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Discriminative Stimulus Properties of Cocaine: Neuropharmacological Characteristics as Derived From Stimulus Generalization Experiments[1,2]

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COLPAERT, F C , C J E NIEMEGEERS AND P A J JANSSEN *Discriminative stimulus properties of cocaine neuropharmacological characteristics as derived from stimulus generalization experiments* PHARMAC BIOCHEM BEHAV **10**(4) 535–546, 1979 —The experiments reported here were undertaken to examine the neuropharmacological characteristics of drugs inducing stimulus generalization with cocaine as a cue Experiment 1 indicated that d-amphetamine (ED_{50} 0 17 mg/kg), l-amphetamine (0 45 mg/kg), methylamphetamine (0 15 mg/kg), methylphenidate (0 55 mg/kg) and nomifensine (0 32 mg/kg) induce stimulus generalization with cocaine in rats trained to discriminate 10 mg/kg cocaine from saline, this generalization occurred in 100% of the animals, proceeded along steep slopes (s 1 27 to 1 88 in log-probit plots), and was not associated with behaviorally toxic effects Amantadine (57 8 mg/kg, s=1 85), apomorphine (0 33 mg/kg, s=1 77), piribedil (8 4 mg/kg, s=10 6) and bromocryptine (>40 mg/kg) also induced stimulus generalization to some extent, but this generalization was partial in some cases, proceeded along a shallow slope with piribedil, and was invariably associated with severe rate depressant effects Ten mg/kg, but not 1 25 mg/kg hydroxyamphetamine induced generalization in 3 out of 8 rats Experiment 2 revealed that tranylcypromine (2 5 mg/kg, s=1 7), fentanyl (0 068 mg/kg, s=1 34), morphine (>10 mg/kg), phencyclidine (0 81 mg/kg, s=1 43), dexetimide (0 44 mg/kg, s=1 43), and benztropine (9 2 mg/kg) induce stimulus generalization with cocaine, whereas lidocaine, procaine, chlordiazepoxide, imipramine, desipramine, mescaline, LSD, isopropamide, and atropine do not Experiment 3 shows that propranolol (1.25 to 40 mg/kg) and isoproterenol (0 63 to 2 5 mg/kg) induce a biphasic generalization with cocaine Experiment 4 discloses that rats trained to discriminate 10 mg/kg propranolol from saline generalize their training drug along a linear gradient, but generalize cocaine along a biphasic gradient It is suggested (a) that stimulus generalization with cocaine may be contingent upon increasing the functional availability of endogenous dopamine and, perhaps, of norepinephrine irrespective of the presynaptic mechanism from which such increase may result and (b) that differential stimulus generalization of drugs with cocaine (in terms of dose, subjects, slope, and rate effects) may parallel their differential primary reinforcing properties

Cocaine cue Drug cue Drug discrimination CNS stimulants Psychotomimetic drugs Dopamine DA agonists Stimulus generalization Propranolol Amphetamines Narcotics Hallucinogens Reinforcement

THE current status of knowledge on the discriminative stimulus properties of drugs [18] indicates that various psychoactive drugs produce discriminative stimuli, or cues, which are pharmacologically specific Most of the research concerned with the discriminative stimulus properties of central nervous system (CNS) stimulant drugs has focused on the amphetamines [38,51], and relatively few data are currently available on the cue produced by cocaine when this drug is applied as the training drug Evidence available at present suggests that, in rats trained to discriminate cocaine from saline, other CNS stimulants such as amphetamine [12, 14, 15, 26, 51], apomorphine [12], and methylphenidate [38] induce stimulus generalization with the training drug Similar data have recently been obtained [1] in monkeys Also, various neuroleptic drugs [12, 14, 51], but not dibenamine, phenoxybenzamine, phentolamine, propranolol, cyproheptadine, or methysergide [12,38] appear to antagonize the cocaine cue. Neuroleptics similarly block d-amphetamine generalization with cocaine [14], and this would seem consistent with the finding [15] that symmetrical cross-generalization of cocaine and d-amphetamine may occur under some conditions (see, however [26])

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The experiments reported here were aimed at providing further data relevant to a neuropharmacological characterization of cocaine's discriminative stimulus properties Using a two-lever fixed-ratio drug discrimination procedure [13], rats were trained to discriminate 10 mg/kg cocaine from saline In animals so trained, stimulus generalization experiments were carried out with a number of compounds which purportedly increase dopaminergic and noradrenergic activity in the brain, as well as with a number of drugs selected from different pharmacological classes. Other experiments involved animals trained to discriminate 10 mg/kg propranolol from saline

EXPERIMENT 1

As pointed out above, the available evidence indicates that some CNS stimulant drugs other than cocaine induce stimulus generalization with cocaine, thus suggesting [12,51] that biogenic amine systems may be involved in the cocaine cue To further verify this hypothesis dose-response generalization studies were carried out with a number of CNS stimulant and/or dopamine agonist drugs

METHOD

Animals

Male wistar strain rats weighing 220 ± 10 g at the beginning of the experiment were used The animals were housed in individual living cages, stored in a continuously illuminated and air-conditioned room (21 ± 1°C; relative humidity 65 ± 5%). Tap water was available freely. Access to dry powdered standard laboratory food was limited to 2 hr a day, as specified below

Discrimination Training

The drug discrimination procedure used here has been described in detail elsewhere [13] Briefly, materials consist of standard animal test cages, fitted with two levers and a food cup, and programmed by solid-state programming equipment. The animals were trained to barpress for food; the response requirement was such that after every 10th press on the appropriate lever, a 45 mg food pellet was delivered through a dispenser (Fixed Ratio· 10 schedule of reinforcement) Following subcutaneous treatment with 10 mg/kg cocaine HCl 30 min before session, the rats were required to press one of the levers (drug lever DL) in order to obtain reinforcement, upon saline injection they were required to press the opposite lever (saline lever· SL) Responses on the incorrect lever produced no programmed consequences. Every week, each rat was run in daily 15 min sessions on 5 consecutive days. The two standard treatments (referred to by D and S, respectively) were given according to two monthly alternating sequences, i.e (1) DSSDS, SDDSS, SDSDD, DSDSD and (2) SDDSS, DSDSD, DSSDD, SDSDS The number of responses on either lever before obtaining the first reinforcement (and, thus, before having made 10 appropriate responses) was recorded after each session (symbol FRF); in addition, all responses emitted during the entire course of the 15 min sessions were noted (symbol TR) The training criterion consisted of 15 consecutive sessions on which FRF did not exceed 12

Stimulus Generalization Experiments

Following training, stimulus generalization experiments

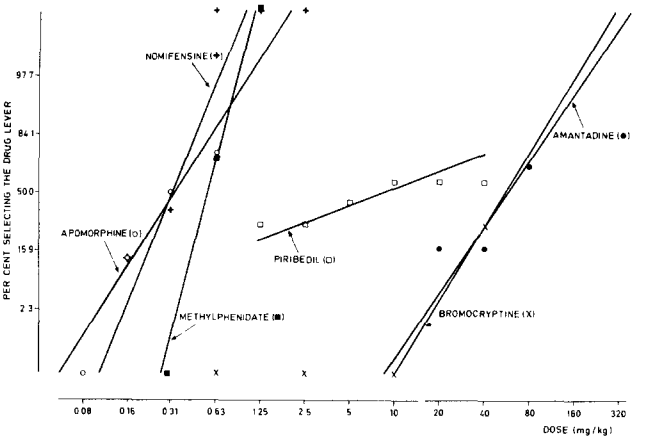

FIG 1 Stimulus generalization gradients of nomifensine, apomorphine, methylphenidate, piribedil, amantadine, and bromocryptine in rats trained to discriminate 10 mg/kg cocaine from saline Log-probit plot, abscissa test dose in mg/kg; ordinate percent of rats selecting the drug lever All drugs were subcutaneously injected 30 min before test.

were run on Wednesdays and Fridays, with the following restrictions During each week, rats making incorrect or inaccurate lever selections (FRF>16) on standard sessions were not tested, or their test result was discarded and the test condition was repeated

The test procedure consisted of treating the animals with the test drug being studied, and allowing them to select one of the two levers. That is, the lever on which the rat totalized 10 responses first was considered as the selected lever, and subsequent reinforcement was made contingent upon pressing (Fixed Ratio: 10) the selected lever Stimulus generalization with cocaine is said to occur whenever an animal selected the DL upon being treated with a test compound The degree of stimulus generalization is expressed by the percentage of animals which select the DL; the generalization is said to be partial if increasing the dose of the test compound to a maximal level makes some but not all animals select the DL Complete generalization and lack of generalization are denoted as 100% of the animals selecting the DL or the SL, respectively Recording of FRF and TR proceeded as during training sessions. In the following data reports, rate of responding (TR) under test conditions will be expressed as a percentage of responding under the saline condition; this notion of response level thus provides a direct indication of the extent to which any test condition increased or decreased responding relative to the no-drug (saline) control level. One hour following any (training/test) session, the animals were allowed to feed freely for 2 hr. On weekends, a similar 2 hr feeding period was scheduled between 10 and 12 a m.

In the first group of trained rats (n=8), all animals were tested with 20–80 mg/kg amantadine HCl, 0 08–0 63 mg/kg apomorphine HCl, 0 63–40 mg/kg bromocryptine mesylate, 0 31–1 25 mg/kg methylphenidate HCl, 0.16–2.5 mg/kg nomifensine, and 1.25–40 mg/kg piribedil The sequence in which different drugs were tested, was randomized for each rat individually, a similar randomization was applied to the sequence in which the different doses of these drugs were tested All injections were subcutaneous, 30 min before test, the injection volume was 1 ml/100 g body weight

All animals of a second group (n=8) were tested with 0 08–0.63 mg/kg d-amphetamine sulphate, 0 16–1 25 mg/kg l-amphetamine sulphate, 0.08–0 31 mg/kg methylamphetamine and 1 25 and 10 mg/kg hydroxyamphetamine HBr. Sequences of tests and injection conditions were similar to those in the first group

RESULTS

Data on acquisition of discriminative responding and on absolute response rates for the training conditions were similar to those obtained earlier [14] under identical conditions, and will not be detailed here. The overall response rate for the rats used in Experiment 1 was 1163 (± 39) under the saline condition, and 1007 (± 27) for the 10 mg/kg cocaine condition.

Direct and Indirect Agonists

The results of the stimulus generalization experiments carried out in group one are summarized in Fig. 1 and Table 1 It was found that nomifensine, ED_{50}. 0.32 (0.22–0.46) mg/kg [44] and methylphenidate, ED_{50} 0.55 (0 43–0.71) mg/kg, induced stimulus generalization in all animals tested; at these doses, the drugs failed to produce any statistically significant ($p>0.05$) effect on either FRF value, response rate, or on the percent of responses on the selected lever. Apomorphine was equipotent with nomifensine in terms of its ED_{50} value, 0.33 (0.19–0.58) mg/kg, but its generalization (doses 0.16 to 0.63 mg/kg) with cocaine was associated with marked rate depressant effects. Apomorphine, at a dose of 0 31 mg/kg, also attenuated the accuracy of lever selection (increased FRF value), and at the doses 0.31 and 0.63 mg/kg, the drug reduced the percent of responses on the selected lever Over a wide dose range (i.e., 1.25 to 40 mg/kg) piribedil appeared to induce only partial stimulus generalization; at different doses, the generalization always occurred in the same animals, and 3 out of 7 rats selected the saline lever at all doses (Fig 1). While leaving further parameters unaffected, piribedil generalization was associated with marked rate depressant effects (Table 1), and doses higher than 40

TABLE 1

RESULTS OF STIMULUS GENERALIZATION EXPERIMENTS WITH DOPAMINE AGONIST AND/OR CNS STIMULANT DRUGS IN RATS TRAINED TO DISCRIMINATE 10 MG/KG COCAINE FROM SALINE

Test Drug	Dose (mg/kg)	N	DL Selected (%)	FRF		Response Level (%)	% on Selected Lever
Amantadine	20	6	17	10	(10–10)	81* (± 6 0)	100 (92 3–100)
	40	6	17	10	(10–18)	80* (± 5 7)	99 9 (98.8–100)
	80	6	67	10 5	(10–12)	61* (± 6 0)	99 4 (90 1–100)
Apomorphine	0 08	8	0	10	(10–11)	104 (± 7 1)	99 9 (82 0–100)
	0 16	8	13	10	(10–15)	81* (± 5 4)	99 5 (86 8–100)
	0 31	8	50	11*	(10–15)	74* (± 5 5)	98 5* (82 2–100)
	0 63	8	75	10	(10–11)	54* (± 9 8)	98 3 (85 3–100)
Bromocryptine	0 63	7	0	10	(10–16)	86* (± 2 0)	99 9 (99 6–100)
	2 5	7	0	10	(10–12)	87 (± 10 2)	100 (99 4–100)
	10	7	0	10	(10–10)	74* (± 11 7)	100 (99 4–100)
	40	7	29	10	(10–12)	78* (± 6 3)	100 (93 6–100)
Methylphenidate	0 31	7	0	10	(10–11)	103 (± 3 1)	100 (99 9–100)
	0 63	7	71	10	(10–11)	102 (± 2 8)	100 (99 9–100)
	1 25	7	100	10	(10–10)	98 (± 6 4)	100 (95 7–100)
Nomifensine	0 16	8	13	10	(10–10)	106 (± 4 0)	100 (91 9–100)
	0 31	8	38	10	(10–12)	103 (± 6 1)	99 8 (99 1–100)
	0 63	8	100	10	(10–11)	101 (± 5 2)	99 4 (92 4–100)
	1 25	8	100	10	(10–16)	101 (± 7 0)	100 (88 9–100)
	2 5	8	100	10	(10–16)	90 (± 9 2)	100 (98 9–100)
Piribedil	1 25	7	29	10	(10–12)	69* (± 3 8)	100 (92 8–100)
	2 5	7	29	10	(10–18)	53* (± 7 6)	99 8 (95 2–100)
	5	7	43	10	(10–12)	56* (± 9 5)	99 8 (99 5–100)
	10	7	57	10	(10–17)	27* (± 4 0)	100 (98 5–100)
	20	7	57	10	(10–12)	27* (± 5 2)	100 (97 0–100)
	40	7	57	10	(10–13)	16* (± 5 7)	99 9 (87 0–100)

Symbols, N number of rats tested "DL Selected" represents the per cent of animals selecting the drug lever tested out of those rats which made a sufficient number of responses to show lever selection FRF (median and 95% confidence limits, C L) represents the total number of responses made on either lever before 10 responses were made on the selected lever, as the selected lever can be either the DL or the SL, the FRF notion does not by itself specify on which lever these responses were made Response Level (Mean ± 1 SEM) represents the total number of responses expressed as a per cent of total responding on the most recently preceding saline control session "% on Selected Lever" (median and 95% C L) represents the per cent of total responses which was made on the selected lever * denotes $p<0$ 05 for the difference between test- and control data (Wilcoxon test, [50])

TABLE 2

RESULTS OF STIMULUS GENERALIZATION EXPERIMENTS WITH AMPHETAMINES IN RATS TRAINED TO DISCRIMINATE 10 MG/KG COCAINE FROM SALINE SYMBOLS AS IN TABLE 1

Test Drug	Dose (mg/kg)	N	DL Selected (%)	FRF	Response Level (%)	% on Selected Lever
d-Amphetamine	0 08	6	0	10 (10–10)	118* (± 6 1)	100 (99 2–100)
	0 16	6	33	10 (10–12)	103 (± 5 6)	99 7 (90 7–100)
	0 31	6	100	10 (10–11)	97 (± 3 8)	99 3 (92 8–99 7)
	0 63	6	100	10 (10–10)	84 (± 13 0)	100 (98 1–100)
l-Amphetamine	0 16	7	14	10 (10–10)	101 (± 2 5)	100 (98 1–100)
	0 31	7	14	10 (10–11)	103 (± 3 9)	100 (99 9–100)
	0 63	7	71	10 (10–10)	98 (± 6 4)	100 (98 0–100)
	1 25	7	100	10 (10–17)	104 (± 8 6)	99 9 (95 0–100)
Methylamphetamine	0 08	7	14	10 (10–11)	99 (± 4 3)	100 (99 8–100)
	0 16	7	57	10 (10–10)	104 (± 8 4)	100 (60 3–100)
	0 31	7	86	10 (10–11)	103 (± 7 5)	100 (99 9–100)
Hydroxyamphetamine	1 25	8	0	10 (10–12)	95 (± 3 7)	100 (99 6–100)
	10	8	38	10 (10–10)	64* (± 3 6)	99 9 (93 8–100)

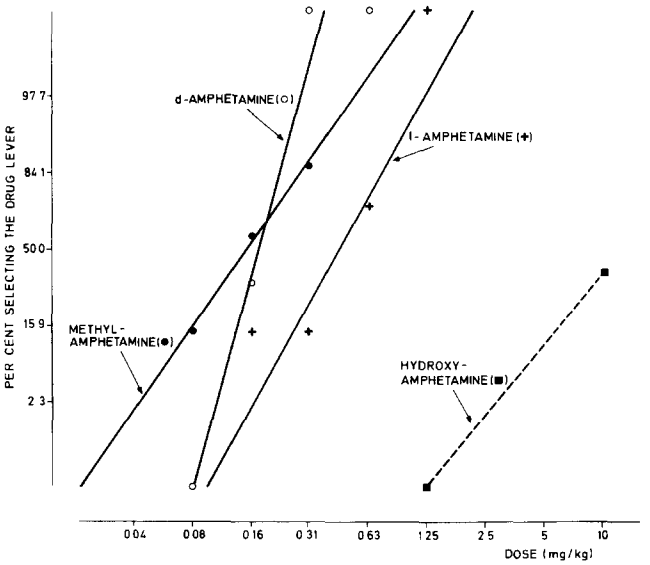

FIG 2 Stimulus generalization gradients of d-amphetamine, methyl-amphetamine, l-amphetamine, and hydroxyamphetamine in rats trained to discriminate 10 mg/kg cocaine from saline Legend as in Fig 1

mg/kg were not tested because of this behavioral toxicity Large doses (i e , 20–80 mg/kg) of amantadine, ED_{50} 57 8 (35 3–94 6) mg/kg, and bromocryptine, ED_{50} >40 mg/kg, induced stimulus generalization which was associated with significant rate of depressant effects.

Thus, of the drugs tested here, only nomifensine and methylphenidate induced up to 100% generalization without, in addition, producing rate-depressant or other deleterious effects on performance Also, the slopes of the stimulus generalization gradients (Fig. 1) of methylphenidate (s=1.27) and nomifensine (s=1 44) were relatively steep Stimulus generalization of the direct agonists failed to reach the 100% level at the doses studied, and was invariably associated with rate-depressant effects The slopes of apomorphine (s=1 77) and amantadine (s=1 85) were slightly, but not significantly, shallower than those of methylphenidate and nomifensine Comparison of all 5 slopes revealed that only that of piribedil (s=10.6) deviated from parallelism ($p<0$ 05) with other drugs

Amphetamines

The results of the stimulus generalization experiments carried out in group two are summarized in Fig. 2 and Table 2 The data indicate that all three centrally acting amphetamines induced stimulus generalization with cocaine, methylamphetamine, ED_{50} 0 15 (0.094–0.24), mg/kg; s=1.88, and d-amphetamine, ED_{50} 0.17 (0 13–0 23) mg/kg, s=1 27, were virtually equipotent, but l-amphetamine, ED_{50} 0.45 (0 31–0.65) mg/kg, s=1 65, was 2 6 times less potent than the d-isomer There were no significant differences in slope ($p>0$ 05). At doses inducing up to 100% (d-amphetamine, l-amphetamine) or 86% generalization (methylamphetamine), these drugs had no detectable deleterious effects on either FRF value, response level, or percent of responding on the selected lever (Table 2) After 1 25 mg/kg hydroxyamphetamine, all rats selected the saline lever, but 3 out of 8 animals selected the drug lever at the 10 mg/kg dose This dose also produced a significant rate-decreasing effect (Table 2)

EXPERIMENT 2

The second experiment was aimed at further determining the degree of specificity of the discriminative stimulus properties of cocaine To this end, a number of drugs selected from distinct pharmacological classes was submitted for stimulus generalization tests in rats trained to discriminate 10 mg/kg cocaine from saline

TABLE 3

RESULTS OF STIMULUS GENERALIZATION EXPERIMENTS WITH A NUMBER OF PHARMACOLOGICALLY HETEROGENEOUS COMPOUNDS IN RATS TRAINED TO DISCRIMINATE 10 MG/KG COCAINE FROM SALINE SYMBOLS AS IN TABLE 1

Test Drug	Dose (mg/kg)	N	DL Selected (%)	FRF	Response Level (%)	% on Selected Lever
Lidocaine	10	6	0	10 (10–15)	102 (± 3 6)	100 (99 5–100)
Procaine	10	6	0	10 (10–11)	95 (± 7 4)	99 9 (92 3–100)
Chlordiazepoxide	10	7	0	10 (10–13)	92 (± 8 1)	99 7 (97 2–100)
Imipramine	40	6	0	10 (10–10)	60* (± 6 4)	99 8 (97 2–100)
Desipramine	5	6	0	10 (10–10)	80 (± 11 0)	99 5 (93 1–100)
Tranylcypromine	0 63	6	0	10 (10–10)	105 (± 4 9)	100 (100–100)
	2 5	6	50	10 (10–12)	70* (± 18 0)	99 7 (84 4–100)
Mescaline	80	6	0	16* (11–19)	40* (± 7 4)	88 2* (69 9–96 2)
LSD	0 31	6	0	10 (10–11)	49* (± 5 1)	99 8 (95 6–100)
Fentanyl	0 04	13	15	10 (10–14)	62* (± 5 3)	99 8 (99 0–100)
	0 08	10	60	10 (10–19)	26* (± 11 0)	99.2 (92 1–100)
Morphine	5	6	0	10 (10–11)	54* (± 7 9)	100 (99 1–100)
	10	11	9	10 (10–18)	17* (± 5 1)	95 5 (93 5–100)
Phencyclidine	0 31	7	0	10 (10–10)	107 (± 3 1)	100 (99 9–100)
	0 63	7	29	10 (10–14)	65* (± 9 6)	98 5 (68 9–100)
	1 25	7	86	12 (10–18)	38* (± 7 7)	98 8 (98 5–100)

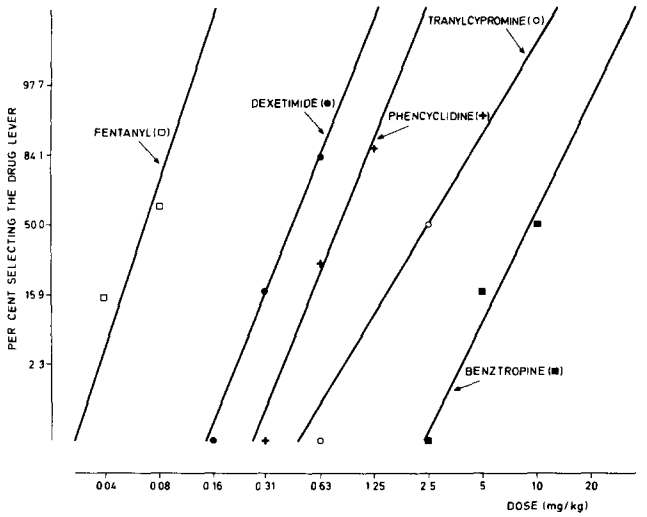

FIG 3 Stimulus generalization gradients of fentanyl, dexetimide, phencyclidine, tranylcypromine, and benztropine in rats trained to discriminate 10 mg/kg cocaine from saline Legend as in Fig 1

METHOD

Animals, discrimination training, and the procedure used in stimulus generalization experiments were similar to those of Experiment 1.

A pool of 21 rats newly trained to discriminate 10 mg/kg cocaine HCl from saline was used for the testing of 10 mg/kg lidocaine HCl, 10 mg/kg procaine HCl, 10 mg/kg chlordiazepoxide HCl, 40 mg/kg imipramine, 5 mg/kg desipramine HCl, 0.63 and 2 5 mg/kg tranylcypromine sulphate, 80 mg/kg mescaline sulphate, 0 31 mg/kg lysergic acid diethylamide (LSD), 0 04 and 0 08 mg/kg fentanyl citrate, 5 and 10 mg/kg morphine HCl, and 0 31 to 1 25 mg/kg phencyclidine HCl Out of the pool of 21 rats, 6 to 13 animals were randomly selected for test on each drug dose

A second set of experiments was carried out on 6 other trained rats which were tested with 0.16 to 1 25 mg/kg ispropamide CH_3I, 0.16 to 0.63 mg/kg dexetimide HCl, 2.5 to 10 mg/kg benztropine mesylate, and 0.31 to 1.25 atropine sulphate.

All drugs and saline were subcutaneously injected, 30 min before test. At the doses used here, all drugs listed above are known to be pharmacologically active in other *in vivo* assays; the doses were selected so as to largely exceed lowest effective doses. Of those drugs which, in preliminary experiments, failed to induce any generalization at different doses, only one dose was tested for the purpose of the experiments reported here

RESULTS

Miscellaneous Compounds

At a dose equal to the cocaine training dose, the local anaesthetics lidocaine and procaine failed to induce stimulus generalization with cocaine in any of the rats tested (Table 3) Lack of generalization was also found with the benzodiazepine chlordiazepoxide, the tricyclic antidepressants imipramine and desipramine, and with the hallucinogens mescaline and LSD. Significant ($p<0.05$) rate-depressant effects were observed with 40 mg/kg imipramine, 0.31 mg/kg LSD and with 80 mg/kg mescaline; in addition, mescaline increased the FRF value, and attenuated the percent of responding on the selected lever (Table 1)

To a varying extent, stimulus generalization (Fig. 3) was observed with the monoamine oxidase inhibitory tranylcypromine, ED_{50}. 2.50 (1 37–4 55) mg/kg; s=1.70, the narcotic analgesics fentanyl, ED_{50} 0 068 (0 047–0 097) mg/kg; s=1.34, and morphine, ED_{50}>10 mg/kg, and with the psychotomimetic phencyclidine, ED_{50}: 0.81 (0 55–1 18) mg/kg; s=1.43. Fentanyl (0 04 and 0 08 mg/kg), morphine (5

TABLE 4

RESULTS OF STIMULUS GENERALIZATION EXPERIMENTS WITH ANTICHOLINERGIC DRUGS IN RATS TRAINED TO DISCRIMINATE 10 MG/KG COCAINE FROM SALINE SYMBOLS AS IN TABLE 1

Test Drug	Dose (mg/kg)	N	DL Selected (%)	FRF	Response Level (%)	% on Selected Lever
Isopropamide	0 16	6	0	10 (10–11)	20* (± 4 1)	99 6 (98 3–100)
	0 31	6	0	10 (10–11)	22* (± 2 0)	99 3 (97 8–100)
	0 63	6	0	10 (10–10)	15* (± 2 4)	99 8 (94 3–100)
	1 25	6	0	10 (10–10)	17* (± 1 3)	100 (95 1–100)
Dexetimide	0 16	6	0	10 (10–13)	19* (± 5 5)	98 8 (96 9–100)
	0 31	6	17	10 (10–12)	9* (± 1 5)	96 3 (68.1–100)
	0 63	6	83	11 5* (11–15)	6* (± 0 6)	86 4* (77 1–98 6)
Benztropine	2 5	6	0	12 5 (10–19)	16* (± 4 6)	91 7 (76 2–98 1)
	5 0	6	17	10 5 (10–13)	7* (± 0 8)	92 8 (83 3–100)
	10	6	60	10 (10–10)	7* (± 2 5)	92 3 (67 9–100)
Atropine	0 31	6	0	10 (10–11)	19* (± 2 4)	90 3* (71 5–98 8)
	0 63	6	0	10 (10–13)	10* (± 2 6)	99 4 (88 9–100)
	1 25	6	0	10 (10–15)	16* (± 3 0)	99 3 (98 2–100)

and 10 mg/kg), tranylcypromine (2 5 mg/kg) and phencyclidine (0.63 and 1 25 mg/kg) reduced response rate, but had no effect on other parameters (Table 3)

Anticholinergics

Isopropamide (0 16 to 1 25 mg/kg) made all rats select the saline lever, and reduced response rate about equally at the different doses tested (Table 4). A similar result was obtained with atropine, except that 0 31 mg/kg of this drug also attenuated the percent of responding on the selected lever.

A dose-related stimulus generalization (Fig. 3) was obtained with dexetimide, ED_{50}· 0.44 (0.33–0.58) mg/kg, s=1 43, and benztropine, ED_{50}· 9.20 (5.64–15 0) mg/kg; s=1.54; both drugs decreased response rate, and 0 63 mg/kg dexetimide and 2.5 mg/kg benztropine attenuated the percent of responding on the selected lever (Table 4).

Comparison of slopes of the stimulus generalization gradients (Fig 3) of fentanyl, dexetimide, phencyclidine, tranylcypromine, and benztropine, failed to reveal any significant deviation ($p>0$ 05) from parallelism

TABLE 5

GENERALIZATION OF *dl*-PROPRANOLOL WITH COCAINE IN RATS TRAINED TO DISCRIMINATE 10 MG/KG COCAINE FROM SALINE THE DATA ARE REPRESENTED FOR RATS INDIVIDUALLY (– SALINE LEVER SELECTED, + DRUG LEVER SELECTED)

Rat #	Propranolol Dose (mg/kg) 1 25	2 5	5	10	20	40
1	–	–	–	–	–	–
2	–	–	–	–	–	–
3	–	–	–	–	–	–
4	–	–	–	–	–	–
5	–	–	–	–	+	–
6	–	–	–	+	+	–
7	–	–	+	+	+	+
8	–	+	+	+	+	+
9	–	+	+	+	+	+
Σ	0	2	3	4	5	3

EXPERIMENT 3

As pointed out in the Discussion section, the results of Experiments 1 and 2 suggest that stimulus generalization with cocaine occurs with drugs (1) which possess primary reinforcing properties in laboratory animals, and (2) whose mechanism of action at the neuronal level may imply some increase of central dopaminergic activity Goldberg and Gonzalez [31] have reported that propranolol interacts with behavior maintained by cocaine injections. The interaction consisted of progressive decreases in the responding of squirrel monkeys during sessions of cocaine self-administration, and resembled the effects of increasing the cocaine unit dose above the optimal dose for high response rates [32]. The authors considered several possible explanations for this propranolol effect, i.e (1) a propranolol-induced increase of the steady-state plasma level of cocaine through haemodynamic mechanisms [8,9], (2) some interaction of propranolol with the effects of cocaine in the central nervous system, or (3) an inhibitory effect of propranolol on cocaine metabolism in the liver. However, several recent findings suggest that propranolol itself may exert significant central effects Thus, significant amounts of propranolol are found in the CNS upon peripheral administration [6,42]; the drug has marked effects on central monoamine metabolism [58,59], and inhibits the behavioral responses of rats to increased 5-hydroxytryptamine in the CNS [35] Experiment 3 verified to what extent propranolol might mimic cocaine's discriminative stimulus properties

METHOD

Other conditions being equal to those used in the previous experiments, 10 rats newly trained to discriminate 10 mg/kg

TABLE 6

RESULTS OF STIMULUS GENERALIZATION EXPERIMENTS WITH β-AGONIST AND -ANTAGONIST DRUGS IN 9 RATS TRAINED TO DISCRIMINATE 10 MG/KG COCAINE FROM SALINE SYMBOLS AS IN TABLE 1

Test Drug	Dose (mg/kg)	DL Selected (%)	FRF	Response Level (%)	% on Selected Lever
Propranolol	1 25	0	10 (10–10)	104 (± 2 4)	100 (99 9–100)
	2 5	22	10 (10–10)	109 (± 4 7)	100 (97 4–100)
	5	33	10 (10–14)	114* (± 7 2)	99 9 (99 3–100)
	10	44	10 (10–15)	106 (± 5 0)	100 (99 6–100)
	20	56	10 (10–12)	101 (± 8 4)	99 8 (95 9–100)
	40	33	10 (10–10)	71* (± 3 7)	100 (99 4–100)
Practolol	2 5	0	10 (10–10)	96 (± 3 6)	100 (99 9–100)
	5	0	10 (10–10)	101 (± 5 7)	100 (99 8–100)
Isoproterenol	0 63	11	10 (10–10)	23* (± 5 8)	100 (99 6–100)
	1 25	33	10 (10–11)	8* (± 2 3)	100 (75 2–100)
	2 5	22	10 (10–15)	5* (± 1 8)	100 (84 0–100)
Salbutamol	1 25	0	10 (10–14)	55* (± 3 5)	100 (96 0–100)
	2 5	0	10 (10–11)	43* (± 5 6)	99 8 (99 4–100)
	5	11	10 (10–14)	31* (± 6 4)	100 (97 8–100)
	10	11	10 (10–16)	36* (± 6 8)	99 4 (80 0–100)

cocaine HCl from saline, were used for testing of 1 25 to 40 mg/kg dl-propranolol HCl, 2 5 and 5 mg/kg practolol, 0.63 to 2.5 mg/kg isoproterenol HCl, and 1 25 to 10 mg/kg salbutamol As one animal died in the course of the experiments, data are reported for the remaining 9 animals only.

All drugs and saline were subcutaneously injected 30 min before test The sequence of drug testing was as described for experiment 1

RESULTS

Individual data on drug lever selection following various doses (1 25 to 40 mg/kg) of dl-propranolol are given in Table 5 It was found that 4 out of the 9 animals tested selected the saline lever at all doses (Rats 1 to 4 in Table 5) The other 5 rats selected the drug lever in a manner which was directly related to dose up to the 20 mg/kg dose level. However, 2 of the 5 rats which had shown stimulus generalization with cocaine at some lower dose(s), selected the saline lever following 40 mg/kg propranolol Higher doses were not tested because preliminary experiments had shown that 80 mg/kg propranolol would induce ill effects, whereas doses $\geq$160 mg/kg were lethal Except for a rate increase at 5 mg/kg, and a rate decrease at 40 mg/kg, propranolol had no significant effects on other parameters of performance (Table 6)

In contrast with propranolol, the other β-antagonist tested here, practolol (2 5 and 5 mg/kg), failed to induce stimulus generalization in any of the same 9 animals. The β-agonists isoproterenol (0 63 to 2 5 mg/kg) and salbutamol (5 and 10 mg/kg) led some of the rats to select the drug lever, but the maximal response amounted to only 33% (Table 6) At all doses tested, the latter two drugs severely depressed response rate, but exerted no effects on the FRF value or on the percent of responding on the selected lever

EXPERIMENT 4

Experiment 3 indicates that dl-propranolol induces partial generalization with cocaine in rats trained to discriminate 10 mg/kg cocaine from saline The generalization is partial in that it is observed in only part of the animals, and because it occurs within a limited portion of the propranolol dose-range only. Experiment 4 aimed to verify the possible symmetry of the limited stimulus similarity of cocaine and propranolol To this end, rats were trained to discriminate 10 mg/kg propranolol from saline, and stimulus generalization experiments were carried out with cocaine as well as with β-agonists and -antagonists.

METHOD

Other conditions being equal to those used in the previous experiments, 6 rats were trained to discriminate 10 mg/kg dl-propranolol HCl from saline.

After training, all 6 rats were tested with 0.31 to 40 mg/kg dl-propranolol, 0.63 to 10 mg/kg cocaine HCl, 10 mg/kg practolol, 1 25 mg/kg isoproterenol HCl, and 5 mg/kg salbutamol All drugs and saline were subcutaneously injected, 30 min before test. The sequences of drug testing were as described for Experiment 1

RESULTS

The 6 rats trained to discriminate 10 mg/kg propranolol from saline required a median number of 30 5 sessions (limits· 19–45) to reach a criterion of 10 consecutive (training drug/saline) sessions on which FRF$\leq$12 The results of the stimulus generalization experiments carried out in these animals are summarized in Table 7. It was found that stimulus generalization of propranolol doses (0 31 to 5 mg/kg) lower than the training dose, proceeded in a manner

TABLE 7

RESULTS OF STIMULUS GENERALIZATION EXPERIMENTS WITH PROPRANOLOL, COCAINE, AND OTHER DRUGS IN RATS TRAINED TO DISCRIMINATE 10 MG/KG PROPRANOLOL FROM SALINE SYMBOLS AS IN TABLE 1 ALL RESULTS, EXCEPT THOSE OBTAINED WITH 10 MG/KG PROPRANOLOL, ARE BASED ON A SINGLE DETERMINATION IN SIX RATS

Test Drug	Dose (mg/kg)	DL Selected (%)	FRF	Response Level (%)	% on Selected Lever
Propranolol	0 31	0	10 (10–11)	111 (± 5 5)	99 5 (98 2–100)
	0 63	33	10 (10–11)	150* (± 35 0)	100 (99 9–100)
	1 25	50	10 (10–14)	87 (± 15 0)	99 4 (96 2–100)
	2 5	67	12 5 (10–19)	118 (± 9 3)	99 8 (98 9–100)
	5	100	10 5 (10–14)	86 (± 14 0)	97 0 (91 8–100)
	10	100	10 (10–10)	110 (± 13 0)	100 (99 2–100)
	20	100	10 (10–14)	102 (± 13 0)	100 (99 6–100)
	40	100	10 (10–16)	80 (± 11 0)	99 9 (96 3–100)
Cocaine	0 63	0	10 (10–10)	105 (± 2 5)	100 (99 9–100)
	1 25	33	10 (10–14)	111 (± 5 7)	100 (97 4–100)
	2 5	33	10 (10–17)	106 (± 4 8)	100 (94 7–100)
	5	20	10 (10–12)	77 (± 20 0)	100 (95 5–100)
	10	17	10 (10–10)	94 (± 14 0)	100 (99 9–100)
Practolol	10	0	10 (10–10)	105 (± 4 2)	100 (96 7–100)
Isoproterenol	1 25	0	10 (10–10)	45* (± 11 0)	99 6 (99 0–100)
Salbutamol	5	0	10 (10–18)	56* (± 8 4)	99 8 (92 9–100)

that was linearly related to dose, ED_{50} 1 25 (0.76–2 06) mg/kg s=2 15 Also, doses higher than the training dose elicited 100% drug lever selection, and it follows that the stimulus generalization gradient of propranolol in rats trained to discriminate 10 mg/kg of this drug from saline, is monophasic. Exception being made for a statistically reliable rate increasing effect at 0 63 mg/kg, propranolol exerted only erratic effects on response rate, and failed to significantly affect other parameters of discriminative performance.

Four of the 6 animals used here selected the saline lever at all cocaine doses tested, one animal selected the drug lever at doses 1.25 to 10 mg/kg, whereas the 6th animal did so at doses 1.25 and 2.5 mg/kg only Thus, in terms of percent effect, cocaine induced stimulus generalization with propranolol in some animals (Table 7), and its gradient resembles that of propranolol or isoproterenol in rats trained to discriminate cocaine from saline (Table 5). At the doses tested here, cocaine had no significant effect on the further parameters of performance

Finally, 10 mg/kg practolol, 1 25 mg/kg isoproterenol, and 5 mg/kg salbutamol induced saline lever selection in all animals tested, the latter two drugs also significantly reduced response rate (Table 7)

DISCUSSION

The studies presented here were undertaken to examine the neuropharmacological characteristics of the discriminative stimulus properties of cocaine through stimulus generalization experiments in rats trained to discriminate 10 mg/kg cocaine from saline

A first series of experiments involved drugs which presumably increase dopaminergic activity in the brain either directly by mimicking DA at its receptor sites, or indirectly by increasing the presynaptic release of DA and/or by blocking its re-uptake at DA nerve terminals Two of these drugs, i e., methylphenidate and nomifensine, are compounds which, like cocaine [27], act by indirectly increasing the functional availability of endogenous DA [7], methylphenidate and nomifensine were found (Fig 1) to induce stimulus generalization with cocaine in up to 100% of the rats tested This generalization proceeded along steep gradients (s: 1.27 and 1 44, respectively), and occurred in the absence of any deleterious effect on discriminative responding as measured by FRF value, response rate, or percent of responding on the selected lever (Table 1) Under similar experimental conditions, cocaine itself appears [14,15] only slightly less potent (ED_{50}~0.8 mg/kg), and yields a steep slope (s~2 0) at doses which are similarly devoid of behaviorally toxic effects Another pattern of results was obtained with the purported direct DA agonists amantadine [55], apomorphine [19], bromocryptine [21,43], and piribedil [20,22] At the doses studied, all four drugs induced some degree of stimulus generalization with cocaine, but a 100% effect was observed with none of these agonists Whereas the generalization gradients of amantadine and apomorphine were about as steep as those of methylphenidate and nomifensine, piribedil produced an exceptionally shallow dose-response (Fig 1) However, any generalization occurring with these 4 compounds was invariably associated with severe rate depressant effects, and nearly lethal doses of amantadine and bromocryptine were required to attain a 50% level of stimulus generalization with 10 mg/kg cocaine This behavioral and physiological toxicity made it impossible to

further verify whether the generalization of the direct agonists was perhaps only partial. While these data are evidence that both indirectly and directly acting DA agonists may induce stimulus generalization with cocaine, it is also apparent that the parameters of the experimental conditions used here quite clearly differentiate these two groups of compounds Thus, although the data so far suggest that increasing the functional availability of endogenous DA and, perhaps, other neurotransmitters is a sufficient condition for causing stimulus generalization with cocaine, it is left undetermined whether the purported DA mimicking action of the direct DA agonists would also fulfill a similarly sufficient condition. The two direct agonists which are shown here to induce the highest incidence of generalization and with slopes similar to those of the indirect agonists, have been found to also act indirectly by either promoting DA release (amantadine; [55]) or inhibiting DA uptake (apomorphine, [30]) Piribedil, which appeared to induce at least partial generalization albeit with a shallow slope, also increases noradrenaline (NA) turnover in the rat brain [20,22] Thus, it is conceivable that part if not all of the generalization found here with the direct DA agonists results from their indirect effects on DA and NA metabolism or release, and it cannot be concluded that their purported ability to mimick the postsynaptic action of DA is a sufficient condition for these drugs to induce stimulus generalization with cocaine

A second series of experiments involved the amphetamines [23], which are thought to act by promoting catecholamine release and inhibiting their uptake (e g , [10, 36, 37]). It was found (Fig 2) that the centrally acting amphetamines methyl, d-, and l-amphetamine, induce complete stimulus generalization with 10 mg/kg cocaine, the stimulus generalization gradients of these compounds display steep slopes (s 1 27 to 1.88) and no behaviorally disruptive effects were observed (Table 2). This pattern of results is entirely similar to that obtained with methylphenidate and nomifensine (Experiment 1) or with cocaine itself [14] Thus, however different the manner in which methylphenidate, nomifensine, methylamphetamine, d- and l-amphetamine, and cocaine affect DA synthesis, release, and uptake [7, 28, 36, 37, 41], all these drugs indirectly increase the functional availability of DA, and are quite similar to one another in generalizing with the cocaine cue Hydroxyamphetamine induced 0 and 38% generalization at doses 1 25 and 10 mg/kg, respectively (Table 1) While the latter compounds has *in vitro* catecholamine releasing properties similar to the centrally acting amphetamines [11,57], it only poorly penetrates the brain [34], and the hydroxyamphetamine data are consistent with the hypothesis that the cocaine cue originates from the central action(s) of this drug

The 1 2 6 d- to l-amphetamine potency ratio found here compares reasonably well with biochemical and behavioral data [37, 41, 52] indicating a similar ratio for the effects of the enantiomers on DA, but not on NA activity This may suggest that although the indirect agonists studied here may affect different neurotransmission systems, their generalization with cocaine may be primarily contingent upon their ability to increase dopaminergic activity The present 1 2 6 ratio also corresponds with that found in rats trained to discriminate amphetamine from saline [37,49], though Schechter [48] recently obtained a d- to l-amphetamine potency ratio for cuing activity of 1 4 9 Another seeming inconsistency has also arisen in regard to the relative cuing potency of cocaine and d-amphetamine [15,26], and for an understanding of these phenomena it might be useful to determine whether the potency ratios of drugs in drug discrimination experiments may perhaps be co-determined by training dose [15] At any rate, the ratio found here is clearly suggestive of a dopaminergic rather than a noradrenergic mediation of the cocaine cue, and is consistent [14] with clinical data [2] on the psychotomimetic effects of the amphetamine enantiomers

The specificity tests carried out in Experiment 2 (Table 3) indicate that 10 mg/kg lidocaine or procaine fail to generalize with 10 mg/kg cocaine, thus suggesting that the local anaesthetic properties of cocaine do not significantly contribute to its cue The failure of chlordiazepoxide, mescaline, and LSD to induce any generalization is suggestive of some degree of pharmacological specificity of this cue Also, the lack of stimulus generalization obtained with imipramine and desipramine is consistent with the d- to l-amphetamine potency ratio found here, in suggesting that blockade of NA uptake is not a sufficient condition for drugs to induce stimulus generalization with cocaine In view of the above discussion, the phencyclidine generalization (Fig. 3) can be understood in terms of the drug's ability to inhibit DA uptake [29]

A similar argument may apply to tranylcypromine which inhibits monoamine oxidase and hence potentiates the neuronal action of endogenous DA. Finally, the generalization of fentanyl and, perhaps, morphine with cocaine (Table 3) is consistent with recent data [1] that morphine is generalized with cocaine in monkeys trained to discriminate the latter from saline Narcotic drugs are known (e g [30]) to interfere with DA metabolism, and there is suggestive evidence (discussed in [19]) that these drugs indirectly increase DA activity in the brain The generalization of dexetimide and benztropine with cocaine (Fig. 3) seems to challenge the specificity of the cocaine cue However, the doses at which this generalization occurs are far beyond those exerting central anticholinergic activity [40], and it is known [24] that benztropine blocks DA uptake That isopropamide and atropine fail to generalize with cocaine suggests that neither peripheral nor central anticholinergic activity is a sufficient condition for drugs to induce stimulus generalization with cocaine, and it seems the more unlikely, therefore, that the generalization observed with dexetimide and benztropine would result directly from their central anticholinergic properties Although this generalization was associated with severe rate-depressant effects, ispropamide had similar effects, and this depression may merely result from a reduced salivary secretion impairing food intake [16]

Experiment 3 indicates, quite surprisingly, that propranolol and, to some extent, isoproterenol are generalized with cocaine in rats trained to discriminate 10 mg/kg cocaine from saline This generalization was partial in terms of both subjects and dose (Table 5), and the shape of its gradient resembles that of mixed narcotic agonists-antagonists in rats trained to discriminate the narcotic agonist fentanyl from saline [17] However, although propranolol may similarly act as a mixed agonist-antagonist at β-adrenergic receptors [47], the failure of the agonist practolol and the antagonist salbutamol to induce an appreciable degree of generalization (Table 6) may suggest that mere β-agonist or -antagonist activity is not a sufficient condition for drugs to produce the cocaine cue Also, the presynaptic effects of these drugs [56] may not clarify the observed generalization because these seem only to result in an inhibition of NA release Experiment 4 further indicates that rats can be trained to discriminate 10 mg/kg propranolol from saline, and that prop-

ranolol's gradient in rats so trained is linear (Table 7) The discriminative stimulus similarity of propranolol and cocaine was then found to be symmetrical not only in that cocaine induced stimulus generalization with propranolol, but also in that this generalization was similarly partial This phenomenon of symmetrical partial stimulus generalization between drugs is unprecedented and warrants further investigation Any interpretation of the phenomenon is speculative at this stage because too little is known of how propranolol and related drugs may affect central neurotransmission processes [58,59]

Thus, of all drugs examined here, methylphenidate, nomifensine, methylamphetamine, d-amphetamine, and l-amphetamine were found to substitute for cocaine as a discriminative stimulus, like cocaine itself, their generalization may occur in 100% of the rats tested, it proceeds along relatively steep generalization gradients, and is not associated with behaviorally toxic effects Similar to cocaine, these drugs indirectly increase the functional availability of endogenous DA through presynaptic mechanisms (release, reuptake) A second group of drugs found here to generalize with cocaine belong to different pharmacological classes, but may have in common that they can act as indirect DA agonists; this applies to amantadine, apomorphine, fentanyl, morphine, phencyclidine, tranylcypromine, benztropine and, perhaps, dexetimide Stimulus generalization of these compounds with cocaine is characterized by the fact that it is invariably associated with rate depressant effects; their gradients are similar to those of the first group Thirdly, piribedil also generalizes with cocaine; this generalization was found to proceed along a particularly shallow gradient, and to be associated with severe rate-depressant effects Finally, the generalization of propranolol with cocaine differed from that of the preceding groups of compounds in that it was biphasic. On the basis of this data it seems reasonable to propose as a working hypothesis that stimulus generalization with cocaine occurs with drugs which belong to different pharmacological classes but may have in common that they increase the functional availability of endogenous DA in central neurons, quite irrespective of what indirect, presynaptic mechanism produces this increase

A second suggested neuropharmacological characterization may become apparent from comparative data on drug self-administration Thus, much like cocaine [33], methylphenidate [60], nomifensine [61], and the centrally acting amphetamines [4] are self-administered by laboratory animals and can substitute for cocaine in animals self-administering the latter drug A comparative experiment in monkeys [4] on methylphenidate, d- and l-amphetamine has revealed relative self-administration potencies similar to those found here. Of the second group of compounds found here to induce at least some degree of stimulus generalization with cocaine, apomorphine [5], fentanyl [54], morphine [62], and phencyclidine [3] are known to be self-administered by laboratory animals Tranylcypromine, benztropine and dexetimide do not seem to have been studied in this respect Interestingly, those two direct DA agonists (amantadine, bromocryptine) which were found here to generalize only partially and at near-lethal doses, have been found by Woods [61] not to sustain self-administration behavior at lower intravenous doses Piribedil which we found here to induce partial generalization with a shallow gradient, was identified by Woods [61] as a compound which, although self-administered, generated less consistency of the maintenance responding across sessions than amphetamine Finally, propranolol has been found [31] to exert effects on cocaine self-administration which are similar to those of increasing the cocaine unit dose Though this finding is amenable to several interpretations [31], it would also be consistent with the hypothesis that, as in the present experiments, propranolol may partially mimick the cocaine action which is responsible for cocaine self-administration Therefore, the present data are compatible with the tentative suggestion that drugs which induce stimulus generalization with the cocaine cue, can also act as primary reinforcers in laboratory animals While it remains unclear to what extent drug discrimination- and self-administration data are mutually predictive, it does seem possible at this stage that a correspondence might exist between the extent of stimulus generalization of drugs with cocaine on the one hand, and consistency of their self-administration on the other This conclusion is further supported by the fact that DA receptor blockade through haloperidol or related drugs, not only blocks the cocaine cue or generalization of amphetamine [14], but also decreases the reinforcing action of various drugs shown here to generalize with cocaine [25, 45, 63, 64] Thus, the presumed role of DA in the reinforcing action of cocaine [46] and related drugs is consistent with the two neuropharmacological characteristics of the cocaine cue tentatively identified here

In conclusion, the studies reported here suggest that compounds which induce stimulus generalization with cocaine as a discriminative stimulus (1) can indirectly increase the functional availability of endogenous DA and, perhaps, of NA through a variety of presynaptic mechanisms, and (2) can act as primary reinforcers in laboratory animals In as much as the primary reinforcing effects of these compounds is consequent upon their indirect DA agonist activity, these two neuropharmacological characteristics may be based on a single action at the neuronal level

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