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Propranolol-Induced Increases in Target-Biting Attack

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MATRAY-DEVOTI, J. AND G. C. WAGNER. *Propranolol-induced increases in target-biting attack.* PHARMACOL BIOCHEM BEHAV 46(4) 923–925, 1993.—The effect of a beta-adrenoreceptor blocking agent on defensive aggression in mice was evaluated. Acute doses of *d,l*-propranolol (0.2, 0.4, 0.8, 1.6, 3.2, 6.4, and 12.8 mg/kg) were administered to male Rockland-Swiss mice prior to testing in a target-biting paradigm. Baseline conditions established a high target-biting rate immediately after animals received a 2 mA tail shock, an intermediate biting rate during a 2-min intershock interval, and a low biting rate during a 15-s tone stimulus preceding the next shock. Every dose of propranolol increased target-biting rates above baseline during each interval with one exception: 0.4 mg/kg decreased the biting rate immediately after delivery of the tail shock. The overall increase in aggression observed following dosing with propranolol was not expected from a review of the clinical literature. These results are discussed in reference to propranolol's known effects on the brain serotoninergic systems and the use of an animal model of defensive aggression.

Propranolol Target biting Aggression Rockland-Swiss mice Serotonin

THE aggression-modulating properties of the beta-blocker propranolol have been widely observed and reported. Clinically, this drug's antiaggressive properties have proven useful in treating a variety of aggression-producing mental disorders in children and adults (11,16,17,20,22,28). Likewise, in animal models, propranolol's effects on both offensive and defensive aggression in rodents have been tested.

Offensive aggression has proven vulnerable to the suppressive effects of propranolol. For examle, DaVanzo et al. (5) saw that propranolol caused a linear dose-dependent decrease in reversal of aggression in CD-1 mice tested in a resident-intruder paradigm. Poli and Palermo-Neto (14) administered propranolol to 4-week isolated or amphetamine-treated mice (Swiss albino) and observed increased latency to, decreased duration of, and decreased number of attacks on an intruder mouse. Weinstock and Weiss (26) tested male mice (Sabra Hebrew University strain) after 4 weeks of isolation and found that propranolol decreased the number of attacks and increased the latency to attack. Finally, in a study by Yoshimura et al. (27), male ICR albino mice, treated with propranolol, again showed a dose-dependent decrease in aggression towards an intruder. This latter study was of interest because only the highest dose of propranolol decreased locomotion below control levels, indicating that the propranolol-induced decrease in aggression was most likely not consequent to nonspecific sedative effects of the drug.

Defensive behaviors, too, have proven sensitive to this beta-blocker's aggression-reducing effect, but these effects are more equivocal. Acute doses of propranolol have been reported to suppress shock-induced fighting in rats. Hegstrand and Eichelman (8) gave a 2 mA shock for 0.5 s presented every 7.5 s for 50 shocks to paired rats (Sprague-Dawley). Rats were injected daily with either 5 or 10 mg/kg twice each day of *d,l*-propranolol for 15 days. Shock-induced fighting was decreased significantly following the acute dose (day 1) of propranolol at both dose levels, but increased markedly above baseline and control levels after 13 days of dosing. Ray et al. (18,19) tested aggressive albino rats of either sex in a foot shock-induced fighting paradigm and found that low doses of *d,l*-propranolol potentiated, and high doses inhibited, fighting. When Swiss male mice were tested for foot shock-induced aggression after dosing with propranolol, no changes were seen compared to control levels (21) although these same doses enhanced the antiaggressive effects of benzodiazepines when given together. Finally, aggressive behavior induced, or enhanced, by various pharmacological agents has been successfully suppressed by higher doses of propranolol and other beta-blockers (9,13–15,18,21,26). Thus, although propranolol succesfully reduces aggression in humans and animals engaged in offensive behaviors, its effects on defensive behaviors may actually be biphasic, with low doses enhancing attack probability. Thus, the present study was designed to assess the

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effects of propranolol on defensive target biting over a full range of doses.

METHOD

Subjects

Subjects were 24, 60-day-old male Rockland-Swiss mice (maintained as an outbred strain in a closed colony) housed individually in a colony room with a 12 L : 12 D cycle. Mice had free access to food and water throughout the day.

Apparatus

The apparatus has been described in detail elsewhere (25). Mice were confined in an opaque, plastic cylinder (2.8 cm inner dia., 9.8 cm long). Their tails were passed through a slot at the rear of the cylinder and taped in position with Dermiclear (Johnson & Johnson) tape. The cylinder was placed in a larger outer chamber such that the leading edge of the bite target (model 278-1631 cable ties, Radio Shack) was within easy reach of the mouse. The target was attached to a model 16082 omnidirectional switch (Gerbrands). The tail was rubbed with electrode paste, and two brass bar electrodes (1.0 cm apart) were placed over the tail approximately 1.5 cm from its base. A GE 1813 session light was mounted 1.0 cm over the target. Each outer chamber was equipped with an 8-cm loudspeaker mounted 10 cm above the target.

Treatment

d,l-Propranolol (Aldrich Chemical Co., Milwaukee, WI), dissolved in 0.9% saline, was administered intraperitoneally, 30-min presession. Concentrations ranged from 0.2 to 1.28 mg/ml given in a volume of 0.1 ml/10 g to achieve doses of 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, and 12.8 mg/kg. Saline, delivered at the same volume, served as control. The various doses of propranolol or saline were administered randomly, such that animals were not dosed with drug on 2 consecutive days.

Procedure

At the same time each day (during the light cycle), 20-min target-biting sessions were conducted 5 days per week. During the first week, tail shock was not applied. Afterwards, a 2.0 mA, 0.15-s tail shock was delivered by an AC shock generator on a fixed-time, 2-min schedule. A 2,500-Hz, 70 dB tone (conditioned stimulus, CS) preceded the tail shock for 15 s, terminating with the onset of the shock. Target bites over the 2-min trial were collected in eight 15-s bins, each cumulated over the session. Programming and recording equipment were in a separate room.

RESULTS

When dosed with saline, biting rates were highest in bin 1 (32.9 ± 10.6), the 15 s immediately following application of the 2 mA shock. Bins 2 through 7, covering the next 90 s, induced an intermediate rate of target biting (23.1 ± 9.0). A tone was sounded during the final 15 s preceding the application of the next shock. Mice exhibited the lowest rate of target biting during this bin (bin 8; 8.4 ± 3.5). Nonparametric sign tests revealed that bin 1 target biting was significantly greater than bins 2–7 ($p < 0.05$) which, in turn, was significantly greater than target biting during bin 8 ($p < 0.05$).

Propranolol caused a dose-dependent increase in target-biting rates observed during bin 1, bins 2–7, and bin 8 (Fig. 1). A repeated measures ANOVA revealed a significant effect of propranolol dose, $F(7, 255) = 6.05$, $p < 0.01$, as well as bin, $F(2, 255) = 18.47$, $p < 0.01$, but no dose by bin interaction. With respect to individual bins, a repeated measures, one-way ANOVA revealed a significant effect of dose, $F(7, 85) = 2.23$, $p < 0.039$, for bin 1, but not bins 2–7 or bin 8. Finally, post hoc analysis (Fisher's LSD) of bin 1 target biting indicated significantly greater target biting following doses of 6.4 and 12.8 mg/kg as compared to baseline. For bins 2–7, post hoc analysis indicated significantly greater target biting rates following a dose of 12.8 mg/kg as compared to baseline and for bin 8, post hoc analysis indicated significantly greater target biting rates following a dose of 12.8 mg/kg as compared to baseline.

DISCUSSION

The results of this study run counter to what was expected from a perusal of the clinical literature. Rather than decreasing the aggressive response, propranolol appears to have increased shock-induced target biting. A possible biphasic response to propranolol has been hinted at in other research, where acute doses of 1 and 3 mg/kg *d,l*-propranolol potentiated, and 10 mg/kg inhibited foot shock aggression in rats (18,19). In addition, chronic dosing with propranolol also facilitated shock-induced fighting in rats (8).

Although propranolol is known to be a potent blocker of beta-adrenergic receptors, this action might not be responsible for the observed aggression enhancing effects. Doses of various beta-blocking agents, including propranolol, which were sufficient to reverse murine aggression caused upregulation of beta receptors in all or some of the following brain areas: limbic system, olfactory bulbs, hypothalamus, septum, amygdala, cortex, midbrain, cerebellum, pons and medulla (5). It is important to note, however, that labetalol, although reversing isolation-induced mouse aggression, did not produce appreciable upregulation of brain receptors. These results suggest there may be no correlation of beta blockade with the observed antiaggressive effects of these drugs.

Serotoninergic systems have been widely implicated in reg-

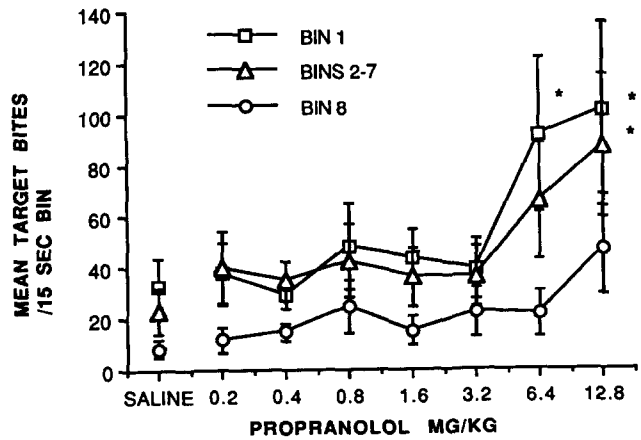

FIG. 1. Mean number of biting attacks following the administration of saline or propranolol: Bin 1 = 15 s immediately following the 2.0 mA tail shock; bins 2–7 = 90 s intershock interval; bin 8 = 15 s during a 2,500-Hz, 70-dB tone immediately prior to the next shock. Bars = standard error of mean, *$p < 0.05$ (post hoc Fisher's LSD as compared to baseline).

ulation of the aggressive response in both humans and animals (10,24), and it has been well established that propranolol acts as a serotonergic antagonist (6,7,12,23). For instance, 5-methoxy-N′,N′-dimethyltryptamine (5MEODMT) produces a characteristic serotonin syndrome that was prevented by treatment with *d,l*-propranolol (23).

In addition, the K^+-evoked release of labelled 5-HT was inhibited by *l*-, but not *d*-, propranolol in a dose-dependent fashion (12). Finally, stereoselective binding of propranolol to 5-HTIA, 5-HT_{1B} and 5-HT_{1C} sites was observed, with the *l*-isomer binding more potently than the *d*-isomer (1). Thus, the increased aggression observed in this study following propranolol may be related to its antagonistic action in the brain serotonergic system. Continued study of propranolol's effects on defensive aggressive behavors should prove helpful in determining the mechanisms of this type of aggression.

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