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Dopamine and Sexual Behavior in the Male Rabbit

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ÅGMO, A., R. G. PAREDES, J. I. RAMOS AND J. L. CONTRERAS. *Dopamine and sexual behavior in the male rabbit.* PHARMACOL BIOCHEM BEHAV **55**(2) 289–295, 1996.—Male rabbits were treated with the dopamine releasing drug amphetamine or the dopamine D_1/D_2 receptor antagonist *cis*(Z)-flupenthixol. Amphetamine, 1 to 4 mg/kg, had no effect on sexual behavior. Flupenthixol, 2 mg/kg, reduced the proportion of rabbits that ejaculated and the number of ejaculations per test. Lower doses were ineffective. Castrated males were treated with both drugs at two intervals after castration, 19–21 and 27–29 days postcastration, respectively. Amphetamine was without effect while flupenthixol, 1 mg/kg, reduced sexual behavior at the test 19–21 days postcastration. At the second test, sexual behavior was almost completely absent in control animals. Therefore, no further reduction could be observed after treatment with flupenthixol. Another group of animals was castrated and given androgen replacement. Testosterone decanoate was injected once weekly at a dose of 3 mg/kg. This treatment maintained a stable, low sexual activity. In these animals, amphetamine was again ineffective whereas flupenthixol, 1 mg/kg, inhibited sexual behavior. Gross motor function was evaluated in a water escape test. Amphetamine was inactive, and the effective dose of flupenthixol was 10 mg/kg. This dose is far above the dose required for inhibiting sexual behavior. In sum, facilitated dopaminergic transmission does not seem to affect on sexual behavior in the male rabbit, whereas reduced dopaminergic activity disrupts this behavior. **Copyright © 1996 Elsevier Science Inc.**

Male rabbits Sexual behavior Dopamine Motor functions

MUCH data suggest that dopamine antagonists reduce male rat sexual behavior, particularly the aspects associated with sexual motivation (19,37). It seems, though, as if most of these effects could be attributed to motor actions of the drugs (4,10). However, in male rats without sexual experience, dopamine antagonists reduce sexual behavior independently of their motor actions (6).

Stimulation of dopaminergic neurotransmission with receptor agonists have yielded conflicting results. Several studies have shown that low doses of the dopamine agonist apomorphine facilitates sexual behavior (17,22,29,30,34,35). Large doses, 300 μg/kg and more, mainly stimulating postsynaptic receptors, have either inhibitory (29,42) or facilitatory effects (9,40). Equally conflicting results have been obtained with the dopamine D_2 agonist LY163502 (16,20). From these studies it is difficult to draw any clear-cut conclusion as to the role of dopamine receptors in the control of sexual behavior in the male rat.

Studies with the dopamine releasing drug amphetamine have provided less confusing results. In sexually active, experienced males, the drug has no effect (4,7) or stimulates sex behavior (13,17). In males where the activation of sexual behavior is difficult because of castration, lack of sexual experience or lesion of the prefrontal cortex, a consistent facilitation of sexual behavior is observed after treatment with amphetamine or amfonelic acid (4,6,7). This facilitation is limited to motivational aspects, that is, reduced mount and intromission latencies, whereas no effect is observed on the behavior once

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it is initiated. It seems, then, as if dopamine releasing drugs facilitate sexual behavior, at least under some conditions.

The above-mentioned studies have been performed in the rat. The effects of dopaminergic agents on sexual behavior have been little studied in other species. There is one report showing that amphetamine is ineffective in sexually experienced hamsters (14), and cocaine has been found to reduce sexual behavior in the rhesus monkey (39). Low doses of apomorphine have been reported to reduce the postejaculatory interval in this species, while higher doses lengthened the ejaculation latency (38). However, a thorough study of the effects of apomorphine on male rhesus behavior reported only minor changes, and the authors concluded that the effects of low doses were not meaningful. Large doses, however, were disruptive to sexual behavior (15). In the human male, antipsychotics may reduce libido and have frequently adverse effects on erectile mechanisms (41). To the contrary, dopamine agonists may facilitate erection and enhance libido, although few controlled studies are available (41).

The rather inconsistent effect on sexual behavior of dopaminergic agents and the paucity of data from species other than the rat prompted us to evaluate the role of dopamine in the control of this behavior in the rabbit. In the present study, the effects of amphetamine and *cis*(Z)-flupenthixol were evaluated in intact, sexually experienced rabbits, in castrated males shortly after castration, and in long-term castrated animals given low doses of testosterone. The animals were also tested in a water escape task, to detect any nonspecific effect on motivation or motor function.

METHOD

Subjects

New Zealand White rabbits (Bioterio México, Mexico City) were used in all experiments. Males weighed between 3.0 and 4.5 kg, and the females between 2.5 and 3.5 kg. They were housed individually in stainless steel cages under a natural light/dark cycle (sunrise between 0600 and 0700 h and sunset between 1800 and 1900 h, depending on the season). Food (Albamex rabbit pellets) and tap water were always available.

All females were ovariectomized under pentobarbital anesthesia (30 mg/kg intravenously, IV) at least 2 weeks before being used in sex behavior tests. One week before the first test, the females were given a SC injection of estradiol valerianate (Schering Mexicana), 2.5 mg in 0.25 ml corn oil. This injection was repeated once a week, and maintained an excellent receptivity for 2 to 4 months.

The males were subjected to several screening tests with receptive females. Only males that ejaculated at least once in three consecutive tests were included in the experiments. Some of the sexually active males were castrated under pentobarbital anesthesia (30 mg/kg, IV). A bilateral scrotal incision was made, and the testicles with adjacent epididymis were removed. Starting 4 weeks after castration, some males were given a weekly SC injection of testosterone decanoate (TD, Organon Mexicana), 3 mg/kg in 0.1 ml/kg of corn oil. Unpublished data from this laboratory show that this dose maintains a sexual behavior considerably below normal for several months. Indeed, the behavioral effect is similar to that observed after treatment with 1 mg/kg/day of TP (24). When sexual behavior had reached a stable, low level, drug treatments were initiated.

Drugs

D-Amphetamine sulfate (Sigma, St. Louis, MO) and *cis*(Z)-flupenthixol HCl (Lundbeck, Copenhagen, Denmark) were dissolved in physiological saline just before use, and were injected SC in the back in a volume of 1 ml/kg b.wt. The interval between injection and behavioral observation was 30 min for flupenthixol and 40 min for amphetamine. All doses given in the text and tables refer to the salt.

Behavioral Testing Procedure

At the tests, the male was placed in an observation cage (thick wire mesh, 100 × 50 × 40 cm high) 5 min before that a receptive female was introduced. The following behavioral parameters were recorded: mount latency, time from introduction of the female until the first mount with pelvic thrusting; ejaculation latency, time from introduction of the female until the first ejaculation (rabbits ejaculate normally upon each vaginal penetration); postejaculatory interval, time from one ejaculation until the next mount. The number of mounts and ejaculations was also recorded. The test lasted 10 min. A detailed description is found elsewhere (1,8).

Immediately after the sex behavior test, the animals were subjected to a water escape task (36). A cylindrical water tank, diameter 124 cm and 27 cm deep, was used. Fresh water (about 15°C) was filled up to 7 cm from the upper edge. The rabbits were gently dropped into the water in the middle of tank. Control rabbits swam rapidly to the border and jumped out of the water, without showing any discomfort. The escape time was defined as the time necessary for the rabbits to be entirely out of the water. One escape test consisted of three trials, separated by 1 min. An escape time of 300 s was used as cutoff. In case that an animal did not immediately swim, it was removed from the water tank. This latter event did not occur in the present experiments, however. Some animals that did not participate in experiments on sexual behavior were used for testing some doses of flupenthixol in escape tests.

Immediately after the escape test, a righting reflex test was performed. The animal was turned on its back, and released one meter above a thick rubber foam mattress. The righting reflex was considered adequate if the animal landed on all four paws.

Design

Two groups of intact animals were used. One (n = 12) was treated with amphetamine, 0, 1, 2, and 4 mg/kg, according to a Latin square design. A second group of 10 animals was given flupenthixol, 0, 1, and 2 mg/kg.

Castrated animals were tested at two intervals after castration, 19–21 days and 27–29 days postcastration. Previous studies have shown that sexual behavior is much reduced 21 days after castration in the New Zealand White rabbit, and almost completely absent 28 days after (3). Two groups of 10 animals each were used. The first group was treated with amphetamine, 2 mg/kg, and saline, and the other with flupenthixol, 1 mg/kg, and saline. The reason for using the 1 mg/kg dose of flupenthixol was that earlier studies in the rat have shown that castrated animals are more sensitive to dopamine antagonists than intact ones (4,6). The drug treatments were counterbalanced at each of the postcastrational intervals.

Two groups of 10 animals each were castrated and later treated with TD. Sex behavior tests were started 3 weeks after beginning of hormone treatment. Again, amphetamine, 2 mg/

TABLE 1

SEXUAL BEHAVIOR IN INTACT MALE RABBITS TREATED WITH DIFFERENT DOSES OF AMPHETAMINE

	Amphetamine Dose (mg/kg)			
Behavior Parameter	0	1	2	4
Mount %	92	92	92	75
Ejaculation %	92	92	92	75
Mount latency	0.8 ± 0.24	2.3 ± 1.02	1.4 ± 0.56	0.9 ± 0.57
Ejaculation latency	1.1 ± 0.38	2.3 ± 1.03	1.4 ± 0.58	0.9 ± 0.57
Postejaculatory interval	2.8 ± 0.66	2.7 ± 0.61	3.2 ± 0.66	3.1 ± 0.49
Number of mounts	3.5 ± 0.48	3.4 ± 0.66	3.6 ± 0.63	2.5 ± 0.68
Number of ejaculations	2.5 ± 0.43	2.4 ± 0.38	2.3 ± 0.31	1.9 ± 0.43

Data are mean ± SEM. Latencies and the postejaculatory interval are expressed in min. $n = 12$.

kg, and flupenthixol, 1 mg/kg were used. Drug and saline were counterbalanced in each group.

One additional group of four animals was used for testing large doses of flupenthixol, 5 and 10 mg/kg, at several intervals after drug treatment (30, 120, and 240 min) in the escape test. Here, a Latin square design was used for drug administration.

The interval between drug treatments in the sex behavior experiments was not shorter than 48 h and not longer than 120 h. In the additional escape test experiment, an interval between drug injections of 1 week was used.

Statistical Analysis

The proportion of rabbits displaying mount and ejaculation was evaluated with Cochran's Q test or McNemar's test for the significance of changes when only two treatments were compared. Where appropriate, the binomial test was used instead of the McNemar test. The latencies were analyzed with parametric ANOVA or the *t*-test when appropriate. When post hoc tests proved necessary, the Tukey HSD test was used. Only animals that actually mounted or ejaculated were included in these analyses. The number of mounts and ejaculations was analyzed with Friedman's ANOVA or the Wilcoxon test. Because many of the castrated animals made 0 mounts and ejaculations, the distribution of the raw data was drastically skewed. Parametric tests were, therefore, not considered convenient.

The mean escape time over the three trials of each test was calculated for each subject. These means as well as righting reflex data were evaluated with parametric ANOVAs. In case of significance, Tukey's HSD test was used for a posteriori comparisons.

RESULTS

As shown in Table 1, amphetamine had no stimulatory effect on sexual behavior in intact animals. If anything, it seemed as if the largest dose, 4 mg/kg, reduced behavior. The effect was not significant, however (all $ps > 0.3$). Flupenthixol, at the largest dose, 2 mg/kg, reduced the proportion of animals displaying ejaculation, $Q(3) = 9.727$, $p < 0.05$; binomial $p = 0.016$ for flupenthixol, 2 mg/kg, compared to saline, as well as the number of ejaculations, $\chi^2(3) = 7.831$, $p < 0.05$; Wilcoxon's matched-pairs signed-ranks test showed $z = 2.366$, $p = 0.018$, for saline compared to flupenthixol, 2 mg/kg (Table 2). Lower doses were ineffective (all $ps > 0.1$).

In castrated animals, amphetamine was ineffective both at days 19–21 and 27–29 postcastration (all $ps > 0.5$) (Table 3). Flupenthixol, 1 mg/kg, significantly reduced the proportion of animals that displayed mounts (binomial $p = 0.031$) and the number of mounts was, consequently, also reduced at the first postcastrational interval (Wilxocon's matched-pairs signed-ranks test $z = 2.201$ $p = 0.028$). No significant effect on ejaculatory behavior was found, but this was due to the low initial

TABLE 2

SEXUAL BEHAVIOR IN INTACT MALE RABBITS TREATED WITH DIFFERENT DOSES OF FLUPENTIXOL

	Flupentixol Dose (mg/kg)			
Behavior Parameter	0	0.5	1	2
Mount %	70	50	40	30
Ejaculation %	70	50	30	0*
Mount latency	2.6 ± 1.45	1.0 ± 0.84	3.5 ± 1.59	2.2 ± 2.01
Ejaculation latency	3.7 ± 1.47	1.7 ± 1.42	4.6 ± 2.28	—†
Postejaculatory interval	2.1 ± 0.70	0.4 ± 0.26	0.7 ± 0.63	—†
Number of mounts	2.3 ± 0.63	1.8 ± 0.62	1.5 ± 0.69	0.8 ± 0.44
Number of ejaculations	1.8 ± 0.51	1.4 ± 0.54	0.8 ± 0.51	0*

Data are mean ± SEM. Latencies and the postejaculatory interval are expressed in min. $n = 10$.

*Different from saline, $p < 0.05$, †no data were obtained.

TABLE 3

SEXUAL BEHAVIOR IN CASTRATED MALE RABBITS TREATED WITH AMPHETAMINE, 2 MG/KG, AT TWO INTERVALS AFTER CASTRATION

	Postcastration Days 19–21		Postcastration days 27–29	
Behavior Parameter	Saline	Amphetamine	Saline	Amphetamine
Mount %	50	50	10	10
Ejaculation %	20	10	0	0
Mount latency	3.0 ± 1.77	2.8 ± 1.61	—*	—*
Ejaculation latency	0.5 ± 0.61	—*	—*	—*
Postejaculatory interval	2.6 ± 1.08	—*	—*	—*
Number of mounts	2.0 ± 0.96	2.2 ± 1.21	0.1 ± 0.12	1.1 ± 1.13
Number of ejaculations	0.6 ± 0.42	0.4 ± 0.43	0	0

Data are mean ± SEM. Latencies and the postejaculatory interval are expressed in min. $n = 10$.

*Data were obtained from 1 or 0 animals; hence, no mean was calculated.

activity of the animals. In fact, flupenthixol almost eliminated sex behavior. At the second postcastrational interval, control sexual activity was already so low that no further reduction could reach statistical significance. Data are shown in Table 4.

In castrated, testosterone-treated animals, amphetamine lacked effect (all $ps > 0.5$). However, flupenthixol, 1 mg/kg, reduced the proportion of animals that mounted (binomial $p = 0.031$) as well as the number of mounts (Wilcoxon's matched-pairs signed ranks test $z = 2.022$, $p = 0.042$). In fact, sexual behavior was completely eliminated by flupenthixol. No significant effect could be found on ejaculatory behavior, but this was again due to the low sexual activity after saline. No effect on latencies or on the postejaculatory interval could be observed because none of these parameters could be recorded in the flupenthixol treated animals (Table 5).

Amphetamine had no effect on water escape behavior (data not shown). Flupenthixol was also ineffective in the doses used in the sex behavior experiments ($F(3, 27) = 0.486$, NS (Fig. 1A). However, in the additional experiment where larger flupenthixol doses were used, a clear and long-lasting effect was obtained with 10 mg/kg. This was shown by the ANOVA, where the interaction dose × time was significant, $F(4, 12) = 4.369$, $p < 0.05$. There was no main effect of dose, $F(2, 6) = 3.594$, NS, or of time, $F(2, 6) = 2.287$, NS. Tukey's HSD test showed that the effect was present already 30 min after treatment, but had weaned off at 240 min posttreatment. Data are shown in Fig. 1B.

There was no drug effect on the righting reflex (data not shown).

DISCUSSION

Present data show that amphetamine is unable to stimulate male rabbit sexual behavior in any of the conditions used. Some of these conditions are particularly favorable for detecting stimulatory effects of drugs (castrated animals with low sexual activity). Furthermore, the doses used are similar to those reported to stimulate copulation in the rat (4,6). There is no reason to believe, then, that the lack of effect of amphetamine is due to inadequate doses. Because this drug stimulates not only dopamine but also noradrenaline release (27), it could be argued that the lack of effect is a consequence of opposing actions of these transmitters. This is unlikely, however, because studies in the rat have shown that noradrenaline does not contribute to the effects on sexual behavior observed after treatment with amphetamine (4,6,7). Furthermore, brain concentrations of amphetamine are increased after castration (12,31), and dopamine release induced by this drug is enhanced in the castrated rat (21). If these observations hold for the rabbit, then the ineffectiveness of amphetamine

TABLE 4

SEXUAL BEHAVIOR IN CASTRATED MALE RABBITS TREATED WITH FLUPENTIXOL, 1 MG/KG, AT TWO INTERVALS AFTER CASTRATION

	Postcastration Days 19–21		Postcastration days 27–29	
Behavior Parameter	Saline	Flupentixol	Saline	Flupentixol
Mount %	60	10*	20	0
Ejaculation %	20	0	0	0
Mount latency	3.6 ± 1.82	—*	5.7 ± 1.15	—†
Ejaculation latency	4.1 ± 1.11	—*	—†	—†
Postejaculatory interval	2.8 ± 1.31	—*	—†	—†
Number of mounts	1.9 ± 0.60	0.5 ± 0.50*	0.6 ± 0.42	0
Number of ejaculations	0.5 ± 0.32	0	0	0

Data are mean ± SEM. Latencies and the postejaculatory interval are expressed in min. $n = 10$.

*Different from saline, $p < 0.05$, †data were obtained from 1 or 0 animals; hence, no mean was calculated.

TABLE 5

SEXUAL BEHAVIOR IN CASTRATED MALE RABBITS GIVEN WEEKLY INJECTIONS OF TD, 3 MG/KG, AND TREATED WITH AMPHETAMINE, 2 MG/KG, OR FLUPENTIXOL, 1 MG/KG

Behavior Parameter	Saline	Amphetamine	Saline	Flupentixol
Mount %	60	60	50	0*
Ejaculation %	30	40	20	0
Mount latency	3.2 ± 1.47	2.5 ± 0.92	3.9 ± 0.71	—†
Ejaculation latency	5.9 ± 0.77	6.1 ± 2.38	4.7 ± 2.60	—†
Postejaculatory interval	—†	—†	—†	—†
Number of mounts	2.2 ± 0.77	2.7 ± 1.03	1.71 ± 0.61	0*
Number of ejaculations	0.4 ± 0.26	0.4 ± 0.18	0.3 ± 0.21	0

Data are mean ± SEM. Latencies and the postejaculatory interval are expressed in min. $n = 10$.

*Different from saline, $p < 0.05$ †data were obtained from 1 or 0 animals; hence, no mean was calculated.

in the castrated animals cannot be due to altered metabolism or to weak actions on dopaminergic systems. It is suggested that enhanced dopaminergic neurotransmission does not facilitate sexual behavior in the rabbit. This does not exclude, obviously, that amphetamine might be effective in situations specifically designed to evaluate the appetitive aspects of sexual behavior. However, whereas instrumental responses reinforced by access to a receptive female are more sensitive to dopaminergic blockade than actual copulatory behavior, the contrary seems to be the case after stimulation of dopaminergic activity with amphetamine (19).

The reasons for the different effect of amphetamine in rats and rabbits are not known, but some speculations can be made. In the rat, dopamine release in the nucleus accumbens and in the preoptic area is activated by sexually relevant stimuli, such as the sight or smell of a receptive female (18,24,28). The amount of release activated by such stimuli appears to determine whether the male engages in sexual activity or not, at least in castrated or inexperienced animals (23,43). In the rabbit, it is not known whether sexual activity stimulates dopamine release and if such release is a determinant of sex behavior. Present data suggest that this is not the case, but only studies of in vivo dopamine release could provide definitive evidence.

The dopamine antagonist *cis*(Z)-flupenthixol is different from most currently used antagonists in the way that it has almost equal affinity for the dopamine D_1 and D_2 receptors (25). Like most neuroleptics, this drug is also an antagonist at noradrenaline α_1 receptors (25). It seems, however, that this latter effect does not contribute to the drug's actions on sex behavior (4,6,7). Flupenthixol reduced sexual behavior in intact and castrated rabbits at a dose of 2 and 1 mg/kg, respectively. These doses had no effect in the escape test, suggesting that possible motor effects or a generalized lack of motivation to engage in any behavior were not the cause of the reduced sex behavior. Indeed, a dose of 10 mg/kg was necessary to produce effects in the escape test. It seems, then, that blockade of dopaminergic receptors disrupts sexual behavior in the absence of gross motor effects. This indicates that dopamine, in some way or another, is necessary for the activation of sexual behavior. The basic effect obtained with flupenthixol was reduced mount and ejaculation percentage. Because fewer animals copulated, the number of mounts and ejaculations was also reduced. There was no effect on laten-

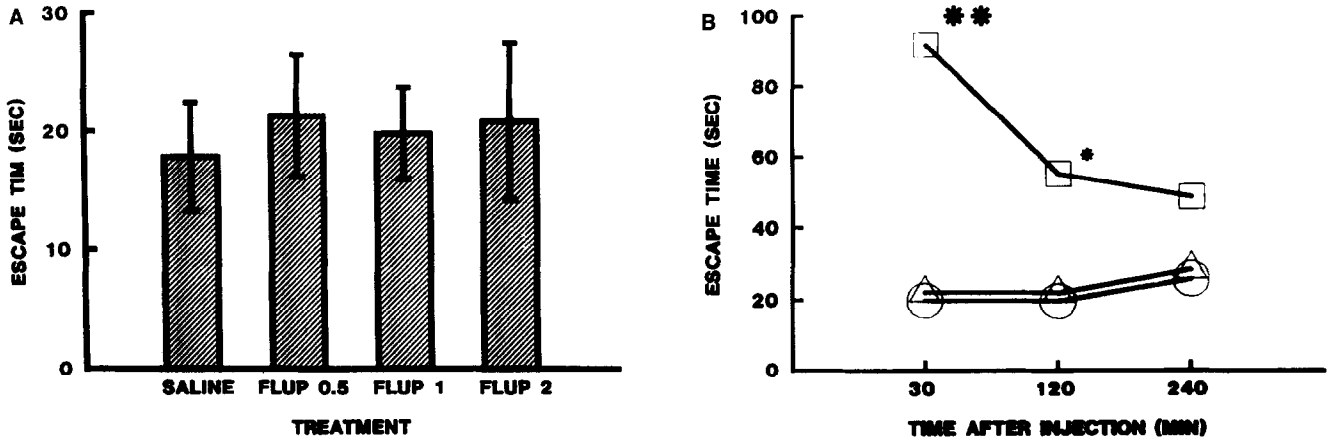

FIG. 1. Escape time in male rabbits treated with flupenthixol at a test performed immediately after the sex behavior test ($n = 10$) (A) and in an additional group of animals that were treated with larger doses of the drug than those that were used in tests for sexual behavior ($n = 4$) (B). Data are mean ± SEM. FLUP, flupenthixol. Dose in mg/kg: ○, saline; △, flupenthixol, 5 mg/kg; □, flupenthixol, 10 mg/kg. *Different from saline, $p < 0.05$; **$p < 0.01$.

cies. Thus, the drug reduced the likelihood that an animal would engage in copulation in an all-or-none way. A similar effect of dopamine antagonists is observed in male rats without sexual experience (6). The most parsimonious explanation for this is that dopamine has a permissive role in the control of sexual behavior. Some level of activation is necessary for the behavior to occur, but if this level is reached dopamine has no further influence. The results obtained with amphetamine suggest that an endogenous, physiological release always is above this limit. If not, amphetamine would have facilitated the behavior.

The castrated animals were more sensitive to the actions of flupenthixol than the intact ones. This could suggest hypersensitive dopamine receptors. In fact, castration has been reported to reduce dopamine concentrations and release in some brain structures and to increase them in others (11,32). This might produce hypersensitive receptors at some brain sites. However, there is no evidence showing that responses to neuroleptics are enhanced in castrated animals. It is more likely that the reduced sexual motivation found after castration (26) renders the animals more sensitive to the disruptive effects of dopamine receptor blockade.

Dopamine antagonists induce penile erection in rabbits (33). It is not likely, therefore, that the inhibition of sexual behavior observed after treatment with flupenthixol is a consequence of erectile dysfunction. In fact, treatments interfering with penile function have quite different behavioral effects (2).

Present data show both similarities and differences between the rabbit and other species. Dopamine antagonism have effects similar to those reported in the rat and human. One important difference with regard to the rat is that flupenthixol, in the rabbit, reduced sexual behavior in a dose much lower than the one required for producing gross motor deficiencies or amotivation. In the intact rat, only doses that much reduce ambulatory activity and induce loss of motor coordination are effective (4,5). It appears, though, that dopamine antagonism has basically the same effect on sexual behavior in all species so far studied.

The absence of effect of dopaminergic stimulation in the rabbit, even in castrated males, constitutes an apparent difference from the rat. However, it must be remembered that the actions of dopaminergic stimulants, in the intact rat and in the primate, are quite variable between studies and experimental procedures (see the introductory paragraphs). At best, it could be considered that facilitated dopaminergic neurotransmission has a stimulatory effect in some conditions. This effect is absent in the rabbit. This suggests that the consequences of dopaminergic stimulation depend not only on the experimental situation but also on the species studied.

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