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Effects of the dopamine autoreceptor antagonist (−)-DS121 on the discriminative stimulus properties of *d*-amphetamine and cocaine

David Clark [a,*], Madlen Exner [a], Lesley J. Furmidge [a,1], Kjell Svensson [b,2], Clas Sonesson [b]

[a] *Centre for Substance Abuse Research, Department of Psychology, University of Wales, Swansea, SA2 8PP, UK*
[b] *Department of Pharmacology, University of Goteborg, Goteborg, Sweden.*

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Abstract

(−)-DS121 [*S*-(−)-3-(3-cyanophenyl)-*N*-*n*-propyl piperidine) is a recently synthesised phenylpiperidine derivative suggested to be a dopamine receptor antagonist acting preferentially at dopamine autoreceptors. The drug exerts 'agonist-like' behavioural effects by enhancing dopamine release, but also shares properties in common with neuroleptics. The ability of (−)-DS121 to both generalise to and antagonise the stimulus effects of psychostimulants was determined in rats trained to discriminate *d*-amphetamine (0.5 mg/kg) or cocaine (5.0 mg/kg) from saline in a two-lever, food-reinforced, drug discrimination task. (−)-DS121 (3.5–14.0 mg/kg) produced small, but significant, increases in drug lever-appropriate responding in both *d*-amphetamine and cocaine-trained rats. However, there was no indication of a dose-dependent effect in either case. On the other hand, (−)-DS121 dose-dependently reduced response rate. Caffeine produced a higher level of drug lever-appropriate responding than (−)-DS121 in *d*-amphetamine-trained rats. (−)-DS121 (7.0–14.0 mg/kg) also weakly antagonised the cueing properties of both *d*-amphetamine and cocaine. A marked response disruption with the drug combination precluded testing of higher doses of (−)-DS121. A combination of subthreshold doses of (−)-DS121 (3.5 mg/kg) and *d*-amphetamine (0.0625 mg/kg) produced a significant degree of drug lever-appropriate responding, suggesting a synergistic interaction between these drugs. However, such an interaction was not noted with a higher dose of (−)-DS121, or when this drug was administered with a low dose of cocaine (0.25 mg/kg). These results show that (−)-DS121 can exert both weak agonistic and antagonistic effects in animals trained to discriminate between *d*-amphetamine (or cocaine) and saline. They argue against a close similarity between the subjective effects of (−)-DS121 and the psychostimulants.

Keywords: (−)-DS121; Dopamine autoreceptor antagonist; Dopamine D_3 receptor; D-Amphetamine; Cocaine; Drug discrimination; Caffeine

1. Introduction

Carlsson and colleagues (Svensson et al., 1986; Hajos et al., 1988; Waters et al., 1990) have described two aminotetralin derivatives which act as antagonists at dopamine receptors but produce a paradoxical mild behavioural stimulation in rodents. (+)-AJ76 [*cis*-(+)-1*S*,2*R*-5-methoxy-1-methyl-2-(*n*-propylamino)-tetralin] and (+)-UH232 [cis-(+)-1*S*,2*R*-5-methoxy-1-methyl-2-(di-*n*-propylamino)-tetralin] enhance extracellular dopamine levels in an impulse- and Ca^{2+}-dependent manner and induce a reserpine-sensitive increase in locomotor activity. These dopamine 'agonist-like' effects were hypothesised to be due to preferential blockade of dopamine autoreceptors located on the somatodendritic region of dopamine neurons and on dopamine nerve terminals.

Blockade of dopamine autoreceptors by (+)-AJ76 and (+)-UH232 is indicated by their antagonism of the inhibitory effects of apomorphine on dopamine cell firing and the apomorphine-induced reversal of the increase in dopamine synthesis produced by γ-butyrolactone (Svensson et al., 1986; Bergstrom et al., 1988; Piercey and Lum, 1990). (+)-AJ76 and (+)-UH232

* Corresponding author. Tel. (0)792-295279, fax (0)792-295679.
[1] Current address: Dept. Preclinical Veterinary Sciences, Royal (Dick) School of Veterinary Sciences, The University of Edinburgh, Edinburgh, U.K.
[2] Current address: CNS Research, The Upjohn Company, Kalamazoo, MI 49001, USA.

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also act as weak postsynaptic dopamine receptor antagonists, since they reduce the locomotor stimulatory effects of apomorphine and *d*-amphetamine. The ability of these drugs to antagonise apomorphine-induced excitation of globus pallidal neuronal activity (Bergstrom et al., 1988) and *d*-amphetamine-induced inhibition of nigral dopamine cell firing (Piercey and Lum, 1990) has also been taken as an indication of postsynaptic dopamine receptor antagonism. (+)-AJ76 and (+)-UH232 interact with dopamine D_2 receptors but also show high affinity, and a small degree of selectivity, for the D_3 receptor subtype (Sokoloff et al., 1990).

The phenylpiperidine (−)-DS121 (*S*-(−)-3-(3-cyanophenyl)-*N*-*n*-propyl piperidine) (Sonesson et al., 1993) is a more recently synthesised dopamine receptor antagonist which exhibits a very similar pharmacological profile to (+)-AJ76 and (+)-UH232. In brief, the behavioural stimulation produced by this drug is blocked by reserpine, α-methyl-*p*-tyrosine or dopamine receptor antagonists, whilst the dose-dependent elevation in dopamine release in the dorsal and ventral striatum is sensitive to both tetrodotoxin and Ca^{2+}. Antagonistic effects of the drug at dopamine autoreceptors are indicated by its ability to reverse the effects of apomorphine on dopamine cell firing and on dopamine synthesis in the γ-butyrolactone model. Although (−)-DS121 also blocks postsynaptic dopamine receptors, this effect appears to be weak and there are indications that the drug possesses a higher preference for dopamine autoreceptors than (+)-AJ76 and (+)-UH232 (Svensson et al., 1993; Waters et al., 1993).

The behavioural stimulation induced by (−)-DS121 and the aminotetralin derivatives is similar, although less pronounced, to that of the psychostimulants cocaine and *d*-amphetamine. These psychostimulants also enhance extracellular dopamine levels (Sharp et al., 1987; Moghaddan and Bunney, 1989) and their ability to increase dopamine function in the nucleus accumbens has been intimately linked to their powerful rewarding or euphoric effects and consequent abuse liability (Wise and Bozarth, 1987). By enhancing dopamine release in the nucleus accumbens, (−)-DS121 might also produce rewarding effects which could lead to abuse of the drug. Similarly to the psychostimulants (Spyraki et al., 1982a,b), (−)-DS121 induces a conditioned place preference in rodents (Kling-Petersen et al., 1994), suggesting reinforcing properties of the drug.

In the present paper, we have used drug discrimination procedures to determine further whether the behavioural effects of (−)-DS121 resemble those produced by *d*-amphetamine and cocaine. These procedures are based on the fact that animals can be trained to use drug-induced internal states as biologically relevant interoceptive stimuli (cues) which signal the availability of reinforcement (Overton, 1987). The interoceptive stimulus properties of cocaine and *d*-amphetamine in the rat, which have been shown to be dependent on mesoaccumbens dopamine functional activity (Nielsen and Scheel-Krüger, 1986; Wood and Emmett-Oglesby, 1989), are likely to be related at least in part to subjective aspects of their reinforcing effects. Therefore, a study of the effects of (−)-DS121 in rats trained to discriminate *d*-amphetamine (or cocaine) from saline should provide information of relevance to the subjective effects of the drug in man and its potential abuse liability.

Our first aim was to establish whether (−)-DS121 possesses similar discriminative stimulus properties to *d*-amphetamine and cocaine. For comparative purposes, we have also examined the ability of caffeine to substitute for *d*-amphetamine. Caffeine has been shown to enhance locomotor activity in rodents (Dews, 1986) and at least partially substitute for the psychostimulants (Holloway et al., 1985; Harland et al., 1989). Given that (−)-D121 exhibits both 'agonist-like' and antagonist effects in different pharmacological models (Waters et al., 1993), we have also determined whether the drug can alter the discriminability of *d*-amphetamine and cocaine.

2. Materials and methods

2.1. Animals

Eighteen male, Sprague-Dawley albino rats (Harlan Olac, Bicester, UK) were food-deprived to approximately 85% of their free feeding weights (initial weight 250–300 g) by restricting food intake to an average of 20 g rat chow per day. Water was freely available. The rats were housed in pairs in a room maintained at a constant temperature (21–23°C). Lights were on from 07:00 to 19:00.

2.2. Apparatus

The experiments were conducted in four identical, commercially manufactured operant boxes (Campden Instuments, Loughborough, UK), measuring 20 cm high with a 25 × 23 cm grid floor. Each chamber contained two retractable levers mounted on one wall, with a food hopper positioned equidistant between the levers. Food pellets were delivered by automatic dispensers. The boxes were dimly lit by a centrally positioned 2.8-W light and were enclosed in light- and sound-attenuating chambers. Fans provided ventilation and masking noise.

The operant boxes were controlled by a Amstrad PC1640 computer located in a different room. They were connected to an interface designed and built in the Department, which in turn was linked to the com-

puter via a PC-63 relay output card, and a PC-14A input/output and timer card (Amplicon, Brighton, UK). Software written in TopSpeed Modula-2 (Jensen and Partners UK, London) controlled the levers and food dispensers in the operant boxes, and recorded the number of lever presses and relevant latencies.

2.3. Drug discrimination procedures

The discrimination procedures were similar to those we have described in detail elsewhere (Exner et al., 1989). Initially, the rats were randomly assigned to either the *d*-amphetamine or cocaine study and also to one of the four operant boxes. For each box, half of the animals in each study were randomly assigned to the right lever as the drug-appropriate lever and the other half to the left lever. This arrangement, and the fact that saline and drug sessions followed each other in a pseudo-random order, served to control for the development of position cues based on olfactory stimuli by animals that were run in the same box (Extance and Goudie, 1981).

Throughout the *d*-amphetamine study, rats were injected intraperitoneally (i.p.) with either 0.5 mg/kg of the training drug, or 0.9% saline, 15 min before being placed in the operant boxes. In the other study, the rats received either 5.0 mg/kg cocaine, or 0.9% saline, 15 min before the test session.

Only the correct lever was present during the initial phase of training. Animals were injected with saline and trained to press the saline-appropriate lever for food pellets. Following reliable performance under the saline condition, they learnt to respond on the drug-appropriate lever following *d*-amphetamine (or cocaine) injections. Saline and drug sessions were then carried out each day on a random basis with the restriction that neither condition occurred more than 3 days in a row. The rats were trained to respond on a FR20 schedule on each lever using an ascending FR schedule independently for each condition.

Discrimination training was initiated once the rats were responding reliably on the FR20 schedule. During these training sessions of 20-min duration, both levers were available, but only responses on the appropriate lever were reinforced on an FR20 schedule. Incorrect responses were recorded but had no programmed consequences. The time in s to complete the first 20 responses on the correct lever (latency) and the percentage of drug lever responses prior to delivery of the first food pellet (100 × drug lever responses divided by drug + saline lever responses) were recorded. A response rate measure was derived by calculating the number of responses per min before delivery of the first reinforcer.

Discrimination training continued 6 days a week until the rats reached criterion performance (nine out of ten consecutive sessions with more than 80% correct lever presses before the first reinforcement was delivered). Each animal was then used in the (−)-DS121 studies. No reinforcement was given during test sessions; the rat was removed from the operant box on completion of 20 responses on either of the levers. The number of drug- and saline-appropriate lever responses, and the latency to complete 20 responses on either of the levers, were recorded. Each latency value was converted to a response rate measure.

The ability of (−)-DS121 to substitute for *d*-amphetamine or cocaine was initially examined. Animals were administered different doses of (−)-DS121 30 min before the experimental sessions. A similar procedure was adopted in the subsequent antagonism studies; in this case, (−)-DS121 was administered 15 min before *d*-amphetamine or cocaine, and animals were placed in the operant boxes 15 min later. Drug interaction studies were then carried out; animals received different doses of *d*-amphetamine (or a single dose of cocaine), with or without (−)-DS121, at the time intervals indicated above. After completion of these studies, the *d*-amphetamine-trained rats were tested with various doses of caffeine administered 30 min prior to the session. In all studies, drug doses were administered in a random order.

Test sessions were separated by at least one *d*-amphetamine and one saline baseline session. A particular baseline session was randomly designated as the control session for either the saline or drug condition in each study. If discrimination performance deteriorated between test sessions, further training was carried out until performance restabilised. If under any condition an animal failed to respond with at least ten lever presses in a session, the data were considered unreliable and excluded from analysis. Similarly, data were not analysed if less than half of the rats tested under a condition failed to respond with at least ten presses.

2.4. Statistical analyses

The effects of drugs on the percent drug lever responding and response rates were analysed using the SAS-GLM procedure one-way analysis of variance (ANOVA) for a repeated measures design (SAS Institute, Cary, NC, USA). Provided that this procedure yielded significant overall F-values ($P < 0.05$), comparisons between means were carried out using Duncan's multiple comparison procedure.

2.5. Drugs

The following drugs were administered intraperitoneally (i.p.) in 0.9% saline: (*d*)-amphetamine sulphate, cocaine hydrochloride, caffeine (Sigma Chemi-

cal Co., Poole, UK); (−)-DS121 hydrochloride [S-(−)-3-(Cyanophenyl)-*N*-*n*-propyl piperidine] (Department ofPharmacology, University of Goteborg, Sweden). All drugs were injected in a volume of 1 ml/kg.

3. Results

3.1. (−)-DS121 in d-amphetamine discrimination rats

When administered alone, (−)-DS121 produced a small but significant increase in responding on the drug-appropriate lever in rats trained to discriminate *d*-amphetamine from saline [one-way ANOVA: $F(4,29) = 63.04$, $P < 0.0001$]. However, there was no evidence of a dose-dependent drug effect (Fig. 1A). Duncan's multiple comparison procedures revealed that whilst both 3.5 mg/kg and 14.0 mg/kg (−)-DS121 significantly increased drug lever-appropriate responding, an intermediate dose (7.0 mg/kg) was without effect. No individual animal responded primarily on the drug lever (i.e. at the > 83% criterion level) after any dose of (−)-DS121.

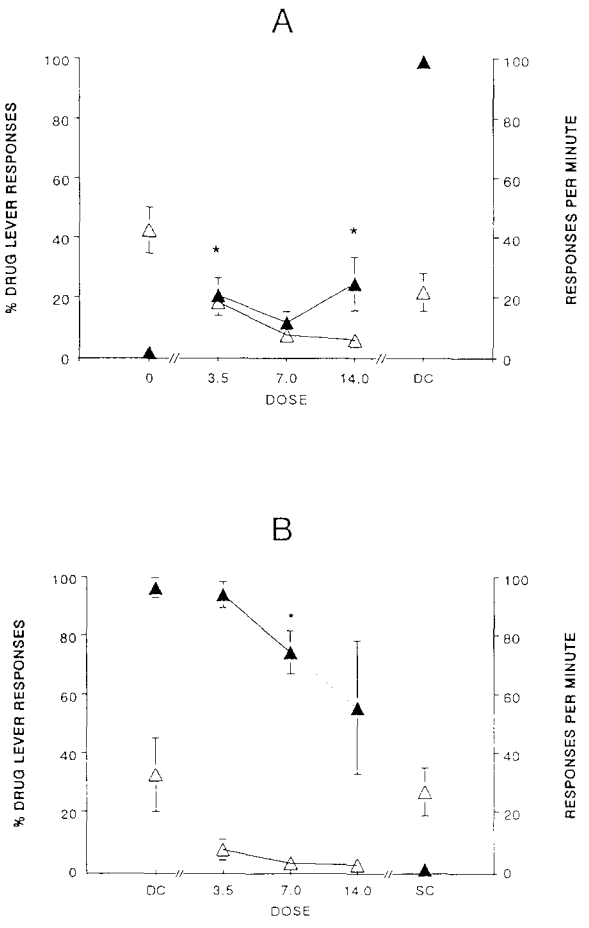

Fig. 1. Ability of (−)-DS121 to (A) substitute for, and (B) to antagonise, the discriminative stimulus properties of 0.5 mg/kg *d*-amphetamine. Filled triangles represent the percentage of drug lever (DL) responses (±S.E.M.) in test sessions. Empty triangles (±S.E.M.) represent the number of responses per min at different drug doses. Asterisks indicate scores for percent drug lever responses that (A) differ significantly from saline performance ($P < 0.05$) or (B) differ significantly from *d*-amphetamine performance. See text for significant changes in response rate. Control performance (±S.E.M.) for saline (SC) and for *d*-amphetamine (DC) are shown on the left and right side of the dose response curve (see Methods). If less than half the animals responded with at least ten lever presses, their percent drug lever data were excluded from analysis. Data for these instances are included in the figure but connected by a dotted line only. Eight animals participated in the substitution study and seven in the antagonism study.

Table 1
Percentage drug lever responding (±S.E.M) after combinations of various doses of (−)-DS121 (0–7.0 mg/kg) and *d*-amphetamine (0 or 0.0625 mg/kg)

	Dose of (−)-DS121 (mg/kg)			
	0	1.75	3.5	7.0
Saline	4.8±4.5	5.9±5.5	10.1±5.3	17.3±6.4
Amp (0.062 mg/kg)	12.5±11.1	16.5±8.8	39.0±13.3 [a]	26.4±7.6

[a] Significantly ($P < 0.05$) higher level of drug lever responding than after drug vehicles or either drug alone.

Animals administered 7.0 mg/kg (−)-DS121 in combination with *d*-amphetamine (0.5 mg/kg) responded less on the drug-appropriate lever than in *d*-amphetamine control sessions [$F(3,15) = 130.54$, $P < 0.0001$; Fig. 1B]. A lower dose of (−)-DS121 was without effect, whilst 14.0 mg/kg produced a pronounced reduction in responding such that more than 50% (4/7) of the animals did not complete the minimum requirement of ten lever presses. In the three animals which responded reliably, drug lever-appropriate responding was further reduced to 55.5 ± 22.7% of control levels.

Animals were administered low doses of (−)-DS121 (1.75–7.0 mg/kg) in combination with saline or a subthreshold dose of *d*-amphetamine (0.0625 mg/kg). A one-way ANOVA revealed significant differences between the drug conditions [$F(8,41) = 21.3$, $P < 0.0001$]. The level of drug lever-appropriate responding after 0.0625 mg/kg *d*-amphetamine alone and after any dose of (−)-DS121 administered alone was not significantly different to that observed for in vehicle control condition (Table 1). Furthermore, drug lever responding was at vehicle levels after the combination of *d*-amphetamine and the lowest dose of (−)-DS121. However, after the combination of 0.0625 mg/kg *d*-amphetamine and 3.5 mg/kg (−)-DS121 drug lever-appropriate responding was at a higher level than after the vehicle control or either of the drugs administered alone. This finding indicates a small degree of synergism between the two drugs. However, this synergism was not maintained at the highest dose of (−)-DS121. Drug lever responding following the drug combination was significantly greater than after the drug vehicles or

d-amphetamine alone, but not after (−)-DS121 (7.0 mg/kg) alone.

In the substitution study, (−)-DS121 dose dependently reduced response rates [$F(4,32) = 7.69$, $P < 0.0001$]. Even 3.5 mg/kg (−)-DS121 was effective, whilst none of the seven animals responded ten times on the levers when administered 28.0 mg/kg (Fig. 1A). All doses of (−)-DS121 (3.5–14.0 mg/kg) reduced response rates when administered with 0.5 mg/kg *d*-amphetamine [$F(3,18) = 3.59$, $P < 0.035$], and only three of eight animals responded more than ten times after the highest dose tested (Fig. 1B). The reductions in response rate observed with 3.5–7.0 mg/kg (−)-DS121 in the interaction study were not exacerbated by the low dose of *d*-amphetamine [$F(8,48) = 3.79$, $P < 0.002$ followed by Duncan's test] (data not shown).

In these studies, and those described below, casual observations revealed that (−)-DS121-treated animals which failed to respond on the levers remained alert; in most instances, they appeared mildly stimulated.

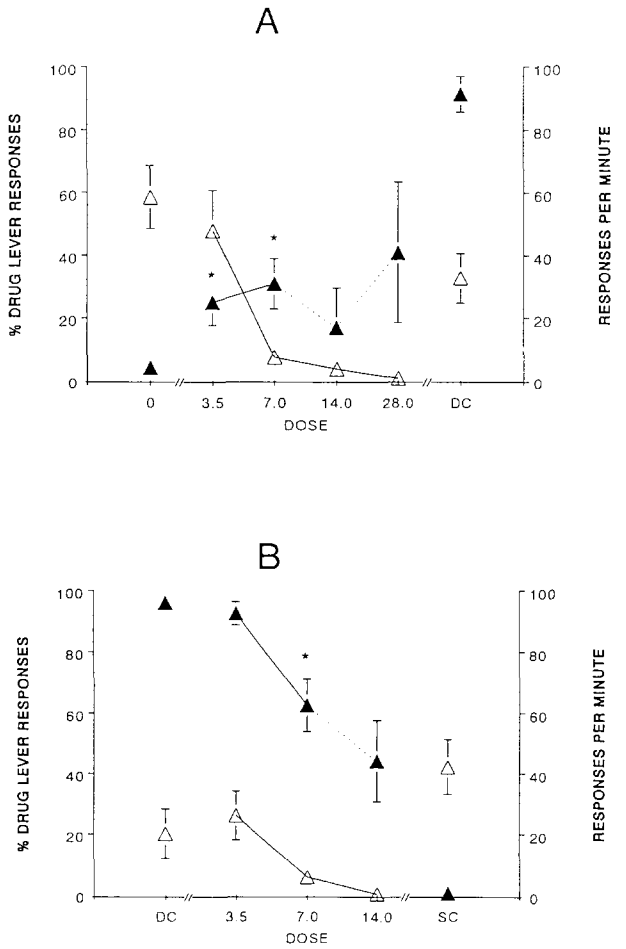

Fig. 2. Ability of (−)-DS121 to (A) substitute for, and (B) to antagonise, the discriminative stimulus properties of 5.0 mg/kg cocaine. Filled triangles represent the percentage of drug lever (DL) responses (±S.E.M.) in test sessions. Empty triangles (±S.E.M.) represent the number of responses per min at different drug doses. Ten animals participated in the substitution study and eight animals in the antagonism study. See Fig. 1 for further details.

Table 2
Percentage drug lever responding (±S.E.M) after combinations of doses of (−)-DS121 (0–3.5 mg/kg) and cocaine (0 or 2.5 mg/kg)

	Dose of (−)-DS121 (mg/kg)	
	0	3.5
Saline	1.7 ± 1.1	29.2 ± 12.0
Cocaine (0.25 mg/kg)	40.2 ± 16.0	48.3 ± 14.0

3.2. (−)-DS121 in cocaine discrimination rats

(−)DS121 (3.5–7.0 mg/kg) partially substituted for cocaine, although there was no indication of dose dependency [$F(3,24) = 31.40$, $P < 0.0001$; Fig. 2A]. Only four of ten animals responded reliably after 14.0 mg/kg (average drug lever responses: 16.9 ± 6.3%), whilst only two of five pressed after the next highest dose. No individual rat responded primarily on the drug lever (i.e. at the > 83% criterion level) after any of these doses of (−)-DS121.

(−)-DS121 (7.0 mg/kg) produced a small reduction in drug lever appropriate-responding when combined with the training dose of cocaine, whilst a lower dose was without effect [$F(3,20) = 91.27$, $P < 0.0001$; Fig. 2B]. Only three of eight animals completed ten responses after the 14.0 mg/kg dose.

In pilot work, we were unable to find an appropriate single dose of cocaine which was just subthreshold for inducing drug lever responses for all animals due to individual variability in responsiveness to the drug. Therefore, the ability of (−)-DS121 to influence the cueing properties of 0.25 mg/kg cocaine was examined. The one-way ANOVA revealed a significant effect of drug condition [$F(4,27) = 8.77$, $P < 0.0001$]. (−)-DS121 (3.5 mg/kg) produced a level of drug lever appropriate-responding which was not significantly different to that observed in the vehicle session. Drug lever responding after 0.25 mg/kg cocaine was at a level intermediate to that observed in the cocaine and vehicle control sessions. This effect was not influenced at all by (−)-DS121 (Table 2).

When administered alone, (−)-DS121 dose dependently reduced response rates with a threshold dose of 3.5 mg/kg [$F(4,36) = 9.11$, $P < 0.0001$; Fig. 2A]. Rats administered cocaine responded at a slower rate than saline-treated animals [$F(3,21) = 5.03$, $P < 0.0088$]. They responded at an even slower rate when administered cocaine with 7.0 mg/kg (−)-DS121, but this effect did not reach statistical significance (Fig. 2B). In the interaction study, the ANOVA did not reveal significant effects of drug condition [$F(4,27) = 2.13$, $P > 0.05$; data not shown].

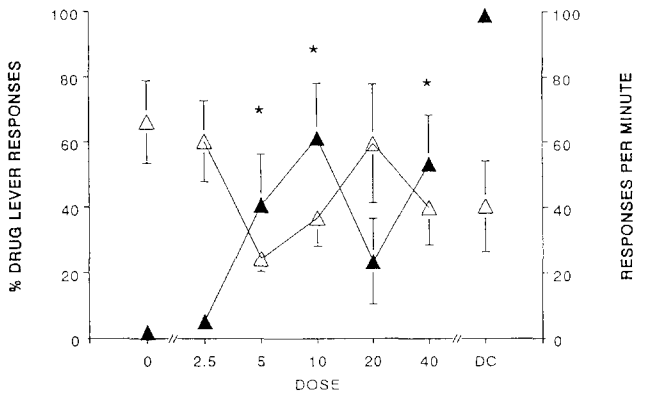

Fig. 3. Ability of caffeine to substitute for the discriminative stimulus properties of 0.5 mg/kg *d*-amphetamine. Filled triangles represent the percentage of drug lever (DL) responses (±S.E.M.) in test sessions. Empty triangles (±S.E.M.) represent the number of responses per min at different drug doses. Eight animals participated in the study. See Fig. 1 for further details.

3.3. Caffeine in d-amphetamine discrimination rats

Administration of caffeine resulted in an increase in drug lever-appropriate responding [$F(6,42) = 7.90$, $P < 0.0001$]. Duncan's tests revealed a significant partial substitution with 5–10 and 40 mg/kg, but not with the 20 mg/kg dose (Fig. 3). In the vast majority of cases, animals responded almost entirely on either the drug- or saline-appropriate lever. Caffeine failed to significantly reduce response rates [$F(6,42) = 2.08$, $P < 0.09$; Fig. 3).

4. Discussion

The phenylpiperidine (−)-DS121 has recently been shown to be a mild stimulant, inducing a reserpine-sensitive increase in locomotor stimulation, a conditioned place preference, and a marked elevation of dopamine release. These effects were suggested to be due to selective blockade of dopamine D_2/D_3 autoreceptors. Higher doses of (−)-DS121 also reduced the locomotor stimulation produced by apomorphine and *d*-amphetamine, suggesting some degree of drug interaction with postynaptic dopamine receptors (Svensson et al., 1993; Waters et al., 1993).

In the present studies, (−)-DS121 (3.5–14.0 mg/kg) failed to produce discriminative effects which were identical to those produced by either *d*-amphetamine (0.5 mg/kg) or cocaine (5.0 mg/kg). Although a significant partial substitution was noted in both cases, the mean levels of drug lever-appropriate responding were low (21–39%), there was no indication of dose dependency, and no individual animal responded entirely on the drug-appropriate lever in any experimental session. In contrast, rats trained to discriminate *d*-amphetamine from saline responded entirely on the drug lever in a significant number of experimental sessions when administered caffeine. The overall level of partial substitution with this drug was higher than that noted with (−)-DS121. Previous studies have shown that caffeine can partially substitute for both *d*-amphetamine and cocaine (Holloway et al., 1985; Harland et al., 1989).

The increase in drug lever responding with (−)-DS121, which occurred with doses shown to increase dopamine release (Sonesson et al., 1993; Waters et al., 1993), suggests some degree of similarity between the subjective effects of (−)-DS121 and the psychostimulants, albeit less than that noted between caffeine and *d*-amphetamine. Alternatively, it might be argued that the (−)-DS121-induced increase in drug lever responding is of no direct relevance, reflecting simply a disruptive effect of the drug resulting in loss of discriminative control. There are some indications from the *d*-amphetamine interaction study that this explanation is less likely. A combination of subthreshold doses of (−)-DS121 (3.5 mg/kg) and *d*-amphetamine (0.0625 mg/kg) produced a level of drug lever-appropriate responding which was significantly higher than that observed with either drug alone. This effect suggests a synergistic interaction between the drugs, although complete substitution was again not observed. This form of synergistic interaction was not apparent when a higher dose of (−)-DS121 was used, probably reflecting a shift from selective autoreceptor antagonism to an additional blockade of postsynaptic D_2/D_3 receptors.

Postsynaptic dopamine receptor actions of (−)-DS121 are indicated by the ability of the drug to reduce the discriminative effects of both *d*-amphetamine and cocaine. In these cases, there was a tendency for dose-dependent effects of the drug, although such a conclusion is limited because only some animals responded at high doses. (−)-DS121 also reduced the locomotor activity produced by *d*-amphetamine and apomorphine, and it increased intracranial self-stimulation thresholds in a manner similar to dopamine receptor antagonists (Bozarth, personal communication). Moreover, the drug reduced the break point for animals self-administering cocaine on a progressive ratio schedule, and reduced responding on a standard fixed ratio schedule (Smith et al., 1993).

The present mixed agonist/antagonist-like activity of (−)-DS121 is similar to that which we have previously reported for the partial dopamine D_2 receptor agonists preclamol [(−)-3-PPP] (which has a similar chemical stucture) and SDZ 208-911 in *d*-amphetamine discrimination rats (Exner and Clark, 1992). The particular effect exerted by preclamol was shown to depend on the dose of *d*-amphetamine used. Preclamol partially antagonised the discriminative effects of the training dose of *d*-amphetamine, but it significantly

enhanced drug lever-appropriate responding when combined with an ineffective dose of the psychostimulant. No change in discrimination was noted when preclamol was administered with an intermediate dose of *d*-amphetamine. These results were interpreted in terms of classical receptor theory, which predicts that the effects of a partial agonist depend in part on the relative concentrations of transmitter and drug competing for common receptor sites (Kenakin, 1987).

These findings suggest a partial dopamine receptor agonist profile for (−)-DS121. For example, the drug enhanced the discriminative (present findings) and locomotor activating (Waters et al., 1993) effects of a low dose of *d*-amphetamine, whilst acting as an antagonist when administered with a higher dose of the psychostimulant. Moreover, whilst (−)-DS121 reduced the discriminative effects of the training dose of cocaine, it failed to influence the mean drug lever response levels observed after a lower dose of cocaine that engendered only 50% drug lever responding. However, there is one important difference between (−)-DS121 and the partial dopamine D_2 receptor agonists preclamol and SDZ 208-911. Administration of the latter drugs, but not (−)DS121, resulted in individual animals responding entirely on the drug lever in substitution tests (Exner and Clark, 1992). Therefore, if (−)-DS121 does exert partial agonist effects, it clearly possesses lower intrinsic efficacy at postsynaptic D_2/D_3 receptors than preclamol and SDZ 208-911.

Callahan and colleagues (Callahan et al., 1992) have reported that the putative dopamine autoreceptor antagonist (+)-AJ76 (Svensson et al., 1986) partially substitutes for cocaine; we have noted similar effects of this drug in animals trained to discriminate *d*-amphetamine from saline (Furmidge, 1990). However, (+)-AJ76 failed to attenuate the discriminative effects of cocaine (Callahan et al., 1992). In contrast, (−)-DS121 exerted weak antagonism in the present cocaine (and *d*-amphetamine) animals. These findings, along with the observation that (+)-UH232 (Svensson et al., 1986) neither mimics nor antagonises the discriminative properties of cocaine (Callahan et al., 1992), indicates subtle differences in the profile of these putative dopamine autoreceptor antagonists.

As reported earlier for (+)-AJ76 (Furmidge, 1990; Callahan et al., 1992), (−)-DS121 produced a clear dose-dependent reduction in overall response levels when administered alone or in combination with the psychostimulants. However, animals did not resemble those administered dopamine receptor antagonists; they remained alert and, in fact, generally appeared mildly stimulated. Similar observations have been noted in the intracranial self-stimulation paradigm (Bozarth, personal communication).

The present study demonstrates that the phenylpiperidine derivative (−)-DS121 exerts both agonist- and antagonist-like activity in animals trained to discriminate psychostimulants from saline. (−)-DS121 has recently been reported to induce a conditioned place preference in rats, suggesting that it may possess rewarding or euphoric properties. However, the drug does not support self-administration behaviour when substituted for cocaine in previously trained rats; rather, as outlined above, (−)-DS121 acts more like a dopamine receptor antagonist in this paradigm (Smith et al., 1993). In rats responding for electrical stimulation of the brain, the drug has been found to either significantly increase stimulus thresholds (Bozarth, personal communication), in a manner similar to dopamine antagonists, or produce a non-significant trend in this direction (Kling-Peterson et al., 1994). These findings, along with the present drug discrimination data, provide encouraging evidence to suggest that (−)-DS121 would not possess a significant abuse potential. In addition, this drug and others with a similar profile could prove to be useful therapeutic agents for psychostimulant abuse. Given their mild stimulant effects, they might be effective in reducing craving during withdrawal from either amphetamine or cocaine. Future studies assessing the subjective effects of these drugs in human volunteers are of particular importance in this regard.

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