

Acute and Chronic Effects of Propranolol on Extinction of Rewarded Running in the Rat

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TERRY, P., N. WRAY AND P. SALMON. *Acute and chronic effects of propranolol on extinction of rewarded running in the rat.* PHARMACOL BIOCHEM BEHAV 36(2) 249-253, 1990. — Three experiments examined the effect of propranolol injected IP on a series of 16 extinction trials at 24-hour intertrial intervals after continuously rewarded running. In Experiment I, propranolol (1, 5 or 10 mg/kg) was injected, in different groups, shortly before or shortly after each extinction trial, but without effect. In Experiment II, the same doses were injected daily for 18 days preceding extinction, to allow longer for any long-term drug effect to accumulate. Propranolol (1 mg/kg) facilitated extinction. In Experiment III, a single dose (7.5 mg/kg) was injected before or after extinction trials as in Experiment I; the acute effect was to impair extinction. These results are consistent with previous findings in the Skinner box that propranolol has an acute disinhibitory effect on nonrewarded responses and a long-term inhibitory one. These effects have different dose-response relationships.

Beta-adrenoceptor Propranolol Extinction Runway Rat

THEORETICALLY, beta-adrenergic blocking drugs should be effective treatments for anxiety. First, they can reduce the sympathetically mediated physiological arousal which may underlie or exacerbate anxiety in some conditions (27). Secondly, and more controversially, certain beta-blockers which reach appreciable concentrations in the central nervous system after systemic administration might antagonize transmission in the central noradrenergic structures which, it has been argued, mediate the behavioural effects of anxiety (7,21). Nevertheless, the evidence concerning the effectiveness of beta-blockers in reducing anxiety is limited and contradictory. In studies of acute anxiety reactions, for example to public speaking or stage performances, a single administration of a beta-blocker has sometimes been reported to reduce anxiety and improve performance (2, 9, 10, 16). It is less clear, however, that beta-blockers reduce anxiety in routine treatment of longer-term anxiety disorders. Despite isolated positive reports (1, 5, 11), many studies have yielded negative results [e.g., (17,27)] and it has been argued that this family of drugs is of little value in anxiety (8,18).

The principal beta-blocking drug used in these studies has been propranolol, and one explanation for this drug's failure to show anxiolytic effects upon long-term administration has been sug-

gested by some recent studies of its behavioural effects in rats (22,23). These concerned the inhibition of responding by nonreward; this has been argued to be a model of anxiety, and disinhibition of this behaviour is a characteristic effect of anxiolytic drugs (6,7). An acute effect was to increase the rate of nonrewarded responding on a schedule of differential reinforcement of low rates of response (DRL 20 sec); on this schedule only interresponse times exceeding 20 sec are rewarded, and animals learn to reduce shorter latency responding. When propranolol was administered daily during acquisition of this schedule, however, a separate drug effect developed which opposed the acute one (i.e., suppression of short latency nonrewarded responses was facilitated), and which did not depend on the drug's presence in the body at the time of testing (i.e., it developed even when animals were drugged after each day's training). The long-term effect tended to outweigh the acute one; a similar process in people could help to account for the absence of an anxiolytic effect of long-term administration.

The acute disinhibition by propranolol of nonrewarded behaviour has been described in a further schedule in the Skinner box: successive discrimination between periods of random interval (RI 20 sec) reward and of nonreward (24). Since a disinhibitory effect

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on nonrewarded responding is characteristic of anxiolytic drugs (6), it is possible that the acute effects of propranolol in rats are related to its anxiolytic properties in man. However, the possibility cannot be excluded that some other effect of propranolol, for example on measuring out periods of time, could explain the effects on DRL and successive discrimination.

The first aim of the present series of experiments was to confirm whether both the acute and long-term effects of propranolol extend to a simpler paradigm of nonreward in which timing is not involved: the extinction of continuously rewarded running in the straight alley with a 24-hour intertrial interval. Acute and long-term effects were distinguished in the way described by Salmon and Gray (22): by comparing groups given drug either before or after each daily trial. A long-term effect is seen in the comparison of postinjected animals with saline controls.

The second aim was to begin to explore the relationship between the two effects. The simplest hypothesis is that the long-term effect reflects some adaptive change in the neurochemical system which mediates the acute one (22). We should then expect to find that the two effects show a similar dose-response relationship. We therefore examined each effect at three different doses.

In Experiment I, these were injected either before or after extinction trials. Results were unclear, and the next two experiments were attempts to create the conditions under which either the acute or the long-term effect would be seen. In Experiment II, rats were drugged after each trial only, with drug administration beginning 18 days before extinction so as to increase the opportunity for a long-term effect to accumulate. In Experiment III, we studied the highest dose of propranolol which was effective at acutely disinhibiting nonrewarded responding in recent Skinner-box experiments (26).

METHOD

Subjects

Male Sprague-Dawley rats (N=50, Experiment I; N=44, Experiment II; N=35, Experiment III), obtained from Olac Ltd. (Bicester, UK), were caged in groups of 4 (Experiment II) or 5 (Experiments I and III) and tested in the light phase of a 24-hour light/dark cycle. They were maintained on 23-hour food deprivation for 2 weeks before testing, and fed in their home cages after any behavioural testing was complete. Water was freely available in the home cages. Mean weights at the start of training were 298 g (Experiment I), 350 g (Experiment II) and 307 g (Experiment III).

Apparatus

A straight runway made of black perspex was divided into 3 sections separated by remotely operated aluminum doors: start-box (20 cm long), run section (110 cm) and goal box (20 cm). The walls were 32 cm high. A food magazine was mounted in the end wall of the goal-box. Run time was measured from the breaking of a photobeam 14 cm into the run section to the breaking of one 3.5 cm before the goal-box door. This measure is unaffected by variations in emergence time from the start-box and in tray-approach behaviour in the goal-box. For comparison, total running time was timed from the opening of the start-box door to the breaking of a photobeam immediately before the food magazine. In addition, emergence time was measured from opening the start-box door to breaking the first photobeam, and goal time between breaking the second and final photobeams. Illumination was by a 40-W bulb directed at the ceiling above the start-box. After each trial the runway was wiped with a damp cloth soaked in

a mild detergent solution. Animals were confined singly in waiting boxes before and after testing.

Behavioural Training

The training procedure was similar for each experiment. After 14 days of handling (1 min/day each), rats were familiarized with the alley over 2 days. On the first, they were placed in the runway in cage groups for 10 min; 40 × 45 mg (Noyes) reward pellets were distributed along the runway. On the second day, each rat was placed in the runway individually for 5 min, with 10 pellets spread over the goal-box floor and twenty in the food tray. Acquisition training began on the next day, at the rate of 1 trial/day. The food magazine contained twenty reward pellets. The rat was placed in the start-box, and the door opened 5 sec later. From the 5th trial the goal-box door was closed immediately after the final photobeam was broken, confining the rat for 90 sec. Training continued for 17 days in Experiment I, when running times appeared stable over successive days; this value was also adopted for Experiments II and III. Extinction followed the same procedure, except that no reward was given; the rats were simply confined in the goal-box for 60 sec. If any of the measured times (emergence, run and goal) reached 60 sec, the rat was removed to the waiting box and credited with a time of 60 sec for that and subsequent stages of the runway. If this occurred on two consecutive days, the rat was deemed to have extinguished and was credited with times of 60 sec for each stage of the runway thereafter. Extinction trials continued for 16 days.

Drug Administration

Racemic propranolol was injected IP in 1 ml isotonic saline/kg body weight. Doses refer to the HCl salt.

Experiment I. One rat failed to run consistently and was discarded. The remaining animals were allocated after acquisition training to seven groups matched for mean weight and mean running time over the final three acquisition trials. On each of these trials all rats were injected with saline 12–20 min before and 10–12 min after testing. The same intervals applied during the subsequent extinction trials, on which three drug groups received propranolol at 1, 5 or 10 mg/kg before testing and saline afterwards. Three other drug groups were injected with saline before testing and with propranolol at the same three doses afterwards. The saline control group received equivalent volumes of saline both before and after test (N=7 in all groups).

Experiment II. The rats were allocated before the start of training to 4 groups. For reasons unconnected with the experiment, four rats were eliminated early in acquisition. One group (N=11) was a saline control; the others received propranolol at doses of 1 mg/kg (N=9), 5 mg/kg (N=11) and 10 mg/kg (N=9). Injections started on the second day of runway familiarization, and were given 10–12 min after testing. There were, therefore, 18 injections before extinction began.

Experiment III. Saline injections were given 12–20 min before and 10–12 min after each of the final three acquisition trials. The rats were then allocated to three groups, matched for mean weight and running time over the previous three trials. Five rats were excluded for failing to run consistently, N=10 for all groups. One group received 7.5 mg/kg propranolol before test, and saline afterwards; another received saline before test and propranolol afterwards; the third was a saline control (as in Experiment I).

Statistical Method

Run and total times during extinction and the last 3 acquisition

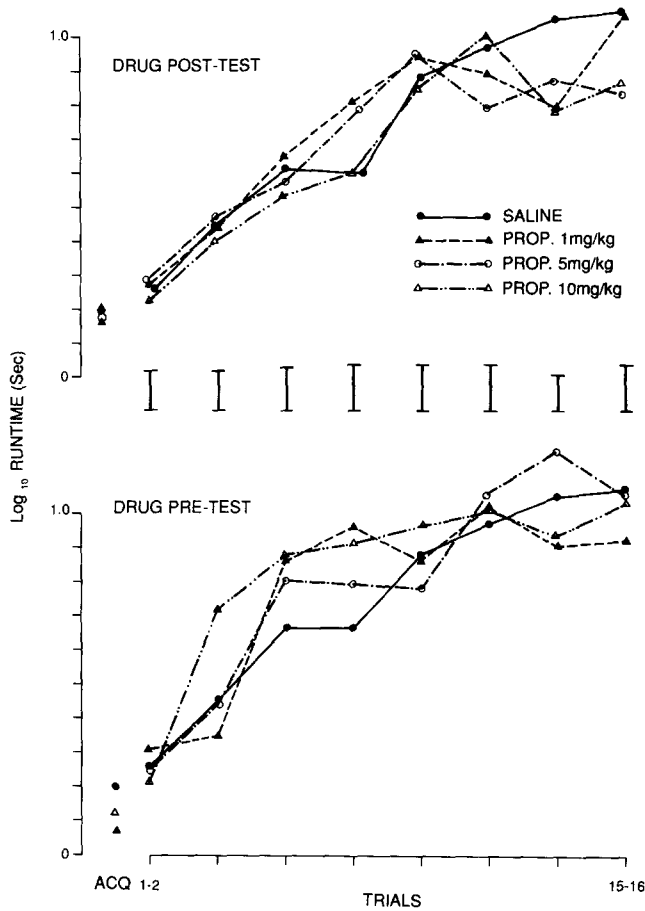


FIG. 1. Mean transformed running times on the final acquisition trial, and averaged over pairs of extinction trials, in groups injected pre- or posttrial in Experiment I. As an index of variability, bars show the pooled SEM for each pair of trials.

trials were subjected to log₁₀ transformation to normalize their distributions before analysis of variance using the GENSTAT 5 program (Rothampstead Experimental Station). Analyses included the between-subjects factor Drug, and the within-subject factor Trial. The final acquisition trial was included as the first level of this factor in the analysis of extinction. A separate analysis was carried out on the last 3 acquisition trials. A polynomial expansion for analysis of linear, quadratic and cubic trends was fitted to Trial. Trends were assessed a priori; i.e., independently of the overall term [(12), pp. 154-158].

RESULTS

In no experiment did groups differ over the final acquisition trials. Total running time revealed a similar pattern of effects to run time in every experiment; only run time is presented.

Experiment I

There was no significant overall interaction of Drug × Trial, $F(96,688) = 0.083, p > 0.10$; nor were any of the component interactions of Drug × trends of Trial significant [$F(6,688) = 1.05, 1.28$ and 0.63 for interactions with linear, quadratic and cubic terms, respectively, $ps > 0.10$]. Means are presented in Fig.

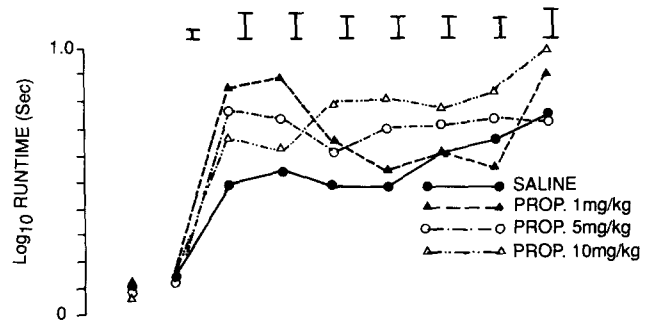


FIG. 2. Mean transformed running times on the final acquisition trial and averaged over pairs of extinction trials in groups injected posttrial in Experiment II. As an index of variability, bars show the pooled SEM for each pair of trials.

1; this confirms clearly that being drugged after training had no effect, although there is a suggestion that receiving 10 mg/kg before training might have slowed running.

Experiment II

Figure 1 shows mean Run time over successive trials. Extinction over early trials was markedly facilitated by 1 mg/kg, although running times subsequently shortened so as to return to Saline levels. This effect was confirmed by the interaction of Drug × cubic trend of Trial, $F(3,576) = 4.92, p < 0.01; t = 3.75, p < 0.001$ (Table 1). A similar pattern was present, but without statistical support, at 5 mg/kg. The effect at 1 mg/kg was significant also by comparison with the 5 or 10 mg/kg groups ($t = 3.50, t = 2.75$, respectively; $p < 0.01, p < 0.01$; Table 1).

It is clear from Fig. 1 that this facilitation of extinction in early trials was absent at the highest dose, 10 mg/kg, although running times appeared to lengthen in this group as extinction continued. This comparison of 10 mg/kg with each of the groups receiving lower doses is confirmed by the interaction of Drug × linear trend of Trial, $F(3,576) = 2.86, p < 0.05$. Linear regression coefficients were greater (reflecting shorter times initially, but longer ones later) at 10 mg/kg than at 1 or 5 mg/kg ($t = 3.00, t = 2.13$, respectively; $p < 0.01, p < 0.05$; Table 1). Although the 10 mg/kg group appeared to develop longer running times than Saline, also, as extinction continued, there was no evidence that this was a real effect; the difference in linear coefficients over Trial only approached significance ($t = 1.75; p < 0.10$).

Experiment III

Drug interacted with Trial, $F(32,430) = 1.66, p < 0.05$, and with the linear and quadratic components of Trial [linear: $F(2,430) = 7.01, p < 0.001$; quadratic: $F(2,430) = 6.70, p < 0.001$]. Figure 2 shows that, despite the predrugged rats having run more slowly at the start of extinction than did the other groups (on trial 2 the comparison with Saline just reached significance; $t = 1.96, p = 0.05$), running times subsequently declined least in these animals; only by the final trials did they approach those in Saline and postinjected animals. The resulting divergence of the predrugged group from Saline and postinjected animals during the course of extinction is confirmed in the difference of quadratic trends (respectively: $t = 2.50, p < 0.05; t = 3.50, p < 0.001$; Table 1). Postdrugged rats did not differ significantly from Saline until the final few trials when they began to run more rapidly (Drug × linear component of Trial: $t = 2.17, p < 0.05$).

TABLE 1
GROUP MEAN TREND COEFFICIENTS FOR TRIAL TERMS WHICH INTERACTED
SIGNIFICANTLY WITH DRUG

		Propranolol				
		Saline	1 mg/kg	5 mg/kg	10 mg/kg	SED
Experiment II	Linear	0.033	0.023	0.030	0.047	0.008
	Cubic	0.0007	0.0022	0.0008	0.0011	0.0004
		Propranolol				
		Saline	Pretest	Posttest	SED	
Experiment III	Linear	0.049	0.026	0.036	0.006	
	Quadratic	-0.0025	0.0010	-0.0039	0.0014	

Pooled standard errors of differences of means are derived from the analysis of variance.

DISCUSSION

Although neither pre- nor posttrial drug injections had any significant effect in Experiment I, changes in procedure revealed an effect of both treatments in the subsequent experiments. In Experiment II a longer period was allowed for a long-term drug effect to accumulate, by starting daily posttrial injections 18 days before extinction began. Under this regime, propranolol significantly facilitated extinction. The existence of a long-term effect of propranolol which facilitates inhibition of nonrewarded responses, builds up over repeated daily injections and is independent of the presence of the drug in the circulation, has been described in the acquisition of a different schedule in which animals learn to suppress nonrewarded responses [DRL (22)]. The present findings therefore suggest a general effect on nonrewarded responding.

Two features of this long-term effect are of note. First, it was greatest at the lowest dose (1 mg/kg); indeed, it lacked statistical support at higher doses (5 and 10 mg/kg). An explanation for this sensitivity to low doses is not apparent. There have, however,

been other reports that propranolol has behavioural effects at doses in this range. For example, it has been found that at doses of 0.4–1.0 mg/kg, propranolol (and its non-beta-blocking isomer, dextro-propranolol) reduced open-field activity which had been induced by injection of amphetamine or by isolated housing (29–31). Second, the facilitation was seen in the early stages of extinction; the advantage over Saline was lost once asymptotic running had been approached. Again, the explanation is not clear. One possibility is that behaviour is most vulnerable to this drug effect during the period when extinction is occurring most rapidly; alternatively, the long-term effect may weaken as drug administration continues.

Experiment I revealed no disinhibitory effect of pretrial injections. In our studies of nonrewarded responding in the Skinner box (26), we had found a unimodal dose-response relationship; disinhibition was seen at a maximum dose of 7.5 mg/kg. At 10 mg/kg, both rewarded and nonrewarded responding were suppressed. In the first of the present experiments, animals injected pretrial with this same dose appeared to run most slowly; it seemed possible that reducing the dose to 7.5 mg/kg might reveal disinhibition. Therefore, in Experiment III, 7.5 mg/kg was injected in the same design as Experiment I. The results were consistent with this analysis; preinjection of propranolol at this dose significantly retarded extinction. This was despite a lengthening of running times by comparison with Saline in the early trials [it is possible that this is a result of the change in state from acquisition training (19)]. As would be expected from the results of Experiment II, there was no facilitatory effect of postinjection on extinction at this relatively high dose.

Taken together with previous results in the Skinner box (24,26), these effects may reflect a general ability of propranolol acutely to antagonize the inhibitory effects of nonreward, although it is not clear why this property should emerge over a wider range of doses in the Skinner box than in the runway. It is possible that this effect on nonreward is part of an even more general action since similar effects, with broadly comparable dose-response functions, have been observed on responding suppressed by punishment (23,24). This would add to the resemblance between this drug's behavioural effects and those of conventional anxiolytics, and suggests that propranolol may also have anxiolytic properties. By this reasoning, however, the long-term effect suggests that this drug might also have an anxiogenic action. There are two ways in which this might become apparent clinically. One is by summing with the acute effect so that, after repeated administration, propranolol no longer has any anxiolytic effect (22). Such a mechanism could account for the frequent failure of

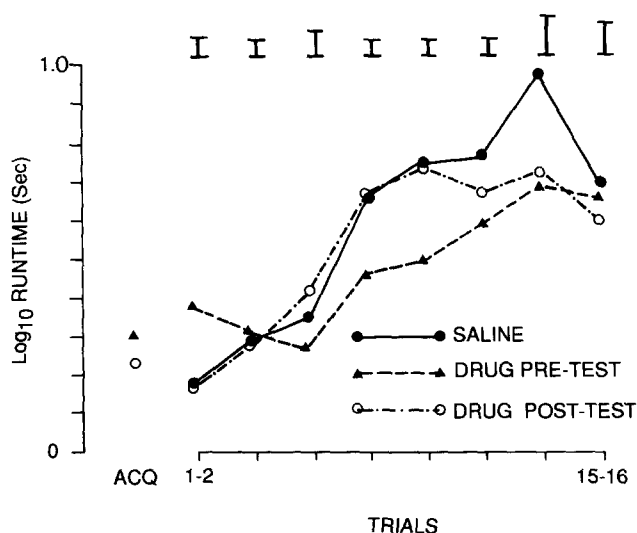


FIG. 3. Mean transformed running times on the final acquisition trial and averaged over pairs of extinction trials in groups receiving propranolol (7.5 mg/kg) or saline in Experiment III. As an index of variability, bars show the pooled SEM for each pair of trials.

propranolol to be beneficial in the long-term treatment of anxiety. Alternatively, the long-term effect could outweigh the acute one. Reports that depression and anxiety have been induced or exacerbated during propranolol treatment (13, 20, 28, 32) might reflect this process. Our results suggest that the anxiolytic-like effect of propranolol can be dissociated from the opposite long-term one. It may be possible to identify other beta-blockers which exert the short-term effect but do not share the pharmacological property which causes the long-term one.

Alternative explanations are possible. For instance, propranolol might affect memory for the nonrewarded trial. In view of evidence that it or other beta-blockers administered shortly before or after single aversive learning trials can facilitate subsequent retention (14,15), a memory-facilitating effect might explain the more rapid extinction after repeated administration at 1 mg/kg. Alternatively, since noradrenergic activation may improve retention (4), an amnesic effect of propranolol might be suggested to explain the resistance to extinction in animals drugged pretest at 7.5 mg/kg. These explanations are, however, less easily applied to the acute disinhibitory or long-term inhibitory effects of propra-

nolol on steady-state performance in the Skinner box; in the schedules studied [successive discrimination (24,25) DRL (23) or fixed interval performance (26)], drugs are injected before or after 30-minute sessions in which nonrewarded and rewarded responses are intermingled.

The pharmacological mechanism of the acute and long-term effects cannot be inferred from the present results. Nevertheless, the difference between their dose-response relationships argues against our previous hypothesis that the long-term inhibitory effect resulted from an adaptive, opponent response in the beta-adrenergic or other receptor systems which underlie the acute effect (22). Instead, it is possible that long-term treatment recruits a separate mechanism, which is not activated acutely.

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