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Effects of Four Beta-Adrenergic Receptor Antagonists on Male Rat Sexual Behavior

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SMITH, E. R., J. MAURICE, R. RICHARDSON, T. WALTER AND J. M. DAVIDSON. *Effects of four beta-adrenergic receptor antagonists on male rat sexual behavior*. PHARMACOL BIOCHEM BEHAV **36**(4) 713–717, 1990.—Antihypertensive medication has been reported to cause serious sexual side effects in men. Frequently mentioned as causing sexual dysfunction are beta-adrenergic receptor antagonists. The purpose of this study was to examine in detail the effects of beta blockers on adult male rat sexual behavior. Thirty minutes following a single subcutaneous injection of propranolol, pindolol, atenolol or labetalol, mating tests were conducted. The mixed $beta_1$- and $beta_2$-adrenergic antagonists, propranolol and pindolol, profoundly inhibited male sexual behavior. At the 5 and 10 mg/kg doses, propranolol inhibited ejaculatory behavior to the extent that only 9.1 and 8.3% respectively showed the behavior while pindolol reduced this behavior to 36.4% (16 mg/kg). These drugs also adversely affected various parameters of behavior in a dose-dependent manner. The selective $beta_1$ antagonist, atenolol, had only minor effects and labetalol even less so at the doses tested. It was suggested that the strongly inhibitory effects of propranolol and pindolol on male rat sex behavior may well be due to their $5\text{-}HT_{1A}$ antagonistic binding properties rather than their beta-antagonistic properties.

Beta-adrenergic antagonists Propranolol Pindolol Atenolol Labetalol Sexual behavior
Ejaculatory behavior $5\text{-}HT_{1A}$-antagonists Sexual dysfunction Impotence and antihypertensives

REPORTS of sexual dysfunction resulting from antihypertensive drugs are common (4,5), though controlled studies are still very sparse (6,7). Of the various types of medication, major culprits appear to be the beta-adrenergic receptor blockers. Virtually no systematic investigations have been performed in animals, although Ahlenius and Larsson (2) have recently reported that pindolol blocks the stimulatory effect of 8-OH-DPAT on sexual behavior in male rats, even though they found no effect of pindolol alone.

The present experiments were designed to determine if a variety of beta-adrenergic receptor blockers had any significant effect on the sexual behavior of normal male rats, when administered via a single subcutaneous injection. The following beta blockers were selected for investigation: (±)propranolol, a mixed $beta_1$- and $beta_2$-adrenergic antagonist; (±)pindolol, a mixed $beta_1$- and $beta_2$-adrenergic antagonist; (±)atenolol, a selective $beta_1$-adrenergic antagonist which is hydrophilic (17), and (±)labetalol, a mixed alpha- and beta-adrenergic antagonist with other binding properties, which has been investigated in human male sexual behavior (13).

METHOD

Animals

Adult male Long-Evans rats were obtained as naive animals (Simonsen Labs., Gilroy, CA), housed 3–4 per cage, provided food and water ad lib and maintained in an air-conditioned, light-controlled room with a reversed 14:10 light/dark cycle (lights off 1100 hr, lights on 2100 hr). All animals received preexperimental mating behavior tests to provide sexual experience, and those animals included in the studies showed the complete mating behavior sequence on at least four tests prior to experimentation.

Drugs

(±)Atenolol, (±)propranolol hydrochloride and (±)pindolol were obtained commercially (Sigma, St. Louis, MO). (±)Labetalol hydrochloride was kindly supplied by GLAXO Group Research (Greenford, Middx., England). Immediately prior to testing, drugs were dissolved in normal saline; all were injected subcutaneously.

Stimulus females used in mating behavior tests were rendered receptive and proceptive via SC injections of 150 μg estradiol benzoate 48 hr before and 750 μg progesterone 4–6 hr before testing (both in 0.15 ml sesame oil).

Mating Behavior Test

Males were placed in the observation cages a minimum of 3–5 min before a receptive/proceptive female was introduced and observations began. The male was allowed to mate until the beginning of the second copulatory series, or for 15 min if no intromission occurred or for 30 min after the first intromission if no ejaculatory behavior was displayed.

The following parameters were recorded: mount latency (ML), the time from onset of the test to the first mount with or without penile insertion; intromission latency (IL), the time from the

introduction of the female to the first intromission; ejaculation latency (EL), time from the first intromission to ejaculatory behavior; postejaculatory interval (PEI), time from ejaculatory behavior to the first intromission of the second copulatory series; mount frequency (MF), the number of mounts prior to ejaculatory behavior; intromission frequency (IF), the number of intromissions before ejaculatory behavior; copulatory efficiency (CE), the number of intromissions divided by the total number of mounts with and without penile insertion; and intercopulatory interval (ICI), the average time between intromissions (ICI = EL/IF + 1), or if no ejaculatory behavior occurred, ICI = 30/IF. If the male failed to intromit by seven minutes, the female was rapidly replaced by another without restarting the time clock. Testing was performed in the lights off period.

Experimental Design

The basic design for all drug studies was crossover with each animal serving as its own control. During week 1, half the animals received drug and half vehicle; in week 2 all rats were tested without treatment; and during week 3, those animals that had received drug during week 1 were injected with vehicle and those that had received vehicle in week 1 were administered drug.

Males were sexually experienced and divided into groups balanced for behavioral parameters. Doses of drugs tested were as follows: propranolol, 2.5 (n = 12), 5 (n = 12) and 10 mg/kg body weight (n = 12); pindolol, 2 (n = 12), 4 (n = 12), 8 (n = 9) and 16 mg/kg (n = 11); atenolol, 3 (n = 10), 6 (n = 11), 12 (n = 12) and 18 mg/kg (n = 12); and labetalol, 2 (n = 13), 4 (n = 13), 8 (n = 12) and 16 mg/kg (n = 12). Mating behavior tests were begun 30 min postinjection. The males used in the pindolol experiment were the same as those used in the labetalol study after a rest of four weeks and with the groups being balanced for behavior parameters and prior drug treatment

Statistics

Data were analyzed nonparametrically (16); Fisher's exact probability test was used for percentage data, Wilcoxon matched-pairs for the behavioral parameters and Kruskal-Wallis followed by the Mann-Whitney test for dose-response data. Before exploring dose-response effects, the vehicle values were analyzed for variance by the Kruskal-Wallis test. If no significant effects were found, the drug values were further analyzed. Behavioral parameters evaluated were from animals positive for the behavior with the following exceptions: For ML, if a male did not mount or intromit, it was assigned the maximum latency of 15 min for ML and no other measures were included from this animal. For IL, if a male mounted but did not intromit, it was assigned the maximum latency of 15 min for IL only, and for EL, if a male intromitted but did not show ejaculatory behavior, it was assigned the maximum latency of 30 min for EL only.

RESULTS

Administration of a single subcutaneous injection of two of the four beta-adrenergic receptor antagonists markedly inhibited the numbers of animals displaying ejaculatory behavior (Fig. 1). Propranolol at the 5 and 10 mg/kg doses significantly ($p<0.01$) reduced the percent of rats ejaculating as did pindolol at the 16 mg/kg dose ($p<0.005$) when compared to the vehicle control. In contrast, atenolol and labetalol did not show this effect.

For propranolol and pindolol, percentages of animals intromitting and mounting were not significantly affected except in the case of the highest dose of pindolol, i.e., 16 mg/kg (Fig. 2). No

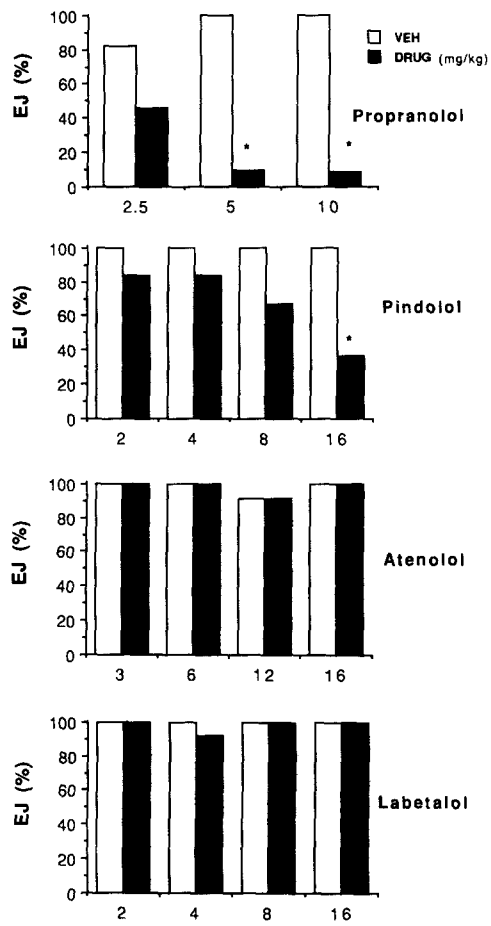

FIG. 1. The effects of four beta-adrenergic receptor blockers on the percentage of rats displaying ejaculatory behavior (EJ); *$p<0.01$.

such effects were seen with atenolol and labetalol. For these beta blockers, 100% of the animals mounted and intromitted at every dose (data not displayed) except for the 4 mg/kg labetalol dose when 12/13 (92.3%) rats intromitted.

Data for the behavioral parameters are presented in Tables 1–4. For propranolol (Table 1), ejaculatory behavior latency (EL) was significantly increased while copulatory efficiency (CE) was significantly decreased at all doses tested. The postejaculatory interval (PEI) was also significantly increased at the 2.5 mg/kg dose; study of effects of higher doses was precluded due to disintegration of the behavior. At the 2.5 mg/kg dose, intromission frequency (IF) showed a strong tendency to increase ($p = 0.068$). When intromission frequency for those animals which intromitted without showing ejaculatory behavior in 30 min were included in this "modified" IF determination, then 2.5 mg/kg propranolol significantly increased this measure (Wilcoxon matched-pairs, $p = 0.028$), medians: vehicle = 6.0, 2.5 mg = 9.5, No. of rats = 10. Intercopulatory interval (ICI) showed a significant relationship (Fig. 3) with increasing doses [Kruskal-Wallis: vehicle ($p = 0.352$); propranolol ($p = 0.039$)].

Generally, similar results were obtained with pindolol (Table 2). In this instance, moreover, mount latency (ML), intromission latency (IL) and mount frequency (MF) were also significantly increased. Dose-response relationships were found for ML [Kruskal-Wallis: vehicle ($p = 0.242$); pindolol ($p = 0.005$)], EL

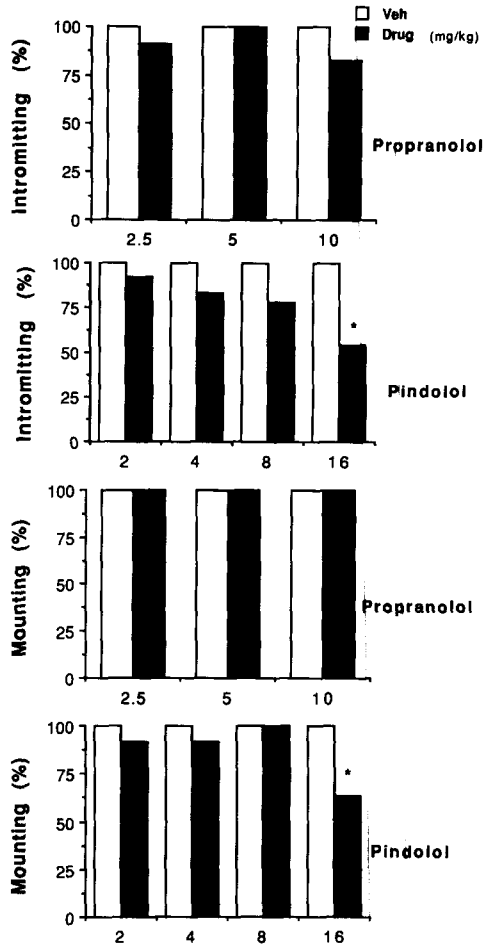

FIG. 2. Effects of (±)propranolol and (±)pindolol on the percentage of animals mounting and intromitting; *$p<0.025$.

[Kruskal-Wallis: vehicle ($p=0.529$); pindolol ($p=0.007$)], ICI [Kruskal-Wallis: vehicle ($p=0.444$); pindolol ($p=0.002$)] and CE [Kruskal-Wallis: vehicle ($p=0.848$); pindolol ($p=0.031$)]. These relationships are illustrated in Fig. 4.

The effects of atenolol and labetalol on the parameters of mating behavior are presented in Tables 3 and 4. Drug effects were minimal. At the lowest dose tested (3 mg/kg), atenolol caused a relatively small though significant increase in EL and ICI and a decrease in CE. At the 6 mg/kg dose, there was a significant decrease in IL and a significant increase in IF. However, these results may be misleading since the vehicle values at the 6 mg dose were markedly different from all the other control values for these parameters [i.e., Vehicle-IL (6 mg) = 0.95 vs. 0.11, 0.19, 0.19, 0.19 for the other doses]. Labetalol showed virtually no effect except for a slight increase in ML and a somewhat larger one in IL at the 8 mg/kg dose.

DISCUSSION

The mixed $beta_1$- and $beta_2$-adrenergic receptor antagonists, propranolol and pindolol, profoundly inhibit the display of male sexual behavior in rats following an acute subcutaneous injection of these agents. This applies to the percentage of animals showing ejaculatory behavior as well as to a variety of behavioral parameters. Ejaculatory behavior latency (EL), intercopulatory interval (ICI) and copulatory efficiency (CE) showed major deterioration from both drugs. These parameters were altered in a dose-dependent manner for pindolol and to some extent for propranolol. The low dose of propranolol also significantly increased intromission frequency. Likely, more significant inhibitory behavior would have appeared in propranolol- and pindolol-treated rats were it not for the complete failure of ejaculatory behavior and intromission with these drugs.

TABLE 1

EFFECTS OF PROPRANOLOL (mg/kg) ON THE PARAMETERS OF MATING BEHAVIOR† IN MALE RATS (MEDIANS)

Dose	ML (min)	IL (min)	EL (min)	CE (min)	PEI (min)	IF	MF
Veh	0.05	0.10	9.50	0.70	5.40	6	2
2.5	0.10	0.23	23.90*	0.34*	6.45*	10	12
N	(11)	(11)	(9)	(11)	(5)	(5)	(5)
Veh	0.05	0.10	11.40	0.57	ISD	ISD	ISD
5.0	0.10	0.25	30.0*	0.38*	ISD	ISD	ISD
N	(11)	(11)	(11)	(11)	(1)	(1)	(1)
Veh	0.05	0.13	9.83	0.48	ISD	ISD	ISD
10.0	0.16	0.26	30.0*	0.27*	ISD	ISD	ISD
N	(12)	(12)	(10)	(12)	(1)	(1)	(1)

*$p<0.05$, Wilcoxon matched-pairs test in this and subsequent tables.

†Assigned maximum latencies: if no mounting, assigned 15 min ML only; if mounting but no intromission, assigned 15 min IL only; if intromitting but no ejaculatory behavior, assigned 30 min EL only in this and subsequent tables.

ISD = insufficient data.

The inhibitory behavioral changes resulting from propranolol and pindolol are the inverse of the stimulatory effects of 5-HT_{1A} receptor agonists on male rat mating behavior (3, 9–11, 15). This converse relationship is displayed in the agonist-induced decrease in EL and ICI and an increase in CE. An apparently ubiquitous effect of 5-HT_{1A} drugs is reduction of the ejaculatory threshold, as represented by reduced IF (3, 8–11, 15). Propranolol and pindolol tended to increase IF, but so many animals failed to ejaculate at the most effective doses that either this measure could not be calculated, or there were too few animals represented.

Recently, Ahlenius and Larsson (2) reported that (±)pindolol (4 mg/kg) blocked the facilitation of male rat sex behavior induced by the prototypical 5-HT_{1A} agonist, 8-OH-DPAT. These authors, however, did not find any significant effect of the racemic mixture

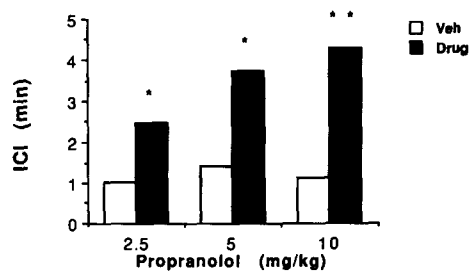

FIG. 3. Dose-response relationship of propranolol's effect on the intercopulatory interval (ICI); *$p<0.005$ compared to vehicle; **$p<0.005$ compared to vehicle; and $p<0.018$ compared to the 2.5 mg/kg dose, Mann-Whitney test.

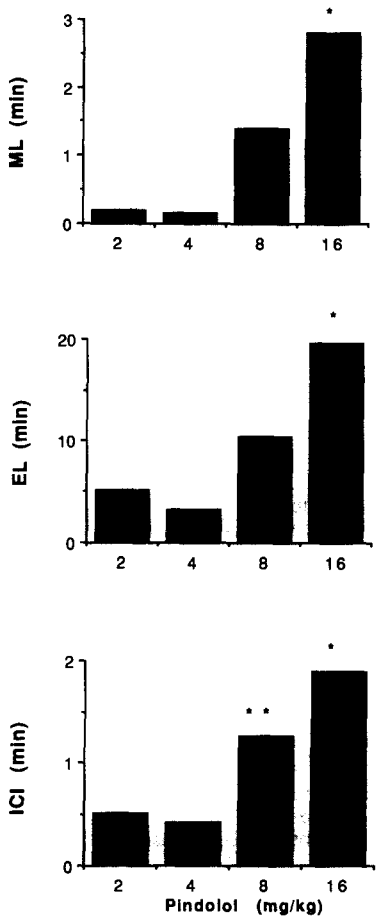

FIG. 4. Dose-response relationships of pindolol's effects on various parameters of rat male behavior; ML (mount latency, $*p=0.0026$ 16 mg vs. 2 mg, $p=0.0031$ vs. 4 mg and $p=0.0874$ vs. 8 mg); EL (ejaculatory behavior, $*p=0.0307$ 16 mg vs. 2 mg, $p=0.0014$ vs. 4 mg and $p=0.0637$ vs. 8 mg); ICI (intercopulatory interval; $*p=0.0067$ 16 mg vs. 2 mg and $p=0.0011$ vs.4 mg; $*p=0.0112$ 8 mg vs. 4 mg and $p=0.0774$ vs.2 mg) and CE (copulatory efficiency, $*p=0.0038$ vs. 4 mg), Mann-Whitney test.

of pindolol alone (2–8 mg/kg) on male sex behavior. They had previously reported unpublished observations in a book chapter (1) that (−)pindolol and (−)alprenolol caused inhibitory effects on male sex behavior as well as antagonizing 8-OH-DPAT-induced stimulatory effects. A possible explanation for the difference in comparing their published report and our present findings may be that they used an intraperitoneal route of drug administration while we used a subcutaneous one, and many beta blockers are known to undergo strong first-pass effects. Interestingly, they administered the (−)isomer of pindolol subcutaneously. Nevertheless, the fact that (±)pindolol did antagonize the stimulatory effect of 8-OH-DPAT on male sex behavior suggests that it may well be the 5-HT_{1A} antagonistic binding properties of pindolol and propranolol that are responsible for most if not all of the inhibitory effects on male sexual behavior observed in the present studies. Both pindolol and propranolol have been shown to bind significantly to the 5-HT_{1A} receptor (12).

That there was very little effect of the selective $beta_1$-adrenergic receptor antagonist, atenolol, on male sexual behavior may be due to one or more factors. First, this drug is sufficiently hydrophilic to be blocked by the blood-brain barrier; mating

TABLE 2

EFFECTS OF PINDOLOL (mg/kg) ON THE PARAMETERS OF MATING BEHAVIOR‡ IN MALE RATS (MEDIANS)

Dose	ML (min)	IL (min)	EL (min)	PEI (min)	ICI (min)	CE	IF	MF
Veh	0.18	0.15	4.00	5.50	0.46	0.75	7	2
2.0	0.20	0.30	5.20*	6.10	0.52	0.52	10	6.5†
N	(12)	(11)	(11)	(10)	(11)	(11)	(10)	(10)
Veh	0.10	0.20	3.00	5.20	0.38	0.82	6	3
4.0	0.15	0.20	3.28	6.15	0.42	0.80	7.5	2
N	(12)	(11)	(10)	(10)	(10)	(11)	(10)	(10)
Veh	0.10	0.20	4.5	5.55	0.45	0.70	7	1.5
8.0	1.40*	3.35*	10.4	6.58	1.26*	0.38*	6	10.5
N	(9)	(9)	(7)	(6)	(7)	(9)	(6)	(6)
Veh	0.20	0.25	2.55	5.25	0.31	0.83	8	1.5
16.0	2.80*	2.6	19.6*	7.70	1.90*	0.39*	7.5	13.0*
N	(11)	(7)	(6)	(4)	(6)	(7)	(4)	(4)

$*p<0.05$; $†p=0.051$.
‡Assigned maximum latencies.

behavior effects are most likely to be centrally mediated (14). Second, the $beta_1$ selectivity of atenolol may be responsible for its minimal effects, and atenolol does not bind to the 5-HT_{1A} receptor (S. Peroutka, personal communication). In this context, it is noteworthy that Ahlenius and Larsson (2) also found no significant effect of the selective $beta_1$-adrenergic antagonist, betaxolol (2–8 mg/kg) on male sex behavior nor did it antagonize 8-OH-DPAT's stimulatory effect.

The ineffectiveness of labetalol on male rat sexual behavior may also be due to several factors. First, our doses may have been below the effective range because of constraints due to labetalol's poor aqueous solubility. Alternatively, it may be that this drug lacks 5-HT_{1A} antagonistic binding properties. On the other hand, the $alpha_1$-adrenergic antagonist activity of labetalol (17) may

TABLE 3

EFFECTS OF ATENOLOL (mg/kg) ON THE PARAMETERS† OF MATING BEHAVIOR IN MALE RATS (MEDIANS)

Dose	ML (min)	IL (min)	EL (min)	PEI (min)	ICI (min)	CE	IF	MF
Veh	0.08	0.11	4.01	5.55	0.36	0.71	9.5	5
3.0	0.10	0.14	5.56*	5.69	0.52*	0.57*	9	8.5
N	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Veh	0.15	0.95	4.20	5.30	0.60	0.58	5	4
6.0	0.08	0.15*	3.48	5.45	0.48	0.55	8*	4
N	(11)	(11)	(11)	(11)	(11)	(11)	(11)	(11)
Veh	0.10	0.19	4.85	6.18	0.57	0.61	9	4.5
12.0	0.11	0.19	5.24	6.08	0.52	0.49	8	3
N	(12)	(12)	(12)	(10)	(12)	(12)	(10)	(10)
Veh	0.14	0.19	5.08	5.93	0.48	0.61	7.5	5.5
18.0	0.15	0.20	4.80	5.88	0.49	0.71	10	4.5
N	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

$*p<0.05$.
†Assigned maximum latencies.

TABLE 4

EFFECTS OF LABETALOL (mg/kg) ON THE PARAMETERS† OF MATING BEHAVIOR IN MALE RATS (MEDIANS)

Dose	ML (min)	IL (min)	EL (min)	PEI (min)	ICI (min)	CE	IF	MF
Veh	0.10	0.11	2.75	5.45	0.34	0.82	8	2
2.0	0.10	0.11	2.95	5.75	0.31	0.80	8	2
N	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)
Veh	0.10	0.18	3.76	5.85	0.43	0.73	7	3
4.0	0.10	0.15	3.80	5.95	0.37	0.82	7.5	2
N	(13)	(12)	(12)	(12)	(12)	(13)	(12)	(12)
Veh	0.10	0.10	3.15	5.45	0.30	0.72	9	3.5
8.0	0.13*	0.20*	3.78	5.85	0.34	0.79	14	2.5
N	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
Veh	0.10	0.18	2.75	5.90	0.33	0.70	7.5	3
16.0	0.13	0.20	3.20	5.73	0.33	0.77	9	3.5
N	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

*$p<0.02$.

†Assigned maximum latencies.

have confounded the results.

These experiments indicate that acutely administered beta blockers can markedly affect male sexual behavior in normal rats. The ability of a particular beta-blocking drug to induce these adverse changes may reside in the drug's ability to bind to the 5-HT_{1A} receptor and have little or nothing to do with its beta-adrenergic binding properties. Nevertheless, further study is needed before this hypothesis is firmly established.

Finally, these experiments may have provided a rat model for beta blocker-induced sexual dysfunction in men. In support of this is the observation that atenolol appears to be much less deleterious to rat male sexual behavior than propranolol and other beta blockers, a condition also observed in men.

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