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Interactions Between Stimulants and Depressants on Schedule-Controlled Behavior[1]

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FORD, R. D., R. H. RECH AND D. TOBIN. *Interactions between stimulants and depressants on schedule-controlled behavior.* PHARMAC. BIOCHEM. BEHAV. 12(5) 657–661, 1980.—Interactions between *d*-amphetamine and diazepam, *d*-amphetamine and methaqualone, and cocaine and diazepam were examined on one-hour daily sessions of an FI-30 schedule of food-reinforced behavior in rats. Administered singly, *d*-amphetamine and cocaine increased overall responding at one intermediate dose (1 and 10 mg/kg, respectively) and decreased response rates and reinforcements at the highest doses (3 and 10 for *d*-amphetamine; 18 and 30 for cocaine). Diazepam caused a dose-related increase in response rate from 0.3 to 3 mg/kg, less of an increase at 10 mg/kg, and no increase or a decrease at 30 mg/kg. Methaqualone administered singly in doses from 1.0 to 30 mg/kg caused only a dose-related decrease in response rate and, at the highest doses, also decreased the number of reinforcements. Combining a fixed dose of 0.3 mg/kg *d*-amphetamine with various doses of diazepam did not alter behavior from diazepam alone except at 30 mg/kg; at this dose combination the diazepam-alone decreases in response rate and reinforcements were antagonized. The combination of 1.0 mg/kg *d*-amphetamine with the dose-range of diazepam generally potentiated the rate increasing effects of the drugs given singly. When *d*-amphetamine was combined with lower doses of methaqualone the rate-increasing effects of the former drug were potentiated. Combining higher doses of this depressant with *d*-amphetamine hardly affected rate as related to the methaqualone-alone decrease, but the combination did increase number of reinforcements earned. A low dose (3 mg/kg) of cocaine antagonized the increase in response rate by 1 and 3 mg/kg of diazepam, while a higher dose (10 mg/kg) of cocaine enhanced the increase in rate by 0.1 and 10 mg/kg diazepam. The results support other studies that interactions between these drug classes are complex, poorly dose-related, and not predictable on the basis of the effects of the agents administered singly.

d-Amphetamine Diazepam Methaqualone Cocaine Depressants Stimulants
Schedule-controlled behavior

INTERACTIONS between stimulants of the amphetamine type and central nervous system (CNS) depressants of the barbiturate type have been studied in a variety of behaviors [1, 2, 3, 9, 13, 17, 18, 20, 21, 22, 25, 26]. In some cases when the drugs increased responses separately the combination increased responses more than either drug alone [2, 3, 18, 20, 21, 22, 25, 26]. In a few instances the term potentiation, a greater increase than expected from the additive effects of the drugs given singly, appeared to be appropriate. In other studies or in those measuring more than one component of behavior, the one drug that was active in modifying behavior (increase or decrease) was enhanced or antagonized by combination with the second drug [1, 2, 3, 9, 13, 17, 18, 22]. Attempts to explain the drug interactions on the basis of a reduction in "fear" reactions or state dependency [25], the level of baseline responding or initial effects of the drugs [2, 3, 13], or delayed metabolism of the amphetamine-type drug [1,17] have not been very satisfactory. The studies of multiple components indicated that even dose-response patterns of the combinations afforded little predictability. Furthermore, a dose combination of two drugs synergyzing to increase one component of behavior may interact with antagonism on another component.

Previous studies have often utilized a fixed-interval (FI) operant schedule of reinforcement ([2, 13, 22] in pigeons; [13] in cats). This is a sensitive measure of drug effects on schedule-controlled behavior [12]. Moreover, especially if response rates within the intervals are analyzed separately as early and late components [13], rate-dependent influences of the drugs or their combination may be determined in the same behavioral session. We chose to study the effects of *d*-amphetamine-diazepam combinations on FI-30 in rats, there apparently being no previous extensive analysis of this drug combination on operant behavior in this species. Furthermore, the effects of this combination were compared with those of *d*-amphetamine plus methaqualone and cocaine plus diazepam, examining another non-barbiturate CNS depressant and central sympathomimetic-type stimulant, respectively. Thus, the interaction between *d*-amphetamine and diazepam was explored for generalization to similar type agents. The behavioral effects of these drug interactions are of more than academic interest, since there is concern that

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dangerous drug interactions are becoming more common in the drug abuse patterns of our society [23].

METHOD

Animals

Ten naive female Sprague-Dawley rats (Spartan Farms, Haslett, MI) weighing from 210 to 247 g were used in this study. The subjects were deprived of food until each had reached 85% of free-feeding weight and subsequently maintained at this weight by adjusted feeding after each experimental session. The animals were housed individually in home cages with free access to water.

Apparatus

The experiments were conducted in Lehigh Valley Electronics 143-20-215 operant chambers equipped with one response bar and set in ventilated sound attenuating cubicles. The required force of a successful bar press was approximately 15 g. Centered in the wall containing the response bar was a food hopper attached to a dispenser delivering 45 mg Noyes food pellets. A 6-W bulb illuminated the chamber. Electromechanical programming equipment was used to control experimental contingencies and record data.

Procedure

Rats were trained to bar press for food on CRF (each press presenting a pellet) and then gradually shaped to a 30-sec fixed-interval (FI-30) schedule of food presentation for one-hour daily sessions [8]. Rates of responding during the first, middle and last 10-second segments of the 30-sec intervals were recorded separately. Drug studies were initiated only after the typical scalloped FI-30 pattern of responding became stable (about 45 days) within 10–15% day-to-day variations around the mean value. All subjects had been assigned randomly to one of the three drug-treatment groups prior to training.

Diazepam and methaqualone were suspended in 0.5% aqueous methylcellulose. *d*-Amphetamine sulfate and cocaine hydrochloride were dissolved in distilled water, doses being expressed in terms of the salt. All injections were intraperitoneal in a volume of 1 ml/kg. Control injections, 0.5% methylcellulose and/or distilled water, were tested the day before each drug session. All injections were given 15 min prior to a session and drug sessions were separated by at least 5 days. Three rats were devoted to amphetamine-diazepam studies, 3 rats to amphetamine-methaqualone interactions and 4 rats to the cocaine-diazepam combination. However, one of the 3 rats selected beforehand to be studied for amphetamine-diazepam interactions failed to maintain a stable baseline pattern of FI-30 responding during drug studies. This animal was deleted, leaving only two subjects in this group. In each case half of the animals received one of the two drugs first and the other half the other drug first. The fixed doses of amphetamine or cocaine that were combined with diazepam or methaqualone were determined for their effects when given alone before, during and after the determination of the dose-response curves for the combination. Doses of drugs and drug combinations were administered in ascending or descending order. In the case of the group of 3 rats (amphetamine-methaqualone) drugs were given in ascending order in two rats and in descending order in one rat.

The data were expressed and analyzed by the method of McMillan and Leander [16]. The range of responses for each group under control (vehicle) conditions and for the fixed doses of amphetamine or cocaine was determined for multiple injections. The range of response scores was also determined for sessions following single or combined treatments involving diazepam or methaqualone and the values compared with those of the vehicle, stimulant drug alone, or depressant drug alone days.

RESULTS

The FI-30 schedule induced the typical scalloped pattern of responding during control sessions that has been extensively described by others [2, 8, 12, 18]. Few responses occurred in the first 10-sec segment of the intervals and most responses occurred in the last 10-sec segment. The drugs and drug combinations generally altered this scalloped pattern as described for cats by Richelle [18]. That is, the lowest doses of the stimulants increased responding in the first and second segments, intermediate doses increased it in the first and decreased it in the last segment, and the largest doses decreased response rate in all segments. Diazepam in low to intermediate doses tended to increase responding in all segments while large doses (10, 30 mg/kg) decreased it, especially in the last segment of the interval. Methaqualone in any effective dose only decreased rate, especially in the third segment. The combinations of stimulants and depressants, at low to intermediate doses of the depressant drugs, increased responses in all segments of the interval. The combinations including high doses of the depressants produced variable results (see below).

The effects of *d*-amphetamine and diazepam alone and in combination are shown in Fig. 1. The increase by *d*-amphetamine alone became prominent only at the 1 mg/kg dose. Larger doses not only reduced drastically the overall rate of responding, but also decreased comparably the number of intervals during which there was any response. Thus, the number of reinforcements earned (bottom panel in Fig. 1) was decreased in like manner. Diazepam alone increased overall rate, except at the 30 mg/kg dose. This latter dose reduced responses to less than a third of control values. Nevertheless, the temporal spacing was less affected, as indicated by the earning of over 50% of control number of reinforcements following this dose. The combination of 0.3 mg/kg *d*-amphetamine with the various doses of diazepam yielded a pattern very similar to diazepam alone, with the exception of the 30 mg/kg dose. At this dose the inclusion of the stimulant antagonized the decrease for both the response rate and reinforcements earned. The larger dose of *d*-amphetamine (1.0 mg/kg) plus various doses of diazepam showed a potentiation at 0.3, 1.0, 10.0 and 30.0 mg/kg of diazepam (greater than the additive increases from the drugs as administered singly). The largest dose of diazepam plus 1.0 mg/kg *d*-amphetamine also resulted in the antagonism of the reduced number of reinforcements caused by diazepam alone at this dose. Responding in all segments of the interval was increased by the combination of *d*-amphetamine 1 mg/kg and every dose of diazepam relative to the influence of diazepam alone. Despite the testing of only two subjects with this combination, the results were quite similar for the various treatments between the two subjects and resembled the effects of stimulant-benzodiazepine combinations on unpunished responding as reported in cats [18] and pigeons [2].

The administration of methaqualone in doses of 1 to 30

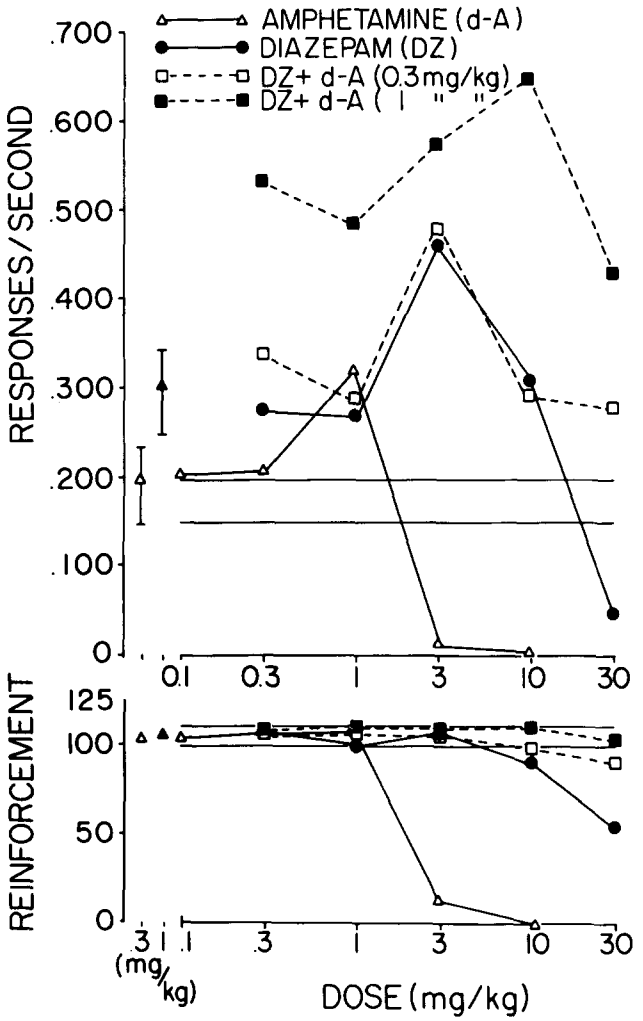

FIG. 1. Effects of *d*-amphetamine, diazepam and drug combinations on the rate of responding and reinforcements per session under an FI-30 schedule of reinforcement. Abscissa: dose, log scale on the right; isolated points at the left show the mean of 3 sessions for the 2 rats following *d*-amphetamine doses of 0.3 (open triangles) and 1.0 (closed triangles) mg/kg, the vertical lines indicating the range above and below the mean. Points along the log scale are the mean response of 2 rats for one session. The horizontal lines indicate the range of means for vehicle controls. Ordinates: response-rate and number of food pellets presented during an hour session.

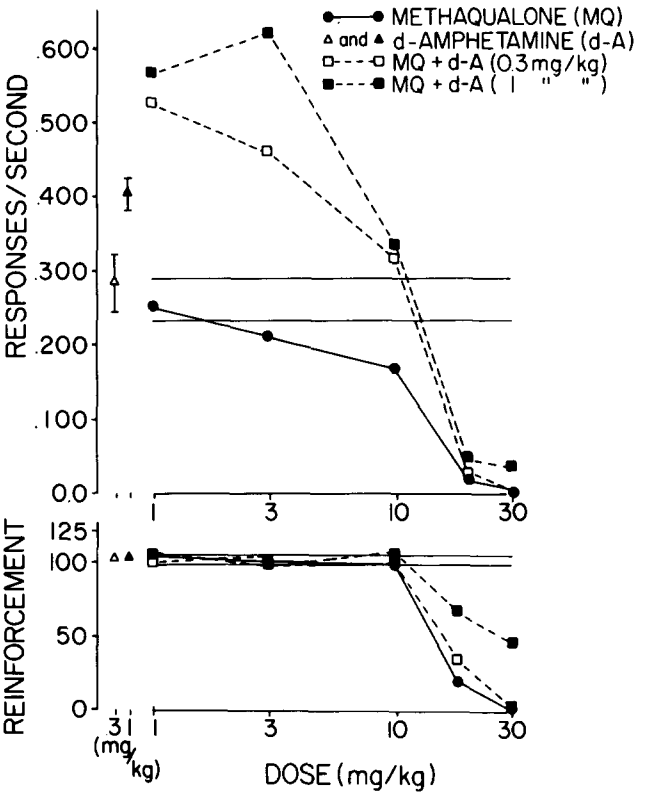

FIG. 2. Effects of *d*-amphetamine, methaqualone and the combination on rate of responding and reinforcements received per session under the FI-30 schedule. See Fig. 1 legend for details of the meaning of symbols and designations on the abscissa and ordinates, except that these results are derived from 3 rats.

mg/kg produced a dose-related decrease in FI-30 response rate (Fig. 2). However, the depressant reduced the number of reinforcements only at the two largest doses (18 and 30 mg/kg). The effects of *d*-amphetamine (0.3 and 1.0 mg/kg) alone were similar to those depicted in Fig. 1. The combinations of *d*-amphetamine and methaqualone at the lower doses resulted in greater stimulation than with the stimulant alone. Combinations of *d*-amphetamine with 10 mg/kg methaqualone antagonized the depression of rate by this dose of methaqualone given singly. However, the stimulant combined with 18 or 30 mg/kg methaqualone produced very little antagonism of the marked depression of these doses of methaqualone alone. On the other hand, the decrease in reinforcements by these doses of methaqualone singly was partly antagonized by combination with 1 mg/kg *d*-amphetamine. Therefore, while the combined effects did not appreciably restore response rates, the spacing of responses improved to allow for fewer intervals without a single response. The marked decrease in response rate, especially in the third segment of the interval, by 18 or 30 mg/kg of methaqualone given singly was very little antagonized by combining the depressant with either dose of *d*-amphetamine.

Analysis of interactions of the last pair of drugs, cocaine and diazepam, yielded the most complex results (Fig. 3). Cocaine alone increased responses above vehicle controls only at 10 mg/kg. Despite this increase in rate, this dose of the stimulant caused a small decrease in number of reinforcements. This reflects a greater number of intervals during which no response was made, *e.g.*, a disruption of the temporal spacing of responses. Larger doses of cocaine (18 and 30 mg/kg) decreased both response rates and number of reinforcements comparably. Diazepam alone in doses of 0.1 to 30 mg/kg produced an inverted U-shaped dose-response curve as seen in Fig. 1. However, the data in Fig. 3 illustrate that in this group 30 mg/kg diazepam did not cause a decrease in response rate from vehicle controls, although a decrease in number of reinforcements was evident. When 3 mg/kg cocaine was combined with various doses of diazepam, the stimulant antagonized the anticipated increase after 1.0 and 30 mg/kg diazepam. The combination of 3 mg/kg cocaine and 10 or 30 mg/kg diazepam resulted in a response rate increase not differing from these doses of diazepam alone. Nevertheless, this combination did decrease rein-

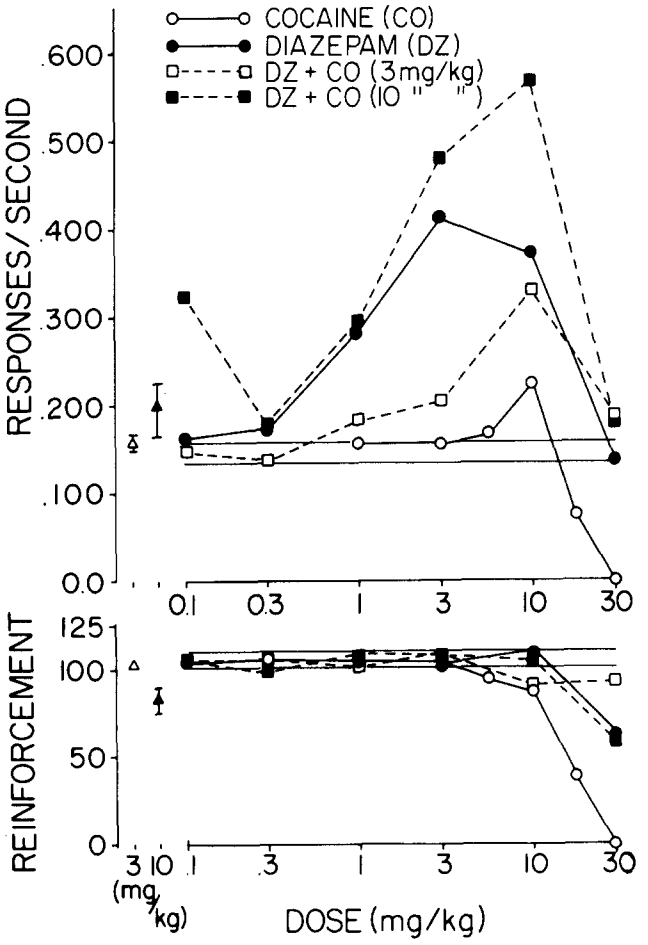

FIG. 3. Effects of cocaine, diazepam and the combination on the rate of responding and reinforcements per session under the FI-30 schedule. See Fig. 1 legend for details of the meaning of symbols and designations on the abscissa and ordinates, except that these results are derived from 4 rats.

forcements, the spacing of responses becoming more variable than after vehicle or diazepam alone. Following the combination of 10 mg/kg cocaine and various doses of diazepam, only after 0.1 and 10 mg/kg of the depressant was the response rate greater than after diazepam alone. The reinforcements earned after this combination did not differ from the pattern after diazepam alone. The combination of cocaine with 30 mg/kg diazepam also failed to reverse the decreased response rate in the third segment of the interval as produced by diazepam alone. Therefore, the combined effects of cocaine and diazepam may decrease or increase the FI-30 response rate relative to diazepam alone, or cause no change, dependent upon the particular doses of both the stimulant and the depressant in the combination.

DISCUSSION

The effects of amphetamine-diazepam combinations on FI-30 responding in the rat were similar to the interactions between these drugs in cats [18] and of amphetamine with chlordiazepoxide on unpunished behavior in pigeons [2]. That is, the increase in responses after the combination showed synergism (greater effect than either drug alone) or potentiation (greater than the additive increases of the individual drugs) with many of the dose combinations. Combinations involving larger doses, which singly produced a decrease from control responding, produced either synergism or antagonism, depending on the study cited. The operant schedule of Barrett and Witkin [2] for unpunished responding was a VI-3 min procedure, perhaps accounting for some minor differences in comparing results with ours. Barrett and Witkin used a multiple schedule incorporating FI-5 min, but this latter was associated with punishment, which changes the character of the response to *d*-amphetamine. In any case, the present results are in agreement with the proposals that the interaction is complex [2, 3, 18, 21] and is not easily explained in terms of the effects of the drugs administered separately. We had come to this conclusion previously on the basis of acute and chronic interactions between *d*-amphetamine and diazepam on punished behavior of rats [9].

The interaction of methaqualone with *d*-amphetamine on FI-30 responding indicated that potentiation of the increased response rate by *d*-amphetamine alone occurred after combination with a depressant that itself did not increase responding. This suggests that methaqualone has little disinhibiting influence in its own right, but may become so when combined with *d*-amphetamine. Although the inclusion of the stimulant did not antagonize the marked depression of response rate by the larger dose of methaqualone, the combination did result in an improvement in spacing of responses and thus in the number of reinforcements attained.

The results with cocaine and diazepam combinations indicate that this stimulant may decrease, increase or not change response rate from that of diazepam alone according to the particular dose combinations studied. Also, the addition of cocaine to higher doses of diazepam tended to disrupt the spacing of responses more than the depressant alone, rather than reverse this effect as was true for the *d*-amphetamine-diazepam interaction.

It is clear from these results that the interactions between *d*-amphetamine and methaqualone or cocaine and diazepam are at least as unpredictable as those between *d*-amphetamine and diazepam. This supports well the thesis advanced by others [2, 3, 21, 22, 26] that the combined effects of centrally-acting agents may present a qualitatively different state than the effects of the drugs administered separately. It is likely that the stimulant drugs involved produce their dose-related increases and decreases in operant responding by mechanisms very different than those accounting for the dose-related increase or decrease in response rate as observed with the depressants. Thus, the combination of these influences may create essentially a different order of integration in brain circuitry, especially as regards more sophisticated patterns of learned behavior.

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