognition or behavior in primates is unknown. In these studies, we sought to learn whether specific antagonism of D_4 DRs would affect performance of a task dependent on the frontostriatal system. The effects of NGD94-1 (2-phenyl-4(5)-[4-(2-pyrimidinyl)-piperazin-1-yl)-methyl]-imidazole dimaleate), a potent and selective D_4 DR antagonist and haloperidol, a non-specific D_2-like DR antagonist, on the performance of an object retrieval/detour task by monkeys were examined. The effects of these antagonists on the object retrieval task were evaluated in normal control monkeys and in subjects repeatedly exposed to phencyclidine (PCP), to induce frontal cortical dopaminergic and cognitive dysfunction. NGD94-1 (1–5 mg/kg) reversed the cognitive deficits of PCP pre-treated monkeys, whereas haloperidol (25 μg/kg) exacerbated PCP-induced performance impairments. A low dose of NGD94-1 failed to affect performance of control subjects, while both haloperidol and a high dose of NGD94-1 impaired control performance. These data show, for the first time, that D_4 DRs modulate the cognitive functions of the frontostriatal system.

Key words Prefrontal cortex · Psychotomimetic · Memory · Dopamine · Primate · D_4 receptor

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Introduction

D_4 dopamine receptors (DRs) are enriched in the primate prefrontal cortex (Mrzljak et al. 1996), a brain region involved in cognitive processes (Goldman-Rakic 1987, 1996; Petrides 1996; Robbins 1996). Lesions to subregions of the prefrontal cortex have been shown to impair spatial working memory and to induce deficits in response inhibition, planning and cognitive flexibility in monkeys (Jacobsen 1936; Goldman et al. 1971; Dias et al. 1996a,b). In addition, dopaminergic depletion in prefrontal cortex impairs delayed alternation performance, which involves spatial working memory and response inhibition (Brozoski et al. 1979; Roberts et al. 1994), and improves attentional set-shifting, a task which includes components of set-shifting and response inhibition (Roberts et al. 1994). In addition, a recent study has shown that dopamine release in prefrontal cortex is specifically increased during performance of a test of working memory function, as opposed to a control task (Watanabe et al. 1997).

Within the primate prefrontal cortex, the D_1-like subtype of DRs are localized largely in dendritic spines of pyramidal cells of layers II, III and V (Bergson et al. 1995). These receptors appear to be critically involved in regulating the working memory functions of the prefrontal cortex, since blockade of D_1-like DRs by intra-prefrontal administration of a selective D_1 DR

antagonist impaired performance of an oculomotor variant of the delayed response task by monkeys (Sawaguchi and Goldman-Rakic 1991). In contrast, raclopride, which blocks D_2 and D_3, but not D_4, DRs, failed to affect performance (Sowagvchi and Goldman-Rakic 1991). Similar effects are seen following systemic administration of these selective agents to monkeys (Arnsten et al. 1994, 1995).

Within prefrontal cortex, the subtype of D_4 DRs appears to be localized to GABAergic interneurons (Mrzjlak et al. 1996). Despite this fact, little is known about the potential functional relevance of D_4 DRs to cortical cognitive function. This is due largely to the relative paucity of compounds which can selectively block this particular receptor. Previously, clozapine was utilized as a non-selective antagonist of the D_4 DR. Clozapine administration alleviated the benzodiazepine inverse agonist-induced working memory deficits in monkeys (Murphy et al. 1996; 1997). In addition, the cognitive deficits exhibited by monkeys after long-term phencyclidine (PCP) treatment were ameliorated by clozapine (Jentsch et al. 1997b).

Recently, several selective D_4 DR antagonists have been synthesized, including NGD94-1, 2-phenyl-4(5)-[4-(2-pyrimidinyl)-piperazin-1-yl)-methyl]-imidazole dimaleate (Tallman et al. 1997). These new pharmacological probes should be useful for studying the in vivo functions of these receptors in awake, behaving subjects. While it appears that D_4 DR antagonists are devoid of the behavioral actions which are typical of classical D_2-like DR antagonists [e.g., inhibition of apomorphine-induced stereotypy and pre-pulse inhibition deficits or antipsychotic efficacy (Bristow et al. 1997; Kramer et al. 1997)], the effects of manipulation of the D_4 DR on tests of frontal cortex function are unknown.

In the current studies, the effects of the specific D_4 DR antagonist NGD94-1 and haloperidol, a D_2-like DR antagonist, were examined in monkeys performing a variant of the object retrieval/detour task, a test of frontostriatal function. In particular, these antagonists were administered to both control monkeys and subjects that had undergone long-term exposure to PCP to induce frontal cortical cognitive and dopaminergic deficits (Jentsch et al. 1997b). Furthermore, the ability of a selective D_4 DR antagonist to affect monoaminergic transmission was assessed by sampling cisternal cerebrospinal fluid after drug administration. These results strongly suggest that D_4 DRs modulate prefrontal cortical cognitive functions.

Materials and methods

Animals

Subjects were male and female young-adult vervet (*Cercopithecus aethiops sabaeus*) monkeys of the St Kitts Biomedical Research Foundation (St Kitts, West Indies). The monkeys were housed in standard, stainless steel primate cages in an outdoor, covered facility. All subjects had ad libitum access to water and were fed (monkey chow and fresh fruit) in excess immediately following cognitive testing every day. Care of the subjects was in accord with the NIH Guide for the Care and Use of Animals in Research, and all experimental protocols were approved by the appropriate institutional animal care and use committees.

Chronic drug treatments

All subjects were repeatedly treated with either phencyclidine hydrochloride (Research Biochemicals Inc., Natick, Mass., USA) or sterile saline. PCP was dissolved in 0.1 ml/kg sterile saline and injected intramuscularly at a dose of 0.3 mg/kg. Control injections consisted of an equivalent volume of saline. Treatments occurred twice daily (7:30 a.m. and 3:30 p.m.) for 14 consecutive days, resulting in a total of 28 injections over 2 weeks.

Cognitive testing

Testing was performed exactly as previously described (Taylor et al. 1990a,b; Jentsch et al. 1997b). Cognitive testing occurred in the home cage, to which a custom-designed and constructed Wisconsin General Test Apparatus was affixed, and consisted of two phases: (1) an initial 4-day acquisition period and (2) a subsequent drug assessment period. All testers were blind to the treatment conditions of the subjects.

In this task, the subjects watch (through a transparent screen) as a reward (a slice of banana) is placed in a small transparent box which is fixed to a tray of the testing apparatus and that is open on only one side. The position of the reward in the box (front, middle, corner), the position of the box on the tray (left, right, middle) and the orientation of the open side of the box relative to the subject (front, left, right) were all varied. The transparent screen was then raised, and subjects were allowed unlimited time and reaches to retrieve the reward (as long as they continued attempting to respond, a 3-min period of inactivity resulted in a scored "failure" on the trial).

The trial structure used in the current studies were identical to those published previously (Taylor et al. 1990a,b). The first day of testing consisted of 11 trials which were stimulus-driven trials, e.g., all trials involved a direct reach for the reward which was placed in the monkey's line-of-sight. Subsequently, test sessions consisted of 20 trials, in which the trials were more difficult. Trials requiring either direct (line-of-sight) reaches or detour reaches were intermixed on days 2–4 and subsequent test days. On days 2–4, four of the 20 trials involved direct reaches, whereas the other 16 trials required detour reaches. In addition, day 4 and subsequent days were the most "difficult", consisting of sequences of trials which included identical reach sequences followed by a subsequent switch in the direction of the box (e.g., left, left, left, right).

All reaches were hand-scored by the tester at the time of testing. The data were subsequently entered into a computer file by a second technical person who was likewise blind to treatment and testing conditions. These data files were later compiled for several variables by an automated statistical analysis program (see Statistical analysis below). Measures of performance included: *correct* (retrieval of the reward on the trial); *success* (retrieval of the reward on the first reach of the trial without touching any of the closed, transparent faces of the box); *motor problems* (reaching into the open side of the box but failing to retrieve the reward or dropping the reward); *response initiation latency* (time from raising the screen at the start of each trial until the subject made contact with the test box or reward); *total reaches* (number of reaches on a trial); *barrier reaches* (responding at the closed, transparent, side of the box); and *perseverative reaches* (a trial in which the first reach was

made into a closed, transparent face of the box and which was a repeat of the last, rewarded reach on the previous trial). Barrier reaches were scored as any reach into a closed side of the box, including both 'line-of-sight' reaches, as well as other reaches. In general, however, barrier reaches were largely in the line-of-sight.

After the initial 4-day acquisition testing period, subjects were tested every other day on a trial sequence which consisted of both line-of-sight reaches and detour reaches. Drug administrations were given after group comparisons for a particular day confirmed that PCP-treated subjects were still exhibiting significant performance deficits. Performance for each animals on drug was compared with that of the previous test session (drug versus baseline; paired, within-subjects comparisons).

Drug reversal studies

NGD94-1 (Neurogen Corporation, Branford, Com., USA) or haloperidol (as the lactate, Solopak Industries, Elk Grove Village, Ind., USA) were prepared in sterile saline. NGD94-1 was administered at 1 or 5 mg/kg intramuscularly 45 min prior to testing. Haloperidol was given at 0.025 mg/kg intramuscularly 30 min prior to testing.

Cerebrospinal fluid sampling and metabolite quantification

At the conclusion of cognitive testing, all subjects were treated with saline or NGD94-1 (1 mg/kg), and 1 h later, cisternal cerebrospinal fluid was collected under ketamine anesthesia. Samples were frozen on liquid nitrogen and later stored at −70°C until assay for homovanillic acid (HVA) concentrations using high pressure liquid chromatography with electrochemical detection performed according to previously published methods (Jentsch et al. 1997a). Concentrations were expressed as ng metabolite per ml of cerebrospinal fluid.

Statistical analysis

All data were tabulated by an automated program using the SAS (SAS Institute Co., Cary, N.O., USA) statistical analysis package running on a Power Macintosh. Statistical evaluations employed analyses of variance. Data expressed as percentiles (which have a binomial distribution; e.g. success, correct and perseveration) were arcsin transformed. Analysis of variance was used to determine significant main effects (e.g. group: saline- versus PCP-treated) and interactions. Post hoc analyses using Scheffe's *F*-test determined whether there were significant differences between the groups when there were significant interactions. These analyses, importantly, determined whether PCP-treated subjects exhibited cognitive deficits, as compared with control monkeys, before pharmacological reversal of any impairments was examined. Effects of acute, ameliorative drug treatments were determined by paired *t*-tests, since performance of each animal on drug was compared with its baseline performance. CSF metabolite data were analyzed by Mann-Whitney *U*-test (Statview 4.02; Abacus Concepts, Berkeley, Cal, USA).

Results

Performance impairments induced by long-term PCP treatment

Two-week, subchronic treatment with PCP induced marked and persistent performance impairments on an object retrieval/detour task as assessed 7 days after the final drug administration ($F_{1,14} = 15.6$, $P = 0.001$). This overall reduction in successful performance was due to increased propensity for PCP-treated monkeys to make barrier reaches ($F_{1,14} = 7.6$, $P = 0.02$) and to perseverate in responses ($F_{1,14} = 11.3$, $P = 0.005$). PCP-treated subjects required significantly more reach attempts per trial to retrieve the reward ($F_{1,14} = 8.6$, $P = 0.01$). These performance deficits, however, were not associated with significant occurrence of motor problems or increased response initiation latencies.

These performance deficits lasted throughout the drug challenge time period. All drug challenges were given within a 1-month time period following cessation of PCP treatment. A significant effect of drug treatment on successful task performance was still exhibited by PCP-treated monkeys at 1 month after PCP administration ($F_{1,14} = 7.34$, $P = 0.02$). In addition, performance after acute drug challenges always returned to baseline (i.e., PCP-treated subjects showed continued deficits), indicating that any measured effects were transient and drug-induced.

Reversal of PCP-induced deficits by NGD94-1, a selective D_4 DR antagonist

Figure 1 shows the effects of NGD94-1 in PCP-treated and control subjects. At a lower dose (1 mg/kg),

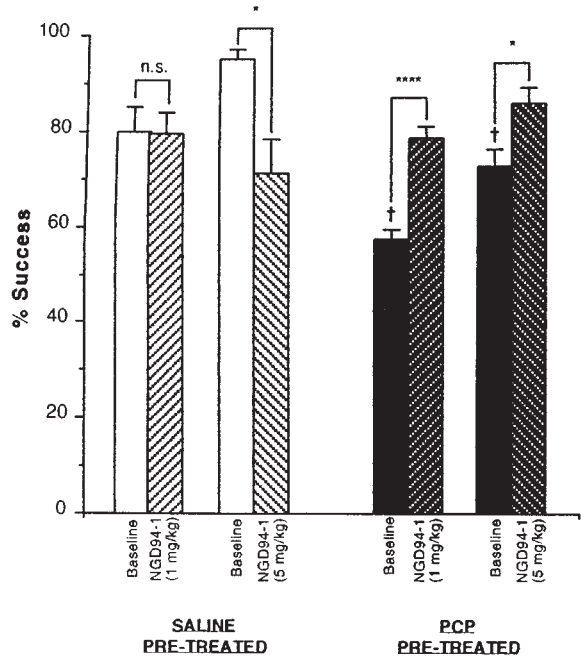

Fig. 1 Performance deficits in PCP pretreated monkeys were ameliorated by NGD94-1, a selective dopamine D_4 receptor antagonist, while performance of controls (saline pretreated) was either not affected or was impaired after NGD94-1 administration. Significantly impaired relative to saline-treated controls: $P < 0.001$ by analysis of variance and Scheffe's *F*-test. Significantly different from baseline: $*P < 0.05$, $****P < 0.0001$ by paired Student's *t*-tests. *n.s.* not significantly different from baseline

NGD94-1 significantly reversed the impaired successful performance of PCP-treated subjects (from 58% to 79% accuracy; $t_{dep} = 5.7$, $df = 7$, $P = 0.0007$). In addition, a higher dose ameliorated the PCP-induced impairments (from 73% to 86% accuracy; $t_{dep} = 3.4$, $df = 5$, $P = 0.02$). At both doses, NGD94-1 reduced barrier reaching (1 mg/kg: $t_{dep} = -5.4$, $df = 7$, $P = 0.001$; 5 mg/kg: $t_{dep} = -7.2$, $df = 5$, $P = 0.0008$) and perseverative responding (1 mg/kg: $t_{dep} = -2.4$, $df = 7$, $P = 0.04$; 5 mg/kg: $t_{dep} = -7.4$, $df = 5$, $P = 0.0007$). In contrast, response initiation latencies were unaffected by NGD94-1 treatment in PCP-treated monkeys (1 mg/kg: $t_{dep} = -1.08$, $df = 7$, $P = 0.32$; 5 mg/kg: $t_{dep} = -2.32$, $df = 5$, $P = 0.07$), nor were motor problems affected (1 mg/kg: $t_{dep} = -0.55$, $df = 7$, $P = 0.60$; 5 mg/kg: $t_{dep} = -2.0$, $df = 5$, $P = 0.36$).

A different set of effects were noted in control subjects. At the lower (1 mg/kg) dose, accurate performance was unaffected ($t_{dep} = -0.19$, $df = 7$, $P = 0.85$). In contrast, successful performance was slightly impaired at the 5 mg/kg dose ($t_{dep} = -3.8$, $df = 5$, $P = 0.02$). At both doses, NGD94-1 failed to affect response initiation latencies (1 mg/kg: $t_{dep} = 1.54$, $df = 7$, $P = 0.17$; 5 mg/kg: $t_{dep} = -0.12$, $df = 4$, $P = 0.91$) or motor problems (1 mg/kg: $t_{dep} = 1.0$, $df = 7$, $P = 0.35$; 5 mg/kg: $t_{dep} = 0$, $df = 4$, $P = 1$).

Exacerbation of PCP-induced performance deficits by haloperidol

Haloperidol administration (0.025 mg/kg) impaired performance of both control and PCP-treated subjects (Fig. 2). In monkeys that had been previously treated subchronically with PCP, haloperidol further reduced successful performance ($t_{dep} = -5.4$, $df = 14$, $P = 0.002$), increased barrier reaching ($t_{dep} = 3.8$, $df = 14$, $P = 0.009$) and tended to increase perseveration ($t_{dep} = 2.4$, $df = 14$, $P = 0.051$). Haloperidol also induced motoric deficits in PCP-treated monkeys ($t_{dep} = 4.1$, $df = 14$, $P = 0.007$).

A similar profile was seen in control subjects. Haloperidol administration reduced success ($t_{dep} = -7.5$, $df = 14$, $P = 0.0003$), increased barrier reaches ($t_{dep} = 5.9$, $df = 14$, $P = 0.001$), potently increased perseverative responding ($t_{dep} = 11.3$, $df = 14$, $P = 0.0001$) and tended to increase motor problems ($t_{dep} = 2.3$, $df = 14$, $P = 0.06$).

Effects of NGD94-1 on dopamine metabolite concentration in cerebrospinal fluid

Cerebrospinal fluid levels of HVA were measured in control and PCP-treated subjects after an acute saline or NGD94-1 challenge, and the data are shown in Fig. 3. NGD94-1 failed to affect HVA levels relative to saline in control subjects ($z = 0$, $P = 0.99$), but in PCP-treated subjects, NGD94-1 significantly increased HVA concentrations in the CSF ($z = -2.3$, $P = 0.02$).

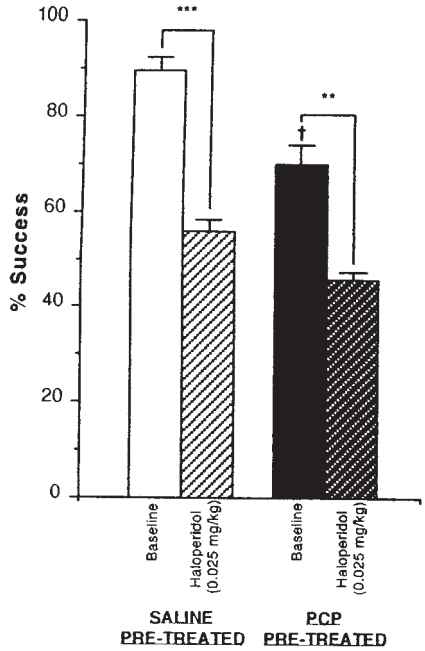

Fig. 2 Haloperidol, a non-specific dopamine receptor antagonist, impaired performance of control (saline pretreated) subjects and worsened deficits in PCP pretreated monkeys. Significantly impaired relative to saline-treated controls: $P < 0.001$ by analysis of variance and Scheffe's *F*-test. Significantly different from baseline: $^{**}P < 0.01$, $^{***}P < 0.001$ by paired Student's *t*-tests

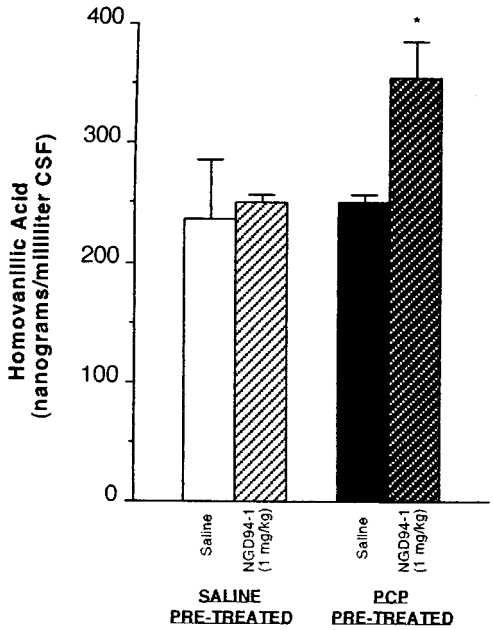

Fig. 3 NGD94–1 administration increased cerebrospinal fluid levels of homovanillic acid in PCP pretreated monkeys but failed to alter the same in control (saline pretreated) subjects. *Significantly increased relative to saline treatment: $P < 0.05$ by Mann-Whitney *U*-test

Discussion

Selective blockade of D_4 DRs led to reversal of the object retrieval/detour performance impairments in monkeys that had been previously treated subchronically with PCP. Furthermore, NGD94-1 increased the accumulation of HVA in the cisternal cerebrospinal fluid of PCP-treated monkeys. The current data suggest that selective D_4 DR antagonists modulate cognitive functions of the frontostriatal system in monkeys and demonstrate that these agents may also regulate dopaminergic transmission in vivo. In particular, the effects of NGD94-1 were evident in monkeys which exhibited behavioral and dopaminergic dysfunction induced by long-term PCP exposure (Jentsch et al. 1997b).

Anatomical localization of the cognitive effects of NGD94-1

D_4 DRs are enriched in the primate prefrontal cortex, exhibiting a pattern of localization to GABAergic interneurons (Mrzljak et al. 1996). Thus, the cognitive effects of the D_4 DR antagonist observed in the current study may be mediated by effects in this cortical region. The object retrieval/detour task is clearly linked with the frontostriatal system; large frontal lesions or more selective lesions of the dorsolateral prefrontal cortex impair task performance (Moll and Kuypers 1977; Diamond and Goldman-Rakic 1985; Dias et al. 1996b). In addition, dopaminergic dysfunction within the basal ganglia induced by MPTP administration results in object retrieval/detour performance deficits (Schneider and Kovelowski 1990; Taylor et al. 1990a,b).

Recently, D_1 and D_4 DRs have been postulated to modulate two distinct effects of dopamine on cortical circuitry (Goldman-Rakic 1998). First, dopamine can affect the firing of pyramidal cells through direct synaptic or non-synaptic stimulation of D_1 DRs which are localized predominantly on this cell type (Bergson et al. 1995). Second, dopamine can modulate the firing of GABAergic interneurons via a D_4 DR mechanism, thus indirectly modulating cortical output (Mrzljak et al. 1996). Thus, the effects of the D_4 DR antagonist observed in the current study may be mediated by modulation of feed-forward inhibitory circuits in cerebral cortex.

A primary target of frontal cortical efferents is the corpus striatum (Alexander and Crutcher 1990), and dopamine function in the caudate nucleus has also been implicated in the neural circuitry underlying performance of some cognitive tasks (e.g., object retrieval/detour and delayed response; Schneider and Kovelowski 1990; Taylor et al. 1990a,b). While the cognitive dysfunction induced by systemic D_1 DR antagonist administration has been shown to be due, in part, to local actions in prefrontal cortex (Sawaguchi and Goldman-Rakic 1991), D_1 DRs are enriched in the caudate nucleus (Bergson et al. 1995), as well. In contrast, D_4 DRs seem to be virtually absent from all substructures of the corpus striatum, including the caudate nucleus, putamen and nucleus accumbens (Mrzljak et al. 1996). Thus, the D_4 DR antagonist effects on object retrieval/detour task performance observed in the current study appear to be mediated by altered cortical circuitry.

D_4 DR antagonist modulation of central dopaminergic transmission

In the current study, NGD94-1 administration to PCP pretreated monkeys was observed to increase cerebrospinal fluid concentrations of HVA, an indication of activation of central dopaminergic transmission (Elsworth et al. 1987). Subchronic PCP treatment reduces prefrontal cortical dopaminergic transmission (Jentsch et al. 1997b), and the degree of reduction in dopamine transmission correlates positively with the degree of impairment of performance on the object retrieval/detour task (our unpublished observations), suggesting that dopaminergic dysfunction in prefrontal cortex is directly involved in the cognitive impairments. It is noteworthy that this selective change in cortical dopamine transmission is not immediately reflected in global measures of dopaminergic transmission (CSF HVA levels), since we did not observe a reduction in CSF HVA concentrations in PCP-treated monkeys at baseline. This is consistent with the notion that cortical dopamine turnover only constitutes a portion of cisternal HVA concentrations. It is thus likely that the increase in cisternal HVA after NGD94-1 does not reflect a selective change in cortical dopamine turnover, but rather, a more generalized effect. Nevertheless, since dopaminergic hypofunction probably subserves a component of the cognitive deficit in PCP-treated subjects, "re-activation" of cortical dopaminergic transmission via D_1 DRs induced by NGD94-1 administration may subserve its superlative cognitive effects. In contrast, the exacerbation of cognitive deficits by haloperidol may be explained by its high degree of occupancy of both post-synaptic D_1-like and D_2-like DRs, further reducing transmission at the D_1 subtype of DRs, which is known to be critically involved in regulating working memory functions (Sawaguchi and Goldman-Rakic 1991).

The mechanism by which NGD94-1 increases cerebrospinal fluid levels of homovanillic acid (and presumably augments dopaminergic transmission) is likewise unclear. D_4 DRs are localized on the GABAergic neurons of the substantia nigra pars reticulata (Mrzljak et al. 1996), placing them within the feedback, regulatory circuit which controls dopamine neuron firing. D_4 DRs may thus regulate dopamine neuronal firing via this circuit.

Differential effects of NGD94-1 in control and PCP-treated subjects

It is currently unclear why the effects of D_4 DRs are specifically observed in PCP-treated animals, as opposed to control subjects. While improvements in performance are always difficult to observe in control subjects, especially under task conditions that support high levels of successful performance in control subjects (like object retrieval), this possibility may not totally explain the effects of NGD94-1 reported here, since the highest dose of NGD94-1 actually impaired performance in control subjects. Thus, there may be different actions of this drug in control and PCP-treated subjects.

The neural mechanisms which subserve this potential differential response are not known. If D_4 DR antagonists modulate dopamine neuron firing by a feedback pathway, it is possible that differential states of basal activity of dopaminergic cells in control and drug-treated animals (i.e., reduced basal activity in PCP-treated animals) results in altered responses to drug administration. Alternatively, D_4 DRs could be fundamentally altered (distribution or density) after subchronic PCP treatment. In the rodent, long-term exposure to the PCP congener MK-801 has been shown to down-regulate both D_1 and D_4 DRs in the hippocampus (Healy and Meador-Woodruff 1996a). Unfortunately, in an analogous study, the authors were unable to detect D_4 DR transcripts in frontal cortex, reporting only a decrease in D_1 DR mRNAs after subchronic MK-801 treatment (Healy and Meador-Woodruff 1996b). Nevertheless, a drug-induced change in the function of D_4 DRs alone or in the relative modulation of cortical circuitry by D_1 and D_4 DRs may subserve the different consequences of drug administration in control and drug-treated monkeys.

Effects of D_4 DR antagonists on rodent behavior

Based upon the observation that the non-selective D_4 DR antagonist clozapine had a unique profile of effects in several rodent behavioral assays, such as blockade of PCP-induced hyperactivity (Maurel-Remy et al. 1995) and pre-pulse inhibition deficits (Bakshi et al. 1994), several groups have investigated the behavioral effects of novel and selective D_4 DR antagonists, largely on tests of striatal function. L-745,870 and U-101,387G, both highly selective D_4 DR antagonists, have failed to reduce amphetamine-induced hyperactivity (Merchant et al. 1996; Bristow et al. 1997), and L-745,870 failed to block apomorphine-induced stereotypy. In addition, D_4 DR antagonists appear not to impair conditioned avoidance responding or produce catalepsy in rats (Bristow et al. 1997), nor to affect PCP-induced hyperlocomotion, social isolation or stereotypy (Sams-Dodd 1998). Recently, however, another group has reported that specific dopamine D_4 DR antagonists do block apomorphine-induced deficits in pre-pulse inhibition (Mansbach et al. 1998), though another group failed to find a similar effect (Bristow et al. 1997). Since these tests, in general, measure subcortical function, the lack of effects may not be very revealing. Further tests for drug effects on the function of frontal cortex, where D_4 DRs are enriched, are necessary to elucidate the actions of this receptor subtype. In addition, studies of selective D_4 DR antagonists on primate behavior must be further pursued.

Conclusions

The results of the current study demonstrate that modulation of D_4 DRs can affect performance of tasks dependent on the frontostriatal system. In addition, our data suggest that D_4 DRs may modulate central dopaminergic transmission in vivo. Importantly, the behavioral and biochemical effects of manipulation of D_4 DRs were largely observed in subjects with frontal cortical cognitive and dopaminergic deficits which had been induced by chronic exposure to the psychotomimetic NMDA antagonist PCP. Further studies of the effects of selective D_4 DR ligands on the functions of the prefrontal cortex, such as spatial or object working memory or attentional-set shifting, are warranted. The effects of these ligands on cognitive functioning in animals with experimentally induced dopaminergic dysfunction in prefrontal cortex (induced by 6-OHDA, MPTP or chronic PCP) should be compared with effects in control subjects. Further studies of the mechanisms subserving the beneficial cognitive effects of D_4 DR antagonists on frontal cortical tasks should give further insight into dopaminergic receptor mechanisms in prefrontal cortex.

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