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Effect of Administration of an Analog of LHRH on Appetitive Learning in Young and Middle-Aged Female Rats

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NAUTON, P., N. GIRY, M.-A. BRUHAT AND J. ALLIOT. *Effect of administration of an analog of LHRH on appetitive learning in young and middle-aged female rats.* PHARMACOL BIOCHEM BEHAV 43(4) 1005–1013, 1992.—Hypothalamic luteinizing hormone-releasing hormone (LH-RH) had been reported to induce changes in defensive learning. In middle age, females exhibit a decline in their reproductive axis. Several studies in rodents suggested that hypothalamic LHRH function deteriorated in middle-aged females. Our experiments compare T-maze learning in young and middle-aged female rats and study the effect of administration of an analog of LHRH, D-Trp^6-LHRH. The ovarian action of the analog was studied and a gonadectomized control group was added. No differences were observed between young and middle-aged females in acquisition, retention, and reversal of a simple discrimination in the T-maze. However, after removal of motor and spatial cues acquisition of the discrimination on visual cues was impaired in middle-aged females compared to young mature ones. Administration of D-Trp^6-LHRH enhanced performance during the visual discrimination in younger females and had no action in middle-aged ones, whereas it inhibited ovary function in both groups. Ovariectomy had no effect. These results suggest a direct effect of the analog of LHRH on the CNS and show that this peptide fails to counteract the deleterious effect of age on performance.

LHRH Learning and memory Aging Females

HYPOTHALAMIC luteinizing hormone-releasing hormone (LHRH) produces specific effects on reproductive (20,29) and nonreproductive behavior (8,23,25). Administration of about 100 μg LHRH modifies performance during defensive learning (24,26). Also, dense hippocampal concentration of gonadotropin-releasing hormone (GnRH) receptors have been described (21) and GnRh binding sites were also found in other limbic structures such as septum, amygdala, and entorhinal cortex. Together, these data suggested a possible action of LHRH on learning and memory as other neurosecretory peptides of hypothalamic origin.

In a previous study, we demonstrated a modification of working memory in middle-aged females (2), while males showed no changes. The female reproductive axis in most mammals exhibits an age-related decline. There is a gradual change from a cyclic to a noncyclic mode of function (10, 32,33) detectable during middle age. Several studies in rodents have suggested that hypothalamic function deteriorates in middle-aged females. Changes in the diurnal rhythms of neurotransmitter activity occur in hypothalamic areas that control gonadotropin release (34) during middle age. The mean levels of in vivo LHRH secretion in ovariectomized rats treated with oestrogen and progesterone had been shown to be higher in young rats than in middle-aged ones (30,31). More recently, Barnea and Bhasker (3) found a greater secretory response of the LHRH neurons in ovariectomized aging females compared to younger ones and an attenuated steroid regulation of LHRH secretion in old animals. Hence, changes in cognitive performance (2,18) observed in females may be linked to changes in hypothalamic LHRH.

Accordingly, we designed experiments to compare T-maze learning in young and middle-aged female rats and study the effect of administration of LHRH. As LHRH has a short duration of action, an agonist D-Trp^6-LHRH, was used. However, chronic administration of such a potent agonist as D-Trp^6-LHRH has a marked inhibitory effect on reproductive func-

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tion [see (12)] and can result in chemical castration. Therefore, a surgical gonadectomized group was added as control.

METHOD

Animals

Sixty-eight female rats of the LOU strain (Wistar-derived strain) purchased from INRA Center (Theix, France) were used. They were housed at 21 ± 0.5°C and 60 ± 10% humidity in same-age groups of three and were handled and weighed daily throughout experimentation.

The dates of birth of all animals were known. At the beginning of the experiment, animals were grouped as follows: 36 4-month-old females and 32 12-month-old females. At the end of the experiment, rats were, respectively, 8 and 16 months old.

During training, rats were maintained under 23-h food deprivation. Food was given ad lib for 1 h , at the end of training, between 5:00 and 6:00 p.m. Water was available ad lib. Animals submitted to this regimen maintained their body weight; we had already shown that they have an unmodified basal level of adrenal and plasma corticosterone compared to rats fed ad lib (1).

Water and food were given ad lib between successive training sessions.

Surgery and Treatment

D-Trp^6-LHRH was used. In this analog, the replacement of Gly^6 by a deamino acid enhances stability toward enzymatic degradation and increases receptor binding affinity (12).

Treated rats were subcutaneously injected with long-lasting microcapsule formulations (800 μg/kg releasing continuously 5 μg/day over at least 28 days). This dosage form has been shown to be more effective than daily drug administration and more convenient to administer (11).

Control and gonadectomized rats were given an SC injection of 0.25 ml vehicle. Injections were given 10 days before behavior testing.

Gonadectomy was performed under pentobarbital anesthesia (0.5 mg/kg pentobarbital to 6%) preceded by 0.025 mg atropine sulfate. Controls and D-Trp^6-LHRH-treated rats were anesthetized and sham operated. The recovery period was 20 days.

At the end of the experiment, rats were sacrificed by decapitation. Ovaries were weighed and frozen at −25° while awaiting analysis of estradiol (E2) and progesterone levels.

Procedure

Discriminative learning in a T-maze. Rats were tested in a T-maze, 10 cm wide and 15 cm high, consisting of an 80-cm straight alley, two 55-cm arms, and two 20-cm goal boxes. The arms and goal boxes differed visually: One was black and the other white. Each arm was closed by a flap of the same color, hinged to the top: The rat swung the flap open as it entered the arm.

After habituation to the apparatus lasting 2 days, a pellet of food (Quaker cereal) was placed in the white-left goal box and each rat was submitted to one daily trial for 6 days. Training took place between 2:00 and 4:00 p.m. For each trial, the arm chosen and the latency to enter it were recorded. If the rat did not enter either arm within 180 s (refusal of choice), the trial was stopped and the animal taken from the apparatus and placed in its home cage.

Retention and reversal. Two weeks after the last training session, each rat was submitted to a daily retention trial lasting 3 days in the same conditions. On the fourth day, the pellet of food was placed in the black-right goal box and rats were given one daily trial for 6 days in a reversal paradigm.

Each age group was divided as follows: 36 young females into 12 controls sham-operated and injected with vehicle, 12 ovariectomized animals injected with vehicle, and 12 injected with D-Trp^6-LHRH and sham operated; and 32 middle-aged females into 10 controls sham-operated and injected with vehicle, 11 ovariectomized animals injected with vehicle, and 11 injected with D-Trp^6-LHRH and sham operated.

Rats were paired by previous performance into the three groups. Twenty days after ovariectomy and 10 days after administration of D-Trp^6-LHRH, animals underwent retraining in the T-maze in the conditions of reversal. The following day, the visual and kinesic cues were removed: Both arms and goal-boxes were colored like the straight alley. The flaps remained black and white and were put at random on the left or right. Rats had to learn to choose the arm closed by the black flap. Hence, they had to ignore spatial and kinesic cues and use only the visual cue.

Open field. As D-Trp^6-LHRH had been shown to have a potent inhibitory effect in mice in the open-field test (19), exploratory activity was tested twice in the open field, first after acquisition of the T-maze, prior to retention, and second after gonadectomy and injection of LHRH. The open field, measuring 1 × 1 m, was divided into 10 × 10-cm squares. Locomotion, central ambulation, rearing, grooming, and defecation were measured over a 5-min period.

Statistical Analysis

The correct choices were compared by χ^2 analysis. Analysis of variance (ANOVA) with repeated measures was performed on the latencies of choices.

RESULTS

Influence of Age on Learning

The results are presented in Figure 1.

1. During acquisition of the T-maze, latency of choice decreased, $F(5, 330) = 21.5$, $p < 0.001$, and the number of correct choices increased. However, no difference was observed between the two groups. The older rats chose faster than the younger ones but the differences were not significant due to the wide intragroup variations.
2. Interruption of training induced, for both groups, an increase in the latency of choice, $F(1, 66) = 12.32$, $p < 0.001$, on the first trial of retention compared to the end of acquisition. There was a main effect of age during retaining, $F(1, 66) = 4.7$, $p < 0.05$: Middle-aged females chose faster than younger ones.
3. During reversal, the difference in the mean running time was maintained between young and middle-aged females. However, the learning of reversal was identical for the two groups.
4. Testing in the open field revealed only a difference in total locomotion, $F(1, 66) = 5.99$, $p < 0.002$, between the two groups. There was an increase in locomotion in middle-aged rats.

Other parameters were not modified, $F(1, 66) < 0.2$, n.s. (see Table 1A).

Conclusion. There was no difference in learning, retention,

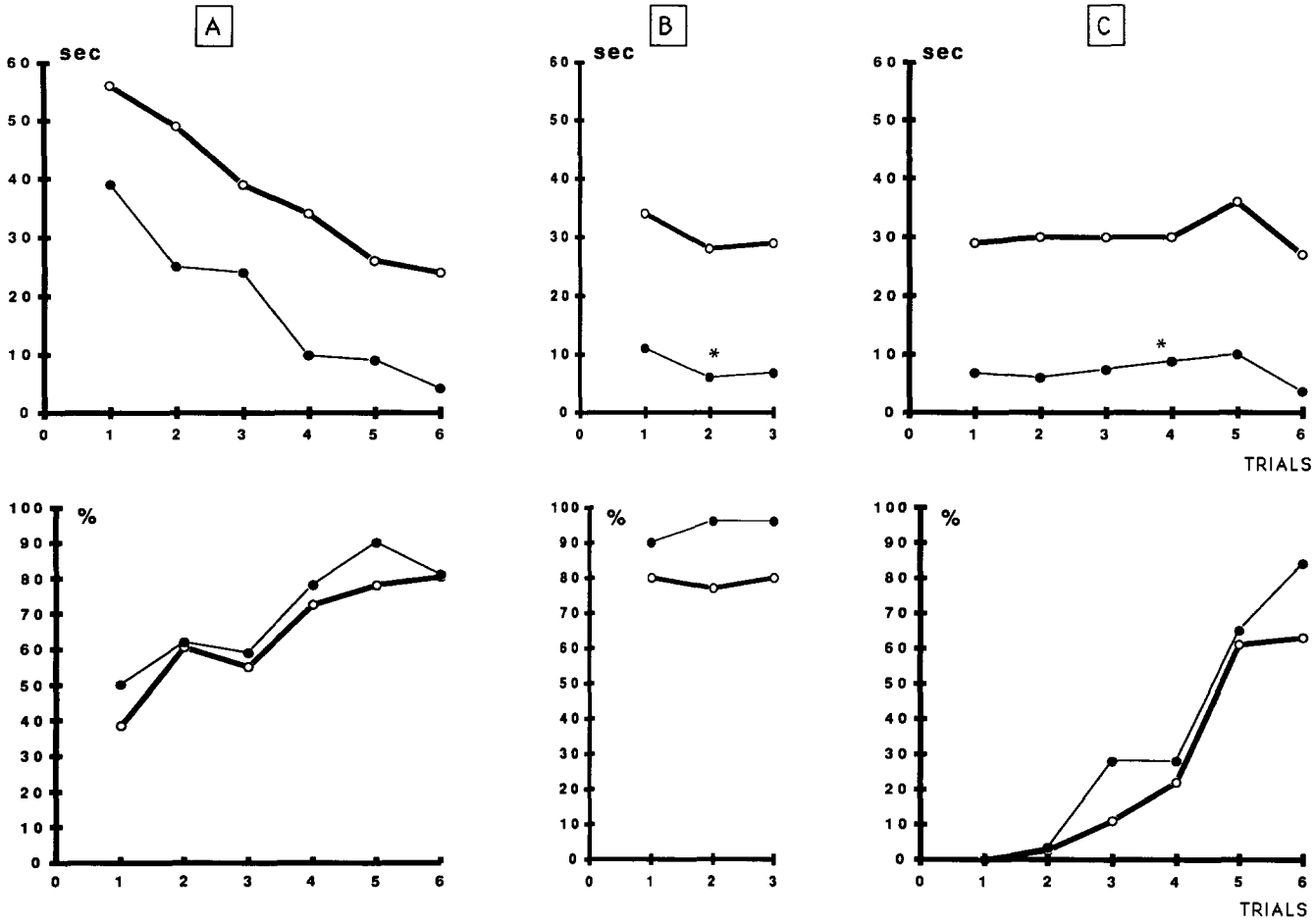

FIG. 1. Acquisition (A), retention (B), and reversal (C) of the discrimination in the T-maze. Middle-aged females (●) showed lower latencies of choices (top) than younger females (○). The decrease of latencies was significant in retention and reversal. However, there was no difference in the percentage of correct choices (bottom) between the two groups throughout the three phases of training. *Indicates a main effect of age on the latencies.

and reversal of the T-maze between young and middle-aged females. However, a clear-cut decrease in choice latencies was seen in the middle-aged group throughout the training that cannot be explained by a difference of general activity.

Effect of Gonadectomy and D-Trp^6-LHRH

Retention of the T-maze (Fig. 2). As previously seen, the latency of choice was greater in young rats than in older ones, $F(1, 65) = 4.7, p = 0.05$. There was no difference in correct choices between controls, ovariectomized, and injected rats, regardless of age group, either in retention or reacquisition ($\chi^2 < 1.45$, n.s.). Animals in general showed an enhancement of correct choices more obvious in middle-aged ($\chi^2 = 6.24$, $p < 0.02$) than in younger ones ($\chi^2 = 3.84, p = 0.05$) during retraining.

Acquisition on visual cue. Acquisition was measured by the increase in the correct choices made when the black flap was placed on the left arm, which was previously nonreinforced (Fig. 3). The number of correct choices on this side increased throughout the training, $F(1, 65) = 6.8, p = 0.02$. For the first time, younger rats learned faster: Comparison using a paired t-test showed that the left correct choices increased on the third day while they increased only in the sixth trial for middle-aged females. Moreover, though, no significant difference was seen in the ovariectomized groups; marked enhancement of the efficiency of injected young rats was observed. Figure 4 shows that the preference for the previously reinforced right side, stronger in all groups, specifically in the older groups, has disappeared only in the injected young group ($\chi^2 = 4.2, p < 0.05$).

It is noteworthy that injection had no effect on middle-aged rats. The two injected groups differed significantly with regard to side preference ($\chi^2 = 5.3, p < 0.05$).

Open-field behavior. Open-field activity is presented in Table 1. In the second test, as in the first, ANOVA revealed a main effect of age only on total locomotion, $F(1, 65) = 4.1$, $p = 0.054$.

No effect of treatment (Table 1B) was found for either the second test or evolution between the first and second tests.

When the open-field activity data were analyzed separately for each age, only the effect of treatment on grooming reached an acceptable level of significance in the younger group, $F(2, 35) = 3.3, p = 0.05$, due to a decrease in the injected group (2 vs. 9).

Hormone levels. Ovary weight and E2 and progesterone

TABLE 1

ACTIVITY IN THE OPEN FIELD BEFORE (A) AND AFTER (B) TREATMENT WITH THE ANALOG OF LHRH OR GONADECTOMY

TABLE 1A

Animals	Total Locomotion	Central Locomotion	Rearings	Grooming	Defecations
Youngers					
a	332	57	27	2.6	−0.4
b	60.9	16	5.9	2.2	1.15
Middle aged					
a	360*	58	26	2.4	0.36
b	31.6	15.1	5.2	1.5	0.9

TABLE 1B

Animals Treatment	Total Locomotion	Central Locomotion	Rearings	Grooming	Defecations
Youngers					
Controls					
a	323	58	18	2	0.4
b	42.6	14.6	4.3	1.1	1.1
Gonadectomized					
a	310	54.2	22.5	1.4	0.1
b	38.4	15	5.7	1.3	0.3
Injected D-Trp^6 LHRH					
a	338	51	21.3	0.9†	0
b	57.5	14.2	7.1	0.8	0
Middle aged					
Controls					
a	352.2*	58	18.4	2.2	0
b	32.4	12.3	4.8	1.8	0
Gonadectomized					
a	330	61	17.3	1.91	0.4
b	52	22.2	5.3	1.4	1.1
Injected D-Trp^6 LHRH					
a	326	48	18	2,1	0
b	68	17.3	5.9	1.9	0

*Significant decreased with respect to youngers.(a), mean; (b), standard deviation.
†Significant decrease with respect to controls of the same group.

levels were identical in the two groups, $F(1, 41) < 1.37$, n.s. (Table 2).

There was an effect of injection on the weight of ovaries, $F(1, 41) = 58$, $p < 0.0001$, which decreased in injected groups. There was no difference in E2 levels, $F(1, 41) = 0.41$, n.s., but the progesterone level fell, $F(1, 41) = 21.45$, $p < 0.0001$.

DISCUSSION

Changes in Learning and Memory During Aging

There was no age difference in learning, retention, and acquisition of reversal of discrimination in the T-maze. This had already been observed in a previous experiment (27). Barnes et al. (5) also reported that young and old animals learn to find the correct goal in a T-maze equally rapidly. This agrees with general findings that age-related impairment is a function of task complexity.

As stressed by Barnes (4), animals can use different strategies in the two-choice discrimination problem in the T-maze: They can remember where the goal is in the environment, based upon the distal cues in the testing room (spatial strategy), remember to turn right or left for reward (response strategy), or remember a salient cue in the arm itself and always choose this arm (cue strategy). It has been found that older rats rarely use spatial memory whereas young rats frequently do.

In the second part of the experiment, spatial and motor strategies were irrelevant. Animals could only use the salient visual cue. In this condition, impairment appeared in middle-aged females compared to younger ones. Several explanations can be proposed for this, but the design of the experiment does not enable us to decide between them. First, the impairment may be due to the increase in complexity of the task. Second, older rats may be unable to use cue strategy. Third, middle-aged rats may show more perseverative behavior that may be associated with a more rigid response strategy, as has been shown for older animals (13,14). However, it can be

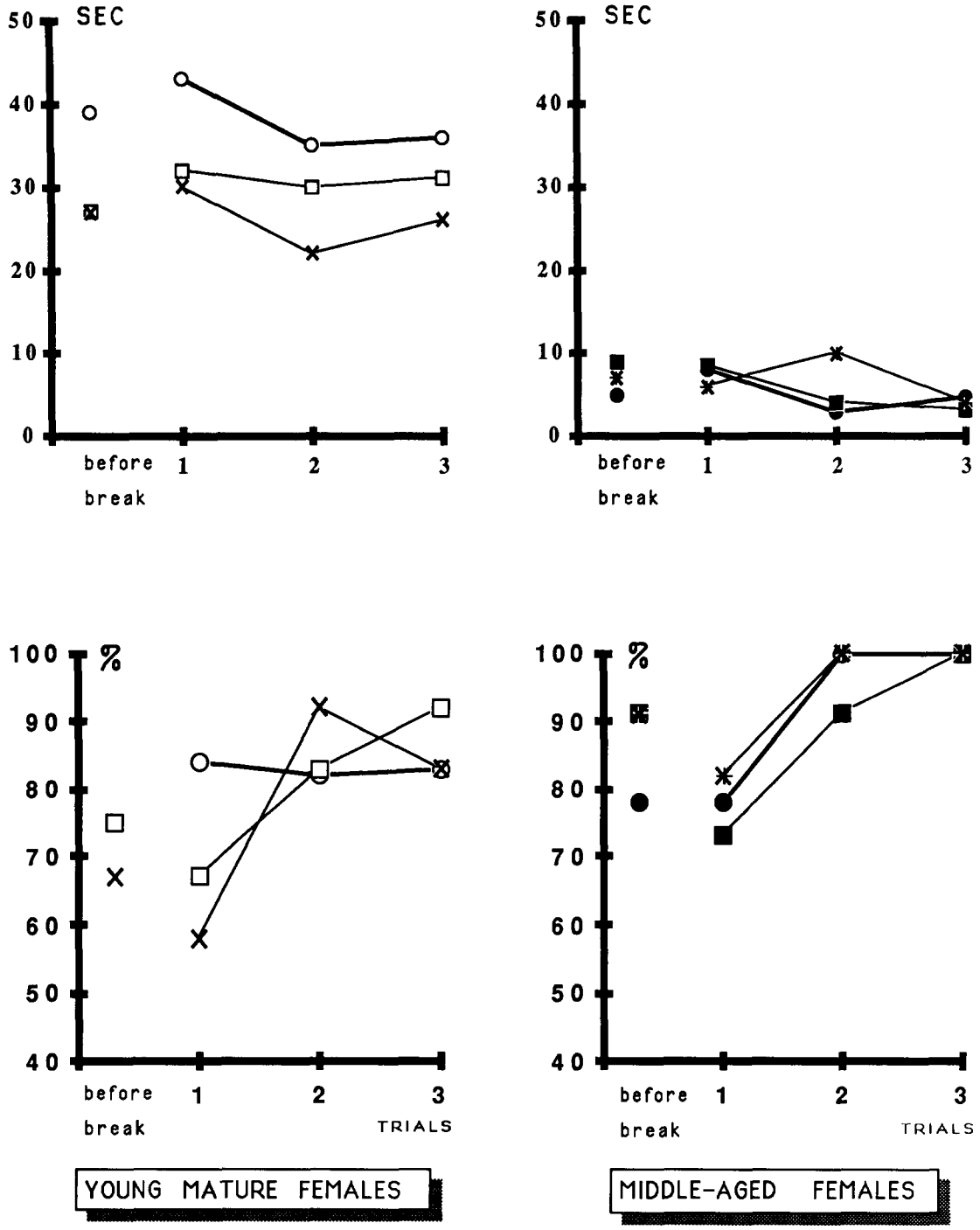

FIG. 2. Effect of gonadectomy and D-Trp^6-LHRH administration on retention. Latencies of choices (in seconds) are shown in the upper part of the figure and percentage of correct choices in the lower part. Middle-aged females chose faster than youngsters ($p = 0.05$) regardless of treatment. Gonadectomized groups (□, ■), injected with analog of LHRH (X, XX), were not different from controls (○, ●) in each group of age.

noted that no perserverative response was seen in reversal in middle-aged animals.

A striking effect of age was seen on the latencies of choice. They were always shorter in the middle-aged group. This had already been observed in another experiment (27) and is certainly related to the greater locomotor activity in the open field. This augmentation of locomotor activity is a novel finding and may be strain dependent.

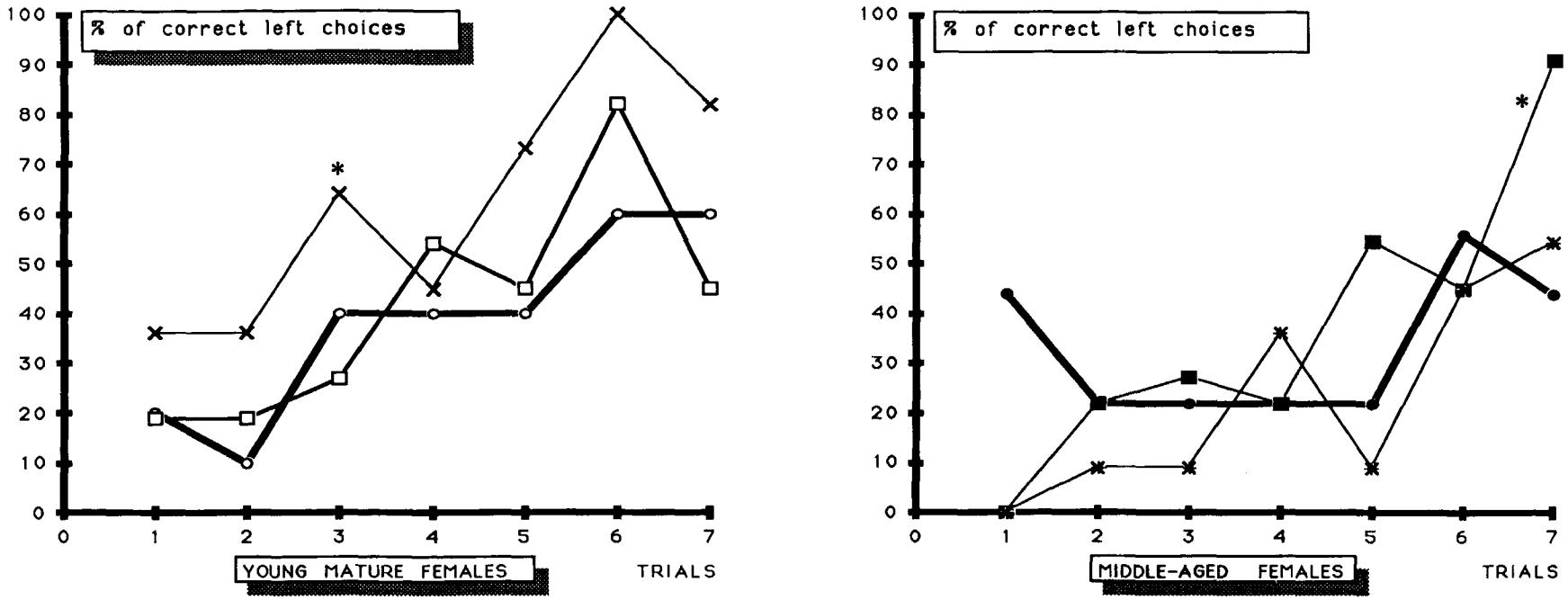

FIG. 3. Percentage of correct left choices (previously nonreinforced side) during visual discrimination in gonadectomized (□, ■), injected with analog of LHRH (X, XX), and control (○, ●) females. Number of correct choices on this side increased throughout training in both groups. However, learning was faster in youngers. Moreover, although no significant difference was seen in the ovariectomized groups marked enhancement of the efficiency of injected young rats was observed. *Indicates that correct choices of the whole group of age was significantly improved in the trial compared to first one.

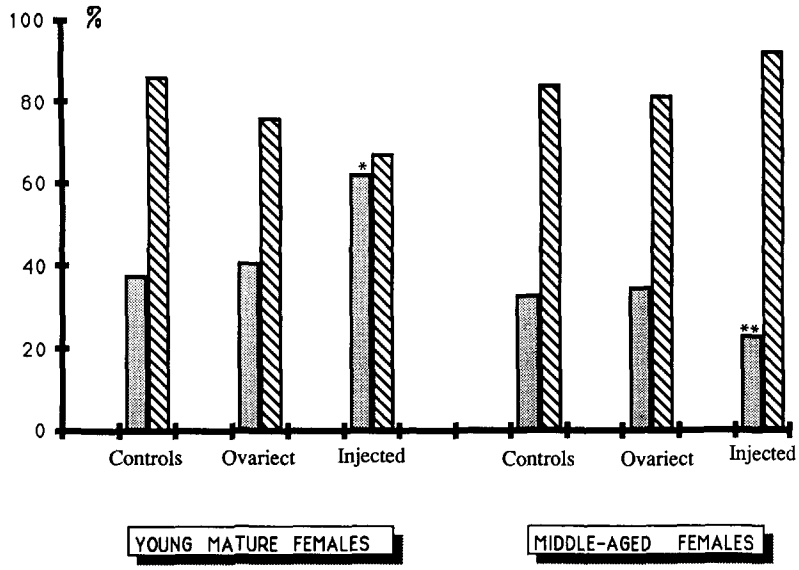

FIG. 4. Mean correct choices of right side (▨) (previously reinforced) and left choices ( ) (previously nonreinforced side). The preference for the previously reinforced right side is stronger in all groups, specifically in older groups. The preference disappeared only in the injected young group (*different compared to controls of the same group of age). **Injected middle-aged group differed significantly with regard to side preference compared to injected younger group.

It can be noted that peripheral hormonal levels, similar in the two groups, cannot account for the behavioral differences. Rats were food restricted; this food restriction induces a blockade of cycles and a state of pseudopregnancy, allowing a comparative study between young mature and middle-aged female rats in similar peripheral reproductive hormonal states.

Effects of D-*Trp*^{6}*-LHRH*

Administration of the analog of LHRH reduced ovary weight and decreased the ovary progesterone content, whereas E2 content was not modified. Thus, as expected, administration of D-Trp^6-LHRH resulted in inhibition of the ovaries. The mode of action of this analog is undoubtedly complex,

TABLE 2

MEAN (A) AND STANDARD DEVIATION (B) OF OVARY WEIGHT AND HORMONE LEVELS IN CONTROL AND D-TRP^6 LHRH-TREATED YOUNG AND MIDDLE-AGED FEMALES

	Ovary Weight (mg)	E2 (pg/mg)	Progesterone (ng/mg)
Youngers			
Control			
a	31	6.7	30.9
b	1.9	0.6	2.1
Injected D-Trp^6-LHRH			
a	20*	15.74	12.4*
b	0.3	0.8	23.4
Middle aged			
Control			
a	34	15.9	28.9
b	8.7	20.3	17.7
Injected D-Trp^6-LHRH			
a	21*	12.8	13.3*
b	5.5	18.2	15.5

There was no difference between younger and middle-aged females. Treatment with analog of LHRH reduced ovaries weight and decreased progesterone content in both groups whereas E2 content was not modified.
*Significantly different ($p < 0.05$) compared to controls.

possibly involving down regulation of ovarian luteinizing hormone (LH) and follicle-stimulating hormone (FSH) receptors and a direct antigonadal effect (6,17). Thus, LHRH receptors have been characterized in rat ovarian tissue, in particular on luteal cells (6), leading to a reduced progesterone secretion. Our results agree with these data and show that the antigonadal action was similar in the two age groups.

The main results for the behavioral effect of the analog D-Trp^6-LHRH are as follows:

1. Administration of D-Trp^6-LHRH did not modify general activity as measured in the open field. In mice, Kadar et al. (19) found a potent inhibitory effect for injection of 100 μg/kg of this analog in the open-field test: Ambulation, rearing, and grooming were significantly reduced. In our experiment, only grooming decreased in the injected group. Discrepancies could be attributed to the species, dose, and mode of administration of the peptide. These data show that the dose used in our experiment was relatively moderate.
2. Administration of D-Trp^6-LHRH enhanced the acquisition of the visual discrimination of the T-maze in young mature females. LHRH has been found to modify passive and active avoidance responses in male rats. Both enhancement (8,26) and impairment (25) have been reported. It seems that the effect observed depended upon the time of injection, injected dose (23), and intensity of the foot-shock applied (24). This study shows that LHRH may also affect positively reinforced tasks. However, although the data obtained suggest an improvement in acquisition another interpretation is possible: As shown in Fig. 3, the left correct choices are significantly enhanced but the right correct choices are simultaneously decreased (90 to 70%), as if rats are leaving perseverative responses in previously reinforced right side and adopting a perseverative response in the left side. Thus, the analog of LHRH may be promoting the change of strategy, not the learning.

   The literature reports either facilitation of conditioned avoidance response (9) or absence of effect in a differential reinforcement of low rates (DRL) task after ovariectomy (22). In this experiment, ovariectomy is ineffective in modifying performance. Consequently, a direct action on the CNS is probable. This is also supported by the fact that middle-aged females showed an ovarian response to the analog of LHRH without showing any behavioral response.
3. Administration of D-Trp^6-LHRH had no action on middle-aged females, whereas it inhibited ovary function in both groups. It failed to counteract the deleterious effect of age on performance, showing that the deficit in learning was not linked to a deficit in LHRH. Further evidence is the ineffectiveness of ovariectomy in young rats. Ovariectomy led to a >50% reduction in net stimulated release of LHRH in young rats but did not alter the release of LHRH in middle-aged females (3); however, it may be that the response of hypothamic and/or other central LHRH receptive cells (in particular those present in limbic structures) is adversely affected in middle age.

   A large amount of data suggests that the deficit in aging females is not in the secretory machinery of the LHRH neuron itself but rather in other inputs that govern the function of the hypothalamic axis. An indirect action of D-Trp^6-LHRH, for example, through the ovarian progesterone (28), is also possible.

In addition, several neurotransmitters are known to regulate the reproductive axis in young female rats (15). Considerable data suggest that norepinephrine, dopamine, and serotonin exert important neurochemical influences on LHRH release. Lower activities of catecholamines and a higher activity of serotonin in the hypothalamus of old rodents have been reported (7,16). Changes in diurnal rhythms of neurotransmitter activity occur during middle age in female rats (33). Changes in the activity of these neurotransmitters could also play a role in the deficit observed in middle-aged rats and the ineffectiveness of administration of LHRH. Due to the subtle complexity of the deterioration of the reproductive system, the difference in behavioral effects of the LHRH along between young and middle-aged females remains unexplained; further work on this is planned.

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