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COMPARISON OF THE DISCRIMINATIVE STIMULUS PROPERTIES OF COCAINE AND AMPHETAMINE IN RATS

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1 Water-deprived rats were trained to press either the left or the right bar in a test chamber according to whether they were injected with a central nervous system stimulant or 0.9% w/v NaCl solution (saline). Correct responses were reinforced with water.

2 Different groups of rats learned to discriminate amphetamine or cocaine from saline. Dose-response curves and ED_{50} values were then determined in brief test sessions when no responses were reinforced.

3 In a crossover study, cocaine was tested in the rats trained to discriminate amphetamine from saline, and *vice versa*. The two drugs were largely interchangeable, but the ED_{50} values were increased, indicating a possible, subtle difference in their discriminative stimulus properties.

4 The results indicate the importance of complete crossover designs in combination with dose-response determinations when attempting to classify drugs according to their discriminable properties.

Introduction

Many psychoactive drugs, including amphetamine, can serve as discriminative stimuli in the sense that rats can be trained to make different behavioural responses depending on whether they have received drug or 0.9% w/v NaCl solution (saline) (Overton, 1971; Harris & Balster, 1971; Schechter & Rosecrans, 1973). Once discriminative control has been established with a drug, other substances may then be substituted. As a rule, closely-related substances produce the response associated with the drug used in training but compounds from different pharmacological classes produce the response previously associated with saline (Overton, 1971, 1974). It has therefore been proposed that their discriminative stimulus properties may be useful for classifying drugs (Barry, 1974) and further information about the specificity of drug-produced stimuli would clearly be valuable.

Many behavioural effects of amphetamine and cocaine are similar (Woods & Downs, 1973), but little is known about the similarity or otherwise of their discriminative stimulus properties. Huang & Ho (1974) have reported that at a single dose level, cocaine produced the drug response in rats trained to discriminate amphetamine from saline. In the present experiments, the ability of rats to discriminate cocaine from saline was examined with a procedure known to yield good discriminative control with amphetamine (Kuhn, Appel & Greenberg, 1974). Different rats were trained with amphetamine and cocaine and, after discriminative control had developed, dose-response and crossover experiments were carried out to compare these drugs further. A preliminary account of this work has been published (D'Mello & Stolerman, 1977a).

Methods

Animals

In these experiments 8 female, Sprague-Dawley rats were used, weighing 200–250 grams. They were housed individually in a room of controlled temperature (22–24°C) and a regular day-night cycle was imposed by electric lighting (light from 08 h 00 min to 20 h 00 min). The rats were allowed access to water for 1 h each day, but food was available at all times except during training sessions. The animals were run at the same time each day, 5 days a week, and were divided into 2 groups of 4 rats each, trained with amphetamine and cocaine respectively.

Apparatus

A standard experimental chamber (Campden Instruments) contained within a sound-insulated, ventilated enclosure was used throughout. The chamber contained two response bars separated by a recess in which water (nominally 0.08 ml) could be presented by a dipper mechanism. White noise at

78 dB (ref. 0.0002 dynes/cm^2) was present at all times to mask extraneous sounds. Solid-state programming and recording equipment was located in an adjacent room.

Acquisition of drug-saline discriminations

The procedure was similar to that described in detail by Kuhn *et al.* (1974). The rats were first trained to press bars for water reinforcement which was made available on a tandem variable-interval 1 min fixed-ratio 10 schedule (tand VI 1 FR 10). In this schedule, the 10th bar-press (FR 10) was reinforced after a randomly determined, variable interval (VI) of time (mean = 1 min; range 14–108 seconds). Responses during the intervening periods were recorded but were not reinforced. On any given day, either the left or right bar was removed (in an alternating sequence) to avoid giving the rats a choice before discriminative stimuli (drug injections) were presented. Sessions lasted for 30 minutes.

After this preliminary training to establish a baseline of responding, both bars were made available simultaneously and drug injections were begun. In order to minimize effects due to any possible position preferences, the 4 rats trained on each drug were divided into 2 sub-groups. For one sub-group, responding on the left bar was reinforced whenever a drug had been injected, whereas the other sub-group was reinforced for responding on the right bar after drug. Responses on the opposite bars were reinforced after saline injections. Ten consecutive responses on the correct bar were now required for reinforcement, so as to minimize any tendency for the rats to press the two bars alternately. Incorrect responses reset the FR counter to zero. Constant doses of 1.0 mg/kg (amphetamine) and 10.0 mg/kg (cocaine) were used throughout training, and were selected on the basis of previous work (Kuhn *et al.*, 1974; Huang & Ho, 1974). Drug and saline injections were given in a randomized sequence except that the same injection was not given for more than three successive sessions. Overall, each rat received an equal number of drug and saline injections.

After 30 days on the training regimen described above, accuracy of discriminative control by the drug injections was assessed during short (5 min) extinction sessions during which no water was presented regardless of which bar was pressed. This was necessary since the water itself could indicate which bar was correct during training sessions. The VI component of the tandem schedule made it very difficult for the rats to discriminate extinction test sessions from training sessions. From this stage, training sessions were shortened to 25 minutes.

Test phase

After about 40 training sessions, satisfactory discriminative control by the drugs had developed. Dose-response curves were then established. The rats trained on amphetamine-saline discrimination were tested with either saline or amphetamine 0.10, 0.32 or 1.0 mg/kg, whereas the rats trained on cocaine-saline discrimination were tested with either saline or cocaine (1.0, 3.2 or 10.0 mg/kg). Saline and the three drug doses were tested twice in each rat, in counterbalanced sequences which were different for each rat (total of 8 tests per rat). In order to simplify statistical analysis, the mean of the two tests was used as the score for each rat at a given dose.

The rats were run only for 5 min extinction sessions on days when test doses were administered. All test days were preceded by a saline training day to minimize residual drug effects, and a training day with amphetamine (1 mg/kg) or cocaine (10 mg/kg) was given once a week. Thus, during each week, test doses were given on Tuesdays and Fridays, with saline training on Mondays and Thursdays and drug training on Wednesdays (Kuhn *et al.*, 1974).

Next, in the crossover phase of the experiments, the dose-response curves were redetermined, but this time the rats trained on amphetamine were tested with cocaine and *vice versa*. The doses of each drug and the experimental design were the same as when the dose-response curves were first established. Training with saline and the original drugs continued on the intervening days.

Drugs

Cocaine hydrochloride (B.P.) and (+)-amphetamine sulphate (S.K.F.) were dissolved in saline and injected intraperitoneally in a volume of 1 ml/kg. Control injections consisted of isotonic saline. All doses were calculated as salts.

Results

Acquisition of drug-saline discriminations

Cumulative response records for a representative rat (no. 1) trained to discriminate amphetamine from saline are shown in Figure 1. In such records, the slope of the trace is proportional to the response rate. The baseline of responding before any drug injections was characterized by rapid runs of about 10–15 responses separated by brief pauses. Typically, rat no. 1 pressed the bar about 1200 times in the 30 min sessions and was reinforced about 25 times. The rates and patterns of responding were similar for left and right bars, which were presented on alternate days.

During the first few sessions of discrimination training, the rat pressed the wrong bar very frequently, as can be seen from the short travel of the pen in the cumulative records in Figure 1(1). The pen was reset by every incorrect response and thus, the height of the trace indicates the number of consecutive correct

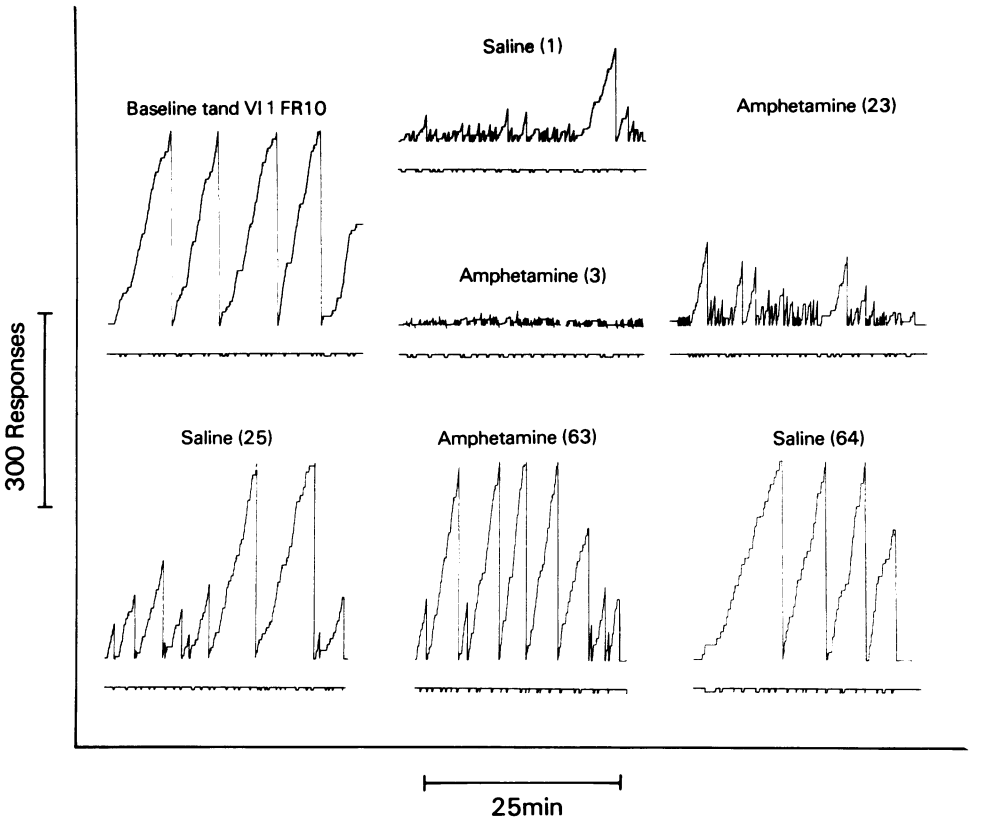

Figure 1 Representative performance of rat no. 1 during development of discriminative control by amphetamine (1 mg/kg) and saline administered 30 min before sessions. Each record shows complete performance for a session on tand VI 1 FR 10. Abscissae, time; ordinates, cumulative number of responses. Short diagonal strokes on the cumulative records indicate reinforcements. The pen was reset after about 300 responses, or when the rat pressed the wrong bar. Downward deflections of the event recorder (horizontal line) indicate periods when FR component was operative. Figures in parentheses indicate total number (drug and saline) of discrimination training sessions.

responses. After about 20 sessions, a distinct change in responding was evident: fewer presses on the wrong bar (errors) were made with the result that the original baseline pattern of responding became clearly evident again (e.g. Figure 1(25)). Asymptotic performance was attained after 35 and more sessions, and was characterized by very few errors. Typically, pauses were shorter after the injection of amphetamine than after saline and thus, the drug increased total responses per session by about 40%. However, pause durations and response totals varied considerably from day to day under both saline and drug conditions.

The results shown in detail for rat no. 1 were generally similar to those obtained from the other animals; the most notable exceptions were with rats no. 3 and no. 6, which usually paused more between runs of responses. However, there was an occasion during discrimination training when responding on the drug bar was totally suppressed in rats no. 3 and no. 6, which were then retrained from the beginning (continuous reinforcement) in 2–3 sessions. This did not seem to impair subsequent learning to discriminate between drug or saline administration. Asymptotic performance for another rat (no. 2) trained on amphetamine-saline discrimination is shown in Figure 2, along with that for 2 of the 4 rats trained on cocaine. The cumulative records for amphetamine- and cocaine-trained rats were similar at all stages of the experiment and are not therefore presented in further detail.

The mean numbers of correct responses and of errors during the VI component of the schedule are shown in Figure 3. The results for rats no. 3 and no. 6

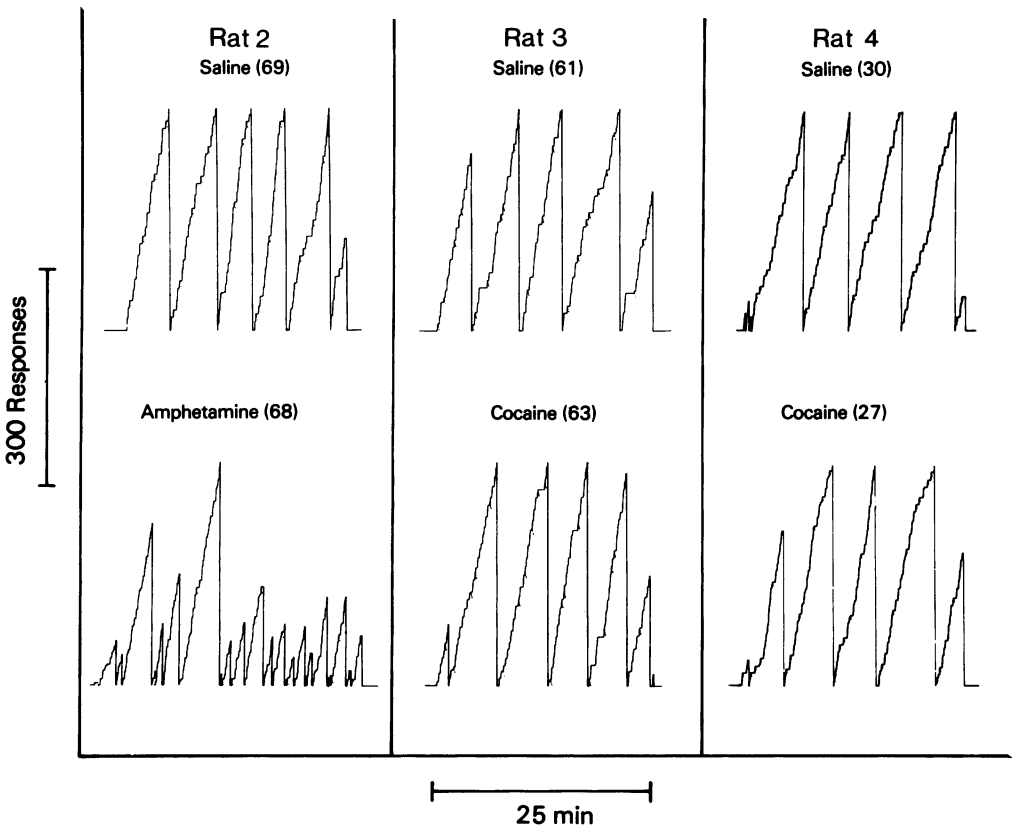

Figure 2 Representative asymptotic performance of one rat (no. 2) trained to discriminate amphetamine (1 mg/kg) from saline and of 2 rats (nos 3 and 4) trained to discriminate cocaine (10 mg/kg) from saline. Abscissae, time; ordinates, cumulative numbers of responses. The recorder pen was reset after 300 responses, or when the rats pressed the wrong bar. Figures in parentheses indicate number of discrimination training sessions.

are omitted for the whole five-day period within which they were retrained. Correct responses remained substantially constant during training, at about 1000 in 30 min, whereas errors fell progressively to an average of about 10. There were no marked differences in the rates at which errors declined over sessions according to whether the drug was amphetamine or cocaine. However, the absolute numbers of responses after amphetamine as compared with saline were increased markedly in 3 of the 4 rats (Table 1), and the mean increase for the group as a whole was statistically significant ($t=4.15$, d.f. 3, $P<0.05$). Cocaine on the other hand tended to reduce the overall number of responses, but not to a significant extent.

These results provided evidence for discriminative control by amphetamine and cocaine, but were not conclusive since during the training sessions, the presentation of the very first reinforcer indicated which bar the rats should press to obtain water. From that point in the session, the rats could have maximized reinforcement without using the drug as a cue. The usual tests for bar choice in the absence of reinforcement were therefore carried out, and the results from these 5 min extinction test periods given after 30–35 training sessions are shown in Table 2.

It can be seen that all rats responded predominantly on the appropriate bar according to the injection of drug or saline, regardless of whether this bar was on the left or right side of the chamber. The mean scores for saline and drug conditions differed significantly for both amphetamine ($t=8.68$, d.f. 3, $P<0.01$) and cocaine ($t=9.03$, d.f. 3, $P<0.01$). The arc-sin transformation was used in calculating the values of t as is usual for percentage scores (Winer, 1971).

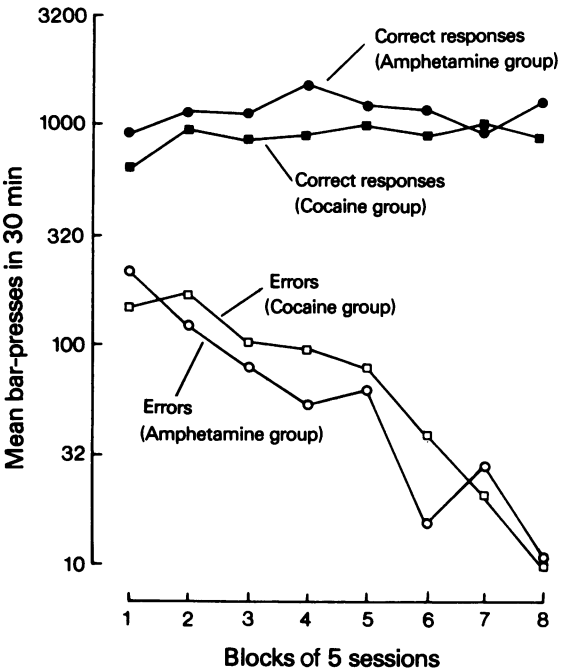

Figure 3 Acquisition of discriminative control by amphetamine (1.0 mg/kg) and cocaine (10.0 mg/kg) in 2 groups of 4 rats each. Responses on the correct bar remained approximately constant for both the amphetamine (●) and cocaine (■) groups, while responses on the wrong bar were drastically reduced (○ amphetamine group; □ cocaine group). Each point is the mean of results from both drug and saline sessions, of which there were equal numbers overall.

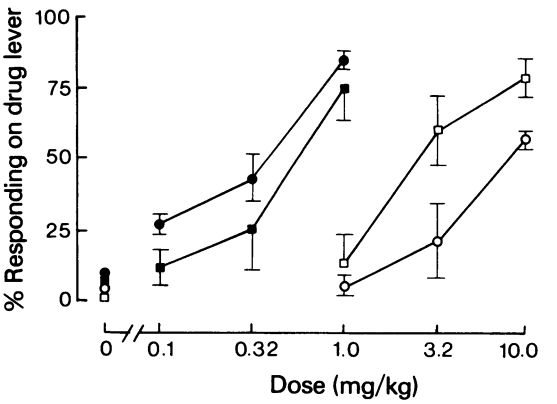

Figure 4 Percent responding (means ± s.e.) on drug bar as a function of drug and dose. Results are shown for tests with amphetamine in rats trained on amphetamine (●) or cocaine (■), and for tests with cocaine in rats trained on cocaine (□) or amphetamine (○). Each dose was given twice to all rats and thus each point represents the mean of 8 observations obtained during 5 min extinction tests. Some standard errors have been omitted for clarity.

Test phase

Dose-response curves obtained during extinction test sessions are shown in Figure 4. After saline injection, responses on the bar appropriate for drug averaged only about 5% of the total number of responses. Regardless of whether the drug injected was amphetamine or cocaine, the larger the dose, the greater the percentage of responding which was on the bar appropriate for drug. Analysis of variance revealed that the slopes of the various dose-response curves did not differ significantly, nor were there any significant deviations from linearity.

The results from the crossover phase showed that in sufficient doses, cocaine increased responding on the bar appropriate for drug in rats originally trained to discriminate amphetamine from saline. Similarly, amphetamine increased responding on the bar appropriate for drug in rats trained to discriminate cocaine from saline (Figure 4). However, the dose-

Table 1 Mean numbers of responses (bar-presses) during training sessions: the scores for each rat are means for the first 12 saline and drug sessions respectively and include all bar-presses during both components of the tand VI 1 FR 10 schedule

Rat no.	*Saline*	*Amphetamine*	*Difference %*
1	1481	2113	+42.7
2	1854	2003	+ 8.0
6	346	486	+40.5
8	1466	2025	+38.1
Means	1287	1657	+32.3
	Saline	*Cocaine*	*Difference %*
3	639	555	−13.1
4	1661	1528	− 8.0
5	1263	1282	+ 1.5
7	1373	1049	−23.6
Means	1234	1104	−10.8

Amphetamine (1 mg/kg) was injected 30 min before, and cocaine (10 mg/kg) 15 min before, 30 min training sessions. Saline was injected either 30 min or 15 min before sessions, to match the interval between drug injection and training for each group.

response curves were shifted during the crossover phase of the experiment, indicating possible changes in the apparent potencies of the drugs. Statistical support for these effects was then sought by comparisons of ED_{50} values derived from the dose-response curves.

An ED_{50} was defined according to Barry (1974) as that dose of drug which would have been expected to produce 50% responding on the bar previously associated with drug. Thus ED_{50} values were calculated for both drugs in each rat from linear regression equations determined by the method of least squares. Table 3 shows that the mean ED_{50} was 0.30 mg/kg for amphetamine in rats trained with amphetamine (1 mg/kg), which compares well with the published value of 0.23 mg/kg (Kuhn *et al.*, 1974). The four ED_{50} values were then compared statistically by means of a two-factor (2 x 2) analysis of variance. This analysis confirmed the significantly higher log ED_{50} for cocaine as compared with amphetamine ($F=97.2$, d.f. 1,6, $P<0.001$). The mean difference between the log ED_{50} values for amphetamine-trained and cocaine-trained rats was not significant ($F=1.38$, d.f. 1,6), indicating that the drug which was used for training did not influence the overall sensitivity of the rats to the stimuli from the two drugs. However, a significant interaction indicated that the overall ED_{50} was increased during the crossover phase of the study ($F=12.3$, d.f. 1,6, $P<0.05$), which confirms the statistical reliability of the shifts in dose-response curves apparent in Figure 4. Thus, Table 3 shows that the potency of cocaine relative to that of amphetamine varied by a factor of about 7, depending on whether the drugs were compared in the rats trained on amphetamine or on cocaine.

Table 2 Percentage responding on drug bar during 5 min extinction sessions: each score is the result of a single test given after 30–35 training sessions

Rat no.	*Saline*	*Amphetamine*
1	20.9	91.4
2	0.0	76.4
6	3.1	97.8
8	1.5	99.8
Mean ± s.e.	6.4 ± 4.9	91.4 ± 5.3
	Saline	*Cocaine*
3	5.3	100.0
4	4.5	78.7
5	2.3	70.4
7	9.6	94.5
Means ± s.e.	5.4 ± 1.5	85.9 ± 6.9

Amphetamine, cocaine or saline was injected before test sessions in which both bars were present but no reinforcers were presented. Bar choice was therefore determined solely by the drug or saline injection. Doses and injection-test intervals were the same as during previous training sessions (see Table 1).

Discussion

It was established that cocaine (10 mg/kg) could serve as a discriminative stimulus indicating which of two bars rats should press to obtain water. Discriminative control developed at about the same rate, and to the same extent as with amphetamine (1 mg/kg). Amphetamine, but not cocaine, also increased the total numbers of responses on both bars. The results with amphetamine are very similar to those of Kuhn *et al.* (1974) with respect to the development of discriminative control, changes in response rate and the general suitability of the tandem VI FR schedule for such experiments. The apparent lack of effect of cocaine on response rate during the acquisition of discriminative responding does not necessarily represent a real difference from amphetamine since only one dose of each drug was examined at that stage. In appropriate doses cocaine, like amphetamine, can increase rates of operant responding on suitable schedules of reinforcement (Smith, 1964; Benesova, 1967).

The cumulative records showed that responding on the tandem schedule was characterized by brief pauses between runs of rapid responding. Evidently runs of responses served as cues which temporarily inhibited further performance in the absence of any

Table 3 ED_{50} values (mg/kg ± s.e.) for amphetamine and cocaine in rats trained to discriminate these drugs from saline

	Test drug		*Relative potency*
Training drug	*Amphetamine*	*Cocaine*	*Amphetamine : Cocaine*
Amphetamine	0.30 ± 0.07	10.1 ± 2.7	*33.7 : 1*
Cocaine	0.62 ± 0.18	2.8 ± 0.4	*4.5 : 1*

ED_{50} values were determined from linear regression of percentage drug-bar responding on log dose. All data based on responding during 5 min extinction tests.

programmed, sensory stimuli. This performance resulted in a frequency of reinforcement near to the maximum allowed by the schedule, and at the same time minimised unreinforced responding. Amphetamine reduced pausing, but the typical pattern of responding was still clearly apparent.

To a considerable extent, cocaine and amphetamine were interchangeable. Huang & Ho (1974) have found that cocaine (7.5 mg/kg) produced responding appropriate for drug in rats trained with amphetamine (0.8 mg/kg) as the discriminative stimulus. Ando (1975) has reported that at a single dose level, cocaine substituted for amphetamine in one rat. However, in rats trained with mescaline (10 mg/kg), or Δ^9-tetrahydrocannabinol (4 mg/kg), neither amphetamine nor cocaine elicited the drug response (Barry & Kubena, 1972; Winter, 1975). More precise analysis of the present results indicated that increased doses were needed when amphetamine or cocaine were substituted for each other. This suggests that there may be a subtle difference in the discriminable effects of the drugs, but other explanations should also be considered.

A gradual development of tolerance could account for the shift in dose-response curves during the crossover phase of the study. This seems unlikely since the rats had been drugged repeatedly prior to even the first dose-response determinations. As a rule, tolerance to the discriminable properties of drugs has not been found unless much larger doses are administered in addition to the doses used for training (Hirschorn & Rosecrans, 1974; York & Winter, 1975). Even with opiate drugs, repeated ED_{50} determinations can yield very consistent results (Colpaert, Kuyps, Niemegeers & Janssen, 1976), but comparable information for amphetamine and cocaine does not seem to be available. In summary, the development of tolerance in the present experiments cannot be excluded altogether but it seems unlikely.

It is known that ED_{50} values for the discriminable properties of drugs increase as the dose used for training increases (Harris & Balster, 1971; Overton, 1974), so the apparent shifts in dose-response curves in the crossover phase of the present experiments may have been a consequence of the doses used in training. This possibility can be excluded; if the two drugs were really completely interchangeable, but one group was trained on a relatively lower dose than the other, that one group should have been more sensitive to both drugs. This was not the case; the overall difference between the ED_{50} values due to the use of either amphetamine or cocaine during training was insignificant, whereas there was a statistically reliable difference in ED_{50} values between the original and crossover phases of the study. The similar rates at which discriminative control developed with the two drugs also suggest that equivalent doses were used.

The present results therefore strengthen previous evidence of considerable similarities between the behavioural effects of cocaine and amphetamine. For example, both drugs can facilitate locomotor activity, induce stereotyped behaviours, either increase or decrease rates of operant responding, and serve as positive reinforcers (Woods & Downs, 1973). Very similar patterns of responding can be maintained when either cocaine or amphetamine serve as reinforcers (Goldberg, 1973). Mixtures of cocaine with chlordiazepoxide can increase the locomotor activity of mice to a much greater extent than cocaine alone (D'Mello & Stolerman, 1977b), and this action of cocaine is also similar to that of amphetamine (Rushton, Steinberg & Tomkiewicz, 1973). However, there are differences in the interactions of cocaine and amphetamine with iproniazid, α-methyltyrosine and haloperidol (Smith, 1965; Simon, Sultan, Chermat & Boissier, 1972). The results from the crossover phase of the present study also suggest that the effects of amphetamine and cocaine may not be identical, in this case with respect to their discriminable properties. This supports a more general point made by Overton (1974), who commented critically on the common strategy of training with only one drug, and then testing for the ability of other substances to substitute. Complete crossover designs in combination with ED_{50} determinations greatly increase the expenditure of time and effort, but seem to be necessary when attempting to compare and classify drugs according to their properties as discriminative stimuli.

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