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Regulation of Working Memory by Dopamine D_4 Receptor in Rats

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Working memory is regulated by neurotransmitters in prefrontal cortex (PFC), including dopamine and norepinephrine. Previous studies of dopamine function in working memory have focused on the D_1 and D_2 receptors, with most evidence suggesting a dominant role for the D_1 receptor. Since the dopamine D_4 receptor is highly expressed in PFC, we hypothesize that it may also contribute to working memory. To test this hypothesis, we examined behavioral effects of L-745,870, a highly selective, centrally active, D_4 antagonist, using a delayed alternation task in rats. Task performance was dose-dependently affected by the D_4 antagonist, depending on individual baseline functional status of working memory. In rats with *good* baseline performance, the D_4 antagonist had no effects at low doses, whereas high doses disrupted working memory. In rats with *poor* baseline working memory, the D_4 antagonist significantly improved working memory at low doses, and higher doses were not distinguishable from vehicle controls. Effects of the D_4 antagonist among poor performers were most robust when task demand for working memory was high, with lesser effects at lower demand level, suggesting that such effects were selective for working memory. The present findings indicate a significant role of the D_4 receptor in working memory, and suggest innovative, D_4-based, treatment of cognitive deficits associated with neuropsychiatric disorders.
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INTRODUCTION

Working memory is a mechanism that maintains information over a short period of time (Baddeley, 1986). Such information is held 'on-line' temporarily, and used to guide future response selection. Working memory is essential for virtually all complex behaviors. A trivial example is using a telephone number several seconds after it was read from a directory. Without the guidance of working memory, components of higher-order behavior become temporally disconnected from each other. As a component of complex cognitive processes, working memory has become a central construct in cognitive neuroscience.

As with many other forms of memory, working memory is dependent on many interconnected brain regions, but a great deal of research supports the conclusion that prefrontal cortex (PFC) is critically important. Working memory is impaired in human subjects with lesions in the frontal cortex, and particularly the dorsolateral PFC (Freedman and Oscar-Berman, 1986; Verin *et al*, 1993). Ablation of PFC in non-human primates leads to poor performance in tasks that require working memory (Battig *et al*, 1960; Goldman *et al*, 1971). Deficits of working memory are also characteristic of rats with lesions to the medial PFC—the rodent equivalent of the dorsolateral PFC in primates (Kolb *et al*, 1974; Larsen and Divac, 1978).

Working memory is regulated by various neurotransmitters found in PFC, particularly dopamine. Lesioning the mesocortical dopamine pathway from the ventral tegmental area to PFC results in impaired working memory in both primates (Brozoski *et al*, 1979) and rats (Bubser and Schmidt, 1990; Simon, 1981). Deficits induced as such can be rescued with the dopamine precursor L-DOPA, or the dopamine agonist apomorphine, to directly implicate dopaminergic mechanisms (Brozoski *et al*, 1979; Stam *et al*, 1989). Recent studies in human subjects have also provided evidence indicating that working memory is modulated by dopaminergic transmission (Mattay *et al*, 2000).

The receptor basis for dopamine action in working memory has been extensively studied with selective ligands. These studies have demonstrated an important role of the D_1-like (D_1,D_5) receptors. Blockade of the D_1-like receptors in PFC disrupts working memory (Arnsten *et al*, 1994; Sawaguchi and Goldman-Rakic, 1991). In animals with

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dopamine depletion, occurring either naturally with aging, or induced by reserpine treatment or chronic stress, the D_1 partial *agonist* SFK-38393 improves working memory (Arnsten *et al*, 1994; Mizoguchi *et al*, 2000). However, an overflow of dopamine activity, either by excessive dopamine release or overstimulation of postsynaptic D_1 receptor, can impair working memory (Arnsten and Goldman-Rakic, 1998; Cai and Arnsten, 1997; Murphy *et al*, 1996; Zahrt *et al*, 1997). These findings suggest that optimal functioning of PFC requires an intermediate level of dopamine input.

Studies of the D_2-like (D_2, D_3, D_4) receptors have yielded inconsistent, and sometimes conflicting results. Chronic exposure to the D_2-like receptor antagonist haloperidol results in disrupted working memory (Castner *et al*, 2000). Acute challenge with various D_2-like receptor antagonists has been reported to impair working memory and delay-specific PFC neuronal activity in some studies (Arnsten and Goldman-Rakic, 1998; Didriksen, 1995; Murphy *et al*, 1996), but not others (Aultman and Moghaddam, 2001; Bushnell and Levin, 1993; Sawaguchi and Goldman-Rakic, 1994; Verma and Moghaddam, 1996; Williams and Goldman-Rakic, 1995). Working memory deficits induced by the noncompetitive NMDA antagonist ketamine (Verma and Moghaddam, 1996), the benzodiazepine inverse agonist FG-7142, or physiological stress (Arnsten and Goldman-Rakic, 1998) are attenuated by D_2-like receptor antagonists. These observations suggest that, although the D_1 (or D_5) receptor is a major constituent of working memory, D_2-like receptors may also participate in its regulation.

Dopamine D_4 receptor is a member of the D_2-like receptor family with limited anatomical distribution (Van Tol *et al*, 1991). In mammalian species, D_4 receptor is detected mainly in the corticolimbic areas, with particularly high levels in PFC (Oaks *et al*, 2000; Tarazi and Baldessarini, 1999). Because of this unique distribution, we hypothesize that D_4 receptor may play a significant role in working memory. In the present study, we examined behavioral effects of L-745,870, a highly selective D_4 receptor antagonist, using a continuous delayed alternation task, a commonly used paradigm to assess working memory in rat (Dember and Fowler, 1958).

MATERIALS AND METHODS

Subjects

Male Sprague–Dawley rats (4–8 months old; Charles River Labs., Wilmington, MA) were housed in groups of 2–3 under a 12-h artificial daylight/dark schedule (on, 0700–1900). A total of 18 rats were included in the experiment. Daily food intake was restricted to approximately 17 g of standard rat chow, and body weight was maintained at 85–90% of free-feeding weight. Water was freely available. Rats were handled extensively before training.

Working memory was assessed using a standard T-maze. The main alley ($18 \times 60\,cm^2$) was separated from a starting box ($18 \times 24\,cm^2$) and two goal arms ($13 \times 40\,cm^2$) by opaque guillotine doors. At 2 cm from the end of each goal arm, a barrier blocked a food reward (1/6 Froot Loop cereal) from view. A large amount of reward was placed outside both goal arms to mask olfactory cues. The maze was located in the same position in a room with several easily identifiable visual cues, and cleaned with 50% ethanol between each animal.

Training

In the first 3–5 days, cage-mates were placed on the maze in pairs, and allowed to explore and consume rewards spread in the goal arms. In the following 3–5 days, rats were placed in the maze individually, with rewards behind barriers.

Training sessions were conducted 5 days/week (Monday through Friday). Each session consisted of 11 trials (a forced trial followed by 10 choice trials). In the forced trial, a randomly selected goal arm was blocked by a guillotine door, and a reward was placed in the other arm. A rat was placed in the starting box, and the guillotine door separating the starting box from the main alley was raised immediately. Once the rat entered the open arm, the guillotine door was closed behind it. In choice trials, both arms were accessible, but reward was available only in the arm not entered in the previous trial. Entry into the arm visited in the previous trial was registered as an error of working memory. Rats were allowed 10 s to consume the reward.

Habituation to injection (needle poke, twice/week for 4 weeks) started when performance of the rats in sessions without delay reached $\leqslant 1$ error/session on 2 consecutive days. During this period, rats were placed in a holding cage for approximately 10 min after the needle poke but prior to the sessions so that they became fully habituated to the procedure. Initially, needle poke significantly decreased the number of correct trials. However, towards the end of the 4-week habituation, needle poke no longer had any effect on performance.

Testing

Effects of L-745,870 (Merck; Rahway, NJ) were examined with three different delays between trials (0, 30, or 120 s; each tested in a different session), during which rats were placed in a holding cage next to the maze. L-745,870 was administered intraperitoneally (i.p.) at doses of 0 (20% β-hydroxypropyl-cyclodextrin as vehicle control), 15, 50, 150, 500, or 5000 μg/kg at 40 min prior to the start of behavioral testing. At this dose range, L-745,870 is centrally active and selective for the D_4 receptor, and has negligible action at other receptors (Patel *et al*, 1997).

Testing was carried out on Tuesdays and Fridays, with at least a 72-h washout period between testing sessions to minimize carry-over artifacts of previous drug administration. Performance was maintained by training sessions that did not involve delays on the remaining weekdays. The dosing sequence was randomized using a balanced Latin square design. All rats received all doses of L-745,870 (and a vehicle) once for each delay condition.

Data Analysis

Since rats were used repeatedly, data were analyzed using ANOVA of repeated measures with *post hoc* Dunnett's *t*-test. Probability $\leqslant 0.05$ was the criterion for statistically significant effect. Data are presented as mean $\pm$ SEM. Since working memory is dependent on an optimal level of

dopamine activity (see Introduction), we hypothesize that the D_4 antagonist may have different actions depending upon basal dopamine activity, and hence baseline performance. Accordingly, an average-split analysis was carried out. In this analysis, data obtained from rats with good baseline performance (above average) were separated rats with poor baseline performance (below average). Nonparametric Spearman rank correlation analysis was performed to determine whether effect of D_4 antagonist was associated with individual baseline performance.

RESULTS

Performance of rats decreased as task demand for working memory increased (Figure 1). The mean number of correct trials was 9.96 ± 0.12, 8.17 ± 0.22, and 6.69 ± 0.22 at 0, 30, and 120 s delay, respectively. In theory, the number of correct trials at chance performance is 5 (50% × total of 10 choice trials). To truly reflect working memory, we designed a working memory index (WMI), calculated as ([correct trials -5]/5) × 100. Accordingly, WMI was 99.2, 63.4, and 33.8 at 0, 30, and 120 s delay, respectively.

At 0-s delay, performance was not affected at any dose of L-745,870 (Figure 2a). However, at 30 (Figure 2b) and 120 s delay (Figure 2c), performance was significantly improved at doses of 15 and 150 μg/kg, respectively.

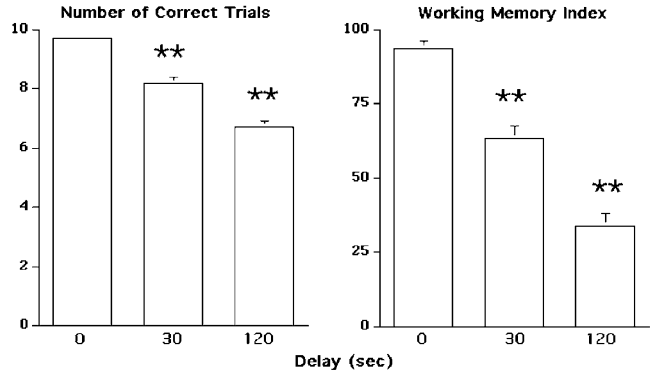

Figure 1 Performance of the rats in delayed alternation task as a function of delay. (**), $p \leqslant 0.01$. $N = 18$.

Next, we separated data from rats with relatively good (above average; Figure 3) *vs* poor (below average; Figure 4) baseline working memory, as determined with data obtained with vehicle injection at 30 and 120 s delays. In rats with good baseline performance, L-745,870 resulted in a significant *decrease* of WMI in sessions with a 30 s delay at 500 and 5000 μg/kg, with no effect at lower doses of 15–150 μg/kg (Figure 3a). In sessions with a 120 s delay, WMI was significantly decreased at 5000 μg/kg (Figure 3b). In rats with relatively poor baseline performance, treatment with L-745,870 at doses of 15 and 50 μg/kg yielded significantly *increased* WMI in sessions with a 30 s delay, whereas performance returned toward control values at higher doses (Figure 4a). In sessions with a 120 s delay, WMI was significantly increased at 15, 50, and 150 μg/kg (Figure 4b).

Improvement in WMI in the rats with poor baseline performance by low doses of L-745,870 also was dependent on the delay. At a 30 s delay, WMI was increased by a maximum of 77% (from 45.2 ± 4.8 to 80.0 ± 9.0) at 15 μg/kg, and somewhat less at higher doses (Figure 4a). At a 120 s delay, WMI was increased by up to 3.86-fold (from 10.0 ± 2.8 to 48.6 ± 13.0) at 150 μg/kg, with lesser increases at lower or higher doses (Figure 4b). A Spearman correlation analysis indicated that improvement of working memory performance with the D_4 antagonist was significantly inversely correlated with individual baseline performance (Figure 5).

DISCUSSION

Dopamine D_4 receptor is expressed preferentially in the limbic system and cortical areas, particularly in PFC (Oaks *et al*, 2000; Tarazi and Baldessarini, 1999). Several previous studies have examined cognitive effects of D_4 antagonists. Using an object retrieval/detour task in monkeys (a test of frontostriatal function), Jentsch *et al* (1999) found that behavioral deficits induced by the NMDA antagonist phencyclidine could be reversed with the selective D_4 antagonist NGD94-1. The D_4-selective antagonist PNU-101,387G has been reported to prevent working memory deficits induced by the benzodiazepine inverse agonist FG-7142 in monkeys (Arnsten *et al*, 2000). These studies implicate D_4 receptor in cognitive functions generally, but

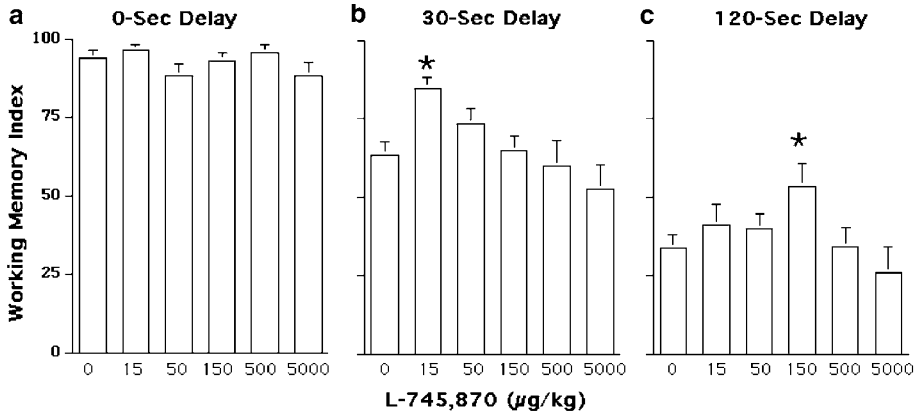

Figure 2 Effects of L-745,870 on delayed alternation task performance at various delays. (*), $p \leqslant 0.05$. $N = 18$.

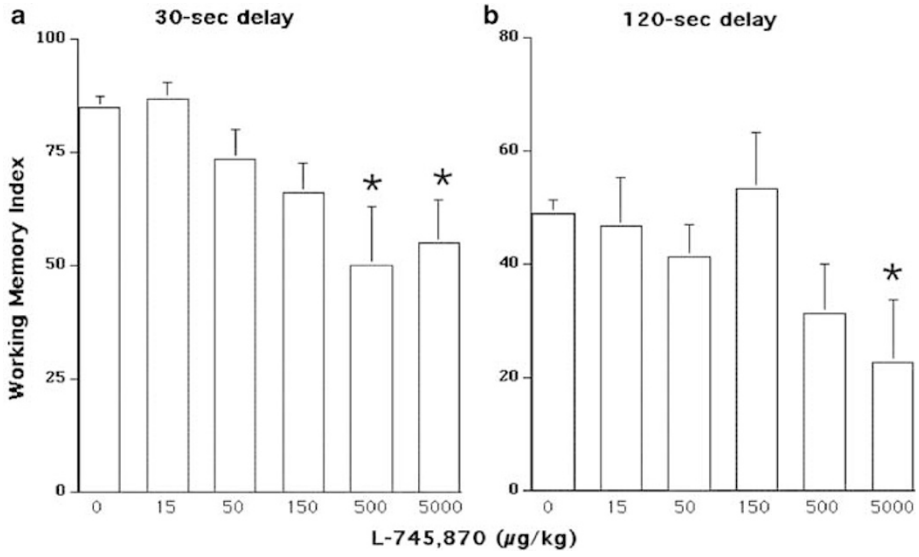

Figure 3 Effects of L-745,870 on working memory in rats with above-average baseline performance. (*), $p \leqslant 0.05$ in comparison to vehicle controls. $N = 8$ at 30 s, and 9 at 120 s delay.

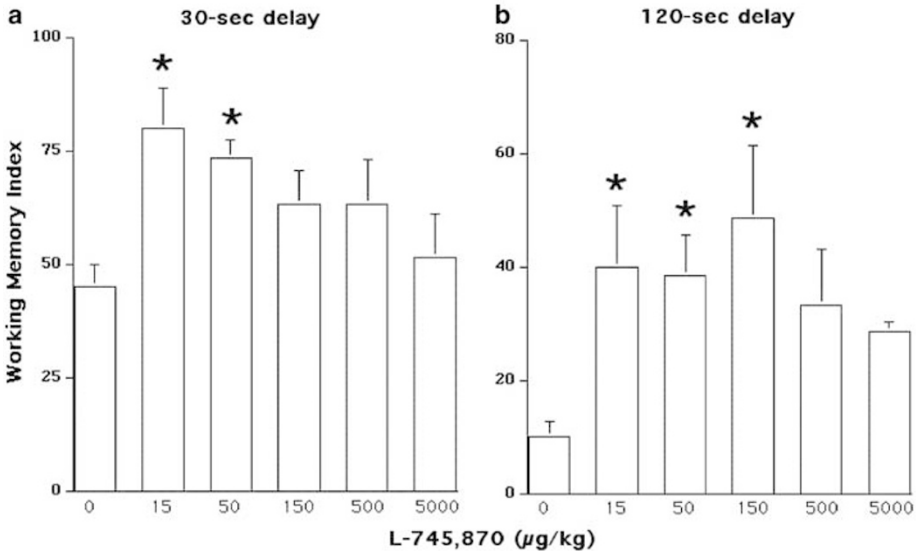

Figure 4 Effects of L-745,870 on working memory in rats with below-average baseline performance. (*), $p \leqslant 0.05$ in comparison to vehicle controls. $N = 10$ at 30 s, and 9 at 120 s delay.

explicit involvement in working memory *per se* was uncertain since the D_4 antagonist may have produced improvements in cognitive function by interacting with the agents used to disrupt working memory.

In the present study, we used a delayed alternation task to test for a role of the D_4 receptor in working memory in rats. Consistent with previous reports (Dember and Fowler, 1958), performance of rats in this task was dependent on the length of the intertrial delay, during which the rats must remember which arm of the T-maze was visited in the preceding trial. The number of correct trials and the WMI decreased significantly with increasing delays between trials, indicating construct validity of the procedure as a paradigm for working memory.

The present results indicate that dopamine regulates working memory by multiple mechanisms that evidently include a D_4 component. Changes of WMI by L-745,870 were not randomly distributed among various doses of L-745,870. Instead, such changes followed particular patterns (inverted U-shape dose-response in poor performers, disruption by high doses in good performers). These observations suggest that the observed drug effects were related to altered levels of D_4 receptor activation.

In addition, we found that effects of the D_4 antagonist were dependent on both individual baseline working memory level and dosage. In rats with above-average baseline performance, low doses of L-745,870 had little effect, but disrupted working memory at higher doses. In rats with below-average baseline performance, L-745,870

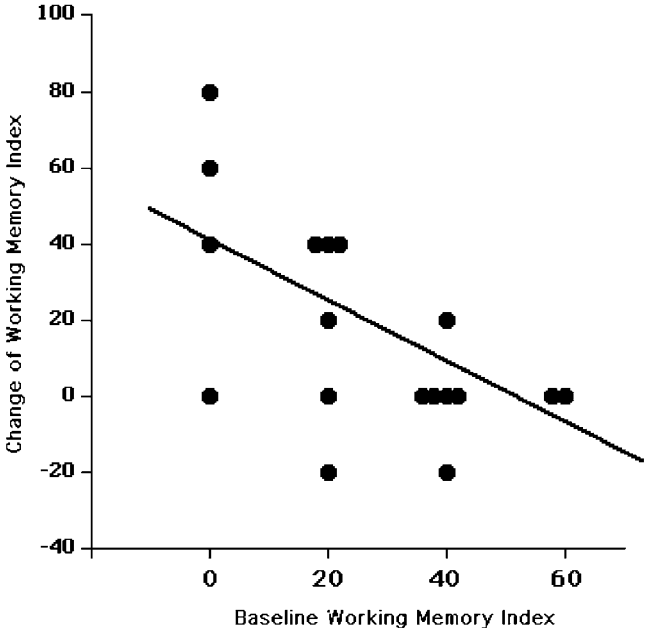

Figure 5 Relationship between baseline performance and effect of 50 μg/kg L-745,870 on working memory. $N = 18$. Spearman $r_s = 0.59$, $p \leqslant 0.05$.

produced an inverted U-shape dose-response. At low doses, L-745,870 (15–150 μg/kg) resulted in a significant improvement of working memory. At higher doses (500 and 5000 μg/kg), working memory returned toward vehicle control levels. These findings suggest that working memory is differentially regulated by the D_4 receptor, depending on baseline working memory function.

Based on the inverted U-shape dose-response found with the D_4 antagonist in rats with relative poor baseline, it is reasonable to conclude that optimal working memory requires an intermediate level of D_4 receptor stimulation. We further speculate that signal transduction mediated by D_4 receptor may be overactive in subjects with poor working memory. Thus, reducing D_4 receptor stimulation with low doses of an antagonist in these rats enhanced working memory.

Enhancement of performance in the delayed alternation task by L-745,870 was dependent on task demand for working memory. At a 0 s delay (minimal demand for working memory), performance of the rats was not affected by any dose of L-745,870. At a 120 s delay (relatively high demand), the WMI in rats with poor baseline performance was increased by up to nearly four-fold by the D_4 antagonist. At an intermediate level of demand for working memory (30 s delay), L-745,870 produced a significant, but somewhat smaller increase in WMI (up to 80%) in rats with poor baseline performance. These findings suggest that the effects of L-745,870 on delayed alternation task performance reflect changes in working memory.

An important distinction between the present experiments and several previous studies that reported behavior effects of L-745,870 (Mansbach *et al*, 1998; Patel *et al*, 1997; Zhang *et al*, 2001, 2002) was the finding of significant effects at much lower doses, with presumably greater selectivity at the D_4 receptor. Although we do not have direct evidence for the *in vivo* specificity for the D_4 receptor, other studies using surrogate markers such as plasma prolactin level (Patel *et al*, 1997) indicate that L-745,870 is devoid of any noticeable affect on the D_2 receptor at doses used in this study.

Consistent with the view that an optimal level of dopaminergic functioning is required for working memory functioning are human studies indicating that working memory, and function of PFC in general, may depend on individual levels of dopamine signaling. One such observation is the inverse correlation of working memory to the activity of catechol-*O*-methyltransferase (COMT, an enzyme that converts dopamine to the inactive metabolite 3-methoxytyramine), based on inheritance of specific alleles of the COMT gene (Mattay *et al*, 2003). In order to establish a relationship between working memory and the D_4 receptor, further experiments using reliable methods to quantify the density and function of the D_4 receptor are required. These might include specific testing of memory and other cognitive functions with a range of doses of D_4 antagonists that have already been proven to be safe and well tolerated by human subjects, including L-745,870 (Kramer *et al*, 1997).

Specific mechanisms by which D_4 antagonists produce cognitive effects are unknown. We propose that PFC is a leading candidate for such actions since PFC is vitally important for working memory (Goldman-Rakic, 2001) and since D_4 receptor mRNA and proteins are highly expressed in PFC (Oaks *et al*, 2000; Tarazi and Baldessarini, 1999). During working memory tasks, certain groups of pyramidal neurons in PFC increase firing rate after presentation of a spatial cue (for a review, see Goldman-Rakic, 2001). These neurons remain activated in the delay period (during which the spatial cue is removed), and cease firing when a response is executed. Failure of these neurons to maintain activity during the delay period is associated invariably with performance errors. These observations demonstrate that working memory is in part encoded and maintained by pyramidal neurons in PFC. There is evidence that the same neurons are modulated by D_4 receptor. Notably, several immunocytochemical studies indicate that D_4 receptor resides in pyramidal neurons in PFC (Ariano *et al*, 1997; Mrzljak *et al*, 1996; Wedzony *et al*, 2000). The presence of D_4 receptor in pyramidal neurons places this receptor in an ideal location to modulate working memory. Indeed, electrophysiological studies using D_4 selective ligands or knockout mice provided strong evidence that physiological property of PFC pyramidal neurons is regulated by D_4 receptor in normal condition (Rubinstein *et al*, 2001; Wang *et al*, 2002).

By simultaneously recording multiple PFC neurons in behaving monkeys, Goldman-Rakic and her colleagues provided evidence that pyramidal neurons representing working memory inhibit activity of surrounding units via GABAergic interneurons (Constantinidis *et al*, 2002; Rao *et al*, 1999). Through this collateral pathway, GABAergic interneurons sharpen the presentation of working memory. The presence of D_4 receptor in the GABAergic interneurons in PFC (Mrzljak *et al*, 1996; Wedzony *et al*, 2000) raises the possibility that D_4 antagonists may also regulate working memory indirectly through GABAergic interneurons.

A subpopulation of the D_4 receptor is present in presynaptic terminals in nucleus accumbens as evidenced by experiments that combined electronic microscopy with immunocytochemistry (Svingos *et al*, 2000). Although such findings have not been replicated in PFC, dopamine release in PFC has been shown to be increased in D_4 receptor knockout mice (Rubinstein *et al*, 1997), and in response to D_4 antagonists (Broderick and Piercey, 1998; Millan *et al*, 1998). These observations suggest that D_4 antagonist may affect working memory by modulating dopamine release in PFC.

Lesions to hippocampus (Aggleton *et al*, 1986), and closely associated structures, including the fornix (Pisa, 1981) and the septal area (Brito and Thomas, 1981), also produce a deficit in working memory as measured using delayed alternation. Significant levels of the D_4 receptor in hippocampus (Oaks *et al*, 2000; Tarazi and Baldessarini, 1999) raise the possibility that behavioral effects of L-745,870 observed in the present study may include actions in the hippocampal complex. Adding one more dimension of complexity, the D_4 receptor has high affinity for both dopamine and norepinephrine (Lanau *et al*, 1997). Since hippocampus as well as PFC is innervated by both catecholamines, it is conceivable that the behavioral effects of the D_4 antagonist observed in this study may reflect combined effects of both catecholamines in both brain regions.

Finally, the present findings suggest that the D_4 receptor might play a role in neuropsychiatric disorders involving working memory deficits, such as schizophrenia and attention-deficit/hyperactivity disorder (ADHD). D_4 receptor was initially implicated in schizophrenia by the relatively high D_4 receptor affinity for clozapine, an atypical antipsychotic agent (Oaks *et al*, 2000; Tarazi and Baldessarini, 1999). Subsequent clinical trials with D_4 receptor antagonists have failed to show antipsychotic efficacy of these agents (Corrigan *et al*, 2004; Kramer *et al*, 1997). However, possible effects of such treatment on cognitive deficits might have been overlooked since these studies were conducted in acutely ill psychotic patients, using clinical symptom rating scales. Further studies on chronically ill schizophrenia patients, aimed at quantitative assessments of specific cognitive functions and social functioning, are needed to adequately evaluate D_4 receptor as a potentially important therapeutic target. Genetic studies have strongly implicated D_4 receptor polymorphism in ADHD (La Hoste *et al*, 1996; Faraone *et al*, 2001). Using young rats with neonatal 6-hydroxydopamine lesions as a model for ADHD, we reported that locomotor hyperactivity in this model was inhibited by several selective D_4 antagonists as by the stimulant methylphenidate, but not antagonists that bind preferentially to the D_2 or 5-HT_{2A} receptor (Davids *et al*, 2002; Zhang *et al*, 2001, 2002). Given a hypothesized role of working memory deficits in ADHD (Pennington and Ozonoff, 1996; Denney and Rapport, 2001), beneficial effects of L-745,870 on cognition identified in the current study encourage further consideration of D_4 antagonists as novel treatments for clinical ADHD and other disorders of attention and cognition.

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