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Effects of an Antitussive Mixture and Its Constituents in Rats Discriminating Methamphetamine from Saline

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ANDO, K. AND T. YANAGITA. *Effects of an antitussive mixture and its constituents in rats discriminating methamphetamine from saline.* PHARMACOL BIOCHEM BEHAV 41(4) 783–788, 1992.—The discriminative effects of over-the-counter antitussive syrup containing dihydrocodeine (DHC), methylephedrine (MEP), caffeine (CAF), and chlorpheniramine (CPA) were compared with those of methamphetamine (MA) in a drug discrimination experiment using rats. Rats were trained to discriminate the effects of MA at 0.5 mg/kg SC and saline for food reinforcement under the fixed-ratio 10 schedule in a two-lever operant chamber situation. In substitution testing using a cumulative dose procedure by the subcutaneous route, DHC (4 and 8 mg/kg, expressed hereafter as referred to cumulative dose) or CPA (16–64 mg/kg) individually did not produce MA lever selection. On the other hand, MEP (128 mg/kg) and CAF (64 mg/kg) produced MA lever selection 41.5 and 57.2% of the time, respectively. The complete mixture (16 mg/kg DHC + 32 mg/kg MEP + 33.2 mg/kg CAF + 6.4 mg/kg CPA) produced MA level selection 65.8% of the time. The partial mixture containing only MEP + CAF at the above doses produced MA lever selection 95.6% of the time. Thus, the complete mixture only partially substituted for MA in rats while the partial mixture containing MEP and CAF completely substituted for MA.

Drug discrimination Methamphetamine Antitussive mixture Dihydrocodeine Methylephedrine Caffeine Chlorpheniramine Rats

OVER-THE-COUNTER antitussive syrups are drug mixtures of which abuse has been reported among adolescents in Japan. These syrups usually contain antitussives such as dihydrocodeine (DHC), bronchial muscle relaxants as well as sympathomimetics such as methylephedrine (MEP), CNS and respiratory stimulants such as caffeine (CAF), and antihistamines such as chlorpheniramine (CPA). Although these combination mixtures are usually expected to produce enhancement of antitussive effect and reduction of side effects by interaction of the constituents, these mixtures at high doses have been found to produce effects (e.g., hallucinations, delusions, manic depression) resembling those of methamphetamine (MA) in abusers (9). Previously, antitussive mixtures were found to be self-administered intravenously in rhesus monkeys at our laboratory, consistent with such mixtures having abuse potential. In addition, the efficacy of the reinforcing effects of DHC was demonstrably enhanced by interaction with the other constituents such as MEP, CAF, and CPA (11). Although antitussive mixtures can function as reinforcing stimuli, their discriminative stimulus effects, which are likely to underlie their abuse, have not yet been well characterized.

The purpose of the present study was to examine the ability of an antitussive mixture to produce MA-like discriminative stimulus effects in rats and evaluate the role of its constituents in producing these effects.

METHOD

Subjects

Twenty-four male Sprague Dawley rats (jcl:SD, Clea Japan Inc., Tokyo) weighing between 310 and 390 g at the start of discrimination training were used. They were housed in individual cages in an animal room at controlled temperature (22 ± 2°C). Rats received 15 g of food (CE2, Clea Japan Inc., Tokyo) per rat per day and water was available freely in the animal room.

Apparatus

Discrimination training was conducted in operant chambers. Each chamber was housed in a sound-attenuating box with fan ventilation. On one wall of the chamber, a light

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was mounted centrally above a food cup, which was located between two response levers. Food (50-mg pellet, Clea Japan Inc., Tokyo) was delivered by a pellet dispenser (Model G 5100, Ralph Gerbrands Co., Arlington, MA). Response recording and scheduling of reinforcement contingencies were performed by an LSI-11 microcomputer (Digital Equipment Co., Maynard, MA) using software developed at this laboratory.

Discrimination Training

Rats were trained to press a lever for food as a reinforcer. Lever-pressing behavior was shaped by progressively requiring more lever presses per reinforcement. When 10 lever press responses were required for reinforcement, rats were then trained to press one of the levers (MA lever) for food reinforcement after MA administration and the other lever (saline lever) for food reinforcement after saline administration. For this training, either MA at 0.5 mg/kg or physiological saline at 1 ml/kg was administered subcutaneously 10 min before each daily session. A session was terminated after 100 reinforcements or 30 min, whichever came first. After MA administration, every tenth consecutive response on the MA lever was reinforced but responses on the saline lever were not reinforced. After saline administration, every tenth consecutive response on the saline lever was reinforced but responses on the MA lever were not reinforced. The training sessions were generally conducted 6 days a week, during which MA and saline were administered according to a single alternation schedule (i.e., MA, saline, MA, saline, . . .) for sessions 1–20, followed by a double alternation schedule (i.e., MA, MA, saline, saline, MA, MA, . . .) after session 21. To determine whether the discrimination training had been successfully established, training criterion was set. The criterion was that at least 80% of the responses 1) for the first food pellet in the session and 2) for the session overall were made to the appropriate lever for at least five consecutive training sessions.

Substitution Testing

After establishment of the discrimination, the substitutability of the discriminative effects of various drugs described below for those of the training dose (0.5 mg/kg, SC) of MA was tested using a cumulative dose procedure (2,12). In this procedure, the dose–effect relationships of test drugs were determined in multiple test periods using different doses of the same drug administered on the same day. Each period consisted of administration of saline or a dose of a drug followed by a 10-min rest interval and concluding with a 2-min test session. The first period of each day of testing was always performed by using saline at 1 ml/kg via the same administration route as that to be used in the following test drug periods. After the period with saline, the next period using a test drug was conducted in the same manner, beginning with administration of the drug at an initial dose (X mg/kg) and ending with the 2-min test session after a 10-min rest interval. In the succeeding periods, the same drug was tested next at the same dose (cumulative dose, $2X$ mg/kg), then at twice the initial dose (cumulative dose, $4X$ mg/kg), and so on, doubling the dose in each period as a rule. In the case of drug mixtures, each dose of each constituent was increased in the same manner as above. The interval of each administration was 13 min (a 10-min rest interval after administration, a 2-min test session, and 1 min for administering a drug to several rats). During the 2-min test sessions in each period, the procedure was identical with that during the training sessions except for the 2-min duration of the test session and the fact that every tenth consecutive response on either lever produced food reinforcement. The 1-day substitution tests were interspersed with daily discrimination training sessions and were only held after the discrimination training criterion described in the discrimination training section had been maintained for at least three consecutive discrimination training sessions. In the substitution testing, complete substitution of each dose of a test drug for the training dose of MA was defined in terms of a substitution criterion that required that at least 80% of the overall lever-press responses be made to the MA-appropriate lever in at least one of the test sessions for a test drug or a drug mixture.

Drugs

Methamphetamine hydrochloride (Dainippon Pharmaceutical Co., Osaka), *l*-ephedrine (Dainippon Pharmaceutical Co., Osaka), cocaine hydrochloride (Takeda Pharmaceutical Co., Osaka), dihydrocodeine sulphonate (Takeda Pharmaceutical Co., Osaka), caffeine anhydrous (Kantou Chemical Co., Tokyo), chlorpheniramine maleanate (Iwaki Pharmaceutical Co., Tokyo), and *dl*-methylephedrine hydrochloride injection (Tanabe Pharmaceutical Co., Osaka) were obtained commercially. These drugs were dissolved or diluted in physiological saline. The concentrations of all drugs were adjusted so as to result in a constant volume of 1 ml/kg. The antitussive mixture and various combinations of the constituents of the mixture were prepared by mixing each constituent dissolved or diluted in physiological saline in the same proportions as the corresponding constituents of the over-the-counter antitussive syrup BRON W (S.S. Pharmaceutical Co., Tokyo). The complete mixture contained 4 mg DHC, 8 mg MEP, 8.3 mg CAF, and 1.6 mg CPA per 1 ml. All administrations were given subcutaneously except for cocaine, which was given intraperitoneally. All drug dosages were given in terms of the weight of the salt.

RESULTS

Within 37 sessions (50 days), 16 of 24 rats attained the training criterion for the establishment of discrimination between MA at 0.5 mg/kg SC and saline. These rats were used in the following substitution testing while the other eight rats were excluded from the present experiment.

In each of the 1-day substitution tests with various drugs using the cumulative dose procedure, saline was tested first. In each of the saline test sessions given before each drug testing, the mean percent of MA-appropriate responses out of the total number of responses ranged between 0.0–1.1% and the means of total response rate per min ranged between 51.7–79.5 (Tables 1–4).

In the substitution test with MA, the mean percent of MA-appropriate responses increased and the mean response rate decreased, both dose dependently (Table 1). Since the mean percent of MA-appropriate responses was 92.2% at the cumulative dose of 1 mg/kg SC of MA and 15 of 16 rats showed at least 80% of MA-appropriate responses at this dose, the effects of MA at this cumulative dose substituted for MA at the single training dose (0.5 mg/kg SC). On the other hand, repeated subcutaneous administrations of saline caused almost 100% of the mean percent of saline-appropriate responses over six saline test sessions (Table 1). The means of total response rate per min were consistent over these test sessions, ranging between 70.2–80.7 across sessions.

In the substitution test with cocaine, the mean percent of

TABLE 1

SUBSTITUTION TESTS FOR THE DISCRIMINATIVE EFFECTS OF MA AT 0.5 mg/kg SC WITH OTHER DOSES OF MA AND WITH REPEATED ADMINISTRATION OF SALINE IN A CUMULATIVE DOSE PROCEDURE BY SUBCUTANEOUS ROUTE

Drug	Cumulative Dose (mg/kg)	% MA-Appropriate Responses*	Response Rate Per Min*	*n/N*†
Saline	1 ml/kg	0.6 ± 0.5	66.8 ± 4.0	0/16
Methamphetamine	0.13	4.5 ± 3.0	72.4 ± 3.6	0/16
Methamphetamine	0.25	31.8 ± 11.1	54.9 ± 5.4	4/16
Methamphetamine	0.5	77.4 ± 10.1	45.9 ± 5.4	12/16
Methamphetamine	1.0	92.2 ± 6.3	34.8 ± 5.4	15/16
Saline	1 ml/kg	0.2 ± 0.1	70.2 ± 2.9	0/16
Saline	2 ml/kg	0.1 ± 0.1	78.9 ± 4.1	0/16
Saline	3 ml/kg	0.1 ± 0.1	78.2 ± 4.0	0/16
Saline	4 ml/kg	0.3 ± 0.3	80.4 ± 4.2	0/16
Saline	5 ml/kg	0.2 ± 0.1	80.7 ± 4.3	0/16
Saline	6 ml/kg	0.0 ± 0.0	76.7 ± 3.8	0/16

*The mean percent of MA-appropriate responses and the mean response rate per min during each 2-min test session are presented with standard errors.

†*n/N* indicates the number of rats showing at least 80% of MA-appropriate responses (*n*) out of the total number of rats tested (*N*).

MA-appropriate responses increased and the mean response rate decreased, both dose dependently (Table 2). Since the mean percent of MA-appropriate responses was 83.3% and 10 of 12 rats showed at least 80% of MA-appropriate responses with cocaine at the cumulative dose of 24 mg/kg IP, cocaine at this dose substituted completely for MA. At this dose of cocaine, no response was observed in 2 of 14 rats, and thus these rats were excluded from the analysis.

In the substitution test with *l*-ephedrine, the mean percent of MA-appropriate responses increased and the mean response rate decreased, both dose dependently (Table 2). The mean percent of MA-appropriate responses was 78.3%, and 11 of 14 rats showed at least 80% of MA-appropriate responses with *l*-ephedrine at the cumulative dose of 32 mg/kg SC.

In the substitution tests with each constituent of the antitussive mixture, the mean percent of MA-appropriate responses did not increase with DHC or CPA even at cumulative doses, where the response rate decreased markedly with DHC and grossly observable sedative effects continued until the next day with CPA (Table 3). Almost no rats showed substitution of these drugs for MA. With MEP and CAF, the mean percent of MA-appropriate responses increased and the mean response rate decreased, both dose dependently (Table 3). The mean percent of MA-appropriate responses was 41.5% with MEP at the cumulative dose of 128 mg/kg SC and 57.2% with CAF at the cumulative dose of 64 mg/kg SC. Less than half the rats showed at least 80% of MA-appropriate responses with these drugs at the above doses, and the mean response rate markedly decreased with CAF at the above dose.

TABLE 2

SUBSTITUTION TESTS FOR THE DISCRIMINATIVE EFFECTS OF MA AT 0.5 mg/kg SC WITH COCAINE AND *l*-EPHEDRINE IN A CUMULATIVE DOSE PROCEDURE BY INTRAPERITONEAL ROUTE AND SUBCUTANEOUS ROUTE, RESPECTIVELY

Drug	Cumulative Dose (mg/kg)	% MA-Appropriate Responses*	Response Rate Per Min*	*n/N*†
Saline	1 ml/kg	0.2 ± 0.1	79.5 ± 4.8	0/14
Cocaine	8	42.9 ± 13.7	76.6 ± 8.4	6/14
Cocaine	16	64.3 ± 13.3	69.3 ± 7.4	9/14
Cocaine	24	83.3 ± 11.2	59.7 ± 9.2	10/12
Saline	1 ml/kg	0.1 ± 0.1	69.1 ± 4.2	0/14
l-Ephedrine	8	2.7 ± 2.5	67.5 ± 5.6	0/14
l-Ephedrine	16	28.3 ± 12.3	48.7 ± 7.4	4/14
l-Ephedrine	32	78.3 ± 11.3	37.2 ± 8.6	11/14

*The mean percent of MA-appropriate responses and the mean response rate per min during each 2-min test session are presented with standard errors.

†*n/N* indicates the number of rats showing at least 80% of MA-appropriate responses (*n*) out of the total number of rats tested (*N*).

TABLE 3

SUBSTITUTION TESTS FOR THE DISCRIMINATIVE EFFECTS OF MA AT 0.5 mg/kg SC WITH EACH CONSTITUENT OF AN ANTITUSSIVE MIXTURE IN A CUMULATIVE DOSE PROCEDURE BY SUBCUTANEOUS ROUTE

Drug	Cumulative Dose (mg/kg)	% MA-Appropriate Responses*	Response Rate Per Min*	n/N†
Saline	1 ml/kg	0.3 ± 0.2	77.9 ± 4.1	0/14
Dihydrocodeine	4	7.8 ± 7.7	45.4 ± 6.8	1/14
Dihydrocodeine	8	0.0 ± 0.0	33.4 ± 7.6	0/14
Saline	1 ml/kg	0.1 ± 0.1	71.8 ± 4.9	0/14
dl-Methylephedrine	64	25.8 ± 11.5	68.7 ± 10.3	3/14
dl-Methylephedrine	128	41.5 ± 13.7	55.7 ± 10.7	5/13
Saline	1 ml/kg	0.1 ± 0.1	73.0 ± 3.9	0/13
Caffeine	16	15.4 ± 10.4	73.7 ± 5.5	2/13
Caffeine	32	23.3 ± 10.9	58.6 ± 6.9	2/13
Caffeine	64	57.2 ± 11.8	11.6 ± 2.8	6/13
Saline	1 ml/kg	1.1 ± 0.8	67.9 ± 4.1	0/14
Chlorpheniramine	16	7.4 ± 7.1	70.4 ± 4.3	1/14
Chlorpheniramine	32	7.6 ± 7.0	66.9 ± 5.1	1/14
Chlorpheniramine	64	0.6 ± 0.5	62.0 ± 5.3	0/14

*The mean percent of MA-appropriate responses and the mean response rate per min during each 2-min test session are presented with standard errors.

†*n/N* indicates the number of rats showing at least 80% of MA-appropriate responses (*n*) out of the total number of rats tested (*N*).

In the substitution test with the complete mixture containing DHC, MEP, CAF, and CPA, the mean percent of MA-appropriate responses increased dose dependently with the value of 65.8% at the highest cumulative doses (DHC at 16, MEP at 32, CAF at 33.2, and CPA at 6.4 mg/kg) and 8 of 12 rats showed at least 80% of MA-appropriate responses at the above doses (Table 4). The mean response rate decreased dose dependently with this complete mixture. With the partial mixture lacking DHC, the mean percent of MA-appropriate responses increased dose dependently: The mean percent was 72.2% at the highest cumulative doses (MEP at 32, CAF at 33.2, and CPA at 6.4 mg/kg). The mean response rate did not change markedly with this partial mixture even at the highest cumulative doses and 8 of 12 rats showed at least 80% of MA-appropriate responses at the above doses. With the partial mixture lacking MEP, the mean percent of MA-appropriate responses increased dose dependently with the value of 62.3% at the highest cumulative doses (DHC at 16, CAF at 33.2, and CPA at 6.4 mg/kg) and half the rats showed at least 80% of MA-appropriate responses at the above doses. The mean response rate decreased dose dependently with this partial mixture. With the partial mixture lacking CAF, the mean percent of MA-appropriate responses increased dose dependently but with the value of 33.2% at the highest cumulative doses (DHC at 16, MEP at 32, and CPA at 6.4 mg/kg) and only one of six rats showed at least 80% of MA-appropriate responses. The mean response rate decreased dose dependently with this partial mixture. With the partial mixture lacking CPA, the mean percent of MA-appropriate responses increased dose dependently with the value of 68.9% at the highest cumulative doses (DHC at 16, MEP at 32, and CAF at 33.2 mg/kg) and six of nine rats showed at least 80% of MA-appropriate responses at the above doses. The mean response rate decreased dose dependently with this partial mixture. Finally, with the partial mixture containing only CAF and MEP the mean percent of MA-appropriate responses increased dose dependently with the value of 95.6% at the highest cumulative doses (MEP at 32 and CAF at 33.2 mg/kg) and all rats tested showed at least 80% of MA-appropriate responses at the above doses. The mean response rate decreased at the highest cumulative doses with this partial mixture.

DISCUSSION

In the present study, discrimination between MA at 0.5 mg/kg SC and saline was established in rats. The dose of MA for discrimination training was selected based on data obtained from a schedule-controlled behavior experiment in rats performed at our laboratory where MA at 0.5 mg/kg SC clearly increased response rate. The discriminative effects of MA were compared to those of the constituents contained in an antitussive syrup, as well as to prototypic psychomotor stimulants such as cocaine and *l*-ephedrine in rats. The administration route for the constituents of the antitussive mixture, as well as *l*-ephedrine, was matched to the route used for MA in the discrimination training. Cocaine was not administered subcutaneously but intraperitoneally because subcutaneous administration of this drug caused inflammation at the injection site. In the substitution tests, a cumulative dose procedure was used to obtain results efficiently. MA at the cumulative dose of 0.5 mg/kg substituted partially and at the cumulative dose of 1 mg/kg substituted completely for MA at the single training dose (0.5 mg/kg). Under the identical cumulative dose procedure, cocaine at the cumulative dose of 24 mg/kg IP substituted for MA. The similarity of the discriminative

TABLE 4

SUBSTITUTION TESTS FOR THE DISCRIMINATIVE EFFECTS OF MA AT 0.5 mg/kg SC WITH COMBINATIONS OF CONSTITUENTS OF AN ANTITUSSIVE MIXTURE IN A CUMULATIVE DOSE PROCEDURE BY SUBCUTANEOUS ROUTE

Drug* (mg/ml)	Cumulative Dose (ml/kg)	% MA-Appropriate Responses†	Response Rate Per Min†	n/N‡
Saline	1	0.1 ± 0.1	70.4 ± 3.9	0/14
Complete mixture [DHC	1	0.3 ± 0.3	68.7 ± 5.2	0/14
(4) + MEP (8) + CAF	2	39.8 ± 12.0	45.8 ± 7.4	4/14
(8.3) + CPA (1.6)]	4	65.8 ± 14.1	25.0 ± 7.5	8/12
Saline	1	0.0 ± 0.0	57.1 ± 4.2	0/12
	1	8.3 ± 8.3	63.9 ± 6.4	1/12
Mixture lacking DHC [MEP	2	42.2 ± 14.6	63.9 ± 8.6	5/12
(8) + CAF (8.3) + CPA (1.6)]	4	72.2 ± 12.2	52.8 ± 9.1	8/12
Saline	1	0.1 ± 0.1	61.3 ± 4.8	0/12
	1	8.8 ± 8.3	57.1 ± 6.6	1/12
Mixture lacking MEP [DHC	2	37.3 ± 13.9	56.3 ± 6.9	4/12
(4) + CAF (8.3) + CPA (1.6)]	4	62.3 ± 12.4	22.3 ± 5.4	6/12
Saline	1	0.3 ± 0.3	51.7 ± 4.6	0/10
	1	0.0 ± 0.0	51.5 ± 7.8	0/10
Mixture lacking CAF [DHC	2	10.5 ± 10.0	28.2 ± 6.8	1/10
(4) + MEP (8) + CPA (1.6)]	4	33.2 ± 15.3	17.5 ± 7.0	1/ 6
Saline	1	0.1 ± 0.1	59.3 ± 5.0	0/11
	1	20.0 ± 13.3	39.7 ± 4.7	2/10
Mixture lacking CPA [DHC	2	33.6 ± 14.9	20.5 ± 2.2	3/10
(4) + CAF (8.3) + MEP (8)]	4	68.9 ± 15.4	10.3 ± 2.7	6/ 9
Saline	1	0.0 ± 0.0	57.8 ± 5.1	0/11
	1	9.1 ± 9.1	63.5 ± 5.1	1/11
Mixture lacking DHC and CPA	2	28.5 ± 13.8	64.1 ± 5.8	3/11
[CAF (8.3) + MEP (8)]	4	95.6 ± 1.8	34.3 ± 5.8	11/11

*The relative concentrations of constituents are equivalent to those in an over-the-counter antitussive mixture. (DHC), dihydrocodeine; (MEP), *dl*-methylephedrine; (CAF), caffeine; (CPA), chlorpheniramine.

†The mean percent of MA-appropriate responses and the mean response rate per min during each 2-min test session are presented with standard errors.

‡*n/N* indicates the number of rats showing at least 80% of MA-appropriate responses (*n*) out of the total number of rats tested (*N*).

effects of cocaine and amphetamines has been reported in other studies (1,3,4,5,8). The repeated saline administration in the present procedure consistently produced saline-appropriate responses. These facts indicate that the present cumulative dose procedure is appropriate for observation of discriminative effects of various drugs in substitution for MA.

In the substitution tests with each constituent of the antitussive mixture, MEP at 128 mg/kg alone and CAF at 64 mg/kg alone substituted only partially for MA, that is, the mean percent of MA-appropriate responses was less than 80% and only some rats showed substitution for MA with these drugs. It was also demonstrated that efficacy and potency of MEP in terms of partial substitutability for MA were lower than those of *l*-ephedrine. On the other hand, neither DHC nor CPA substituted for MA. In the substitution test with the complete antitussive mixture in which the relative concentrations of each constituent were matched to the proportions found in the over-the-counter antitussive syrup, the complete antitussive mixture substituted only partially for MA. In this case, one third of the rats showed the substitution for MA at the highest cumulative dose of the complete mixture. It should be mentioned that this dose is comparable to consumption of eight 120-ml bottles of the syrup by a 60-kg person, while in fact abusers actually do ingest up to several bottles of this syrup a day (9), although the pharmacodynamics and pharmacokinetics of the mixture under the present experimental conditions in rats and actual abuse in humans may differ.

The roles of the discriminative effects of each constituent in the complete mixture were analyzed by testing partial mixtures. The partial mixtures lacking either any of DHC, MEP, CAF, or CPA substituted only partially for MA. The partial substitutability for MA with the partial mixture lacking CAF was the lowest among these four partial mixtures. The response rate per minute for the partial mixtures containing DHC at their highest doses was lower than the response rate for the partial mixture lacking DHC. These results seem to

indicate that CAF has a positive role in the substitution for MA, and DHC has higher response-rate-decreasing effects. On the other hand, the combination of CAF and MEP alone showed complete substitution for MA. This may indicate that CAF and MEP produce a synergistic effect in terms of substitution for MA. The role of CPA was considered to reduce the synergism of these drugs because the mean percent of MA-appropriate responses with the partial mixture of CAF, MEP, and CPA were lower than with the partial mixture of CAF and MEP alone. The similar synergism in the discriminative effects of other antitussive mixtures was also reported by investigators who demonstrated that the mixture containing caffeine, ephedrine, and phenylpropanolamine substituted for amphetamine and cocaine in rats but each constituent individually did not (6,7).

Although the complete mixture does not appear to have strong MA-like stimulus effects, some of its constituents appear to have stimulant properties. MEP and CAF produced partial substitution for MA when given alone, but produced complete substitution when given together. The results suggest that the MA-like stimulus effects of the CAF and MEP mixture are reduced by additional DHC and CPA and that the present complete mixture has a limited role for MA-like stimulus effects in the abuse of the antitussive mixture.

Although the role of DHC in the complete mixture in terms of substitution for MA was minor in the present experiment, it is considered that the stimulus effects of the antitussive mixture need additional characterization, perhaps by examining their resemblance to those of DHC or other constituents. It has been reported that neither CAF nor MA substituted for the same complete mixture used as a training drug in rats, while DHC and Δ^9-tetrahydrocannabinol did substitute for the complete mixture (13), and further that the reinforcing efficacy of DHC was increased with the combination of MEP, CAF, and CPA in rhesus monkeys (11). It was also demonstrated that place preference conditioning in rats was enhanced by the combination of DHC and CPA in comparison with DHC alone (10). These facts may indicate that the complete antitussive mixture also has some different stimulus properties from those of MA.

Under the present experimental condition using rats, it was concluded that the discriminative effects of the complete antitussive mixture were partially similar to MA and that CAF and MEP by their interaction play primary roles in producing MA-like discriminative stimulus effects while DHC and CPA play roles in reducing MA-like effects.

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