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d-Amphetamine and Phencyclidine Alone and in Combination: Effects on Fixed-Ratio and Interresponse-Time-Greater-than-t Responding of Rats[1]

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POLING, A., J. CLEARY, K. JACKSON AND S. WALLACE. d-*Amphetamine and phencyclidine alone and in combination: Effects on fixed-ratio and interresponse-time-greater-than-t responding of rats.* PHARMAC. BIOCHEM. BEHAV. **15**(3) 357–361, 1981.—The effects of three doses of *d*-amphetamine (0.5, 1.0, and 2.0 mg/kg) and phencyclidine (0.5, 1.0, and 2.0 mg/kg), alone and in combination, were assessed in rats performing under fixed-ratio 30 and interresponse-time-greater-than-15-sec food reinforcement schedules. When given alone, phencyclidine and *d*-amphetamine produced similar increases in responding under the interresponse-time-greater-than-t schedule, and decreases in responding under the fixed-ratio 30 schedule. Each drug decreased the number of reinforcers (food pellets) earned relative to control values under both schedules. The effects of the two drugs in combination were nearly always less than additive. That is, the effects of a given dose of phencyclidine and *d*-amphetamine together were less than an arithmetic summation of the effects of the drugs given alone.

Phencyclidine *d*-Amphetamine Drug interactions Schedule-controlled behavior Fixed-ratio schedule Interresponse-time-greater-than-t schedule Operant behavior Rats

IN recent years, the behavioral and biochemical actions of phencyclidine (PCP) have been examined carefully, probably due to the drug's broad spectrum of action and recognized abuse potential [1,11]. Prior investigations indicate that the behavioral effects of PCP are not mediated through an isolated interaction with dopaminergic, serotonergic, or cholinergic systems, although the drug does affect each of these systems [17,26]. Like its neuropharmacological actions, the behavioral actions of PCP are complex, dose-dependent, and species-specific. The drug is a potent psychotomimetic in humans, and has become a favored although a dangerous drug of abuse [11].

Interestingly, in a variety of species, PCP affects schedule-controlled behavior in a manner highly similar to *d*-amphetamine [1, 15, 24, 25], which apparently facilitates the release and interferes with the reuptake of norepinephrine and dopamine [22]. The effects of both drugs are rate-dependent. That is, low-to-moderate doses increase the rate of operants maintained at a low rate in the absence of drug, while decreasing high-rate operants. High doses nonselectively suppress responding (for reviews of rate-dependency see [10,21]).

The present study investigated the effects of PCP and *d*-amphetamine, alone and in combination, on the schedule-controlled performance of rats. Through intent as well as misinformation, humans commonly self-administer PCP in combination with other drugs, including stimulants such as the amphetamines [11]. The effects of PCP in combination with several other drugs on unlearned behaviors have been examined (see [20]). Interactions between PCP and pentobarbital [4,5], and between PCP, physostigmine, and atropine [7], also have been studied in nonhumans responding under schedules of operant reinforcement, but nothing is known concerning the effects of PCP and *d*-amphetamine combinations on operant responding.

Balster and Chait [2] examined the actions of such combinations with respect to drug-induced stereotypy in the rat. PCP when given alone at low doses had no effect, but potentiated the stereotypy produced by *d*-amphetamine. Higher doses of PCP produced stereotypy when given alone, but did not enhance the stereotypy induced by *d*-amphetamine. The generalizability of these findings to schedule-controlled responding is unclear. The present experiment assessed how PCP and *d*-amphetamine given alone and in combination would affect responding maintained at widely different rates under fixed-ratio and interresponse-time-greater-than-t (also known as differential-reinforcement-of-low-rates, or DRL) schedules. Earlier studies of drug combinations rarely have

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examined performance under a range of conditions, although it is to be expected that current environmental contingencies strongly affect the behavioral actions of drug combinations, as they do the actions of single drugs [22].

METHOD

Subjects

Eight experimentally naive adult male Sprague-Dawley rats, maintained at 80% of free-feeding weights, served as subjects. They were individually housed with unlimited access to water in a constantly illuminated room maintained at 23°C.

Apparatus

Four identical Plexiglas and aluminum operant conditioning chambers were used. Each chamber was 21 cm high, wide, and long. The work panel, fabricated of aluminum, was equipped with a response lever horizontally centered 8 cm above the chamber floor, and a feeder trough located 5 cm to the left of the lever. Noyes 45 mg rat pellets could be delivered via the trough when desired. A 15-W white house light above the chamber's transparent ceiling provided constant ambient illumination while an exhaust fan provided ventilation and masking noise. Solid state programming equipment was used to control experimental events and to record data.

Behavioral Procedure

The rats were first trained to lever press under a fixed-ratio 1 (FR 1) schedule, where a food pellet followed each lever press. After ten 30-min sessions of exposure to this schedule, all subjects responded consistently. At this time, they were randomly divided into two groups of four. For one group, the FR 1 was gradually lengthened across 12 sessions to a FR 30 schedule, where food followed every thirtieth lever press. The second group was exposed to an interresponse-time-greater-than-t (IRT>t) schedule. Under the IRT>t schedule, a food pellet followed the first response emitted at least a specified number (t) of seconds after receipt of the preceding pellet; each response emitted before that time reset the interval. The second group of rats was initially exposed to an IRT>5-sec schedule that was lengthened across 12 sessions to IRT> 15 sec. Here, for food to be delivered responses had to be separated in time by at least 15 sec.

The terminal schedules described above were in effect throughout the balance of the study. Each subject was exposed to one 30-min session per day, six days per week. Number of responses emitted and number of reinforcers (food pellets) earned per session were recorded.

Pharmacological Procedure

The effects of three doses of *d*-amphetamine sulfate (0.5, 1.0, and 2.0 mg/kg) and phencyclidine hydrochloride (0.5, 1.0, and 2.0 mg/kg) were evaluated alone and in combination (doses refer to the total salt). Drugs were given only when an individual subject's performance was stable across three consecutive control sessions, in which 0.2 ml injections of isotonic saline were given intraperitoneally 20 min prior to the experimental session. Responding was assumed to be stable when the mean rate of responding varied by less than 10% across three consecutive sessions. The effects of PCP were evaluated first, then the effects of *d*-amphetamine, and finally the effects of the two in combination. Each rat received each dose of PCP and *d*-amphetamine on one occasion, in an irregular order that varied across subjects. The nine combinations of PCP and *d*-amphetamine doses also were given to each subject. Each rat received each combined dose once, in an irregular sequence that varied across subjects. When given alone and in combination, phencyclidine hydrochloride and *d*-amphetamine sulfate were dissolved in isotonic saline to an injection volume of 0.2 ml and given intraperitoneally 20 min prior to the experimental session. Thus, conditions of injection were identical during control, single drug, and multiple drug sessions.

One rat in the FR 30 group died of respiratory infection midway through the PCP injection regimen. This subject was not replaced and its data are not reported, thus the FR 30 group consisted of three rather than four animals.

RESULTS

During baseline (non-drug) sessions, rates of responding under the IRT>15-sec schedule were much lower than those maintained by the FR 30 schedule. Across all control sessions (the three sessions immediately prior to each drug administration), mean response rate for rats exposed to FR 30 was 71.8 responses per minute, with a range across subjects of 43–91. Corresponding mean response rate for the group of rats exposed to the IRT>15-sec schedule was 4.8 responses per minute, with a range of 4.3–5.7. Control rates prior to individual drug administrations are presented in the figure legends.

Figure 1 shows the effects of PCP and *d*-amphetamine alone on responding under the two schedules. For simplicity, all data are expressed as percent of baseline (the three sessions immediately prior to drug administration) rate. PCP and *d*-amphetamine produced similar effects. However, mean group response rate under the IRT>15-sec schedule was increased relative to control values by each drug, while decreases in responding were observed under the FR 30. Repeated measures analysis of variance indicated overall effects to be statistically significant ($p<0.01$) for each drug under both schedules. Group data are generally indicative of individual performance under both schedules. Across doses, PCP alone increased IRT>15-sec responding in 11 of 12 instances (4 rats × 3 doses); this drug reduced FR 30 responding in 7 of 9 instances (3 rats × 3 doses). *d*-Amphetamine increased IRT>15-sec response rates on 10 of 12 occasions, and reduced FR 30 responding in all cases.

Figure 2 shows the effects of the two drugs given alone on group reinforcement rate (number of food pellets delivered per min). Since reinforcement rate is directly proportional to response rate under fixed-ratio schedules, drug effects on response and reinforcement rates were identical under the FR 30 schedule. The IRT>15-sec schedule does not prescribe a direct relationship between response and reinforcement rates. However, both PCP and *d*-amphetamine decreased group reinforcement rate to below control levels under this schedule. These effects were, like changes in response rate, generally consistent across subjects.

Figures 3 and 4 show the effects of the two drugs in combination on group response and reinforcement rates. Under the FR 30 schedule, all combined doses reduced group response and reinforcement rates relative to control values: across doses, these effects were statistically significant (repeated measures analysis of variance, $p<0.01$). For individ-

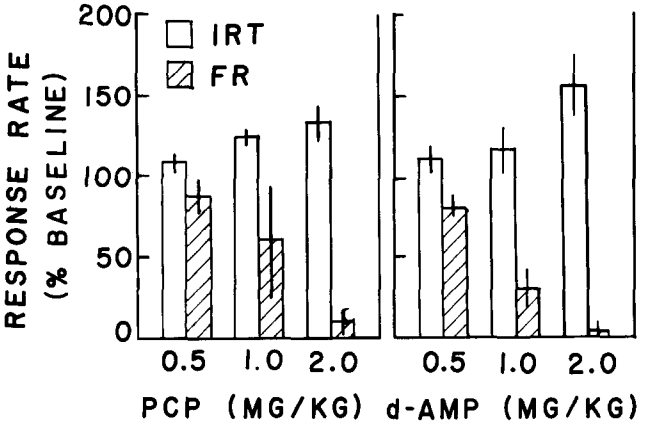

FIG. 1. Effects of PCP and *d*-amphetamine alone on the mean group response rate of rats responding under FR 30 or IRT>15-sec schedules of food reinforcement. Response rates during sessions in which a drug was given are expressed as a percentage of the rate obtained across the three control sessions immediately prior to drug administration. Vertical lines represent ± 1 standard error (SE). Reading from left to right across the figure, mean control response rates (and SEs) in responses per min for each drug administration were: FR=59.3(2.9), 43.3(2.9), 52.3(2.9), 62.3(4.9), 54.7(10.1), and 70.0(9.3); IRT=5.4(0.6), 5.7(0.6), 5.0(0.5), 5.0(0.4), 4.9(0.6), and 5.3(0.7).

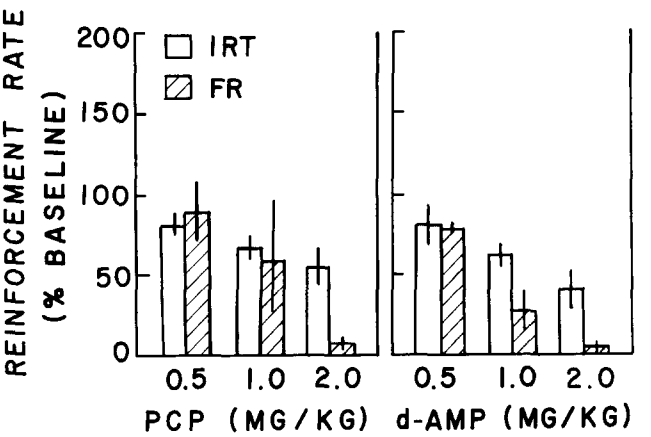

FIG. 2. Effects of PCP and *d*-amphetamine alone on the mean group reinforcement rate of rats responding under FR 30 or IRT>15-sec schedules of food reinforcement. Reinforcement rates during sessions in which a drug was given are expressed as a percentage of the rate obtained across the three control sessions immediately prior to drug administration. Vertical lines represent ± 1 standard error (SE). Mean control reinforcement rates (reinforcers per minute) for individual drug administrations for the FR group are proportional to (0.33 of) and can be derived from the response rates given in Fig. 1. Reading from left to right across the figure, mean control reinforcement rates (and SEs) for the IRT group were 1.5(0.3), 1.4(0.1), 1.8(0.3), 1.9(0.2), 1.9(0.4), and 1.7(0.3) reinforcers per min.

ual subjects, across all doses PCP and *d*-amphetamine combinations reduced response (and consequently reinforcement) rate in 27 of 27 (3 rats × 9 administrations) instances. However, under the FR 30 schedule the effects of combinations of PCP and *d*-amphetamine typically were less than predicted by simple additivity (see [14]). That is, the effects of a given dose of PCP and *d*-amphetamine together were less than an arithmetic summation of the effects of the drugs given alone or, simply put, rats exposed to combined doses of PCP and *d*-amphetamine responded more often under a FR 30 schedule than expected given the effects of the individual drugs.

Changes in group responding produced by PCP and *d*-amphetamine under the IRT>15-sec schedule also were less than predicted by an additive model, although the departure from additivity was small except when the highest dose of *d*-amphetamine was given. This dose of *d*-amphetamine (2.0 mg/kg), combined with any dose of PCP, reduced IRT>15-sec responding to below control values. In contrast, all other drug combinations increased group responding to above control values. The effects of drug combinations under the IRT>15-sec schedule were not statistically significant across all doses (repeated measures analysis of variance, $p>0.05$), as expected given the dissimilar effects associated with high and low doses of *d*-amphetamine. In all instances, however, rats responded more slowly under the IRT>15-sec schedule than predicted by an additive model, while subjects had responded more rapidly under the FR 30 schedule than additivity would predict.

All drug combinations reduced the group reinforcement rate under the IRT>15-sec schedule. This overall effect was statistically significant (repeated measures analysis of variance, $p<0.01$), and also was observed with individual subjects in 35 of 36 instances. However, the magnitude of this effect was never greater than predicted by summating the

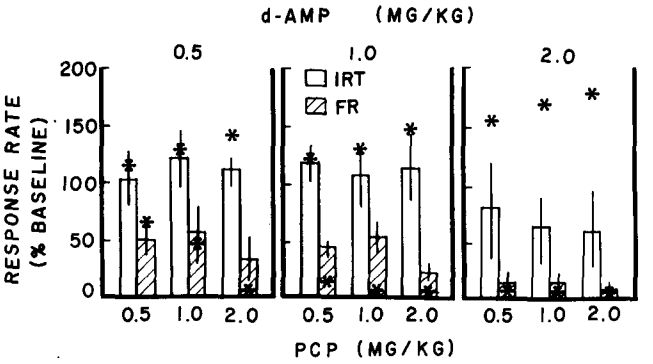

FIG. 3. Effects of PCP and *d*-amphetamine combinations on the mean group response rate of rats responding under FR 30 or IRT>15-sec schedules of food reinforcement. Response rates during sessions in which drugs were given are expressed as a percentage of the rate obtained across the three control sessions immediately prior to drug administration. Vertical lines represent ± 1 standard error (SE). Asterisks represent values predicted by an additive model, where the effects of individual drugs (Fig. 1) are summated to predict their combined effects. Reading from left to right across the figure, mean control rates (and SEs) in responses per min for each drug administration were: FR=87.3(2.7), 83.3(12.4), 84.7(4.3), 75.7(3.3), 84.0(13.0), 76.7(7.4), 82.7(11.9), 90.7(2.9), and 80.7(3.8); IRT=4.5(0.4), 4.8(0.4), 4.7(0.4), 4.4(0.3), 4.3(0.4), 4.6(0.3), 4.6(0.2), 4.6(0.4), and 4.4(0.5).

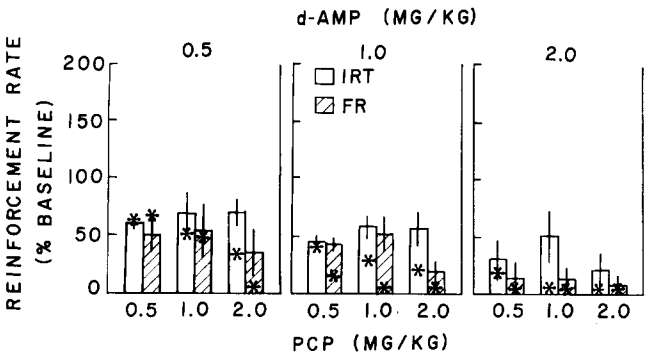

FIG. 4. Effects of PCP and *d*-amphetamine combinations on the mean group reinforcement rate of rats responding under FR 30 or IRT>15-sec schedules of food reinforcement. Reinforcement rates during sessions in which drugs were given are expressed as a percentage of the rate obtained across the three control sessions immediately prior to drug administration. Vertical lines represent ± 1 standard error (SE). Asterisks represent values predicted by an additive model, where the effects of individual drugs (Fig. 2) are summated to predict their combined effects. Here and in Fig. 3, additive values less than 0% are graphed as 0%. Mean control reinforcement rates (reinforcers per minute) for individual drug administration for the FR group are proportional to (0.33 of) and can be derived from the response rate given in Fig. 2. Reading from left to right across the figure, mean control reinforcement rates (and SEs) for the IRT group were 2.1(0.4), 1.9(0.4), 2.0(0.3), 1.9(0.3), 2.1(0.3), 1.9(0.3), 2.0(0.2), 2.2(0.4), and 2.1(0.4) reinforcers per min.

relative reinforcement loss produced by PCP and *d*-amphetamine alone. The finding that PCP and *d*-amphetamine, alone and in combination, produced appreciable decreases in reinforcement rate at doses that did not greatly increase response rate suggests that the drugs did not simply increase "bursting" (bouts of rapid responding) immediately after food presentation, for such bursting would have little effect on overall reinforcement rate. Unfortunately, since interresponse time distributions were not collected, the precise nature of the drug-induced response rate increases and reinforcement rate decreases could not be accurately determined.

DISCUSSION

A large number of studies have explored the effects of *d*-amphetamine alone on schedule-controlled behavior in rats and other species (e.g., [3, 8, 10, 12, 16, 18, 19, 23, 24, 25]). In general, results have been similar to those of the present study: High non-drug response rates, like those maintained under the FR 30 schedule, are reduced by low-to-moderate doses of the drug, while low non-drug response rates, like those engendered by the IRT>15-sec schedule, are increased at the same doses. PCP reportedly affects operant behavior much like *d*-amphetamine (e.g., [1, 4, 6, 7, 15, 17]), as it did in the present study.

More noteworthy than the effects of the single drugs were their combined actions. With respect to both response and reinforcement rates, PCP and *d*-amphetamine usually produced infraadditive effects, although in many cases departures from additivity were small. It is of some interest that, under the FR schedule, rats responded more rapidly (and received more food pellets) when given drug combinations than predicted on the basis of an additive model, while under the IRT>t schedule they responded less rapidly (and received more food pellets) than additivity would predict. The appropriate interpretation of these findings is unclear.

To some extent, they suggest that PCP and *d*-amphetamine are antagonists, although the mechanism of this interaction is speculative. Dews [9], however, has offered a provocative behavioral analysis of apparent drug antagonism on operant baselines that Chait and Balster [4] considered in relation to their finding that PCP and pentobarbital combinations produced infraadditive effects on the lever pressing of squirrel monkeys maintained by variable-interval schedules of food reinforcement. This analysis notes that many drugs (including PCP and *d*-amphetamine) produce rate-dependent effects, as discussed above. When two drugs with such effects are given together under conditions where either alone would reduce responding (e.g., under the FR schedule in the present study), "the combination might cause less of a decrease in responding than expected since each drug is acting upon a baseline that is lowered by the other drug" ([4], p. 205). On the other hand, when non-drug rates are low and individual drugs increase responding (as under the IRT>t schedule), the two drugs in combination might cause less of an increase in responding than expected since each drug is acting upon a baseline that is raised by the other drug. Such an analysis is generally consistent with our findings. For example, the greatest relative antagonism of PCP's effects under the IRT>15-sec schedule occurred with the highest dose of *d*-amphetamine, which produced the greatest increase in response rate when given alone, while lower doses of *d*-amphetamine, which produced lesser increases in responding, were associated with weaker apparent antagonism. These results are in keeping with a rate-dependent analysis of drug interaction such as that advanced by Dews [9], as are those of Chait and Balster [4].

It should be noted that in the present study and in earlier operant studies of PCP in combination with other drugs [4,7], dose-response curves for the individual drugs were first determined, then their combined actions were assessed. This raises the possibility that any infraadditive effects observed when drug combinations were given may reflect tolerance resulting from multiple exposure to either or both of the individual drugs. This possibility could best be evaluated by determining dose-response curves for the individual drugs before and after the combinations were evaluated. However, it seems unlikely that the infraadditive effects of PCP and *d*-amphetamine observed in the present study resulted from the development of tolerance to either or both of the individual drugs, for two reasons: (1) Drugs were given no more often than once a week, and usually far less often. Several studies have failed to demonstrate tolerance to PCP and *d*-amphetamine when administered under such a regimen (e.g., [3, 16, 18, 24, 25]). (2) Doses of each individual drug were given in an irregular order across subjects, yet a given dose produced similar effects across subjects regardless of order of administration. Thus it seems improbable that tolerance strongly contributed to the observed effects of drug combinations.

Nonetheless, this possibility emphasizes the difficulties inherent in conducting and interpreting studies designed to evaluate drug combinations. Despite these problems, the increasingly common practices of polydrug use and abuse [11] persuasively argue for empirical analyses of drug interactions, and the behavioral variables that influence them.

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