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DISCRIMINATIVE STIMULUS PROPERTIES OF COCAINE

EFFECTS OF APOMORPHINE, HALOPERIDOL, PROCAINE AND OTHER DRUGS

T. U. C. JÄRBE
University of Uppsala, Department of Psychology, Box 227, S-751 04 Uppsala and Department of Applied Psychology, Box 1225, S-751 42 Uppsala, Sweden

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Summary—In pigeons trained to discriminate between the presence and absence of 3 mg/kg of cocaine, combinations of intramuscularly injected (i.m.) procaine (0.7–7.0 mg/kg) plus cocaine (0.3–3.0 mg/kg) did not alter the drug (cocaine)–dose generalization curve as compared to cocaine alone although tests with large doses of procaine given alone (30.0 and 56.0 mg/kg) engendered dose-related responding appropriate to cocaine. Apomorphine (0.56 mg/kg, i.m.) also elicited more than 50% cocaine-appropriate responding, as did doses of 10 mg/kg of intragastrically administered cocaine, given by gavage at the opening of the proventriculus; of the two treatment-test intervals (15 and 30 min) examined the generalization effect was greater at 30 min as compared to 15 min after administration. D-Lysergic acid diethylamide (0.1 mg/kg) morphine (3.0 mg/kg), pentobarbital (10.0 mg/kg), and Δ^9-tetrahydrocannabinol (0.3 mg/kg) caused less than 16% pecking responses on the cocaine-appropriate key. The discriminative stimulus effects of cocaine (3.0 mg/kg) were attenuated in a dose-related manner by the neuroleptic haloperidol (dose range tested: 0.1–1.0 mg/kg). Neither the antagonism, nor the substitution tests with haloperidol were accompanied by a significant change in the percentage of responding on the initially selected position (key) by the pigeons.

Key words: cocaine cue, procaine, haloperidol, apomorphine, other drugs, pigeons.

Drug discrimination learning in animals is a relatively recent assay for *in vivo* assessment of "subjectively" experienced effects of drugs in subhuman subjects. Most commonly, animals are trained to emit one response when influenced by the training drug dose and to emit the alternative, opposite response when trained without drug in two-choice settings (e.g. Järbe and Swedberg, 1982). This technique has served as a behavioural marker using a variety of drugs in recent years (for review see Colpaert and Slangen, 1982).

The concensus today from drug discrimination studies, conducted with the CNS psychomotor stimulant cocaine, must be that its stimulus effects are related to changes in catecholaminergic transmission (Ho and Silverman, 1978; Silverman and Ho, 1977). Thus, the response learned in the presence of a CNS stimulant drug is generalized by the animal to other substances which are believed to enhance catecholaminergic transmission (Ando, 1975; Ando and Yanagita, 1978; Colpaert, Niemegeers and Janssen, 1979; D'Mello and Stolerman, 1977; Ho and McKenna, 1978; Ho, McKenna and Huang, 1976; Järbe, 1981, 1982; Stolerman and D'Mello, 1981; Porsolt, Pawelec and Jalfre, 1982). More specifically a dopaminergic mediation is suggested by the antagonism of the cocaine cue by the neuroleptic haloperidol and related agents (Colpaert, Niemegeers and Janssen, 1978a, 1978b; Järbe, 1978; McKenna and Ho, 1980) whereas purported noradrenargic and serotonergic blockers did not attenuate the cocaine cue (Järbe, 1978; McKenna and Ho, 1980); admittedly, however, not all cocaine-induced discriminations reported were substantially reversed by pretreatment with haloperidol (Colpaert, Niemegeers and Janssen, 1976b; Cunningham and Appel, 1982).

A loss of reinforcement contingencies (e.g. Wise, 1982) was suggested by Colpaert *et al.* (1978a, 1978b) to explain the observation that rats did not exclusively press the rewarding, initially selected bar throughout sessions when haloperidol was tested together with cocaine or amphetamine; haloperidol was not tested singly and therefore this was examined in the present study.

The relationship between cocaine and other agents exhibiting local anaesthesia is unclear. Local anaesthetics other than cocaine are generally considered to be devoid of reinforcing ("euphorigenic") properties (Ritchie, Cohen and Dripps, 1970) but recent data in animals suggest that procaine and related short-acting esteratic agents are self-administered to an extent greater than control values (Ford and Balster, 1977; Garza and Johansson, 1982; Hammerbeck and Mitchell, 1978; Johansson, 1980; Woolverton and Balster, 1979, 1982) suggesting abuse potential. Street samples of cocaine often are adulterated, not uncommonly with procaine; a 30/70% ratio estimate between cocaine/procaine has been suggested (Anonymous, 1980). To examine their stimu-

lus properties, cocaine and procaine were tested singly or in combination.

Contrary to earlier beliefs (Ritchie *et al.*, 1970), cocaine is also active when given orally to man (Post, Kotin and Goodwin, 1974; Van Dyke, Jatlow, Ungerer, Barash and Byck, 1978; Wilkinson, Van Dyke, Jatlow, Ungerer, Barash and Byck, 1980) and pigeons (Järbe, 1981), observations consistent with traditional modes of administration of preparations from *Erythroxylon coca* by South American indians (Gay, Inaba, Sheppard, Newmeyer and Rappolt, 1975; Mortimer, 1974). The intragastric route of administration was used to evaluate the effects of cocaine at two intervals after administration in pigeons trained to discriminate between the presence and absence of 3 mg/kg of cocaine. The specificity of the present drug discrimination was tested with morphine, pentobarbital, Δ^9-tetrahydrocannibinol and lysergic acid diethylamide and these substances mainly produced responding appropriate for no drug.

METHODS

Animals

Five mature, male White Carneaux pigeons with a mean free-feeding weight of 610.1 g (SEM ± 49.15, were used; they were the same as used in a previous study (Järbe, 1981). The birds were reduced to about 80% of their weights after having been on a free-access food-regimen for about 3 months in the laboratory. The 80% weights were maintained between sessions by the food presented during the sessions and by post-session supplemental feedings. Water and crushed oyster shell grit were always available in the home cages. Between experimental sessions the birds were individually housed in a colony room (lights from 07–19 hr; temp. 20–22°C; relative humidity 50–60%), housing altogether 12 pigeons.

Apparatus

The experimental chamber, adapted after Ferster and Skinner (1957), was sound-attenuated and ventilated. The response keys 2 cm in diameter and dimly illuminated with white light, were mounted 10 cm apart on the front panel of the chamber, each key 19 cm above the chamber floor. The opening of the key contacts defined a key-pecking response. The food magazine was located between the response keys, 4 cm above the floor of the chamber. The reward was a 4 sec access to grain. The key light went off simultaneously with the 4 sec operation of the grain magazine and illumination of food by the magazine light. A dim-light bulb illuminated the chamber. Conventional relay programming and recording equipment, located in a room adjacent to that of the chamber, were used.

Procedure

Discrimination training. The birds had originally been trained to respond on either of the two keys to obtain food according to a fixed ratio (FR1) schedule of reinforcement. Thereafter the requirement for obtaining food was increased until a fixed ratio 15 schedule was in operation, i.e. the pigeons had to peck the key 15 times in order to produce access to food for 4 sec. In the drug-discrimination sessions, the birds had to respond on the appropriate key to get access to the food. Which key was correct depended upon whether cocaine or saline had been administered prior to the training session. Responses on the inappropriate key had no programmed consequences. The order of administration of cocaine and saline in the sessions was irregular with the restriction that the same training condition never occurred more than twice in succession, that the first and second session treatments in any week never were the same, and that over a 2 week period an approximately equal amount of training sessions had been distributed between both training conditions. The animals were trained once a day for 3 to 5 days a week for 20 min per session or until food had been presented 52 times, whichever occurred first. The pigeons were placed in the chamber immediately after injection and remained there until the training session started 15 min later. The activation of the house light and illumination of the response keys signalled the start of a session. The masking noise and exhaust fans were always in operation. In order to avoid potential interanimal cues the order in which the birds were trained during a given day was mixed (Extance and Goudie, 1981).

Testing. After the birds reliably discriminated between the training conditions (3 mg/kg of cocaine and 1 ml/kg of saline), test sessions were interspersed between the regular training days; the criterion for entering the test phase was that the bird should have selected the correct key (left or right) at the onset of each training session during at least 8 out of 10 consecutive training days. Unlike regular training, both keys were activated throughout a test session and the birds consequently could obtain rewards by pecking on either of the keys (cf. Järbe, 1981, Järbe, Swedberg and Mechoulam, 1981; Porsolt *et al.*, 1982). As in training, food was presented according to a fixed ratio (FR-15) schedule of reinforcement, i.e. 15 pecking responses had to be accumulated on one of the two keys to obtain a 4 sec access to food. Except otherwise indicated, six rewards could be obtained in a test session. Animals were tested two or three times each 2-week period; each test was preceded by at least one correct cocaine and one correct saline training session. The birds were placed in the chamber immediately after the injection and remained there until the session started when intervals of 30 min or less were tested; otherwise the pigeons were returned to their home-cages after the injection and were left there until 15 min remained of the injection-test interval at which time they were placed in the experimental chamber; 15 min later the test session started. The order of tests was mixed. When

two drugs were given injections were on opposite sides of the breast muscle.

Drugs. Cocaine hydrochloride, morphine hydrochloride (ACO, Sweden), apomorphine hydrochloride, lysergic acid diethylamide tartrate (LSD-25, Sandoz, Switzerland), procaine hydrochloride (Sigma) and pentobarbital sodium (Abbott, U.S.A.) were dissolved in saline shortly before administration. Freshly prepared suspensions of (−)-Δ^9-tetrahydrocannabinol (Δ^9-THC, UN Narcotics Lab., Switzerland) contained 10% propylene glycol (v/v) 1% Tween-80 (v/v) and saline (Sofia, Kubena and Barry, 1974). Intramuscular (i.m.) injections were given in a constant volume of 1 ml/kg in the breast muscle. Combinations of cocaine and procaine were given as a single injection; solutions were prepared such that the mixture contained 30% cocaine and 70% procaine. When cocaine and saline were administered by gavage at the opening of the proventriculus with a stainless steel animal-feeding tube, the volume was 2 ml/kg. Doses refer to the forms indicated.

Data analyses. The principal datum is the percentage of responses on the drug-associated position (% RDP) out of the total number of responses emitted during a session. Other data recorded and calculations made were: position selection (left or right key) expressed as the number of tests where the pigeons selected the drug-associated position (DP selected); accuracy of the selection which is expressed as the number of responses emitted before the first reinforcement (FRF, median and 95% confidence limits, CL, two-tailed; in most instances, 95% CL is equal to the range for a given set of tests); the percentage of responding on the first, initially-selected key out of the total number of responses emitted during a session (median and 95% CL, symbol: percentage on the first selected key). Time level (mean ± SEM) is expressed as the quotient between the most recently preceding vehicle session and the drug session; a score above 1.0 means an increased response rate and/or a decrease in the latency to initiate responding. The statistics used are indicated in the appropriate sections.

RESULTS

Stimulus effects of mixtures of cocaine and procaine

Figure 1 shows the percentage drug-associated responses for testing mixtures of cocaine and procaine (30 and 70%, respectively) as well as cocaine alone in pigeons trained to discriminate between the presence and absence of the effects induced by 3 mg/kg of cocaine. Both cocaine alone and the combination of cocaine plus procaine caused dose-related generalization gradients which were very similar to one another, suggesting that the addition of procaine did not alter the cocaine cue appreciably. The median effective doses (ED_{50}) of cocaine were 1.30 mg/kg (cocaine plus procaine) and 1.24 mg/kg

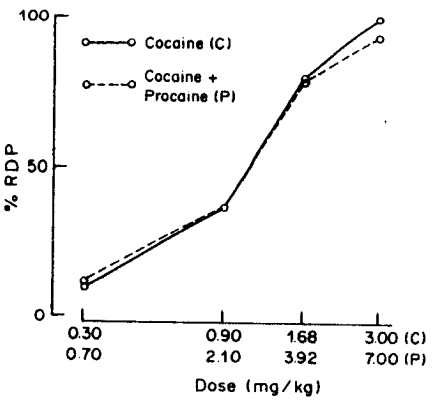

Fig. 1. Generalization tests with combinations of cocaine and procaine. Y-axis, percentage responding on the drug-associated key position (% RDP): X-axis, dose in mg/kg of cocaine (C) or combinations of cocaine plus procaine (P) administered intramuscularly 15 min prior to testing. Each data point represents the mean performance of 5 pigeons, trained to discriminate between the presence and absence of 3 mg/kg of cocaine. Data points were determined on separate days.

(cocaine alone), respectively, according to the procedure of Barry (1974); the corresponding estimates according to the procedure by Litchfield and Wilcoxon (1949) were, respectively: 0.94 and 0.90 mg/kg. For all determinations the median first reinforcement was 15, and the 95% confidence limits, 15–19; the median for the percentage of responding on the first selected key was 100 except in one case (procaine 7 mg/kg plus cocaine 3 mg/kg) where it was 99.5% although birds occasionally were observed to change key in these tests.

Generalization tests with procaine and apomorphine

Table 1 shows the percentage drug-associated responses as well as the time needed to obtain six rewards (time level) caused by three different doses of either procaine and apomorphine in the five birds trained to discriminate between cocaine and saline; data are shown separately for animals responding within 20 min after initiation of the test session and the cumulative effects of birds responding within the interval of 20 to 30 min after the test session proper began. At the largest doses tested of procaine (56 mg/kg) and apomorphine (0.56 mg/kg), respectively, more than 50% drug-associated responses were observed. This was accompanied by significantly increased time levels. According to the procedure by Barry (1974), the ED_{50} values were, respectively: 35 mg/kg (procaine) and 0.48 or 0.45 mg/kg for apomorphine at the two time intervals (20 and 30 min), respectively. For all determinations the median first reinforcement was 15 and the 95 confidence limits, 15–18. On five occasions the animals switched side during the test sessions. The median percentage of responding on the first selected key was 100%, except in one case (procaine 56 mg/kg) where the median was 75% (range: 16–100%).

Table 1. Generalization tests with procaine HCl and apomorphine HCl in pigeons ($n = 5$) trained to discriminate between 3 mg/kg of cocaine HCl and saline

Drug	Dose (mg/kg)	*n* tested (20′) *n* responding (20′)	DP selected	% RDP (20′)	Time level	*n* tested (30′) *n* responding (30′)	DP selected	% RDP (30′)	Time level
Procaine	10.0	5/5	0	0.0	1.08 (0.15)	5/5	0	0.0	1.08 (0.15)
Procaine	30.0	5/5	2	39.7	0.61 (0.15)	5/5	2	39.7	0.61 (0.15)
Procaine	56.0	5/4	3	82.3	0.22 (0.05)*	5/4	3	82.3	0.22 (0.05)*
Apomorphine	0.10	5/5	1	20.0	0.75 (0.38)	5/5	1	20.0	0.75 (0.38)
Apomorphine	0.30	5/4	2	29.6	0.87 (0.27)	5/5	3	42.7	0.70 (0.27)
Apomorphine	0.56	5/2	1	58.1	0.25 (0.19)*	5/4	2	54.1	0.20 (0.18)*

All drugs were injected intramuscularly 15 min prior to sessions. Data, one determination per bird for each drug and dose, are presented for the animals responding (at least 15 pecking responses) within 20 min (20′) and 30 min (30′), respectively, since initiation of testing as signalled by the onset of houselight and illumination of the two response keys, i.e. 15 min after injection of the compounds. Data for the 30 min test period represent the cumulative percentages; % RDP = percentage of responses directed to drug (cocaine) appropriate position. Time level (mean, and within brackets ± SEM) denotes the time needed to produce six rewards; the scores are expressed as quotient between the most recently preceding vehicle session and the test session. Scores above 1.0 indicate increased response rate and/or a reduced latency to initiate responding. ED_{50} values (Barry, 1974) were 35 mg/kg for procaine and 0.48 or 0.45 mg/kg for apomorphine at the two injection test intervals, respectively. $^*P < 0.05$ (*A*-test, two-tailed; McGuigan, 1965). DP = drug-associated position.

Table 2. Effects of haloperidol alone or in combination with cocaine in pigeons trained on a cocaine–saline discrimination

Drug	Dose (mg/kg)	Time (min)	Drug	Dose (mg/kg)	Time (min)	*n* tested *n* responding	DP selected	% RDP (1–6 rft)	Time level	% RDP (7–15 rft)	Time level	Percentage on the first selected key
Haloperidol	0.1	60	Saline	—	15	5/5	1	3.3	0.86 (0.07)	0.0	0.78 (0.08)	100 (6.7–100)
Haloperidol	0.3	60	Saline	—	15	5/5	0	0.0	0.75 (0.11)	3.0	0.80 (0.12)	100 (93.3–100)
Haloperidol	1.0	60	Saline	—	15	5/4	0	0.0	0.80 (0.07)	4.0	0.65 (0.10)*	99.5 (93.3–100)
Haloperidol	0.1	60	Cocaine	3.0	15	10/10	5	46.2	0.64 (0.18)	37.3	0.71 (0.13)†	100 (80.7–100)
Haloperidol	0.3	60	Cocaine	3.0	15	10/10	4	41.5	0.36 (0.19)*	37.8	0.46 (0.19)*	100 (81.0–100)
Haloperidol	1.0	60	Cocaine	3.0	15	10/9	3	33.3	0.47 (0.12)*	30.0	0.69 (0.07)*	100 (100–100)

Haloperidol was injected 60 min prior to testing followed either by saline (upper section) or 3 mg/kg of cocaine (lower section) 15 min prior to the test session proper began. Cue determination in each of the 5 pigeons was done with haloperidol plus saline whereas two observations per dose in these pigeons are the bases for the values pertaining to the haloperidol–cocaine combinations (2×5 observations per haloperidol dose). The number of subjects (n) = 5 for all statistical analyses, hence the replication was treated separately. $^*P < 0.10$; $^†P < 0.05$ (*A*-test, two-tailed; McGuigan, 1965). % RDP = percentage of responses directed to drug-appropriate position. DP = drug-associated position.

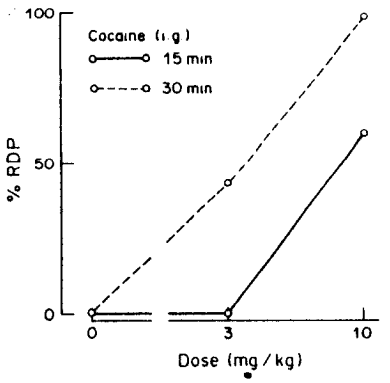

Fig. 2. Generalization tests after intragastric (i.g.) administration of cocaine. Y-axis, percentage responding on the drug-associated key position (% RDP); X-axis, dose in mg/kg of intragastrically administered cocaine. Each data point represents the mean performance of 5 pigeons, trained to discriminate between the presence and absence of 3 mg/kg of intramuscularly administered cocaine. Each dose and time interval (15 or 30 min after application) were determined on separate test days.

Antagonism of the cocaine cue by haloperidol

Table 2 shows the results of testing haloperidol alone (0.1–1.0 mg/kg), given 60 min prior to sessions, as well as testing halperidol together with the cocaine training stimulus (3.0 mg/kg). Haloperidol alone resulted in one bird initially selecting the drug-associated key, hence the low value (6.7%) noted in the column, *percentage on the first selected key*, whereas for the remainder of the session, subsequent rewards were obtained from the saline, non-drug associated key. The two larger doses (0.3 and 1.0 mg/kg) of haloperidol produced primarily responding appropriate for the non-drug condition, the drug-associated position selected was 0 in both instances and only 3 to 4% of the pecking responses were on the drug key throughout the entire session comprising 15 rewards. There was a tendency towards dose-related changes in time level probably reflecting a reduced rate of key pecking in comparison to the corresponding saline training sessions. Median first reinforcement was 15 (15–15) throughout. Haloperidol attenuated the cocaine cue (lower section of Table 2) as revealed by the progressively smaller number of animals selecting the drug-associated position (DP selected) as well as the total number of pecking responses directed to the drug key position (% RDP). Median percentage on the first selected key was 100% and the 95% confidence limits ranged between 81 and 100%.

A comparison between percentage drug-associated responses for the first six reinforcements (1–6 rft) and the percentage drug-associated responses for the remaining nine reinforcements (7–15 rft) in these 15-reward sessions was not significant ($P > 0.05$, two-tailed A-test; McGuigan, 1965), meaning no significant change in percentage drug-associated responses between the initial segment and the later section of the test probes. There was a tendency towards an increased time to produce the rewards; thus the rate of responding and/or the time until the first pecking-response of combinations of haloperidol and cocaine did not become normalized, i.e. were not equal to the values noted during saline training sessions. The median first reinforcement was 15, except on the 2nd determination of the interaction of 0.1 mg/kg of haloperidol and cocaine where it was 16 (95% CI: 15–16); in the other instances the upper limit of the 95% CI varied between 15 and 20 (2 × 5 tests) with a mean of 1.8 ($n = 9$) "incorrect" responses before the first reinforcement.

Generalization of intragastric application of cocaine

Figure 2 shows the effects (% RDP) of administering various doses (0–10 mg/kg) of cocaine in intragastric (i.g.) application to the 5 pigeons trained to discriminate between the presence and absence of 3 mg/kg of cocaine given intramuscularly; the intragastric route of administration was evaluated both at 15 and 30 min after administration. The effect of intragastric administration appeared stronger after the longer administration-test interval (30 min), since all birds selected the cocaine-associated position from the outset in tests with 10 mg/kg of cocaine whereas only 3 birds did so at this dose of cocaine (10 mg/kg), when the test was carried out 15 min after application. Responding after administration of 3 mg/kg of cocaine administered intragastrically followed the above described pattern in that three at the 30 min interval, as opposed to none of the birds tested at 15 min after intragastric application selected the cocaine key, although one of the birds selecting the drug-key changed after the first reinforcement at the longer interval. The median first reinforcement was 15 throughout, and for the 15 min interval the 95% confidence limits were 15–16; and for the 30 min interval they were 15–15, except for tests with 10 mg/kg of cocaine where the limits were 15–26. Dose-effect estimates (ED_{50}) for the 15 and 30 min intervals were, respectively (Barry, 1974): 9.2 and 3.6 mg/kg.

Compounds not maintaining cocaine-appropriate responding

Morphine, pentobarbital and Δ^9-THC resulted in 0 percentage drug-associated responses when tested by substitution in birds regularly maintained on a cocaine vs saline discrimination; a similar test with LSD-25 produced 16 percentage drug-associated reaponses. These data are shown in Table 3. Although there was a tendency for a change in time level with all four drugs, a statistically-significant effect is found only for the tests with LSD. Median first reinforcement was 15 (95% CL: 15–15) throughout, and all reinforcements were obtained from the initially selected key.

Table 3. Generalization tests with lysergic acid diethylamide tartrate (LSD-25), morphine HCl, pentobarbital sodium (P-barb.), and *l*-delta-9-tetrahydrocannabinol (Δ^9-THC) in pigeons trained to discriminate between 3-mg/kg of cocaine HCl and saline

Drug	Dose (mg/kg)	Time (min)	*n* tested / *n* responding	DP selected	% RDP	Time level
LSD-25	0.1	15	4/4	1	15.7*	0.22 (0.16)†
Morphine	3.0	15	4/3	0	0.0	0.56 (0.21)
P-barb.	10.0	15	4/4	0	0.0	0.66 (0.12)
Δ^9-THC	0.3	90	4/3	0	0.0	0.47 (0.13)

Each drug and dose represent the average performance of the four birds participating in these tests. Tests were of 20 min duration after initiation of the test session proper. Time in minutes indicates the time period elapsing after the injection until testing. Time level (mean ± SEM) denotes the time needed to produce six rewards; the scores are expressed as quotient between the most recently preceding vehicle session and the test session. Scores above 1.0 mean increased response rate and/or decreased latency to initiate responding. *One bird only performed 15 pecking responses (on the non-drug associated key). †$P < 0.05$ (*A*-test, two-tailed; McGuigan, 1965). % RDP = percentage of responses directed to drug-appropriate position. DP = drug-associated position.

Performance levels during training conditions with cocaine and saline

The quotients for state-appropriate, correct key selection in the regular maintenance sessions (saline vs 3 mg/kg of cocaine) that intervened between test days were for the five birds, respectively: 1.21, 1.12, 1.10, 1.00 and 1.00 (mean: 1.086 SEM: ±0.045), meaning that 3 of the birds made more errors (exceeded the limit of an FRF of 29) in sessions with cocaine as compared to the training sessions with saline. In terms of percentage of correct responding, this amounts to 91.3% (±SEM: 3.3) for the sessions with cocaine, and the corresponding values for the training sessions with saline were 98.8% (±SEM: 1.3), respectively ($0.05 < P < 0.10$, two-tailed *A*-test; McGuigan, 1965). Throughout the median first reinforcement and 95% confidence limits were 15 for each bird and training condition, respectively. Sessions with cocaine regularly took longer than the training sessions with saline, i.e. time levels were below 1.0 ($P < 0.05$, two-tailed *A*-test; McGuigan, 1965).

DISCUSSION

The findings of the present investigation, using pigeons trained to discriminate between the presence and absence of 3 mg/kg of intramuscularly administered cocaine were: (a) that neither haloperidol alone, nor combinations of cocaine and haloperidol induced any significant changes in the percentage of responding on the initially selected key; haloperidol attenuated the cocaine cue but caused negligible cocaine-appropriate responding when tested alone; (b) that the addition of procaine did not markedly change the generalization curve for cocaine, although large doses of procaine by itself caused cocaine-like responding; (c) that intragastric application of cocaine can produce stimulus effects comparable to those of cocaine administered intramuscularly, the potency shown to vary with the interval examined after application; and (d) that the purported dopamine agonist, apomorphine, exerted at least 50% responding appropriate to cocaine, whereas representatives from four other pharmacological classes mainly induced responding appropriate for the non-drug, saline-training condition.

Colpaert *et al.* (1978a, 1978b) argued that the initial bar selection indicated the ability of the rat to detect the cue effects of psychomotor stimulants such as *d*-amphetamine and cocaine when tested in combination with neuroleptics; the lack of continued responding on the initially selected bar after combinations of haloperidol and psychomotor stimulants therefore reflected loss of reinforcement contingencies (cf. Beninger and Freedman, 1982; Tombaugh, Szostak and Mills, 1983; Wise, 1982) rather than, for example, limited antagonism (Järbe, 1982). A similar effect was observed after fentanyl–haloperidol combinations in one experiment (Colpaert, Niemegeers and Janssen, 1977a) but to less a degree in another study (Colpaert, Niemegeers and Janssen, 1976c). Also pimozide, another neuroleptic, resulted in a deterioration of responding on the initially selected bar when tested with fentanyl (Colpaert, Niemegeers and Janssen, 1977b). At the very least the present data suggest that not all haloperidol–cocaine combinations result in significant changes in responding on the initially selected manipulandum; similar results were obtained when testing haloperidol alone. Likewise, combinations of apomorphine and haloperidol did not result in significant changes in responding on the initially selected bar by rats (Colpaert, Leysen, Niemegeers and Janssen, 1976a) suggesting that the differential effects were not due to different procedures or species used. Additional research is required to clarify the issue further but the data argue against a simplistic view concerning postulated interference with dopaminergic reward mechanisms. The observation that haloperidol attenuated the cocaine cue is consistent with the majority of studies of cocaine discrimination published, although exceptions to this rule have been noted (see introduction as well as Shearman and Lal, 1981). Arguing against a "true" dopaminergic involvement, an endogenous cocaine-like substance was recently

proposed based on findings that agents which preferentially inhibited type B monoamine-oxidase showed generalization effects in rats trained to discriminate between cocaine (5 mg/kg) and the no drug condition (Colpaert, Niemegeers and Janssen, 1980; see, however, also Goudie, 1982).

Being a nitrogeneous compound, procaine can penetrate into the CNS, although doses larger than those needed for local anaesthesia is required (Ritchie *et al.*, 1970). In large doses both drugs cause convulsions and respiratory arrest but, unlike cocaine, procaine does not block reuptake of catecholamines; however, being a monoamine oxidase inhibitor (Hrachovec, 1972; MacFarlane, 1973) procaine could potentially enhance catecholaminergic transmission. This could be one reason why large doses of procaine caused cocaine-like responding in this study (see also Järbe, 1981). Rats trained to discriminate between procaine (54.6 mg/kg) injected intraperitoneally (i.p.) and saline also caused procaine-like responding when tested with cocaine and other esteratic local anaesthetics as well as with *d*-amphetamine (Woolverton and Balster, 1982); the potency factor was about 9 whereas in the present study cocaine exhibited at least twice that potency over procaine in terms of stimulus effects. In addition, McKenna and Ho (1980) noted around 55% drug (cocaine)-appropriate responding with procaine (20 mg/kg) in rats discriminating between 10 mg/kg of cocaine and saline; this effect, however, was associated with a decrease of the rate of bar-pressing behaviour. In yet another study with rats (Huang and Wilson, 1982), procaine (5–30 mg/kg) did not cause more than about 10% cocaine appropriate responding and therefore procaine did not qualify as a substitute for the cocaine training stimulus (5 mg/kg, i.p.), thus questioning the generality of the above finding of at least partial generalization; the local anaesthetic lidocaine, however, resulted in a maximum of about 50% responding appropriate to cocaine in the latter study. That local anaesthesia is not primarily responsible for the discriminations so far presented has been suggested earlier (e.g. Colpaert *et al.*, 1979; Järbe, 1981) but the question of the degree of overlap between the stimulus effects of procaine and cocaine requires additional investigation. However, the present results, together with previous data (Järbe, 1981), suggest common features in the stimulus effects between these two local anaesthetics in pigeons. Obviously large doses of procaine ($\geq$30 mg/kg; see McMillan, Dearstyne and Engström, 1975, for behavioural effects of local anaesthetics in pigeons) were needed to bring about the at least partial generalizations between cocaine and procaine in the pigeons and this might explain the lack of effect when the two drugs were tested in combination. Thus, no change of the dose–response curve was observed when procaine was added to cocaine as compared to cocaine alone. The relatively large doses of procaine needed to produce stimulus effects, at least partly similar to those of cocaine and for the ability of procaine to serve as a reinforcer in monkeys (Woolverton and Balster, 1982) suggest that the actions of adulterated street samples can be ascribed mainly to cocaine rather than to procaine; in addition the half-life of intravenously applied procaine is very short (Seifen, Ferrari, Seifen, Thompson and Chapman, 1979), suggesting the need for continuous administration to obtain sustained levels of procaine in an organism.

That intragastrically administered cocaine can substitute for cocaine given intramuscularly has been shown previously in pigeons (Järbe, 1981; see also introduction), the new finding being that this route of administration is more effective at 30 min than at 15 min. This is reminiscent of data in man (Van Dyke *et al.*, 1978) where physiological and subjective effects began to appear 30 min after oral administration and reached the greatest values 30–45 min thereafter. The change in percentage drug-associated responses between the two intervals tested again reinforces the suggestion that more than one interval should be examined when the time-course of the agent (or, in this case the route of administration) is not well known (Järbe and McMillan, 1980; Järbe *et al.*, 1981). In addition the data support the idea that local anaesthesia is not responsible for the cocaine–saline induced discrimination.

Of the other psychotropic compounds tested it was only the dopamine agonist apomorphine that resulted in more than 50% responding appropriate to cocaine. This degree of generalization is greater than that noted earlier (Järbe, 1981), which may be partly ascribed to the difference in the training doses used, 3 and 5.6 mg/kg, respectively. In rats, a greater degree of generalization between CNS motor stimulants and apomorphine is often observed (Ho and Silverman, 1978), the effect, however, being determined by the training dose in a fairly complex manner (Colpaert and Janssen, 1982; Stolerman and D'Mello, 1981). Thus, CNS motor stimulants and apomorphine may have discriminative stimulus attributes in common but the cue effects certainly are not identical (Järbe, 1981; Schechter, 1980; Stolerman and D'Mello, 1981).

As emphasized by Colpaert and colleagues (e.g. Colpaert and Janssen, 1982; Colpaert, Niemegeers and Janssen, 1978c), cocaine–saline discriminations in rats are characterized by a "bias" towards the lever associated with cocaine, i.e. the rats made more errors in saline-training sessions than when trained with cocaine (range, 2.5–10 mg/kg). In contrast, the pigeons in this study made more errors with cocaine, as compared to saline training sessions, although the statistical analysis fell short of significance; in the earlier study (Järbe, 1981) the means for correct selections were 97.6 and 99.5% for the two training conditions, respectively, indicating an even smaller difference in bias. Although it is beyond the scope of the present paper to discuss the implications of response-bias, it may suffice to note that this could

explain the difference in the generalization gradients for cocaine observed in pigeons and rats.

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