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Effects of Propranolol, Buspirone, pCPA, Reserpine, and Chlordiazepoxide on Open-Field Behavior

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ANGRINI, M., J. C. LESLIE AND R. A. SHEPHARD. *The effects of propranolol, buspirone, pCPA, reserpine, and chlordiazepoxide on open-field behavior.* PHARMACOL BIOCHEM BEHAV **59**(2) 387–397, 1998.—The study examined the possibility that propranolol, buspirone, pCPA, and reserpine have antianxiety effects by comparing their effects with those of chlordiazepoxide on an open-field test of emotionality in rats. The effects of intraperitoneal injections of *d,l,* propranolol (5, 10, 20 mg/kg), buspirone (1.25, 2.5, 5 mg/kg), reserpine (0.5 mg/kg), parachlorophenylalanine (pCPA) (100 mg/kg), and chlordiazepoxide (CDP) (2.5, 5, 10 mg/kg) were compared with performance of rats under saline or water using an open-field test on 5 successive days. Significant effects were found on peripheral movements, rearing, grooming, immobility, and defecation. The patterns of effects of high doses of propranolol and buspirone resembled those of CDP, while pCPA had some of the effects of CDP, and reserpine produced few effects. With propranolol, buspirone, and CDP, there was evidence of dose sensitivity. The effects of repeated testing across 5 days were different from these of CDP or other drugs. The results are consistent with the hypothesis that the effects of propranolol and buspirone on open-field behavior are anxiolytic, and may be mediated by action on the same brain systems. © 1998 Elsevier Science Inc.

Open field Anxiety Chlordiazepoxide Propranolol Buspirone Parachlorophenylalanine Reserpine

ALTHOUGH propranolol has often been used to treat human clinical anxiety [(48); see (6) and (22) for reviews], studies in behavior pharmacology have produced inconclusive results as to its antianxiety effects. While propranolol has been shown to have an antianxiety effect on conditioned suppression (40), reliable effects with a conflict procedure have not always been obtained (43), and punished responding has been released by propranolol in pigeons (21) but not in rats (40). Additionally, propranolol is known to have 5-HT antagonist properties (16). Use of a neophobia procedure, and comparison with methysergide and beta-blockers lacking 5-HT antagonist activity, has suggested that 5-HT mechanisms mediate some antianxiety actions of propranolol (44).

Because of the inconsistent effects on conditioned behavior obtained in previous studies, the present study examined the effects of propranolol on unconditioned behavior in Broadhurst's open field. The open-field test has been widely used as a measure of emotionality in rodents (4,12,13), and it has also been used to study the effects of antianxiety and other classes of drugs on the behavior occurring in this novel environment (2,14,18,36). The effects were compared with those of chlordiazepoxide (CDP), as a reference anxiolytic, and with other drugs that may act through 5-HT systems. These were buspirone, reserpine, and parachlorophenylalanine (pCPA).

Buspirone is a 5-HT_{1A} partial agonist, and is widely used in the treatment of clinical anxiety (45), but has not always had antianxiety effects in behavioral pharmacology studies (37,41). There have, however, been some positive findings: buspirone increased punished responding in rats, although with an effect smaller than that of CDP (42); prolonged treatment with high doses of buspirone has anxiolytic action in the plus-maze (15,46); and 5-HT_{1A} drugs have been found to have an antianxiety effect in pigeons under a punishment procedure (8). However, other animal studies have failed to find a consistent antianxiety effect (41).

While some studies showed pCPA, a 5-HT depletor, to have some antianxiety effects (24,39), others found that pCPA had no significant effect in a conflict procedure (10). Similarly, although reserpine depletes central 5-HT, it also de-

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pletes catecholamines and it has not consistently been found to have an antianxiety effect in behavioral procedures. However, a review of early studies reported an effect on conditioned suppression (34). It was included in the present study to control for nonspecific drug effects.

Given the lack of consistency in the reported behavioral effects of propranolol, the likely involvement of 5-HT mechanisms in any of its central effects, and some inconsistency in the behavioral effects of other drugs that reduce activity of 5-HT systems, the present study sought to resolve some of the issues by comparing the effects of five drugs in one procedure. The open-field test and procedure used closely resembled that of Broadhurst (12,13). This was done to make it possible to compare the present results directly with other published studies [e.g., (9,36)]. Given the complexity of unconditioned anxiety-related behavior (26), it is unlikely that comparisons can validly be made with other so-called open-field procedures, such as those where food or water is located at the center of the apparatus [e.g., (11,47)]. Additionally, it is important to note that multiple measures and repeated sessions in the open field may be required to detect anxiety-related effects (29). A major feature of the present study, which distinguishes it from many recent studies, is that testing was continued for 5 days. This enabled us to assess whether the changes that occur in open-field behavior as animals adapt to this novel, stressful environment resemble those produced by anxiolytic agents.

METHOD

Subjects

One hundred sixty Sprague–Dawley albino male rats bred at the University of Ulster, 100–150 days old and weighing between 350–650 g at the time of testing, were used. Animals were not handled prior to testing. Water and food were available ad lib, the rats were housed in plastic cages (55 by 33 by 20 cm) in groups (4–6) in controlled room temperature (22 ± 1°C) with a 12 L:12 D cycle (with lights on from 0800h).

Drugs

Drugs were dissolved in 0.9% saline and 1% Tween (except buspirone, which was dissolved in water). Injections were given by the intraperitoneal route in a volume of 1 ml/kg of body weight. Animals received 5 daily injections of one of the following drugs: *d,l,* propranolol (5, 10, or 20 mg/kg) or saline and Tween; buspirone (1.25,2.5, or 5 mg/kg) or water; CDP (2.5, 5 or 10 mg/kg) or saline and Tween. Propranolol, buspirone and CDP injections were given 15–30 min prior to open-field testing. Reserpine (0.5 mg/kg), pCPA (100 mg/kg) injections were given for 8 days, 3 days before testing and 5 days during testing with injections occurring 15–30 min after testing. A group of 10 rats was given each drug dose, four control groups of 10 rats were given saline and one control group of 10 rats was given water. Drugs were obtained from Sigma-Aldrich Company Ltd., Poole, UK. The forms of drugs used, all expressed as salts, were *d,l,* propranolol hydrochloride, buspirone hydrochloride, CDP hydrochloride, reserpine, and *d,l*-pCPA methyl ester hydrochloride.

Apparatus and Procedure

The open field that was used is similar to Broadhurst's (12). This apparatus is a round arena with a diameter of 88 cm and a circular wall 30 cm high, situated on a wooden floor. The floor and the wall are painted white. The field consists of three concentric circles, an inner circle of 20 cm diameter, a second circle of 50 cm diameter, and the outside circle defined by the arena wall. The outer two circles are divided into roughly equal size areas by radial lines. The outside, or peripheral circle is divided into eight areas, and the second circle into four areas. A ceiling light is situated 175 cm above the arena floor, white net cloth is draped from the ceiling and dropped outside the arena wall. The level of illumination is 600 lx. A white noise generator supplies a background noise of 93 dB.

Testing was carried out between 1000 and 1500 h, with individual animals being tested at the same time each day. The open field was washed with soap and water before each animal was introduced into the apparatus. Animals were placed individually in the center of the arena and observed for 10 min. A hand counter and timer were employed to score movement (number of floor areas entered with the four paws) in the outer circle or periphery, crossing to the central area, movements in the central area (defined as for peripheral movement), rearing (number of times the animal stood on its hind legs), time spent grooming (face and head washing, body licking, scratching), immobility (a 1-min interval in which none of the other behavior categories occurred). Each of these categories was scored in each 1-min interval of the 10-min period, except for defection, which was counted at the end of the 10-min period.

Measures and Statistics

Total score for each rat was computed for the first 5-min period of the test for the following measures: peripheral movements, central movements, rearing, grooming and immobility. These scores were also computed for the second 5-min period of the test. However, activity levels were invariably lower in the second period and effects of drugs broadly resembled those occurring in the first 5-min. Consequently, those results are not reported here, nor are the crossing scores that showed few between-group differences. Other scores, including defecation over 10 min, were subjected to a drug condition × days analysis of variance using MANOVA one-way analysis of variance with repeated measures in SPSS-X. A preliminary MANOVA comparing the five saline- or water-administered groups showed that there were significant differences between them on some measures. Consequently, the results reported below compare each drug group with the saline or water group tested at the same time.

RESULTS

Figure 1 shows the effects of all drug treatments on peripheral movement scores in the open field. While reserpine had no significant effects, pCPA decreased the number of movements, $F(18, 1) = 35.83$, $p < 0.001$, and, for those drugs where three doses were administered, propranolol decreased the movements at all doses [at 5 mg/kg, $F(18, 1) = 10.21$, $p < .01$, at 10 mg/kg, $F(18, 1) = 13.3$, $p < 0.01$, and at 20 mg/kg, $F(18, 1) = 60.25$ $p < 0.001$], CDP 5 mg/kg had no effect while CDP 2.5 mg/kg, and CDP 10 mg/kg both decreased movements [at 2.5 mg/kg, $F(18, 1) = 5.76$, $p < 0.05$, and at 10 mg/kg, $F(18, 1) = 15.42$, $p < 0.001$], buspirone had no effects at the two lower doses, but it decreased movements at the highest dose, $F(18, 1) = 108.36$, $p < 0.001$. In summary, a decrease in peripheral movements occurred with pCPA and at least with the highest dose administered for propranolol, buspirone and CDP. Peripheral movements decreased across days with all drugs and doses of drugs [pCPA: $F(72, 4) = 9.72$, $p < 0.001$; reserpine:

$F(72, 4) = 8.07$, $p < 0.001$; propranolol: 5 mg/kg: $F(72, 4) = 13.75$, $p < 0.001$; 10 mg/kg: $F(72, 4) = 21.83$, $p < 0.001$; 20 mg/kg: $F(72, 4) = 9.52$, $p < 0.001$; CDP 2.5 mg/kg: $F(72, 4) = 13.95$, $p < 0.001$, 5 mg/kg: $F(72, 4) = 9.37$, $p < 0.001$; 10 mg/kg: $F(72, 4) = 12.24$, $p < 0.001$; buspirone 1.25 mg/kg: $F(72, 4) = 3.79$, $p < 0.01$; 2.5 mg/kg: $F(72, 4) = 2.54$, $p < 0.05$; 5 mg/kg: $F(72, 4) = 21.92$, $p < 0.001$]. There were no significant drug × days interactions.

Figure 2 shows the drug effects on movements in the central area of the open field. Reserpine had no significant effect while pCPA reduced movements, $F(18, 1) = 5.85$, $p < 0.05$. For those drugs where three doses were administered, CDP increased the amount of movements at the lowest dose, $F(18, 1) = 9.34$, $p < 0.01$, but not at the higher doses; buspirone had no significant effects at the two lowest doses and decreased movements at the highest dose [5 mg/kg, $F(18, 1) = 105.11$,

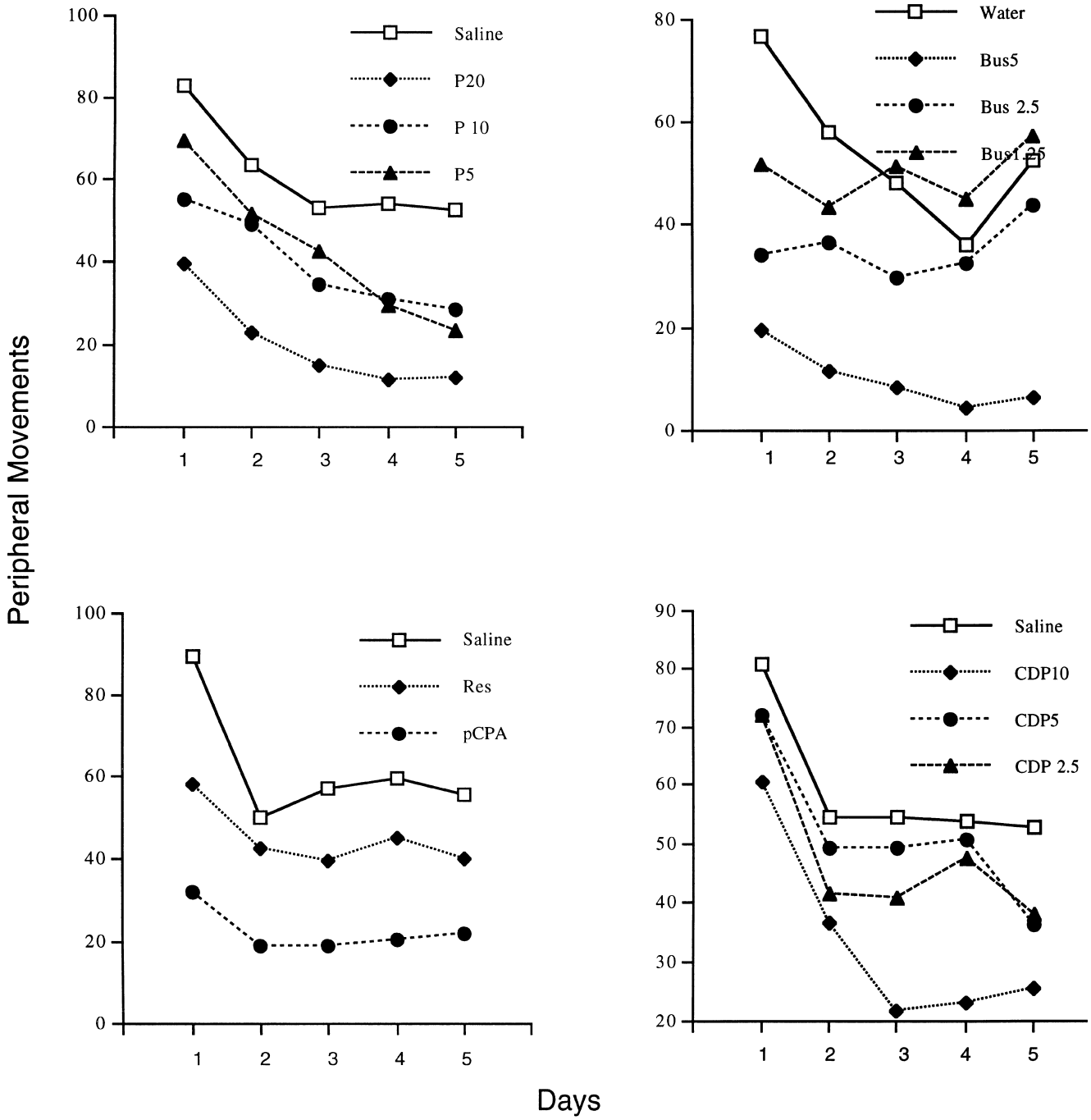

FIG. 1. Mean peripheral movements for groups of rats given saline or propranolol (20, 10, or 5 mg/kg), top left panel; water or buspirone (5.0, 2.5, or 1.25 mg/kg), top right panel; saline or pCPA (100 mg/kg) or reserpine (0.5 mg/kg), lower left panel; saline or CDP (20, 10, or 5 mg/kg), in the first 5 min of five successive test sessions.

$p < 0.001$]. Propranolol increased movements at all doses [5 mg/kg, F (18, 1) = 10.07, $p < 0.01$; 10 mg/kg F(18, 1) = 7.56, $p < 0.05$; 20 mg/kg, F(18, 1) = 9.71, $p < 0.01$). In summary, effects on this measure were variable across drugs. The central movements decreased across days with all drugs at all doses [reserpine: F(72, 4) = 5.99, $p < 0.01$; pCPA; F(72, 4) = 4.32, $p < 0.01$; propranolol 5 mg/kg, F (72, 4) = 13.59, $p < 0.001$; 20 mg/kg, F(72, 4) = 13.72, $p < 0.001$; CDP, 5 mg/kg, F(72, 4) = 3.29, $p < 0.05$; 10 mg/kg, F(72, 4) = 8.93, $p < 0.001$; buspirone 1.25 mg/kg, F(72, 4) = 3.34, $p < 0.05$; 2.5 mg/kg, F(72, 4) = 3.20, $p < 0.05$; 5 mg/kg, F(72, 4) = 108.36, $p < 0.001$]. In the case of propranolol, there was a significant interaction between

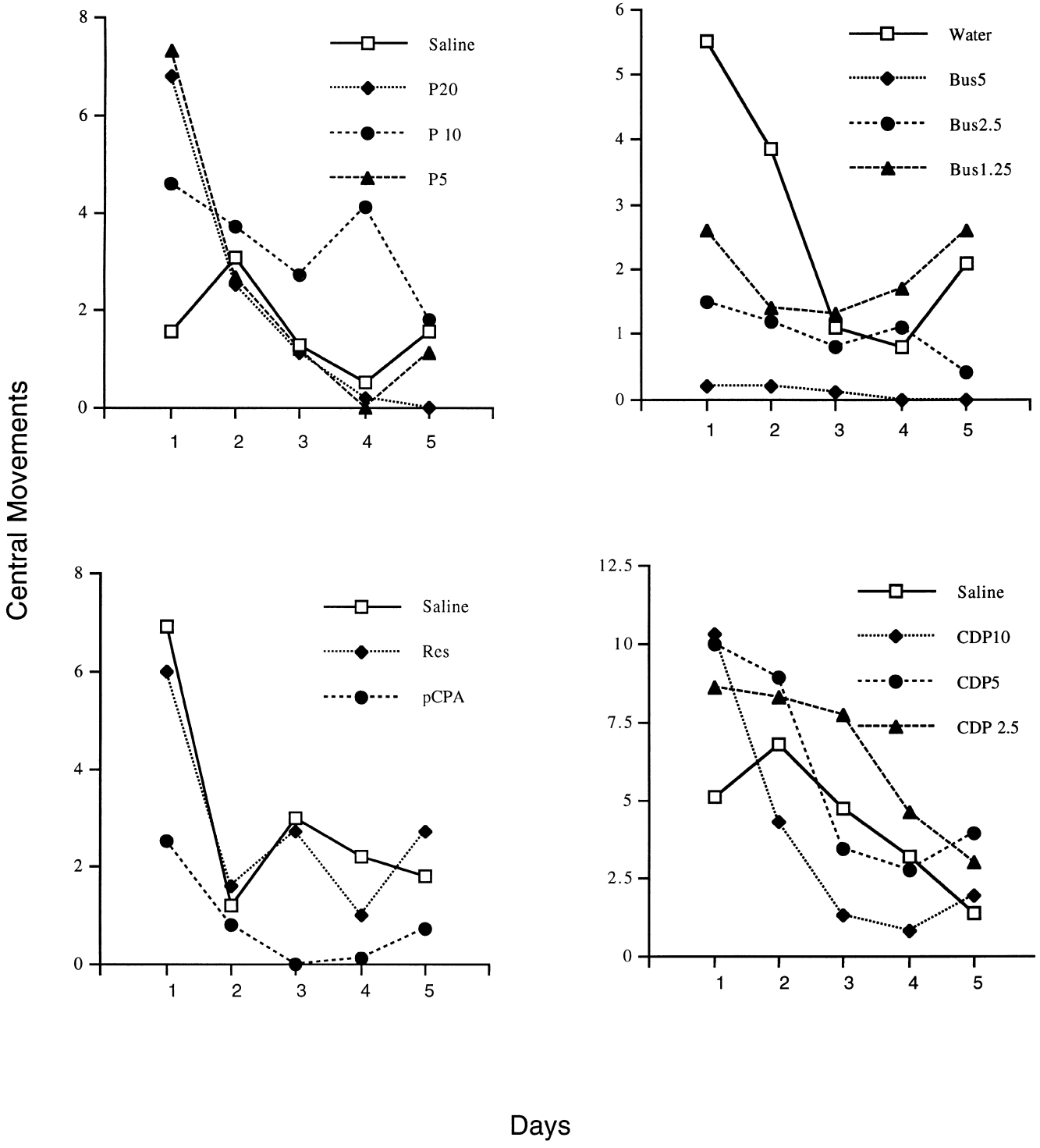

FIG. 2. Mean central movements. Details as for Fig. 1.

drug treatment and days at two doses (5 mg/kg, $F(72, 8) = 6.22$, $p < 0.001$; 20 mg/kg, $F(72,8) = 6.78$, $p < 0.001$].

Drug effects on rearing are shown in Fig. 3. Propranolol at 20 mg/kg, $F(18, 1) = 18.09$, $p < 0.001$, and buspirone at all doses [1.25 mg/kg, $F(18, 1) = 7.70$, $p < 0.05$; 2.5 mg/kg, $F(18, 1) = 12.78$, $p < 0.01$; 5 mg/kg, $F(18, 1) = 109.26$, $p < 0.001$] and CDP at 10 mg/kg, $F(18, 1) = 6.75$, $p < 0.05$] decreased rearing, while the other drugs had no significant effects. In summary, a decrease in rearing occurred with at least with the highest dose administered for propranolol, buspirone and CDP, but not with reserpine or pCPA. Rearing decreased across days with all drug treatments except pCPA [reserpine, $F(72,4) = 9.95$, $p < 0.001$; propranolol 5 mg/kg, $F(72, 4) = 18.45$, $p < 0.001$; 10 mg/kg, $F(72, 4) = 5.91$, $p < 0.01$; 20 mg/kg, $F(72, 4) = 16.99$, $p < 0.001$; CDP 2.5 mg/kg, $F(72, 4) = 4.34$, $p < 0.01$, 5 mg/kg, $F(72, 4) = 8.57$, $p < 0.001$; 10 mg/kg, $F(72,4) = 12.03$, $p < 0.001$; buspirone 1.25 mg/kg, $F(72, 4) = 4.43$, $p < 0.01$; 2.5 mg/kg, $F(72, 4) = 3.25$, $p < 0.05$; 5 mg/kg,

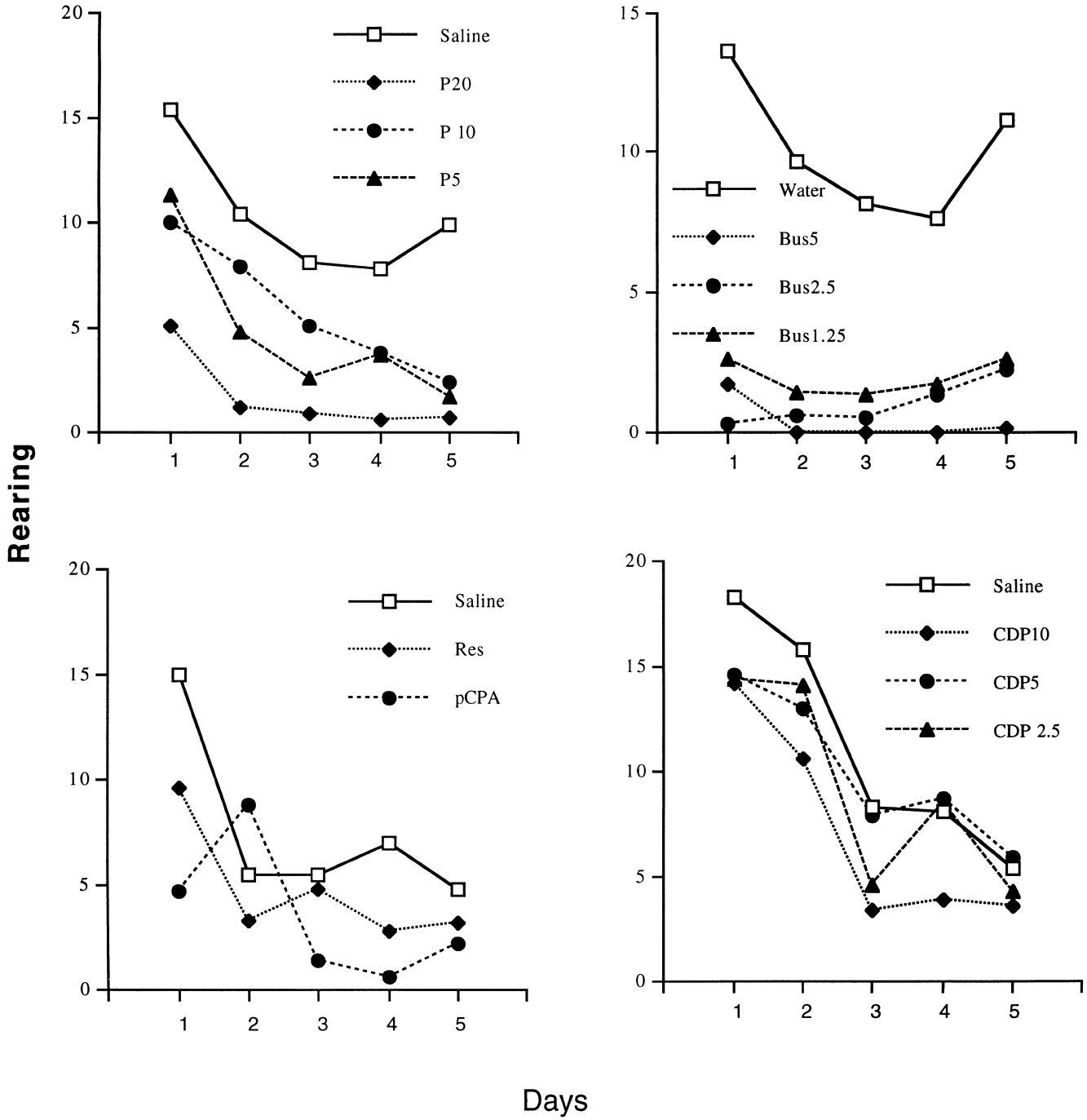

FIG. 3. Mean rearing scores. Details as for Fig. 1.

$F(72, 4) = 6.26$, $p < 0.01$]. With buspirone there was a significant interaction between drug treatment and days at the two highest doses [2.5 mg/kg, $F(72, 8) = 3.67$, $p < 0.01$; 5 mg/kg, $F(72, 8) = 6.26$, $p < 0.01$].

Drug effects on grooming are shown in Fig. 4. Reserpine and pCPA had no significant effects, but propranolol decreased grooming at the two highest doses [10 mg/kg, $F(18, 1) = 19.19$, $p < 0.001$; 20 mg/kg, $F(18, 1) = 28.81$, $p < 0.001$], and grooming decreased at all doses for buspirone and CDP [buspirone 1.25 mg/kg, $F(18, 1) = 6.42$, $p < 0.05$; 2.5 mg/kg, $F(18, 1) = 8.38$, $p < 0.01$; 5 mg/kg, $F(18, 1) = 23.93$, $p < 0.001$] CDP 2.5 mg/kg, $F(18, 1) = 19.49$, $p < 0.001$; 5 mg/kg, $F(18, 1) = 12.19$, $p < 0.01$; 10 mg/kg, $F(18, 1) = 13.69$, $p < 0.01$). In summary, a decrease in grooming occurred with at least with the highest dose administered for propranolol, buspirone, and CDP, but not with reserpine or pCPA. Grooming increased across days

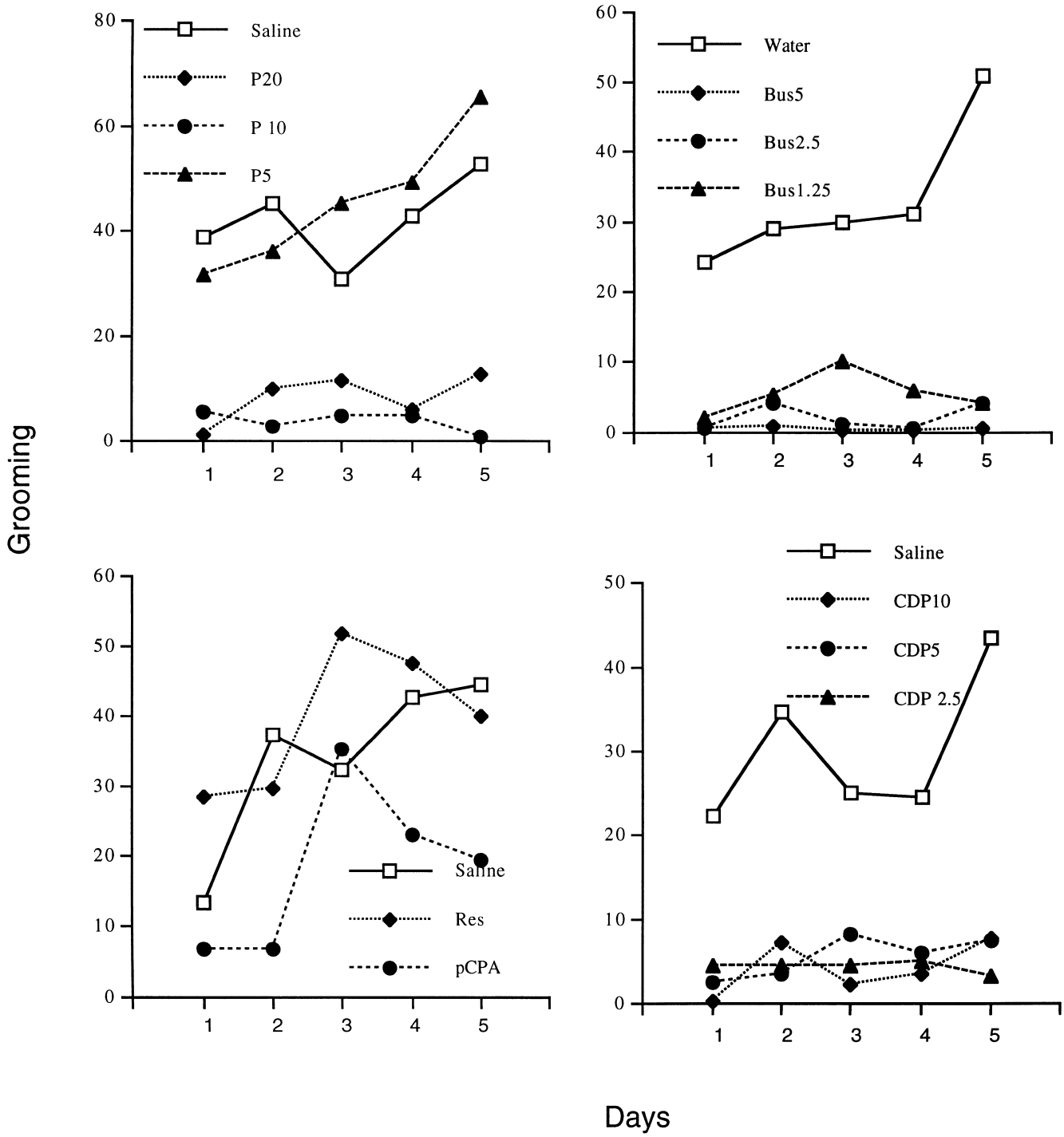

FIG. 4. Mean grooming scores. Details as for Fig. 1.

with pCPA, $F(72, 4) \times 4.42$, $p < 0.01$, and with the lowest dose of buspirone [1.25 mg/kg, $F(72, 4) = 3.34$, $p < 0.05$] but not with CDP, propranolol, or reserpine. Significant drug × days interactions occurred with one dose of CDP [5 mg/kg, $F(72, 8) = 3.04$, $p < 0.05$] and the two highest doses of buspirone [2.5 mg/kg, $F(72, 8) = 2.83$, $p < 0.05$; 5 mg/kg, $F(72, 8) = 16.50$, $p < 0.001$].

Drug effects on immobility scores are shown in Fig. 5. Reserpine and pCPA increased immobility [reserpine: $F(18, 1) = 4.88$, $p < 0.05$; pCPA: $F(18, 1) = 37.72$, $p < 0.001$]. For those

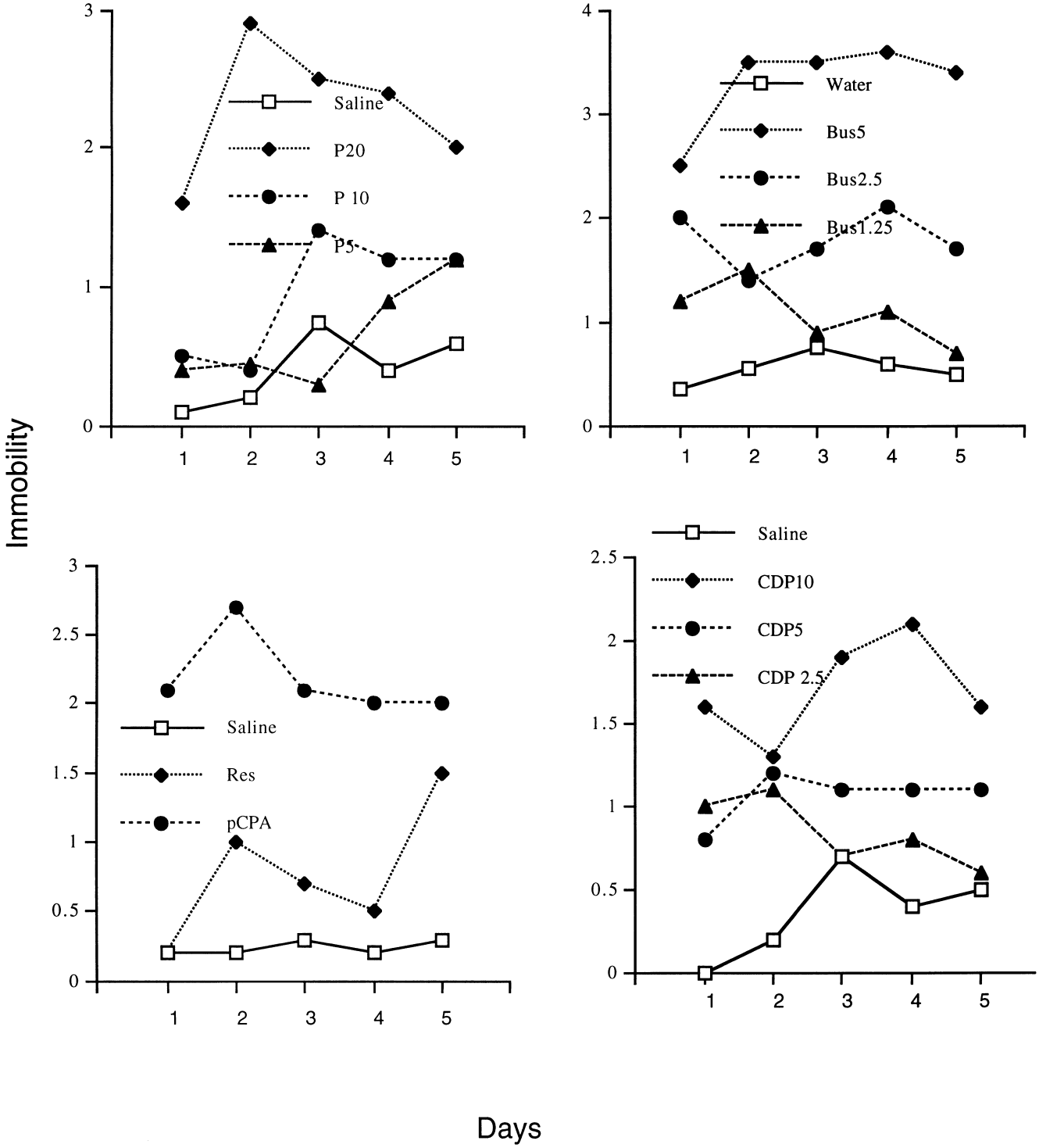

FIG. 5. Mean immobility scores. Details as for Fig. 1.

drugs administered at three doses, this effect occurred only at the highest dose for propranolol (20 mg/kg, $F(18, 1) = 15.14$, $p < 0.001$] and at the two highest doses of buspirone [2.5 mg/kg, $F(18, 1) = 11.98$, $p < 0.01$, 5 mg/kg, $F(18, 1) = 23.93$, $p < 0.001$], and at the two highest doses of CPD [5 mg/kg, $F(18, 1) = 7.40$, $p < 0.05$; 10 mg/kg, $F(18, 1) = 66.02$, $p < 0.001$]. There were no significant effects of days or drug × days interactions.

The effects of the drugs on defecation scores (over the 10-

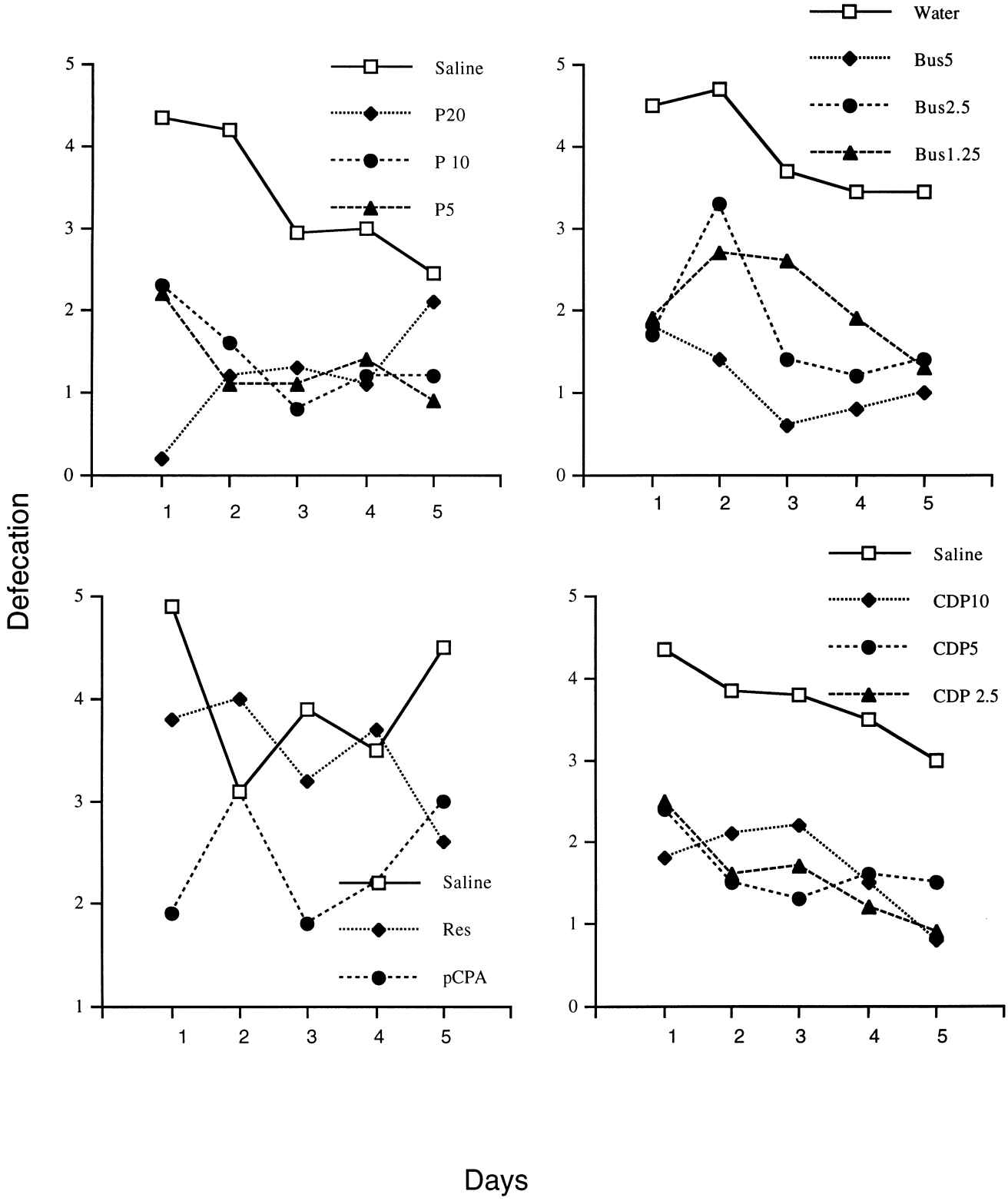

FIG. 6. Mean defecation scores for each 10-min session. Other details as for Fig. 1.

min session) are shown in Fig. 6. All drug treatments except reserpine decreased defecation scores [pCPA: $F(18, 1) = 8.36$, $p < 0.01$; propranolol 5 mg/kg, $F(18, 1) = 3.12$, $p < 0.05$; 10 mg/kg, $F(18, 1) = 9.97$, $p < 0.01$; 20 mg/kg, $F(18, 1) = 11.99$, $p < 0.01$; CDP 2.5 mg/kg, $F(18, 1) = 5.25$, $p < 0.05$; 5 mg/kg, $F(18, 1) = 7.27$, $p < 0.05$; 10 mg/kg, $F(18, 1) = 7.97$, $p < 0.05$; buspirone 1.25 mg/kg, $F(18, 1) = 12.56$, $P < 0.01$; 2.5 mg/kg, $F(18, 10 = 19.71$, $p < 0.001$, 5 mg/kg $F(18, 1) = 93.8$, $p < 0.001$). There were no significant effects of days or drug × days interactions.

DISCUSSION

The overall effects are summarized in Table 1. This shows significant increases (+), decreases (−), and where there was no effect (o), for each drug at each dose and each measure of open field behavior. As indicated in the Results section, there was a high degree of similarity of action of CDP, propranolol, and buspirone. Excluding the effects on central movements (as there were few consistent drug effects this measure is not included in the table), these three drugs had the same effects at the highest dose administered on all five of the behavioral measures reported in Table 1. Additionally, no effect was obtained with at least one lower dose with three of the measures for propranolol, two measures for buspirone and with three of the five measures with CDP. There is, thus, strong evidence that all three drugs had the same profile of behavioral actions, and dose sensitivity was seen in a majority of cases. Profiles of effects for the other two drugs were different: reserpine, which was included to control for nonspecific drug effects, had only one significant effect (on immobility), and pCPA shared some of the effects of high doses of CDP, propranolol, and buspirone, but had no effect on either rearing or grooming.

Table 1 also presents the days effects for the behavioral measures. Because days effects were very consistent across drugs and doses, it is possible to summarize all these effects in one line of the table (a small number of exceptions are indicated). Across days, peripheral movements, central movements, and rearing declined but other behaviors did not change systematically. This profile of effects is different in three out of the five sensitive measures from that of the highest doses of CDP, propranolol, and buspirone.

Because there were only a small number of significant days × drug interactions reported earlier—6 out of a possible 66—they are not included in the table. Two of these occurred with central movements, a measure that was not systematically affected by drug treatments. Of the remaining four, two occurred between the effects of buspirone (2.5 and 5 mg/kg) and days on grooming and one between the effect of a dose of CDP (5 mg/kg) and days on grooming. These occurred because grooming was heavily suppressed across days with those drugs but increased under saline (see Fig. 4). The fourth interaction was obtained between the effects of the highest dose of propranolol and days on defecation. This occurred because defecation was suppressed on all days with the drug, but declined across days under saline.

To summarize the findings of the present experiment, CDP, propranolol, and buspirone all had similar effects on open field behavior, but these were different from the effects of reserpine or pCPA, or the typical days effects. The effects of the various drugs on each type of behavior will be discussed first, and then the degree of support for the anxiolytic action of each drug will be reviewed. Finally, implications for possible neurochemical mechanisms of action will be assessed.

Two of the open-field measures used, peripheral movements, and immobility are generally regarded as related to attempts to escape (5), while central movements are more strongly related to exploratory behavior. While only two of the drugs affected central movements and these effects were in different directions (propranolol producing an increase and pCPA a decrease), all the drugs increased immobility (at least at high doses) and four decreased peripheral movements. Thus, there was substantial evidence that attempts to escape reduced with CDP, propranolol, buspirone, and pCPA. That these drugs tended to reduce locomotor behavior was perhaps, surprising as, although some theorists predict a complex relationship between open field behavior and the effects of anxiolytics (26), increases in locomotion are generally ob-

TABLE 1

EFFECTS OF DRUGS DOSES ON FIVE MEASURES OF OPEN-FIELD BEHAVIOR

	Peripheral Movements	Rearing	Grooming	Immobility	Defecation
P 5 mg/kg	−	0	0	+	−
P 10 mg/kg	−	0	−	0	−
P 20 mg/kg	−	−	−	+	−
Bus 1.25 mg/kg	0	−	−	0	−
Bus 2.5 mg/kg	0	−	−	+	−
Bus 5 mg/kg	−	−	−	+	−
CDP 2.5 mg/kg	−	0	−	0	−
CDP 5 mg/kg	0	0	−	+	−
CDP 10 mg/kg	−	−	−	+	−
pCPA	−	0	0	+	−
Res	0	0	0	+	0
Days effects	−	− (ex.pCPA)	0 (ex. Bus 1.25&pCPA)	0	0

"+" Indicates a significant increase.
"−" Indicates a significant decrease.
"0" Indicates no effect.
"P" Indicates propranolol.
"Bus" Indicates buspirone.
"Res" Indicates reserpine.

tained with CDP in the open field and with other behavioral tests for anxiolytics [e.g., (17)]. Because care was taken in the present study to make the open field stressful with the presence of loud noise and bright lights, it is unlikely that the direction of the relationship in our results comes about because the open field was less stressful than that used in other published studies. In a study with rats using a different type of open field (29), there was higher ambulation in a strain of rats that generally showed greater emotionality, and this is consistent with the present findings of locomotion being reduced by CDP and other drugs that may have anxiolytic action.

Rearing has also been regarded as an aspect of exploratory behavior in some studies (29,31), but other studies suggested that anxiolytic agents decrease rearing (30,47). In the present study, rearing was decreased by propranolol, buspirone, and CDP (at least at the highest doses). These findings are consistent with the previous finding that a more emotional strain of rats showed higher rearing scores in an open field than did a less emotional strain (29), and with earlier reports of reductions in rearing in the open field produced by anxiolytics (26).

Grooming increases with fear in rodents (5), and a number of studies have found that antianxiety drugs decrease grooming in an open field [e.g., (9,20,35)]. In the present study, propranolol, buspirone and CDP all decreased grooming (at least at the highest doses), while reserpine and pCPA did not. These findings strengthen the view that propranolol, buspirone, and CDP all had antianxiety effects.

Defecation has long been regarded an indicator of high emotionality (5,12,13,27), although drug-induced changes in defecation have sometimes been attributed to peripheral factors not associated with anxiety (5,25). In the present study, all the drugs except reserpine, which has been used as a depression-inducing agent in the open field (1,2), reduced defecation, and it is unlikely that any of these effects were due to peripheral actions of the drugs.

The general picture that emerges in the present study is one of similarity of action of CDP, propranolol, and buspirone. The effects of pCPA were less similar and those of reserpine were apparently different. However, unlike the other drugs, only one dose level of reserpine and pCPA were employed, and it is possible that some effects were masked that might have been shown if a range of doses had been examined. The single-dose strategy was used because of the narrow dose range at which each of these agents has been found to be behaviorally effective in our own laboratory and elsewhere, but it constrains our interpretation of the results.

Looking across the whole experiment, CDP produced significant changes in five measures of behavior, and similar (significant) changes were produced by propranolol and buspirone, which, given that CDP is generally regarded as a reliable indicator of anxiolytic behavioral effects, is strong evidence for anxiolytic action of all three drugs. This conclusion is consistent with the clinical use of both propranolol and buspirone in treatment of anxiety.

The effects of pCPA and reserpine are harder to interpret because of the use of single dosages. However, these drugs did not appear to have the same effects as the other three in the open-field test. While reserpine was originally introduced as a major tranquilizer, some recent behavioral studies have classed it as anxiogenic, and a depression causing agent (1,2), and pCPA is not widely used clinically because of its toxicity.

As buspirone and propranolol have similar effects on anxiety-related behavior in the present study, it may be that they are affecting the central nervous system in a similar manner. In recent years serotonin, or 5-HT, has been found to be involved in anxiety and the effects of antianxiety drugs (7,23,28), and it may be propranolol, originally used as a beta-adrenergic blocker, has antianxiety effects through its central effects on the 5-HT system (25,33). For example, beta-adrenergic-blocking drugs, including propranolol, inhibit the postsynaptic central 5-HT–mediated response while not affecting dopaminergic transmission (15). Similarly, while some authors have attributed the reduction of locomotor activity in the open field by buspirone to dopamine receptor blockade [e.g., (3)], others have attributed the effects of buspirone to pre- or postsynaptic 5-HT antagonism (19,28), and reductions in locomotor activity in rats with buspirone have been related to both dopaminergic and 5-HT_{1A} agonist effects (38).

As noted earlier, the 5-HT depletors, reserpine and pCPA, produced different patterns of results in the present study. However, the effects of pCPA were more similar to those of the putative antianxiety drugs, and it may be that the effects of reserpine in the open field resulted from suppression of dopaminergic activity (1,32).

In the present study, the drugs were administered daily for 5 days and open-field behavior was measured each day. Although it was possible that repeated dosing would have cumulative effects that were different from the initial effect of the drug, there was no evidence for this, or for drug tolerance over this period. The number of days $\times$ drug interactions was very small, which suggests that even with pCPA and reserpine, which have long-term neurochemical depletion effects, the effective dose did not change across days.

The use of a design in which the animals were tested across 5 successive days enabled us to investigate whether the anxiolytic action of CDP and other drugs was mimicked by the habituation to the stressful open field test, which occurs with repeated exposure. This was not the case: although there were reliable days effect, the general profile of the effects of days was different from that of anxiolytic drugs.

Overall, the findings of the present study suggest that both propranolol and buspirone, which have sometimes been reported to be ineffective in standard behavioral pharmacological procedures used for evaluating anxiolytic agents, had antianxiety effects on open-field behavior, and it may be that these were mediated by similar effects on the 5-HT system, although this conclusion remains speculative in the absence of neurochemical data. These drug effects validate the use of the open-field test (uncontaminated by the introduction of food or water) for detection of possible 5-HT–mediated antianxiety effects. It might be that other possibly anxiolytic drugs, which have inconsistent effects in other anxiety related procedures, could usefully be analyzed with this procedure. Although testing occurred over 5 days in the present study, analysis of the results suggested that the habituation to the open field that was observed did not resemble the effects of anxiolytic drugs.

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