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Investigations into the nature of a 7-OH-DPAT discriminative cue: Comparison with D-amphetamine

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Abstract

In the present study, separate squads of rats were trained to discriminate either the dopamine D_3 receptor preferring ligand 7-hydroxy-2-(di-*N*-propylamino)-tetralin (7-OH-DPAT) (0.03 mg/kg) from saline, or D-amphetamine (0.3 mg/kg) from saline using a standard operant schedule (FR10 schedule reinforcement). Following stable acquisition of responding, tests of generalisation and antagonism were conducted. A number of dopamine agonists having high dopamine D_2-like receptor (D_2, D_3 or D_4) affinity generalised to the 7-OH-DPAT, but not amphetamine, cue. The dopamine $D_{1/5}$ receptor agonist SKF38393 showed no generalisation to either drug cue. Subsequent correlational analysis suggested that this effect was most likely mediated through the dopamine D_3 receptor. The dopamine $D_{2/3}$ receptor antagonist raclopride significantly attenuated both cues. The failure of these drugs to generalise to amphetamine, suggest that there is little involvement of the dopamine D_3 receptor subtype in mediating its discriminative stimulus properties. © 1997 Elsevier Science B.V.

Keywords: Dopamine D_3 receptor; Drug discrimination; 7-OH-DPAT (7-hydroxy-2-(di-*N*-propylamino)-tetralin); D-Amphetamine; (Rat)

1. Introduction

Since the discovery of the dopamine D_3 receptor by Sokoloff et al. (1990) there have been a number of apparently selective agonists identified for this subtype. These include 7-hydroxy-2-(di-*N*-propylamino)-tetralin (7-OH-DPAT), quinpirole, quinelorane (LY-163502) and (+)-(4a*R*,10b*R*)-4-propyl-3,4,4a,10b-tetrahydro-2H,5H-1-benzopyrano [4,3-b],4(oxazin-9-ol) (PD128907) (Levesque et al., 1992; Pugsley et al., 1995; Sautel et al., 1995). By the use of such drugs, various workers have been engaged in attempts to ascribe behavioural or physiological functions to this subtype. For instance, Millan et al. (1995) found that the potency of certain dopamine agonists to produce hypothermia in rats, correlated most strongly with their dopamine D_3 receptor binding affinity. Similarly, Caine and Koob (1993) observed correlations between dopamine D_3 receptor affinity and the potency of three dopamine receptor agonists to reduce rates of cocaine self-administration in rats. These latter findings were of particular interest for they suggest that the rewarding effects of psychostimulants may be mediated via the dopamine D_3 receptor.

Recently, McElroy (1994) reported that rats may be trained to discriminate 7-OH-DPAT from saline using a two lever operant procedure. Drug discrimination techniques can provide a reliable means to obtain quantitative in-vivo data on drug potency and have been frequently used in the pharmacological analysis of various drugs, including psychostimulants (e.g., see Brauer et al., 1997 for a recent review). Until recently little was known about the nature of the 7-OH-DPAT cue, for in the McElroy study no tests of generalisation or antagonism were conducted. However, Sanger et al. (1997) have recently presented evidence that the pharmacology of a 7-OH-DPAT cue was most consistent with a dopamine D_3 receptor mediated response. It was an aim of the present study to further investigate the nature of a 7-OH-DPAT cue by means of generalisation tests using a range of dopamine agonists of varying D_3 receptor selectivity. Furthermore, given the findings of Caine and Koob (1993), the profile of

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a 7-OH-DPAT cue was compared to a psychostimulant (D-amphetamine) cue. The discriminative stimulus properties of psychostimulants are thought to at least partially underlie their rewarding effects.

Part of this work was presented at the 1995 Society for Neuroscience meeting in San Diego (Varty et al., 1995).

2. Materials and methods

2.1. Animals and housing

Twenty-four male Wistar rats (starting weight 300–350 g) were used for these studies. On arrival at the holding facility, the animals were singly housed and placed on a restricted diet of 15 g chow daily, plus pellets earned during the daily operant sessions. Water was available ad-libitum. The holding room was maintained at constant temperature (22 ± 1°C) and humidity (50%), the lights on period was 07.00–19.00 h.

2.2. Drug discrimination procedure

Eight operant chambers were used for these studies (Campden Instruments, UK). Each operant chamber ($25 \times 23 \times 21$ cm) had a working front panel, which consisted of a central food magazine with a hinged perspex panel, placed 0.5 cm above the floor, and two retractable levers positioned 3 cm on either side of the food magazine. Positioned above each lever, and also in the roof of the chamber were lights which illuminated during the training and testing sessions. The presentation of levers, delivery of food pellets (45 mg Noyes pellets) and response recording were controlled by a microcomputer.

Initially, the rats were placed in the operant chambers with both levers presented, for a 20 min session. Both levers were active on an FR1 schedule. Following acquisition of lever responding, the FR was gradually increased to a final ratio of 10. At this point either the left or right lever was assigned as active.

Next, the animals were randomly allocated to one of two groups: those to be trained to a 7-OH-DPAT cue, and those trained to a D-amphetamine cue ($n = 12$ per group). In each group, animals were assigned to specific 'drug' and 'saline' levers, i.e. a rat may be assigned the left lever as the 'drug lever' and therefore the 'right lever' as the saline lever, and vice versa, such that half the group were allocated drug to each lever. Care was also taken to ensure that consecutive rats in the chamber were not always on the same lever, to minimise the influence of inter-animal olfactory cues on choice of lever responding (Extance and Goudie, 1981). On training days, rats were injected with either saline or training drug, and after an appropriate pretreatment time, placed into the chamber with both levers presented but only the specific lever active under an FR10 schedule. Sessions would end after 20 min or after 50 reinforcements had been obtained, whichever occurred sooner. Animals were considered to have learnt the discriminative cue when they made no more than 5 incorrect responses, before 10 correct responses, for at least 5 consecutive test sessions.

Tests of generalisation and antagonism were then undertaken. In each case, the animals were placed in the chambers after drug (or vehicle) pretreatments and both levers were active under FR10. The percentage of drug lever responding was determined (no. of drug lever response/total no. of lever presses $\times$ 100) as was the rate of responding (total no. of lever presses/time to complete the session). Animals were run 5 days/week with drug testing on Tuesday and Friday, subject to the animals showing appropriate control of responding on the intervening days.

2.3. Drugs and injections

Drugs used and their source (in parenthesis) were as follows: 7-OH-DPAT hydrobromide, 8-OH-DPAT hydrobromide and (+)-PD128908 hydrochloride (Semat, St. Albans), apomorphine hydrochloride, cocaine hydrochloride, D-amphetamine sulphate (Sigma, UK), bromocriptine mesylate (Tocris Cookson, Bristol), quinelorane and quinpirole hydrochloride (Eli Lilly, Indianapolis, USA), SKF38393 hydrochloride, WAY100135 and domperidone (Glaxo, Ware) and raclopride tartrate (Astra, Sweden).

All drugs were freshly prepared on the day of the experiment, except 7-OH-DPAT and D-amphetamine which were prepared every 3 days. All drugs were injected subcutaneously in the flank, except cocaine and quinpirole which were injected intraperitoneally. Drugs were dissolved in saline, with the exceptions of apomorphine which required the addition of 0.1% ascorbic acid, bromocriptine which was made up in a 25% ethanol solution in saline, and WAY100,135 which required the addition of 1 M hydrochloric acid before addition of saline and buffering back to neutral pH. A dose volume of 2 ml/kg was used and all drug doses refer to base. Pretreatment times were as follows: bromocriptine 60 min; raclopride, domperidone, WAY100135 30 min; UH-232 20 min; all others 10 min.

2.4. Data analysis and statistics

The percentage of drug lever responding was determined (no. of drug lever response/total no. of lever presses $\times$ 100) as was the rate of responding (total no. of lever presses/time to complete the session). Data is expressed as the mean of 3–10 animals per group. Drug ED_{50}'s and 95% confidence limits were determined using the statistical program BDHS version 2.0. Correlations between variables was determined using SPSS.

3. Results

3.1. 7-OH-DPAT discriminative cue

Animals were successfully trained to a 7-OH-DPAT cue after an average of 32 sessions. Initially a training dose of 0.05 mg/kg was used, but only 50% of the animals successfully completed a significant proportion of responses on the drug lever, the remainder exhibited a severe reduction in response rate. Therefore the training dose was reduced to 0.03 mg/kg, and consequently, 11 out of 12 animals displayed stable generalisation to the 7-OH-DPAT cue, with a significant, measurable rate of response (typically 0.3–0.4 lever presses/s). One animal failed to learn the cue by 70 training sessions and was omitted from the studies.

3.1.1. Tests of generalisation

7-OH-DPAT (0.003-0.05 mg/kg, $n = 6–9$ per dose) produced a dose-dependent increase in drug lever responding (i.e. 0.003 mg/kg = 12 ± 9%, 0.03 mg/kg = 92 ± 4%), and an accompanying dose-dependent decrease in the rate of responding (i.e. 0.003 mg/kg = 0.81 ± 0.08 lever presses/s, 0.03 mg/kg = 0.32 ± 0.04 lever presses/s). Apomorphine (0.003–0.1 mg/kg, $n = 5–10$ per dose), quinpirole (0.001–0.03 mg/kg, $n = 4–8$ per dose), quinelorane (0.00003–0.01 mg/kg, $n = 4–7$ per dose) and (+)-PD128907 (0.003–0.1 mg/kg, $n = 3–9$ per dose) each produced a significant generalisation to the 7-OH-DPAT discriminative cue (see Fig. 1). At higher doses of each of these drugs, there was a significant dose-dependent decrease in response rate on the drug lever. SKF38393 (0.5–32 mg/kg, $n = 4–10$ per dose), bromocriptine (1–30 mg/kg, $n = 5–6$ per dose), cocaine (3–10 mg/kg, $n = 4$ per dose), and 8-OH DPAT (0.03–0.1 mg/kg, $n = 5–7$ per dose) each failed to generalise to the 7-OH-DPAT cue (Table 1). At higher doses, these drugs produced significant decreases in the response rate whilst still producing no marked generalisation.

3.1.2. Antagonist studies

Raclopride (0.01–0.1 mg/kg) produced no generalisation when tested alone against the 7-OH-DPAT cue, but produced a clear antagonism of the cue (% 7-OH lever response: 7-OH = 91 ± 3%; raclopride (0.03 mg/kg) = 2 ± 2%; raclopride + 7-OH = 53 ± 9%), with no effect on the rate of responding (Fig. 2). At higher doses of raclopride there was no increase in antagonism, however, the rate of response was decreased dramatically making lever selection difficult to interpret (i.e. rate at 0.03 mg/kg =

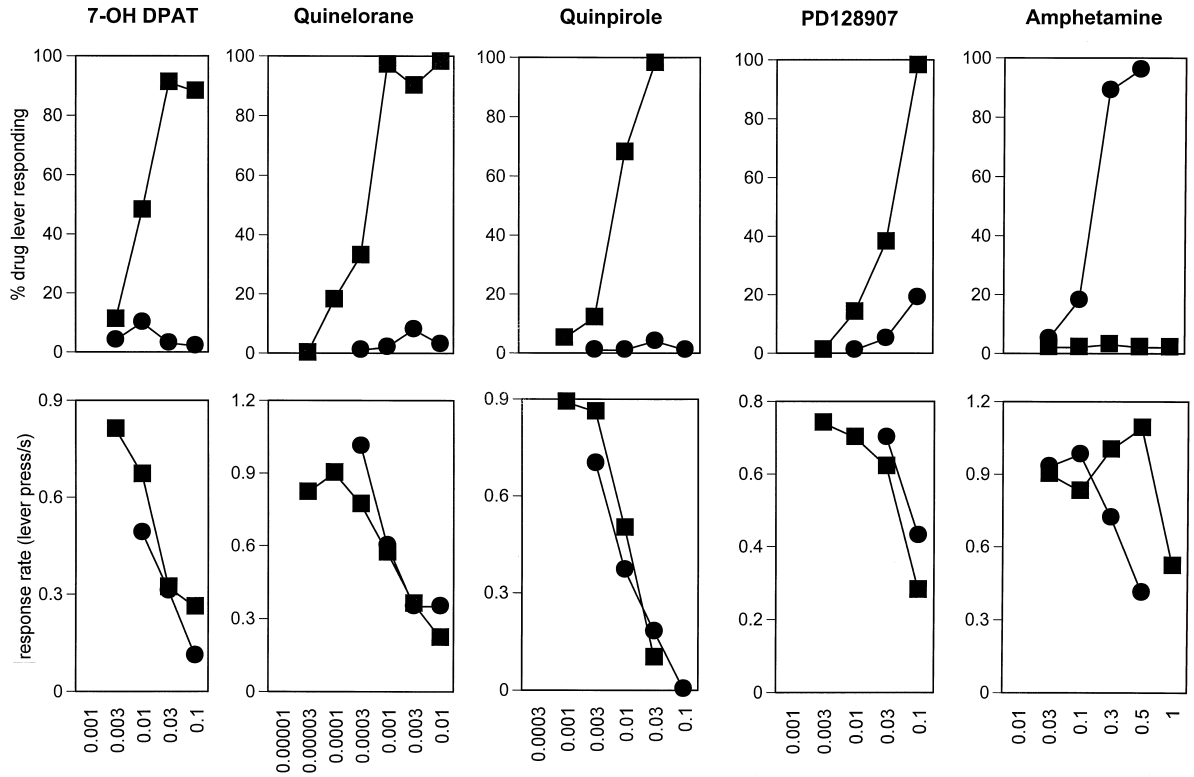

Fig. 1. Results of generalisation tests in rats trained to discriminate either 7-OH-DPAT (0.03 mg/kg, ■) or amphetamine (0.3 mg/kg, ●) from saline. Rats were pretreated with different doses of 7-OH-DPAT ($n = 4–9$ per group), quinelorane (4–7 per group), quinpirole (4–8 per group), PD128907 (4–9 per group), or amphetamine (4–9 per group). The upper panels represent the percentage of responding on the drug paired lever. The lower panel represents the response rate (no. lever presses/s) attained during the test session. Drug ED_{50}'s for generalisation and response rate from the 7-OH-DPAT study are presented in Table 2.

Table 1
Effect of various drugs on generalisation and response rate to a 7-OH-DPAT (0.03 mg/kg) or D-amphetamine (0.3 mg/kg) cue

Drug	Dose (mg/kg)	7-OH-DPAT cue		D-amphetamine cue	
		% correct	response	% correct	response
Apomorphine	0.01	13 ± 6	0.57 ± 0.07	—	—
	0.03	43 ± 19	0.38 ± 0.10	10 ± 8	0.43 ± 0.1
	0.1	95 ± 4	0.25 ± 0.10	10 ± 10	0.35 ± 0.1
	0.3	—	—	NR	NR
Cocaine	1	—	—	1 ± 1	0.75 ± 0.15
	3	0	0.93 ± 0.08	50 ± 19	1.04 ± 0.05
	10	0	0.97 ± 0.08	93 ± 7	0.55 ± 0.15
Bromocriptine	3	1 ± 1	0.81 ± 0.04	0	1.08 ± 0.13
	10	4 ± 3	0.88 ± 0.06	0	1.11 ± 0.1
	30	7 ± 5	0.9 ± 0.05	50 ± 50	0.19 ± 0.1
SKF38393	2	2 ± 2	0.81 ± 0.04	0	0.99 ± 0.04
	8	3 ± 1	0.88 ± 0.06	0	0.96 ± 0.07
	32	1 ± 1	0.7 ± 0.02	—	—
8-OH-DPAT	0.03	4 ± 2	0.91 ± 0.07	—	—
	0.075	10 ± 10	0.76 ± 0.24	—	—
	0.1	33	0.26 (4NR)	—	—

NR = no responders. Response rate is expressed in lever presses/s.

0.24 ± 0.06 presses/s; rate at 0.1 mg/kg = 0.09 ± 0.03 presses/s). (+)UH-232 (0.1–3 mg/kg, $n = 4$–8 per dose) produced no generalisation to the 7-OH-DPAT cue, however, there was a modest attenuation of the cue (see Fig. 2) with a slight reduction in response rate. At the higher dose of 3 mg/kg the effect was not as marked. Domperidone (5 mg/kg) had no effect against the 7-OH-DPAT cue (see Fig. 2). WAY-100135 (3 mg/kg) produced no generalisation to the 7-OH-DPAT cue when tested alone and had no effect on the 7-OH-DPAT cue (i.e. % 7-OH lever response: 7-OH = 92 ± 5%; WAY (3 mg/kg) = 2 ± 2%; WAY + 7-OH = 89 ± 7%).

3.1.3. Tests of correlation

Drug potencies for generalisation to the 7-OH-DPAT cue and to reduce rates of responding were determined and are summarised in Table 2. There was a highly significant correlation between drug potencies on each response (coefficient = 1, $p < 0.001$). Further correlations were made between drug ED_{50} on the generalisation test and functional potencies at a dopamine D_2 or D_3 receptor system (Sautel et al., 1995, see Table 2 for values). A significant correlation was found with the dopamine D_3 but not D_2 receptor ($D_3 = 0.99$, $p < 0.001$; $D_2 = 0.23$, $p = 0.66$).

3.2. Amphetamine discriminative cue

Eleven out of twelve animals learnt the amphetamine discriminative cue (0.3 mg/kg) after an average of 30 training sessions. The final rat was omitted from the study as it failed to show reliable amphetamine responding by 70 sessions.

Both amphetamine (0.03–0.5 mg/kg, $n = 4$–9 per dose; Fig. 1) and cocaine (1–10 mg/kg, $n = 4$–6 per dose; Table 1) produced a dose related increase in drug lever responding (e.g. amphetamine 0.03 mg/kg = 5 ± 3%, 0.5 mg/kg = 96 ± 2%). There was also a dose dependent decrease in the rate of responding on either lever (see Fig. 1 and Table 1). The direct DA agonists apomorphine (0.03–0.3 mg/kg, $n = 3$–5 per dose), quinpirole (0.003–0.1 mg/kg, $n = 4$–5 per dose), quinelorane (0.0003–0.01 mg/kg, $n = 4$–5 per dose), (+)-PD128907 (0.03–0.3

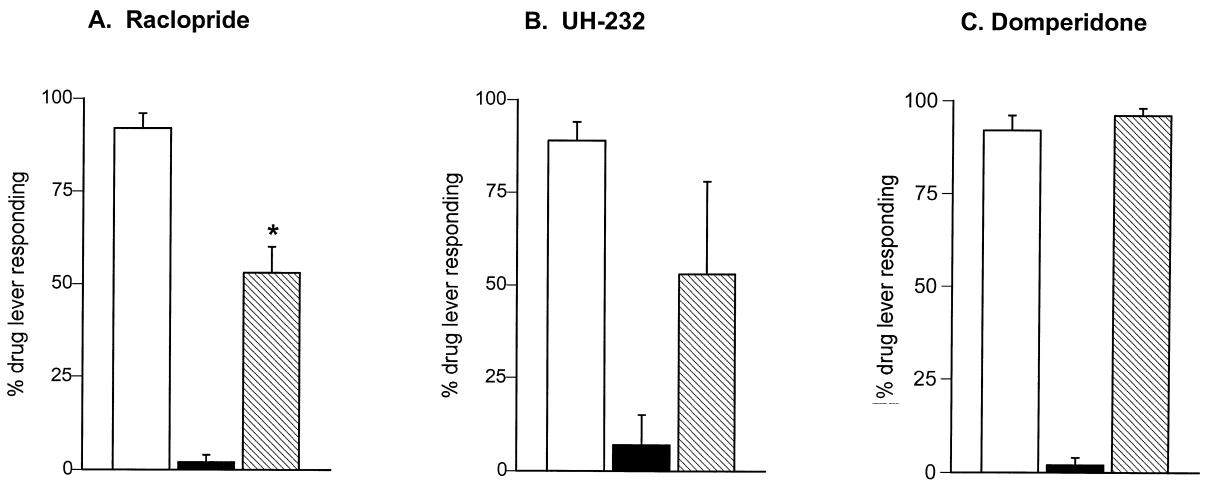

Fig. 2. Effect of raclopride (0.03 mg/kg), UH-232 (1 mg/kg) and domperidone (3 mg/kg) to antagonise a 7-OH-DPAT-induced cue (0.03 mg/kg). * $p < 0.05$ vs. 7-OH-DPAT/saline response (*t*-test). (open bar) = 7-OH-DPAT alone, (filled bar) = test compound alone, (hatched bar) = 7-OH-DPAT + test compound. Data show the percentage of responding on the 7-OH-DPAT paired lever. Response rates were as follows: raclopride 0.76 ± 0.05 responses/s, raclopride + 7-OH 0.24 ± 0.06 responses/s ($n = 3$–8 per group); UH-232 0.74 ± 0.10 responses/s, UH-232 + 7-OH 0.17 ± 0.06 responses/s ($n = 4$–6 per group); domperidone 0.32 ± 0.07, domperidone + 7-OH 0.19 ± 0.06 responses/s ($n = 5$ per group).

Table 2
ED_{50} determinations and confidence limits for drug potencies to generalise to a 7-OH-DPAT cue, and to reduce response rate

	Drug discrimination			Response rate			Functional activity[a]	
	ED_{50} (mg/kg)	lower 95%	upper 95%	ED_{50} (mg/kg)	lower 95%	upper 95%	D_2	D_3
7-OH-DPAT	0.01	0.006	0.016	0.013	0.004	0.034	2.7	0.39
Apomorphine	0.029	0.012	0.072	0.015	0.009	0.024	2.3	2.2
Quinpirole	0.006	0.002	0.04	0.008	0.001	—	2.8	0.86
Quinelorane	0.0004	0.0001	0.001	0.0008	0.0003	0.002	3.2	0.15
PD128907	0.025	0.012	0.06	0.029	0.011	0.14	34	0.64
Bromocriptine	> 30	—	—	> 30	—	—	1.8	12

[a] Functional activity is derived from Sautel et al. (1995).

mg/kg, $n = 4–5$ per dose), 7-OH-DPAT (0.01–0.1 mg/kg, $n = 4–6$ per dose) and SKF38393 (2–8 mg/kg, $n = 4$ per dose) each failed to produce any significant generalisation to the amphetamine cue (see Fig. 1, Table 1), although partial generalisation was seen following bromocriptine (30 mg/kg, $n = 4–5$ per dose). At higher doses of each drug, there were significant reductions in response rate. Doses were increased until effects on rate made lever selection uninterpretable.

Raclopride produced a dose related attenuation of the amphetamine cue (e.g. amphetamine lever response: 0.001 mg/kg $79 \pm 13\%$, 0.01 mg/kg $42 \pm 16\%$, 0.1 mg/kg $16 \pm 11\%$; $n = 5–8$ per dose). In this instance, response rates were partially reduced by raclopride (e.g. 0.01 mg/kg = 0.57 ± 0.15; 0.1 mg/kg 0.38 ± 0.07 responses/s; $n = 5–8$ per dose).

4. Discussion

In the initial study by McElroy (1994), male Sprague–Dawley rats were trained to a dose of 0.05–0.1 mg/kg 7-OH-DPAT. Despite showing robust stimulus generalisation at these doses, there was a marked reduction in response rate. In the present study, we found that these doses were too high in that the low response output made lever selection difficult to assess. At the lower dose of 0.03 mg/kg, reliable stimulus control was evident and response rates were at a reasonable level (typically 25–50% of controls, 200–500 responses/20 min). A number of dopamine agonists of mixed dopamine D_2-like receptor affinity substituted for 7-OH-DPAT, and at equivalent doses reduced response rate, indeed there was a highly significant correlation between ED_{50} doses required to generalise to the 7-OH-DPAT cue and to reduce the rate of responding. However, it seems unlikely that the rate depressant effects of these drugs served as the cue, for the 5-HT_{1A} receptor agonist, 8-OH-DPAT and the dopamine $D_{2/3}$ receptor antagonist raclopride, both reduced response rate, but neither engendered appropriate drug-lever responding. Of further note, the failure of 8-OH-DPAT to markedly generalise, and lack of blockade with the selective 5-HT_{1A} receptor antagonist, WAY100135, suggests negligible involvement of this receptor subtype in the discriminative properties of 7-OH-DPAT.

In terms of the dopaminergic nature of the 7-OH-DPAT cue, it seems most likely to be mediated via a dopamine D_2-like receptor. Firstly, all the compounds which generalised have relatively high affinity at these sites, secondly the 7-OH-DPAT cue was attenuated by raclopride, and thirdly the dopamine $D_{1/5}$ receptor agonist SKF38393 failed to substitute, at doses which do generalise to a $D_{1/5}$ cue (Reavill et al., 1993). Because raclopride has relatively low affinity for the dopamine D_4 receptor (Seeman and Van Tol, 1994), it seems unlikely that this subtype is of importance. Thus the main comparison was between the D_2 and D_3 receptor. Recently, Sautel et al. (1995) reported on the functional potencies of a range of dopamine agonists in a mitogenesis assay using transfected CHO cell lines expressing either human D_3 or D_2 receptors. Comparison of these data with the present studies suggest that the pharmacological profile of the various dopaminergic drugs to generalise to the 7-OH-DPAT cue was most consistent with a D_3, rather than D_2 receptor interaction. Sanger et al. (1997) have reported similar findings using rats trained to discriminate a higher dose of 7-OH-DPAT (0.1 mg/kg) from saline. Furthermore, given the high correlation between ED_{50} doses required to reduce response rate and generalise to the 7-OH-DPAT cue, the rate depressant effects of these drugs are also consistent with a dopamine D_3 receptor mediated effect. This too is in line with the observations of Sanger et al. (1996) looking at rates of food responding under an FR10 schedule. However, antagonist studies using centrally active dopamine D_2 and D_3 receptor-selective ligands are necessary to further validate these preliminary observations. Although UH-232 shows some antagonist selectivity for the dopamine D_3 receptor (Sokoloff et al., 1990; Waters et al., 1993), this has been recently questioned by Griffon et al. (1995) who suggest it may have partial agonist properties. This may explain its very modest attenuation of the 7-OH-DPAT cue. The peripheral dopamine D_2-like receptor antagonist domperidone (Champion, 1988), a compound with nanomolar affinity for the D_3 receptor (Sokoloff et al., 1990; Millan et al., 1995) did not block the cue, consistent with this being a centrally mediated response. Of final note

from the antagonist studies, neither raclopride nor UH-232 modified the rate depressant effects of 7-OH-DPAT. This is most likely because these antagonists were tested at doses close to that which reduce rates of operant responding.

Comparison between the 7-OH-DPAT and amphetamine cue clearly showed no overlap. Thus compounds which generalised to the 7-OH-DPAT cue failed to generalise to amphetamine, at least to any significant degree in the dose range studied. Similarly, cocaine which completely substituted for amphetamine, failed to generalise to a 7-OH-DPAT cue. The observation that none of the dopamine compounds produced any marked substitution for amphetamine contrasted with some studies suggesting that D_2-like, but not necessarily D_1-like receptor (Nielsen et al., 1989; Furmidge et al., 1991; Reavill et al., 1993) agonists may generalise to amphetamine, although Van Groll and Appel (1992) failed to report significant amphetamine generalisation following dopamine D_1 or D_2 receptor agonist pretreatment. Differences in training dose, schedule, drug sensitivity of rat strain used, may explain these differences. For instance, in the Furmidge et al. (1991) study, doses of quinpirole around 0.1 mg/kg were required to produce significant amphetamine responding (see also Van Groll and Appel, 1992), yet in the present study these doses completely suppressed response rate to a level making lever selection uninterpretable. In any case, the finding that none of the dopamine D_2-like receptor agonists generalised at doses which do to 7-OH-DPAT is clearly inconsistent with the amphetamine cue being mediated through D_3 receptor activation. Recently, Acri et al. (1995) and Spealman (1996) have suggested that certain dopamine D_3 receptor-preferring ligands such as 7-OH-DPAT and PD128907 can engender cocaine appropriate responding, suggestive of a D_3 receptor involvement to the cocaine discriminative cue. In as much as an amphetamine and cocaine cue may be similar, both in terms of pharmacology (Van Groll and Appel, 1992; Woolverton and Johnson, 1992) and neuroanatomical locus (Nielsen and Scheel-Krüger, 1986; Callahan et al., 1994), clearly our results are inconsistent with this view and it will require further studies, again using subtype selective antagonists to resolve this issue.

Thus in conclusion, using a range of dopamine agonists of varying D_2/D_3 receptor selectivity, subsequent correlational analysis is most consistent with a 7-OH-DPAT cue being mediated through the dopamine D_3 receptor subtype, i.e quinelorane > quinpirole > 7-OH-DPAT > apomorphine = PD128907 > bromocriptine. These conclusions broadly agree with the observations of Sanger et al. (1997) and in general, this rank order of potency is similar to that reported by Storey et al. (1995) regarding hypoactivity, Sanger et al. (1996) regarding decreases in operant response rates, and Kreiss et al. (1995) regarding the inhibition of dopamine cell firing in the substantia nigra pars compacta. Each of these effects correlate best with a dopamine D_3 receptor mediated response. The availability of truly subtype selective antagonists with demonstrable CNS penetration will either confirm or refute these correlations.

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