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Contrasting Interactions of Pipradrol, *d*-Amphetamine, Cocaine, Cocaine Analogues, Apomorphine and Other Drugs with Conditioned Reinforcement

T. W. Robbins[1], B. A. Watson[1], M. Gaskin[1] and C. Ennis[2]

[1] Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK
[2] Wyeth Laboratories, Maidenhead, Berkshire, UK

Abstract. The effects of various psychomotor stimulant drugs and drugs outside this class were examined on the efficacy of stimuli previously paired with reinforcement or reward (conditioned reinforcers, CR) in controlling responding. Pipradrol (5–45 μmol/kg), *d*-amphetamine (1.25–15.0 μmol/kg), and the cocaine analogues WIN 35,428 (0.1–30.0 μmol/kg) and in one of two determinations WIN 35,065-2 (0.1–29.0 μmol/kg) all generally increased responding on a lever providing CR, but did not change or decreased responding on a lever providing no CR (NCR). Cocaine (5–125 μmol/kg) and chlordiazepoxide (3.75–60.0 μmol/kg) had no significant effects. Morphine (3.2–32.0 μmol/kg) and α-flupenthixol (0.02–2.0 μmol/kg) generally reduced responding on both levers. Apomorphine (0.1–1.0 μmol/kg) generally increased responding on both levers. Neurochemical data showed that *d*-amphetamine was generally more potent than pipradrol in its effects on in vitro monoamine uptake and release.

Key words: Conditioned reinforcement – Reward – *d*-Amphetamine – Pipradrol – Cocaine – Cocaine analogues – Apomorphine – Morphine – α-Flupenthixol – Chlordiazepoxide – Psychomotor stimulants – Uptake – Release – Monoamines – Dopamine – Rat

There is evidence that, under some circumstances, psychomotor stimulant drugs can enhance the effectiveness of stimuli associated with reinforcement which become conditioned reinforcers (CR) Beninger et al. 1980; Hill 1970; Ridley et al. 1981; Robbins 1976, 1978; Robbins and Koob 1978). One way of testing this is to pair a stimulus such as a light with an event such as the delivery of food, water or intracranial stimulation, and then to examine the potency of the light as a CR by making its presentation contingent upon pressing a previously inactive or absent lever (CR lever). Pressing a second lever in the chamber has no effect (no CR, NCR) and is used as a control for non-specific increases in responding. Using this method, Robbins (1976, 1978) showed that pipradrol, a methylphenidate-like stimulant (Scheel-Krüger 1971), greatly increased responding on the CR lever, but had no effect, or even decreased responding, on the NCR lever. A control experiment (Robbins 1976) showed that pipradrol exerted no significant rate-increasing effect if the light had previously been only randomly correlated with water and was not therefore a CR. Therefore, the rate-increasing effect appeared to depend on the positive pairing of the light with the unconditioned reinforcer and had a degree of behavioural specificity.

The aim of the present experiments was to provide data comparing the effectiveness of a variety of other psychomotor stimulants besides pipradrol, including *d*-amphetamine, cocaine and two phenyltropane analogues of cocaine, that have attracted interest because of their greater behavioural potency than cocaine (D'Mello et al. 1981; Spealman et al. 1977) and because of their marked effects on central catecholamines (Heikkila et al. 1979). Since many of the behavioural effects of the psychomotor stimulants depend upon the central catecholamines dopamine (DA) and noradrenaline (NA), the effect of the DA receptor agonist apomorphine (AP) was examined. The pharmacological specificity of the enhancement of the effect of CR by psychomotor stimulants was further examined by testing the effects of drugs outside the psychomotor stimulant class. These were morphine, chlordiazepoxide (CDP) and the neuroleptic α-flupenthixol, a DA receptor antagonist.

The effects of pipradrol and *d*-amphetamine on CR have been compared in two previous investigations (Beninger et al. 1981; Robbins 1978). In both cases, pipradrol was found more effective: indeed, the effects of *d*-amphetamine were not significant. Since the neurochemical effects of pipradrol have previously been little investigated (Ferris et al. 1972; Scheel-Krüger 1971), the comparison between these two compounds is extended by including a neuropharmacological analysis of their effects upon the in vitro release and blockade of uptake of the monoamines DA, NA and 5-hydroxytryptamine (5-HT) as possible correlates of the observed behavioural effects.

Materials and Methods

Behavioural Experiments. Male hooded Lister rats (Olac, Bicester, UK) were used. They weighed 200–350 g at the beginning of the experiments and were generally housed three to a cage with food (Diet 41 B pellets) continuously available, but with access to water restricted to 1 h/day. The rats were housed under natural daylight in a temperature-controlled (21 °C) colony, and had no previous drug or experimental history.

Three rodent chambers (Campden Instruments, London, UK) were used. Each operant chamber was supplied with two levers, a water dipper behind a translucent Plexiglas panel, a house light (2.6 W 24 V) and a light (2.6 W 24 V) situated

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above the reinforcement tray where the dipper delivered water (0.06 ml) through a hole. Further details of the apparatus can be found in Robbins (1978).

Design. Different groups of drug-naive rats (generally $N = 6$) were used to study each drug. For some drugs, replications of the dose-response determinations were run, sometimes under slightly different conditions. This was done partly to provide standard data (e.g. for pipradrol) for comparisons with concurrent determinations with other compounds, and partly to explore the procedural variables that might contribute to the observed effects (e.g. for AP). However, in general, no differences were found between replications following analysis of variance with a repeated-measure design. Therefore, for the purpose of presentation, data for a given drug were pooled over the separate determinations.

Training. In phase 1, rats were initially trained to associate a light and the noise of the dipper elevation with water. The CR was the compound (light plus dipper noise) stimulus. In phase 2, the effectiveness of the CR was tested under drug and control conditions. Rats were trained to approach the water dipper when elevated behind the hinged panel and to drink. They were then put onto the following schedule of water presentation. Initially (three or four sessions of 15-min duration), water was delivered for 7.5 s every 30 s following the end of the last presentation (i.e. fixed time, FT 30 s) for a total of 20 presentations per session. Preceding each dipper elevation, the tray light was switched on for 0.5 s. The rats were then trained so as to maximize the stimulus control of the light plus dipper noise, over panel pushing by the use of intermittent unpredictable schedules of water presentation. A random time (RT) schedule was used which operated until 30 presentations of water had occurred per session. The RT schedule did not operate and the house light was switched off for the duration that the rat pushed the panel (and activated its microswitch) when the CR or water were absent. After an inappropriate panel push and the withdrawal of the rat's head from the reinforcement tray, the RT schedule was restarted after a delay of at least 3 s. Thus the presentation of the CR and water could never begin whilst either the animal was pushing the transparent panel, or for at least 3 s after the end of an inappropriate panel push. Initially, a RT 6-s schedule was in operation (two or three sessions) before the rats were transferred to the final training schedule (RT 30 s). The rats were trained under this schedule for 10 – 12 sessions, until the group as a whole had reached a certain mean criterion of performance. This criterion was that the proportion of time spent panel pushing during the presentation of CR or water was 60 % or more of the total time spent panel pushing. This value was generally close to the asymptotic proportion attained by the group as a whole. The rats were then placed into the test (phase 2).

Testing. During phase 1, the two levers had been present in most conditions (see below), although lever pressing had had no programmed effect other than being recorded. In phase 2, water was no longer presented (i.e. extinction). However, the tray light (0.5 s) followed by the brief (0.3 s) elevation of the dipper (compound CR) occurred following responding on one (the CR lever) of the two levers present in the chamber. The presentation of CR was placed onto a random interval (RI) 5-s schedule. Responding on the other lever (NCR) had no programmed effect other than being recorded. The lever providing CR was counterbalanced over rats, but generally placed on the side on which the rats had pressed least during training. The exceptions were for one group of rats receiving pipradrol and one group receiving *d*-amphetamine, for which the CR was placed randomly on one of the two levers independently of responding during training, as in previous studies (e.g. Robbins 1978). There were no significant differences between the groups receiving the CR on the least-preferred, or a randomly selected lever in these experiments. Sessions were 30-min long and occurred at least 72 h apart. Drug doses, as well as an injection of vehicle (control treatment), were administered according to Latin-square designs.

Drug Groups. Two groups of six rats received pipradrol dissolved in the vehicle (distilled water : polyethylene glycol, 2 : 1) used in a previous study (Robbins 1978). The third group ($N = 6$) received the same doses dissolved in hot distilled water for comparison with *d*-amphetamine dissolved in hot distilled water.

Two groups of rats ($N = 6$ and 5/group) received *d*-amphetamine dissolved in saline, and a third group ($N = 6$) received the drug dissolved in distilled water.

Two groups of six rats received AP after the usual training procedures. A third group of six rats received the same training conditions, except that this group had a session prior to any training to establish individual preferences for pressing levers. The levers were then removed from the operant chamber in phase 1 and replaced prior to phase 2. The 'levers absent' group and one of the 'levers present' groups were run contemporaneously.

The effects of cocaine (two groups, $N = 6$ and 5/group), WIN 35,428 (two groups, $N = 6$/group) and WIN 35,065-2 (two groups, $N = 6$/group) were measured in parallel, in two separate determinations which used slightly different dose ranges. Other drugs studied were morphine ($N = 6$), CDP ($N = 6$) and α-flupenthixol ($N = 6$).

Drugs. Details of drugs, doses, solvents and administration are listed. Doses are expressed in μmol/kg to facilitate comparisons of potency. The approximate mg/kg equivalent of the salt is given in parentheses.

Pipradrol HCl (Merrell, Cincinnati, USA), in doses of 5, 10, 15, 30 and 45 μmol/kg (1.5, 3.0, 4.5, 9.0, 13.5 mg/kg), was dissolved in hot distilled water or a mixture of distilled water and polyethylene glycol (2 : 1) and injected IP. *d*-Amphetamine sulphate (Smith Kline and French, Welwyn Garden City, UK), in doses of 1.25, 2.5, 5.0, 10.0 and 15.0 μmol/kg (0.25, 0.5, 1.0, 1.9, 2.9 mg/kg), was dissolved in 0.9 % saline or distilled water. Cocaine HCl (May and Baker, Sagatal, UK) was dissolved in 0.9 % saline and given in the following two series of doses: 5, 13, 40, 67 and 121 μmol/kg (1.7, 4.4, 13.6, 22.8, 41.4 mg/kg); 25, 50, 75 and 125 μmol/kg (8.5, 17.0, 25.5, 42.5 mg/kg). WIN 35,428 (as the 1,5-naphthalenedisulphonate salt, M.W. = 841 g: 66 % of salt is free base) (Sterling-Winthrop, Rensselaer, NY, USA) was dissolved in distilled water and given in the following two series of doses: 1, 3, 10, 17 and 30 μmol/kg (0.4, 1.3, 4.2, 7.1 and 12.6 mg/kg); 0.1, 0.3, 1, 3 and 10 μmol/kg) (0.04, 0.12, 0.42, 1.3, 4.2 mg/kg). WIN 35,065-2 (as the 1,5-naphthalenedisulphonate salt, M.W. = 805 g; 64.5 % of salt is free base) (Sterling-Winthrop, Rensselaer, NY, USA) was dissolved in distilled water and given in the following two series of doses: 1, 3, 10, 16 and 29 μmol/kg (0.4, 1.2, 4.0, 6.4, 11.7 mg/kg); 0.1, 0.3, 1.0, 3.0

and 10.0 μmol/kg (0.04, 0.12, 0.40, 1.2, 4.0 mg/kg). All of these psychomotor stimulants were injected IP 15 min prior to the beginning of the session.

AP HCl (Macfarlan-Smith, Edinburgh, UK) was dissolved by slow warming in 0.2% ascorbate in 0.9% saline and given SC in the flank at doses of 0.1, 0.3, 1.0, 3.0 and 10.0 μmol/kg (0.03, 0.09, 0.30, 0.90, 3.0 mg/kg) 2 min prior to the beginning of the session. Morphine HCl (May and Baker, Sagatal, UK) was dissolved in 0.9% saline and given in doses of 3.2, 17.6 and 32.0 μmol/kg (1.0, 5.6, 10.0 mg/kg). CDP HCl (Roche, Nutley, NJ, USA) was dissolved in 0.9% saline and given in doses of 3.75, 7.5, 15.0, 30.0 and 60.0 μmol/kg. (1.3, 2.6, 5.1, 10.2, 20.4 mg/kg). α-Flupenthixol dihydrochloride (Lundbeck, Copenhagen, Denmark) was dissolved in 0.9% saline and given in doses of 0.02, 0.06, 0.2, 0.6 and 2.0 μmol/kg (0.01, 0.03, 0.1, 0.3, 1.0 mg/kg). Morphine, CDP and α-flupenthixol were each injected IP 30 min prior to the beginning of the session. All drugs were administered in a volume of 0.1 ml/100 g body weight.

Measures and Statistical Analysis. Responding on the CR and NCR levers was measured by solid-state counters. Analysis of variance was used to analyse the absolute numbers of responses on the CR and NCR levers (CR factor) over dose (dose factor) of drug, including the control condition. An 'effect of CR' refers to significantly more responses made on the CR as compared to the NCR lever. All data were subjected to a square-root transformation to reduce heterogeneity of variance (Winer 1971). Post hoc comparisons of particular doses with control were made using Dunnett's *t*-test.

Neurochemical Effects of Pipradrol and d-Amphetamine Uptake Studies. Male Sprague-Dawley rats (160 – 200 g) were decapitated, the striatum or cortex dissected out and synaptosomes prepared according to the method of Gray and Whittaker (1962). The uptake of radioactively labelled neurotransmitter was measured, as described by White and Keen (1970), over a range of concentrations of *d*-amphetamine and pipradrol ($10^{-7} - 10^{-4}$ *M*).

The labelled neurotransmitters were all obtained from Amersham International (London, UK) and were ^{3}H-DA (7.5 Ci/mmol^{-1}), ^{3}H-NA (9.6 Ci/mmol^{-1}) and ^{14}C-5-HT (58 mCi/mmol^{-1}).

Release Studies. Male Sprague-Dawley rats (160 – 200 g) were decapitated and the striatum, cortex or hypothalamus dissected out. The brain tissue was chopped into 250 × 250 μm slices using a McIlwain tissue chopper. The slices were preloaded with tritiated neurotransmitter and superfused as described previously (Ennis et al. 1981). After a 50-min superfusion the slices were superfused with Krebs-Henseleit solution containing modifying drug for 12 min followed by a further 12 min with drug-free medium. The total percentage efflux of radioactivity released above basal values during 24 min following addition of the modifying drug was calculated. Effects of a range of concentrations of *d*-amphetamine and pipradrol were determined ($10^{-7} - 10^{-4}$ *M*).

The following compounds were used: ^{3}H-DA (40 Ci/mmol^{-1}) and ^{3}H-NA (32 Ci/mmol^{-1}) (Amersham International, London, UK); ^{3}H-5-HT (24 Ci/mmol^{-1}; New England Nuclear, Boston, MA, USA).

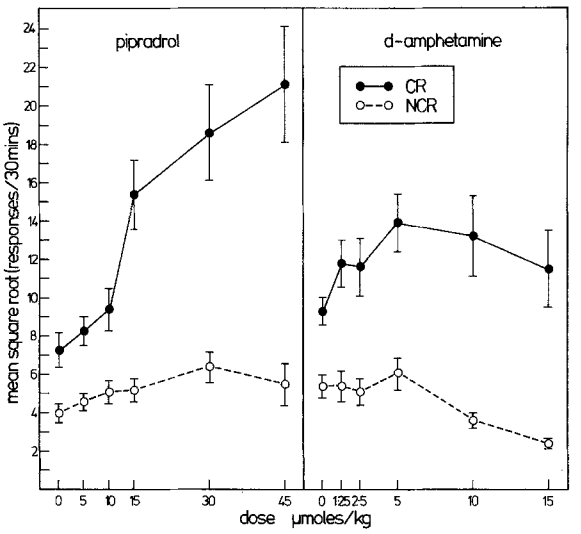

Fig. 1. Effect of pipradrol ($N = 18$) and *d*-amphetamine ($N = 17$) on responding on a lever providing conditioned reinforcement (*CR*) and a lever providing no conditioned reinforcement (*NCR*): *abscissa*, log dose in μmol/kg (mg/kg equivalents given in text); *ordinate*, mean lever presses/30 min ± 1 SEM. Square-root transformed data are presented

Results

Effects of Pipradrol and d-Amphetamine. Figure 1 shows the effects of pipradrol and *d*-amphetamine upon lever pressing with CR. Neither drug showed significant differences among replications, hence combined data are presented. Pipradrol produced a dose-dependent increase in responding on the CR lever from a mean of 66.8 responses/30 min in the control condition to a maximum mean of 594.5 responses/30 min at 45 μmol/kg. There was no significant increase in responding on the NCR lever. This selective increase in responding was confirmed by the highly significant interaction between dose and CR ($F = 12.48$, $df = 5,75$, $P < 0.001$).

d-Amphetamine produced smaller increases in responding on the CR lever, from a control mean of 94.0 responses/30 min to a maximum mean of 235.4 responses/30 min at 5 μmol/kg. In contrast, there were reductions in responding on the NCR lever. The dose- × -CR interaction, however, was only barely significant ($F = 2.69$, df 5,70, $P < 0.05$).

The slightly different patterns of responding on the CR and NCR levers and the different degrees of variability in responding produced by these two drugs makes comparisons of their potency and effectiveness difficult. However, comparing the means for CR and NCR rates in Fig. 1, it appears that the ratios of responding on the CR and NCR levers are roughly similar at certain doses (e.g. at 30 μmol/kg pipradrol and 10 μmol/kg *d*-amphetamine). This suggests that both drugs enhanced the control over responding by CR to a similar extent, although *d*-amphetamine produced this effect at lower doses. However, despite this apparently greater potency, *d*-amphetamine was more variable in this effect than pipradrol and was also less effective in increasing overall levels of responding.

Effects of Cocaine, WIN 35,428 and WIN 35,065-2. Figure 2 shows the two separate determinations of the effects of cocaine and the two cocaine analogues. Cocaine produced

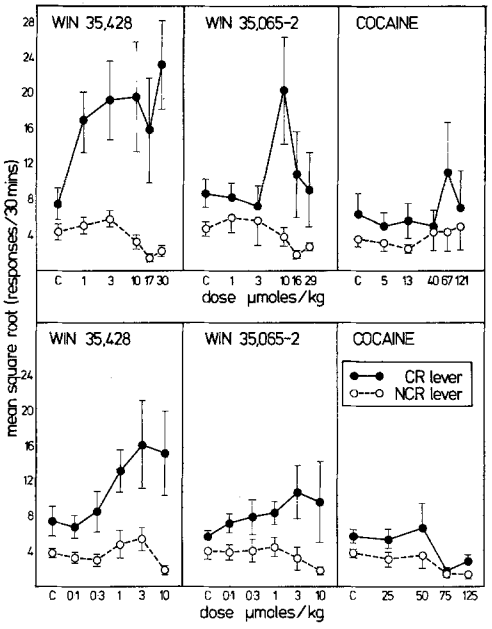

Fig. 2. Effects of cocaine ($N = 11$) and the cocaine analogues WIN 35,428 ($N = 12$) and WIN 35,065-2 ($N = 12$) on responding on a lever providing conditioned reinforcement (*CR*) and a lever providing no conditioned reinforcement (*NCR*): determination 1 (*top*); determination 2 (*bottom*). Other details as in Fig. 1

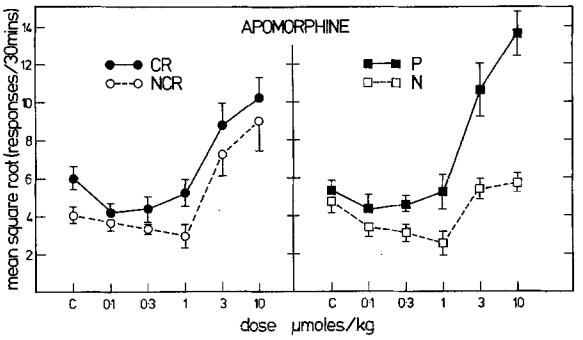

Fig. 3. Effects of apomorphine ($N = 18$) on responding on a lever providing conditioned reinforcement (*CR*) and a lever providing no conditioned reinforcement (*NCR*) (*left-hand-side*). The same data are presented (*right-hand side*) so as to illustrate that apomorphine-induced stimulation of responding was restricted mainly to one lever. The effects of apomorphine are shown for the lever responded on the most at the highest dose (preferred lever, P) and for the lever responded on the least at the highest dose (nonpreferred lever, N), as calculated for each rat. This mode of presentation serves to show a selective stimulatory effect of apomorphine, but unrelated to the CR contingency. Other details as for Fig. 1

rather variable and non-significant changes in responding on the CR and NCR levers (dose-×-CR interactions $F < 1.00$, *df* 5,25; $F = 1.1$, *df* 4,16 respectively). The overall effect of dose was also nonsignificant in both determinations and the overall effect of CR was significant in determination 2, but not in determination 1.

By contrast, for WIN 35,428, there were clear dose-related effects. Figure 2 shows dose-dependent increases in responding on the CR lever, but reductions on the NCR lever. In both cases, there were significant interactions of dose with CR ($F = 4.75$, *df* 5,25, $P < 0.001$; $F = 2.62$, *df* 5,25, $P < 0.05$ respectively). The lowest dose at which these effects were significant in both determinations was 1 μmol/kg.

Figure 2 shows similar effects for WIN 35,065-2, but these were less consistent. In determination 1 (1–29 μmol/kg) there was a significant dose-×-CR interaction ($F = 3.29$, *df* 5,25, $P < 0.05$) that was due almost entirely to the significant effect of 10 μmol/kg, but in determination 2 this interaction was not significant ($F = 1.33$, *df* 5,25). Evidently, the range of doses used in these experiments determined to some extent the size of the effect.

Effects of AP. There were no differences among the three replications for AP, hence combined data are presented in Fig. 3. This shows that AP produced dose-dependent changes in response rate, but, surprisingly, in a similar fashion on both CR and NCR levers. Low doses tended to reduce responding whereas high doses increased it. Statistical analysis revealed a significant main effect of dose ($F = 32.3$, *df* 5,75, $P < 0.001$). The reductions in rate produced by 0.1 and 0.3 μmol/kg were not significant, but 3.0 and 10.0 μmol/kg had significant rate-increasing effects. The mean control rate of responding was 29.1 responses/30 min whereas 10 μmol/kg increased this to a mean of 123.0 responses/30 min. The rate-increasing effects occurred indiscriminately upon both CR and NCR levers. The dose-×-CR interaction did not approach significance ($F = 0.25$, *df* 5,25) and the main effect of CR was not significant ($F = 3.91$, *df* 1,15).

Although the impression gained from the group means, shown in the left panel of Fig. 3, might be that individual rats were responding equally on both the CR and the NCR levers, this was not the case. An alternative arrangement of the data is shown on the right panel of Fig. 3, according to which responses are classified not as CR or NCR, but as 'preferred' (P) or 'nonpreferred' (N) for each rat. The P lever is defined simply as that lever responded on most at the highest dose of AP: therefore, it is not necessarily the preferred lever prior to drug treatment or under control conditons. This analysis shows that the rate-increasing effect of AP was mainly confined to the P lever. An analysis of variance (using the factor P versus N rather than CR versus NCR) revealed a significant dose-×-P interaction ($F = 12.22$, *df* 5,75, $P < 0.001$). Therefore, AP produced selective increases in responding (i.e. on one lever rather than the other), but these increases were largely independent of whether responding produced CR.

Effects of Morphine, CDP and α-Flupenthixol. Figure 4 shows the effects of the three drugs outside the psychomotor stimulant class. Morphine produced general reductions in responding ($F = 7.3$, *df* 3,15, $P < 0.01$) with no significant dose-×-CR interaction ($F < 1.0$, *df* 3,15), but a significant overall effect of CR.

CDP had a biphasic effect, with low doses increasing and high doses decreasing the rate. However, the main effect of dose was not significant. ($F = 1.54$, *df* 5,25), nor was there a significant dose-×-CR interaction ($F = 1.12$, *df* 5,25). Again, the main effect of CR was significant.

α-Flupenthixol significantly reduced responding ($F = 5.6$, *df* 5,25, $P < 0.01$). There was a tendency for responding to be reduced to a greater extent on the lever providing CR, but this was not significant (dose-×-CR interaction $F = 1.69$, *df* 5,25). The main effect of CR also failed to reach significance ($F = 4.75$, *df* 1,5). Therefore these three drugs had

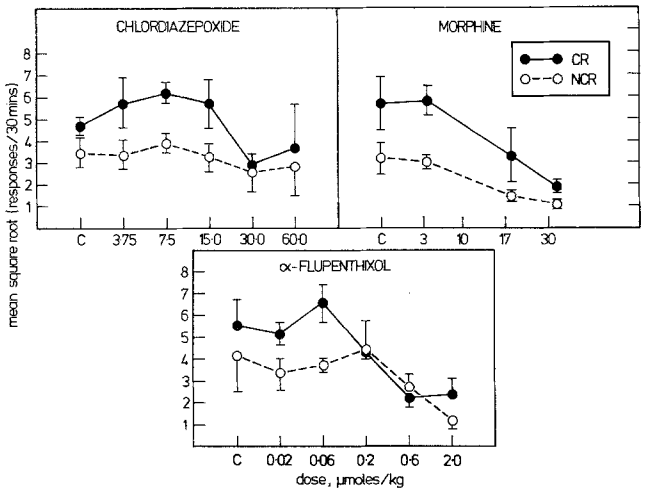

Fig. 4. Effects of morphine ($N = 6$), chlordiazepoxide ($N = 6$) and α-flupenthixol ($N = 6$) on responding on the lever providing conditioned reinforcement (*CR*) and on the lever providing no conditioned reinforcement (*NCR*). Other details as for Fig. 1

Table 1. Effects of pipradrol and *d*-amphetamine on monoamine release and uptake

	Release [EC_{50} + SEM (μ*M*)][a]	
	d-Amphetamine	Pipradrol
^{3}H-Dopamine	3.5 ± 0.15	114.8 ± 13.8
^{3}H-Noradrenaline	2.1 ± 0.06	58.8 ± 5.2
^{3}H-5-Hydroxytryptamine	26.3 ± 0.12	79.4 ± 6.6
	Uptake [IC_{50} ± SEM (μ*M*)][b]	
^{3}H-Dopamine	0.39 ± 0.04	0.17 ± 0.01
^{3}H-Noradrenaline	0.08 ± 0.002	0.17 ± 0.02
^{3}H-5-Hydroxytryptamine	4.49 ± 0.79	106.0 ± 40.0

[a] EC_{50} values for the release of tritium from slices of striatum, cortex or hypothalamus preloaded with ^{3}H-dopamine, ^{3}H-noradrenaline and ^{3}H-5-hydroxytryptamine. All determinations were performed in duplicate ($N = 4$)

[b] IC_{50} values for the inhibition of synaptosomal uptake of labelled monoamine neurotransmitter. All determinations were performed in triplicate ($N = 3$)

different effects from those of the psychomotor stimulants, consisting mainly of reductions in responding in the case of morphine and α-flupenthixol. None of these drugs significantly enhanced the control of responding by CR.

Neurochemical Effects of d-Amphetamine and Pipradrol. Comparative effects of *d*-amphetamine and pipradrol on in vitro release and uptake of the monoamines DA, NA and 5-HT are shown in Table 1. Both compounds appeared much less potent as inhibitors of 5-HT than of catecholamine (DA, NA) uptake. Pipradrol appeared to be slightly more potent than *d*-amphetamine in inhibition of DA, but less potent with respect to NA. In terms of release, pipradrol was much less potent than *d*-amphetamine with respect to all three monoamines, especially DA. The EC_{50} for pipradrol for 5-HT release is so close to its IC_{50} for inhibition of 5-HT uptake that it is impossible to distinguish between these two effects.

Discussion

Perhaps the most important finding of the present experiment was the failure of the DA receptor agonist AP to interact with conditioned reinforcers in the same way as pipradrol and *d*-amphetamine. Systemically administered AP produced rate-increasing effects in responding, which were mainly restricted to one of the two levers present. However, these effects were not selective for the lever providing CR. In this respect, the effects of AP were independent of the feed-back provided by the compound stimulus previously paired with water. This suggests that the behavioural effects of AP are less under the influence of the previous history of the subject than those of *d*-amphetamine, pipradrol and the cocaine analogues. In view of the often-described similarities in behavioural effects between amphetamine-like drugs and AP (e.g. Fog 1969), the present contrasting effects suggest that further comparisons between these drugs might be important in determining the functions of the central DA system.

Given the multiple neurochemical effects of *d*-amphetamine, as well as of pipradrol and the cocaine analogues shown in previous studies (Ferris et al. 1972; Heikkila et al. 1979; Moore 1978; Scheel-Krüger 1971) and in the present one, it is tempting to argue that the findings with AP argue against a major contribution of DA in the interaction with CR found with the stimulants. However, such scepticism may be premature. The rate-increasing effects of pipradrol on the CR lever can be antagonized by DA depletion induced by injection of the neurotoxin 6-hydroxydopamine into the caudate nucleus and the nucleus accumbens (Robbins and Everitt 1982). An alternative way of explaining the effects of AP is to suggest that the occupation of DA receptors by this drug may occur relatively independently of the organism's behaviour. In contrast, drugs such as *d*-amphetamine and pipradrol may effect a presynaptic release of DA (Von Voigtlander and Moore 1973), which is more susceptible to modulation by presynaptic influences, for example, at the cell body or nerve terminal. These arguments are in accord with those used by Herberg et al. (1976) and Crow (1976) to account for rate-increasing effects of amphetamine, but the lack of rate-increasing effects of AP, upon responding reinforced by intracranial stimulation. Butcher (1968) and deOliveira and Graeff (1972) also observed respectively great variability, or only reductions, in schedule-controlled behaviour in rats. The implication is that stimulus control over responding is likely to be less effective with AP and other direct DA agonists as compared with amphetamine-like drugs.

The effects of AP stand in great contrast to those of pipradrol, where the rate-increasing effect is tied much more to the lever providing CR. The present results with pipradrol replicate previous results (e.g. Beninger et al. 1980, 1981; Hill 1970; Robbins 1976, 1978). The effects are reproducible with quite small ($N = 6$) groups of rats, although the size of the effect and the decrease or lack of change in responding on the NCR lever may depend on such factors as strain of rat and schedule of presentation of CR: compare these results with those of Beninger et al. (1981) and Robbins (1978).

The present study has added to the findings with pipradrol by showing that other drugs of the psychomotor stimulant class, notably *d*-amphetamine and two phenyltropane analogues of cocaine, can have similar qualitative effects, but drugs outside this class (specifically morphine, CDP and α-flupenthixol) do not. The results with *d*-amphetamine may

appear to contrast with previous negative findings with this drug (Beninger et al. 1981; Robbins 1978). Indeed, the significant effects with *d*-amphetamine were obtained at lower doses than those with pipradrol, suggesting a greater potency for *d*-amphetamine. However, the results were also more variable with *d*-amphetamine, as previously observed (Robbins 1978), and only attained significance with a large number ($N = 17$) of subjects. The overall rate-increasing effect of *d*-amphetamine was also weaker and more variable than that of pipradrol.

These behavioural results were somewhat paralleled by the neurochemical data (Table 1), obtained with a different rat strain, showing that *d*-amphetamine was generally more potent than pipradrol in blocking uptake and facilitating release of the monoamines NA, DA and 5-HT. Nevertheless, the reasons for the greater variability and weaker rate-increasing effect with *d*-amphetamine are not obvious from these data. In considering other possibilities it may be relevant that amphetamine and methylphenidate-like drugs such as pipradrol differ in their mode of catecholamine release, methylphenidate and pipradrol predominantly acting on the reserpine-sensitive pool (Scheel-Krüger 1971). A further, perhaps more likely possibility is that pipradrol has fewer autonomic (e.g. pressor) effects than amphetamine (Brown and Werner 1954) which may detract from rate-increasing behavioural effects, particularly in extinction. In support of this speculation, central injections of *d*-amphetamine into the region of the nucleus accumbens produce larger effects on CR than with systemic administration, which would be more likely to have peripheral effects (J. Taylor, unpublished data).

The fact that the cocaine analogues WIN 35,428 and, to a lesser extent, WIN 35,065-2 also enhanced responding with CR suggests that blockade of re-uptake of the catecholamines (DA, NA) may be sufficient to produce this behavioural effect, since these drugs, while being potent inhibitors of re-uptake comparable to *d*-amphetamine and pipradrol, are ineffective in facilitating monoamine release (Heikkila et al. 1979). Indeed, it is notable that the effects of WIN 35,428 were at least as large as those of pipradrol and were obtained at lower doses. The greater efficacy of the cocaine analogues over cocaine and, in turn, the greater potency of WIN 35,428 over WIN 35,065-2 corresponds with their relative potencies in blocking catecholamine uptake (Heikkila et al. 1979). Cocaine was largely ineffective in the present experiments with large variability. Previous work has also failed to show a significant effect of cocaine with CR when compared to control (Beninger et al. 1981). It is possible that stronger effects with cocaine could be obtained with a shorter interval between injection and test, since cocaine has a relatively short duration of action (D'Mello et al. 1981; MacPhail and Seiden 1975).

The pharmacological specificity of the effects of the psychomotor stimulants can be seen from the lack of interaction of morphine, CDP and α-flupenthixol with CR. Particularly striking were the results with CDP, since this drug is well-known to produce substantial increases in responding in simple extinction situations (Gray 1977).

A degree of behavioural specificity of the effects of pipradrol was previously established, but this has not yet been achieved for the effects of *d*-amphetamine or the cocaine derivatives described in this study. The relationships of the enhanced effectiveness of CR with psychomotor stimulants to the rate-dependent and perseverative actions of those drugs have been discussed (Robbins 1976, 1978) and remain beyond the scope of the present article. However, elucidation of the behavioural mechanism underlying the increased effectiveness of CR with amphetamine-like drugs may do much to explain their psychological effects.

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