Psychopharmacology (2008) 196:643–648
DOI 10.1007/s00213-007-0999-1

ORIGINAL INVESTIGATION

Selective PDE inhibitors rolipram and sildenafil improve object retrieval performance in adult cynomolgus macaques

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Received: 7 March 2007 / Accepted: 23 October 2007 / Published online: 23 November 2007

Abstract
Rationale Selective phosphodiesterase (PDE) inhibitors improve the formation of hippocampus-dependent memories in several rodent models of cognition. However, studies evaluating the effects of PDE inhibition on prefrontal cortex-dependent cognition and in monkeys are rare.
Objectives The present study investigates the effect of the PDE4 inhibitor rolipram and the PDE5 inhibitor sildenafil on object retrieval performance. Object retrieval is a prefrontal cortical-mediated task, which is likely to capture attention and response inhibition.
Materials and methods The ability to retrieve a food reward from a clear box with an open side positioned in various orientations was assessed in adult male cynomolgus monkeys (*Macaca fascicularis*).
Results Rolipram (0.003–0.03 mg/kg, intramuscular [i.m.]) and sildenafil (0.3–3 mg/kg, i.m.) dose-dependently increased correct first reaches during difficult trials, reaching significance at 0.01 and 1 mg/kg, respectively. For both drugs, correct reaches were increased approximately 20%; that is, performance was improved from ~50 to ~70% correct.
Conclusions Both rolipram and sildenafil improved object retrieval performance, thus demonstrating the cognition-enhancing effects of PDE inhibition on a prefrontal task of executive function in monkeys.

Keywords Attention · Executive function · Phosphodiesterase · PDE4 · Rolipram · PDE5 · Sildenafil · Cognition · Cyclic AMP · Cyclic GMP · Object retrieval · Monkey · Primate

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Introduction

Second messenger cyclic nucleotides, i.e., cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), have been strongly implicated in processes of synaptic long-term potentiation (LTP; Frey et al. 1993; Zhuo et al. 1994) and have cognition-enhancing properties (Bernabeu et al. 1996; Blokland et al. 2006; Prickaerts et al. 2002a; Prickaerts et al. 2005). cAMP and cGMP are hydrolyzed by phosphodiesterase (PDE) enzymes, and inhibitors of PDEs (PDE-Is) produce cognition-enhancing effects in animal models of cognition. In this field, research has focused on PDE4 and PDE5 inhibitors (Blokland et al. 2006; Rose et al. 2005; Rutten et al. 2006) and more recently PDE2 (Boess et al. 2004; Rutten et al. 2007b) and PDE10 (Rodefer et al. 2005) inhibitors. For example, inhibition of PDE2, PDE4, and PDE5 can improve memory in the object recognition task in rodents (Boess et al. 2004; Prickaerts et al. 2004; Rutten et al. 2007b).

Moreover, the cAMP-selective PDE4-I rolipram is an effective performance enhancer in the passive avoidance task (Egawa et al. 1997; Imanishi et al. 1997), fear-conditioning test (Barad et al. 1998), and radial arm maze (Zhang and O'Donnell 2000). The cGMP-selective PDE5-I

sildenafil has been shown to enhance performance in the object recognition task, in the T-maze, and spatial plus maze (Devan et al. 2006; Devan et al. 2004; Patil et al. 2006; Prickaerts et al. 2004). In addition, sildenafil improved object recognition memory in mice (Rutten et al. 2005), and another PDE5-I, zaprinast, improved performance in a passive avoidance task in neonatal chicks (Campbell and Edwards 2006). Taken together, these results confirm the beneficial effects of PDE inhibition on cognition involving the hippocampus.

The present study assesses the effects of PDE inhibition on object retrieval (OR) performance, a task of prefrontal cognition, in monkeys. OR (also known as the detour reaching task) involves attention, response inhibition, and planning (i.e., executive function; Diamond et al. 1989). Because the prefrontal cortex is not well represented in rodents (especially the dorsolateral prefrontal cortex) and considerable debate exists on whether the rodent prefrontal cortex subserves the same behavioral functions as the primate/human prefrontal cortex (Brown and Bowman 2002; Uylings et al. 2003), tests of prefrontal functioning (i.e., executive function) are preferentially carried out in monkeys. Successful completion of the OR task requires various hypothetical steps. An animal must appreciate the contradiction between visual and tactile input, ignore the incorrect input, remember the previous incorrect approach, and formulate a novel approach to obtain the reward, which acts against the innate tendency of perseveration toward sustained sensory stimulation (Lipina and Colombo 2001). Direct support for the involvement of the frontal cortex in OR comes from studies in which lesions of the frontal cortex impaired, while lesions of the hippocampus did not impair, performance in the task (Diamond et al. 1989; Wilkinson et al. 1997). Furthermore, deficits in OR tasks have been documented in monkeys after treatment with methylphenyl tetrahydropyridine (Schneider and Roeltgen 1993; Taylor et al. 1990a; Taylor et al. 1990b), phencyclidine (Jentsch et al. 2000; Jentsch et al. 1999a; Jentsch et al. 1999b), and after excitotoxic lesioning with quinolinic acid of the striatum (Roitberg et al. 2002). The effect of PDE-Is in the OR task have, to our knowledge, never been evaluated before in unimpaired monkeys.

As mentioned above, improvement in hippocampus-dependent *memory* tasks in rodents is well established through PDE inhibition. However, no evidence exists on the effects of rolipram or sildenafil on prefrontal cortex-dependent tests of *executive function*. As the PDE4 enzyme is omnipresent throughout the brain and PDE5 is expressed in the hippocampus, cortex, and cerebellum (van Staveren et al. 2004), we hypothesized that OR performance would be improved by the PDE4 and PDE5 inhibitors rolipram and sildenafil, respectively.

Materials and methods

Subjects

Fourteen adult (age 5–12 years; weights 6–9 kg) male cynomolgus macaques (*Macaca fascicularis*) were housed in same-sex pairs in a colony room maintained at 21±2°C, 40±10% humidity, and on a normal 12-h light/dark cycle (lights on at 7:00 A.M.). Food (Purina High Protein no. 5045) and water were available ad libitum. All experimental procedures were approved by the Institutional Animal Care and Use Committee of Roche Palo Alto and were in accordance with National Institutes of Health guidelines.

Object retrieval task

The OR task has been previously described by Diamond et al. (1989). Briefly, this task requires a monkey to reach into a clear acrylic box (dimensions=5×5×5 cm) with one open side, to retrieve a food treat (cubes of apple or pear, 1–2 cm^2). The box was positioned in front of the monkey and outside of the home cage, with the open side facing left, right, or toward the monkey. Food treats were placed on the outer edge, inner edge, or deep within the box. A test session consisted of 17 trials with nine "easy" food retrievals (i.e., placement of the food reward on the inner or outer edges of the box or when the opening is toward the monkey) and eight "difficult" food retrievals (i.e., placement of the food reward deep within the box and the open side facing left or right, see Fig. 1). The order of presentation never varied (Table 1), there were no contingencies for incorrect reaches (i.e., monkeys typically acquired the treat after the incorrect reach) or dropped treats, and trials were terminated if there were no reaches within 3 min. The box was cleaned diligently between trials to minimize cues that could influence the task and subsequent task performance. After an initial period (1 week) to acclimatize the monkeys to the apparatus and procedure, tests were conducted twice a week.

Drugs

Rolipram (0.003, 0.01, 0.03, and 0.1 mg/kg; Sigma Chemicals, St Louis, MO) and sildenafil (0.3, 1, and 3 mg/kg; Sequoia Research Products Limited, Pangbourne, UK) were prepared fresh daily in a suspension of 10% cremaphore/90% saline and administered 30 or 60 min before testing, respectively. Drugs were administered via intramuscular injection (i.m.) in a volume of 0.1 ml/kg. Compounds were typically administered on Tuesday and Friday each week. Weekly test sessions were comprised of a vehicle session and a drug test session. Drug administration and behavioral measurement were completed blind,

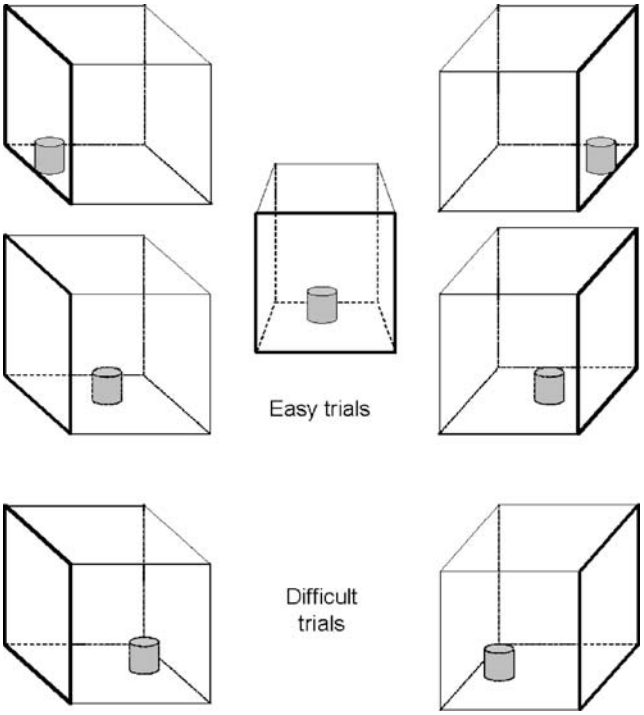

Fig. 1 A schematic overview of possible trials in the object retrieval (detour-reaching) task. The transparent box containing a food reward is depicted form the monkey's point of view. The *top* five orientations depict easy trials, and the *bottom* two orientations depict difficult trials

and each drug–dose combination was tested once. Drug doses were administered in a pseudorandom order.

Data analysis

The mean percent correct first reaches for easy and difficult food retrievals were analyzed with a one-factor (Dose) repeated-measures analysis of variance. When significant effects were demonstrated, a post-hoc Dunnett analysis comparing dose conditions to vehicle performance was performed. For all tests, the significance level was 0.05 (two-tailed).

Results

During vehicle sessions, monkeys readily reached for the food treats, successfully acquiring the treat on the first reach 100±0% during easy trials and 52±3% during difficult trials. Over the course of the experiment (2 months), there were no changes in vehicle performance.

The PDE4 inhibitor rolipram (0.003–0.1 mg/kg, i.m.) dose-dependently increased correct first reaches during difficult trials ($F[3, 55]=13.5$, $p<0.05$), reaching significance at 0.01 mg/kg (Fig. 2a). At the highest dose tested without side effects (0.03 mg/kg), the percentage correct first reaches were increased approximately 20 to 71±3%. Note that at 0.1 mg/kg (data not shown), emesis was observed in all but two monkeys; these results were therefore excluded from analysis.

The PDE5 inhibitor sildenafil (0.3–3 mg/kg, i.m.) dose-dependently increased correct first reaches during difficult trials ($F[3, 50]=8.6$, $p<0.05$), reaching significance at 1 mg/kg (Fig. 2b). At the highest dose tested (3 mg/kg), correct reaches were increased approximately 20 to 73±3%. No side effects were observed.

Neither rolipram nor sildenafil altered performance during the easy trials, with the exception of the high dose of rolipram (0.1 mg/kg), in which monkeys failed to perform the task (data not shown) because of emetic side effects.

Discussion

The present study demonstrates performance-enhancing effects of two selective PDE-Is on OR performance in monkeys. OR is subserved by the prefrontal cortex and/or fronto-striatal pathways, within which modulation of dopamine and acetylcholine transmission are involved in attention, response inhibition (i.e., executive function), and working memory in rodents and primates (Jentsch et al. 2000; Lipina and Colombo 2001; Palfi et al. 1996; Ramos et al. 2003; Wilkinson et al. 1997). To our knowledge, this is the first study to investigate the effects of PDE5 inhibition on executive function in monkeys. Of note, two previous studies have investigated the effects of sildenafil on cognition-related variables in humans. In these studies, sildenafil was shown to enhance simple reaction times and to some extent enhancement of focused attention (Grass et al. 2001; Schultheiss et al. 2001). However, these findings have not been further

Table 1 Primate object retrieval: trial order

Trial number	Description	Level
1	LOS—line of sight	Easy
2	LOS—line of sight	Easy
3	RO—right outside	Easy
4	RD—right deep	Difficult
5	RO—right outside	Easy
6	RI—right inside	Easy
7	RD—right deep	Difficult
8	LO—left outside	Easy
9	LD—left deep	Difficult
10	LO—left outside	Easy
11	LI—left inside	Easy
12	LD—left deep	Difficult
13	LD—left deep	Difficult
14	RD—right deep	Difficult
15	LD—left deep	Difficult
16	RD—right deep	Difficult
17	LOS—line of sight	Easy

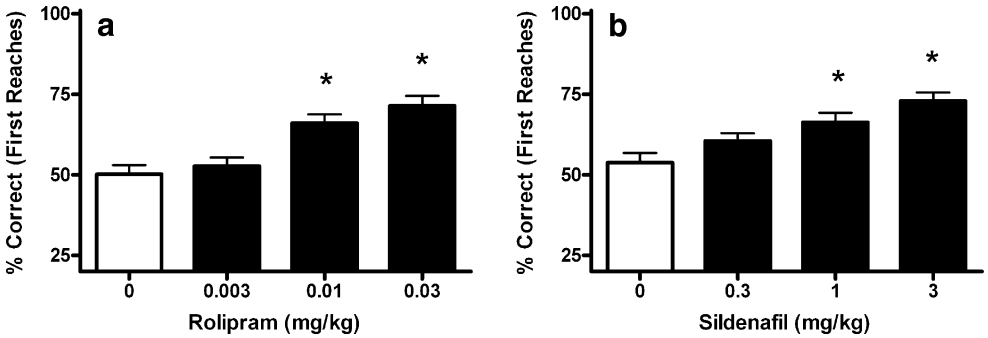

Fig. 2 The effects of PDE-I on object retrieval (OR) performance (mean values and SEM) **a** The effects of the PDE4 inhibitor rolipram and the PDE5 inhibitor sildenafil (**b**) on the percentage correct first reaches on difficult trials in the OR task. *Asterisks* indicate significant differences from baseline ($P<0.05$)

described in the literature. The effects of the PDE4 inhibitor rolipram on executive function have yet to be assessed in humans. Thus, the current results complement and extend to the cognition-enhancing effects of PDE inhibition.

Previous studies have repeatedly shown that PDE-Is can have cognition-enhancing effects, mainly in hippocampus-dependent memory tasks, in rodents. For example, the PDE4 inhibitor rolipram improved long-term memory in the object recognition task, in passive avoidance learning, and fear conditioning (Barad et al. 1998; Rutten et al. 2006; Zhang et al. 2005). In addition, rolipram had performance-enhancing effects in a prefrontal cortex-dependent working memory task, i.e., delayed alternation, in young rats and young monkeys (Ramos et al. 2003). Results from the present study corroborate the cognition-enhancing effects of low-dose (0.01 mg/kg) rolipram treatment in a prefrontal cortex-dependent task, although the present OR task does not involve working memory but requires attention and response inhibition (i.e., executive function; Diamond et al. 1989). Furthermore, in aged mice, rolipram ameliorated the age-related deficits in the passive avoidance task, a test of hippocampus-dependent memory. In contrast, rolipram impaired prefrontal cortex-dependent working memory performance in aged rodents and aged monkeys. With advancing age, opposite profiles between the function of protein kinase A (PKA) in the hippocampus and prefrontal cortex were suggested to explain these results; that is, the prefrontal cortex showed indices of increased PKA activity, while the hippocampus exhibited evidence of decreased PKA activity (Ramos et al. 2003). Although in the present study, cognition-enhancing effects on executive function were observed after rolipram treatment in young monkeys, the possible cognition-impairing effects of rolipram on prefrontal cortex-dependent tests in aged monkeys should be further investigated.

Compared to PDE4 inhibition, the cognition-enhancing effects of PDE5 inhibition have not been studied as extensively. However, a growing number of studies have shown cognition-enhancing effects of PDE5-Is in multiple tests and in multiple species. PDE5-Is improved cognitive performance in object recognition and inhibitory and passive avoidance tasks (Baratti and Boccia 1999; Prickaerts et al. 2005; Prickaerts et al. 2004; Prickaerts et al. 2002b; Rutten et al. 2005; Shafiei et al. 2006; Singh and Parle 2003). In addition, the inhibition of PDE5 reversed memory deficits induced by scopolamine, diabetic neuropathy, or nitric oxide (NO) synthase inhibitors in rats (Devan et al. 2006; Devan et al. 2004; Patil et al. 2004; Prickaerts et al. 1997). To our knowledge, no literature exists on the possible cognition-enhancing effects of PDE5 inhibitors in nonhuman primates. Furthermore, the effects of PDE5 inhibition on prefrontal cortex-depending cognition, i.e., working memory and executive function, are unknown.

The underlying mechanisms of PDE-Is and cognition enhancement are still elusive, but several possible pathways have been described. Possible mechanisms of action for rolipram and sildenafil are based on the proposed underlying signaling pathways of LTP. Both cAMP and cGMP have been strongly implicated in hippocampal LTP (Frey et al. 1993). Activation of LTP-related signaling pathways of cAMP/PKA/cAMP response element-binding protein (CREB) and cGMP/protein kinase G (PKG)/CREB have been implicated as the underlying mechanisms for the cognition-enhancing effects of PDE4 and PDE5 inhibitors (Bernabeu et al. 1996; Blokland et al. 2006; Lu and Hawkins 2002; Prickaerts et al. 2002a; Rutten et al. 2007b). A very recent study suggested another pathway through which cGMP can influence cognitive processes. This study showed that the hippocampal NO/cGMP pathway directly stimulates the postsynaptic cAMP/PKA/CREB pathway (Matsumoto et al. 2006). Alternatively, cGMP has also been found to maintain LTP via a presynaptic cGMP/PKG pathway (Zhuo et al. 1994). However, the present study involves prefrontal cortex-dependent behavior, and it remains to be proven that the above mentioned hippocampal LTP mechanisms of synaptical strengthening are also applicable in the prefrontal cortex. Of note, the effects of rolipram on prefrontal cortex performance were explained via activation of the postsynaptic PKA pathway (Ramos et al. 2003). Thus, both cGMP and cAMP can activate cellular cascades resulting in CREB phosphorylation, which could induce long-lasting changes in neuronal signaling and may thereby explain the performance enhancement observed in the present study.

Apart from LTP-related mechanisms of action, the effects of rolipram and sildenafil on prefrontal functioning in the OR may be explained by their stimulatory effect on neurotransmission. Because rolipram is independent of a specific receptor system, it is suggested that rolipram may ameliorate physiological abnormalities that occur secondary to alterations in dopaminergic, glutamatergic, serotonergic, and/or adrenergic transmission (Maxwell et al. 2004; Rutten et al. 2007a). Elevated cAMP levels are thought to excite noradrenergic and dopaminergic neurotransmitter systems (Schoffelmeer et al. 1985), thus enhancing their availability, hence also enhancing synaptic transmission. Similar to rolipram, sildenafil is a drug that is not linked to specific neurotransmitter systems. Modulatory activity of sildenafil was suggested on central dopaminergic pathways (Ferrari et al. 2002). Dopaminergic dysfunction in prefrontal cortex may subserve at least a component of the impaired OR/detour performance in deficit models (Jentsch et al. 1999a). Moreover, serotonin depletions of the prefrontal cortex in the common marmoset result in deficits in the acquisition of the OR task (Walker et al. 2006). Hence, activation of cGMP or cAMP may improve dopaminergic turnover and prefrontal functioning in the OR task. Thus far, it remains unclear which of these abovementioned mechanisms are involved in the prefrontal cortex and how they explain cognition enhancement by inhibition of PDEs in the OR task.

To summarize, previous research demonstrated the cognition- and largely memory-enhancing effects of PDE4 and PDE5 inhibition in rodents. The results from the current study extend these cognition-enhancing effects of PDE-Is in rodents to nonhuman primates. More specifically, rolipram and sildenafil improve OR performance, thus demonstrating that PDE4 and PDE5 inhibition enhance performance in a cognitive domain involving executive function (and attention) mediated by the prefrontal cortex.

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