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(–)Ephedrine and Caffeine Mutually Potentiate One Another's Amphetamine-Like Stimulus Effects

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YOUNG, R., M. GABRYSZUK, R. A. GLENNON. *(−)Ephedrine and caffeine mutually potentiate one another's amphetamine-like stimulus effect*. PHARMACOL BIOCHEM BEHAV **61**(2) 169–173, 1998.—Using rats trained to discriminate 1 mg/kg of (+)amphetamine (ED_{50} = 0.4 mg/kg) from saline vehicle in a two-lever drug discrimination procedure, it was shown that (−)ephedrine (ED_{50} = 4.5 mg/kg), but not (+)ephedrine, substitutes for the (+)AMPH stimulus. It was also shown that caffeine (ED_{50} = 12.9 mg/kg) can substitute for (+)amphetamine in a dose-related fashion. Doses of (−)ephedrine and caffeine, which produced ≤1% drug-appropriate responding when administered alone, were able to enhance each other's stimulus effects when administered in combination such that there was a twofold leftward shift in their respective dose–response curves. Furthermore, stimulus generalization occurred when a dose of caffeine that produced saline-appropriate responding when administered alone was administered in combination with (+)ephedrine. It would appear that low doses of (−)ephedrine and caffeine may mutually potentiate one another's stimulus effects in (+)AMPH-trained rats, and that a combination of caffeine and (+)ephedrine result in altered stimulus character when compared to comparable doses of either agent administered alone. © 1998 Elsevier Science Inc.

Ephedrine Caffeine Amphetamine Stimulants Drug abuse Herbal dietary supplements

AMPHETAMINE (AMPH) and caffeine are prototypical central stimulants (6,8). Although AMPH may possess some therapeutic indications, it is also a drug of abuse. Caffeine, in contrast, is a socially accepted constituent of numerous beverages and various over-the-counter medications. Nevertheless, caffeine may also possess some abuse potential (7). Related in structure to AMPH are two other stimulants: ephedrine and norephedrine (or phenylpropanolamine). Ephedrine and norephedrine, β-hydroxy analogs of methamphetamine and AMPH, respectively, can be found in over-the-counter decongestants and diet aids. In the 1970s "amphetamine look-alike" drugs began to appear on the clandestine market (16). These "look-alikes" contained caffeine, ephedrine, and norephedrine, either alone or in binary or ternary combinations (16). This prompted investigators to question whether any of these agents might be capable of producing amphetamine-like stimulus effects in animals.

What are the effects of ephedrine, norephedrine, and caffeine in (+)AMPH-trained animals? Early on it was demonstrated a (+)AMPH stimulus generalizes to (±)ephedrine (11). A subsequent study reported only partial generalization, but only two doses of (±)ephedrine were examined (9). Results with (±)norephedrine also have been somewhat inconsistent. In rats trained to discriminate 1 mg/kg of (+)AMPH from vehicle, (±)norephedrine doses of 10 to 40 mg/kg produced >90% (+)AMPH-appropriate responding (14). However, earlier studies (examining only two drug doses) reported a maximum of 56–75% (+)AMPH-appropriate responding (9,11). Racemic norephedrine substituted for (+)AMPH in three of four pigeons (2) and in two of four monkeys (20). Norephedrine substituted for (+)AMPH in humans (1,12), and the two agents reportedly produced similar subjective effects (1). Results with caffeine have been more consistent. Nearly all studies have concluded that caffeine produces partial general-

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ization [30–78% (+)AMPH-appropriate responding] in rats and pigeons (2,9,13,18,19). However, most studies examined only two or three doses of caffeine.

More recently, ephedrine, norephedrine, and caffeine have themselves been employed as training drugs. For example, rats have been trained to discriminate (±)ephedrine (5) and an extract of ephedra (4). Stimulus generalization occurred upon administration of (±)norephedrine to the (±)ephedrine-trained rats (5), and to (+)methamphetamine in the ephedra extract-trained animals (4). Administration of caffeine resulted only in partial generalization (~50% drug-appropriate responding) in the former group, but in stimulus generalization in the latter group. Rats have been trained to discriminate both (±)norephedrine (17.8 mg/kg) (5) and (+)norephedrine (20 mg/kg) (15) from vehicle. Administration of (±)AMPH and (±)ephedrine resulted in stimulus generalization in the former group of animals, but caffeine produced only partial generalization in both groups. With animals trained to discriminate caffeine from vehicle, (+)AMPH, (±)AMPH, (±)ephedrine, (−)ephedrine, (±)norephedrine, and (+)norephedrine produced only partial generalization (caffeine training dose = 20 to 42 mg/kg) (5,10,15). However, Mumford and Holtzman (17) demonstrated that the caffeine training dose is a critical factor in stimulus generalization studies. That is, (+)AMPH generalized in rats trained to discriminate 10 mg/kg of caffeine from vehicle, but not in rats trained to discriminate 30 or 56 mg/kg (10,17). See Griffiths (8) for additional discussion.

In an attempt to gain further insight into these potentially complex interactions, ephedrine, norephedrine, and caffeine have been examined as binary and ternary mixtures, both as training drugs and in tests of stimulus generalization. Schechter (19) demonstrated that caffeine [at 15 mg/kg, which by itself produces ~44% (+)AMPH-appropriate responding] potentiated the stimulus effects of a low dose of (+)AMPH. Holloway et al. (9) later argued that the stimulus effects of ephedrine, norephedrine, and caffeine are additive. That is, a dose of caffeine (32 mg/kg) that by itself produces 57% (+)AMPH-appropriate responding, plus a dose of (±)ephedrine that by itself produces 20% (+)AMPH-appropriate responding, produced 85% (+)AMPH-appropriate responding when administered in combination. Similar results were reported for combinations of caffeine plus (±)norephedrine (9). Likewise, doses of caffeine, (±)ephedrine and (±)norephedrine as ternary mixtures resulted in (+)AMPH stimulus generalization in (+)AMPH-trained rats, whereas any one of the three agents, administered alone, only resulted in partial generalization (9). These same authors replicated and extended their findings in a follow-up study (5). However, examining caffeine and (+)norephedrine, alone and in combination, Mariathasan and Stolerman (15) concluded that there is no synergistic relationship between caffeine and norephedrine, and that a mixture of caffeine plus norephedrine was no more AMPH-like than norephedrine alone.

Obviously, questions remain. However, the results may not be as conflicting as they first seem. Many of the investigations, particularly those involving caffeine in tests of stimulus generalization, did not examine complete dose–response relationships. Furthermore, it has been demonstrated that when caffeine is used as training drug, the training dose has a significant impact on the results of stimulus generalization (8,10, 17). Secondly, many, if not nearly all, studies employed ephedrine and norephedrine as racemic mixtures without regard to the possible differences in the activity of the individual optical isomers. And finally, with regard to the possible additivity of effects of caffeine, ephedrine, and/or norephedrine combinations, essentially all studies employed "potentiating" doses of agents which, by themselves, produced partial generalization.

The purpose of the present study was severalfold: (a) to examine the two optical isomers of ephedrine in (+)AMPH-trained animals to determine whether or not any differences exist, (b) to conduct a thorough dose–response investigation of the effect of caffeine in rats trained to discriminate (+)AMPH from vehicle, and last, (c) to examine the effect of subthreshhold (i.e., saline-like) doses of caffeine and the individual optical isomers of ephedrine to determine whether or not there is any interaction.

METHOD

Nine male Sprague–Dawley rats, weighing 350–400 g at the beginning of the study, were used. The animals were housed individually and, prior to the start of the study, their body weights were reduced to approximately 80% of their free-feeding weight. During the entire course of the study, the animals' body weights were maintained at this reduced level by partial food deprivation; in their home cages, the animals were allowed drinking water ad lib. The rats were trained (15-min training session) to discriminate intraperitoneal injections (15-min presession injection interval) of 1.0 mg/kg of (+)AMPH from vehicle (sterile 0.9% saline) under a variable-interval 15-s schedule of reward (i.e., sweetened milk) as previously described in detail (21). Briefly, daily training sessions were conducted with (+)AMPH or saline; on every fifth day, learning was assessed during an initial 2.5-min nonreinforced (extinction) session followed by a 12.5-min training session. For four of the animals, the left lever was designated the drug-appropriate lever, whereas the situation was reversed for the remaining animals. Data collected during the extinction session included responses per minute (i.e., response rate) and number of responses on the drug-appropriate lever (expressed as a percent of total responses). Animals were not used in the stimulus generalization studies until they made greater than 80% of their responses on the drug-appropriate lever after administration of (+)AMPH, and less than 20% of their responses on the same drug-appropriate lever after administration of saline, for 3 consecutive weeks.

Tests of stimulus generalization were conducted to determine if the (+)AMPH stimulus would generalize to (−)ephedrine, (+)ephedrine, caffeine, and combinations of these drugs: fixed dose of caffeine (3.0 mg/kg) with various doses of (−)ephedrine, fixed doses of (−)ephedrine (2.0 mg/kg or 4.5 mg/kg) with various doses of caffeine, and a fixed dose of (+)ephedrine (12 mg/kg) with various doses of caffeine. During this phase of the study, maintenance of the (+)AMPH-saline discrimination was insured by continuation of the training sessions on a daily basis (except on a generalization test day; see below). On 1 of the 2 days before a generalization test, half of the animals would receive (+)AMPH and half would receive saline; after a 2.5-min extinction session, training was continued for 12.5 min. Animals not meeting the original criteria (i.e., >80% of total responses on the drug-appropriate lever after administration of training drug, and <20% of total responses on the same lever after administration of saline) during the extinction session were excluded from the next generalization test session. During the investigations of stimulus generalization, test sessions were interposed among the training sessions. The animals were allowed 2.5 min to respond under nonreinforcement conditions; the animals were then removed from the operant chambers and returned to their home cages. An odd number of training sessions (usually five) sepa-

rated any two generalization test sessions. Doses of the test drugs or combination of drugs were administered in a random order, using a 15-min presession injection interval, to groups of four to eight rats. If a particular dose of a challenge drug resulted in disruption of behavior (i.e., no responding), only lower doses would be evaluated in subsequent weeks. Stimulus generalization was said to have occurred when the animals, after a given dose of challenge drug or combination of drugs, made ⩾80% of their responses (group mean) on the (+)AMPH-appropriate lever. Animals making fewer than five total responses during the 2.5-min extinction session were considered as being disrupted. Where stimulus generalization occurred, ED_{50} values were calculated by the method of Finney (3). The ED_{50} doses are doses at which the animals would be expected to make 50% of their responses on the drug-appropriate lever.

Drugs

S(+)Amphetamine sulfate was available from previous studies, (−)ephedrine HCl ([1R,2S]-(−)-2[methylamino]-1-phenylpropan-1-ol HCl), (+)ephedrine HCl ([1S,2R]-(+)-2-[methylamino]-1-phenylpropan-1-ol HCl), and anhydrous caffeine were obtained from Sigma-Aldrich Corp. (St. Louis, MO). Solutions of all drugs were made fresh daily in 0.9% sterile saline, and all agents were administered via intraperitoneal injection in a 1.0 ml/kg injection volume. All doses refer to the weight of the salt.

RESULTS

(−)Ephedrine was examined at doses of 2.0, 4.0, 6.0, and 8.0 mg/kg; (+)ephedrine was examined at eight different doses ranging from 2.0 to 15 mg/kg. The (+)AMPH stimulus (ED_{50} = 0.4 mg/kg; 95% CL = 0.3–0.5 mg/kg) generalized to (−)ephedrine in a dose-related fashion (ED_{50} = 4.5 mg/kg; 95% CL = 3.2–6.3 mg/kg) (Fig. 1). In contrast, administration of (+)ephedrine resulted in a maximum of 50% drug-appropriate responding at 12 mg/kg, in 43% drug-appropriate responding at 13 mg/kg, and in disruption of behavior at 14 and 15 mg/kg. Thus, the (+)AMPH stimulus generalized to (−)ephedrine but only partially generalized to (+)ephedrine. Six different doses of caffeine were examined in the (+)AMPH-trained animals; the (+)AMPH stimulus generalized to caffeine (ED_{50} = 12.9 mg/kg; 95% CL = 7.7–21.8 mg/kg) in a dose-related fashion (Fig. 2). Response rates were not appreciably altered after administration of (+)AMPH, saline, (−)ephedrine, or caffeine; however, decreased response rates (≈40–60%) were observed after administration of 12 mg/kg and 13 mg/kg of (+)ephedrine. The slope of the dose–effect function of caffeine (slope = 3.56) was not statistically different [Students' *t*-test; t(6) = 0.79, $p > 0.05$] from the slope of the dose–efect function of (−)ephedrine (slope = 6.37).

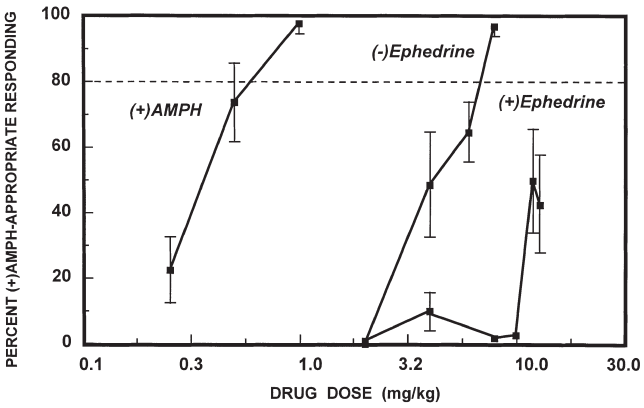

FIG. 1. Effect (±SEM) of doses of (+)AMPH, (−)ephedrine, and (+)ephedrine administered to rats trained to discriminate 1.0 mg/kg of (+)AMPH from saline vehicle. Five to nine animals were used to examine each dose of (+)AMPH and (−)ephedrine; (+)ephedrine doses of 15.0 mg/kg and <12.0 mg/kg were examined in four animals, whereas doses of 12.0, 13.0, and 14.0 mg/kg were examined in nine animals. Doses of (+)ephedrine higher than those shown (i.e., 14.0 and 15.0 mg/kg) resulted in disruption of behavior (i.e., four of nine and one of four animals responding, respectively).

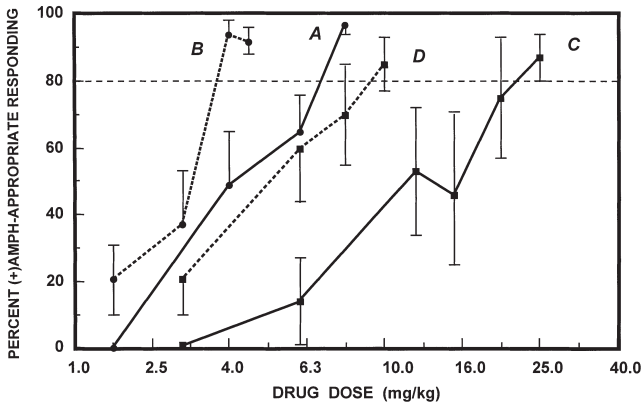

FIG. 2. Effect (±SEM) of doses of (−)ephedrine administered alone (A) or in combination with 3.0 mg/kg of caffeine (B), and of caffeine administered alone (C) or in combination with 2.0 mg/kg of (−)ephedrine (D), in rats trained to discriminate 1.0 mg/kg of (+)AMPH from saline vehicle. Six to nine animals were used to evaluate doses of agents. Data for (−)ephedrine administered alone (i.e., curve A) are taken from Fig. 1.

Doses of (−)ephedrine were reexamined in the presence of a fixed dose of caffeine (3.0 mg/kg, which by itself produced 1% (+)AMPH-appropriate responding) (Fig. 2). Stimulus generalization occurred in a dose-related manner, and an ED_{50} dose for (−)ephedrine was calculated for the combination (ED_{50} = 2.8 mg/kg; 95% CL = 1.9–4.2 mg/kg). The reverse experiment was also conducted; that is, doses of caffeine were reexamined in the presence of a fixed dose of (−)ephedrine (2.0 mg/kg, which by itself produced 0% (+)AMPH-appropriate responding) (Fig. 2). Stimulus generalization occurred to the combination. The ED_{50} dose of caffeine in the presence of 2.0 mg/kg of (−)ephedrine was calculated (ED_{50} = 5.2 mg/kg; 95% CL = 3.6–7.6 mg/kg). The slope of the dose–effect function of caffeine (slope = 3.37) in the presence of 2.0 mg/kg of (−)ephedrine was not statistically different [Students' $t(4) = 1.64$, $p > 0.05$] from the slope of the dose–effect function of (−)ephedrine (slope = 6.94) in the presence of 3.0 mg/kg of caffeine. Furthermore, the slopes of the caffeine + (−)ephedrine curve (slope = 3.37) and (−)ephedrine + caffeine curve (slope = 6.94) are nearly identical to the slopes of the caffeine and (−)ephedrine curves when the drugs were administered alone (slopes = 3.56 and 6.37, respectively).

Administration of the ED_{50} dose of (−)ephedrine (4.5 mg/kg) to (+)AMPH-trained rats resulted in 46% drug-appropriate responding (Fig. 3). The ED_{50} dose of (−)ephedrine was then administered in combination with various doses of caffeine. Caffeine doses of 0.5, 1.0, and 2.0 mg/kg plus 4.5 mg/kg of (−)ephedrine resulted in 40 to 50% (+)AMPH-appropriate responding. However, doses of 3.0 and 6.0 mg/kg of caf-

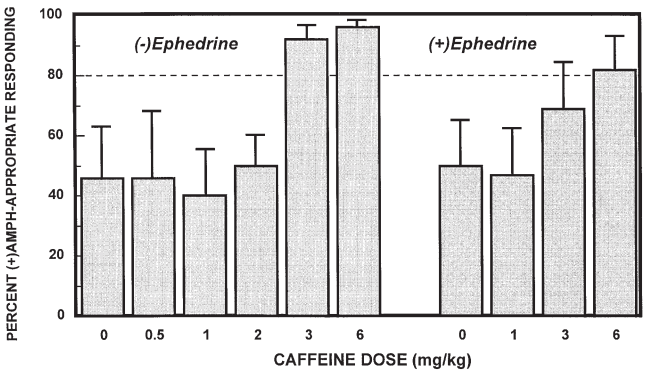

FIG. 3. Effects (±SEM) of caffeine doses administered in combination with 4.5 mg/kg of (−)ephedrine, and in combination with 12.0 mg/kg of (+)ephedrine (n = 4–6 animals at each dose or dose combination).

feine, which produced saline-like effects (i.e., 1 and 14% drug-appropriate responding, respectively) when administered alone, in combination with the ED_{50} dose of (−)ephedrine resulted in 92 and 96%, drug-appropriate responding, respectively. The animal's response rates were not substantially different after administration of (+)AMPH, saline, or any of the above (−)ephedrine–caffeine dose combinations.

(+)Ephedrine produced a maximum of 50% (+)AMPH-appropriate responding (at 12 mg/kg; see Fig. 1); higher doses of (+)ephedrine resulted in disruption of behavior. Administration of 12 mg/kg of (+)ephedrine in combination with 1.0 and 3.0 mg/kg of caffeine resulted in 47 and 69% (+)AMPH-appropriate responding, respectively, and with 6.0 mg/kg of caffeine resulted in stimulus generalization (i.e., 82% drug-appropriate responding; Fig. 3). Animal's response rates were slightly (≈20–30%) decreased after administration of the (+)ephedrine–caffeine dose combinations.

DISCUSSION

A search of the literature suggests that this is the first time that both optical isomers of ephedrine have been examined and compared in (+)AMPH-trained animals. The (+)AMPH stimulus generalized completely only to (−)ephedrine, whereas (+)ephedrine resulted only in partial generalization. In fact, at the dose of (−)ephedrine (8.0 mg/kg) that produced 97% (+)AMPH-appropriate responding, (+)ephedrine produced only 2% drug-appropriate responding. This may explain why only partial generalization was observed in a prior study using racemic ephedrine (9). The (+)AMPH stimulus also generalized to caffeine. Other studies have employed doses of caffeine comparable to (and larger than) those used herein; thus, it is difficult to explain why others have observed only partial generalization. Although differences in animal species may offer a partial explanation, this is not particularly satisfying because even investigations using rats as subjects have failed to observe stimulus generalization. Different (+)AMPH training doses or other procedural differences (e.g., schedule of reinforcement) might be responsible, at least in part, for findings of partial generalization. In fact, Holtzman (10) has found that different strains of rats may be differentially sensitive to the effects of caffeine. Furthermore, it might be noted that (+)AMPH substituted for caffeine in rats trained to discriminate 10 mg/kg of caffeine from vehicle (17).

It has been argued that the effects of ephedrine and caffeine are additive (9). The results of the present study would suggest that the interaction is seemingly more complex than this. That is, a fixed dose of (−)ephedrine [which produced 0% (+)AMPH-appropriate responding when administered alone] caused a twofold parallel leftward shift of the dose–response curve of caffeine, and a fixed dose of caffeine [which produced 1% (+)AMPH-appropriate responding when administered alone] caused a twofold parallel leftward shift of the dose–response curve of (−)ephedrine. Consistent with these observations is that a fixed dose of caffeine (i.e., 3.0 mg/kg), that produced 1% (+)AMPH-appropriate responding, administered in combination with the ED_{50} dose of (−)ephedrine, resulted in (+)AMPH stimulus generalization. Significant differences between this and previous studies (5,9) is that (−)ephedrine was used in place of (±)ephedrine, and the potentiation studies used doses of "potentiating" agents that (a) were 10-fold lower than those used previously, and that (b) produced ⩽1% drug-appropriate responding when administered alone.

Particularly noteworthy is that administration of a low dose of caffeine (i.e., one that produced saline-appropriate responding when administered alone) in combination with a dose of (+)ephedrine, an agent that failed to produce >50% drug-appropriate responding when administered alone, resulted in stimulus generalization. This would appear to be the first reported instance where a dose of an agent (i.e., caffeine) that produces saline-like effects can seemingly alter the stimulus properties of a second agent both in a quantitative and qualitative fashion. That is, although the (+)AMPH stimulus only partially generalized to (+)ephedrine [i.e., maximum (+)AMPH-appropriate responding = 50%, at 12 mg/kg], administration of this same dose together with a 6.0 mg/kg dose of caffeine results in complete stimulus generalization. Caffeine seems capable of making (+)ephedrine appear more "amphetamine-like" to the (+)AMPH-trained animals. At this time, it is unknown how this effect is produced, but additional investigation is certainly warranted.

Overall, the results of the present investigation cast the effect of ephedrine and caffeine, administered singly or in combination, in new light. (−)Ephedrine, but not (+)ephedrine, is capable of producing >80% (+)AMPH-like drug-appropriate responding; to this extent, (−)ephedrine is approximately 10-fold less potent than (+)AMPH. Caffeine is also capable of producing similar effects and is approximately 30-fold less potent than (+)AMPH. A saline-like dose of (−)ephedrine (i.e., a dose that produced saline-appropriate responding when administered alone) potentiates the effect of caffeine, and a saline-like dose of caffeine potentiates the effects of (−)ephedrine, as evidenced by twofold parallel leftward shifts in their respective dose–response curves when the agents are administered in combination. In fact, a saline-like dose of caffeine even potentiates the effect of (+)ephedrine, which, by itself, does not produce >50% (+)AMPH-appropriate responding.

Given the nearly ubiquitous, and growing, presence of caffeine in hot and cold beverages, as well as its presence in certain over-the-counter medications, the ramifications of caffeine/stimulant combinations or potentiations (i.e., in the form of drug–drug interactions) requires renewed investigation in that such interactions may have bearing on drug abuse and on accidental overdosing. In addition, various herbal preparations or "dietary supplements" are currently quite popular, and because they are considered nutritional supplements, they are not regulated as drugs by the FDA. Two such preparations are Herbal Ecstacy® (sic) (Global World Media

Corp., Venice, CA) and Herbal XTC® (GH Applied Technologies Inc., Fairfield, CT); both contain caffeine and ephedrine. Because, caffeine and ephedrine may mutually potentiate or modify one another's stimulus effects in (+)AMPH-trained rats, the ephedrine in these preparations may appear more active than had the equivalent amount of ephedrine been administered alone. However, although our preliminary results suggest a drug–drug potentiation, further investigation will be necessary to determine the exact nature of this interaction (i.e., simple additivity of effect or true potentiation).

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