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**A PROFILE OF THE PHARMACOTHERAPEUTIC POTENTIAL OF
THE DOPAMINE AUTORECEPTOR ANTAGONIST
(-)-DS121 USING THE SELF-ADMINISTRATION
PARADIGM IN THE RAT**

By

ANDRA MARIE SMITH

**A thesis submitted to the Faculty of Graduate Studies
and Research in partial fulfilment of the
requirements for the degree of
Master of Science**

Department of Psychology

Carleton University

Ottawa, Ontario

June, 1993

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ABSTRACT

The novel dopamine autoreceptor antagonist (-)-DS121 was tested for its ability to alter cocaine self-administration behavior in rats. Two schedules of reinforcement, fixed ratio (FR1) and progressive ratio (PR), were used to assess the affects of (-)-DS121 on rate of self-administration and breaking point. Pretreatment with (-)-DS121 resulted in a reduced rate of cocaine self-administration behavior, a delayed onset of responding and a significant reduction of breaking point. (-)-DS121 was also substituted for cocaine to determine its abuse liability. (-)-DS121 failed to maintain self-administration behavior. The results from these three experiments demonstrate that (-)-DS121 is effective in blocking the reinforcing properties of cocaine, and that (-)-DS121 does not act as a reinforcer. This profile of (-)-DS121 suggests that it is a promising new candidate for the treatment of cocaine abuse.

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INTRODUCTION

In recent years, cocaine abuse has escalated to overwhelming proportions in North American society. Cocaine has emerged as one of the most abused drugs and in 1984, The National Institute of Drug Addiction labelled cocaine as "the drug of greatest national health concern" (Pollin, 1984).

Cocaine has been implicated in complications of nerve conduction, the cardiovascular system, the sympathetic nervous system and of course, the central nervous system (Ritz et al., 1987). Emergency rooms and hospital beds continue to be filled with patients exhibiting the secondary effects of cocaine abuse such as stroke, respiratory arrest, seizures, psychosis, and myocardial infarction (Estroff and Gold, 1985; Pollack et al., 1989; Rowbotham and Lowenstein, 1990). In 1985, there were approximately 2000 cocaine related deaths in the U.S. alone (NIDA, 1988). There has also been a marked increase in cocaine related fatalities, the crime rate has escalated as addicts require money to support their addiction, and more babies are being born to addicted mothers. For these reasons, there has been a concerted effort to increase knowledge about cocaine and its powerful effects.

Clinical settings, support groups (Ehrlich and McGeehan, 1985; Acee and Smith, 1987; Vandegaer, 1989), self-esteem literature, public awareness campaigns, interpersonal psychotherapy (Horberg and Scholl, 1983; Rounsaville et al., 1985) and other drug abuse related programs have been developed to combat the increasingly prevalent abuse of cocaine. While case studies have documented the very important

role of such treatment interventions, to date they have not resulted in significant or widespread reductions in cocaine abuse (Rounsaville et al., 1985; Galanter, 1987; Home, 1988). More promising success in promoting cocaine abstinence in addicted patients has been obtained when these programs have been combined with the results from another avenue of study, pharmacotherapy.

PHARMACOTHERAPEUTIC INTERVENTIONS

In the last decade, several promising drug therapies have emerged. Certain tricyclic antidepressants, such as desipramine, have appeared to facilitate initial cocaine abstinence (Gawin et al., 1989b). Bromocriptine and amantadine are dopamine (DA) agonists which have reduced or eliminated the withdrawal symptoms associated with cocaine addiction (Giannini et al., 1987; Tennant and Sagherian, 1987; Teller and Devenyi, 1988; Giannini et al., 1989; Pike, 1989). Bromocriptine and desipramine, along with the neuroleptic, flupenthixol decanoate, have also shown promise in their ability to reduce or eliminate cocaine craving (Gawin and Kleber, 1984; Dackis et al., 1985; Gawin et al., 1989a; Jaffe et al., 1989). Another drug shown to have potential is phenelzine. It reverses the biochemical damage caused by chronic cocaine use (Golwyn, 1988) and like the drug buprenorphine, causes extreme dysphoria and physical unpleasantness if cocaine is administered (Resnick and Resnick, 1984; Kosten et al., 1989). While these and other drug therapies are promising in open trials, there has been limited success in double blind studies and

there remains no substantially effective treatment for this potential "epidemic" and its attendant drains on the personal, physical, social and financial fabric of individuals and society. Further research is, therefore, critical.

THE SELF-ADMINISTRATION PARADIGM

For ethical reasons and because of the difficulty in studying the neurophysiological and neuroanatomical effects of cocaine abuse on human subjects, it is essential to have an animal model of cocaine addiction. The study of self-administration behavior by laboratory animals has provided a useful model. In the self-administration paradigm, animals must perform a learned behavioral response, such as lever pressing, to obtain access to the test drug. The drugs that consistently lead to this behavior are considered reinforcing and are likely to have abuse potential in humans. Its accuracy in predicting the propensity of a drug to be abused by humans is now well accepted and is supported by clinical evidence (Griffiths and Balster, 1979; Griffiths et al, 1979, 1980; van Ree, 1979; Schuster and Thompson, 1969; Thompson and Unna, 1977; Griffiths et al., 1978). This paradigm also allows for an examination of the neuroanatomy and neurophysiology involved in the reinforcing effects of these drugs of abuse, including cocaine.

Self-administration studies have shown that like humans, rats, squirrel monkeys, rhesus monkeys, pigtail macaques, baboons, cats, and dogs, will voluntarily self-administer cocaine (Fischman et al., 1990; Pickens, 1968; Goldberg,

1973; Aiger and Balster, 1978; Bedford et al., 1978; Young and Woods, 1980; Griffiths et al., 1975; Balster et al., 1976; Risner and Jones, 1975). Cocaine has, therefore, been classified as one of the most powerful reinforcers in existence (Aiger and Balster, 1978; Woods et al., 1987).

FIXED RATIO SCHEDULE OF REINFORCEMENT

Another use of the self-administration technique is to test drugs which may reduce or eliminate the reinforcing effects of cocaine. On a fixed ratio schedule of administration, it is possible to detect changes in the rate of drug intake. On this schedule, animals that have limited access to infusions of cocaine will stabilize their intake with a regular pattern of lever pressing and therefore, receive approximately the same amount of drug each test session. It has also been demonstrated that if the dose of cocaine is reduced, the rate of self-administration increases as the animals respond more frequently to receive the equivalent amount of cocaine. Rate of self-administration behavior is therefore dependent on the injection dose of cocaine.

Yokel and Wise (1976, 1975) drew the analogy that this increased responding following a reduction in unit dose was similar to the increase in responding observed following DA receptor blockade. This compensatory increase in rate of responding following pretreatment with certain DA antagonists has accordingly been interpreted as a reduction in the reinforcing properties of the cocaine.

PROGRESSIVE RATIO SCHEDULE OF REINFORCEMENT

While fixed ratio schedules of reinforcement have been used in most self-administration experiments, the more complex, progressive ratio (PR) schedule of reinforcement, can provide an additional dependent variable in the study of self-administration behavior. A progressive ratio schedule of reinforcement has emerged as a robust and sensitive schedule that produces significant and interpretable results for self-administration experiments. Hodos (1961) developed this technique using rats that pressed a lever on a schedule of reinforcement in which the number of lever presses required on each consecutive session increased by a fixed increment. He showed that there was a relationship between variations in reward and deprivation parameters and the performance of the rats on the PR schedule.

These results suggested that the PR schedule of reinforcement may be useful in evaluating the relative rewarding properties of certain self-administrable drugs and the motivation of an animal to respond for that drug. The dependent variable used in PR experiments is "breaking point" and has been shown to be a viable addition to rate as a measure of drug reinforcement (Griffiths et al., 1975; Thompson, 1977; Griffiths et al., 1978; Bedford et al., 1978; Griffiths et al., 1979; Hoffmeister, 1979; Risner and Silcox, 1981; Risner and Goldberg, 1983; Roberts, 1989; Roberts et al., 1989a, 1989b). The studies in this thesis use both rate and breaking point as dependent variables.

The response criteria for a PR schedule has varied among self-administration

experiments. Several studies have increased the number of responses required to receive a drug infusion daily (Griffiths et al., 1975, 1978, 1979; Hoffmeister, 1979; Risner and Silcox, 1981; Risner and Goldberg, 1983) while others have increased the response requirement repeatedly throughout the test session (Bedford et al., 1978; Roberts, 1989; Roberts et al., 1989a, 1989b). At some point, the reinforcing effects fail to support continued responding and lever responding ceases. The point at which the animal fails to respond corresponds to the breaking point which is defined as the last response criteria met by the animal prior to a period of one or more hours of no drug infusions. This variable is considered to be a sensitive measure of the maximum reinforcing effect.

THE ROLE OF BIOGENIC AMINES IN COCAINE REINFORCEMENT

Cocaine acts at the synapse to inhibit the reuptake of dopamine (DA), norepinephrine (NE) and serotonin (5-HT), thus prolonging the duration of stimulation of the postsynaptic receptor by these monoamines. The first self-administration experiment that implicated the catecholamines as possible substrates for stimulant reward was reported by Pickens, Meisch and Dougherty (1968). They demonstrated that alpha-methyl-p-tyrosine (AMPT), a tyrosine hydroxylase inhibitor which prevents synthesis of the catecholamines, was effective in blocking the reinforcing properties of methamphetamine.

It was then that the catecholamine hypothesis emerged. It was suggested that

there existed one or more central neural systems which played a critical role in reward phenomena and that form a critical link in the catecholamine-containing neuron reinforcing system (Wise, 1978).

THE ROLE OF NOREPINEPHRINE IN COCAINE REINFORCEMENT

Several studies have eliminated NE as a primary participant in the manifestation of cocaine reward. Many antagonist pretreatments such as phentolamine, phenoxybenzamine and propranolol have not proven to be effective in altering the rate of cocaine self-administration (Wilson and Schuster, 1974; Risner and Jones, 1976; DeWit and Wise, 1977). Roberts and colleagues (1977) have also shown that 6-hydroxydopamine lesions of ascending NE systems do not affect cocaine self-administration behavior. These results and others confirm that NE does not play a primary role in the reinforcing properties of cocaine self-administration.

THE ROLE OF SEROTONIN IN COCAINE REINFORCEMENT

Most of the research on the role of serotonin in self-administration behavior has been performed on amphetamine self-administration. Cocaine self-administration experiments have, however, had similar results. Recently, fluoxetine, a specific 5-HT reuptake inhibitor, has been shown to reduce breaking points and reduce rate of cocaine self-administration (Richardson and Roberts 1991; Carroll et al., 1990a).

McGregor and colleagues (1993) also observed that L-tryptophan, a 5-HT precursor, attenuated cocaine intake on a PR schedule of reinforcement while Carroll and associates (1990b) found that L-tryptophan also attenuated the rate of cocaine self-administration. However, Lacosta (1993) showed that three 5-HT antagonists, MDL 72222, ketanserin and methysergide, had no effect on cocaine self-administration. These results suggest that 5-HT is an important neurotransmitter in the reinforcing properties of cocaine but the nature of its effect remains unclear.

THE ROLE OF DOPAMINE IN COCAINE REINFORCEMENT

DA has emerged as the most significant neurotransmitter involved in the rewarding effects of cocaine. Dopamine antagonists, such as, haloperidol (Roberts and Vickers, 1984), perphenazine (Johanson et al., 1976), pimozide (Yokel and Wise, 1975; Roberts et al., 1977), butaclamol (Yokel and Wise, 1975), chlorpromazine (Wilson and Schuster, 1972), alpha-flupenthixol, suipiride, methoclopramide, thioridazine (Roberts and Vickers, 1984), spiperone, and SCH 23390 (Koob et al., 1987) have all produced increases in the rate of cocaine self-administration.

Results from experiments using a PR schedule of reinforcement also clearly support the suggestion that DA receptor blockade antagonizes cocaine reinforcement (Roberts, 1992). Haloperidol (Roberts and Vickers, 1984) attenuates breaking point on a PR schedule, suggesting that there is a blockade or reduction of the reinforcing properties of the cocaine which result in a lack of motivation for the rats to press the

lever for cocaine.

It can be concluded that cocaine works with dopaminergic neuronal mechanisms to produce reinforcement and maintain self-administration behavior (Roberts et al., 1980). These results and those from neuroleptic trials in the clinical setting (Gawin and Kleber, 1984; Dackis et al., 1985; Gawin et al., 1989a; Jaffe et al., 1989) emphasize the importance of testing the effects of dopaminergic drugs on cocaine self-administration behavior.

THE SEARCH FOR THERAPEUTIC DOPAMINERGIC AGENTS

It has also been important to synthesize and pharmacologically characterize new compounds structurally related to DA with the aim to find agents with a selective affinity for DA-receptors or DA-receptor subtypes. In the 1960's there was an explosion of research into this area and DA antagonists, including the major tranquilizers and antipsychotics, were discovered to play a major role in treating certain psychological disorders, such as schizophrenia. It was then discovered that DA agonists, such as L-DOPA and apomorphine, were effective in treating patients with Parkinsons disease (McDermid et al., 1975).

In an attempt to develop novel, more selective, DA-receptor active agents with potential clinical benefits in the treatment of disorders related to DA dysfunction, a body of research was directed toward DA autoreceptor agonists which were found to produce less sedation and debilitating motor impairments characteristic of the

prevailing drugs being used. The piperidine 3-(3-hydroxyphenyl)-N-n-propylpiperidine (3-PPP) and some 5,6-dioxy-2-aminotetralins were discovered to be effective DA autoreceptor agonists (Hacksell et al., 1981; Hjorth, 1983; Wikstrom et al., 1984, 1985; Johansson et al., 1985).

It was then determined that postsynaptic DA antagonism was also important for potential clinically therapeutic agents as psychosis was ameliorated by drugs which block postsynaptic DA receptors, such as haloperidol. Structure-activity relationship studies which design derivatives and enantiomers of prospective drugs like apomorphine, 3-PPP and the 2-aminotetralins revealed that the (+)-enantiomers of the 2-aminotetralins and the (-)-enantiomer of 3-PPP were effective in both agonist activity at the DA autoreceptor and DA antagonist activity at the postsynaptic receptor (Hjorth et al., 1983; Johansson et al., 1985; Wikstrom et al., 1985; Wikstrom et al., 1984; Svensson et al., 1985). It was also shown, with both behavioral and biochemical data, that the antidopaminergic effect of the (-)-S isomer of 3-PPP was preferentially limbic explaining its ability to prevent serious motor disturbances associated with classical postsynaptic DA receptor antagonists (Hjorth, 1983; Hjorth et al., 1983). These drugs provided new insight into central DA function and were considered as a promising prototype in the development of "2nd generation" antipsychotic and antidyskinetic agents, lacking in the serious disabling extrapyramidal motor side effects (Hjorth et al., 1983; Arnt et al., 1983; Svensson et al., 1985; Wikstrom et al., 1985; Johansson et al., 1985).

UPJOHN'S SYNTHESIS OF NOVEL DOPAMINE COMPOUNDS FOR THE POTENTIAL TREATMENT OF COCAINE ABUSE

Due to cocaine's strong interaction with dopaminergic neuronal mechanisms and the effects that DA antagonists have had on cocaine self-administration it was considered that developments of compounds similar to the drugs mentioned above may play a significant role in the pharmacological treatment of cocaine abuse.

Further development in this area of research has led to the synthesis of a new class of DA receptor antagonists which has provided an alternate avenue of investigation for the treatment of cocaine abuse. This new class of drug, which includes the aminotetralins, (+)-AJ76 (cis-(+)-5-methoxy-1-methyl-2-(n-propylamino)tetralin) and (+)-UH232 (cis-(+)-5-methoxy-1-methyl-2-(di-n-propylamino)tetralin), has mixed agonist/antagonist properties (Svensson et al., 1986; Richardson et al., 1993; Piercey et al., 1992).

Agonists, such as apomorphine, enhance the stimulation of postsynaptic receptors and typically result in locomotor stimulation while antagonists, like haloperidol, block the postsynaptic DA receptors and cause sedation, akinesia and catalepsy. Paradoxically, (+)-AJ76 and (+)-UH232, behave biochemically as DA antagonists, increasing DA synthesis and metabolite formation while behaviorally resulting in weak locomotor stimulation, typical of DA agonists. The antagonist effects result from blocking postsynaptic DA receptors, specifically D3 receptors,

whereas the stimulant effects are dependent on the ability of the drugs to increase DA release by preferentially blocking presynaptic autoreceptors which normally suppress dopaminergic firing rates, synthesis and release (Svensson et al., 1986). Several experiments have been performed with these drugs and their pharmacological profile suggests that while postsynaptic antagonism may block cocaine's euphoric effects, autoreceptor antagonism may prevent the craving and anhedonia experienced during cocaine withdrawal by evoking its weak stimulant effect similar to that of cocaine.

In cocaine self-administration experiments, (+)-AJ76, resulted in a decrease in both the time animals took to self-administer their first six infusions of cocaine (ie. increased rate of intake) and decreased breaking points on a PR schedule of reinforcement. (+)-AJ76 was also able to delay the onset of lever responding for cocaine (Richardson et al., 1993). The results of these experiments suggest that the antagonist/agonist properties of this class of drugs may be useful in the treatment of cocaine abuse.

A PROFILE OF THE NOVEL DA AGONIST/ANTAGONIST (-)-DS121

(-)-DS121, (S-(-)-3-(3-cyanophenyl)-N-n-propyl piperidine) is the most recently synthesized member of this new class of drugs and is a nitrile analogue of 3-PPP as well as an analogue of (+)-AJ76. Consequently, (-)-DS121 may have similar effects on cocaine self-administration but it is more soluble than (+)-AJ76 and therefore easier to test.

Locomotor activity studies have shown that (-)-DS121 causes a mild (+50%) behavioral stimulation in actively exploring rats. In habituated rats, the activity level is potentiated to approximately 700% of controls (Svensson et al., 1993).

Biochemical and physiological data show that (-)-DS121 increases DA synthesis and metabolism and reverses the apomorphine-induced depression of DA synthesis in gamma-butyrolactone (GBL) treated rats. (-)-DS121 also reverses apomorphine- and d-amphetamine-induced depression in substantia nigra and ventral tegmental area neurons, increases DA release in a TTX- and Ca- dependent manner, both in the dorsal and ventral striatum and has a preference for the DA D3 receptor in *in vitro* binding studies (Waters et al., 1993). (-)-DS121 also produces a conditioned place preference (Kling-Petersen et al., 1993). These data demonstrate that (-)-DS121 expresses its antagonist activity at the impulse-controlling autoreceptors similar to (+)-AJ76 and (+)-UH232 and has similar agonist properties that cause motor stimulation and place preference.

(-)-DS121 differs from (+)-AJ76 and (+)-UH232 in results obtained from intracranial self-stimulation experiments. (-)-DS121 does not produce an increase in reward threshold in ICSS experiments, whereas both (+)-AJ76 and (+)-UH232 produce a highly significant increase in reward thresholds (Kling-Petersen et al., 1993). This suggests that (-)-DS121 may have stronger stimulant properties than the other drugs in this class of stimulants.

To date no research has been performed on the effects of (-)-DS121 on cocaine self-administration behavior or on the ability of (-)-DS121 to support self-

administration behavior itself. It would appear, from the above mentioned data, that the antagonist/agonist properties of (-)-DS121 would render it beneficial to the treatment of cocaine abuse. Therefore, the following experiments were performed to investigate the abuse potential of (-)-DS121, and its effects on cocaine self-administration.

EXPERIMENTS

A FR1 schedule of reinforcement was used in Experiment 1 to determine the effects of an acute IP pretreatment of (-)-DS121 on the rate of cocaine self-administration in rats. Experiment 2 was designed to investigate the effect of an acute IP injection of (-)-DS121 on the breaking point of animals self-administering cocaine. Experiment 3 was performed to examine the positive reinforcing properties of (-)-DS121 by examining its ability to maintain self-administration behavior.

GENERAL METHODS

Subjects

Male Wistar rats (Woodlyn Farms, Guelph, Ont.) weighing approximately 300-350 g at the start of each experiment were doubly housed in quarantine for one week. The rats were then moved to another vivarium room with a 12 hour reversed light dark cycle (lights off at 10:00). Food and water were available *ad libitum*.

Training

The rats were food deprived for 24 hours prior to food training. Training involved lever pressing for Noyse food pellets in an operant chamber. A FR1 schedule of reinforcement was used and each rat performed two training sessions, pressing over 200 times each trial.

Cannulation

The cannulae used were continuous from the jugular vein to a fluid swivel. A small length of Silastic tubing was fitted into a wider piece of Silastic tubing which was pushed through a small hole in a piece of Marlex mesh. The Silastic tubing was led through a protective spring and a piece of PE 260 was used to stiffen this leash assembly. The end of the spring was wound through the mesh and the joint was covered with Silastic Silicone sealant so the Silastic tubing was stabilized at a 90 degree angle with no crimp in the cannula. The distal end of the tubing was firmly sealed to a fluid swivel with heat shrink.

Once trained, the rats were deeply anaesthetized with Somnotol (60 mg/kg, IP) and implanted with chronically indwelling jugular cannulae (described above).

Lengthwise incisions were made in the mid scapular area of the back and over the right jugular vein on the ventral side of the animal. The Silastic tubing was then led subcutaneously from the dorsal excision to the ventral opening. The jugular vein was exposed and punctured just enough to feed the tubing through to the heart. The vein was then tied off to stabilize the tubing and the ventral incision was sutured. The dorsal incision was sutured with two of the sutures penetrating the Marlex mesh of the cannula. The rats were then placed in operant chambers and the fluid swivel of the cannula was connected to a counterbalance mechanism on the chamber. The swivels were also attached to a 10 ml syringe which was placed in a syringe driver that activated the release of a drug at 5 RPM. The rats were given access to food and water *ad libitum* and were allowed to recover for approximately 24 hours.

The plexiglass operant chambers were used for both testing and housing and were equipped with water bottle holders, counterbalance supports, stimulus lights and removable levers. A pan of shavings with a wire grid top was used as the floor of the chamber with the shavings being changed every three days.

Following recovery from surgery, rats were trained to self-administer cocaine on a FR1 schedule of reinforcement. Each lever press, in a daily five hour session, resulted in an injection of 0.6 mg of cocaine/0.12 ml saline over 5 seconds. A stimulus light lit up for 20 seconds following the injection and any response on the lever for this 20 seconds was not recorded and no injection resulted (time-out). Each session began with the introduction of the lever into the cage and one "free", priming infusion. Once animals reached a stable baseline of three consecutive days of

responding with no more than ± 2 infusions difference between the days, one of three experiments was performed.

Drug

Cocaine hydrochloride was supplied by NIDA (Bethesda, MD) and was prepared in 0.9% saline. DS-121 was received from The Upjohn Company (Kalamazoo, MI). The (-)-DS121 was prepared each day of use and 0.9% saline was used as the vehicle solution.

EXPERIMENT 1

METHODS AND RESULTS

Methods

Once a stable baseline of responding for cocaine was achieved (as above), a pretreatment injection of one of three doses of (-)-DS-121 (vehicle, 7.5 mg/kg, 15 mg/kg) was administered intraperitoneally (IP) half an hour prior to the session. The vehicle pretreatment was saline (0.5 ml). Animals were not included in the study if their rates did not return to baseline levels in the days following the injection. A oneway ANOVA was performed on the number of injections of cocaine self-administered in the 5 hour test session and a Student-Newman-Keuls test was performed to identify significant effects ($p < 0.05$).

The time to initiate the first injection of cocaine was analyzed at the 15 mg/kg dose of (-)-DS121. A Kruskal-Wallis oneway ANOVA was performed followed by Mann-Whitney U tests to reveal significant relationships.

Results

Figure 1 illustrates the rate of cocaine self-administration following intraperitoneally administered (-)-DS121 (vehicle, 7.5 mg/kg, 15 mg/kg). It would appear that there is a dose dependent decrease in rate of responding. It is clear that the (-)-DS121 had an effect on each animals' rate of responding and Figure 2 shows, distinctly, how the animals at both 7.5 and 15 mg/kg varied in their rate of responding for cocaine. Figure 3 shows the event records of the eight animals

FIGURE 1. The effect of (-)-DS121 pretreatment on the rate of cocaine self-administration in 5 hours, on a FR schedule of reinforcement. The mean ($\pm$ SEM) number of injections for the day of pretreatment with (-)-DS121 (7.5 or 15 mg/kg) or saline (1.0 ml) are shown. Eight animals were tested at the 15 mg/kg dose and six were tested following saline and the 7.5 mg/kg dose.

FIGURE 2. The effect of (-)-DS121 pretreatment on the rate of cocaine self-administration by individual rats on a FR schedule of reinforcement. A scatterplot of the number of cocaine injections self-administered in 5 hours for individual rats following pretreatment with saline (open squares), 7.5 and 15 mg/kg (-)-DS121 (filled squares).

FIGURE 3. The event records of eight animals pretreated with (-)-DS121 (15 mg/kg) including a representative baseline event record. Percent baseline scores are also included for each event record. Each vertical line represents an injection of cocaine for a 5 hour test session.

RAT NUMBER

EVENT RECORD

PERCENT BASELINE

BASELINE

97.2

1

8.3

2

17

3

54.6

4

62.5

5

38

6

114

7

126

8

120

pretreated with 15 mg/kg of (-)-DS121 on a FR1 schedule of reinforcement and illustrates, again, the variability that resulted from administration of (-)-DS121. This obvious variability explains the lack of significant DOSE effect when the mean number of injections in the 5 hour session following pretreatment were submitted to a oneway ANOVA ($F=2.104$, $df(2,17)$, $p<0.153$).

The variability in Figure 3, for the time to initiate responding for cocaine, also explains the lack of overall significance revealed with a Kruskal-Wallis oneway ANOVA of the time taken to initiate responding following pretreatment with (-)-DS121 ($p<0.055$). There was, however, a significant delay at the 15 mg/kg dose of (-)-DS121 when data were analyzed by a Mann-Whitney U test ($p<0.046$). Rats 1,2,4,5 and 8 delayed the onset of responding for cocaine by 10 minutes or more compared with the baseline day. Figure 4 shows the event records of the animals pretreated with the 7.5 mg/kg dose of (-)-DS121. Although the results are not significant when submitted to a Mann-Whitney's U test ($p<0.081$), rats 4,5,6 showed a delayed response pattern following administration of (-)-DS121.

FIGURE 4. The event records of the six rats pretreated with (-)-DS121 (7.5 mg/kg) including a representative baseline event record. The percent baseline scores of rate are included for each event record. Each vertical line represents an injection of cocaine over 5 hours.

RAT NUMBER

EVENT RECORD

PERCENT BASELINE

BASELINE

97.2

1

93.3

2

106

3

108

4

113

5

115

6

117

EXPERIMENT 2

METHODS AND RESULTS

Methods

Subsequent to a stable baseline (as above), rats were changed to a PR schedule of reinforcement. There was an exponential increase in the number of responses required to receive an infusion of cocaine (1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, etc.). Following three days of stable baseline, with breaking points that did not vary by more than ± 2 from each other, rats were injected (IP) with one of three doses of DS-121 (vehicle, 7.5 mg/kg, 15 mg/kg) half an hour prior to their five hour session. Saline (0.5 ml) was used as the vehicle pretreatment. The rats were returned to a FR1 schedule for three days following 4 days post-treatment to ensure the cannulae were not malfunctioning.

The dependent variable used for the statistical analysis was breaking point. Breaking point was defined as the number of infusions received prior to a period of one hour with no injections. Breaking points were analyzed with a oneway ANOVA and a Student-Newman-Keuls analysis ($p < 0.05$).

Results

Figure 5 demonstrates the results of experiment 2 which measured the ability or motivation of the rats to "work" for injections of cocaine on a PR schedule of

FIGURE 5. The effect of (-)-DS121 pretreatment on the breaking points reached by animals self-administering cocaine on a PR schedule of reinforcement. The mean ($\pm$ SEM) breaking point values for the day of pretreatment with (-)-DS121 (7.5 and 15 mg/kg) and saline (1.0 ml) are shown. Six animals were tested at each dose. An asterisk (*) indicates a statistically significant change in breaking point from saline levels ($p < 0.000$) as revealed by Student-Newman-Keuls analysis ($p < 0.05$).

of reinforcement. The breaking point data were submitted to a oneway ANOVA and revealed a significant overall DOSE effect ($F = 17.06$, $df(2,15)$, $p < 0.000$) when compared with the saline scores. Student-Newman-Keuls analysis demonstrated that the 15 mg/kg dose of (-)-DS121 significantly reduced breaking point, while 7.5 mg/kg (-)-DS121 did not have a significant effect. A representative example of the cumulative records of animals pretreated with (-)-DS121 and a baseline day are presented in Figure 6.

Several animals failed to return to baseline levels of responding following pretreatment with (-)-DS121. These animals did not show cannulae malfunction, however, as they returned to a high level of responding when changed to a FR1 schedule of reinforcement.

FIGURE 6. The cumulative records of one rat self-administering cocaine on a PR schedule of reinforcement and pretreated with (-)-DS121. Baseline data are included to compare with the (-)-DS121 pretreated day. Vertical lines represent injections of cocaine and five more days of self-administration were completed to ensure cannulae functioning. Data for the (-)-DS121 drug days were then analyzed by a oneway ANOVA comparing each dose of (-)-DS121 with saline. Multiple comparisons were made using Student-Newman-Keuls tests for significance at $p < 0.05$).

EXPERIMENT 3

METHODS AND RESULTS

This experiment was designed to determine if (-)-DS121 is a self-administrable drug. After a stable baseline of cocaine self-administration was achieved on a FR1 schedule of reinforcement, the cocaine in the syringes was replaced with saline or one of three doses of (-)-DS121 (0.01, 0.32, 1.0 mg/kg/injection). Five days of lever pressing for (-)-DS121 on the FR1 schedule followed and the syringes were then filled.

Figure 7 shows a significant attenuation of self-administration behavior with the substitution of (-)-DS121 for cocaine. The mean number of injections self-administered on the (-)-DS121 or saline substituted days (days 4-8) were submitted to a oneway ANOVA and a significant overall DOSE effect was revealed ($F=3.6$, $df(3,16)$, $p<0.036$). Student-Newman-Keuls analysis revealed that the 1.0 mg/kg/injection dose of (-)-DS121 was the only dose of (-)-DS121 that was significantly different from saline ($p<0.05$). It is clear from Figure 6 that the (-)-DS121 resulted in less self-administration behavior than that of saline and that the effect was dose dependent. The 1.0 mg/kg/injection dose of (-)-DS121 was also significantly lower than the 0.1 and 0.32 mg/kg/injections doses of (-)-DS121 as shown by Student-Newman-Keuls analysis ($p<0.05$).

FIGURE 7. The self-administration behavior of animals given access to (-)-DS121. The mean ($\pm$ SEM) number of injections of (-)-DS121 self-administrated following a stable baseline pattern of cocaine self-administration. Four doses of (-)-DS121 (0.1, 0.32, 1.0 mg/kg/injection) and saline are shown. Day 1 to 3 represent access to cocaine while days 4 to 8 represent access to the test drug solution. Day 9 to 13 represent the replacement of test solution with cocaine.

DISCUSSION

In experiment 1, it was shown that (-)-DS121 is successful in altering the pattern of cocaine self-administration behavior in rats. (-)-DS121 pretreatment was effective in decreasing the rate of cocaine self-administration in five of eight animals and delayed the onset of responding for cocaine in several rats. Experiment 2 supported this ability of (-)-DS121 to alter cocaine self-administration behavior as the results revealed a significant reduction in breaking points following pretreatment with (-)-DS121. Experiment 3 showed that (-)-DS121 was, however, not effective in maintaining self-administration behavior itself. It is well accepted that most drugs which are not self-administered by laboratory animals do not have abuse liability in humans (Griffiths et al., 1979, 1980; van Ree, 1979; Thompson and Unna, 1977; Collins et al., 1984). Therefore, the negative result of Experiment 3 would indicate that intravenous (-)-DS121 does not have reinforcing properties in rats and would be unlikely to have abuse potential in the human population.

The search for pharmacotherapies of cocaine addiction have been focused on dopaminergic compounds. Traditionally, pretreatment with DA antagonists, such as haloperidol and alpha-flupenthixol, have produced an increase in the rate of cocaine self-administration behavior in laboratory animals. This has been interpreted as compensation for the blockade of the reinforcing properties of cocaine caused by the pretreatment. Therefore, these drugs, although effective in blocking the reinforcing properties of cocaine, have the potential to increase addicts' cocaine consumption as

they attempt to overcome the blockade of its reinforcing effects. DA antagonists are also not self-administered by laboratory animals which suggest that they are not reinforcing agents. This is not surprising as it is also well-established that DA antagonists cause dysphoria and extrapyramidal side effects that result in poor patient compliance.

Agonists, in contrast, may be more effective in treating cocaine abuse. Dopamine agonists, such as bromocriptine, apomorphine and others (Dackis and Gold, 1985; Caine and Koob, 1993) have been tested as potential treatments for cocaine abuse. These drugs reduce the craving for cocaine and reduce the intake of cocaine without resulting in the dysphoric side effects associated with DA antagonist drugs. However, these drugs substitute for cocaine and are self-administered themselves. This suggests that the agonist itself may become the abused substance simply replacing the cocaine.

The ideal pharmacotherapy for cocaine abuse would, therefore, be a combination of an antagonist's ability to block the euphoria of cocaine and an agonist's ability to reduce drug intake while not causing any dysphoria or extrapyramidal side effects. It would also be essential that the treatment drug would not itself be self-administered. The results from Experiment 1-3 indicate that (-)-DS121 has this curious mixture of agonist/antagonist properties and provides an "atypical" antagonist profile that is distinguishable from classical neuroleptics.

The ability of (-)-DS121 to reduce breaking points in Experiment 2 is a property characteristic of "typical" DA antagonists, such as haloperidol (Roberts et

al., 1989b) (see Figure 8) and suggest that (-)-DS121 blocks the reinforcing effects of cocaine. Other antagonist properties of (-)-DS121 have been determined from previous behavioral, biochemical and physiological data. These experiments showed that (-)-DS121 blocks the cocaine cue (Piercey et al., 1993). (-)-DS121 also has been shown to increase DA synthesis and metabolism and reverse the apomorphine-induced depression of DA synthesis in gamma-butyrolactone (GBL) treated rats. (-)-DS121 also reverses apomorphine- and d-amphetamine- induced depression in substantia nigra and ventral tegmental area neurons (Waters et al., 1993). These data demonstrate that (-)-DS121 expresses its antagonist activity at the impulse-controlling autoreceptors.

Some of the agonist properties of (-)-DS121 were revealed in the results from Experiment 1. DA agonists, such as methamphetamine, phenmetrazine, apomorphine, bromocriptine, piribedil, amphetamine and cocaine have been shown to decrease rate of cocaine self-administration (Pickens et al., 1968; Wilson and Schuster, 1973; Yokel and Wise, 1978; Herling et al., 1979; Hubner and Koob, 1990; Kleven and Woolverton, 1990). The observed delay in the onset of responding in Experiment 1 is another agonist characteristic of (-)-DS121. It is clear from Figure 9 that amphetamine, a typical agonist, both decreases rate and delays the onset of responding. The ability to delay the craving for cocaine has only been observed following pretreatment with (-)-DS121, amphetamine and (+)-AJ76 at the highest dose (30 mg/kg).

Previous experiments with (-)-DS121 have also revealed the agonist properties

FIGURE 8. The computer-reconstructed cumulative record showing the effect of haloperidol on baseline levels of cocaine self-administration behavior on a progressive ratio schedule of reinforcement. Each vertical increment indicates lever responses and arrows represent an injection of cocaine.

FIGURE 9. The computer-reconstructed cumulative record showing the effect of amphetamine on baseline levels of cocaine self-administration behavior on a progressive ratio schedule of reinforcement. Vertical increments represent lever responses and arrows indicate one injection of cocaine.

of (-)-DS121. Locomotor activity studies have shown that (-)-DS121 acts as a stimulant by increasing locomotor activity (Svensson et al., 1993). Piercey and colleagues (1993) reported that (-)-DS121 partially generalizes to cocaine in a drug discrimination task. It has also been found, in 2-deoxyglucose (2DG) experiments, that (-)-DS121 and cocaine, when administered separately, highlight similar brain regions. When the two drugs are administered together, however, the highlighted regions of the brain resemble those following saline (Piercey et al., 1993). As previously mentioned, (-)-DS121 also produces a conditioned place preference and does not produce an increase in reward threshold in intracranial self-stimulation experiments (Kling-Petersen et al., 1993). These results are characteristic of typical DA agonist drugs (van der Kooy, 1987).

Aside from these exciting agonist/antagonists properties of (-)-DS121, Experiment 3 demonstrated the inability of (-)-DS121 to maintain self-administration behavior. This is typically associated with drugs that have no abuse potential in the human population. These results coincide with ICSS experiments that demonstrate that (-)-DS121 does not result in an increase in reward threshold (Kling-Petersen et al., 1993) as demonstrated by most addictive drugs, such as amphetamine and cocaine (Reid, 1987).

The synthesis of the novel DA autoreceptor antagonists, (-)-DS121, (+)-AJ76 and (+)-UH232 has provided researchers with a unique class of drugs that combines the antagonizing properties of typical DA antagonists, like haloperidol and the agonistic properties of the typical DA agonists, like amphetamine. These autoreceptor

antagonists vary in the ratio of stimulation produced to the amount of DA antagonist activity and this variability places this class of drug on a spectrum for these characteristics. (-)-DS121 appears to be at the most stimulant end of the spectrum while (+)-UH232 is at the neuroleptic end and (+)-AJ76 represents the middle of the spectrum.

A comparison of the three drugs of this novel class shows that (-)-DS121 is most effective in attenuating breaking point and does so at a lower dose than both (+)-AJ76 and (+)-UH232 (see Figure 10). (-)-DS121 also causes a more profound delay in responding at a lower dose than (+)-AJ76 (Richardson, 1993). (-)-DS121 does not cause a significant increase in rate of cocaine self-administration as is observed following pretreatment with (+)-AJ76 (Richardson, 1993). It has also been shown that (-)-DS121 shows a slightly higher preference for the DA autoreceptor than (+)-AJ76 or (+)-UH232. This may explain the more profound ability of (-)-DS121 to reduce the reinforcing properties of cocaine by causing locomotor stimulation.

It has been suggested recently that the D3 DA receptor may be a useful target for new pharmacotherapies for cocaine abuse (Caine and Koob, 1993). The D3 receptor is preferentially localized in mesolimbic and mesocortical areas (Sokoloff et al., 1990) known to be the neuroanatomical substrates for cocaine's rewarding effects (Evenden and Ryan, 1988; Goeders and Smith, 1983). Although it is uncertain at this time whether the preferential binding that this class of drugs have for the D3 receptor is related to their stimulant effects, it is possible to speculate that (-)-DS121 binds more preferentially to the D3 receptor than (+)-AJ76 or (+)-UH232 and may

therefore be more successful at treating cocaine abuse.

From this intriguing combination of postsynaptic and autoreceptor antagonism, it appears that (-)-DS121 has the potential to postsynaptically antagonize cocaine's euphoric effects, while evoking a stimulant effect that is effective in preventing the craving and anhedonia associated with cocaine withdrawal. Further to these exciting results, experiment 2 revealed a carryover effect following pretreatment with (-)-DS121 when animals were self-administering cocaine on a PR schedule of reinforcement. The animals in this experiment never returned to baseline values of breaking points. The most common reason for an unstable baseline is cannulae defect, however, when the rats on PR were returned to a FR1 schedule of reinforcement the rate of responding was similar to when the rats were training to press for cocaine. This disruption in responding suggests that (-)-DS121 has long lasting effects on the reinforcing properties of cocaine.

Taken together, the results from experiments 1-3, suggest that (-)-DS121 is an excellent candidate for the treatment of cocaine addiction.

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