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Potentiation of Cathinone by Caffeine and Nikethamide

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SCHECHTER, M. D. *Potentiation of cathinone by caffeine and nikethamide*. PHARMACOL BIOCHEM BEHAV 33(2) 299–301, 1989.—The drug discrimination paradigm was employed to evaluate the effect of coadministration of both caffeine and nikethamide upon the discrimination of a low dose of cathinone. In rats trained to discriminate between 0.8 mg/kg *l*-cathinone and its vehicle in a two-lever food-motivated operant task, 0.2 mg/kg cathinone produced 29.2% of responses on the cathinone-appropriate lever. This lever was chosen in 0 and 50% of trials with 25 mg/kg nikethamide and 20 mg/kg caffeine, respectively. Coadministration of caffeine, nikethamide, or caffeine plus nikethamide with low-dose cathinone produced strong cathinone-like discriminative performance. This potentiation of cathinone by caffeine and nikethamide is reflective of noncontrolled drugs of abuse containing similar combinations especially for that of antiadipositum X-112, a drug containing all three agents and widely abused in Europe.

Drug discrimination Cathinone Caffeine Nikethamide Dopamine X-112

THE leaves of the Khat shrub (*Catha edulis*) have been chewed for their stimulating properties in certain parts of Africa and the Arab peninsula for many centuries (6). The psychoactive alkaloid isolated from Khat is known as cathinone and it is mainly found in the young leaves of the shrub (3). As the leaves dry, cathinone is metabolized to an active compound known as norpseudoephedrine or cathine. Cathinone is considerably more potent in regard to stimulation of the central nervous system, although the effects of cathinone and cathine are qualitatively analogous and there is much evidence indicating that the total effects observed after Khat chewing can be explained by the pharmacodynamics of these two alkaloids alone (6).

Besides the abuse liability and addictive potential (7) of Khat use, cathine is used as a nasal decongestant, an anorexiant and as a component in multiple drug preparations in Europe and its abuse in these forms has increased over the period of the last few years. A preparation that has a particularly high rate of abuse is known as "antiadipositum X-112," an oral solution which contains d-cathine, caffeine and nikethamide, in a 4 to 10 to 10 ratio, respectively. This solution has been used intravenously by street addicts and it now ranks as the sixth most frequently abused stimulant in the Federal Republic of Germany (8). Furthermore, cathine can be found in that country under 10 additional scheduled trade names, as well as being known as Novese (Restan) in South Africa and by 4 other brand names in Switzerland. In the United States, combination drugs containing caffeine and a phenylethylamine, such as ephedrine and phenylpropanolamine (PPA), are present in many "legal" stimulants sometimes called "turkey drugs" or "look-alike" stimulants (10). Although both ephedrine and phenylpropanolamine produce relatively weak central stimulant effects as compared to amphetamine, it appears that when caffeine is added to these compounds, the effects of each are potentiated (4). Thus, when caffeine is administered to rats trained to discriminate the interoceptive stimulus effects of amphetamine, it produces approximately 55% generalization and similar discriminative performance is seen with both ephedrine and phenylpropanolamine. However, when caffeine is added to either one of these compounds, amphetamine-trained animals generalized to the combination. These results suggest that the combinations found in "turkey drugs" may, indeed, produce subjective effects similar to those produced by amphetamine and help to explain the popularity of these noncontrolled substances at establishments such as "head shops" (10).

Caffeine has, in addition, been shown to potentiate the discriminative effects of amphetamine (12) and animals trained to discriminate cathinone have been reported to generalize to amphetamine (14) and vice versa (1,11). The purpose of the present study was to evaluate the effects of both additives in X-112, viz., caffeine and nikethamide, on animals' ability to discriminate *l*-cathinone. Previous work has shown that although nikethamide (5) and caffeine (2,9) are discriminable, their discriminative effects are not identical to amphetamine. If either, or both, of these drugs can potentiate the effects of cathinone, the reported subjective euphoric effects and, therefore, abuse potential of X-112 may be evidenced.

METHOD

Six male Sprague-Dawley rats were trained to discriminate 0.8 mg/kg *l*-cathinone form its vehicle (distilled water) according to the procedures detailed elsewhere (13). Briefly, the food-deprived rats were trained to press one lever in a two-lever operant chamber for a food reward (45 mg Noyes pellet) following the injection of cathinone and to press the other lever following administration of its vehicle. All injections were made intraperitoneally (IP) and training took place 15 min after injection. The rats were required

TABLE 1

EFFECT OF 0.2 mg/kg CATHINONE, 20 mg/kg CAFFEINE AND 25 mg/kg NIKETHAMIDE UPON PERFORMANCE IN CATHINONE (0.8 mg/kg) TRAINED RATS ALONE AND IN COMBINATION

Cathinone	Caffeine	Nikethamide	Quantal	Quantitative (SD)
*			29.2	34.6 (26.3)
	*		50.0	48.5 (18.3)
		*	0.0	13.0 (0.4)
†	†		100.0	85.8 (1.8)
†		†	83.3	66.6 (2.1)
†	†	†	100.0	89.6 (1.9)

*Drug administered intraperitoneally, by itself, at 15 min prior to testing.

†Drug coadministered (IP) at 15 min prior to testing.

to select (press 10 times first) the appropriate lever, according to the cathinone or vehicle state imposed, in 16 of 20 consecutive sessions.

Once this training criterion was achieved by all 6 rats, various doses of cathinone different from the training dose were administered and a dose-response relationship was determined. The calculated ED_{50} was 0.34 mg/kg, similar to the $ED_{50}=0.27$ mg/kg previously reported (13) in like trained rats, whereas the ED_{16} was shown to be approximately 0.2 mg/kg. It was this latter dose that was selected for continued testing in order to be able to observe possible increased discriminative performance. Interspersed between cathinone maintenance and vehicle maintenance sessions, the animals were tested 15 min after injection with either 0.2 mg/kg cathinone, 20 mg/kg caffeine or 25 mg/kg nikethamide alone or in various combinations. Each treatment and/or combination was tested in each rat on two occasions. The doses of both caffeine and nikethamide were chosen from the available literature (5,9). On these test days, the animals were removed immediately after making 10 responses on either lever.

The percentage of rats selecting (pressing 10 times first) the appropriate lever for cathinone was the quantal measurement and this is presented as percentage of rats making the correct-choice selection on the cathinone-correct lever (an all-or-none effect). In addition, a quantitative measurement representing the total number of presses on both levers made prior to completion of 10 presses on either lever, i.e., the number of presses on the cathinone-correct lever divided by the total responses made (including those on the cathinone lever), times 100.

RESULTS

Cathinone, in its l-isomeric form, was readily capable of controlling differential responding as previously shown in this laboratory (13). Administration of 0.2 mg/kg cathinone on test days produced a quantal response of 29.2% and a quantitative measurement of 34.6% (Table 1). Administration of 20 mg/kg caffeine produced 50% quantal responding, whereas 25 mg/kg nikethamide administered alone produced 0% responding on the cathinone-correct lever (or 100% responses upon vehicle-appropriate lever). Coadministration of 0.2 mg/kg cathinone and 20 mg/kg caffeine produced 100% responding on the cathinone-appropriate lever. The combination of cathinone and nikethamide also raised the cathinone discrimination of 0.2 mg/kg from 29.2 to 83.3% quantal. Lastly, the three agents in combination produced 100% responding on the cathinone lever.

DISCUSSION

In a previously reported study, Huang and Ho (5) observed that the administration of nikethamide at a dose of 25 mg/kg produced 18.8% of all responses on the *d*-amphetamine correct lever in animals trained to discriminate 0.8 mg/kg *d*-amphetamine. Likewise, 15 mg/kg caffeine produced 43.7% (12) and 20 mg/kg caffeine produced 55.1% (9) *d*-amphetamine-like responding in similarly trained rats. The combination of caffeine and low-dose amphetamine produced heightened amphetamine-like responding in rats (12). In addition, complete generalization to the d-amphetamine discriminative cue was found with the triple combination of caffeine, ephedrine and phenylpropanolamine, whereas none of these agents produced more than modest amphetamine-like responding when administered alone (4). The present study extends these observations to include the caffeine and nikethamide potentiation of the cathinone discriminative stimulus.

Although a large number of over-the-counter appetite-suppressants formerly sold in the U.S. contain caffeine in combination with phenylpropanolamine, this latter substance should not be confused with either cathinone or cathine. In fact, phenylpropanolamine is the racemic form of norephedrine, which is the isomer of norpseudoephedrine [cathine; (10)].

The explanation for the previously cited ability of caffeine, ephedrine and phenylpropanolamine to mimic amphetamine in the discriminative stimulus paradigm resides in the possibility that amphetamine's discriminative stimulus is mediated by release of dopamine. Ephedrine and phenylpropanolamine may, likewise, act upon the dopaminergic system and caffeine may add to this effect by its own further releasing of dopamine or by enhancing the effect of the released dopamine at cyclic AMP-linked receptors by its inhibition of phosphodiesterase (4). The same explanations may be offered to explain the present results since cathinone has recently been shown to produce its discriminative stimulus cue via dopaminergic mediation (13). In fact, no major pharmacological difference appears to exist between the Khat alkaloid and the synthetic stimulant amphetamine (6).

This result may also be of interest to increased understanding of the abuse potential of products containing cathinone (or its active metabolite cathine) in combination with caffeine and nikethamide, viz., antiadipositum X-112, where the addition of the easily available caffeine and potentially toxic nikethamide enhance the stimulatory effects of cathine (8).

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