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A new one-trial test for neurobiological studies of memory in rats. II: effects of piracetam and pramiracetam

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The effects of the nootropic drugs Piracetam (Pir) and Pramiracetam (Pram) were evaluated on recognition-memory of rats in a new one-trial test. This test is based on spontaneous exploratory activity and does not involve rule learning or reinforcement. Recognition is measured by the time spent by rats in exploring two different objects, one familiar (the sample), the other new. When the retention interval is 1 min, normal rats spend more time exploring the new object which demonstrates that they recognize the familiar one, but they do not discriminate between the two objects after a 24-h interval. Three doses of Pram (15, 30 and 60 mg/kg) and Pir (100, 200 and 400 mg/kg) were administered i.p. 30 min before the acquisition trial. The doses of 30 mg/kg of Pram and of 400 mg/kg of Pir produced a significant improvement in retention when the intertrial interval was 24 h. This effect was not associated with a change in overall exploratory behavior. This study shows that the new object-recognition test may be a useful tool for pharmacological studies of memory in rats.

INTRODUCTION

The experiments reported in this paper have a double purpose: (1) to check the value of the test described in the preceding article[15] as a tool for the neurobiology of learning and memory in rats; (2) to study the effects of two nootropic drugs, piracetam and pramiracetam.

Piracetam and pramiracetam belong to a new class of drugs called 'nootropic'. Since their appearance in the psychopharmacological field[5,7,18,25,31,38], the action profile of this class of drugs is still not fully determined[17,19,20,23,27] (see refs. 30,50). It has been frequently reported that they improve learning and memory in humans and animals that are senescent or suffering from brain pathologies[9,16,21,22,24,40,44,48,51,55,58], but some results are not very clear-cut[1,5,26,28,35,47,52]. In normal subjects, the effects of their administration remain controversial[3,6,12,14,37,38,41,59]. This is partly due to the fact that many results have been obtained from tests that do not provide unequivocal measures of learning and memory, for instance one-trial tests having no discrimination measures[29,49]. In this respect, our test may help to clarify the issue. In our previous experiments[15], we observed that normal rats are able to discriminate between a familiar and a new object when the retention interval between the sample trial (T1) and the choice trial (T2) is 1 min. They spent more time exploring the new object than the familiar one, which demonstrates that they recognize the latter. With a 24-h retention interval normal rats are unable to discriminate between the familiar and the novel object.

On the grounds of these data, we developed the

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experimental strategy used in the present study. We first explored the effects of different doses of pramiracetam on the 24-h retention interval: the poor performance of normal rats makes the test more sensitive to a facilitatory effect. Then we did a control experiment which was to serve three purposes: (1) to confirm the result obtained with the most effective dose of pramiracetam, (2) to check that control rats had a 'normal' performance level for the 1-min retention interval, (3) to compare the effects of pramiracetam to those of piracetam.

Piracetam was chosen as a reference drug for two reasons: (1) it is the most documented nootropic drug and (2) in an earlier version of our test[14], it improved performances of rats with a 1-h retention interval. We wish to see if this facilitatory action is still detectable on a 24-h retention interval.

EXPERIMENT 1

Methods

Subjects

Forty-three male Wistar rats weighing 200–250 g each were used. They were housed in individual cages and maintained on a 12–12 h light/dark cycle (07.00–19.00 h). Ambient temperature was 23 ± 1 °C. During the entire experiment they had free access to food and water.

Apparatus

The apparatus used was an open box made of wood 65 × 45 × 45 cm (height). The objects to be discriminated were made of glass, plastic or metal and existed in duplicate. Their weight was such that they could not be displaced by rats. The apparatus was placed in a sound-isolated room where the sound-insulation was aided by a masking-white noise of 70 dB above the human threshold. A light bulb fastened in the upper part of the room provided a constant illumination of about 40 lux at the level of the test apparatus.

Behavioural testing

The methods are fully explained in the companion paper. They may be summarized as follows: all rats were submitted to two habituation sessions where they were allowed 2 min to explore the apparatus. Twenty-four hours later, testing began. This experiment comprised 3 sessions separated by 48 h. Each session was made up of two trials. In the first trial (T1), rats were exposed to two identical objects which constituted samples A1 and A2. In the second trial (T2), the rats were exposed again to two objects, one of the samples which is now familiar A and a new object B. In each trial, each object was placed in one of the back corners of the box. The object A presented during T2 was a duplicate of the sample presented in T1 in order to avoid olfactory trails. From rat to rat, the role (sample or new object) as well as the position of the two objects was counterbalanced and randomly permuted during T2. A different pair of objects was used for each session. We shall call O1 and O2, the two objects of each pair. For half of the rats, O1 was the sample A and O2 the new object B. For the other half, the role of O1 and O2 was inversed. These precautions were taken in order to reduce object and place preference effects. It should be stressed that the objects apparently had no natural significance for rats and had never been associated with a reinforcement. The duration of T1 and T2 was 3 min each and the delay between them was 24 h.

Drug treatments

The rats were randomly assigned to 4 groups. The treatment of each group was administered i.p. 30 min before each test session. The control group (C, $n = 11$) received an injection of physiological saline, and the experimental groups received respectively an injection of pramiracetam at a dose of 15 mg/kg (Pram 15, $n = 11$), 30 mg/kg (Pram 30, $n = 10$) and 60 mg/kg (Pram 60, $n = 11$). Both solutions were administered in the volume of 1 ml/kg. Pramiracetam was diluted in an appropriate volume of physiological saline.

Measurements and statistical treatments

The basic measure was the time spent by the rats in exploring the objects during T1 and during T2. Exploration of an object was defined as follows: directing the nose to the object at a dis-

TABLE I

Index of the different variables involved in the object-recognition test

Exploration	*Habituation*	*Discrimination*
e1 = [a1 + a2]	h1 = [e1 − e2]	d1 = [b − a]
e2 = [a + b]	h2 = [(e1/2) − a]	d2 = [b/e2]
		d3 = [d1/e2]

tance $\leqslant 2$ cm and/or touching it with the nose; turning around or sitting on the object was not considered as exploratory behavior.

The time spent in exploring the two identical samples will be represented by a1 and a2; the time spent in T2 in exploring respectively the sample and the new object will be represented by a and b. The following variables were considered: e1, e2, h1, h2, d1, d2 and d3, (see Table I).

(e1) and (e2) measure the exploration of both objects during T1 and T2 respectively, the (h) indexes may be considered as a measure of habituation of the exploratory behavior and the (d) indexes as a mnesic measure reflecting the discrimination between the new and the familiar object.

Within groups, statistical tests were applied to variables (h1), (h2) and (d1). They were based on the paired Student *t*-test. For instance, significance of (h1) for a given group was tested by comparing the mean value of (e1) and (e2) for that group. Between-group comparisons were based on Kruskal–Wallis and post-hoc comparisons according to Conover[10].

Results

(1) Effect of pramiracetam on object and side preferences

Paired Student *t*-test (two-tailed) did not show any significant differences within any group when we compared the exploration time according to the nature of the objects and their location in the apparatus.

(2) Effect of pramiracetam on overall exploratory activity

For each group and for the variables (e1) and (e2), a one-way ANOVA for repeated measures did not show any difference between sessions; therefore their results were pooled. The overall analysis of variance of the pooled results shows significant differences between groups: for (e1), $H_3 = 13.69$, $P \leq 0.005$; for (e2), $H_3 = 11.86$, $P \leq 0.01$.

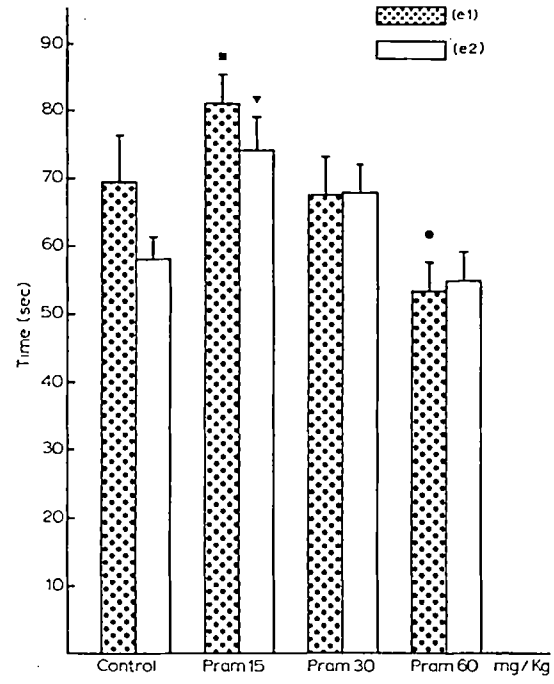

Fig. 1. Mean value (± S.E.M) of the total exploration time during the first trial (e1) and the second trial (e2). For (e1), H(3) = 13.69, $P \leq 0.001$ and for (e2), H(3) = 11.86, $P \leq 0.01$. ■● Compared to control, $t_{39} = 2.021$, $P \leq 0.05$; ■● Compared to Pram 30, $t_{39} = 2.021$, $P \leq 0.05$; ■ Compared to Pram 60, $t_{39} = 3.551$, $P \leq 0.001$; ▼ Compared to Control, $t_{39} = 2.704$, $P \leq 0.01$; ▼ Compared to Pram 60, $t_{39} = 3.307$, $P \leq 0.001$.

Compared to the control, a dose of 15 mg/kg of pramiracetam significantly increases exploratory activity of rats during T1 and T2, whereas a dose of 60 mg/kg significantly decreased exploratory activity during T1.

(3) Effect of pramiracetam on global habituation of exploratory behavior

(a) Within-group test. The significance of the index (h1) was tested by comparing the mean value of (e1) and (e2) within each group (Student *t*-test, two-tailed). The difference between (e1) and (e2) is significant in session 1 only within the

control ($t = 2.83$, $P \leq 0.02$) and the Pram 15 ($t = 3.44$, $P \leq 0.01$) group.

(b) Between-group test. Since the one-way ANOVA for repeated measures for (h1) is significant between sessions in the Pram 15 group, $F_{2,20} = 8.72$, $P \leq 0.002$, the results of the groups were not pooled. Groups were compared session by session. They were only significantly different in session 1, $H_3 = 9.45$, $P \leq 0.03$. Compared to the control, the habituation to the exploration of objects was significantly decreased by a 60 mg/kg dose of pramiracetam.

(4) Effect of pramiracetam on the discrimination between the familiar and the new objects

(a) Within-group tests. The significance of the index (d1) was tested by comparing the mean value of (a) and (b) within each group (Student *t*-test, two tailed). The difference between (a) and (b) is significant only within the Pram 30 group in each session and within Pram 15 and Pram 60 groups in sessions 2 and 3, never in the control group. In other words, the time spent by control rats in exploring the new and the familiar objects did not show discrimination between them.

(b) Between-group tests. Since groups were not significantly different from session to session, the results of all 3 sessions were pooled. The overall analysis of variance gives: $H_3 = 8.126$, $P \leq 0.03$ (see Fig. 2).

Two-by-two comparisons between groups showed that the mean value of the discrimination index (d1) was superior in Pram 15 and Pram 30 as compared to the control.

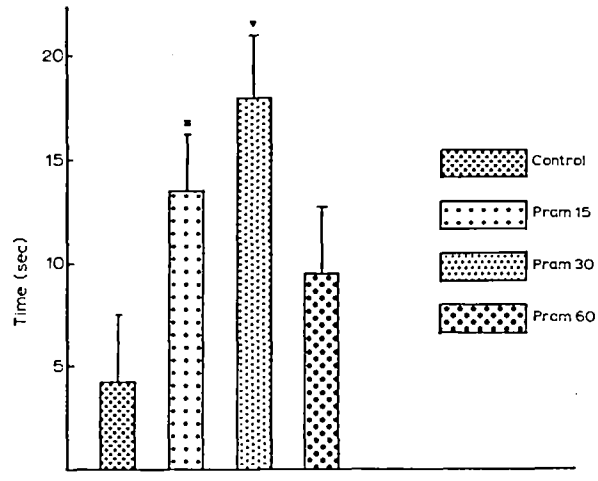

Fig. 2. Mean value (± S.E.M) of the index (d1) for the discrimination between the new and the familiar objects. $H_3 = 8.126$, $P \leq 0.05$. ■ Compared to control, $t_{39} = 2.021$, $P \leq 0.05$; ▼ Compared to control, $t_{39} = 2.704$, $P \leq 0.01$.

In summary, the effect of pramiracetam is dose-dependent: the level of exploratory activity increases with a low dose (15 mg/kg) and decreases with a high dose (60 mg/kg), but it is comparable to the control at an intermediate dose. The effect on recognition-memory follows an inverted U-shape with an increase in effectiveness from the 15 to the 30 mg/kg dose then a decrease from 30 to 60 mg/kg. The facilitatory effect of pramiracetam at a dose of 30 mg/kg is not associated with a change in exploratory activity.

TABLE II

Results of within-groups tests (paired Student t-test) of the discrimination index (d1): comparison within each group of the time spent by rats in exploring the new object (b) to the time spent in exploring the sample (a) in T2. [d1 = (b − a)]

	Session 1			*Session 2*			*Session 3*		
	(d1)	*t*	*P* ≤	*(d1)*	*t*	*P* ≤	*(d1)*	*t*	*P* ≤
Control ($n = 11$)	0.82 ± 1.42	0.58	n.s.	1.73 ± 1.76	0.98	n.s.	1.73 ± 0.007	1.07	n.s.
Pram 15 ($n = 11$)	2.91 ± 1.51	1.92	n.s.	7 ± 1.33	5.27	0.001	3.64 ± 1.32	2.75	0.02
Pram 30 ($n = 10$)	8 ± 1.56	5.14	0.001	4.70 ± 1.94	2.43	0.04	5.40 ± 1.40	4.05	0.003
Pram 60 ($n = 11$)	1.18 ± 2.02	0.59	n.s.	4.18 ± 0.99	4.23	0.002	4.18 ± 1.29	3.24	0.01

EXPERIMENT II

Methods

Subjects

Fifty male Wistar rats weighing 200–250 g each were used. They were housed and maintained in the same conditions as described above.

Behavioral testing

The general methods were the same as in Expt. 1 except that the rats were tested in 4 sessions. The rats were submitted alternatively to two types of sessions. For half, the first session had a 1-min intertrial delay; for the other half a 24-h intertrial delay. For all rats, the delay was 48 h between sessions 1 and 2, 3 and 4, and 72 h between session 2 and 3.

Drug treatments

The rats were assigned randomly to 5 groups (n = 10 each). The treatments of each group were administered i.p. 30 min before each session. The control group received an injection of physiological saline, and the experimental group received respectively an injection of piracetam at a dose of 100 mg/kg (Pir 100), 200 mg/kg (Pir 200) and 400 mg/kg (Pir 400). One group of rats received one dose of pramiracetam 30 mg/kg (Pram 30). Both drugs were diluted in an appropriate volume of physiological saline.

Measurements and statistical treatments

The variables were the same as those considered in Expt. 1. Statistical treatments were performed on:

(a) Data from sessions of the same intertrial delay. Paired Student t-test (two-tailed) was performed within each group on the following variables: (h1), (h2) and (d1).

(b) Differences between groups for each session with the same intertrial delay. The one-way ANOVA for repeated measures was performed on the results of each group for the two sessions having the same intertrial delay; when no differences were observed, the results were pooled. Analyses of variance were used for comparisons between groups.

(c) Differences between sessions with different intertrial delays. Within each group the performances of rats in sessions with a 1-min delay was compared to those in sessions with a 24-h delay. This comparison was performed with the paired Student t-test (two-tailed).

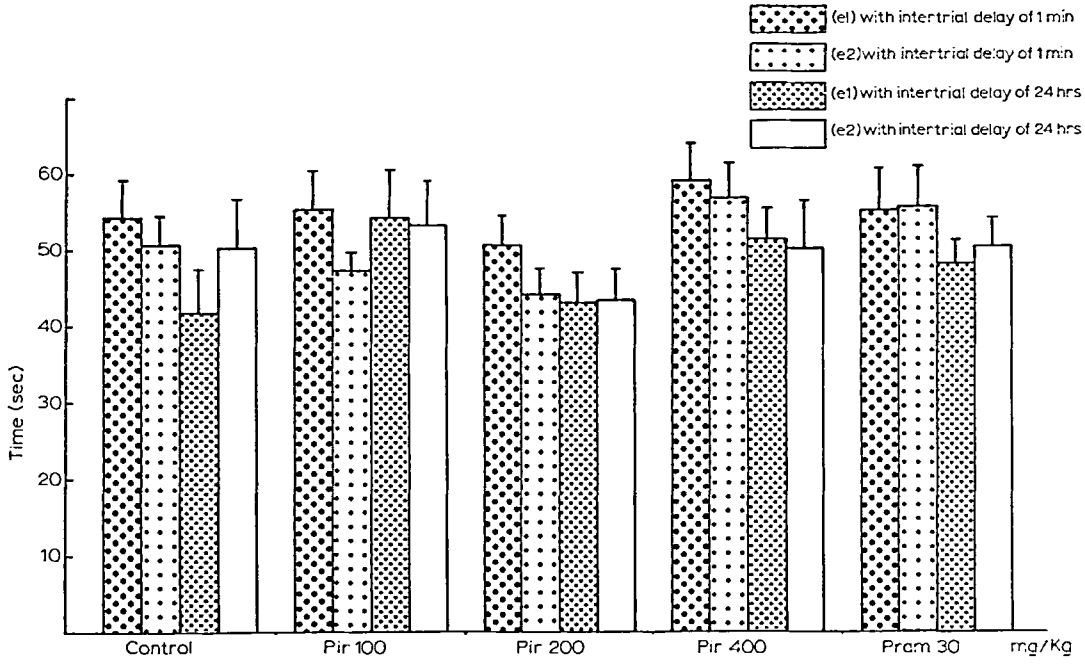

Fig. 3. Mean value (± S.E.M) of the total exploration time during the first trial (e1) and the second (e2) with 1-min and 24-h intertrial delay. $P > 0.10$.

Results

(1) Effect of drugs on object and side preferences

The paired Student *t*-test (two-tailed) did not show any significant differences within any group when we compared the exploration time according to the nature of the objects and their location in the apparatus.

(2) Effect of drugs on overall exploratory activity

For each group, a one-way ANOVA for repeated measures did not show significant differences between each session of the same intertrial delay and, consequently, their results were pooled. The overall analysis of variance of the pooled results was not significant between groups in any session for the total time of exploration during T1 and T2. Moreover, the intertrial delay did not affect (e1) and (e2) within each group.

(3) Effect of the drugs on global habituation of exploratory behavior from T1 to T2

The index (h1) is not significant within any group, which means that within each session the time spent by rats of each group in exploring the objects during T1 is comparable to that spent in T2. There were no significant differences between groups.

(4) Effect of drugs on habituation to the sample

(a) Within-group test. The significance of the index (h2) was tested by comparing the mean value of (e1/2) and (a) within each group (Student *t*-test, two-tailed). (h2) was significant within each group in the two 1-min delay sessions but only in Pir 400 and Pram 30 groups in the second 24-h delay sessions.

For each group a one-way ANOVA for repeated measures did not show significant differences between sessions with the same intertrial delay and, consequently, their results were pooled.

The (h2) habituation index for 24-h delay sessions is significantly inferior to that for 1-min delay in the control, the Pir 100 and the Pir 200 groups, but not in the Pir 400 and Pram 30. In other words, the habituation to the sample was significantly decreased by the 24-h delay in the first 3 groups but not in the last two (see Fig. 4).

(b) Between-group tests. The overall analysis of variance did not show any difference between groups on the 24-h intertrial delay: $H_4 = 7.83$, $P > 0.10$

(5) Effect of drugs on discrimination between familiar and new objects

(a) Within-group tests for each delay. The comparison of (a) to (b) is significant within each

TABLE III

Results of within-group tests of the index of habituation to the sample (h2): comparisons within each group of the average time (e1/2) spent in exploring the samples in T1 to time spent in exploring the sample (a) in T2. [h2 = (e1/2) − a]

	Session 1 (delay 1 min)			*Session 2 (delay 1 min)*			*Session 1 (delay 24 h)*			*Session 2 (delay 24 h)*		
	(h2)	*t*	*P* ≤	*(h2)*	*t*	*P* ≤	*(h2)*	*t*	*P* ≤	*(h2)*	*t*	*P* ≤
Control ($n = 10$)	4.05 ± 1.85	2.19	0.06	7.75 ± 1.98	3.91	0.001	−0.85 ± 1.73	0.49	n.s.	−2.45 ± 1.63	1.5	n.s.
Pir 100 ($n = 10$)	7.65 ± 2.34	3.26	0.01	7.20 ± 1.59	4.52	0.001	−0.35 ± 1.15	0.30	n.s.	3 ± 1.63	1.83	n.s.
Pir 200 ($n = 10$)	6.35 ± 1.16	5.47	0.001	3.35 ± 1.65	2.00	0.07	1.45 ± 1.27	1.14	n.s.	1.20 ± 1.90	0.63	n.s.
Pir 400 ($n = 10$)	7.05 ± 1.42	4.97	0.001	5.30 ± 2.24	2.37	0.04	3.70 ± 1.86	1.98	n.s.	3.55 ± 1.61	2.20	0.06
Pram 30 ($n = 10$)	6.35 ± 2.13	2.98	0.01	6.40 ± 1.84	3.48	0.001	2.30 ± 1.72	1.35	n.s.	3.40 ± 1.24	2.75	0.03

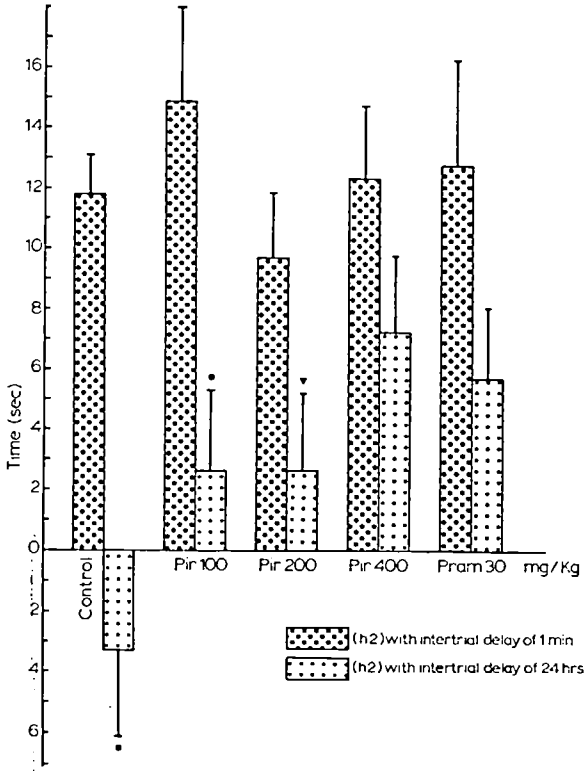

Fig. 4. Mean value (± S.E.M) of the index (h2) for habituation to the sample for 1 min ($H_4 = 1$, $P > 0.10$) and 24 h ($H_4 = 7.34$, $P > 0.10$) intertrial delays. ■ Compared to pooled results of sessions with 1 min intertrial delay, $t = 3.45$, $P \leq 0.005$; ● Compared to pooled results of sessions with 1 min intertrial delay, $t = 3.94$, $P \leq 0.005$; ▼ Compared to pooled results of sessions with 1 min intertrial delay, $t = 2.26$, $P \leq 0.05$.

group in the 1-min delay sessions, but only for Pir 400 and Pram 30 in the 24-h delay sessions.

(b) Within-group test of the influence of the delay. For each group, the one-way ANOVA for repeated measures did not show significant differences between the sessions having the same intertrial delay; their results were pooled.

The comparison within each group of the mean value of (d1) for both the 1-min and the 24-h delay sessions is significant in all groups except in Pram 30. These results mean that the group of rats treated with pramiracetam at a dose of 30 mg/kg performed the discrimination between the new and the familiar object at a comparable level whether the delay was 24 h or 1 min. In the other groups, the level of discrimination after a 24-h delay was significantly inferior to that after a 1-min delay (see Fig. 5).

(c) Between-group tests. The overall analysis of variance is significant between groups only for the 24-h intertrial delay: $H_4 = 15.33$, $P \leq 0.005$ (see Table V).

(6) Effect of drugs on other mnesic indexes

Two other indexes (d2) and (d3) (see Methods) were computed. Between-group comparisons (Table V) showed that these indexes were significantly higher in Pram 30 and Pir 400 than in the Control. However, in the first experiment no dose of pramiracetam had a significant effect on either index.

TABLE IV

Results of within-group tests of the significance of the discrimination (d1) between the familiar and the new objects

Comparisons within each group of the time spent by rats in exploring the sample (a) and the new objects (b) in T2. [d1 = b − a].

	Session 1 (delay 1 min)			*Session 2 (delay 1 min)*			*Session 1 (delay 24 h)*			*Session 2 (delay 24 h)*		
	(d1)	*t*	*P* ≤	*(d1)*	*t*	*P* ≤	*(d1)*	*t*	*P* ≤	*(d1)*	*t*	*P* ≤
Control ($n = 10$)	9.7 ± 2.43	3.99	0.01	10.1 ± 1.72	5.86	0.001	1.12 ± 1.98	0.61	n.s.	0.8 ± 1.27	0.63	n.s.
Pir 100 ($n = 10$)	12 ± 2.44	4.91	0.001	9.8 ± 2.4	4.08	0.01	2.8 ± 3.3	0.92	n.s.	1.7 ± 1.69	1.01	n.s.
Pir 200 ($n = 10$)	9.2 ± 2.01	4.57	0.002	3.7 ± 1.02	3.62	0.01	3.2 ± 1.55	2.06	n.s.	0.2 ± 2.06	0.09	n.s.
Pir 400 ($n = 10$)	14.9 ± 2.92	5.1	0.001	8.6 ± 1.38	6.21	0.001	6 ± 1.71	3.5	0.01	7.2 ± 2.02	3.56	0.01
Pram 30 ($n = 10$)	11 ± 2.42	4.55	0.002	15.1 ± 3.64	4.15	0.01	5.3 ± 0.76	6.96	0.001	10.3 ± 2.76	3.72	0.01

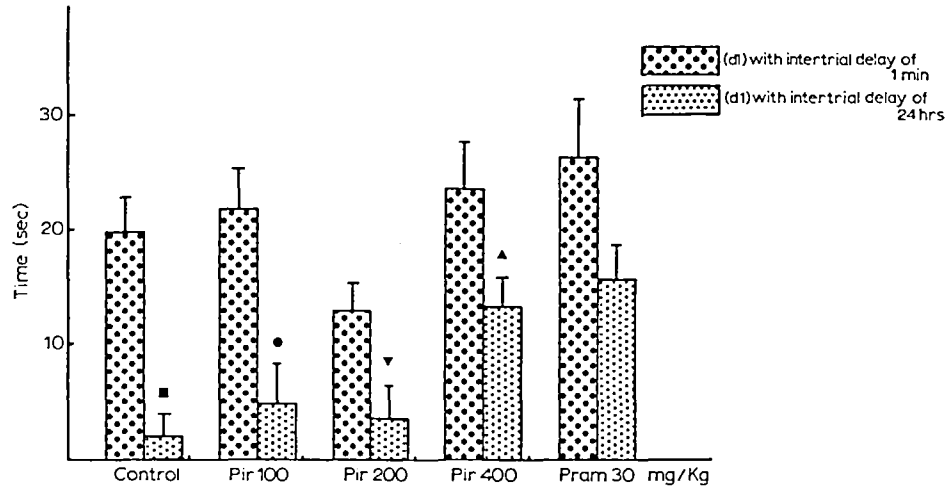

Fig. 5. Mean value (± S.E.M.) of the index (d1) of the discrimination between the familiar and the new object for 1 min ($H_4 = 6.13$, $P > 0.10$) and 24 h ($H_4 = 16.45$, $P \leq 0.01$) intertrial delays. For comparisons between groups see Table V. ■ Compared to pooled results of sessions with 1 min intertrial delay, $t = 6.71$, $P \leq 0.001$; ● Compared to pooled results of sessions with 1 min intertrial delay, $t = 5.49$, $P \leq 0.001$; ▼ Compared to pooled results of sessions with 1 min intertrial delay, $t = 2.75$, $P \leq 0.02$; ▲ Compared to pooled results of sessions with 1 min intertrial delay, $t = 2.42$, $P \leq 0.04$.

TABLE V

Overall analyses of variance for the index measures of recognition memory of rats and 2-by-2 comparisons between groups

	H_4 =	$P \leq$	*Control/ Pir 400*	*Control/ Pram 30*	*Pir 100/ Pir 400*	*Pir 100/ Pram 30*	*Pir 200/ Pir 400*	*Pir 200/ Pram 30*
d1 = b − a'	16.45	0.005	0.01	0.001	0.003	0.01	0.01	0.001
d2 = b/e2	17.58	0.005	0.01	0.001	0.003	0.003	0.01	0.01
d3 = d1/e2	17.40	0.005	0.001	0.001	0.003	0.01	0.01	0.01

DISCUSSION

The main results of our experiment can be summarized as follows:

Experiment 1

(a) Rats treated with pramiracetam are able to discriminate between familiar and new objects after a retention interval which makes this discrimination difficult in controls. The improvement shown with pramiracetam is dose-dependent and the most effective dose is 30 mg/kg.

(b) Pramiracetam also affects overall exploratory activity which is increased by the low dose (15 mg/kg) and decreased by the high dose (60 mg/kg). The intermediate dose (30 mg/kg) has no effect.

Experiment 2

(a) The level of discrimination of all treated rats is comparable to that of controls when tested with an intertrial delay of 1 min.

(b) With a 24-h intertrial delay, only rats treated with pramiracetam 30 mg/kg and piracetam 400 mg/kg discriminate between the familiar and the new objects.

(c) A dose of 30 mg/kg of pramiracetam is more potent than a dose of 400 mg/kg of piracetam, since it is only in the pramiracetam group that the discrimination between the familiar and the new objects shows no difference between a delay of 24 h and of 1 min.

(d) Piracetam and pramiracetam increase habituation to the sample after a 24-h delay; this can

also be considered as an improvement in recognition of this object.

(e) The above effects were not associated with a change in exploratory behavior.

These results seem to confirm the promnesic effects of nootropic drugs; however several questions remain without definite answers:

(1) Why, in many cases, are these drugs ineffective? A possible explanation is that their beneficial action is masked by 'ceiling' effects and can only be detected in non-optimal conditions or in impaired organisms. The significant effects of piracetam were more frequently observed in humans and animals that are senescent or suffering from brain pathologies than in normal subjects (see Introduction). Moreover, piracetam brings about improvement of avoidance behavior in organically normal rats only when this behavior is impaired by previous exposure to uncontrollable shocks based on the 'learned helplessness' paradigm[8]. Hence, we hypothesize that nootropic drugs may have detectable beneficial effects in normal subjects placed in unfavourable conditions. This is clearly the case in our experiments when the retention interval is 24 h.

(2) What form of memory, if any, is facilitated by nootropic drugs? Analyses of amnesic syndromes show that different forms of memory may have unequal susceptibility to brain pathologies or aging. In this respect, 3 main distinctions are frequently made: (1) working vs reference memory, (2) episodic vs semantic memory, and (3) declarative vs procedural memory. In each case, the first form (working, episodic, declarative) is always severely impaired in amnesic patients, whereas the second is usually not affected[32]. In so far as these forms of memory can be measured in animals, it seems that piracetam and pramiracetam have no beneficial effects on working memory performances[6,14,38], but they may improve reference memory[38]. Since our recognition test is based on a short and non-repeated experiment, it can be considered as measuring a form of episodic memory. Furthermore, our test does not involve primary reinforcement such as food, water or electric shocks and in this respect is more similar to a human real life situation than to a standard animal conditioning test. Its sensitivity to piracetam and pramiracetam suggests that these drugs may improve long-term episodic memory of events experienced under low or mild levels of arousal and motivation. This perhaps enters the larger field of the human memory.

(3) What mechanisms are involved in the action of nootropic drugs? Many studies have been devoted to this problem[23,36,39,42–44,46,53,54,56,60], but clear-cut answers have not yet been found. At doses which improve object recognition after a 24-h retention delay, pramiracetam and piracetam do not modify exploratory activity. This suggests that the promnesic effects are not the mere consequence of a global increase of arousal. Another interesting lead is offered by the fact that pramiracetam facilitates hippocampal theta activity[45]. Moreover, it was recently found that the relative power of the 5–11 Hz band of the hippocampal EEG (theta rhythm band) of the awake rat is significantly increased by 30 mg/kg of pramiracetam[11]. This is the dose which had the most reliable promnesic effects in our experiments. Thus a likely mechanism of action of pramiracetam could be the promotion of hippocampal theta activity. Several data suggest that the neurobiological processes reflected by this rhythm may play a role in learning and memory[2,4,13,33,34,57].

Finally, in this study, the new object recognition test that we devised appears to have several interesting properties: (1) sensitivity to drugs; (2) simplicity, which allows the testing of a large number of animals; (3) measurement of a discrimination which allows the control of the treatment side-effects on sensory and motor capacities as well as on arousal levels which is contrary to most one-trial tests. Consequently, this test may well be a useful tool for the neurobiological studies of learning and memory.

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