Pharmacology Biochemistry & Behavior, Vol. 27, pp. 299–306. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

Interactions Between Stimulants: Effects on DRL Performance and Lethality in Rats

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Received 11 July 1985

MICHAELIS, R. C., F. A. HOLLOWAY, D. C. BIRD AND P. L. HUERTA. *Interactions between stimulants: Effects on DRL performance and lethality in rats.* PHARMACOL BIOCHEM BEHAV 27(2) 299–306, 1987.—The Controlled Substances Act of 1970 drastically reduced the supply of amphetamines available to the public. It also inadvertently prompted the emergence of a new drug industry, namely the marketing of caffeine/phenylethylamine combinations packaged to look like many of the previously available amphetamine preparations. The findings of one recent experimental study corroborate anecdotal evidence that the interoceptive "high" produced by these look-alike stimulants mimics that produced by amphetamine. The present study was designed to further characterize the behavioral effects of caffeine/phenylethylamine combinations. The present findings suggest that adding ephedrine and phenylpropanolamine to caffeine markedly enhances the disruption of DRL performance, as well as the lethality of the drug. In addition, different patterns of interactions were obtained between amphetamine and caffeine versus the caffeine/ephedrine/phenylpropanolamine combination.

CNS stimulants Amphetamine Caffeine Phenylethylamines "Look-alike" stimulants
DRL performance Rats

THE Controlled Substances Act of 1970 drastically reduced the supply of amphetamines available to the public. This markedly curtailed the use of amphetamines for nonmedical and recreational purposes. However, it was soon discovered that energizing and mood-elevating effects similar to those produced by amphetamines could be produced by combinations of caffeine and certain phenylethylamines found in over-the-counter nasal decongestants and diet aids. Almost overnight, a nationwide, multimillion dollar industry emerged, marketing these "legal" stimulants packaged to look like previously available amphetamine preparations and touted as "safe" and "legal" recreational drugs [43]. Despite the fact that there is no medical rationale for these caffeine/phenylethylamine combinations, the fact that the individual drugs are recognized as legal over-the-counter entities has enabled unscrupulous entrepreneurs to consistently evade the FDA's efforts to ban the sale of these drug combinations. For example, when the popular triple caffeine/ephedrine/phenylpropanolamine (PPA) combination was reclassified as a new drug entity in 1982 [14], the FDA's ban on the sale of these triple combinations was circumvented by removing either ephedrine or PPA from the drugs, and marketing double combinations.

Most of these "look-alike" combinations contain a large dose of caffeine (up to 400 mg) as their primary ingredient. This is usually supplemented by ephedrine and/or PPA, two phenylethylamines found in many over-the-counter nasal decongestants and diet aids [21]. Not only is there no medical rationale for these drug combinations, but there is clear potential for drug interactions which could involve any one of several neurochemical systems. Ephedrine and PPA are thought to have agonistic effects on noradrenergic [21] and/or dopaminergic [47,48] neurons. In addition, caffeine has been shown to alter the disposition of several endogenous neurotransmitters [4, 5, 15], inhibit cyclic nucleotide phosphodiesterase [8], antagonize the actions of endogenous adenosine at its neuronal receptors [42], and may share theophylline's ability to alter calcium mobility in nerve terminals [30]. Any of the effects attributed to caffeine could interact with a catecholamine agonist effect exerted by the phenylethylamines. It is believed that the major danger from these drug combinations involves the increase in blood pressure produced by noradrenergic hyperstimulation. This has been corroborated by a number of recent case studies [7, 27, 30, 33]. In addition to these reports, there a number of reports of seizures and amphetamine-like psychotic reactions

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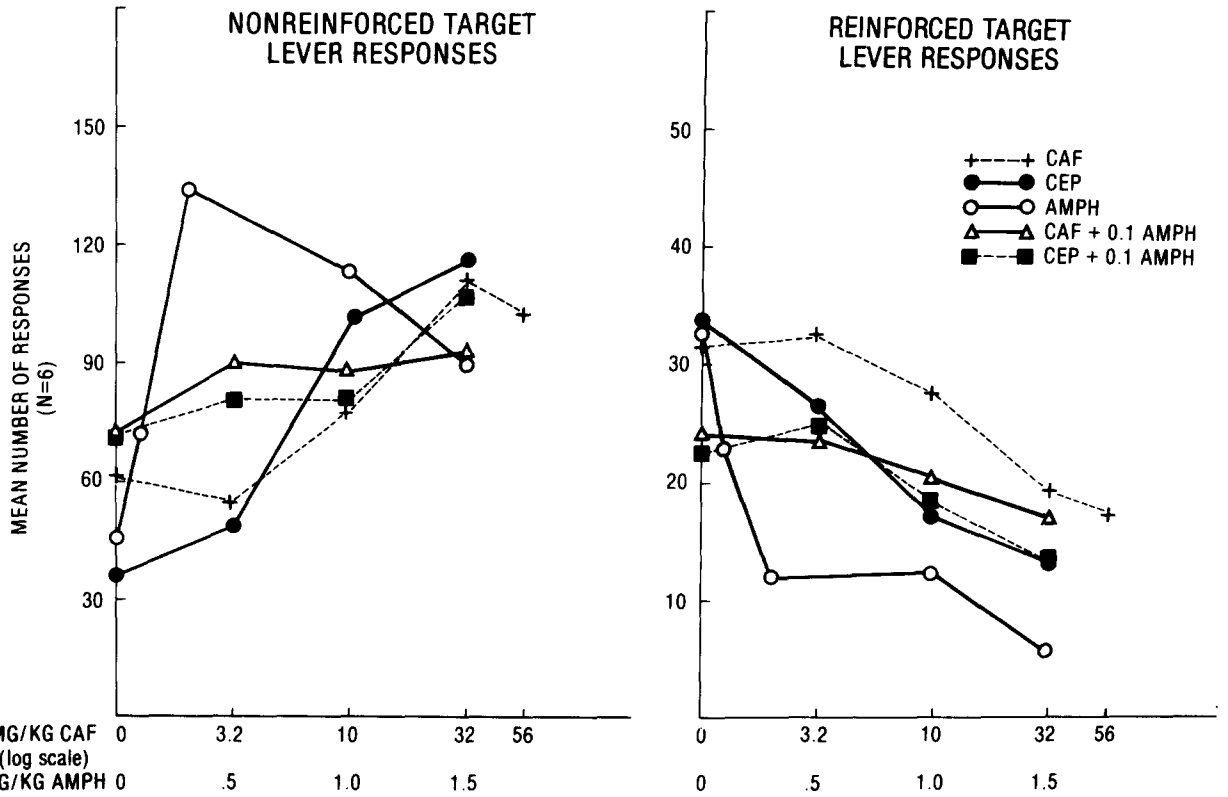

FIG. 1. Effects of drug/dose combinations on nonreinforced and reinforced target lever responses.

following misuse of these drugs [7, 10, 28, 31]. Findings such as these have fueled a heated debate in the medical literature over whether PPA is safe for use in any form [25, 27, 33].

The inexpensive cost, wide availability, and psychotropic effects of these stimulant combinations virtually assure that they will be part of the American drug scene for the forseeable future. This clearly suggests a need for understanding the neurochemical actions and behavioral pharmacology of these drugs. A moderate amount of research has partially characterized the behavioral pharmacology of caffeine and phenylethylamines individually. However, there has been very little research describing the behavioral effects of caffeine/phenylethylamine combinations [19,37]. Ephedrine and PPA are thought to be relatively weak CNS stimulants, and therefore would not be expected to be highly addictive [13, 20, 21]. In addition, although caffeine is one of the drugs most commonly self-administered by humans, its use is most frequently associated with the socially acceptable goal of increasing work output [6]. While some people may feel themselves "dependent" on caffeine's energizing effects, in most cases a headache is the only physical discomfort accompanying withdrawal [11]. Furthermore, these headaches can be treated with aspirin [11], making it relatively easy to stop consuming caffeine, even after chronic high-level intake.

Most experimental studies also suggest that these drugs have limited abuse potential when administered alone. Studies investigating the behavioral effects of the phenylethylamines most similar to ephedrine and PPA have shown them to be much less potent than amphetamine, both as stimulators of locomotor activity and as discriminative stimuli [13,20]. Furthermore, most experimental studies report that caffeine is not readily self-administered by laboratory animals [3, 9, 18, 39, 46]. However, the effect of a number of factors such as drug dose, the species of the subject, or the subject's drug history have not been systematically examined [17,38]. Similar considerations limit the conclusions one can draw regarding the abuse potential of ephedrine and PPA. While one study has reported that baboons trained to self-administer cocaine will not readily self-administer a number of phenylethylamines [16], another study has suggested that phenylethylamines are self-administered by dogs [40].

We have previously reported that certain combinations of caffeine plus ephedrine and/or PPA are capable of mimicking the subjective effects of amphetamine in a drug discrimination paradigm [19]. These findings corroborate anecdotal evidence that caffeine/phenylethylamine "look-alikes" can produce a subjective "high" similar to the "high" achieved after amphetamine ingestion. It has also been reported that simultaneous administration of caffeine enhances amphetamine's discriminative stimulus properties as well as its effects on locomotor activity [37,45]. Given that these look-alikes may frequently be ingested along with authentic amphetamines, these findings clearly highlight the need for further research into the behavioral pharmacology and abuse potential of these look-alike stimulant combinations. Operant schedules which differentially reinforce low rates of responding (DRL schedules) have frequently been used to characterize the behavioral pharmacology of psychotropic drugs. The effects of caffeine and amphetamine on performance under DRL schedules have been reported by several

researchers [2, 24, 29, 34, 35, 41, 44]. In the present study, Experiment I compares the effects of amphetamine, caffeine, and caffeine/phenylethylamine combinations on DRL performance in rats. Experiment II assesses the lethality of these drugs alone and in combination.

EXPERIMENT I: OPERANT PERFORMANCE-DRL 20 SEC

METHOD

Subjects

Six male Sprague-Dawley rats (300–350 g) (Sasco, Inc., Omaha, NE) were individually housed with free access to food and water under a 12-hour light/dark cycle (light onset 0800). Seven days before the beginning of the study, the rats were gradually reduced to 80% of their free-feeding weights. They were maintained at this level throughout the experiment, with an allowance made for normal growth rates. Water was available ad lib throughout the experiment.

Procedure

Subjects were trained and tested in standard two-lever operant chambers. Only one lever, the target lever, was programmed to deliver reinforcement. Presses on the non-target lever had no programmed consequences. Subjects were initially trained to press the target lever for 45 mg food pellets (BioServ, Inc.) under a continuous reinforcement schedule. Once the lever-press response was established, the reinforcement schedule was changed to a DRL schedule, which required subjects to delay each response until a criterion length of time had elapsed since the previous response in order to receive reinforcement. The criterion delay was gradually increased from 5 to 20 seconds, with a limited hold which was gradually increased to 60 seconds. The duration of each training session was 20 minutes. After performance stabilized and each subject met a criterion of no more than three responses per reinforcement, drug testing began. At least three saline-injection sessions were run between successive drug test sessions, with the additional requirement that each subject emit an average of no more than three responses per reinforcement during the saline-injection session immediately preceeding the next drug test session. The number of target lever responses, non-target lever responses, and reinforcements were recorded for each session. The ratio of total responses to number of reinforcements was calculated as an index of the rat's efficiency. In addition, the interresponse time (IRT) distribution was recorded for each session. In the text and figures, Bin 0 refers to responses following IRTs of 0.0–4.9 sec. Bin 1 refers to responses following IRTs of 5.0–9.9 sec. The other Bins follow a similar pattern with respect to the IRTs preceeding their respective responses, except Bin 8, which reflects all responses following IRTs greater than 40 sec. Accordingly, all responses in Bins 4–7 were reinforced, as were most of the responses falling into Bin 8.

Drugs

All drugs were calculated per salt weight except caffeine, which was purchased in free form (Eastman Kodak Company, Rochester, NY). Ephedrine hydrochloride, phenylpropanolamine hydrochloride (PPA), and *d*-amphetamine sulfate were purchased from Sigma Chemical Company, St. Louis, MO. All drugs were dissolved in 0.9% (w/v) saline and injected intraperitoneally 20 minutes before training or testing sessions.

The caffeine/ephedrine/PPA combination (CEP) was constituted in a ratio of 10:2:4, respectively. In the text and figures, doses of the CEP combination refer to the dose of caffeine present in the mixture. The 10:2:4 ratio was used for the CEP combination because this ratio is frequently found in the triple combination look-alike drugs. The CEP doses were chosen to contain the same dose of caffeine as was administered alone, except for the 56 mg/kg dose. The 56:11.2:22.4 mg/kg CEP combination was omitted for behavioral testing because it was felt that doses greater than 32:6.4:12.8 mg/kg present too great a health risk to the subjects (subsequent lethality data indicated an LD50 of 66:13.2:26.4 mg/kg). The doses of amphetamine used were chosen on the basis of previous work done in this laboratory. These doses have been shown to produce a dose-dependent stimulation of locomotor activity in rats, without inducing noticeable degrees of stereotypy. Each dose of each drug or drug combination was administered once to each animal. The order in which drugs were tested was: caffeine, amphetamine, CEP, amphetamine plus caffeine, amphetamine plus CEP.

Data Analysis

The total number of responses, number of target and non-target lever responses, number of reinforcements earned per test session, and the ratio of total responses to reinforcements were analyzed using analyses of variance, with Drug and Dose as within-subject factors. Duncan's Multiple Range Test was used for comparisons between individual drug/dose combinations. In order to analyze IRT distributions, IRTs were grouped in five-second intervals. The number of burst responses, defined as responses following IRTs of 4.9 seconds or less (Bin 0), were analyzed separately from responses following longer IRTs. The number of burst responses occurring per test session and the mean IRT preceeding the remaining responses were also analyzed using analyses of variance and Duncan's Multiple Range Test. The IRT distributions for responses following IRTs longer than 4.9 seconds were compared using the Kolmogorov-Smirnov test.

RESULTS

Figure 1 illustrates the dose-response curves obtained for nonreinforced and reinforced target lever responses after the various drug-dose combinations. In addition, Table 1 provides a detailed comparison of the dose-related changes produced in several DRL performance parameters after the various drug-dose combinations. Figure 2 illustrates the changes in the distribution of IRTs produced by 10 mg/kg caffeine, 0.1 mg/kg amphetamine, the 10 mg/kg CEP combination, and 10 mg/kg caffeine plus 0.1 mg/kg amphetamine. As mentioned earlier, IRTs were grouped in five-second bins for analysis of IRT distributions. In Fig. 2, BIN 0 represents IRTs between 0–4.9 seconds, BIN 1 represents IRTs between 5.0–9.9 seconds, etc., with BIN 8 representing IRTs of 40 seconds or greater.

The initial analysis of variance indicated significant dose-dependent effects for all drugs on all dependent measures (all p's<0.05) with two exceptions. Unlike the other drugs, caffeine had no significant effect on burst responses. In addition, only amphetamine produced significant effects on non-target lever responses.

TABLE 1

EFFECTS OF DRUGS ON DRL PERFORMANCE PARAMETERS*

Drug/Dose (mg/kg)	Total Responses/ Reinforcers		Non-Reinforced Target Responses		Reinforced Responses	
	SAL	Drug	SAL	Drug	SAL	Drug
CAFF						
3.2	2.5 ± 0.45	2.9 ± 0.80	51.0 ± 13.7	55.3 ± 19.7	34.3 ± 1.3	32.5 ± 1.5
10	2.8 ± 0.31	4.3 ± 1.1	59.2 ± 9.8	78.8 ± 20.8	29.0 ± 2.1	27.5 ± 1.7
32	4.0 ± 1.0	7.5 ± 2.8[a]	71.3 ± 17.7	111.0 ± 22.2[b]	29.3 ± 3.3	19.7 ± 2.2[b]
56	3.1 ± 0.60	7.9 ± 2.1[b]	63.3 ± 16.3	103.3 ± 22.8[b]	31.8 ± 2.2	17.7 ± 2.5[b]
CEP						
3.2	2.1 ± 0.21	3.0 ± 0.40	33.0 ± 4.6	48.7 ± 7.4	31.7 ± 2.2	26.5 ± 2.4
10	2.4 ± 0.32	10.0 ± 4.1[a]	41.8 ± 8.3	101.5 ± 17.3[b]	32.0 ± 2.6	17.3 ± 3.3[b]
32	2.0 ± 0.26	10.8 ± 2.3[b]	33.7 ± 8.3	116.5 ± 16.4[b]	37.3 ± 1.9	13.3 ± 1.5[b]
AMPH						
0.10	3.0 ± 0.47	5.7 ± 1.9	52.3 ± 11.8	72.2 ± 14.2	29.0 ± 2.5	22.7 ± 4.1[a]
0.32	3.1 ± 0.55	15.3 ± 4.4[a]	57.2 ± 12.6	134.2 ± 17.4[b]	31.7 ± 3.6	12.3 ± 2.4[b]
1.0	2.3 ± 0.22	12.0 ± 3.2	43.3 ± 6.6	115.2 ± 15.9[b]	33.0 ± 1.3	12.5 ± 1.6[b]
1.5	2.1 ± 0.23	23.6 ± 7.5[b]	40.2 ± 7.4	91.0 ± 40.0[a]	37.0 ± 1.5	5.7 ± 2.1[b]
0.1 AMPH + CAFF						
3.2	1.9 ± 0.16	7.4 ± 3.3[a]	39.0 ± 8.6	90.8 ± 23.7[b]	37.0 ± 1.1	23.8 ± 4.2[b]
10	2.0 ± 0.10	7.2 ± 2.4[a]	41.3 ± 5.4	88.2 ± 15.8[a]	35.3 ± 1.3	20.5 ± 3.6[b]
32	2.0 ± 0.26	7.0 ± 1.3	43.7 ± 12.2	93.7 ± 13.4[b]	34.5 ± 1.5	17.2 ± 1.6[b]
0.1 AMPH + CEP						
3.2	2.0 ± 0.20	4.6 ± 0.82	36.8 ± 7.2	81.5 ± 10.6[a]	35.7 ± 1.3	25.2 ± 2.6[b]
10	2.0 ± 0.25	7.0 ± 1.6	37.2 ± 6.7	81.0 ± 11.9[a]	34.2 ± 1.9	18.8 ± 2.3[b]
32	2.2 ± 0.18	13.1 ± 5.7[b]	42.5 ± 7.9	108.5 ± 31.9[a]	33.3 ± 1.3	13.0 ± 2.2[b]

Drug/Dose (mg/kg)	Burst Responses		Mean IRT† of Non-Burst Responses	
	SAL	Drug	SAL	Drug
CAFF				
3.2	33.3 ± 12.1	35.7 ± 16.0	23.0 ± 0.49	22.1 ± 1.3
10	31.0 ± 6.7	49.8 ± 16.8	21.1 ± 1.1	20.3 ± 1.0
32	42.8 ± 12.3	65.2 ± 20.9[a]	20.6 ± 1.1	17.3 ± 0.60[b]
56	38.5 ± 14.7	55.7 ± 21.3	20.7 ± 1.0	17.2 ± 0.88[b]
CEP				
3.2	13.3 ± 3.0	20.3 ± 4.5	22.7 ± 0.58	22.1 ± 1.7
10	18.8 ± 5.6	44.5 ± 9.5[a]	21.7 ± 0.79	15.7 ± 1.3[b,e]
32	17.8 ± 6.6	57.7 ± 12.9[b]	22.0 ± 0.48	14.3 ± 0.74[b,e]
AMPH				
0.10	23.7 ± 8.4	31.5 ± 8.7	20.5 ± 1.2	18.9 ± 1.7
0.32	32.8 ± 8.9	58.3 ± 14.7	21.0 ± 0.98	13.9 ± 1.1[b,e]
1.0	24.2 ± 4.7	54.8 ± 11.8	22.5 ± 0.97	14.9 ± 0.99[b,e]
1.5	21.7 ± 5.8	59.5 ± 28.0[a]	21.9 ± 0.59	14.4 ± 0.46[b,e]
0.1 AMPH + CAFF				
3.2	16.3 ± 5.3	57.3 ± 15.7[b]	22.0 ± 0.45	18.4 ± 1.2[b,d]
10	18.8 ± 3.3	49.8 ± 8.0[b]	22.2 ± 0.23	17.9 ± 1.2[b,e]
32	15.8 ± 4.5	48.2 ± 5.7[b]	23.2 ± 0.79	15.7 ± 0.25[b,e]

TABLE 1
(CONTINUED)

Drug/Dose (mg/kg)	Burst Responses SAL	Burst Responses Drug	Mean IRT† of Non-Burst Responses SAL	Mean IRT† of Non-Burst Responses Drug
0.1 AMPH + CEP				
3.2	17.3 ± 3.4	39.7 ± 4.0[b]	22.2 ± 0.81	19.1 ± 0.70[d]
10	17.0 ± 4.5	29.5 ± 5.7[a]	23.0 ± 0.82	16.8 ± 0.90[b,e]
32	23.0 ± 1.6	67.0 ± 28.1[a]	21.5 ± 0.79	18.2 ± 2.9[e]

*Significant differences compared to previous day's saline data: [a]=$p<0.05$; [b]=$p<0.01$; [c]=$p<0.001$.
†Accompanied by a significant shift in the IRT distribution (Kolmogorov-Smirnov Test): [d]=$p<0.01$; [e]=$p<0.001$.

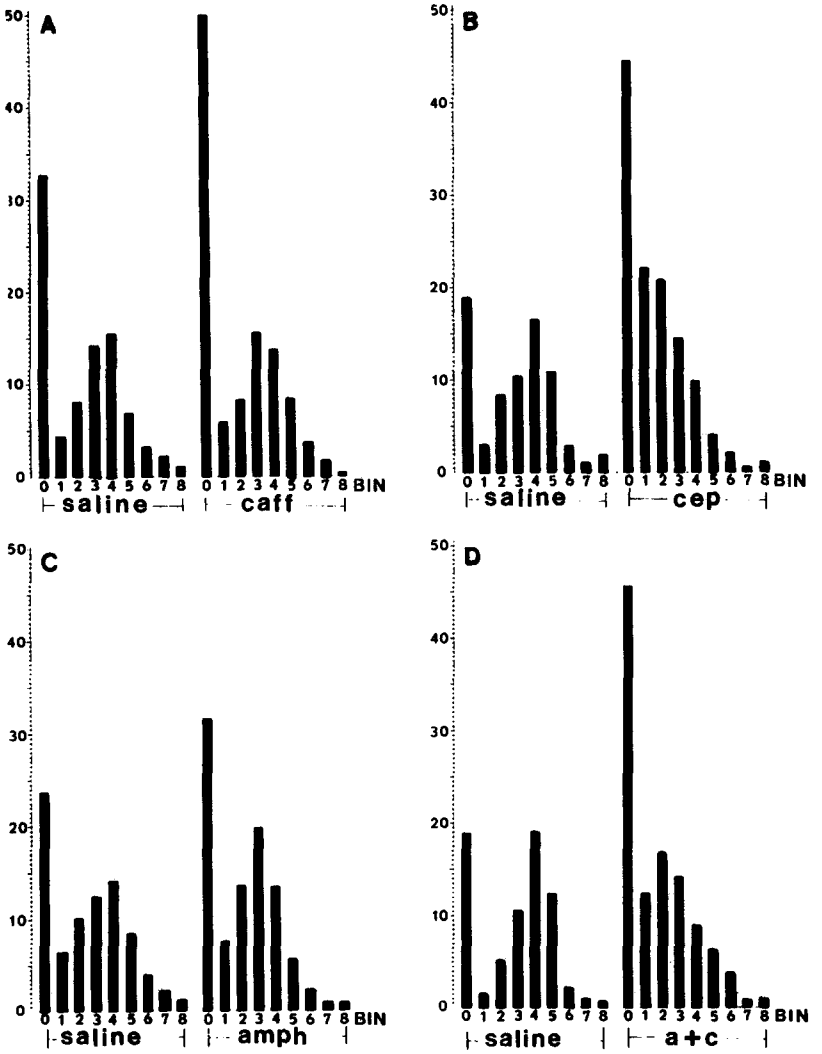

FIG. 2. Comparison of the distribution of IRTs after saline vs. (A) 10 mg/kg caffeine, (B) 10 mg/kg caffeine plus 2 mg/kg ephedrine and 4 mg/kg PPA, (C) 0.1 mg/kg amphetamine, and (D) 0.1 mg/kg amphetamine plus 10 mg/kg caffeine. Y Axis = Mean number of IRTs falling into the appropriate Bin.

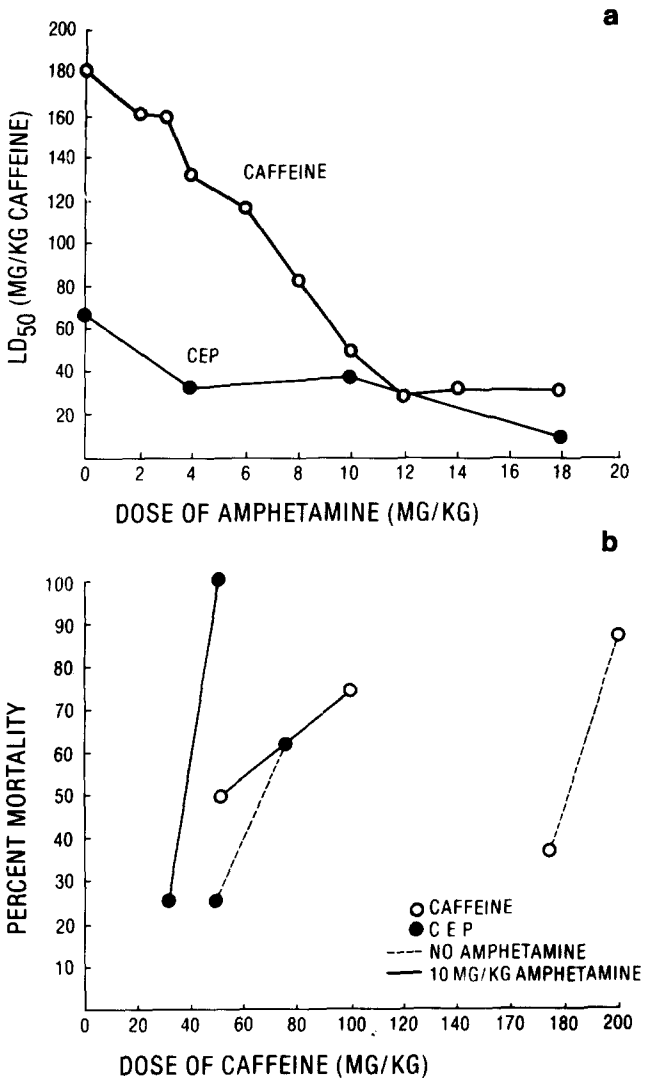

FIG. 3. Lethality of caffeine and CEP alone and in combination with various doses of amphetamine. Top: LD50 of caffeine and CEP alone and in combination with amphetamine. Bottom: percent of subjects dead after injection of caffeine or CEP with or without 10 mg/kg amphetamine.

Efficiency was significantly impaired after both 32 and 56 mg/kg caffeine. Subjects emitted more nonreinforced responses and fewer reinforced responses on the target lever after both of these caffeine doses. Both 32 and 56 mg/kg caffeine decreased the mean IRT of non-burst responses. However, none of the caffeine doses tested significantly shifted the distribution of IRTs.

The CEP combination had markedly stronger effects on DRL performance than did caffeine alone (Fig. 2, panels A vs. B). While 3.2 mg/kg caffeine had no noticeable effects on any of these behavioral measures, the 3.2 mg/kg CEP combination produced several noticeable, although nonsignificant, changes in DRL performance parameters. The two higher CEP doses (which represent higher doses of ephedrine and PPA as well as caffeine) both produced marked decreases in efficiency, involving both increases in nonreinforced responses and decreases in reinforced responses. In addition, these CEP doses produced significant increases in burst responses, decreases in the mean IRT of non-burst responses, and significant shifts in the distribution of IRTs.

Efficiency was significantly impaired by both 0.32 and 1.5 mg/kg amphetamine. In both instances, nonreinforced target lever responses were increased, while reinforced responses were decreased. A similar increase in nonreinforced responses and decrease in reinforced responses was seen after 1.0 mg/kg amphetamine, but the resultant decrease in efficiency was not significant. The only effect produced by 0.10 mg/kg amphetamine was a significant decrease in reinforced responses. The only significant change in burst responses observed after amphetamine was the significant increase seen after 1.5 mg/kg. The three highest amphetamine doses tested significantly decreased the mean IRT of non-burst responses, and significantly shifted the distribution of IRTs. Finally, a significant increase in non-target lever responding was seen after 1.0 mg/kg amphetamine (not shown in table).

The 0.1 mg/kg amphetamine dose markedly enhanced the effects of low doses of caffeine (Fig. 2, panels A, C, D). Neither 3.2 nor 10 mg/kg caffeine alone produced any significant changes in any of the DRL performance parameters. Similarly, the only significant change seen after 0.10 mg/kg amphetamine alone was the decrease in reinforced responses. However, when given together, both these caffeine-amphetamine combinations produced consistent patterns of decreased efficiency, increases in nonreinforced and decreased reinforced responding, increases in burst responding, decreases in mean IRT of non-burst responses, as well as significant shifts in the distribution of IRTs. There was a clear difference in the interactions between 0.1 mg/kg amphetamine and caffeine versus the CEP combination. The 0.1 mg/kg amphetamine dose slightly enhanced the effects of the 3.2 mg/kg CEP combination on DRL performance. However, the effects of higher doses of the CEP combination were not consistently enhanced by the addition of 0.1 mg/kg amphetamine. The higher doses of the CEP combination produced approximately equivalent profiles of changes in DRL performance with and without the addition of 0.1 mg/kg amphetamine.

EXPERIMENT II: LETHALITY

METHOD

Subjects, housing conditions, and drug preparations were as described for Experiment I. The number of rats for each drug/dose condition was 8, with weights ranging from 310–576 g. Some animals had been used in prior studies but at least one week lapsed prior to their use in the present investigation. The animals included the six rats from whom the present DRL data were obtained, as well as some that had a history of ethanol exposure. While it is recognized that the lethality data of these subjects may not be comparable to that of naive rats, it was felt that this issue was of sufficient clinical significance to merit a preliminary investigation. In addition, it was deemed most prudent to use rats who were already scheduled to be sacrificed for this preliminary investigation. Subjects with any prior drug experience were distributed as evenly as possible among the various drug/dose groups. This study assessed the 50% lethal dose (LD50) for amphetamine (2–18 mg/kg, free base), caffeine (10–180 mg/kg, free base), and the CEP combination alone, as well as several combinations of amphetamine (same dose range) plus either caffeine (same dose range) only or the CEP combination (same caffeine dose range). Drugs were injected in-

traperitoneally between the hours of 1600 and 1800. Observations for morbidity or lethality were made within the first four hours after injection and 24 hours after injection.

RESULTS

Figure 3a depicts the LD50 for caffeine and the CEP combination alone and in combination with several doses of amphetamine. The CEP dose is expressed as the dose of caffeine present in the mixture. The LD50 of amphetamine alone in the rat ranges from 60 to 150 mg/kg [16] depending on a variety of factors. The LD50 for caffeine alone (180 mg/kg) was almost three times as high as the LD50 for the CEP combination alone (66 mg/kg).

The interactions between these drugs with respect to their lethal effects were similar to the interactions with respect to DRL performance. As can be seen in Fig. 3a and 3b, amphetamine markedly enhanced the lethality of caffeine, while it only slightly enhanced the lethal effects of the CEP combination. For example, at 10 mg/kg amphetamine (a dose 1/6 the lower limit of reported amphetamine LD50s), the LD50 for caffeine is 50 mg/kg (less than one-third that for caffeine alone) and for the CEP combination is 38 mg/kg (slightly over one-half that for the CEP combination alone).

Figure 3b shows the % of rats dead 24 hours after various caffeine or CEP doses in combination with 10 mg/kg amphetamine. The slopes for the dose-effect curves for caffeine or turkey drug alone are relatively steep but parallel. When combined with 10 mg/kg amphetamine, both the caffeine and CEP curves are shifted to the left, indicating increased lethality. In addition, the slope of the CEP drug combination curve became very steep while the slope for the caffeine curve became more shallow. The latter differences in slope suggest that the nature of amphetamine-caffeine and of amphetamine-CEP interaction is different.

All animals that died did so after one hour, but within the 24-hour post-injection period. While no systematic attempt was made to monitor behavior, most rats displayed one or more of the following signs: piloerection, hyperactivity, convulsive movements, "agitation" or heightened reactivity, salivation, and signs of stereotypy (sniffing and head bobbing).

GENERAL DISCUSSION

The effects of caffeine and amphetamine alone on DRL responding were similar to those reported by other experimenters. Several studies have reported increases in total responses, accompanied by shifts toward lower IRTs and increases in reinforced responses, after administration of these drugs [2, 24, 29, 34, 35, 41, 44]. In addition, the present data clearly demonstrate that addition of ephedrine and PPA to caffeine markedly enhances the effects on DRL responding. This finding, along with the finding that the CEP combination can mimic the interoceptive stimulus effects of amphetamine [19], clearly suggests that these caffeine/phenylethylamine combinations are potent CNS stimulants with behaviorally disruptive effects and abuse potential similar to that of amphetamine. In addition, the lethality data from the present study clearly suggest that these caffeine/phenylethylamine combinations are very dangerous drugs, especially when ingested along with authentic amphetamines.

The interactions between caffeine and the phenylethylamines, including amphetamine, most probably involve catecholaminergic systems. However, the precise neuropharmacological mechanism for these interactions is as yet unclear. There is evidence that ephedrine and PPA are both dopaminergic [47,48] and noradrenergic [21] stimulants. In addition, caffeine's ability to enhance the discriminative stimulus effects of both amphetamine [37] and apomorphine [36] is blocked by haloperidol. This suggests a dopaminergic basis for the interactions between caffeine and the phenylethylamines, perhaps involving caffeine's ability to inhibit a dopamine receptor-linked cyclic nucleotide phosphodiesterase [8]. It has also been shown, however, that noradrenergic receptor blockade antagonizes the lethal effects of caffeine/PPA combinations [22].

Recent surveys of young people clearly suggest that recreational stimulant use is on the rise [1,12]. In addition, confiscated samples of street drugs frequently contain caffeine and/or caffeine-phenylethylamine combinations similar to the CEP combination used in the present study, sometimes mixed with authentic amphetamines [1]. The present study, along with our previous findings [19], clearly suggests that this CEP combination is capable of mimicking the interoceptive "high" and behaviorally disruptive effects produced by amphetamine. These findings suggest that caffeine-phenylethylamine combinations will continue to be popular among people who use stimulants for their energizing or euphoric effects, despite the recent FDA ruling prohibiting the marketing of these drugs. The results of the present study further characterize the behavioral pharmacology of this CEP combination. In addition, they strongly suggest that there is a potential for dangerous interactions among these drugs when any combination of caffeine plus phenylethylamines are ingested together. These findings highlight our need for further knowledge regarding the abuse potential and biomedical hazards associated with these stimulant combinations.

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