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The Inhibitory Effects of Propranolol on Genital Reflexes in Male Rats

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SMITH, E. R., E. J. CETRULO, J. P. DONAHUE, H. SPARROW, J. M. DAVIDSON, B. B. HOFFMAN AND J. T. CLARK. *The inhibitory effects of propranolol on genital reflexes in male rats.* PHARMACOL BIOCHEM BEHAV 52(3) 541–546, 1995.—We have previously reported that propranolol adversely affects sexual behavior in male rats. To elucidate whether the effects of propranolol might involve decrements in ability, we examined two components of sexual function ex copula—ejaculatory reflex capacity and erectile reflexes. In the first study, we examined the effects of various doses of (±)-propranolol (1.25–10 mg/kg) administered subcutaneously. Marked inhibition was observed, evidenced by increases in the latency to ex copula ejaculation and to initial erection and decrements in the number of seminal emissions and in the number of erectile reflexes. Analyses of dose-response relationships indicated that the degree of inhibition increased with increasing dose. In the second study, we evaluated the stereo-selectivity of the responses. Both (+)- and (−)-propranolol (1.25 mg/kg) significantly inhibited ejaculatory reflex potential, and although (+)- and (−)-propranolol significantly inhibited erectile reflexes, (−)-propranolol had a greater effect. The data are interpreted to indicate that a) propranolol-induced sexual dysfunction involves both motivational and ability aspects; and b) propranolol-induced inhibition of genital reflexes may be due, at least in part, to mechanisms other than β-adrenoceptor blockade.

Propranolol β-Adrenoceptor antagonists Genital reflexes Erection Ejaculation

SEXUAL function is regulated by complex interactions between neural and endocrine systems. The nature of sexuality is complex, and cannot be viewed unidimensionally. As a first step in the analysis of sexual function it is necessary to distinguish between arousal (libido) and performance (potency or ability) aspects, as formally proposed by Frank Beach in 1956 (2), and expanded by a number of investigators (3,5,6,16,21). These two aspects of sexual function are readily separable in male rats and men, and exhibit differential hormonal and neurochemical regulation (21).

Several β-adrenoceptor antagonists have been reported to cause sexual problems in men (15,25). Propranolol (Inderal) is commonly used for the treatment of hypertension and is reported to induce sexual dysfunction. We have previously reported that administration of racemic mixtures of either propranolol or pindolol was associated with a marked inhibition of mating behavior in male rats (29). In contrast, other β-adrenoceptor antagonists—atenolol and labetalol—were associated with minor, or no, adverse effects (29). Specifically, we observed an increase in the ejaculatory threshold, and a decrease in copulatory efficacy evident after (−) or (±), but not after (+)-propranolol. These observations are suggestive of possible erectile dysfunction (3,5,6,16,21). Additional support for this possibility is gained from the observed increases in ejaculation latency and intercopulatory interval after (−) and (±), but not after (+)-propranolol (30). In addition, an approximately 50% increase in the postejaculatory interval is evident after (−) and (±), but not after (+)-propranolol was observed (30). The present studies examine the effects of propranolol on genital reflexes ex copula.

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GENERAL METHOD

Adult male Long-Evans rats (Simonsen Laboratories, Gilroy, CA) arrived in the laboratory at 60 days of age. Rats were maintained four per cage under controlled light (lights on 0500–1900 h) and temperature with ad lib access to food and water, except during periods of behavioral observation.

Ex Copula Ejaculation Test

This test was similar to the one used in previously published reports (27,28). Briefly, immediately prior to testing, the penile sheath was retracted manually and the penis was visually inspected for the presence of seminal material [ejaculate (plug)]. If present, the plug was removed. Thereafter, in experimental tests, a subcutaneous (SC) injection of propranolol or vehicle was administered. The rat was then returned to the home cage. Thirty minutes after injection, behavioral testing was initiated. For testing, the rat was picked up, the penile sheath was retracted, and the penis was examined for seminal material. Following this, the penile sheath was returned to the unretracted position, and the rat was coaxed into a clear plastic cylinder. In this state, the rat was observed for 10 min, and the occurrence of (and the latency to the initial) ex copula ejaculation was monitored. Ex copula ejaculation was identified by the expulsion of seminal material, preceded by rapid testicular retractions. In cases where there was testicular retraction but no obvious seminal expulsion, verification of ejaculation was made at the end of the test when the preputial sheath was retracted and a plug was observed. The latency to the initial ex copula ejaculation and the number of occurrences was recorded.

Erectile Reflex Test

Erectile reflexes were monitored immediately following the ex copula ejaculation test. The procedure for evoking erectile reflexes and the criteria for scoring were modified from those of Davidson et al. (17). Briefly, the rat remained in the clear plastic cylinder and the penile sheath was gently retracted with a wooden applicator. The test was considered positive if the rat showed a penile erection within 20 min of sheath retraction. All penile responses that occurred within 10 min of the first erection were scored on an Esterline-Angus event recorder as follows: erection—increased tumescence of the penis, partial or complete, with subsequent detumescence; cup—a complete erection with full flaring of the distal glans penis; quick flip—a rapid dorsiflexion of the penis; and long flip—a slower, more exaggerated, dorsiflexion of the penis.

Drugs

(±)-Propranolol was obtained commercially (Sigma Chemical Co., St. Louis, MO). (+)- and (−)-Propranolol were kindly provided by Wyeth-Ayerst (Philadelphia, PA). Immediately prior to use, drugs were dissolved in physiological saline and injections were SC in a volume of 0.1 ml per 100 grams body weight.

Study 1—Effects of (±)-Propranolol on Genital Reflexes in Male Rats

Twenty-eight males that exhibited erectile reflexes in ≥ three consecutive weekly tests were used. The effects of various doses of propranolol were evaluated using a crossover design, similar to those used in earlier studies (4,8,9,11). On the basis of performance on preexperimental tests, four groups were formed, and the sequence of treatments is illustrated in Table 1. Each male received two doses of (±)-propranolol, with 3 weeks between doses. Following visual inspection of the penis, propranolol or vehicle was administered SC. Thirty minutes later the ex copula ejaculation test was conducted. Following this test, which lasted 10 min, the erectile reflex test was conducted. For analyses, data from groups 1 and 2 were combined, as were those data from groups 3 and 4. The incidence of genital reflexes was evaluated using χ^2-test for independent samples. Behavioral parameters were analyzed using nonparametric, distribution-free, statistics. Overall differences were evaluated using ANOVA (within group, Friedmans; between groups, Kruskal-Wallis) followed by individual comparisons where appropriate (within group, Wilcoxon matched-pairs signed ranks tests; between group, Mann-Whitney *U*-tests).

Study 2—Comparison of (+)- vs. (−)-Propranolol

Following three preexperimental genital reflex tests, 18 rats were randomly assigned to one of four order of treatment groups (Table 2). A crossover design was used, with each rat receiving an injection of 1.25 mg/kg (+)-propranolol, 1.25 mg/kg (−)-propranolol, and two vehicle injections, similar to previously published reports (7,10,12). Following visual inspection of the penis, propranolol or vehicle was administered SC. Thirty minutes later, the ex copula ejaculation test was conducted. Following this test, which lasted 10 min, the erectile reflex test was conducted. For analyses, data from all groups were combined. The incidence of genital reflexes was evaluated using the Cochran *Q*-test. For parameters of behavior, data for the four treatments were initially evaluated using Friedman's ANOVA followed, where appropriate, by Wilcoxon matched-pairs signed ranks tests.

RESULTS

Study 1—(±)-Propranolol Dose-Relatedly Inhibits Genital Reflexes

For each dose, (±)-propranolol was followed by a decrease in the incidence of ex copula ejaculation. Further, when data

TABLE 1

SEQUENCE OF TREATMENTS FOR EVALUATION OF THE EFFECTS OF (+)-PROPRANOLOL ON GENITAL REFLEXES

Week	Group 1 (n = 7)	Group 2 (n = 7)	Group 3 (n = 7)	Group 4 (n = 7)
1	5 mg/kg PROPR	Vehicle	2.5 mg/kg PROPR	Vehicle
2	NONE	NONE	NONE	NONE
3	Vehicle	5 mg/kg PROPR	Vehicle	2.5 mg/kg PROPR
4	NONE	NONE	NONE	NONE
5	1.25 mg/kg PROPR	Vehicle	10 mg/kg PROPR	Vehicle
6	NONE	NONE	NONE	NONE
7	Vehicle	1.25 mg/kg PROPR	Vehicle	10 mg/kg PROPR
8	NONE	NONE	NONE	NONE

PROPR = Propranolol. Injections were SC 30 min prior to ex copula ejaculation tests, which were immediately followed by erectile reflex tests.

TABLE 2

SEQUENCE OF TREATMENTS FOR COMPARATIVE EVALUATION OF THE EFFECTS OF (+)- AND (−)-PROPRANOLOL ON GENITAL REFLEXES

Week	Group 1 (n = 5)	Group 2 (n = 4)	Group 3 (n = 5)	Group 4 (n = 4)
1	1.25 mg/kg (+)-PROPR	Vehicle	1.25 mg/kg (−)-PROPR	Vehicle
2	Vehicle	1.25 mg/kg (+)-PROPR	Vehicle	1.25 mg/kg (−)-PROPR
3	1.25 mg/kg (−)-PROPR	Vehicle	1.25 mg/kg (+)-PROPR	Vehicle
4	Vehicle	1.25 mg/kg (−)-PROPR	Vehicle	1.25 mg/kg (+)-PROPR

PROPR = propranolol. Injections were SC 30 min prior to ex copula ejaculation tests, which were immediately followed by erectile reflex tests.

are compared for those rats exhibiting ex copula ejaculation on the appropriate vehicle test, decreases in the number of ejaculations and increases in the latency to the first ejaculation are evident after 2.5 and 10 mg/kg (Table 3).

(±)-Propranolol at the three highest doses was followed by a decreased incidence of erectile reflexes (Fig. 1A). In addition, there was an increase in the latency to the first erection at all doses (Fig. 1B), a decrease in the number of erections at 2.5, 5, and 10 mg/kg (Fig. 2A), and a decrease in the number of quick flips at 5 mg/kg (Fig. 2B).

In order to assess the dose-effect relationship for the various measures, additional comparisons were made between the pooled data from groups 1 and 2 vs. the pooled data from groups 3 and 4. For the latency to erection, there was no difference between 1.25 and 2.5 mg/kg, but rats treated with 10 mg/kg exhibited elongated latencies relative to 5 mg/kg treated rats. For the numbers of erections, 2.5 mg/kg was more effective than 1.25 mg/kg, and 10 mg/kg was more effective than 5 mg/kg.

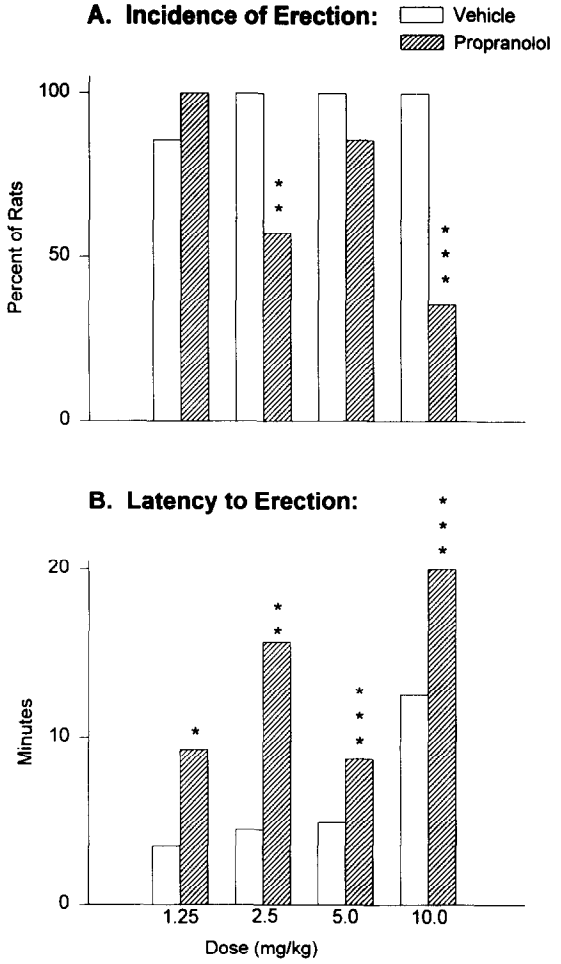

FIG. 1. (A) Propranolol decreases the number of rats showing erection in ex copula tests and (B) increases the latency to the initial erection. Tests were conducted 40 min after SC administration of propranolol or vehicle. (*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.005$).

TABLE 3

EFFECTS OF VARIOUS DOSES OF (±)-PROPRANOLOL ON EX COPULA EJACULATION

Treatment	Incidence (Percent With Ejaculation)	Number of Plugs in 10 Min	Latency to First Ex Copula Ejaculation (Min)
Vehicle	71.4	1.5	4.92
1.25 mg/kg	42.9	1.0	6.46
Vehicle	71.4	1.0	4.83
2.5 mg/kg	14.3*	0†	10.0†
Vehicle	64.3	1.0	4.0
5 mg/kg	35.7	1.0	6.0
Vehicle	50	1.0	5.25
10 mg/kg	14.3‡	0†	10.0*

Groups 1 and 2 were tested after 1.25 and 5 mg/kg, whereas groups 3 and 4 were tested after 2.5 and 10 mg/kg. Data are presented as medians, and only those rats exhibiting ejaculation in the appropriate vehicle test were included in the analyses (* = $p < 0.03$; † = $p < 0.01$; ‡ = $p < 0.05$).

Study 2—Propranolol-Induced Inhibition of Genital Reflexes is Stereo-Selective

In preexperimental tests, an unusually low incidence of ex copula ejaculation was observed. Experimental tests were administered to only the 18 most reliable responders. As in preexperimental tests, relatively few males exhibited ex copula ejaculation following vehicle injection (50% and 55.5% on the first and second vehicle tests, respectively). Treatment with either (+)- or (-)-propranolol resulted in only a slight reduction in incidence (to 33.3% and 38.9%, respectively). Data from those rats exhibiting ex copula ejaculation on the vehicle tests were evaluated further. Both isomers significantly increased the latency to ex copula ejaculation (Fig. 3), but no significant effect on the number of plugs was observed [vehicle = 1.5 vs. (+)-propranolol = 0.5; vehicle = 1.0 vs. (−)-propranolol = 1.0].

Fifteen males displayed erectile reflexes following both vehicle injections, and our analyses is limited to data from these rats. There was a decreased incidence of erectile reflexes after (−)-propranolol [relative to vehicle treatment, but not relative to (+)-propranolol; Fig. 4A]. The latency to the first erection

was increased after (+)- as well as after (−)-propranolol, and was significantly increased following (−)-propranolol when compared to (+)-propranolol (Fig. 4B). Further, both (−)- and (+)-propranolol were associated with decreases in the number of erections (Fig. 5A) and flips (Fig. 5B), but the effect was significantly greater after (−)-propranolol. Additionally, comparison of those eight males that were positive on tests with both (−)- and (+)-propranolol revealed that (−)-propranolol was associated with greater decrements in erectile reflexes, viz increased latency and decreased numbers of erections and cups, corroborating the results of the overall analyses.

DISCUSSION

The results of study 1 clearly demonstrate that acute administration of (±)-propranolol markedly inhibits ex copula ejaculation and erectile reflexes. This inhibition is dose related. This observation supports the suggestion that propranolol-induced copulatory dysfunction may involve erectile/ejaculatory as well as motivational aspects of sexual function.

The data from study 2 demonstrate some degree of stereoselectivity for propranolol-induced inhibition of genital reflexes. Because (−)-propranolol is about 100-fold better at binding to β-adrenoceptors than is (+)-propranolol (19), a greater differential would have been predicted if the effects on genital reflexes were due primarily, or solely, to β-adrenoceptor interactions. This is what is seen with respect to propranolol-induced changes in copulatory behavior (30). For ex copula ejaculation, both isomers reduced the incidence and increased the latency to ejaculation, but no differential effect was noted between the isomers. In erectile reflex tests, both isomers were associated with increased latencies to the initial erection, decreased numbers of erections/test, total erections (erections + cups), decreased numbers of quick flips/test, and decreased numbers of total flips (quick flips + long flips), but (−)-propranolol compared to (+)-propranolol was associated with an increased latency, and decreased frequencies. It should be noted that the dose of (+)- and (−)-propranolol compared were the minimum effective dose for effects on genital reflexes (study 1 and unpublished observations).

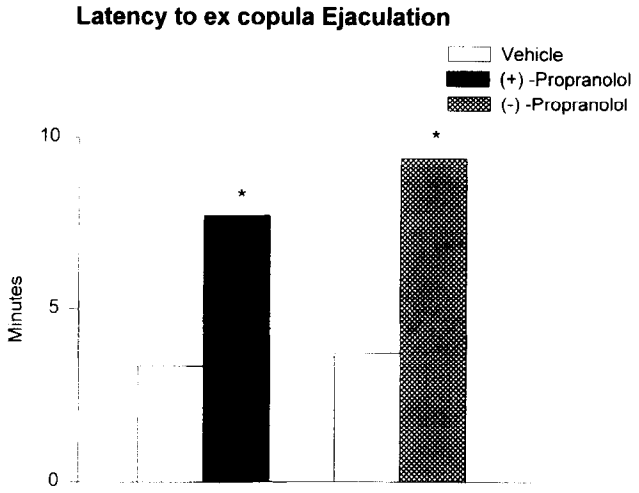

FIG. 3. (+)-Propranolol and (−)-propranolol increase the latency to ex copula ejaculation. Tests were conducted 30 min after SC administration of 1.25 mg/kg or the saline vehicle. (*$p \leq 0.05$; no difference between (+)- and (−)-propranolol).

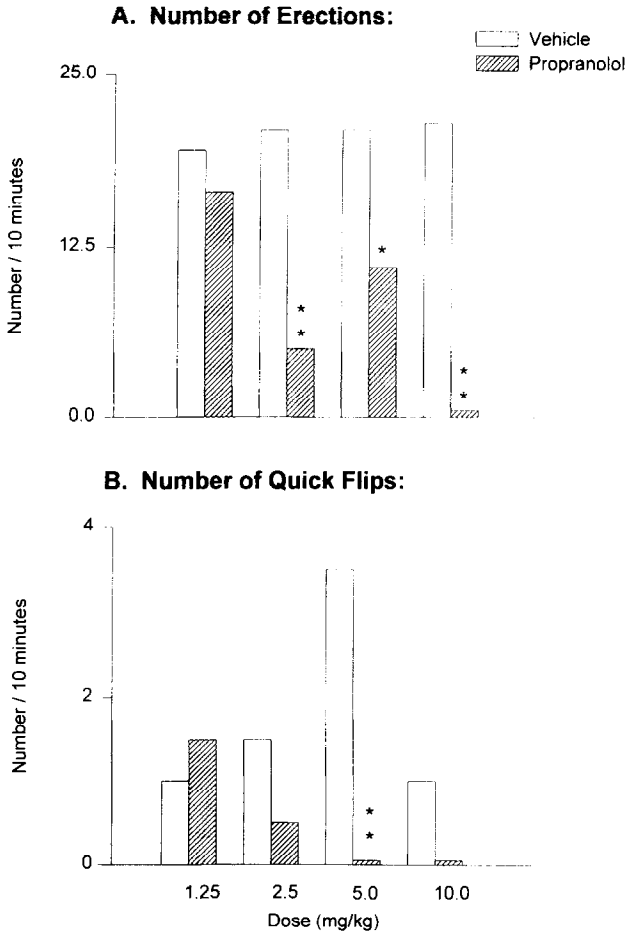

FIG. 2. Propranolol treatment is associated with a decreased number of (A) erections, and (B) quick flips per test. Tests were conducted 40 min after SC administration of propranolol or vehicle. (*$p \leq 0.01$; **$p \leq 0.005$).

Despite the greater effect of the (−)-propranolol, (+)-propranolol did modify genital reflexes. This suggests that, at least in part, the inhibitory effects of propranolol are due to some nonspecific, non-β-adrenoceptor interactions. Both isomers of propranolol have been reported to have local anesthetic properties (1) and, in common with related β-adrenoceptor blockers, to induce perturbations in lipid membranes (24). Irrespective of these caveats, the data do support a stereo-selective effect of propranolol on male sexual function. This inhibition in complex, involving aspects of sexual motivation, as well as aspects of sexual ability. For the effects on mating behavior, β-adrenoceptor and 5-HT_{1A} receptors are implicated [(30), unpublished observations].

It is interesting to note that propranolol is associated with decrements in copulatory performance, as well as decrements in ejaculatory and erectile reflexes ex copula. This is not always the case; these components are differentially modified by a number of pharmacological and steroidal treatments (5,6,16,21). Thus, RDS-127 (a mixed dopaminergic D_2 and 5-HT_{1A} agonist) is associated with a facilitation of ejaculation (both in copula and ex copula), but with decrements in erectile

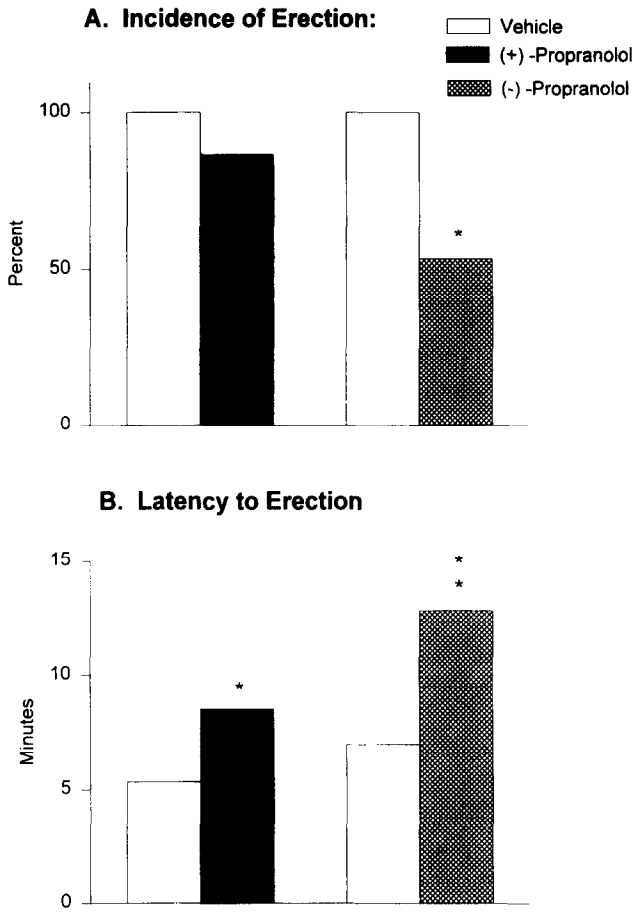

FIG. 4. (A) (−)-Propranolol, but not (+)-propranolol, treatment is followed by a decreased number of rats exhibiting erectile reflexes; (B) (+)-Propranolol and (−)-propranolol increase the latency to first erection. Erectile tests were conducted 40 min after SC administration of 1.25 mg/kg or saline vehicle. (*$p \leq 0.01$; **$p \leq 0.005$; for the latency to first erection, (−)-propranolol > (+)-propranolol, $p \leq 0.05$).

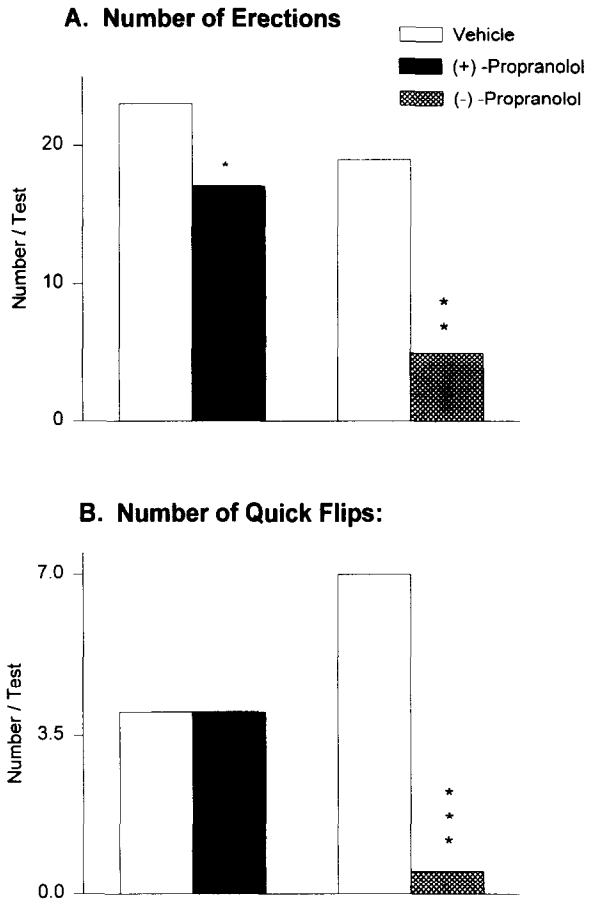

FIG. 5. (+)- and (−)-Propranolol decrease the (A) number of erections and (B) number of quick flips per test. Erectile tests were conducted 40 min after SC administration of 1.25 mg/kg or saline vehicle. (*$p \leq 0.01$; **$p \leq 0.005$; for both the number of erections and the number of quick flips; (−)-propranolol had a greater effect than (+)-propranolol, $p \leq 0.01$).

reflexes (13,14,31). In contrast, chlordiazepoxide has been reported to facilitate erectile reflexes (20).

Recent work from Sachs (26) has stressed the importance of viewing the components of sexual function in context. For example, it is well established that estradiol treatment reinstates copulatory behavior (and in copula erections) but not reflexive erections (18,23). In contrast, testosterone treatment restores mating behavior as well as genital reflexes, whereas dihydrotestosterone treatment restores genital reflexes but not mating behavior (17,21). Thus, the evaluation of sexual function must not be limited to specific contexts, and interpretation of sexual dysfunction must include componential and contextual elements.

In summary, acute SC administration of propranolol is associated with decrements in copulatory performance and in erectile and ejaculatory reflexes. Studies with stereo-isomers suggest that these inhibitory effects are due, in part, to interaction with specific β-adrenoceptors. However, the precise mechanism(s) through which propranolol induces sexual dysfunction is unclear. Propranolol also interacts with 5-HT_{1A} receptors (22). Additional experiments are needed to determine the mechanism of propranolol-induced sexual dysfunction.

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