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Behavioral Interaction Between Cocaine and Caffeine: A Drug Discrimination Analysis in Rats

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HARLAND, R. D., D. V. GAUVIN, R. C. MICHAELIS, J. M. CARNEY, T. W. SEALE AND F. A. HOLLOWAY. *Behavioral interaction between cocaine and caffeine: A drug discrimination analysis in rats.* PHARMACOL BIOCHEM BEHAV **32**(4) 1017–1023, 1989.—The effects of caffeine upon the discriminative and rate-altering effects of cocaine were examined in rats. Using a food-reinforced two-lever operant procedure, 12 Sprague-Dawley male rats were trained to discriminate between 10 mg/kg cocaine and saline. Stimulus generalization tests with both cocaine and amphetamine resulted in a dose-related increase in cocaine-appropriate responding. A variable response rate topography was produced by cocaine. Caffeine also engendered a dose-related increase in cocaine-appropriate responding and resulted in a potency ratio of 15:1 when compared to cocaine. In contrast, increasing doses of caffeine produced a biphasic response rate function (first increases and then decreases). Response choice data suggested a potency relationship of amphetamine > cocaine > caffeine. Caffeine potentiated the discriminative stimulus properties of cocaine. Isobolographic analysis characterized this interaction as simple additivity. However, caffeine's effects upon the rate-altering effects of cocaine resulted in a biphasic interaction pattern. With low doses of cocaine in combination with various doses of caffeine, the interaction for rate reduction is best categorized as "supra-additive," in contrast, increasing either the cocaine dose or caffeine dose could change the interaction to simple additivity and/or infra-additivity.

Drug discrimination Caffeine Cocaine Amphetamine Isobologram Drug interaction

CAFFEINE is one of the most ubiquitous of orally ingested drugs. Its frequency and pattern of use in foodstuffs, beverages, and over-the-counter medications and its presence in "street drugs" increases the likelihood of its joint usage and possible interaction with other drugs, including controlled substances.

Caffeine is generally regarded as a benign psychoactive stimulant, but depending upon the dose, can produce many of the behavioral effects seen with the prototypic psychomotor stimulants cocaine and amphetamine (9). For example, one of these effects, the increase in locomotor activity in rodents (15, 30, 34, 36, 41, 42), can be elicited by each of these stimulants and generally is assumed to result from increased catecholamine concentrations at the synapse (1,37). Growing evidence supports the view that these effects are due to indirect dopamine (DA) agonist effects (4, 7, 13, 17, 42).

McMillen (25) has proposed two subclasses of sympathomimetic behavioral stimulants. One, represented by amphetamine, causes release of endogenous DA, while the second class, represented by cocaine, acts to block reuptake of DA and other catecholamines and serotonin. Postulation of a third subclass, represented by caffeine, seems appropriate. Watanabe and Uramoto (43) have suggested that caffeine stimulates pre- and postsynaptic DA receptors indirectly by 1) modifying the release of DA from nerve endings or 2) through a transynaptic mechanism mediated via a neuronal feedback loop through blockade of the adenosine receptors. Stromberg and Waldeck (38) have suggested that part of the potentiating effects of caffeine upon dopamine-related activity may result from both an increase in cerebral levels of DA and from catecholamine-receptor sensitization. The initial accumulation of DA levels after caffeine administration appears to be due to a reduction in cyclic AMP inactivation (42). Although the pharmacological mechanism of caffeine appears complex, Rall (33) has concluded at least three major modes of action: 1) translocation of intracellular calcium; 2) increasing accumulation of cyclic nucleotides, particularly cyclic AMP; and 3) blockade of adenosine receptors. Taken together, these results suggest three different

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modes of action by which cocaine, amphetamine, and caffeine act as indirect agonists by increasing DA levels at DA terminals.

One possible method of assessing the relative contribution of these indirect acting agonists is to investigate the relative interactions between them using a standard behavioral assay (46). One behavioral assay which seems well suited for the interaction analysis is the drug discrimination procedure (31,44), in which the generalization pattern or profile to other drugs can be characterized. The discriminative stimulus profile of cocaine is well documented in the literature for rats (3, 6, 8, 22), monkeys (12, 47), and pigeons (11, 23, 39). Similarly, the discriminative stimulus properties of caffeine have been described in rats (18, 21, 27, 28, 45). To our knowledge, however, no systematic investigation using this assay has reported the interactive effects between cocaine and caffeine. This laboratory has previously reported the interaction between amphetamine and caffeine (18).

The present study was designed to assess the relative interaction between two of these indirect DA agonists, caffeine and cocaine. Using a standard two-lever drug discrimination training procedure in rats, we investigated the effects of caffeine on both the discriminative stimulus properties and the rate-altering effects of cocaine. These measures have been reported to be partially independent measures (14). *d*-Amphetamine was also tested for comparison purposes.

METHOD

Subjects

Twelve experimentally- and drug-naive male Sprague-Dawley rats (250–275 grams) were purchased from Sasco, Inc. (Omaha, NE) and randomly assigned to three groups. Animals were housed individually in standard suspended wire cages in a colony room maintained under a 12-hour light/dark cycle (lights on at 0630 hours). Water was continously available in the home cages. Rats were reduced to 85% of their free feeding weights and initially maintained at these weights by 45-mg food pellets (BioServ, Inc., Frenchtown, NJ) delivered during the experimental session and supplemental rat chow provided after the session. Over the course of the experiment, supplemental feeding was increased so that weights increased by 10 g per month up to a maximum weight of 450 g.

Apparatus

Experimental sessions were conducted in standard operant chambers (Lehigh Valley Electronics, Lehigh Valley, PA) containing stimulus lamps and two levers mounted equidistant from a recessed food receptacle. Chambers were housed in ventilated, sound-attenuating cabinets. Food pellets were delivered by dispensers mounted outside the chambers. Programming of events and data collection (32) were accomplished with PROMAL software (American Neuroscience Research Foundation, Yukon, OK) on Commodore-64 microcomputers interfaced with the chambers (Rayfield Equipment, Ltd., Waitsfield, VT). Ventilation and masking noise were provided by a fan mounted in the wall of each sound attenuating box.

Training

Subjects were trained to the magazine food delivery system and to operate the saline-appropriate lever by the method of successive approximations.

The illumination of the stimulus and house lights signaled the beginning of the 10-minute experimental sessions. The group of 12 animals was subdivided into 3 squads (N = 4) for lever selection assignments, which were partially counter-balanced. Each response (FR-1) on the saline-appropriate lever was reinforced by the delivery of one 45-mg food pellet into the food cup. Over successive training sessions the schedule of reinforcement was gradually increased from FR-1 to a variable ratio 10 (VR-10, min 5, max 15). Once response rates stabilized on the saline lever ($\pm$ 10% from session to session), training on the opposite cocaine lever began. Intraperitoneal injections of 10 mg/kg cocaine (training dose) were administered 15 minutes prior to the session and subjects were trained to press the lever opposite the one pressed during the previous (no drug) sessions. After responding on the cocaine lever stabilized, cocaine (COC) and saline (SAL) training sessions were scheduled in a double-alternation sequence (i.e., COC/COC/SAL/SAL). Once animals were responding under the VR 5–15 schedule of reinforcement with stable rates, then one day per week the 10-minute training session was extended to 11 minutes. This unique session per week constituted a test/train session in which the first minute was scheduled as an extinction test in which no reinforcers were delivered and provided an index of the subject's ability to discriminate between the two stimuli (19). Training continued until two training criteria were met: 1) discriminative accuracy reached a criterion of 80% or greater during the 1-minute extinction for 9 out of 10 test/train sessions, and 2) rates of responding had a day-to-day stability of $\pm$ 10% on four successive cocaine and four successive saline training days.

Testing

Once criterion discriminative stimulus control was established, dose-response generalization gradients were generated with a single dosing regimen in separate 2-minute extinction tests. Tests were conducted with various doses of compounds administered intraperitoneally in a pseudo-random sequence 15 minutes prior to the test session. Training and test sessions were run five days per week during the initial training and test phases in which the single drug generalization functions were generated. When drug combinations were tested, experimental sessions were shifted to seven days per week. Prior to drug combination tests one injection was administered on one side of the abdomen immediately followed by the second injection on the opposite side. The following dose-response functions were generated: cocaine, amphetamine, caffeine, and various doses of cocaine in combination with various doss of caffeine.

During the testing phase there were three training criteria required prior to testing: 1) one successful test/train session occurred per week in which discriminative accuracy exceeded 80% during the initial 1-minute extinction period, 2) stable response rates ($\pm$ 10%) during intervening training sessions, and 3) greater than 80% discriminative accuracy during the saline and cocaine training sessions. Each test session was preceded by two criterion training days (saline and cocaine). If during a training day subjects failed to meet the training criteria of emitting greater than 80% of the total session responses on the stimulus-appropriate lever, further testing was postponed until criterion performance was reestablished for both training stimuli. With these stringent test criteria, test sessions were run approximately once per week. A typical week training/test schedule follows: train saline, train cocaine, test, train cocaine, test/train saline.

Drugs

(−)Cocaine hydrochloride, *d*-amphetamine sulfate, and caffeine were purchased from Sigma Chemical Company (St. Louis, MO). All drugs were dissolved in 0.9% normal saline and injected intraperitoneally 15 minutes before the session. All doses are

expressed as the salt except for caffeine, which was purchased in free form.

Data Analysis

A test drug and dose was considered to generalize to the 10 mg/kg cocaine training stimulus if >70% of the total session responses were emitted on the cocaine-appropriate lever. Test session discriminative performance is expressed as the percentage of total session responses emitted on the cocaine-appropriate lever. Response choice data were analyzed by one-way (S × T) ANOVA for dose-related effects; individual dose comparisons were made with Duncan's New Multiple Range Test.

Rates of responding are expressed as the total number of responses emitted on either lever throughout the two-minute extinction test session.

Isobolographic analyses were conducted according to Woolverton (46) and Wessinger (44). The ED_{50} values were calculated for both drugs in each rat from linear regression equations determined by the method of least squares. ED_{50} values for % COC-responses and for total responses, as well as 95% confidence limits were calculated for each compound alone and for various doses of cocaine in combination with various doses of caffeine. In order to provide appropriate confidence interval values for the ED_{50} scores derived from differing numbers of subjects tested, the confidence interval was calculated to equal the standard error multiplied by the *t*-score with the appropriate degrees of freedom. The sample size for cocaine combinations with various doses of caffeine were: SAL—11; 3.2 mg/kg—8; 10 mg/kg—9; 25 mg/kg—4; and 32 mg/kg—8 (the 25 mg/kg interaction was the last tested). The sample size for caffeine interactions with various doses of cocaine were: SAL—11; 1.25 mg/kg—8; and 2.5 mg/kg—10. A practical problem in the use of isobolograms (44) is how to determine if the effects of drug combinations deviate significantly from what is predicted from the individual actions of the two drugs. There does not appear to be an adequate statistical test for deviation from the dose-additivity line (44,46). Therefore, the ends of the confidence limits for the ED_{50}s of cocaine and caffeine alone were connected to establish a conservative estimate of dose-additivity. An interaction was concluded to differ from additivity if the group-averaged ED_{50} value for the combination doses fell outside the range of these confidence limits. Response rates are expressed as a percentage of saline response rates. Saline response rates represent the mean rates of responding in eight saline test sessions conducted throughout the length of the study. Response choice ED_{50} values were defined and estimated in a fashion similar to Barry (2) and Woolverton (46). These values were plotted and compared as described for response rate ED_{50}s.

Further analysis of response rate functions were made utilizing a Type II isobologram (26) and tested for statistical significance using a simple *t*-test for dependent samples ($df=6$, p values as stated in text).

RESULTS

Cocaine produced a dose-related increase in the percentage of responses emitted on the cocaine-appropriate lever during two-minute extinction tests (Fig. 1A), ANOVA, $F(5,50)=19.12$, $p<0.001$. Similar results were obtained when generalization tests were conducted for comparison purposes with *d*-amphetamine (Fig. 1A). Dose-related increases in the percentage of cocaine-appropriate lever responses were engendered across a five-fold increase in amphetamine doses, ANOVA, $F(6,42)=23.58$, $p<0.001$. Tests with caffeine produced an intermediate level of generalization to the cocaine stimulus (Fig. 1A). However, even

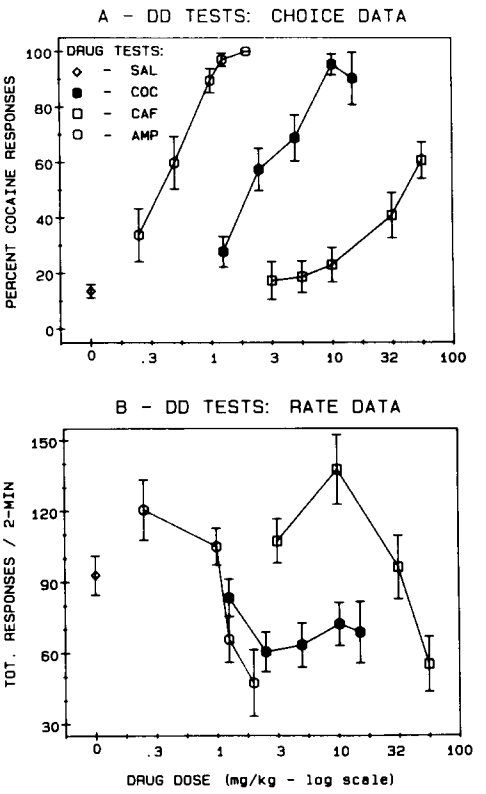

FIG. 1. Dose-related effects of cocaine, *d*-amphetamine, and caffeine upon response choice and response rate in Sprague-Dawley rats (N = 12) trained in a two-choice, appetitively-reinforced drug discrimination task utilizing 10 mg/kg cocaine and saline as discriminative stimuli. Response choice is expressed as the percentage of total session responses (±S.E.M.) emitted on the cocaine-appropriate lever during the two-minute extinction test trials (A—upper panel). Response rates are expressed as the mean number of total session responses (±S.E.M.) emitted on either lever throughout the two-minute extinction test sessions (B—lower panel).

the highest caffeine dose tested (56 mg/kg) failed to completely generalize to the cocaine training dose, ANOVA, $F(5,35)=9.24$, $p<0.001$.

The dose-related effects on response rate (i.e., total number of responses emitted during the two-minute extinction test sessions) are shown in Fig. 1B. Significant dose-related effects on response rate were found for all three drugs (ANOVAs, p's<0.05). While cocaine did not elicit a rate-increasing effect at any test dose, significant rate-decreasing effects were found for the 2.5 and 5.0 mg/kg cocaine doses (p's<0.01). However, *d*-amphetamine elicited rate-increasing effects at the 0.25 mg/kg dose ($p<0.05$) and rate-decreasing effects at the 1.5 and 2.0 mg/kg doses (p's<0.05). Similarly, caffeine elicited rate-increasing effects at the 10 mg/kg dose ($p<0.05$) and rate-decreasing effects at the 56 mg/kg dose ($p<0.05$).

Test sessions were conducted to assess whether or not caffeine in combination with lower doses (1.25, 2.5, and 5.0 mg/kg) of cocaine could engender complete generalization to the cocaine stimulus (Fig. 2A). A dose of 1.25 mg/kg cocaine alone engendered less than 30% drug-appropriate responding across all animals. But the combination of this cocaine dose with caffeine (Fig. 2A) resulted in an increase in cocaine-appropriate responding up to a level greater than 70%. The administration of caffeine with a 2.5 dose of cocaine also potentiated the cocaine cue. Complete

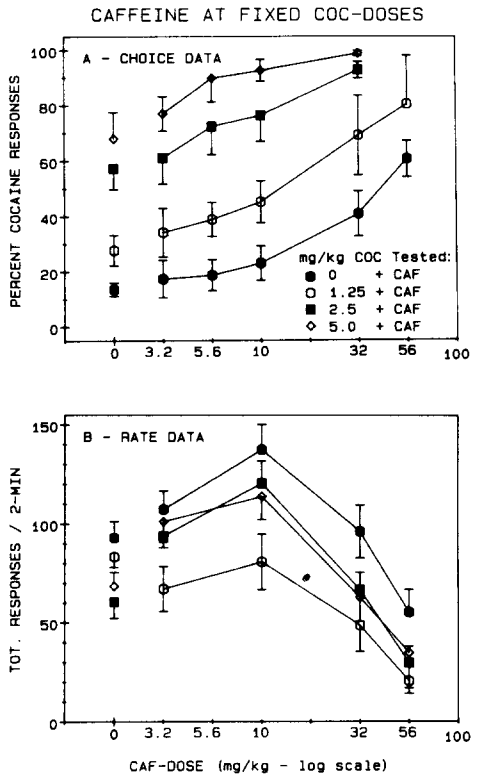

FIG. 2. Dose-related effects of caffeine administered alone or in combination with three doses of cocaine (1.25, 2.5, 5.0 mg/kg) upon response rate and choice. Each point represents the mean percentage (±S.E.M.) of total session responses emitted upon the cocaine-appropriate lever (A—upper panel) during the two-minute extinction test sessions. Response rates (B—lower panel) are expressed as the mean number of total session responses (±S.E.M.) emitted on either lever throughout the two-minute extinction test sessions (N=8 to 10).

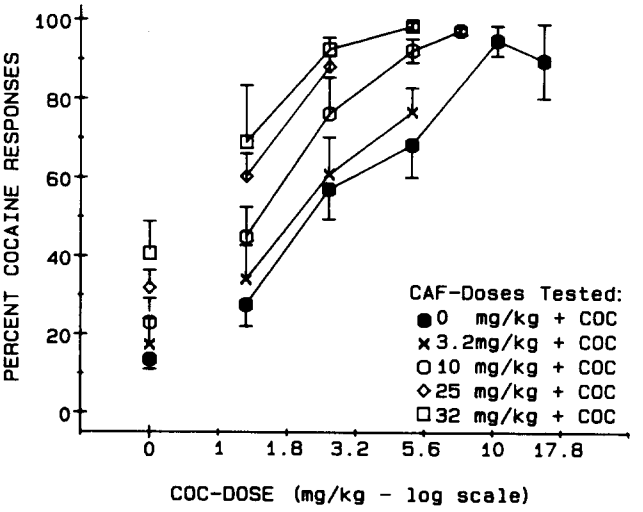

FIG. 3. Dose-related effects of cocaine administered alone or in combination with various doses of caffeine (3.2, 10, 25, or 32 mg/kg) upon response choice. Each point represents the mean percentage (±S.E.M.) of total session responses emitted upon the cocaine-appropriate lever during the two-minute extinction test sessions (N=8 to 11, except for 25 mg/kg caffeine in which N=4).

generalization (greater than 90%) occurred when 2.5 and 5.0 mg/kg cocaine doses were combined with 32 mg/kg caffeine (Fig. 2A). Tests for additivity at each caffeine-cocaine combination were made by dependent *t*-test comparisons of the expected (caffeine alone plus cocaine alone) and actual % COC response values. No test was significant (all t's<1) for all comparisons). Further, the several cocaine-caffeine dose curves did not differ from being parallel with the caffeine-alone curve [$p>0.25$; (40)].

The dose-related effects of caffeine-cocaine combinations on response rates are shown in Fig. 2B. With increasing doses of cocaine in combination with caffeine, the caffeine dose-effect function is shifted downward. The downward shift in the rate function was greater when caffeine was coadministered with 1.25 mg/kg cocaine than when coadministered with 2.5 or 5.0 mg/kg cocaine (see below).

Figure 3 shows the effects of combining 3.2, 10, 25, or 32 mg/kg caffeine with various doses of cocaine upon response choice. Combining various doses of cocaine with these selected doses of caffeine resulted in a leftward shift in the cocaine dose-response function for response choice. Again, *t*-tests for additivity showed no significant differences from values predicted by each dose of cocaine or caffeine alone.

Figure 4A is the dose-additive isobolographic analyses for the discriminative stimulus effects of cocaine across a wide range of caffeine doses. Woolverton (46) has suggested that a distinction between percent effect and percent subjects be identified by the labels ED_{50} and ED-50, respectively. Isobolographic analysis of the ED_{50} values (Fig. 4A) for response choice show a simple-additive effect between caffeine and cocaine. The two doses of cocaine (1.25 and 2.5 mg/kg) tested in combination with a wide range of caffeine doses and four doses of caffeine in combination with various doses of cocaine resulted in values which lie within the theoretical confidence limits for simple additivity (46). The ED_{50} doses of caffeine in combination with various doses of cocaine (closed circles) lie along the theoretical additivity line. However, the ED_{50} values calculated for cocaine in combination with various doses of caffeine (open circles) resulted in a trend toward supra-additivity.

Figure 4B is the dose-additive isobolographic analysis for response rates across a wide range of cocaine and caffeine doses. The ED_{50}s for response rate (group average decrease in response rates to 50% of saline control rates in each animal) resulted in a biphasic response pattern. A low dose of cocaine (1.25 mg/kg) in combination with various doses of caffeine and 25 mg/kg caffeine in combination with several doses of cocaine resulted in a "supra-additive" effect upon response rates. However, increasing either the cocaine or caffeine dose could change the interaction to simple-additivity and/or infra-additivity (46). Similar results were found when ED_{75}s were analyzed by isobolographic analysis (data not shown).

Total responses as a function of cocaine dose are shown in Fig. 5. Points on the lower line represent the total number of responses emitted on either lever during test sessions of cocaine alone. Points on the upper line represent total responses with the averaged dose of caffeine that engendered the maximum rate-increasing effects in each subject during cocaine-caffeine interaction tests. Caffeine alone increased rates maximally at different doses in different rats (mean dose = 7.4 mg/kg, S.E. = 1.3 mg/kg) relative to the average saline response rates (symbol above zero value on the abscissa, *t*-test, $df=6$, $p<0.01$). Cocaine in combination with caffeine resulted in an increase in the caffeine dose required to generate maximum rates (asterisked values above closed circles). The increase in caffeine dose required to engender maximum rate-increasing effects when combined with cocaine was not statisti-

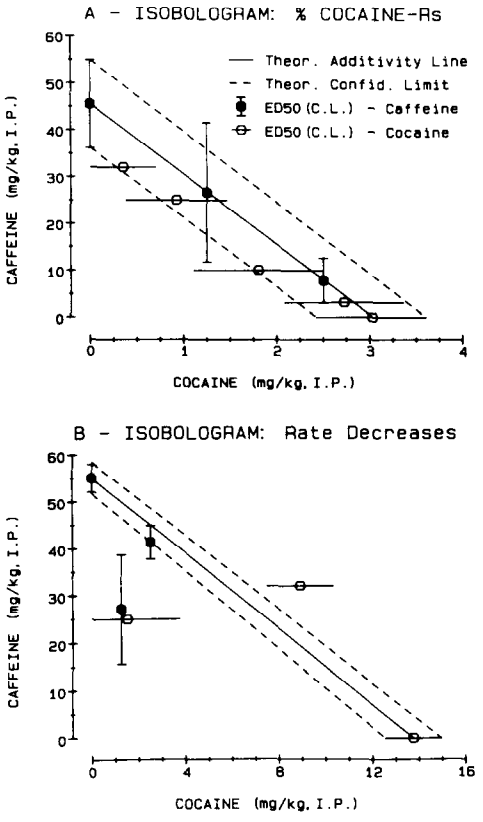

FIG. 4. Dose-additive isobolograms for the behavioral effects of caffeine in combination with cocaine upon response choice and rates. Response choice is expressed as the percentage of total session responses emitted upon the cocaine-appropriate lever (A). Response rates are expressed as the percentage of saline baseline rates which were determined over the entire course of the study. The ED_{50} (and 95% C.L.) of each drug when given alone are presented on the ordinate and abscissa. The diagonal line represents the combinations predicted by dose addition to produce 50% effect. Each point on the graphs represents the ED_{50} value for either caffeine when administered alone with a fixed dose of cocaine (closed circles) or for cocaine when administered with a fixed dose of caffeine (open circles) (N = 8 to 11, except for data generated with 25 mg/kg caffeine where N = 4).

cally significant ($p = 0.052$, t-test, $df = 6$), but suggested an increasing trend. Each point of the maximum caffeine rate function for cocaine-caffeine interactions (solid circles) was significantly greater than the associated cocaine-alone dose response rate (one-tailed t-test, dependent samples, $df = 6$, $p < 0.05$).

DISCUSSION

The discriminative profile of cocaine in the present study was similar to previously published data for rat subjects (8, 16, 24) in that cocaine and amphetamine appear to be interchangeable but differ in potency (8). The ED_{50} was defined according to Barry (2) and D'Mello and Stolerman (8) as that dose of agonist which would have been expected to produce 50% threshold responding on the cocaine-appropriate lever. The mean ED_{50} for cocaine was 3.0 (±0.28) mg/kg and for amphetamine, 0.44 (±0.07) mg/kg. The relative amphetamine:cocaine potency ratio calculated from our data was 1:6.9, slightly higher than the 1:4.5 ratio found by D'Mello and Stolerman (8).

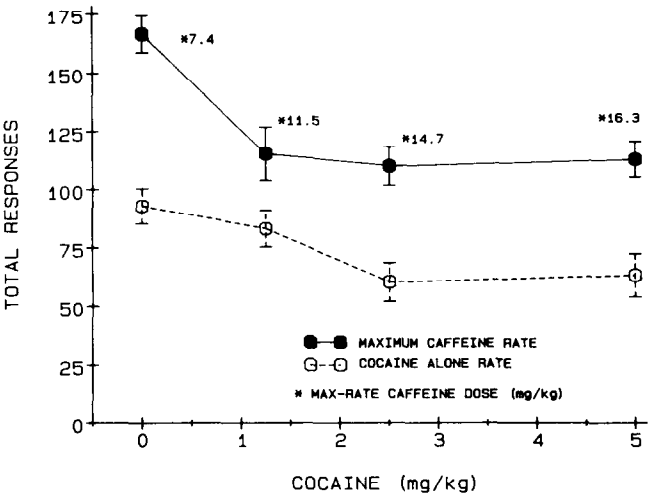

FIG. 5. Modified Type II isobologram (26) for the rate-increasing effects of caffeine. The group averaged dose of caffeine that engendered maximum levels of responding when administered alone or in combination with cocaine (±S.E.M., closed circles) is compared with the level of responding for each cocaine dose when administered alone (±S.E.M., open circles). The averaged caffeine dose for each point is listed for each cocaine-caffeine combination tests (S.E.s for caffeine dose ranged from 1.3 to 3.7 mg/kg).

The caffeine discriminative generalization resulted in a mean ED_{50} value of 45.5 (±9.56) mg/kg caffeine. The resulting caffeine:cocaine potency ratio was 15:1. Holtzman (21) has reported that rats trained to discriminate between 30 mg/kg caffeine and saline in a shock-avoidance/escape paradigm totally generalized to cocaine with a caffeine:cocaine potency ratio of 1:2.17. This disparity between the potency ratios for caffeine and cocaine in the present study and those reported by Holtzman (21) may be due to the differences in training drug or behavioral contingencies employed in the two studies.

In general, the data from the discriminative profile of the present study support the conclusions of Dews (9) in that the three indirect-acting DA agonists share similar behavioral profiles which appear to be dose-dependent.

The interaction between the discriminative stimulus properties of cocaine and caffeine as reflected in data transformation into isobolograms appear to be best categorized as "simple-additivity" (46). This conclusion likely holds only for the drug lever percentages ranging from 25 to 75%. Clearly, at the low and high ends of the % drug lever distributions, ceiling and floor effects are seen. Although all calculated ED_{50} values were within the confidence limits of the simple-additivity line, the cocaine ED_{50}s exhibited a trend toward supra-additivity. This apparent asymmetry is not surprising since there exists an analogous asymmetry between the discriminative stimulus effects of these two drugs with respect to their cross-generalization profiles; i.e., caffeine partially generalized to the cocaine training cue, but cocaine does not generalize to a caffeine training cue (unpublished results).

If one assumes a continuous generalization gradient, at least two interpretations of partial generalization are possible: such data reflect 1) chance, random, or disorganized responding; or 2) a true estimate of the quality or intensity of the drug cue. In the present study, caffeine partially generalized to the cocaine stimulus. Tests of cocaine-caffeine combinations suggested a simple effect- and dose-additive interaction between the two drug stimuli. The

discriminative stimulus properties of caffeine were potentiated additively by cocaine. These data support the notion that discriminative performance, and in particular, partial generalization, may reflect an accurate assessment of the qualitative and/or quantitative similarities between drug stimuli.

The interaction between the rate-altering effects of cocaine and caffeine resulted in a biphasic pattern. A low dose of cocaine (1.25 mg/kg) in combination with a wide range of caffeine (3.2 to 56 mg/kg) resulted in a greater than additive effect upon the rate of responding (Fig. 4B). Transformation of the rate effect data into an isobolograph resulted in the conclusion that low doses of cocaine in combination with caffeine engendered a supra-additive (46) interaction. However, increasing the dose of cocaine with various doses of caffeine *or* combining a high dose of caffeine (32 mg/kg) with a wide range of cocaine doses resulted in either simple additivity and/or infra-additivity (46).

Dews (9) has suggested that the establishment of a physiological interaction between drugs in their effects on behavior requires the demonstration that the combined effects cannot be accounted for by the drugs acting independently. Since drugs affect the rate of responding and since rate of responding can alter the effect of the second drug, physiological potentiation and antagonism cannot be established or refuted without taking account of rate-dependency ralationships (10). Mitchell (26) has suggested a differentiation between Type I and Type II drug interactions. The Type I is represented by situations in which the desired effect can be produced by both substances alone. Figure 4 shows the isobolographic analysis for the rate-decreasing effects elicited by both cocaine and caffeine. The rate-decreasing effects of cocaine and caffeine appear to be of the Type I interaction (26). The Type II interaction occurs when only one of the two substances administered alone produces a specific effect. In the present study, caffeine, when administered alone, elicited a rate-increasing effect that was not seen with the administration of any of the cocaine doses. Figure 5 is a modified Type II isobole for the alteration of the rate-increasing effects of caffeine by cocaine (26). The increase in caffeine dose required when combined with cocaine to engender rate-increasing effects supports the Type I isobole (Fig. 4B) in that 1) the rate-decreasing effects of caffeine were engendered by doses greater than those engendering rate-increasing effects, and 2) the caffeine dose required to elicit rate-decreasing effects was shifted to the right as a result of the shift in the rate-increasing effects. Therefore, the analysis of the Type I isobole suggests the interaction between cocaine and caffeine on the rate-decreasing ED-50's was "infra-additive" at the high cocaine-caffeine doses. This was further supported by the Type II isobole for rate-increasing effects of caffeine.

These data support the notion that caffeine has some degree of abuse potential when used/abused in combination with other psychomotor stimulants. The drug discrimination procedure results in a behavioral endpoint which has been suggested to reflect the type of receptor with which a drug interacts to produce stimulus control of behavior (5, 20, 21, 35). The present study suggests a reciprocal relationship between caffeine and cocaine at the receptor level which influences both stimulus control and rate of ongoing behavior. In the present study, the effect-additive interaction between caffeine and cocaine upon cocaine discriminative choice paralleled the dose-additive effects.

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