Pharmacology Biochemistry & Behavior, Vol. 30, pp. 729–735. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Comparative Effects of Progesterone and Alphaxalone on Aggressive, Reproductive and Locomotor Behaviors[1]

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Received 22 October 1987

FRAILE, I. G., B. S. McEWEN AND D. W. PFAFF. *Comparative effects of progesterone and alphaxalone on aggressive, reproductive and locomotor behaviors.* PHARMACOL BIOCHEM BEHAV 30(3) 729–735, 1988.—Progesterone can reduce aggressive behaviors in rodents under various experimental conditions, but it could be argued that this effect is due to the well known anesthetic/sedative properties of some steroids. We have tested this hypothesis by comparing the effects of progesterone and the anesthetic progestin, alphaxalone, on the aggressive, reproductive and locomotor behaviors of hamsters. Locomotion is used as a sensitive index of sedative/soporific effects. Progesterone reduced aggressive behavior without depressing the general locomotor activity of the animals, and it also facilitated feminine sexual behaviors in both sexes. Alphaxalone induced mild sedation in hamsters but this did not decrease their aggressive display. Alphaxalone did not facilitate feminine sexual behavior in either sex. We proposed that the inhibitory effect of progesterone on hamster aggressiveness is unlikely to follow from the hormone's sedative properties.

Progesterone Alphaxalone Sedative progestins Aggression Lordosis Locomotor activity Hamsters

PROGESTERONE has been shown to reduce aggressive behaviors in rodents under various experimental conditions [4, 5, 10, 21, 23, 24, 27]. The mechanisms by which progesterone may inhibit aggression are not clear. Erpino [5] has argued that progesterone could reduce aggressiveness in mice by inhibiting the production of aggression-promoting pheromones. Payne *et al.* [23,24] have described that in hamsters the female in heterosexual encounters, or the treated individual when one of the members of a pair received progesterone injections, elicited less aggression than the opponent. The authors suggested that there could be a progesterone-dependent olfactory cue mediating the response. In this species ultrasound emissions have been shown to be an important factor in the transition between sexual and aggressive behaviors [9]. It could be that progesterone acts by modulating those ultrasonic and/or olfactory signals to inhibit the aggressive display.

Another explanation could be that the reduced aggressiveness of the progesterone-treated animals is related to the well known anesthetic properties of progestins. Several authors have described the anesthetic properties of steroid hormones. Selye [25] found that progesterone could induce deep anesthesia in rats and mice when administered in high doses and by an intraperitoneal route. Later, Meyerson [19,20], comparing the anesthetic properties of progesterone with other progestins used in the clinic as contraceptives, found that progesterone itself was the most potent anesthetic agent when administered intravenously, followed by medroxyprogesterone.

Hauser *et al.* [17] have described an effect of progesterone in the induction of sleep in cats without reduction in paradoxical sleep time, making it undistinguishable from normal sleep. This sedative action is different from that of the barbiturates, which reduce greatly the REM period. Gyermek *et al.* have reported that some of the progesterone metabolites are considerably more potent hypnotic agents intravenously than some barbiturates (i.e., nembutal), but that their potency decreases when administered intraperitoneally [11].

The anesthetic properties of certain steroids have been related to aggressive behaviors in different ways. It has been reported that the defensive gland of certain beetles contains a combination of several progesterone metabolites. These insects use this glandular secretion in order to induce a reversible paralysis in their depredators [15]. Other authors studying aggression in the mouse model have observed a decrease in the aggressive behavior after treatment with progesterone [4,5]. They suggested that progesterone may have induced an anesthetic or soporific conditions resulting in an aggression decrease, possibly due to raised threshold for response to external stimuli.

In the experiments reported here we have investigated the "sedative hypothesis" by comparing the influences of progesterone and alphaxalone on the aggressive, sexual and locomotor. behaviors of female and male hamsters. Alphaxalone is one of the most potent anesthetic agents in the progestin family and it is the main component of Althesin, a commercial anesthetic which has been used in the clinic

[1]This work has been presented in part in abstract form to the Society for Neuroscience Meeting, New Orleans 1987.

[1,2]. This synthetic progestin has also been used in in vitro assays to study possible mechanisms for the sedative action of progestins [12,13].

Our results show that alphaxalone can induce a mild sedative condition but nevertheless does not affect the aggressive performance of hamsters in our testing paradigm. Therefore, the reduced aggressiveness found in the progesterone-treated animals is not likely to be related to the hormone's anesthetic or sedative properties.

GENERAL METHOD

ANIMALS AND MAINTENANCE

The subjects in these experiments were adult gonadectomized male and female golden hamsters (*Mesocricetrus auratus W.*, Lakeview strain from Charles River Co.) 60 days old at the time of the arrival. Upon arrival animals were housed singly in Plexiglas cages. The animals assigned to the running-wheel activity test were housed individually in Wahmann activity wheel cages. Control animals for the preliminary tests of aggression and the control animals for the sexual behavior tests were housed in groups of three per cage. The colony room was maintained on a 14 hr light, 10 hr dark cycle (lights off at 12:00 noon), and at a constant temperature (about 24°). All animals had free access to food and water.

BEHAVIORAL TESTING

Aggressive Behavior

One week after arrival in our facility every animal passed a preliminary test for their baseline levels of aggression. The test started by introducing a control hamster to the cage of the experimental animal, just opposite to the resident, both being of the same sex, and it finished when the experimental animal showed an attack posture toward the control or after two minutes. All tests showed aggression before the end of the two-minute period and therefore all the animals were included in the study.

Pairs of hamsters were established and assigned to one of the three treatments: progesterone, alphaxalone or control. All animals were matched for sex and body weight, with a minimum allowed difference of 10 g in each pair, and with both members of the pair receiving the same treatment.

A week after the preliminary test every animal received daily injections, during four consecutive days, of progesterone (1 mg/0.2 ml sesame oil SC Progesterone Groups), alphaxalone (1 mg/0.2 ml sesame oil SC Alphaxalone Groups), or oil (0.2 ml sesame oil SC Control Groups), as appropriate for their experimental groups. The minimal progesterone dose that modifies aggressive performance in hamsters has been determined previously [10]. Additionally, we established in preliminary tests the minimal dose for alphaxalone that injected SC can induce a mild sedation, making the animals sleepy and less active during the period of time between the injection and the aggression tests. The treatments were given 1 hr before lights-off in the colony room and the behavioral tests were performed during the last two days, 4–5 hours after the injection.

The tests were conducted in the animal's own home cages (45×20×26 cm), in the colony room and under dim red light. The results were collected during two consecutive days on a home-away rotation. Measures from both days were added and considered as the quantified aggression display of a given pair [10]. Each test was five minutes in duration, in order to limit the intensity of aggression and thus prevent injury. Testing started by placing the "intruder" in the opponent's cage, just opposite the "resident" and it finished by returning the former to its home cage, reversing the procedure on the second day.

During the tests the overall behavior of the animals was recorded by counting and timing those postures displayed in aggressive behavior sequences [7, 8, 10]. The parameters were divided into three categories as follows:

Preaggressive behavior.

Upright position. The two animals were in a position with both forepaws off the substrate showing the complete body length to its opponent, oriented one towards the other. Sometimes they exchanged little pushes with their forepaws or sniffed the area around the opponent's head.

Aggressive behaviors.

Attack. A physical assault by one hamster upon the other. The attacker approached the partner oriented approximately perpendicular to the trunk, facing the flank, having one or both forepaws in contact with some part of the opponent's body, and sometimes biting the flank.

On-back. The hamster in this posture laid on its back or side, and its opponent bent over it perpendicularly, usually sniffing or biting the flank.

Rolling-fight. This behavior represents a violent part of hamster aggressive displays. It has been described before by several authors (see [8]) as "fighting" or lying more or less perpendicularly. As they bit each other, the pair rolled over wildly and occasionally vocalized.

Most of the time postures occurred in the sequence listed here.

Latencies.

Latency to upright. The time in seconds from the start of the test until the first upright position. If no upright position occurred by the end of the tests, the latency was considered to be 600 sec (sum of 300 sec on each of two tests).

Latency to attack. The time in seconds from the start of the test until the first attack position. If no attacks were scored by the end of the tests, this latency was considered to be 600 sec.

These two latencies were chosen for measurement because they indicate the time the animals spent before assuming preaggressive and aggressive behaviors.

Sexual Behavior

Male and female hamsters were tested for feminine sexual behavior in encounters with a stimulus male, followed one hour later by a manual stimulation test.

The first sexual behavioral session was conducted one week after the animals arrived to our facility. All animals were injected with estradiol benzoate (EB, 10 μg/0.1 ml sesame oil, SC) and 48 hours later half of them received progesterone (500 μg/0.1 ml sesame oil, SC) and the other half alphaxalone at the same dose (500 μg/0.1 ml sesame oil, SC). Two animals were wounded during this test and they were excluded from the rest of the study (as shown in Table 4).

The second test session was done two weeks later. The animals were injected with EB (10 μg/0.1 ml sesame oil, SC) followed 48 hours later by progesterone (1 mg/0.2 ml sesame oil, SC) or alphaxalone (1 mg/0.2 ml sesame oil, SC), and they were tested again for their feminine sexual display.

All treatments were given one hour before lights off in the colony room and tests were done 4–5 hours after injection, in the animals' own housing cages (45×20×26 cm) under dim red light. Each test was 5 minutes in duration. Testing

TABLE 1

AGGRESSIVE BEHAVIOR OF FEMALE HAMSTERS*

Group	N	Latency to Upright (sec)	Latency to Attack (sec)	Frequency of Postures Per Session			
				Upright	Attack	On-Back	Rolling Fight
C	8	28 ± 6	92 ± 18†	22 ± 3	48 ± 5†	39 ± 6†	30 ± 6‡
P	8	26 ± 5	244 ± 66	20 ± 2	23 ± 7	17 ± 6	5 ± 3
A	8	20 ± 6	76 ± 24†	21 ± 3	54 ± 7‡	39 ± 5†	21 ± 4

*The data shown are the arithmetic mean of the scores of the n pairs of gonadectomized animals (± SEM).

C=Control group; P=Progesterone-treated group; A=Alphaxalone-treated group. Each group received daily injections (SC) of oil, progesterone or alphaxalone respectively during four consecutive days. The tests were given in the last two days. †$p<0.05$; ‡$p<0.01$. Statistical significance of the differences respect to the P group as estimated by Tukey's test of multiple comparison.

started by placing a control male in the resident's cage and finished by returning the control male to its home cage (after a rest period in a different cage). The control animals were not used more than once each day, and at the time of the tests they had a body weight similar to the experimental animals.

During the tests the overall behavior of the individuals was recorded by counting and timing the sexual behavior display. The aggressive responses during the tests were also noted as described above. The sexual behavioral parameters scored in these tests were as follows:

Latency to lordosis. The time in seconds from the start of the test until the first lordotic posture. If no lordosis had occurred at the end of the test, the latency was considered to be 300 sec.

Time in lordosis. The total time in seconds that the animals spent in the lordotic posture during the test.

Tail-up. The animal in this posture lifted its tail and exposed the ano-genital region to the partner which usually sniffed the area. Sometimes this action induced lateral movements of the tail in the experimental animal. After a number of tail-ups the individual usually performed lordosis.

Rump-movements. These are characteristic movements in which the individual moved its tail and rump area, exposing the ano-genital region to the male control partner.

The number of mounts and mount attempts performed by the control male during the test were also scored, as an indication of the attractiveness and sexual receptivity shown by the experimental animals.

The sexual behavior tests described above (first and second sessions) were followed one hour later by a manual stimulation test of three minutes essentially as described by Kow *et al.* [18]. During the manual stimulation tests only latency to lordosis, time in lordosis and the presence or absence of rump-movements were scored.

Running Wheel Activity

After an habituation period in the activity wheel cages, half of the individuals (four males and three females) were treated during four consecutive days with oil (0.2 ml sesame oil, SC) and four additional days with progesterone (1 mg/0.2 ml sesame oil, SC) and the other half (three males and four females) received oil followed by alphaxalone (1 mg/0.2 ml sesame oil, SC) in the same way. After a recovery period the same sequence was repeated, but reversing experimental treatments.

All progestin treatments were performed at 11:00 hours. Running wheel revolutions were monitored twice daily, at 11:00 and 16:00 hours, in order to record the locomotor activity during the five hour period after the progestin treatments (11:00–16:00 hours). The animals were otherwise minimally disturbed.

Data Analysis

An analysis of variance was applied to the data obtained in the aggressive and sexual behavior tests [6,26], and when statistically significant differences were found, a Tukey's test [22] of multiple comparison was used to establish which conditions were responsible for the observed differences. *t*-Tests were used to analyze the locomotor activity data [6,26].

RESULTS

Aggressive Behavior

Alphaxalone treatment did not have any effect on the expression of the aggressive displays (Tables 1 and 2). The scores of the male and female groups treated with alphaxalone did not differ from those presented by the control groups on any variable. In contrast, when progesterone was used, the treated animals (females and males) showed differences compared to both alphaxalone and control groups. In gonadectomized females, progesterone treatment decreased the number of rolling-fight postures, $F(2,21)=6.83$, $p<0.01$. It also increased the latency to attack, $F(2,21)=4.89$, $p<0.05$, and decreased the frequency of attacks, $F(2,21)=6.46$, $p<0.01$, and on-back postures, $F(2,21)=4.79$, $p<0.05$ (Table 1).

Gonadectomized males treated with progesterone also showed longer latency to attack, $F(2,22)=4.17$, $p<0.05$, and lower frequency of rolling-fights, $F(2,22)=4.17$, $p<0.05$, attacks, $F(2,22)=12.35$, $p<0.005$, and on-back postures, $F(2,22)=10.04$, $p<0.005$ (Table 2).

Sexual Behavior With Stimulus Male

Alphaxalone failed to promote feminine sexual behavior

TABLE 2

AGGRESSIVE BEHAVIOR OF MALE HAMSTERS*

Group	N	Latency to Upright (sec)	Latency to Attack (sec)	Frequency of Postures Per Session			
				Upright	Attack	On-Back	Rolling Fight
C	8	32 ± 5	97 ± 16†	32 ± 4	38 ± 4§	26 ± 4‡	10 ± 4†
P	8	40 ± 9	218 ± 35	24 ± 2	12 ± 2	8 ± 1	1 ± 1
A	9	22 ± 3	141 ± 32	26 ± 3	36 ± 5‡	24 ± 4‡	8 ± 2

*The data shown are the arithmetic mean of the scores of the n pairs of gonadectomized animals (± SEM). Abbreviations as in Table 1.

†$p<0.05$; ‡$p<0.01$; §$p<0.001$. Statistical significance of the differences respect to the P group as estimated by Tukey's test of multiple comparison.

TABLE 3

BEHAVIORAL DISPLAY IN SEXUAL BEHAVIOR TESTS WITH STIMULUS MALE (500 μg PROGESTIN DOSE)*

	Group	Latency to Upright (sec)	Latency to Attack (sec)	Upright	Attack	On-Back	Rolling Fight	Latency to Lordosis	Time in Lordosis	Tail-Up	Mounts and Attempts
♀	P500 n=6	152 ± 66	300 ± 0	1 ± 1¶	0 ± 0	0 ± 0	0 ± 0	17 ± 3#	203 ± 9#	0 ± 0	13 ± 1#
	A500 n=6	21 ± 12	193 ± 43†	5 ±1	6 ± 3†	3 ± 1†	2 ± 1‡	300 ± 0§	0 ± 0§	7 ± 2‡	2 ± 1§
♂	P500 n=6	28 ± 11	300 ± 0	8 ± 2	0 ± 0	0 ± 0	0 ± 0	202 ± 36	72 ± 29	4 ± 1	1 ± 1
	A500 n=6	9 ± 4	183 ± 14‡	11 ± 2	5 ± 1	3 ± 1†	1 ± 0	300 ± 0‡	0 ± 0†	5 ± 1	0 ± 0

*The data shown are the arithmetic mean of the scores of the n gonadectomized animals (± SEM).

P500=Progesterone-treated groups; A500=Alphaxalone-treated groups. All animals received an injection of estradiol benzoate (10 μg/0.1 ml sesame oil SC) and 48 hours later a second one of progesterone (500 μg/0.1 ml sesame oil SC) or alphaxalone (500 μg/0.1 ml sesame oil SC). The tests were given 4–5 hours later.

†$p<0.05$; ‡$p<0.01$; §$p<0.001$. Statistical differences between P500 and A500 within each sex. As estimated by Tukey's test of multiple comparison.

¶$p<0.05$; #$p<0.001$. Statistical differences between P500 females and P500 males as estimated by Tukey's test of multiple comparison.

at any dose (Table 3), whereas progesterone induced sexual responses in both sexes.

Alphaxalone- and progesterone-treated animals showed differences in the latencies to lordosis [$F(1,20)=110.36$, $p<0.005$ at the 500 μg dose; and $F(1,18)=58.98$. $p<0.005$, with 1000 μg] and time in lordosis [$F(1,20)=80.19$, $p<0.005$ at the 500 μg dose and $F(1,18)=92.57$, $p<0.005$ with 1000 μg], with the progesterone groups always showing the shorter latencies and the longer times of sustained lordotic posture (Table 3).

In the progestin-treated female groups, alphaxalone induced a higher number of tail-up postures than progesterone-treated animals at the two doses used [$F(1,20)=12.04$, $p<0.005$ at 500 μg dose and $F(1,18)=12.86$, $p<0.005$ with 1000 μg]. This group also received mount-attempts, but their frequency was significantly lower than progesterone group [$F(1,20)=43.92$, $p<0.005$ at the 500 μg dose and $F(1,18)=31.44$, $p<0.005$ with 1000 μg] (Table 3). During the sexual behavior tests there were aggressive displays only in the alphaxalone-treated animals. At the lower dose of progestin used (500 μg, Table 3) alphaxalone-treated females appeared more aggressive than the progesterone-treated ones as measured by the latency to attack, $F(1,20)=24.62$, $p<0.005$, the number of attacks, $F(1,20)=15.29$, $p<0.005$, and the number of on-back, $F(1,20)=19.90$, $p<0.005$, and rolling-fight postures, $F(1,20)=12.80$, $p<0.005$. At the highest dose used (1000 μg) both groups differed from each other in all the aggressive parameters scored: latency to upright, $F(1,18)=12.77$, $p<0.005$, latency to attack, $F(1,18)=29.28$, $p<0.005$, number of upright postures, $F(1,18)=134.0$, $p<0.005$, and number of attacks, $F(1,18)=19.18$, $p<0.005$, on-back postures, $F(1,18)=101.17$, $p<0.005$, and rolling-fights, $F(1,18)=30.36$, $p<0.005$.

In the feminine sexual behavior tests of the males, the progesterone-treated group also displayed less aggressiveness than the alphaxalone-treated one, as evidenced by longer latencies to attack, $F(1,20)=24.62$, $p<0.005$, fewer on-back postures, $F(1,20)=19.90$, $p<0.005$ with 500 μg dose (Table 3), and lower frequencies of upright, $F(1,18)=134.0$,

TABLE 4

SEXUAL BEHAVIOR IN MANUAL STIMULATION TESTS*

	Group	N	Latency to Lordosis (sec)	Time in Lordosis (sec)
♀	P500	6	2 ± 1§	176 ± 2¶
	A500	6	162 ± 12‡	8 ± 5‡
♂	P500	6	73 ± 25	59 ± 21
	A500	6	180 ± 0‡	0 ± 0†
♀	P1000	6	1 ± 0	179 ± 0
	A1000	5	180 ± 0‡	0 ± 0‡
♂	P1000	6	42 ± 22	117 ± 18
	A1000	5	180 ± 0‡	0 ± 0‡

*The data shown are the arithmetic mean of the scores of the n gonadectomized animals (± SEM).

Same animals as in Tables III tested with manual stimulation.

†$p<0.01$; ‡$p<0.001$. Statistical significance of the differences between the two progestins (progesterone P, and alphaxalone A) at the same dose within each sex, as estimated by Tukey's tests of multiple comparisons.

§$p<0.01$; ¶$p<0.001$. Statistical significance of the differences between males and females at the same dose of progesterone, as estimated by Tukey's test of multiple comparison.

$p<0.005$, and on-back postures, $F(1,18)=101.17$, $p<0.005$ with 1000 μg dose.

There were no sex differences within alphaxalone-treated groups in any parameter related to the feminine sexual display. Progesterone at both doses had a more pronounced effect on females than on males, the former always showing the shortest latencies, receiving the larger number of mounts and sustaining the lordotic posture for a longer time. The difference was significant in the latency to lordosis [$F(1,20)=25.88$, $p<0.005$ at 500 μg dose and $F(1,18)=16.99$, $p<0.005$ with 1000 μg], the time spent in lordosis [$F(1,20)=18.26$, $p<0.005$ at 500 μg, $F(1,18)=33.08$, $p<0.005$ with 1000 μg] and the number of mounts received [$F(1,20)=46.26$, $p<0.005$ at 500 μg, $F(1,18)=12.48$, $p<0.005$ with 1000 μg] (Table 3).

Alphaxalone-treated animals did not show any rump-movements during the tests at any studied dose, while 100% of the females (6/6) and 33% of the males (2/6) treated with progesterone showed them (Table 5).

Sexual Behavior: Manual Stimulation

Alphaxalone did not induce a lordotic response in any group at any dose (Table 4), except for two females treated with 500 μg of alphaxalone, which transiently performed lordosis. Consequently, there were statistically significant differences between the effects of progesterone and alphaxalone treatments on latency to lordosis [$F(1,20)=94.12$, $p<0.005$ at 500 μg and $F(1,18)=168.91$, $p<0.005$ at 1000 μg] and time in lordosis [$F(1,20)=112.96$, $p<0.005$ at 500 μg, $F(1,18)=226.26$, $p<0.005$ with 1000 μg].

There were sex differences among progesterone-treated groups in the latency to lordosis, $F(1,20)=10.38$, $p<0.005$, and time in lordosis, $F(1,20)=48.16$, $p<0.005$, but only at the lower dose used (500 μg). No sex differences were found with 1000 μg of progesterone. There were not any sex differences in the response to alphaxalone.

TABLE 5

PERCENTAGE OF ANIMALS SHOWING RUMP-MOVEMENTS IN SEXUAL BEHAVIOR TESTS

Test	Group	Females	Males
With Stimulus Male	P500	100% (6/6)	33% (2/6)
	A500	0% (0/6)	0% (0/6)
	P1000	100% (6/6)	33% (2/6)
	A1000	0% (0/5)	0% (0/5)
Manual Stimulation	P500	100% (6/6)	83% (5/6)
	A500	0% (0/6)	0% (0/6)
	P1000	100% (6/6)	83% (5/6)
	A1000	0% (0/5)	0% (0/5)

Groups as described in Table 3.

Alphaxalone-treated animals did not show any rump-movements at any dose (Table 5), but 100% of the females (6/6) and 83% of males (5/6) treated with progesterone performed these movements during the tests (Table 5).

Running Wheel Activity

Figure 1 shows the number of running wheel revolutions in a period of five hours (11:00–16:00 hours), during four consecutive days, in groups of females and males treated with oil, progesterone or alphaxalone.

We did not find any statistically significant effect of progesterone on the locomotor activity of the test animals (Fig. 1), although 4/7 (57%) of the males and 5/7 (71%) of the females showed some decrease in the running wheel activity during this period of time.

The alphaxalone treatment did cause a significant decrease in the activity of the males in the first two days [$t(6)=3.63$, $p<0.02$ for the first day and $t(6)=4.12$, $p<0.01$ for the second day] (Fig. 1). The reduction in the locomotor activity was not statistically significant in the females.

GENERAL DISCUSSION

A number of authors have reported that progesterone can reduce the aggressive behavior display in rodents under different experimental conditions [4, 5, 10, 21, 23, 24, 27]. The mechanisms by which progesterone influences this behavior are not fully understood and a variety of hypotheses have been proposed, including the possible existence of a progesterone-dependent olfactory clue [23,24], the inhibition of the production of aggression-promoting pheromones [4,5] and the competition of progesterone for the androgen receptor [4, 5, 28]. Additionally, in hamsters a role for steroids in the modulation of the ultrasonic signals has been proposed, and these are known to be a very important factor in the transition between aggressive and sexual behaviors [9].

Another possible explanation would be that the reduced aggressiveness of progesterone-treated animals is related to the anesthetic properties of the progestin family of compounds. Progesterone might induce an anesthetic or soporific condition in the animals resulting in a decrease of the aggressive display, due to raising the threshold that the stimuli have to elicit a response.

The purpose of these experiments was to explore this last

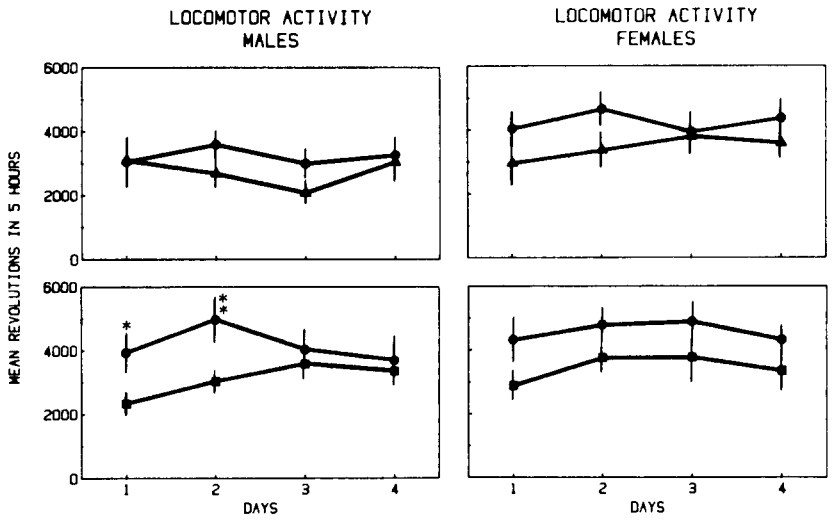

FIG. 1. Running wheel activity for males (n=7) and females (n=7) (mean revolutions in 5 hours per day ±SEM) during 4 consecutive days. ●: oil treatment; ▲: progesterone treatment; ■: alphaxalone treatment. Each animal received an injection of oil (0.2 ml sesame oil SC) during 4 days and progesterone or alphaxalone (either one 1 mg/0.2 ml sesame oil SC) for 4 more days, always at 11:00 hours. *t*-Tests comparisons were made for each day between controls and progestins treatments. $*p<0.02$, $**p<0.01$.

hypothesis, analyzing in parallel the effects of progesterone and a potent anesthetic progestin (alphaxalone) on the aggressive and sexual behaviors and locomotor activity of hamsters.

In our system alphaxalone failed to promote lordotic responses at any studied dose, whereas progesterone induced feminine sexual responses in both sexes. During the sexual behavior tests the alphaxalone-treated hamsters did not display lordosis, instead they consistently showed aggressive behaviors toward the control. This shows that the animals are responding as expected to progesterone and that the synthetic progestin is not able to mimic its effects on the feminine copulatory behaviors under study. The alphaxalone-treated animals displayed what we have interpreted as a precopulatory behavior (i.e., "tail-ups"), while the progesterone-treated ones did not. Interestingly, several natural progesterone metabolites which resemble the structure of alphaxalone have been shown to have a partial effect inducing feminine sexual behavior in rats, hamsters and guinea pigs [3, 16, 29] and they also have anesthetic/sedative properties [14,20].

We used activity in the running wheel to test the soporific effects of both progestins. During this test the animals display spontaneous activity under painless, nonstressing conditions, while they are kept in their own housing cages in their colony room. We have studied the locomotor activity of hamsters to find out if progesterone would decrease their general activity in a manner that could influence the aggressive display. If progesterone could decrease significantly the activity during the five-hour period elapsed between the progestin injections and the behavioral tests, there would exist the possibility that progesterone decreased aggression through sedative or soporific mechanisms. The results showed that progesterone did not decrease significantly the locomotor activity of either females or males during the five-hour period elapsed from the hormonal treatment to the behavioral tests. These data agree with the results of Erpino *et al.* [5] who reported behavioral effects of high doses of progesterone on mice, without apparently reducing the general activity of the animals. However, longer progesterone treatments (8–10 days) can induce decreases in the general locomotor activity of the animals (data not shown). Alphaxalone, when administered SC like progesterone, induced a mild sedative condition which resulted in a decrease in the recorded activity.

Most important, our data show that the reduced aggressiveness, previously found in the progesterone-treated animals [10], is not likely to be related to the hormone's sedative properties, since alphaxalone, administered by the same route as progesterone, induced a mild sedation but it failed to decrease the aggressive display in female and male hamsters. The animals treated with alphaxalone presented a complete aggressive display indistinguishable from the control groups treated with oil. Therefore, we propose that the inhibitory effect of progesterone on hamster aggressiveness is exerted through mechanisms unrelated to its anesthetic/sedative properties.

ACKNOWLEDGEMENT

We are grateful to Dr. K. J. Child from Glaxo Group Research for his generous gift of alphaxalone.

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