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The Dopamine D_3/D_2 Receptor Agonist 7-OH-DPAT Induces Cognitive Impairment in the Marmoset

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SMITH, A. G., J. C. NEILL AND B. COSTALL. *The dopamine D_3/D_2 receptor agonist 7-OH-DPAT induces cognitive impairment in the marmoset.* PHARMACOL BIOCHEM BEHAV **63**(2) 201–211, 1999.—Previous work has shown that dopaminergic systems are involved in cognitive function in the common marmoset. The present study investigated the role of dopamine D_3 receptors in cognitive performance in the marmoset. The effects of the putative dopamine D_3 receptor agonist, 7-OH-DPAT, on performance of a same-day reversal visual object discrimination task were assessed using a miniature Wisconsin General Test Apparatus (WGTA). Within the same test session marmosets acquired a two-choice object discrimination initial task and a reversal task to criterion. 7-OH-DPAT (6–10 μg/kg) significantly impaired reversal task performance only, without affecting acquisition of the initial task. A higher dose of 25 μg/kg 7-OH-DPAT impaired initial task acquisition as well as reversal task acquisition, possibly as a consequence of a nonspecific influence on motor function. The dopamine D_2 receptor antagonist (−)sulpiride (5–10 μg/kg) and the α_2-receptor antagonist yohimbine (50 μg/kg) failed to attenuate the effects of 7-OH-DPAT (6 μg/kg) in this task. In contrast, the dopamine D_2/D_3 receptor antagonist raclopride (50 μg/kg) significantly attenuated the 7-OH-DPAT–induced impairment of reversal task performance. These results suggest that activation of dopamine D_3 receptors produces a selective impairment of aspects of cognitive function in the marmoset. © 1999 Elsevier Science Inc.

Dopamine D_3 receptors Dopamine D_2 receptors Cognition Marmoset

SCHIZOPHRENIA is a neuropsychological disorder with well-characterized disorders in learning and memory. Schizophrenic patients with high negative symptom ratings are more likely to show impairments in information processing and attentional deficits with respect to patients with positive symptoms, as demonstrated by poor performance in cognitive tests (8,32). The cognitive impairments, i.e., the perseverative errors shown in patients with negative symptoms (20), are analagous with those shown in discrimination reversal tasks in both humans and marmosets following administration of dopamine agonists such as amphetamine (23,32). The role of mesocorticolimbic dopamine function in learning and memory processes, in particular those that are involved in executive function and working memory, can be further explored by means of visual discrimination tasks with a reversing reward contingency. The cognitive capabilities required to perform such tasks may be examined more appropriately in the nonhuman primate than the rodent, on the basis of neuroanatomical similarities with humans and the presence of higher cognitive functions required to perform comparable neuropsychological studies in human subjects (33).

Using a miniature version of the the Wisconsin General Test Apparatus (WGTA), common marmosets (*Callithrix jacchus*) trained to carry out a visual discrimination reversal task with competence have been shown to subsequently display an impaired performance following administration of amphetamine (30), which is thought to be mediated by a central dopaminergic excess (23). The specific receptor subtypes that mediate the cognitive processes involved in reversal discrimination have not been defined. Recent studies have shown that the dopamine D_3 receptor is distributed in high densities in discrete areas of the limbic system of the rat (3,15), human

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(27) and marmoset brain (14). The role of the D_3 receptor in behavior has been difficult to characterize due to the lack of D_3 receptor-selective compounds. The dopamine D_3/D_2 receptor agonist 7-OH-DPAT [7-hydroxy-*N*,*N*-di-n-propyl-2-aminotetralin], which displays a 50–100 times higher in vitro affinity for D_3 relative to D_2 receptors (16), has been shown to induce inhibitory effects on motor function (5) in behavioral paradigms of information processing such as prepulse inhibition (4,36), and on passive-avoidance learning (38,42). However, further experimental evidence is necessary to confirm an inhibitory influence of the dopamine D_3 receptor in the expression of cognitive deficits.

The aim of the present study was to investigate the effects of 7-OH-DPAT on cognitive performance in the marmoset by means of visual discrimination reversal task using a miniature WGTA. Radioligand binding studies in vitro have revealed that 7-OH-DPAT possesses appreciable affinity for the dopamine D_2 receptor (13) and the α_2-adrenoceptor (41) in addition to affinity for the D_3 receptor. Therefore, to elucidate the nature of the receptors involved in the cognitive impairment induced by 7-OH-DPAT we examined the ability of the dopamine D_2/D_3 receptor antagonist raclopride, the dopamine D_2 receptor antagonist (−)sulpiride, and the α_2-adrenoceptor antagonist yohimbine to attenuate the impairments in reversal learning.

METHOD

Subjects

Subjects were four drug-naive laboratory-bred (three female, one male, University of Bradford) common marmosets over 18 months of age weighing 290–380 g. Marmosets were housed either in stable single-sex pairs or as a mixed-sex pair where the male partner had been previously vasectomized. Animals were fed at approximately 1600 h with a selection of Mazuri primate diet (SDS Ltd, Essex), fresh fruit, wholemeal bread, or maltloaf. Water was available ad lib. During training and testing, food deprivation was not necessary for maintaining performance of cognitive tasks. Holding rooms were maintained at 25 ± 1°C at a humidity of 55 ± 5%, with a 12-h light–dark cycle (lights on at 0700 h). During the dark period, a single 60-W red bulb was illuminated; this bulb was illuminated for 0.5 h after the main lights were switched on and before they were switched off to simulate dawn and twilight periods.

Assessment of Cognitive Performance of Marmosets Using the Wisconsin General Test Apparatus (WGTA)

Apparatus. Cognitive performance was evaluated in a manually operated, miniature WGTA as described in detail previously (7). The WGTA consisted of a solid box with an illuminated internal chamber. The WGTA interior was separated from a transport box housing the marmoset by an opaque shutter that could be raised or lowered by the operator, allowing the operator to control the marmoset's access to the chamber. Stimuli (junk objects) were presented to the animal by means of a Perspex tray placed in the interior of the WGTA immediately in front of this shutter. This tray contained two food wells placed 14 cm apart that could be baited with food as required, and obscured by covering each well with a stimulus; the animal was required to reach through the bars of the transport box and displace an object to obtain a reward. At the opposite end of the WGTA, a hinged flap allowed access by the operator to the WGTA interior to bait the food wells and to position the test objects over the wells. The operator was able to observe the animal in the transport cage positioned behind the WGTA by means of a smoked Perspex viewing screen.

Training. The WGTA was used to train experimentally naive marmosets to perform a two-choice object discrimination task. In this task, two dissimilar test objects were presented, with one object designated as the rewarded object. The pair of objects were positioned over the food wells with the reward position (left or right well) selected according to a pseudorandom Gellerman schedule (11). A single trial comprised of presentation of the pair of test objects when the screen was raised. The animal was trained to displace the correct, i.e. rewarded, object, and retrieve the reward—a 3-mm cube of bread coated with syrup. Touching the unrewarded object was scored as incorrect. Following the animal's response, the partition between the transport box and the WGTA was lowered to end the trial and the objects were repositioned over the wells. The intertrial interval was maintained at 15 s, with the trial time varying according to the length of time taken by the animal to make a selection. A predetermined criterion set for completion of the simple discrimination task was 90% correct choices in any one test session, i.e. 27 correct object choices within 30 consecutive trials as previously described by Domeney et al. (7).

Visual discrimination reversal task. This task consisted of two serial components—an initial discrimination task followed immediately by a second task with a reversed reward contingency. The performance during learning of an initial task could be compared in the same animal with performance during learning of a subsequent reversal task. Task performance was assessed by the number of trials taken to reach criterion of six correct consecutive trials. The number of incorrect responses (errors) within each block of five trials was used to plot "learning curves" that describe the rate of error during task acquisition. Participation of an animal in this study was determined on the basis of consistent performances in the initial and reversal discrimination tasks on 3 consecutive test days.

The test contingency was carried out on 3 consecutive days (Table 1).

Test day 1. A pair of dissimilar test objects was presented; a red cube (RC) and a blue pyramid (BP), only one of which was rewarded. Left or right positioning of the test objects was determined by means of a pseudorandom schedule (11). The animal was required to displace the rewarded initial object (RC) only, to obtain the reward. To complete the initial task the animal was required to make six consecutive correct choices of the rewarded initial object; if animals failed to reach this test criterion in either 30 trials or in a time period of 30 min, the reversal task was not carried out. On reaching this criterion, the reward contingency was reversed so that the previously unrewarded object (i.e. BP) became the rewarded object. The criterion set for the reversal task was six correct consecutive choices of the new rewarded object. On test day 1 animals received vehicle treatment only; this data was pooled over the course of the studies (7 weeks for the preliminary 7-OH-DPAT study; 6, 4, and 8 weeks for sulpiride, yohimbine, and raclopride studies, respectively; 26 weeks in total) to exclude the possibility of interaction between the different drug dosage regimes and the stability of baseline task performances and, thus, to exclude interference from the effects of repeated testing (1).

Test day 2. The object rewarded in the initial task was always the object rewarded in the reversal task on test day 1

TABLE 1
EXAMPLE OF TASK ORDER FOR ANIMAL A IN 7-OH-DPAT (7DP) STUDY

	Test Day	Week 1	Week 2	Week 3	Week 4	Week 5
	1	VEH	VEH	VEH	VEH	VEH
Initial task		RC v BP	BP v RC	RC v BP	BP v RC	RC v BP
Reversal task		BP v RC	RC v BP	BP v RC	RC v BP	BP v RC
7DP mg/kg	2	0	10	2	5	7.5
Initial task		RC v BP	BP v RC	RC v BP	BP v RC	RC v BP
Reversal task		BP v RC	RC v BP	BP v RC	RC v BP	BP v RC
	3	VEH	VEH	VEH	VEH	VEH
Initial task		RC v BP	BP v RC	RC v BP	BP v RC	RC v BP
Reversal task		BP v RC	RC v BP	BP v RC	RC v BP	BP v RC

RC = red cube; BP = blue pyramid. The first named object in each pair is rewarded.

(BP) followed by reversal of the reward contingency such that RC became the rewarded object (Table 1). Animals received drug or vehicle treatments according to a structured operator-blind counterbalanced schedule (Table 2).

Test day 3. The object rewarded in the initial task was again the object rewarded in the reversal task on test day 1 (RC) followed by reversal of the reward contingency such that BP became the rewarded object (Table 1). Animals received vehicle treatment only; this data was used to assess the posttreatment effects of 7-OH-DPAT.

A 4-week drug-free period was allowed in between each drug study; animals were tested daily for a 1-week period prior to each drug study to ensure baseline performance was maintained.

Assessment of Choice Latency

Choice latency was calculated for individual animals to provide a measure of the competency of performance using the formula:

$$\text{Choice latency} = \frac{\text{Total test time to complete } n \text{ trials (sec)} - [(n-1) \times 15]}{n}$$

TABLE 2
EXAMPLE OF PROCEDURE FOR 7-OH-DPAT STUDY

	Animal			
	A	B	C	D
Week	Treatments (7-OH-DPAT mg/kg/VEH)			
1	0	10	2.5	5
2	7.5	0	10	2.5
3	5	7.5	0	10
4	2.5	5	7.5	0
5	10	2.5	5	7.5
Study extended				
6	0	25	6	0
7	6	0	25	6
8	25	6	0	25
4 week drug-free period				

where n = total number of trials to complete initial plus reversal tasks and the intertrial interval = 15 s.

Drugs

(±) 7-OH-DPAT hydrobromide [7-hydroxy-2-(di-n-propylamino) tetralin. HBr] (RBI, USA), raclopride tartrate (supplied as a gift, Astra, UK), and yohimbine hydrochloride (Sigma, UK) were freshly prepared in 0.9% saline. (−)Sulpiride hydrochloride (RBI, UK) was dissolved in the minimum concentration of hydrochloric acid, diluted in 0.9% saline, and adjusted to pH 7.0 with sodium hydrogen carbonate. All compounds were administered by the subcutaneous route in a volume of 1 ml/kg body weight. All doses are expressed as the base. Following 7-OH-DPAT or vehicle administration animals were returned to the home cage for a 15-min period prior to testing. In antagonism studies, animals were returned to the home cage for a 30-min period following administration of the antagonist or vehicle, followed by administration of 7-OH-DPAT or vehicle as described above. Doses of 7-OH-DPAT were selected to minimize the locomotor stimulant effects and gastrointestinal disturbances associated with higher doses of 7-OH-DPAT in other species (24) and reported by the authors at doses above 0.5 mg/kg in marmosets (39). The minimally effective dose of 7-OH-DPAT was then selected for antagonist studies. Doses of antagonists were selected in order to reduce the likelihood of intrinsic effects on cognitive performance or locomotor activity in the marmoset (19,23). During the pretreatment period and each test session the behavior of the animal was monitored by the operator, and any signs of behavioral changes noted, as responses such as hyperactivity, emesis, sedation, or stereotyped behavior have been reported following the administration of high doses of dopaminergic agents and could cause general disruption of behavior that would exclude animals from the final data analysis (29).

Statistical Analysis

The mean trials to criterion in both the initial and the reversal task and choice latency was calculated for each drug treatment and compared to the respective vehicle or control treatment by means of a one-way ANOVA for repeated measures followed by Dunnett's *t*-test for multiple comparisons. Stability of baseline performance in initial and reversal tasks and posttreatment effects of 7-OH-DPAT were examined by

one-way ANOVA for repeated measures followed by Dunnett's *t*-test.

RESULTS

Effect of Repeated Drug Treatment/Testing on Baseline Performance

Baseline responding in the initial and reversal tasks was not significantly altered during the 26-week duration of the studies, $F(25, 103) = 1.9$, NS. Thus baseline performance did not improve subsequent to repeated testing (26 weeks in total), in agreement with Baker et al. (2), and drug treatments had no detrimental effect on baseline task performances during the course of the studies.

Effects of 7-OH-DPAT on Task Performance

Initial task. 7-OH-DPAT (2.5–10 μg/kg) had no significant effect on mean trials, $F(6, 27) = 1.3$, NS, in the initial acquisition task. A significant impairment in performance of the initial task was, however, produced following the highest dose of 7-OH-DPAT (25 μg/kg; $p < 0.001$) (Fig. 1a). Analysis of the total group errors for the initial task showed no effect of 7-OH-DPAT on the rate of error compared to vehicle except following 7-OH-DPAT 25 μg/kg, where animals continued to

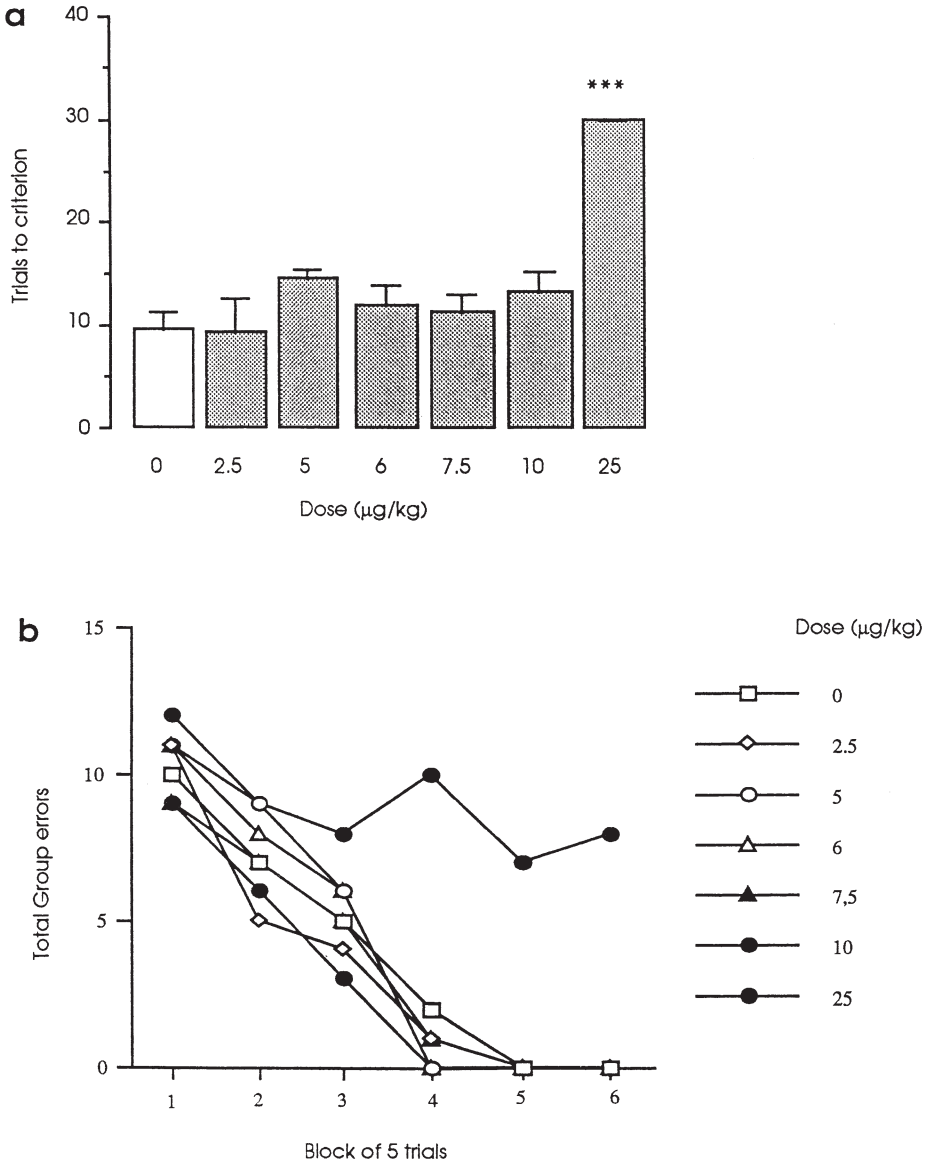

FIG. 1. The effects of 7-OH-DPAT (2.5–25 μg/kg) on performance of an object discrimination initial task. Data are presented as mean ± SEM (a) number of trials to criterion (six correct consecutive responses), and (b) total group errors per block of five trials for the initial discrimination task; $n = 4$ animals per group. Significant impairment in initial task performance following 7-OH-DPAT compared to vehicle treatment is indicated by ***$p < 0.001$; Dunnett's *t*-test.

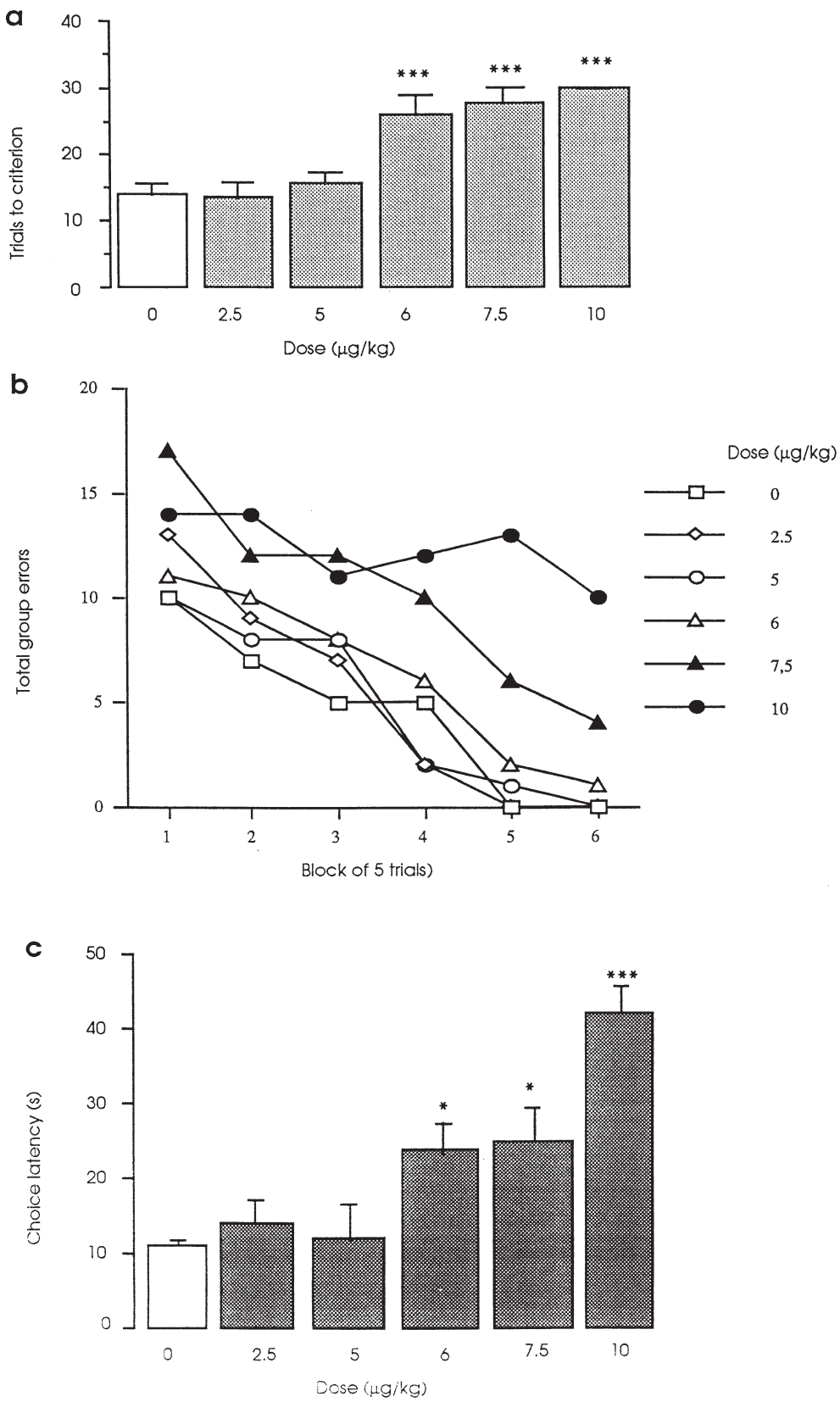

FIG. 2. The effects of 7-OH-DPAT (2.5–10 μg/kg) on performance of an object discrimination reversal task. Data are shown as (a) and (b) in Fig. 1. (c) Mean ± SEM task choice latency for the test session calculated for the total number of trials completed in each test session (initial and reversal tasks). Significant impairments in performance (7-OH-DPAT compared to vehicle treatment) are indicated by $^{***}p < 0.001$; significant impairment in task choice latency $^{*}p < 0.05$ $^{***}p < 0.001$; Dunnett's t-test, $n = 4$ animals per group.

choose the initial (unrewarded) object such that the rate of error did not reach zero and four out of four animals failed to achieve the test criterion of six consecutive correct choices of the initial object in 30 trials at this dose; therefore, the reversal task was not carried out (Fig. 1b).

Reversal task. The administration of 7-OH-DPAT (2.5–10 μg/kg) produced a dose-dependent impairment in performance of the reversal task shown by a significant increase in mean trials to criterion, $F(5, 23) = 10.1$, $p < 0.001$. Post hoc analysis revealed significant ($p < 0.001$) increases in trials to criterion following 7-OH-DPAT at doses of 6–10 μg/kg compared to vehicle treatment (Fig. 2a). Analysis of the total group errors for the reversal task showed that 7-OH-DPAT 2.5–10 μg/kg markedly increased the rate of error in a dose-related manner, as indicated by the displacement of the learning curves following 7-OH-DPAT treatment to the right with respect to the vehicle learning curve (Fig. 2b).

Effects of 7-OH-DPAT on Retention of the Reversal Task

Treatment with 7-OH-DPAT 2.5–10 μg/kg on day 2 did not produce a significant effect on the ability to perform a subsequent retention task, i.e. performance of the initial task on day 3 (i.e. the reversal task performed under the influence of 7-OH-DPAT on the previous test day), $F(5, 23) = 2.2$, NS.

Mean task choice latency. 7-OH-DPAT (2.5–10 μg) caused a significant increase, $F(5, 23) = 10.7$, $p < 0.001$, in mean task choice latency compared to vehicle treatment (Fig. 2c). Post hoc analysis revealed significant increases in mean task choice latency at 6 μg ($p < 0.05$) and 10 μg ($p < 0.001$) 7-OH-DPAT.

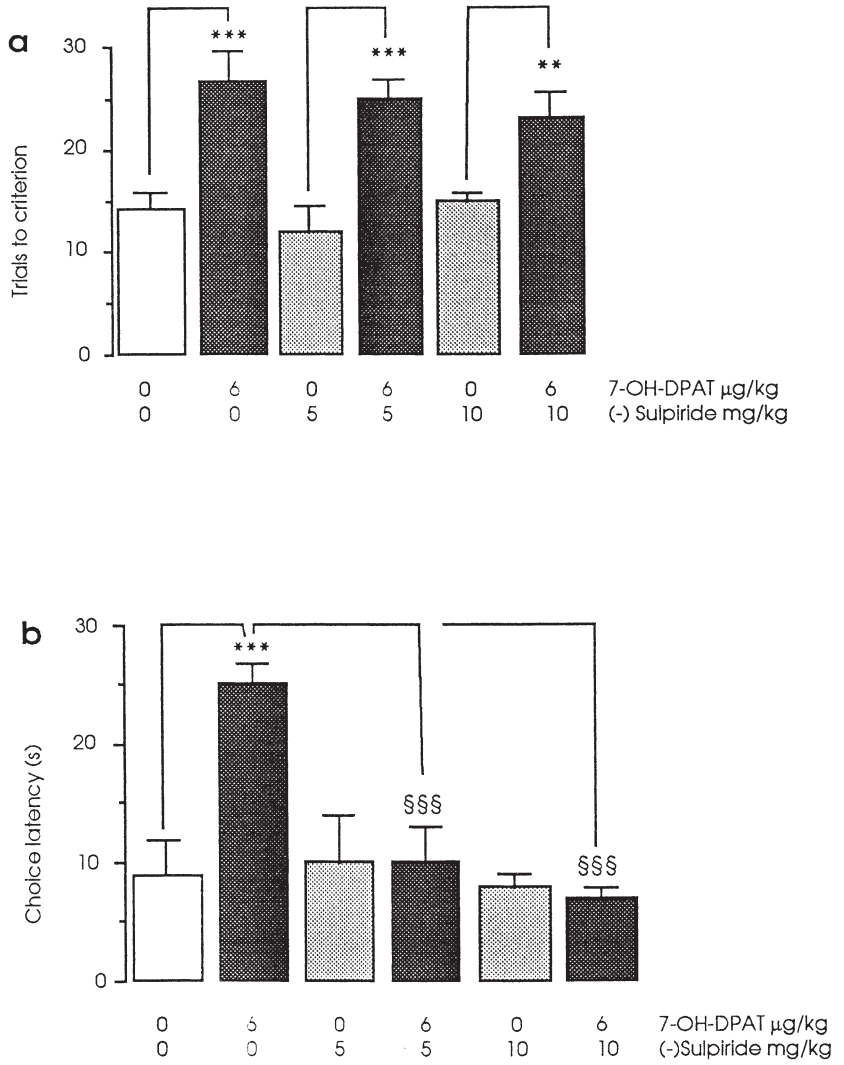

FIG. 3. The effects of (−)sulpiride (5–10 mg/kg) on the impairment in reversal task performance and choice latency induced by 7-OH-DPAT (6 μg/kg). Data are shown as in Fig. 2. Significant impairments in performance and task choice latency (7-OH-DPAT compared with vehicle; sulpiride + 7-OH-DPAT compared with sulpiride + vehicle) are indicated by $^{**}p < 0.01$ $^{***}p < 0.001$; significant improvements in task choice latency (7-OH-DPAT compared with sulpiride + 7-OH-DPAT) are indicated by §§§$p < 0.001$; Dunnett's *t*-test, $n = 4$ animals per group.

Effect of Antagonists on 7-OH-DPAT-Induced Impairments in Task Performance

Impairments in reversal task performance. (−)Sulpiride (5–10 mg/kg) alone had no effect on performance in the initial, $F(2, 11) = 1.2$, NS, or the reversal task, $F(2, 11) = 0.8$, NS, compared to vehicle. (−)Sulpiride (5–10 mg/kg) given prior to treatment with 7-OH-DPAT (6 μg/kg) did not significantly alter initial task performance (data not shown). (−)Sulpiride (20 mg/kg) impaired task performance such that two out of four animals did not reach criterion in the initial task; this dose was, therefore, not tested in the reversal task or in the antagonist studies. (−)Sulpiride failed to attenuate the impairment in reversal task performance induced by 7-OH-DPAT (Fig. 3a and b).

Yohimbine (50 μg/kg) alone had no effect on performance in the initial, $F(1, 7) = 1.9$, NS, or the reversal task, $F(1, 7) = 1.9$, NS, when compared with vehicle. Yohimbine (50 μg/kg) given prior to treatment with 7-OH-DPAT (6 μg/kg) did not significantly alter performance in the initial task (data not shown). Yohimbine (50 μg/kg) failed to attenuate the impairment in reversal task performance induced by 7-OH-DPAT (Fig. 4a and b). Yohimbine (100 μg/kg) induced anxiety-related behaviors (threat postures and vocalization) in three out of four animals tested that disrupted the ability of the animals to perform discrimination tasks such that testing was not carried out.

Raclopride (6–50 μg/kg) alone did not alter performance in the initial, $F(3, 15) = 1.6$, NS, or the reversal task, $F(3, 15) = 0.9$, NS. At a higher dose of 100 μg/kg, raclopride induced somnolence in two out of four animals tested such that the initial task was not completed in the required time; this dose was, therefore, not tested in the reversal task. Pretreatment with raclopride (6–50 μg/kg) prior to 7-OH-DPAT (6 μg/kg) did not significantly alter performance of the initial task when compared with vehicle (data not shown). Treatment with raclopride 6 and 25 μg/kg prior to treatment with 7-OH-DPAT (6 μg/kg) failed to attenuate the increase in trials to criterion induced by 7-OH-DPAT in the reversal task. However, pretreatment with raclopride at a dose of 50 μg/kg produced a significant ($p < 0.001$) improvement in the impairments in reversal task performance induced by 7-OH-DPAT (Fig. 5a and b).

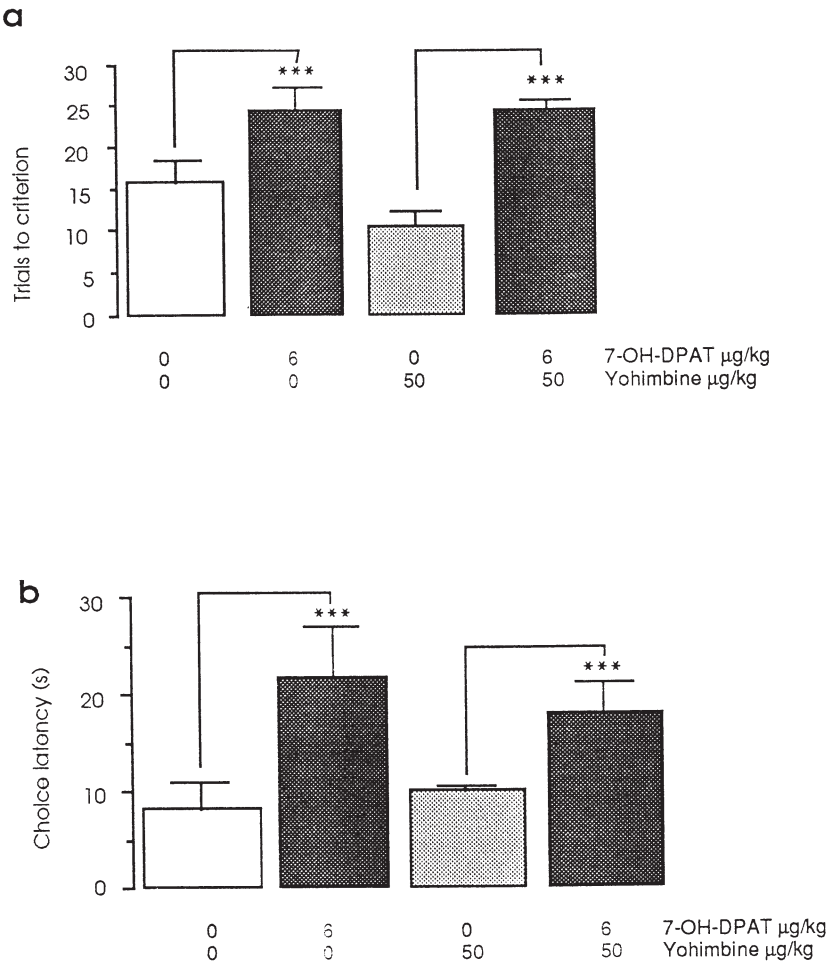

FIG. 4. The effects of yohimbine (50 μg/kg) on the impairment in reversal task performance and choice latency induced by 7-OH-DPAT (6 μg/kg). Data are presented as in Fig. 2. Significant impairments in performance and task choice latency (7-OH-DPAT compared with vehicle; yohimbine + 7-OH-DPAT compared with yohimbine + vehicle) are indicated by ***$p < 0.001$, Dunnett's t-test, $n = 4$ animals per group.

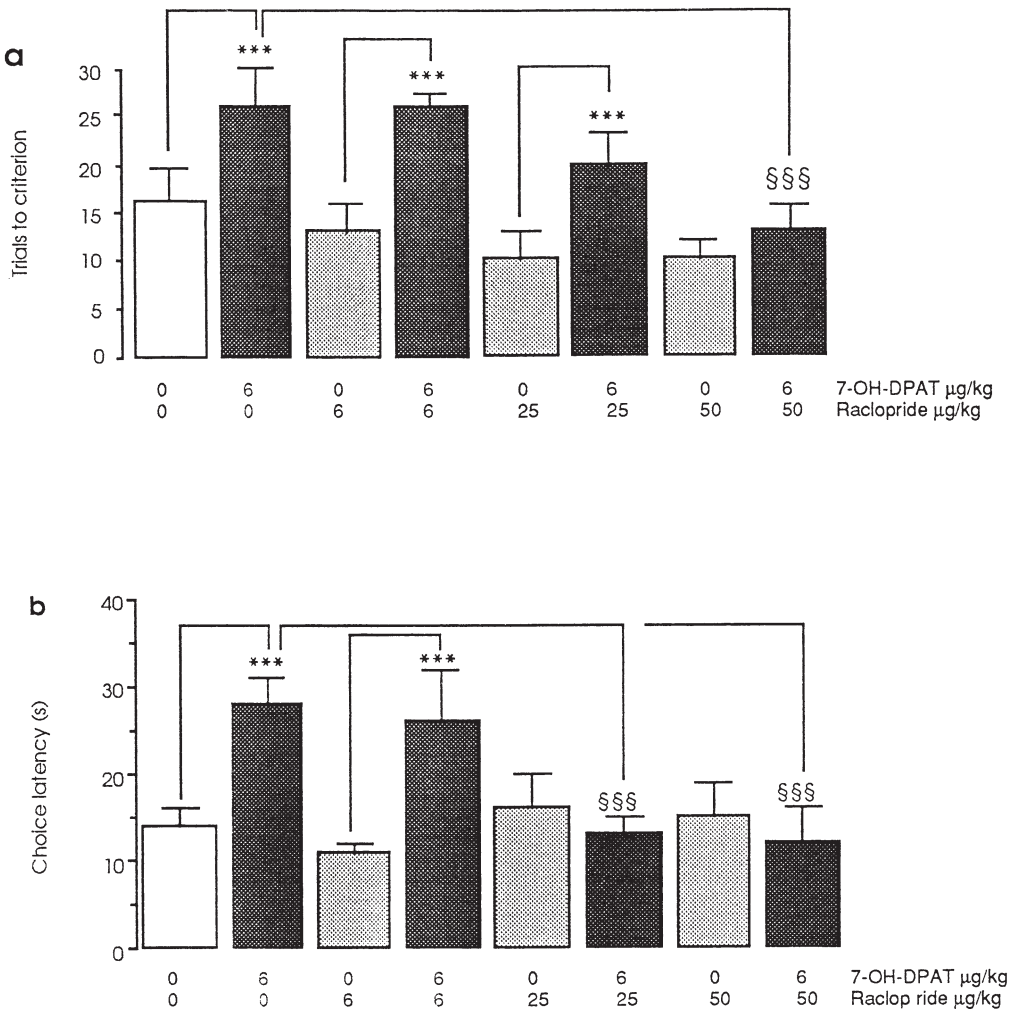

FIG. 5. The effects of raclopride (6–50 µg/kg) on the impairment in reversal task performance induced by 7-OH-DPAT (6 µg/kg). Data are presented as in Fig. 2. Significant impairments in performance and choice latency (7-OH-DPAT compared with vehicle; raclopride + 7-OH-DPAT compared with raclopride + vehicle) are indicated by ***$p < 0.001$. Significant prevention of impairments (raclopride + 7-OH-DPAT compared with 7-OH-DPAT alone) is indicated by §§§$p < 0.001$; Dunnett's *t*-test, $n = 4$ animals per group.

Increase in mean task choice latency. Mean choice latency was not altered by raclopride (6–50 µg/kg), (−)sulpiride (5–10 mg/kg) or yohimbine (50 µg/kg) alone with respect to vehicle treatment. The significant ($p < 0.001$) increase in task choice latency induced by 7-OH-DPAT (6 µg/kg) (Fig. 2c) was not antagonized by prior treatment with yohimbine (50 µg/kg) (Fig. 4c). In contrast, the effect of 7-OH-DPAT (6 µg/kg) on choice latency was significantly ($p < 0.001$) antagonized by treatment with raclopride (25–50 µg/kg) (Fig. 5c) and (−)sulpiride (5–10 mg/kg) (Fig. 3c).

DISCUSSION

In a same-day reversal paradigm used to assess cognitive performance in the marmoset it was found that 7-OH-DPAT was without effect on acquisition of the initial task; however, 7-OH-DPAT induced a significant dose-dependent impairment of reversal task performance, i.e., a significant increase in mean trials to criterion. These effects were observed at doses lower than those previously shown by the authors to induce emesis (0.5–2.0 mg/kg), hypolocomotion (25–50 µg/kg), or hyperactivity (0.75–2.0 mg/kg) in the marmoset (32). The impairment of reversal task performance by 7-OH-DPAT was attenuated by a high dose of raclopride but was not altered by lower doses of raclopride, or by (−)sulpiride or yohimbine.

Repeated drug treatments and testing during the course of the studies (26 weeks in total) had no detrimental effect on the stability of baseline task performances, and drug-induced changes could be readily distinguished.

Acquisition of initial tasks was unaffected by 7-OH-DPAT treatment (2.5–10 µg/kg). At a higher dose of 7-OH-DPAT, 25 µg/kg, performance in the initial task was severely impaired and animals did not achieve the required test criterion for task acquisition in the allowed test time. This effect of 7-OH-DPAT in the initial task is likely to reflect an impairment in motor function, an effect that has been previously observed following 7-OH-DPAT treatment in rats (5) and more re-

cently in the marmoset (39), rather than indicating a specific effect on cognitive function.

In contrast, treatment with 7-OH-DPAT resulted in a significant dose-dependent impairment in performance of the reversal task compared to control animals, as shown by an increase in trials to criterion, with failure to achieve the test criterion for the reversal task following doses of 6 and 10 μg/kg 7-OH-DPAT. Because the initial task was acquired successfully, 7-OH-DPAT treatment did not cause idiosyncratic preference for right or left food wells or impair motor, visual, or perceptual function.

Analysis of the learning curve data for the initial task shows that under control conditions, animals began performing at chance levels (i.e. 10/20 errors = 50% chance of choosing correct object) and made successively fewer errors until the initial object–reward association was acquired, i.e. zero group errors. When the reward contingency was reversed, animals again started performing at chance levels and subsequently relearned a new object–reward association, in agreement with previous work (31). The learning curves following 7-OH-DPAT demonstrate that animals begin performing the reversal task at worse than control, i.e. worse than chance levels, and learn at a slower rate than control. Memory of the initial stimulus–reward association appears to be intact and causes errors in responding when the reward contingency is reversed; the effect of 7-OH-DPAT is likely to be an impairment of task acquisition rather than an effect on memory.

It has been suggested by Ridley and colleagues (31) that perseverative object selection in both initial and reversal acquisition tasks is indicative of stereotyped responding. Because the performance of both initial acquisition and reversal tasks requires the same demands (perception of differences between the two stimuli, reaching to accurately select one of the two stimuli and retrieval of the reward) the failure of animals to reach reversal task criterion following successful completion of the initial task cannot be attributed to any general sensorimotor or aversive effects of 7-OH-DPAT, and so must represent a specific cognitive effect. The increase in task choice latency produced by 7-OH-DPAT suggests an effect to increase the time required for choice making. This may result from a disruption of central cognitive mechanisms involved in arousal and motivation or of higher level choice strategies, causing persistent choices irrespective of the reward potential, an effect that has been induced by amphetamine in the marmoset (22). The lack of effect of 7-OH-DPAT on task retention has shown that the performance of the reversal task that was impaired under the influence of 7-OH-DPAT is not affected on the subsequent test day; i.e. memory of the reward contingency is retained, thus excluding an effect of 7-OH-DPAT on memory processes.

Tests of executive function such as visual discrimination tasks are generally regarded as indicators of prefrontal cortex integrity. However, binding studies have primarily located D_3 receptors in striatal and limbic regions, and not in the prefrontal cortex of the marmoset (14). The integrity of higher cognitive functions such as learning and memory processes may depend upon a relationship between prefrontal cortex and striatal dopamine systems (33). Dopaminergic systems may be responsible for activation of behavioral responses to stimuli that act as cues to signal the availability of a reward. In particular, striatal dopamine neurons may be involved in the initiation and sequential processing of reward-related responses to stimuli and the validation of the outcome of the response (1,37), and may interact with prefrontal cortex dopamine systems to enable reassociation of stimulus–reward associations and modification of the response when the reward contingency changes (9). These processes are analagous to visual discrimination reversal tasks where the initial stimulus–reward response must be inhibited and the alternative stimulus–reward response adopted. Dopamine receptors have been implicated in the autoregulation of dopamine release in the prefrontal cortex (34). The ability of 7-OH-DPAT to disrupt acquisition of the reversal discrimination task may provide evidence for a functional role for the dopamine D_3 receptor in information processing that depends upon intact mesocorticolimbic dopaminergic function. However, the possibility of an interaction with cholinergic mechanisms cannot be excluded, because striatal dopamine D_3 receptors have been shown to inhibit acetylcholine release (35), and the involvement of cholinergic function in learning and memory processes is well documented.

The specific nature of the dopamine receptor mediating the cognitive effects of 7-OH-DPAT is difficult to determine. Although 7-OH-DPAT has been widely reported to possess an affinity for both D_3 and D_2 dopamine receptor subtypes in in vitro radioligand binding studies (13,43), the degree of selectivity for these receptors is dependent on the in vitro assay conditions and may not reflect the affinity of 7-OH-DPAT for D_3 and D_2 dopamine receptors in vivo (17). Recent evidence has indicated that (±)7-OH-DPAT may activate central D_3 dopamine receptors in vivo when administered systemically in the rat at doses lower than 46 μg/kg (10). Thus, at the low concentrations of 7-OH-DPAT (lower than 25 μg/kg) tested in these experiments agonism at the D_3 receptor may predominate.

Several in vitro studies have shown that 7-OH-DPAT also displays a binding affinity for dopamine D_2 receptors. D_2 receptor agonist effects may include stimulation of locomotor activity (observed following high doses of 7-OH-DPAT in the rat (6,13,26) and marmoset (39). The effect of 7-OH-DPAT on reversal learning was attenuated by the D_2 receptor antagonist raclopride at a relatively high dose. Raclopride possesses a high degree of affinity for the D_2 receptor subtype (28) and has been shown at high doses to antagonize the locomotor stimulant effects of 7-OH-DPAT (39) and the D_2 receptor agonist quinpirole (19) in the marmoset, suggesting mediation of the stimulant action of 7-OH-DPAT by activation of D_2 receptors. However, the concentrations of raclopride (higher than 100 μg/kg) and 7-OH-DPAT (higher than 1 mg/kg) used in those studies greatly exceeded the doses used in the discrimination tasks of the present work.

Raclopride has also been shown to possess relatively high binding affinity for dopamine D_3 receptors (21) and in in vivo studies to antagonize 7-OH-DPAT-induced hypothermia, a physiological response thought to be mediated by activation of the dopamine D_3 receptor in the rat (25). The results of the present study could, therefore, be interpreted as a demonstration of the ability of raclopride to antagonize a behavioral response induced by an agonist action of 7-OH-DPAT at the D_3 receptor, providing evidence of a role for the D_3 receptor in cognitive behavior. Although any study of the ability of high doses of raclopride to reverse the behavioral responses to 7-OH-DPAT in the marmoset is confounded by the innate inhibitory effects on task performance displayed here (following a dose of 100 μg/kg raclopride) and locomotor behavior (19), it is envisaged that a carefully selected low dose such as 50 μg/kg raclopride used in the current work may be capable of antagonizing the behavioral effects of agonist action at the D_3 receptor.

Because 7-OH-DPAT possesses an affinity for the dopamine D_2 receptor subtype in binding studies, it is possible, however,

that the inhibitory effects of 7-OH-DPAT on cognitive behavior may result from an action at inhibitory autoreceptors of the D_2 receptor subtype that downregulates dopaminergic function when activated. However, it has been shown that the dopamine D_2 receptor antagonist sulpiride is unable to reverse the locomotor inhibitory effects of 7-OH-DPAT in the rat, despite the proposed high selectivity of (−)sulpiride for the D_2 autoreceptor (12,40).

Results of the present studies showing a lack of effect of (−)sulpiride and lower doses of raclopride on the 7-OH-DPAT induced cognitive impairment suggest that this response to 7-OH-DPAT is not dependent on an agonist action at an inhibitory dopamine D_2 receptor. The present results are in agreement with recently published evidence that (+)7-OH-DPAT induced impairments in passive avoidance learning in mice were not antagonized by (−)sulpiride. The authors proposed that the disruption in memory processes was mediated via an action of (+)7-OH-DPAT at dopamine D_3 and not D_2 receptors (42).

The effect of (−)sulpiride to restore the impairment in task choice latency induced by 7-OH-DPAT in the present study may reflect an involvement of inhibitory dopamine receptors in the mechanism of motivation in choice making. This effect may be manifested in the clinic by treatment with low doses of (−)sulpiride that have been shown to have "alerting" properties, of value in the treatment of withdrawn and apathetic schizophrenic patients (18).

The failure of yohimbine to reverse the impairment induced by 7-OH-DPAT may be indicative of a lack of involvement of the α_2 adrenoceptor in the effects of 7-OH-DPAT. Thus, the affinity of 7-OH-DPAT for α_2 receptors detected by radioligand binding studies (41) may not have a functional component in the behavioral effects of 7-OH-DPAT observed in this study; further studies with higher doses of α_2 receptor antagonists may be necessary to confirm this, but such studies would be confounded by the associated increase in anxiety-related behaviors following such administration in the marmoset.

In conclusion, these studies have established that 7-OH-DPAT induces a reproducible and consistent cognitive deficit in the marmoset. Antagonist studies suggest that the dopamine D_3 receptor is primarily implicated in this cognitive effect of 7-OH-DPAT. However, studies using D_2 and α_2 receptor antagonists were compromised by their extraneous effects on the sensorimotor functions required for performance of tasks. Future studies will investigate the action of dopamine D_3 selective compounds with proven ability to antagonize a behavioral response specifically mediated by D_3 receptor stimulation to determine more intrinsic aspects of the cognitive impairment in visual discrimination task performance induced by 7-OH-DPAT. An insight may thus be provided into the involvement of the D_3 receptor in the disorders of cognitive function such as those that are characteristic of the negative symptomology in schizophrenia.

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