1

OF/DE

1

PM-1 3 1/2" x 4" PHOTOGRAPHIC MICROCOPY TARGET
NBS 1010a ANSI/ISO #2 EQUIVALENT

PRECISIONSM RESOLUTION TARGETS

Direction des acquisitions et
des services bibliographiques

395 rue Wellington
Ottawa (Ontario)
K1A 0N4

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30, et ses amendements subséquents.

Canadă

**AN ANALYSIS OF THE POTENTIAL PHARMACOTHERAPEUTIC
EFFICACY OF AMPEROZIDE IN AN ANIMAL
MODEL OF COCAINE ADDICTION**

**BY
MONIQUE ANDREWS**

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

Department of Psychology

Carleton University

Ottawa, Canada

May, 1994

copyright 1994
Monique Andrews

National Library
of Canada

Acquisitions and
Bibliographic Services Branch

395 Wellington Street
Ottawa, Ontario
K1A 0N4

Bibliothèque nationale
du Canada

Direction des acquisitions et
des services bibliographiques

395, rue Wellington
Ottawa (Ontario)
K1A 0N4

Copyright - votre responsabilité

Copyright - votre responsabilité

The author has granted an irrevocable non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of his/her thesis by any means and in any form or format, making this thesis available to interested persons.

L'auteur a accordé une licence irrévocable et non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de sa thèse de quelque manière et sous quelque forme que ce soit pour mettre des exemplaires de cette thèse à la disposition des personnes intéressées.

The author retains ownership of the copyright in his/her thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without his/her permission.

L'auteur conserve la propriété du droit d'auteur qui protège sa thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

ISBN 0-315-92995-2

Canada

Name MONTIQUE ANDREWS

Dissertation Abstracts International is arranged by broad, general subject categories. Please select the one subject which most nearly describes the content of your dissertation. Enter the corresponding four-digit code in the spaces provided.

Physiological Psychology

SUBJECT TERM

0989 U.M.I.
SUBJECT CODE

Subject Categories

THE HUMANITIES AND SOCIAL SCIENCES

COMMUNICATIONS AND THE ARTS

Architecture 0729
Art History 0377
Cinema 0900
Dance 0378
Fine Arts 0357
Information Science 0723
Journalism 0391
Library Science 0399
Mass Communications 0708
Music 0413
Speech Communication 0459
Theater 0465

EDUCATION

General 0515
Administration 0514
Adult and Continuing 0516
Agricultural 0517
Art 0273
Bilingual and Multicultural 0282
Business 0688
Community College 0275
Curriculum and Instruction 0727
Early Childhood 0518
Elementary 0524
Finance 0277
Guidance and Counseling 0519
Health 0680
Higher 0745
History of 0520
Home Economics 0278
Industrial 0521
Language and Literature 0279
Mathematics 0280
Music 0522
Philosophy of 0998
Physical 0523

Psychology 0525
Reading 0535
Religious 0527
Sciences 0714
Secondary 0533
Social Sciences 0534
Sociology of 0340
Special 0529
Teacher Training 0530
Technology 0710
Tests and Measurements 0288
Vocational 0747

LANGUAGE, LITERATURE AND LINGUISTICS

Language 0679
General 0289
Ancient 0290
Linguistics 0291
Modern 0401
Literature 0294
General 0295
Classical 0297
Comparative 0298
Medieval 0316
Modern 0591
African 0305
American 0352
Asian 0355
Canadian (English) 0593
Canadian (French) 0311
English 0312
Germanic 0315
Latin American 0313
Middle Eastern 0314
Romance 0501
Slavic and East European 0503

PHILOSOPHY, RELIGION AND THEOLOGY

Philosophy 0422
Religion 0318
General 0321
Biblical Studies 0319
Clergy 0320
History of 0322
Philosophy of 0469
Theology 0323

SOCIAL SCIENCES

American Studies 0323
Anthropology 0324
Archaeology 0326
Cultural 0327
Physical 0310
Business Administration 0272
General 0770
Accounting 0454
Banking 0338
Management 0385
Marketing 0501
Canadian Studies 0503
Economics 0505
General 0508
Agricultural 0509
Commerce/Business 0510
Finance 0511
History 0358
Labor 0366
Theory 0351
Folklore 0578
Geography 0366
Gerontology 0351
History 0578
General 0578

Ancient 0579
Medieval 0581
Modern 0582
Black 0328
African 0331
Asia, Australia and Oceania 0332
Canadian 0334
European 0335
Latin American 0336
Middle Eastern 0333
United States 0337
History of Science 0585
Law 0398
Political Science 0615
General 0616
International Law and Relations 0617
Public Administration 0814
Recreation 0452
Social Work 0626
Sociology 0627
General 0938
Criminology and Penology 0631
Demography 0628
Ethnic and Racial Studies 0629
Individual and Family Studies 0630
Industrial and Labor Relations 0700
Public and Social Welfare 0344
Social Structure and Development 0709
Theory and Methods 0999
Transportation 0453
Urban and Regional Planning 0453
Women's Studies 0453

THE SCIENCES AND ENGINEERING

BIOLOGICAL SCIENCES

Agriculture 0473
General 0285
Agronomy 0475
Animal Culture and Nutrition 0476
Animal Pathology 0359
Food Science and Technology 0478
Forestry and Wildlife 0479
Plant Culture 0480
Plant Pathology 0817
Plant Physiology 0777
Range Management 0746
Wood Technology 0306
Biology 0287
General 0308
Anatomy 0309
Biostatistics 0379
Botany 0329
Cell 0353
Ecology 0369
Entomology 0793
Genetics 0410
Limnology 0307
Microbiology 0317
Molecular 0416
Neuroscience 0433
Oceanography 0821
Physiology 0778
Radiation 0472
Veterinary Science 0786
Zoology 0760
Biophysics 0425
General 0996
Medical 0425

EARTH SCIENCES

Biochemistry 0425
Geochemistry 0996

Geodesy 0370
Geology 0372
Geophysics 0373
Hydrology 0388
Mineralogy 0411
Paleobotany 0345
Paleoecology 0426
Paleontology 0418
Paleozoology 0985
Palynology 0427
Physical Geography 0368
Physical Oceanography 0415

HEALTH AND ENVIRONMENTAL SCIENCES

Environmental Sciences 0768
Health Sciences 0566
General 0300
Audiology 0992
Chemotherapy 0567
Dentistry 0350
Education 0769
Hospital Management 0758
Human Development 0982
Immunology 0564
Medicine and Surgery 0347
Mental Health 0569
Nursing 0570
Nutrition 0380
Obstetrics and Gynecology 0354
Occupational Health and Therapy 0381
Ophthalmology 0571
Pathology 0419
Pharmacology 0572
Pharmacy 0382
Physical Therapy 0573
Public Health 0574
Radiology 0575
Recreation 0575

Speech Pathology 0460
Toxicology 0383
Home Economics 0386

PHYSICAL SCIENCES

Pure Sciences

Chemistry 0485
General 0749
Agricultural 0486
Analytical 0487
Biochemistry 0488
Inorganic 0738
Nuclear 0490
Organic 0491
Pharmaceutical 0494
Physical 0495
Polymer 0754
Radiation 0405
Mathematics 0605
Physics 0986
General 0606
Acoustics 0608
Astronomy and Astrophysics 0748
Atmospheric Science 0607
Atomic 0798
Electronics and Electricity 0759
Elementary Particles and High Energy 0609
Fluid and Plasma 0610
Molecular 0752
Nuclear 0756
Optics 0611
Radiation 0463
Solid State 0463
Statistics 0346

Applied Sciences

Applied Mechanics 0984
Computer Science 0984

Engineering 0537
General 0538
Aerospace 0539
Agricultural 0540
Automotive 0541
Biomedical 0542
Chemical 0543
Civil 0544
Electronics and Electrical 0348
Heat and Thermodynamics 0545
Hydraulic 0546
Industrial 0547
Marine 0794
Materials Science 0548
Mechanical 0743
Metallurgy 0551
Mining 0552
Nuclear 0549
Packaging 0765
Petroleum 0554
Sanitary and Municipal System Science 0790
Geotechnology 0428
Operations Research 0796
Plastics Technology 0795
Textile Technology 0994

PSYCHOLOGY

General 0621
Behavioral 0384
Clinical 0622
Developmental 0620
Experimental 0623
Industrial 0624
Personality 0625
Physiological 0989
Psychobiology 0349
Psychometrics 0632
Social 0451

The undersigned hereby recommend to
the Faculty of Graduate Studies and Research
acceptance of the thesis submitted by

Monique Andrews

in partial fulfillment of the requirements
for the degree of Master of Science

A handwritten signature in black ink, appearing to be "G. M. H.", written over a horizontal dashed line.

Chairman, Department of Psychology

A handwritten signature in black ink, appearing to be "C. J. B.", written over a horizontal dashed line.

Thesis Supervisor

Carleton University

May, 1994

ABSTRACT

Amperozide (APZ), which has been classified as an atypical neuroleptic, was examined for its ability to alter cocaine reinforcement. The effects of APZ pretreatment were examined on IV cocaine self-administration reinforced on a fixed (FR) and a progressive ratio (PR) schedule of reinforcement as well as a discrete trials paradigm. Rats were implanted with a chronically indwelling IV cannula and were trained to self-administer cocaine on an FR 1 schedule. Following stable baseline rates of responding rats were tested in one of three procedures. APZ, (2.5 mg/kg, SC) had no effect on rate of cocaine intake on rats responding on an FR 1 schedule. However, APZ pretreatment significantly reduced breaking points across a unit injection dose of cocaine (0.18, 0.37, 0.75, 1.5 mg/kg/inj) in a dose dependent manner on animals responding on a PR schedule. Another group of rats was tested using a discrete trials procedure whereby the rats' access to cocaine was limited to two 10 minute trials every half hour continually over a number of days. This procedure yields a circadian pattern of drug intake restricted to the dark/active phase of the cycle. During each trial animals could receive a single injection of cocaine (1.5 mg/kg/inj) on an FR 1 or an FR 5 schedule. APZ (0.625, 1.25, 2.5 mg/kg, SC) pretreatment produced a dose dependent reduction in drug intake. An additional group of cocaine naive rats was trained to respond for food reinforcement (45 mg Noyes food pellet) on a PR schedule and APZ pretreatment produced a slight but significant dose dependent decrease in overall food intake. These data suggest that APZ has potential therapeutic properties in the treatment of cocaine addiction.

ACKNOWLEDGEMENTS

I would like to thank Dr. David Roberts for providing me with the opportunity to carry out this research and for making the work not only interesting but also enjoyable. Thank you to Mr. Gary Vickers and Mr. Paul Mendella for their technical assistance and Dr. Ikuko Webster for her statistical consulting. Also thanks to Dr. Alison McGregor for the many long sessions of scientific debate. Finally, special thanks go to my parents for providing the support and encouragement I needed to complete this project.

TABLE OF CONTENTS

ABSTRACT	i
ACKNOWLEDGEMENTS	ii
TABLE OF CONTENTS	iii
LIST OF FIGURES	iv
INTRODUCTION	1
Dopamine	2
Serotonin	3
Amperozide	5
Behavioral Profile of APZ	5
Neurochemical Profile of APZ	7
Mechanism of Action of APZ	8
Amperozide and Cocaine	10
 EXPERIMENT 1	 12
Methods and Results	13
Discussion	16
 EXPERIMENT 2	 18
Methods and Results	20
Discussion	26
 EXPERIMENT 3	 27
Methods and Results	27
Discussion	29
 EXPERIMENT 4	 34
Methods and Results	35
Discussion	44
 GENERAL DISCUSSION	 46
 REFERENCES	 50

LIST OF FIGURES

FIGURE 1.	The effect of APZ (2.5 mg/kg, SC) pretreatment on the rate of cocaine self-administration on an FR 1 schedule.	18
FIGURE 2.	The effect of APZ (2.5 mg/kg, SC) pretreatment on breaking point reached by rats self-administering cocaine on a progressive ratio schedule.	24
FIGURE 3.	The cumulative record of baseline and treatment days of a rat administering cocaine on a PR schedule of reinforcement.	25
FIGURE 4.	The effect of APZ pretreatment on total number of reinforcements obtained by bar pressing for food on a progressive ratio.	31
FIGURE 5.	The event records of one animal responding for food on a PR schedule on baseline and treatment days.	32
FIGURE 6.	Illustrates the differences in percent of baseline reached on cocaine and food reinforced responding on the PR schedule.	33
FIGURE 7.	The effect of APZ pretreatment (1.25 & 2.5 mg/kg, SC) on number of cocaine infusions obtained over 24 hours on FR 1 and FR 5 schedules in the discrete trials paradigm.	38
FIGURE 8.	The event records of one animal self-administering cocaine on FR 1 and FR 5 schedules of reinforcement in the discrete trials on 2 baseline days and day of APZ treatment (1.25 & 2.5 mg/kg, SC).	39
FIGURE 9.	The effect of APZ pretreatment (0.625 & 1.25 mg/kg, SC) on number of cocaine infusions obtained over 24 hours on FR 1 and FR 5 schedules in the discrete trials paradigm.	42
FIGURE 10.	The event records of one animal self-administering cocaine on FR 1 and FR 5 schedules of reinforcement in the discrete trials on 2 baseline days and day of APZ treatment (0.625 mg/kg, SC).	43
TABLE 1.	Effect of different manipulations on rate of cocaine intake under an FR schedule and break point under a PR schedule	23

INTRODUCTION

Cocaine abuse in North America has reached epidemic proportions in the last decade and a considerable amount of research has focused on discovering a means to alleviate this problem. The abuse liability of cocaine has been well established in both the clinical and the experimental setting, yet no form of effective intervention has been offered. Numerous pharmacological agents have been analyzed for their therapeutic potential in the treatment of cocaine addiction; the tricyclic antidepressant, desipramine, the neuroleptic flupenthixal decaonate, (Gawin et al., 1989a: 1989b), DA agonists, amantadine and bromocriptine (Dackis et al., 1985; Tennant and Sagherian, 1987) just to name a few. However, while some have shown promise in open clinical trials, there has been no pharmacotherapy discovered to date that has demonstrated significant success.

Analysis of the neural substrates believed to underly cocaine reinforcement indicate that catecholamines play a key role in the reward properties of this drug (Roberts, 1992). It has been well established that cocaine acts as a reuptake inhibitor at dopamine (DA) as well as noradrenaline (NA) and serotonin (5-HT) terminals, which suggests, that the behavioral effects of cocaine are mediated via multiple neurotransmitter interactions. A brief analysis of the DA and 5-HT systems follows.

DOPAMINE

The theory that DAergic neural systems play a critical role in cocaine reinforcement and that the maintenance of this drug taking behavior is reliant on the DA mesocorticolimbic pathway is well supported (Roberts et al., 1980; Koob, et al., 1987). Work from the Roberts' laboratory has indicated that pharmacological manipulation of DA systems can produce an attenuation of the reinforcing properties of cocaine. Most of the research to date has focused on an examination of compounds that act as agonists or antagonists. Specifically, DA antagonists such as pimozide (Yokel and Wise, 1975), haloperidol, alpha-flupenthixal, sulpiride, metoclopramide, thioridazine, (Roberts and Vickers, 1984), spiperone and SCH 23390 (Koob et al., 1987) have all been shown to increase cocaine intake. Such increases have been interpreted as a decrease in reinforcing effect (see below). Lesion studies have also bolstered the DA theory of cocaine reinforcement: 6 OHDA lesions of the mesolimbic DA system abolish responding for cocaine (Pettit, et al., 1984; Roberts and Zito, 1987).

It is without question that the pharmacological manipulations induced following lesion or drug therapy do indeed block cocaine reinforcement via modulation of the DAergic system. Although many of these agents appear to be successful at decreasing some aspect of cocaine reinforcement, these findings do not necessarily translate into a clinical treatment. For example, drugs that attenuate the reinforcing properties of cocaine may in fact increase drug intake; eg., haloperidol, which has also been shown to actually increase cocaine intake with repeated injections

locomotor activity is mediated via indirect blockade of reuptake mechanisms in the NAC.

MECHANISM OF ACTION OF APZ

Typical neuroleptics owe their therapeutic properties to an antagonism of the dopamine D₂ receptor (Meltzer & Stahl, 1976); however, the selective blockade of this receptor complex is also believed to be responsible for the motor disturbances caused by typical neuroleptics. Atypical neuroleptics, like APZ, are shown to have a rather weak affinity for the D₂ receptor (Meltzer, Matsubara & Lee, 1989). It follows that the antipsychotic action of atypical neuroleptic drugs cannot merely be attributed to their D₂ antagonistic properties. Furthermore, APZ is demonstrated to have a potent affinity for the 5-HT₂ receptor complex and it is postulated that its 5-HT antagonistic properties may be responsible for the differences between APZ and other neuroleptics (Svartengren and Simonsson, 1990).

Although APZ appears to attenuate psychostimulant induced increases in DA, the behavioral and neurochemical data suggest this is not mediated via a direct antagonism of the DAergic system. It has generally been accepted that elevated levels of locomotor activity following psychostimulant administration are mediated via enhanced dopaminergic activity. APZ is demonstrated to produce a potent blockade of amphetamine-induced hypermotility; given its weak affinity for D₁ and D₂ receptors, it is not likely that a postsynaptic DA effect is responsible (Svartengren and

1990). By depleting a cocaine sensitive system of 5-HT we may actually be increasing the reinforcing components of this drug and thereby potentiating an increase in cocaine intake. Therefore, it can be argued that 5-HT may play an aversive role and therefore an augmentation of serotonergic transmission would function to decrease cocaine reinforcement. This theory is also supported by data obtained with the 5-HT compounds fluoxetine and L-tryptophan. Fluoxetine, a specific 5-HT reuptake inhibitor and L-tryptophan, a 5-HT precursor, have been shown to attenuate the rewarding aspects of cocaine (Richardson and Roberts, 1991; McGregor, LaCosta, and Roberts, 1993). Accordingly, it is probable that an interaction between the serotonergic and DAergic systems may yield an effective therapeutic response.

However, surprising results have been obtained with some of the 5-HT specific antagonists: MDL 72222, ketanserin and methysergide have no effect on cocaine intake (Lacosta and Roberts, 1993). Furthermore, compounds like fluoxetine have demonstrated variable results across studies: acute vs. repeated treatment with this compound have effected a decrease and an increase, respectively, in cocaine intake (Richardson and Roberts, 1991; Richardson, Smith and Roberts, 1994). Although the argument that the serotonergic system is involved in some aspects of cocaine reinforcement is certainly feasible, these data present a complicated profile for 5-HT.

AMPEROZIDE

The search for effective antipsychotic drugs that do not produce motor disturbances or other adverse side effects has led to the development of a class of compounds that may differ both behaviorally and neurochemically from the typical class. APZ is one such compound that differs from typical neuroleptics with respect to two important features. While typical neuroleptics are effective at alleviating the positive symptoms of schizophrenia, they have very little effect on negative symptoms (Meltzer, Sommers & Luchins, 1986). By contrast, APZ has proven to be effective in the treatment of both positive (hallucinations and delusions) and negative symptoms (withdrawal, lack of motivation and anhedonia) in schizophrenics in early clinical trials (Axelsson et al, 1991). Also, unlike typical neuroleptics, e.g., haloperidol, APZ does not appear to produce motor side effects nor does it induce catalepsy (Gustafsson & Christensson, 1990a), ataxia or sedation (Gustafsson & Christensson, 1990b).

BEHAVIORAL PROFILE OF AMPEROZIDE

The behavioral data published on APZ is limited; however, research to date has reported both similarities and differences in comparison to other typical neuroleptics. APZ is similar to typical neuroleptics in the ability to attenuate locomotion. APZ was demonstrated to dose dependently decrease spontaneous locomotor activity in rats (Kimura, Nomikos & Svensson, 1993), as well as locomotor

activity and exploratory behavior in mice (Gustafsson & Christensson, 1990a). However, in contrast to the motor side effects seen with typical neuroleptics, APZ produced no extrapyramidal side effects in monkeys (Christensson and Gustafsson, 1985). Finally, whereas typical neuroleptics appear to block aggression only in doses that produce sedation and ataxia, APZ appears to have potent anti-aggressive properties without inducing these side effects (Christensson and Bjork, 1990).

Rats show an increase in locomotor activity following administration of psychomotor stimulants (Swerdlow et al., 1986). APZ pretreatment has been demonstrated to attenuate both cocaine and amphetamine-induced hypermotility (Kimura et al., 1993). However, unlike typical neuroleptics such as haloperidol, it appears to have no effect on amphetamine induced stereotypy (Gustafsson & Christensson, 1990). The locomotor effects observed following neuroleptic administration are believed to be mediated via DA receptor blockade (for review see Meltzer & Nash, 1991). It is generally believed that amphetamine induced stereotypy is due to an enhanced DAergic transmission in the striatum (STRM), whereas hypermotility is associated with elevated DA release in the nucleus accumbens (NAC). Given APZ's lack of effect on amphetamine-induced stereotypies, these data suggest a limbic rather than striatal mode of action (Gustafsson & Christensson, 1990a).

NEUROCHEMICAL PROFILE OF AMPEROZIDE

Microdialysis studies have offered a profile of APZ that further implicates a limbic mode of action. APZ induces increases in DA turnover throughout mesolimbic as well as mesocortical brain sites (Pettersson, Johannessen, Hulthe and Enge, 1990). Increases in extracellular DA have been observed in the NAC, (Kimura et al., 1993; Ichikawa & Meltzer, 1992) and medial prefrontal cortex (mPFC) (Pehek, Meltzer and Yamamoto, 1993) following treatment with APZ. By contrast, typical neuroleptics, e.g., haloperidol, have a predominantly striatal effect with relatively slight effects on cortical DA (Pehek et al., 1993). Measures of DA metabolism and rate of synthesis also indicate a specific limbic site of action for APZ. Following APZ administration, increased synthesis and turnover of DA are evident primarily in limbic brain areas, which differs significantly from typical neuroleptics that tend to produce much larger increases in striatal areas. Although these data are not conclusive, they provide strong evidence in support of a mesolimbic site of action for APZ.

Commensurate with APZ's attenuating effect on psychostimulant-induced locomotor activity, it also appears to antagonize psychostimulant-induced increases in extracellular DA concentrations. Pretreatment with APZ inhibits the ability of d-amphetamine to increase DA release in the NAC (Ichikawa & Meltzer, 1992). The inhibition of DA release in the NAC may underly APZ's attenuation of stimulant-induced locomotor activity. Furthermore, the inability of APZ to attenuate amphetamine-induced stereotypy may be due to its lack of D₂ antagonism in the striatum. Finally, it is possible that APZ's ability to block amphetamine-induced

locomotor activity is mediated via indirect blockade of reuptake mechanisms in the NAC.

MECHANISM OF ACTION OF APZ

Typical neuroleptics owe their therapeutic properties to an antagonism of the dopamine D₂ receptor (Meltzer & Stahl, 1976); however, the selective blockade of this receptor complex is also believed to be responsible for the motor disturbances caused by typical neuroleptics. Atypical neuroleptics, like APZ, are shown to have a rather weak affinity for the D₂ receptor (Meltzer, Matsubara & Lee, 1989). It follows that the antipsychotic action of atypical neuroleptic drugs cannot merely be attributed to their D₂ antagonistic properties. Furthermore, APZ is demonstrated to have a potent affinity for the 5-HT₂ receptor complex and it is postulated that its 5-HT antagonistic properties may be responsible for the differences between APZ and other neuroleptics (Svartengren and Simonsson, 1990).

Although APZ appears to attenuate psychostimulant induced increases in DA, the behavioral and neurochemical data suggest this is not mediated via a direct antagonism of the DAergic system. It has generally been accepted that elevated levels of locomotor activity following psychostimulant administration are mediated via enhanced dopaminergic activity. APZ is demonstrated to produce a potent blockade of amphetamine-induced hypermotility; given its weak affinity for D₁ and D₂ receptors, it is not likely that a postsynaptic DA effect is responsible (Svartengren and

Simonsson, 1990). Moreover, the failure of APZ to attenuate apomorphine-induced activity and stereotypy indicates that it does not block postsynaptic DAergic receptors (Waters, Pettersson, Carlsson and Svensson, 1989). Given the complex profile offered, it is possible that APZ effects a functional interaction between different transmitter systems and it is probable that there is more than one pharmacological action of this drug.

It has been hypothesized that the antipsychotic properties of APZ may be associated with 5-HT₂ antagonism. The ability of APZ (Axelsson et al., 1991) and other atypical neuroleptics (Ugedo, Grenhoff and Svensson, 1989) to produce fewer motor side effects may be related to an antagonism of the 5-HT₂ receptor (Eriksson, 1990). Binding studies have shown APZ to possess a potent affinity for the 5-HT₂ receptor, (Eriksson, 1990; Svartengren and Simonsson, 1993), however, contradictory results have been observed in 5-HT systems. Both increases (Kimura et al., 1993) and no effect (Ichikawa & Meltzer, 1992) of APZ have been measured in the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA) from the STRM and NAC. Data indicating a definitive 5-HT role remains to be published; however, a modulatory role for 5-HT on DAergic transmission cannot be ruled out. An inhibitory function for 5-HT on DA has been postulated and it may be that APZ causes a disinhibition of DA via its potent 5-HT affinity. (Gustafsson and Christensson, 1990). This neuroanatomical interaction may occur via serotonergic innervation of the mesolimbic pathway including the ventral tegmental area and NAC (Meltzer and Nash, 1991) and 5-HT may serve a regulatory function on DA systems.

An additional hypothesis holds that a modulatory effect of APZ on DA transporter mechanisms. There is evidence to suggest that APZ's effect occurs at DA reuptake sites (Eriksson, 1990) acting on carrier mediated DA synthesis (Yamamoto & Meltzer, 1992). *In vitro* data demonstrated that APZ inhibited reuptake [³H]-DA in perfused rat striatal tissue as well as stimulated basal release and inhibited amphetamine-induced release of [³H]-DA in both limbic and striatal tissue (Eriksson and Christensson, 1990), indicating that APZ is functioning at the carrier mechanism for DA rather than the autoreceptor. Furthermore, APZ is similar in pharmacological consequence to other DA reuptake blockers, e.g., cocaine. APZ causes increases in DA and is effective at blocking psychostimulant-induced increases in DA. This provides a further indication that APZ is acting at the DA transporter as an uptake/carrier inhibitor (Eriksson & Christensson, 1990).

AMPEROZIDE AND COCAINE

The behavioral and pharmacological data present an interesting profile for APZ. There is sufficient evidence to suggest that APZ has a predominantly mesolimbic site of action (Gustafsson and Christensson, 1990a; 1990b), which is the same brain circuit that is believed to be intricately involved in reward processes (Roberts et al., 1980; Koob, et al., 1987). A considerable amount of evidence also implies that APZ may be acting indirectly as a competitive antagonist for uptake sites and therefore may be effective in blocking the reinforcing properties of cocaine

(Eriksson and Christensson, 1990). These hypotheses offer an explanation of APZ's influence on cocaine mediated behaviors, and although a definitive link has yet to be established, these theories provide promising support for the use of APZ in the treatment of cocaine addiction.

The use of animal models in drug dependency studies has afforded researchers an experimental approach to study the human condition. The self-administration paradigm using the rat has proved successful in elucidating fundamental factors that underlie drug taking behavior. Coupled with a rigorous investigation into the central nervous system it has led to more critical understanding of the anatomy, pharmacology and physiology of cocaine reinforcement.

APZ has recently been observed to decrease rats' preference for an oral solution of cocaine in a two-choice drug discrimination paradigm (McMillen, Jones, Hill, Williams, Bjork and Myers, 1993). Perhaps the most powerful tool to provide support to the therapeutic potential of APZ is an examination of cocaine self-administration behavior (Roberts, Corcoran and Fibiger, 1977). The present thesis offers an examination of APZ on self-administration of cocaine reinforced under a variety of schedules; specifically, fixed and progressive ratio, as well as a discrete trials procedure.

EXPERIMENT 1

The purpose of experiment 1 was to examine the effects of APZ on rate of cocaine intake. The FR 1 schedule has proven to be one of the simplest methods employed in the self administration paradigm, with the dependent variable being rate. Many drug pretreatments have been tested in this paradigm. For example, the dopamine antagonists perphenazine (Johanson et al., (1976), pimozide (Yokel and Wise, 1975; Roberts et al., 1977), butaclamol (Yokel and Wise, 1975), chlorpromazine (Wilson and Schuster, 1972), haloperidol, alpha-flupenthixal, sulpiride, metoclopramide, thioridazine (Roberts & Vickers, 1984), spiperone and SCH 23390 (Koob et al., 1987) have all produced increases in rate of cocaine self administration.

Typically, the interpretation is that an increase in rate of drug intake is indicative of a decrease in reward (Yokel and Wise, 1975; 1976). It appears that animals will alter responding to maintain a certain brain/blood level of drug and an increment or decrement in drug dose will produce a proportional change in responding. Blockade of drug reward via pharmacological manipulations typically leads to an increase in responding for the drug. Furthermore, dopamine receptor blockade is thought to be analogous to decreasing the unit dose of cocaine injection (Roberts et al., 1977).

METHODS

Experiment 1 was designed to assess the effects of APZ on rate using an FR 1 schedule of reinforcement. Animals were required to press a bar only once to receive each cocaine infusion. Once animals reached a stable baseline of responding (no more than a 10% difference across three days) the subjects were pretreated with APZ (2.5 mg/kg, SC), 20 minutes prior to the start of a cocaine self-administration session. Each self-administration session lasted for three hours a day and was run seven days a week.

An overall analysis of rate of cocaine self-administration was completed using a within subjects design oneway ANOVA for the overall main effect of treatment ($p < .01$) and Dunn's procedure was employed to analyze the simple main effect within each hour of treatment ($p < .025$). A total of 6 rats were used in this experiment.

Subjects

Male Wistar rats (Charles River, Quebec) weighing approximately 300-350g served

as subjects. Following a quarantine period of one week, rats were doubly housed in the vivarium with a 12 hour reversed light/dark cycle (lights off at 10am) until the start of the experiment. Food and water were available *ad libitum*.

Training

At the start of the experiment rats were food deprived for 24 hours prior to

food training. Animals were trained to press a lever for food reinforcement, a 45mg Noyes food pellet. An FR 1 schedule of reinforcement was used and rats were required to successfully complete two training sessions; completion of food training occurred when the animal responded at least 500 times/per session in two sessions.

Cannulation

Once trained to lever press for food, rats were anesthetized with Somnotol (60 mg/kg, IP) and implanted with a chronic indwelling silastic jugular cannula (for complete description see Roberts & Goeders, 1987). Incisions were made at the mid-scapular area of the back and over the right jugular vein on the ventral side of the animal. Silastic tubing was led subcutaneously from the dorsal incision to the ventral opening. The jugular vein was exposed and punctured to allow feeding of the silastic tubing through to the heart. The vein was tied off to stabilize the tubing and the ventral incisions sutured. The dorsal incision was sutured and the cannula secured by two sutures which penetrated marlex mesh that was connected to the cannula and sat subcutaneously in the dorsal portion of the animal. The tubing exiting the back was connected through a protective spring to a fluid swivel.

Operant testing chambers

The operant testing chambers, fashioned from plexiglass (25cm X 25cm X 25cm), were used for testing and housing of the animals. Each chamber was equipped with water bottle, counter balance mechanism, stimulus lights and

removable or retractable levers. The animals were placed in the testing apparatus post surgery and the fluid swivel of the cannula was affixed to a counterbalanced arm on the chamber. The swivel was further attached to a 10 ml syringe which was driven by a syringe driven infusion pump (Alzet, 5 rpm motor) when activated.

Cocaine training

Training consisted of daily sessions that began with the insertion of a lever into the test chamber and a single priming injection. Rats were trained to self-administer cocaine on an FR 1 schedule. Each lever press resulted in an injection of cocaine 1.5 mg/kg/inj (0.6 ml of cocaine/0.12 ml of saline) over a five second period. A stimulus light was activated for a 20 seconds following the injection and any response on the operant lever during this "time-out" was not recorded and did not result in an injection.

Drug

Cocaine hydrochloride was supplied by NIDA (Bethesda, MD) and prepared in 0.9% saline. APZ was supplied by Kabi Pharmacia (Malmö, Sweden) and was prepared fresh each day of use in 0.9% saline.

RESULTS

Experiment 1 measured the effect of pretreatment with APZ (2.5 mg/kg, SC) on rate of cocaine self-administration on a FR 1 schedule of reinforcement. The rate data were submitted to a oneway ANOVA, which failed to reveal a statistically significant effect of treatment. Figure 1 illustrates the mean ($\pm$ SEM) number of bar presses for cocaine at each hour of treatment. Post hoc analysis of simple main effects using Dunn's procedure failed to reveal significant effects within each hour of treatment; Hour 1 ($F=0.31, df(5,1)$); Hour 2, ($F=3.24, df(1,5)$); Hour3, ($F=0.0, df(1,5)$).

DISCUSSION

The results of Experiment 1 demonstrate that APZ pretreatment has no effect on rate of drug intake. These results were somewhat surprising. All neuroleptic compounds tested in this laboratory have produced compensatory increases in rate of cocaine self-administration, with the exception of clozapine (Roberts & Vickers, 1984). These include pimozide (Yokel & Wise, 1975) , alpha-flupenthixal, sulpiride, metoclopramide, thioridazine (Roberts & Vickers, 1984) , and spiperone (Koob et al., 1987). Perhaps the most robust and reproducible effects on rate have been observed with the typical neuroleptic, haloperidol, which significantly increases rate with very small doses of the drug (Roberts & Vickers, 1987). APZ, on the other hand, failed to have a significant effect on rate of cocaine intake.

Alterations in rate are difficult to interpret and it is unclear how the failure of APZ to affect rate should be explained. It may be that the APZ dose is not high enough, however this is unlikely given the effects observed in the subsequent experiments. This issue will be further addressed in Experiment 2. It can be also be argued that rate is simply not a sensitive enough measure and it is not as interpretable as one would like given the complexity of the behavior addressed. A decrease in rate of drug intake has been postulated to indicate both an increase or a decrease in reinforcement (Yokel and Wise, 1975; Wilson and Schuster, 1973). Given the conflicting explanations offered, the observation that rate is unaltered here does not necessarily lead to the conclusion that cocaine reinforcement is unaffected. Fortunately, other measures of cocaine reinforcement exist that allow the researcher a more intricate examination of self-administration behavior.

FIGURE 1.The effect of APZ pretreatment on the rate of cocaine self-administration on an FR 1 schedule in a 3 hour session. The mean ($\pm$ SEM) number of cocaine (1.5 mg/kg/inj) injections per hour at baseline (●) and day of treatment (■) with APZ (2.5 mg/kg, SC). N=6.

EXPERIMENT 2

The difficulty in interpreting rate has led to the development of different schedules of reinforcement. One such schedule is the Progressive Ratio (PR) schedule, originally developed by Hodos (1961) and since modified in this lab to provide a rate-free measure of reinforcement (Roberts, 1989; Roberts, Loh and Vickers, 1989). In this procedure, there is an exponential increase in the number of responses required to receive an infusion of cocaine. An animal must initially respond just once on the lever to receive a reinforcement and then response requirement increases along a series of increasing ratios until responding finally stops. Break point is determined by the final ratio achieved; it is defined as the number of injections received prior to a period of one hour during which a response contingency is not met.

Consistent with self-administration paradigms employing the FR schedule, PR studies have typically focused on the effects of lesion and pharmacological manipulation. However, across the variety of compounds that we have examined, there has typically been an inverse relationship between breakpoint and rate. Some of the neuroleptics, such as haloperidol, fall into this category; while demonstrating significant increases in rate, haloperidol has been shown to cause decreases in break point in the PR schedule (Roberts et al., 1989). There is more and more indication that where an alteration in breakpoint exists, rate changes in the opposite direction (see table 1). Given that APZ was observed to have no effect on rate in experiment 1,

an examination of APZ on breakpoint is crucial to our understanding of this compound in relation to cocaine reinforcement. Experiment 2 was designed to assess the effects of acute pretreatment with APZ on cocaine self-administration under a PR schedule.

METHODS

The purpose of Experiment 2 was to examine the effects of pretreatment with APZ on break point of cocaine self-administration. Once animals reached a stable baseline of responding on an FR 1 (no more than a 10% difference between the days) the subjects 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, 178, 219, 268, etc...). In this experiment the dose of cocaine was changed four times; the solution strength cycled through full strength (1.5 mg/kg/inj), one half strength (0.75 mg/kg/inj), one quarter strength (0.37 mg/kg/inj), and one eighth strength (0.18 mg/kg/inj). Subjects were offered each strength solution until three stable baseline days of responding had occurred. Following three days of stable baseline, rats were injected with APZ (2.5 mg/kg, SC) 20 minutes prior to the start of a self-administration session. Each self-administration session lasted for five hours a day and was run seven days a week. Cocaine dose was presented in a latin square design. An overall analysis of treatment was completed using a within subjects, twoway

ANOVA ($p < 0.01$) and Dunn's procedure was employed to analyze the simple main effect of treatment within dose of cocaine ($p < .025$). A total of 7 rats were used in this experiment. Surgery, cannulation, training, etc., were described in Experiment 1. methods.

RESULTS

Experiment 2 measured the effect of pretreatment with APZ (2.5 mg/kg, SC) on break point derived from a PR schedule of cocaine reinforcement. A twoway ANOVA on break point revealed a significant overall treatment effect ($F = 38.68, df(1,6) p < 0.01$) as well as a significant overall DOSE effect ($F = 5.25, df(3,18) p < 0.01$) within subjects.

Figure 2 illustrates the results of experiment 2 which measured the effect of pretreatment with APZ on mean ($\pm$ SEM) breaking points established by a PR schedule. APZ (2.5 mg/kg, SC) pretreatment significantly reduced breakpoint on responding for cocaine at 0.37, 0.75 and 1.5 mg/kg/inj doses. Post-hoc analysis of simple main effects using Dunn's procedure revealed statistical significance on the three larger doses of cocaine; 0.37 mg/kg/inj, ($F = 22.78, df(1,23) p < .025$), as well as 0.75 mg/kg/inj, ($F = 16.26, df(1,23) p < .025$) and 1.5 mg/kg/inj, ($F = 16.26, df(1,23) p < .025$). However, the post hoc analysis failed to reveal a significant effect of APZ on break point at the lowest dose of cocaine (0.18 mg/kg/inj). All animals at these three doses of cocaine showed significant reductions

in breakpoint in comparison to baseline when pretreated with APZ.

The top diagram of figure 3 illustrates an example of a representative cumulative record of animals self-administering cocaine (1.5 mg/kg/inj). The lower diagram of figure 3 illustrates the effect of APZ pretreatment (2.5 mg/kg, SC) on break point.

TABLE 1. Effect of different manipulations on rate of cocaine intake under an FR schedule and break point under a PR schedule.

	Progressive ratio breaking point	Fixed ratio rate	References
Unit dose increases	↑	↓	(Depoortere et al., 1993; Roberts et al., 1989)
amphetamine	↑	↓	in preparation
SCH 23390	↓	↑	(Depoortere et al., 1993; Hubner et al., 1991)
spiperone	↓	↑	(Hubner et al., 1991)
clozapine	↑	↓	(Loh et al., 1992; Roberts et al., 1984)
haloperidol	↓	↑	(Roberts et al., 1984)
(+)AJ 76	↓	↑	(Richardson et al., 1993)

FIGURE 2. The effect of APZ pretreatment on breaking point reached by rats self-administering cocaine on a progressive ratio schedule in a 5 hour session. The mean ($\pm$ SEM) break point is represented across four doses of cocaine (0.18, 0.37, 0.75, 1.5 mg/kg/inj) at baseline (●) and day of treatment (■) with APZ (2.5 mg/kg, SC). The asterisks (*) indicate significant change in break point from baseline levels ($p < 0.025$). N=7.

FIGURE 3. The cumulative record of baseline and treatment day of a rat self-administering cocaine (1.5 mg/kg/inj) on a PR schedule of reinforcement. Vertical lines represent injections. The top diagram of figure 3 is a cumulative data record of baseline breaking point for animal (M878). The lower diagram of figure 3 illustrates the effect of APZ pretreatment (2.5 mg/kg, SC) on break point.

DISCUSSION

APZ (2.5 mg/kg, SC) pretreatment significantly reduced the breaking point for cocaine reinforcement. Although in Experiment 1 APZ (2.5 mg/kg) failed to significantly alter rate of intake, it clearly attenuated the animals' motivation to self-administer cocaine on a progressive ratio schedule. All animals at the top three doses of cocaine showed significant reductions in breakpoint in comparison to baseline. The data illustrated in figure 2 provide a clear representation of this cocaine dose dependent effect. Given APZ's ability to block cocaine induced neurochemical as well as behavioral changes it is reasonable to argue that APZ may be blocking cocaine's reinforcing properties (Kimura et al., 1993).

Our findings however are subject to various interpretations and there are alternative hypotheses that could account for these results. For example, it may be argued that the animal were suffering from motor deficits following APZ pretreatment and interfered with the animals' ability to respond. Therefore, the lower break points observed could be attributed to a nonspecific motoric impairment rather than a blockade in reward. Experiment 3 was designed to address the possible motoric component of APZ via an analysis of responding for food reinforcement on a PR schedule. If APZ does induce motor deficits that render the animal incapable of responding then Experiment 3 should show comparable deficits in responding.

EXPERIMENT 3

The purpose of experiment 3 was to assess the effects of APZ on food reinforcement using an Progressive ratio schedule of reinforcement. It is important to examine the consequences of potential pharmacotherapies for cocaine addiction on other behaviors thought to involve reward processes. This also provides an opportunity to further assess the possible motoric effects of APZ in cocaine naive animals in the food self-administration paradigm.

METHODS

The purpose of experiment 3 was to assess the effects of APZ on responding for food reinforcement using a Progressive Ratio schedule of reinforcement. There was an exponential increase in the number of responses required to receive an infusion of cocaine (see exp. 2 methods for schedule). Following three days of baseline training (no more than a 10% difference between the days) animals were treated with APZ (0.625, 1.25, 2.5 mg/kg, SC) or vehicle 20 minutes prior to the initiation of a food self-administration session. Each self-administration session lasted for two hours a day and was run seven days a week. APZ dose was presented in a latin square design. An overall analysis of the reinforcement data was completed using a within subjects, twoway ANOVA ($p < 0.01$) and Dunn's procedure was employed to analyze the simple main effect of treatment within dose of cocaine ($p < .025$). The

total number of animals used in this experiment was 8.

RESULTS

Experiment 3 measured the effect of pretreatment with APZ (sal, 0.625, 1.25, 2.5 mg/kg, SC) on total number of food reinforcements obtained on a PR schedule of reinforcement. The data were submitted to a twoway ANOVA and revealed a significant overall treatment effect ($F = 24.73, df(1,7)p < 0.01$) and significant treatment by dose effect ($F = 12.38, df(3,21)p < 0.01$) within subjects.

Figure 4 illustrates the results of Experiment 3 which measured the effect of pretreatment with APZ on mean ($\pm$ SEM) number of reinforcements obtained by rats responding for food reinforcement on a PR schedule of reinforcement. APZ pretreatment significantly reduced responding for food reinforcement at 0.625, 1.25 and 2.5 mg/kg/inj doses. Post hoc analysis of simple main effects using Dunn's procedure revealed significant results on the three doses of APZ; 0.625 mg/kg, ($F = 6.74, df(1,20.81)p < .025$), 1.25 mg/kg, ($F = 21.97, df(1,20.81)p < .025$) and 2.5 mg/kg, ($F = 45.62, df(1,20.81)p < .025$) on bar pressing for food reinforcement. However, this analysis failed to reveal a statistical significance ($F = .009, df(1,20.81)$) of saline. Figure 4 provides an illustration of the dose dependent effect of APZ on responding for food on a progressive ratio schedule. All animals showed significant reductions in the total number of reinforcements obtained in comparison to baseline when pretreated with APZ (0.625, 1.25, 2.5 mg/kg, SC).

This dose dependent relationship is also indicated in figure 5; as APZ dose increases, the number of food reinforcements obtained decrease in an inverse fashion. Figure 5 illustrates the event records of one representative animal (M008) responding for food reinforcements within all four pretreatment conditions.

DISCUSSION

The data indicate a slight but significant dose dependent effect of APZ on responding on a PR schedule for food reinforcement. Comparatively, the results obtained on cocaine and food self-administration are somewhat similar. However, it is important to note that the data obtained in Experiment 2 which examined break point of cocaine responding demonstrate a much greater effect following APZ pretreatment. Figure 6. illustrates the marked differences in percent of baseline reached on cocaine and food reinforced responding on the PR schedule. Although, responding for food reinforcement varies in degree from that of cocaine, APZ does appear to affect food reinforced behavior.

One hypothesis could be that APZ causes a decrease in food reward. This interpretation is consistent with a number of other studies that have reported only minimal effects on food intake of animals that have been pretreated with doses similar to those used here. McMillen and his colleagues (1993) demonstrated that APZ pretreatment did slightly decrease food intake but did not significantly reduce body weight of animals that were self-administering cocaine. However, Egbe et al.,

(1990) failed to demonstrate a decrease in responding for food on an FR 40 schedule at doses lower than 3.0 mg/kg, SC of APZ. It should be noted however that this study employed a different measure of food intake and it is possible that the PR schedule provides a more sensitive measure of reinforcement. In conclusion, it is possible that the decreases in number of reinforcements obtained is due to a slight blunting of food reward.

FIGURE 4. The effect of APZ pretreatment on total number of reinforcements obtained by rats bar pressing for food on a progressive ratio in a 2 hour session. The mean ($\pm$ SEM) breakpoint is represented across saline and three doses of APZ (0.625, 1.25, 2.5 mg/kg, SC) at baseline (●) and day of treatment (■). The asterisks (*) indicate significant change in breakpoint from baseline levels ($p < 0.025$). N = 8.

AMPEROZIDE FOOD PR

FIGURE 5. The event records of one animal responding for food on a PR schedule on baseline and treatment days. Each record represents the rat's (M008) total number of reinforcements when responding for food following pretreatment with APZ (saline, 0.625, 1.25, 2.5 mg/kg, SC) 20 minutes prior to the start of a session. The asterisks (*) signal treatment day and the data are presented such that each set of event records denote an increment in APZ dose as signalled below each set.

M 008

	Resp	Inj	FR
III _____	532	15	118
III _____	315	13	77
* III _____	404	14	95
saline			

III _____	264	12	62
III _____	190	11	50
* III _____	111	9	32
0.625 mg/kg			

III _____	245	12	62
III _____	210	11	50
* III _____	106	9	32
1.25 mg/kg			

III _____	214	11	50
III _____	236	12	62
* III _____	61	7	20
2.5 mg/kg			

FIGURE 6. Illustrates the marked differences in percent of baseline reached on cocaine and food reinforced responding on the PR schedule. This bar graph represents the overall total percent of baseline achieved following treatment with APZ (2.5 mg/kg,SC) on cocaine self-administration and food self-administration.

EXPERIMENT 4

Experiment 4 was designed to examine the effects of APZ on responding for cocaine injections over a 24 hour period in a discrete trials paradigm. It has been demonstrated in this lab, as well as others, that animals given unlimited access to high doses of cocaine show elevated subject mortality rates (Bozarth and Wise, 1985). Fitch and Roberts (1993) employed a discrete trials procedure to examine the effect of frequency of access restrictions on the periodicity of cocaine self-administration over a 24 hour period. This design enables the experimenter to vary the time interval between trials during which an animal is free to respond for a single infusion of cocaine. Manipulating the inter-trial interval shifts the pattern of intake from a regular circadian trend to a binge-like drug taking pattern (Wilson et al., 1971). Whereas, 4 trials per hour induces a disruption of sleep/activity cycles, 2 trials elicits a stable responding (Fitch and Roberts, 1993).

Therefore, depending on the access or dose of cocaine used, an erratic pattern of excessive drug intake or a reliable pattern of daily responding is produced. By limiting rats' access to two 10 minute trials/hour, a cyclical pattern of cocaine self-administration is observed. This enables an examination of APZ pretreatment on stable baseline levels of drug responding. Experiment 4 examines the effect of APZ on the periodicity of cocaine self-administration under a discrete trials procedure.

METHODS

This experiment was designed to examine the effects of APZ on responding for cocaine injection over a 24 hour period in a discrete trials paradigm. A trial began with the introduction of a retractable lever into the test chamber. At the start of the experiment each animal was randomly assigned to the FR 1 or FR 5. Completion of the required fixed ratio resulted in a cocaine injection (0.6 mg of cocaine/0.12 ml of saline) which was signalled by a stimulus light for twenty seconds. The trial was terminated and the lever retracted if an injection was collected or if 10 minutes elapsed. The animal was afforded two trials per hour. Please see Experiment 1 for general methods.

Following three days of baseline training (no more than a 10% difference between the days) the subjects received an APZ (1.25, 2.5 mg/kg, SC) pretreatment 20 minutes prior to the initiation of a trial in the cocaine self-administration session. Animals were then re-baselined before the second APZ dose was tested. Also subsequent to completion of treatment with both doses (1.25, 2.5 mg/kg, SC) rats were given one day post treatment before being changed to the alternate FR and re-baselined for three days before testing again. APZ dose and response requirement were presented in a counterbalanced fashion. An overall analysis of the data was completed using a within subjects, threeway ANOVA ($p < 0.01$) and Dunn's procedure was employed to analyze the simple main effect of treatment within dose of cocaine ($p < .029$). The total number of animals used in this experiment was 8.

An additional group of animals was added to this experiment to examine a

lower dose of APZ; the protocol was identical except that animals were only tested with one dose of APZ (0.625 or 1.25 mg/kg, SC) 20 minutes prior to the initiation of a cocaine self-administration. Subsequent to one day post treatment at one of these doses, rats were changed to the alternate FR and re-baselined for three days before testing again at this same dose (0.625 or 1.25 mg/kg, SC). An overall analysis of the data was completed using a between subjects design, threeway ANOVA ($p < 0.01$) and Dunn's procedure was employed to analyze the simple main effect of treatment within dose of cocaine ($p < .029$). $N=5$.

RESULTS

The first part of this experiment was designed to examine the effects of APZ (1.25 and 2.5 mg/kg, SC) on responding for cocaine injection on FR 1 and FR 5 schedules of reinforcement over a 24 hour period in the discrete trials paradigm. The data were submitted to a threeway ANOVA and revealed a significant overall effect of FR ($F=17.20$, $df(1,6)$ $p < 0.01$), APZ ($F=67.79$, $df(1,6)$ $p < 0.01$) and APZ by DOSE ($F=8.07$, $df(1,6)$ $p < 0.01$).

Figure 7 illustrates the effect of APZ pretreatment (1.25 and 2.5 mg/kg, SC) on mean ($\pm$ SEM) number of cocaine infusions obtained over 24 hours on FR 1 and FR 5 schedules of reinforcement. Pretreatment with APZ (1.25 mg/kg, SC) significantly reduced the total number of infusions obtained at the FR 1 schedule ($F=12.00$, $df(1,6)$ $p < .029$) and FR 5 schedule ($F=23.51$, $df(1,6)$ $p < .029$) of

reinforcement. Significant reductions in the number of infusions were also seen when animals were treated with APZ (2.5 mg/kg,SC) at the FR 1 ($F=35.93, df(1,6)p<.029$) and FR 5 schedule ($F=57.15, df(1,6)p<.029$) in the discrete trials paradigm. All animals showed significant reductions in the total number of infusions received in comparison to baseline rates when pretreated with APZ (1.25, 2.5 mg/kg,SC) at both FR 1 and FR 5.

Figure 8 illustrates the event records of animal M984, which are an example of responding patterns observed. It is clear that as dose of APZ is increased, the number of infusions is reduced in a dose dependent as well as a cost benefit manner. Although in this example, at the FR5 schedule of responding, the total number of injections received when pretreated with APZ (1.25 mg/kg) is less than the total number obtained when pretreated with APZ (2.5 mg/kg). Typically, the number of cocaine infusions decreases in an inverse fashion as APZ dose and/or fixed ratio requirement is increased.

FIGURE 7. The effect of APZ pretreatment (1.25 and 2.5 mg/kg, SC) on number of cocaine infusions obtained over 24 hours on FR 1 and FR 5 schedules in the discrete trials paradigm. The mean ($\pm$ SEM) number of infusions/24 hours is represented at baseline (BL) and day of treatment with APZ (1.25 mg/kg, SC) and baseline (BL) and day of treatment with APZ (2.5 mg/kg, SC). Two fixed ratio response requirements are also indicated for each of these conditions; FR 1 (●) and FR 5 (■). The asterisks (*) indicate significant change in total infusions from baseline levels ($p < 0.029$). $N = 7$.

FIGURE 8. The event records of one animal self-administering cocaine on FR 1 and FR 5 schedules in the discrete trials paradigm. The event records of animal M98¹ is a representative example of responding patterns observed on baseline and treatment days. Each record represents the rats' total number of infusions obtained when afforded two 10 minute trials per hour/24 hours at an FR1 and FR5 reinforcement schedule following pretreatment with APZ (1.25, 2.5 mg/kg, SC) 20 minutes prior to the start of a session. Figure 8 illustrates the significant effect of APZ dose and response requirement on cocaine self-administration. The asterisks (*) signal treatment day.

M 984

1.25 mg/kg

	Resp	Inj	FR
26	26	1
28	28	1
*	22	22	1

2.5 mg/kg

25	25	1
25	25	1
*	11	11	1

1.25 mg/kg

99	18	5
119	23	5
*	21	3	5

2.5 mg/kg

115	23	5
117	22	5
*	42	6	5

Dark / Active Cycle

This supplement to the original experiment was designed to examine the effects of APZ (0.625 or 1.25 mg/kg, SC) on responding for cocaine injection on FR 1 and FR 5 schedules of reinforcement over a 24 hour period in the discrete trials paradigm. The data were submitted to a between subjects threeway ANOVA which revealed a significant overall effect of APZ ($F=26.33, df(1,8) p < .01$) on the total number of cocaine reinforcements.

Figure 9 illustrates the effect of APZ pretreatment (0.625 and 1.25 mg/kg, SC) on mean ($\pm$ SEM) number of cocaine infusions obtained over 24 hours on FR1 and FR5 schedules of reinforcement. Pretreatment with APZ (0.625 mg/kg, SC) on total number of infusions obtained at the FR1 schedule or at the FR5 schedule of reinforcement did not reach statistical significance. However, significant reductions in the number of infusions were seen when animals were pretreated with APZ (1.25 mg/kg, SC) at the FR1 schedule ($F=7.64, df(1,8) p < 0.029$) and FR5 schedule ($F=13.16, df(1,8) p < 0.029$) in the discrete trials paradigm. All animals showed significant reductions in the total number of infusions received in comparison to baseline rates when pretreated with APZ (1.25 mg/kg, SC) at both FR 1 and FR 5. However animals pretreated with APZ (0.625 mg/kg) did not differ significantly from baseline when required to respond on either the FR1 or the FR5 schedule.

Figure 10 shows the event records of animal (M214); a representative example of responding patterns observed when bar pressing for cocaine reinforcements. These data demonstrate the effect of APZ dose (0.625 mg/kg, SC) on both the FR1 and FR5 schedules; the number of injections received did not differ significantly from baseline

on either of these schedules. See figure 8 for event records of animals pretreated with APZ (1.25 mg/kg, SC).

FIGURE 9. The effect of APZ pretreatment (0.625 and 1.25 mg/kg, SC) on number of cocaine infusions obtained over 24 hours on FR 1 and FR5 schedules in the discrete trials paradigm. The mean (+SEM) number of infusions / 24 hours is represented at baseline (BL) and day of treatment with APZ (0.625 mg/kg, SC) and baseline (BL) and day of treatment with APZ(0.625 mg/kg, SC). Two fixed ratio response requirements are also indicated for each of these conditions; FR 1 (●) and FR 5 (■) with APZ (1.25mg/kg, SC). The asterisk (*) indicate significant change in total infusions from baseline levels ($p < 0.029$). N = 10.

FIGURE 10. The event records of one animal self-administering cocaine on FR 1 and FR 5 schedules of reinforcement in the discrete trials paradigm. The event records of animal M214 are a representative example of responding patterns observed on baseline and treatment days. Each record represents the rats' total number of infusions obtained when afforded two 10 minute trials per hour/24 hours at an FR1 and FR5 reinforcement schedule following pretreatment with APZ (0.625 mg/kg, SC) 20 minutes prior to the start of a session. The asterisks (*) signal treatment day .

M 214

0.625 mg/kg

Resp Inj FR

	34	34	1
	31	31	1
*		28	28	1
	90	18	5
	102	20	5
*		88	17	5

Dark / Active Cycle

DISCUSSION

Many self-administration paradigms restrict access to 3 or 4 hours a day and this has allowed researchers to study measures such as rate or breakpoint in a very stable drug taking pattern. In both procedures, animals are provided with a noncontingent injection of cocaine at the start of a self-administration session. Essentially, the experimenter 'primes' the animal into responding and a typical self-administration session ensues with the animal responding for injections. However, these schedules only enable us to examine/disrupt the ongoing behavior and basically address issues of drug intake. Whereas these schedules may only offer insight into the animals' motivation to continue drug taking, the discrete trials paradigm affords the experimenter the opportunity to examine the motivational factors implicated in the initiation of cocaine self-administration.

Previous work in this laboratory has determined the parameters of access necessary to elicit normal circadian rhythms in cocaine self-administration. Animals limited access to cocaine to two trials/hour over a 24 hour period show consistent baseline patterns of cocaine intake that are cyclical in nature (Fitch and Roberts, 1993). By establishing stable baselines of cocaine cyclicity the experimenter can predict when a binge will start and therefore can examine effect on patterns of daily intake. Therefore effective pharmacological manipulations would be expected to postpone or shift the time at which an animal initiates responding for cocaine.

Following drug treatment the emergence of two possible patterns of drug intake are postulated. First, the time in which the animal typically starts responding

is postponed but a normal circadian like pattern of cocaine self-administration follows when the animal reinitiates the session; thereby producing an decrease in the overall number of infusions collected. Secondly, the animals' initiation time is shifted but the animal continues responding in a binge like manner into the normally inactive phase of the cycle. Therefore, overall drug intake remains the same or greater. This carryover effect observed may be a compensatory response elicited by the animal's need to achieve or maintain a certain level of cocaine.

We have shown that by pretreating animals with APZ we can effectively postpone the period in which the animal initiates cocaine self-administration and decrease drug intake in a dose dependent manner. The apparent time course of APZ effect was also established (as evidenced by the postponement in initiate) and seems to be somewhere between 4 to 8 hours, depending on APZ dose and response requirement used (see figures 8 and 10). Moreover, APZ did not cause a compensatory shift in responding into the inactive phase of the circadian cycle. Finally, given the minimal response requirements in this paradigm (FR 1 and FR 5), it is unlikely the effects observed can be accounted for by motor deficits.

GENERAL DISCUSSION

The application of different measures of reinforcement in an animal model of drug addiction has helped in the establishment of a more comprehensive understanding of the expression and maintenance of cocaine taking behavior. The self-administration paradigm has provided a sensitive probe into the efficacy of a variety of potentially therapeutic drugs. Given the presumed role of dopamine (DA) in cocaine reinforcement and APZ's proposed mechanism of action, it seemed appropriate to explore the use of this atypical neuroleptic as an anti-cocaine drug in the self-administration paradigm.

In summary, the results presented for Experiment 1 demonstrate that APZ had no effect on rate of cocaine intake. Unfortunately, the varied interpretations of rate make it difficult to address some of the more complex behaviors involved in cocaine reinforcement (Yokel and Wise, 1975; Wilson and Schuster, 1973). An assessment of rate in combination with other schedules of reinforcement, such as progressive ratio and discrete trials may provide more definitive results.

Experiment 2 examined APZ's ability to alter break point and it has demonstrated that pretreatment with this atypical neuroleptic could result in very large decreases on a PR schedule of reinforcement. APZ pretreatment significantly reduced breaking points across the higher dose range for cocaine (0.37, 0.75 and 1.5 mg/kg/inj). Although APZ failed to significantly alter rate of cocaine intake at 2.5 mg/kg, it appeared to attenuate the animals' motivation to self-administer cocaine on a progressive ratio schedule in Experiment 2. It should be reemphasized here that

changes in breakpoint of self-administration are not necessarily reflected in changes in rate of self-administration. Table 1 provides further examples of drugs that fall into this category. Finally, although self-administration of food and cocaine are qualitatively different, the attenuation of food self-administration in Experiment 3, provides further support that APZ is affecting reinforcement systems.

The data presented in Experiment 3 indicate a slight but significant dose dependent effect of APZ on responding for food reinforcement on a PR schedule. These results are consistent with the findings of other researchers examining the effect of APZ on food intake (see Egbe et al., 1990; McMillen et al., 1993). Therefore, it is possible that the decreases observed following APZ pretreatment may be due to a slight blunting of food reward. Alternatively, the slight effects observed on food reinforcement may be the result of proposed motor deficits, however, the finding that rate was unaffected in Experiment 1 provides strong evidence against this possibility. Clearly, further research into APZ effect on food reward properties is required.

The results presented here for Experiment 4 demonstrated that pretreatment with APZ (1.25, 2.5 mg/kg,SC) significantly reduced the total number of infusions obtained over a 24 hour period on both FR 1 and FR 5 schedules of reinforcement. APZ is capable of not only antagonizing cocaine reinforcement, it has also effectively postponed the point at which an animal normally initiates responding. Furthermore, the animals did not attempt to compensate for the reduction in overall cocaine intake by continuing to self-administer into the inactive phase of the cycle and therefore did not disrupt normal circadian patterns. Finally, we were also afforded an indication of

the time course of APZ's effect which appears to fall between 4-8 hours.

Taken together, the findings presented in this analysis of APZ on cocaine self-administration although lending support to its potential as a therapeutic agent, require further examination. Future considerations might include an analysis of repeated APZ treatments on cocaine self-administration paradigm in the discrete trials. Depot injections of the neuroleptics haloperidol and flupenthixol produced long term effects in cocaine self-administration (Richardson et al., in press). In addition, a thorough examination of locomotor activity would provide definitive evidence that APZ's effects on cocaine self-administration are not attributable to widespread motoric impairment.

Finally, the neuromodulatory classification of APZ's cocaine effects remains to be determined. However, APZ's diverse mechanism of action may prove to be an advantage in the overall cocaine clinical picture. A number of different drugs following this type of ambiguous neurochemical profile have presented optimistic data. Surprisingly, a new group of compounds, the aminotetralins, classified as DA D_3/D_2 antagonists have presented an interesting behavioral profile in terms of cocaine reinforcement. Two of these compounds UH-232, (Smith and Roberts, in prep.) and (+)-AJ 76, (Richardson et al., 1993) have been demonstrated to significantly reduce cocaine consumption. Pharmacological agents capable of acting at a number of different receptor sites within as well as between specific neurotransmitter systems may exhibit a behavioral profile that is more conducive to the clinical picture.

Consequently, the potential discovery of an effective therapeutic compound

may involve the pharmacological interaction of a number of neural systems. Clozapine, for example, whose mechanism of action is very poorly understood, has demonstrated significant clinical success in the treatment of schizophrenics who are unresponsive to the D₂ specific antipsychotic drugs (Meltzer et al., 1986; Meltzer, 1989). It not surprising then that APZ is also currently being studied in clinical trials with schizophrenics (Axelsson et al., 1991). Whether APZ's actions are determined to be predominantly serotonergic or dopaminergic in nature, is not the primary argument at issue here. Our purpose has been to examine the potential pharmacotherapeutic efficacy of this compound.

REFERENCES

- Axelsson,R., Nilsson,A., Christensson,E. and Björk,A. (1991) Effects of amperozide in schizophrenia. Psychopharmacology, **104**:287-292
- Bozarth,M.A and Wise,R.A. (1985) Toxicity associated with long term intravenous heroin and cocaine self-administration in the rat. Journal of the American Medical Association, **254**:81-83
- Christensson,E. and Björk,A. (1990) Amperozide: A new pharmacological approach in the treatment of schizophrenia. Pharmacology and Toxicology. **66**(Suppl.1):5-7
- Christensson,E. and Gustafsson,B. (1985) Amperozide, a novel psychotropic compound with specific effect on limbic brain areas. Acta Physiologica Scandanavia,**124**(Suppl. 542):281-287
- Dackis,C.A., Gold,M.S., Davies,R.K. and Sweeney,D.R. (1985) Bromocriptine treatment for cocaine abuse: The dopamine depletion hypothesis. Pharmacology, Biochemistry and Behavior. **15**:125-135

Depoortere, R. Y., Li, D. H., Lane, J. D. and Emmett-Oglesby, M. W. (1993) Parameters of self-administration of cocaine in rats under a progressive ratio schedule. Pharmacology, Biochemistry and Behavior, 45:539-548

Egbe, P., Engel, J., Gustafsson, B. and Christensson, E. (1990) Amperozide and conditioned behavior in rats: Potentiation by classical neuroleptics and alpha-methylparatyrosine. Pharmacology and Toxicology, 66(Suppl.1):18-21

Eriksson, E. (1990) Amperozide, a putative anti-psychotic drug: Uptake inhibition and release of dopamine in vitro in the rat brain. Life Sciences, 47:2111-2117

Eriksson, E. and Christensson, E. (1990) The effect of amperozide on uptake and release of [³H]-dopamine in vitro from perfused rat striatal and limbic brain areas. Pharmacology and Toxicology, 66(Suppl.1):45-48

Fitch, T. E. and Roberts, D. C. S. (1993) The effects of dose and access restrictions on the periodicity of cocaine self-administration in the rat. Alcohol and Drug Dependence, 33:119-128

- Gawin,F.H. Allen,D. and Hunblestone,B. (1989a) Outpatient treatment of "crack" cocaine smoking with flupenthixol decaonate. Archives of General Psychiatry, **46**:322-325
- Gawin,F.H., Kleber,H.D., Byck,R., Rousaville,B.J., Kosten,T.R., Jatlow,P.I. and Morgan,C. (1989b) Desipramine facilitation of initial cocaine abstinence. Archives of General Psychiatry, **46**:117-121
- Gustafsson,B. and Christensson,E. (1990a) Amperozide-a new putatively antipsychotic drug with a limbic mode of action on dopamine mediated behavior. Pharmacology and Toxicology, **66**(Suppl.1):12-17
- Gustafsson,B. and Christensson,E. (1990b) Amperozide and emotional behavior. Pharmacology and Toxicology, **66**(Suppl.1): 34-39
- Hodos,W. (1961) Progressive ratio as a measure of reward strength. Science, **134**:943-944
- Hubner,C.B. and Moreton,J.E. (1991) Effects of selective D1 and D2 dopamine antagonists on cocaine self-administration in the rat. Brain research, **105**:151-156

- Ichikawa,J. and Meltzer,H.Y. (1992) Amperozide, a novel antipsychotic drug, inhibits the ability of *d*-amphetamine to increase dopamine release in vivo in rat striatum and nucleus accumbens. Journal of Neurochemistry,58:2285-2291
- Ichikawa,J. and Meltzer,H.Y. (1992) The effect of chronic atypical antipsychotic drugs and haloperidol on amphetamine-induced dopamine release in vivo. Brain research, 574:98-104
- Johanson,C.E., Balster,R.L. and Bonese,K. (1976) Self-administration of psychomotor stimulant drugs: the effects of unlimited access. Pharmacology Biochemistry and Behavior, 4: 45-51
- Kimura,K., Nomikos,G.G. and Svensson,T.H. (1993) Effects of amperozide on psychostimulant induced hyperlocomotion and dopamine release in the nucleus accumbens. Pharmacology Biochemistry and Behavior, 44:27-36
- Koob,G.F., Vaccarino,F., Amalric,F. and Bloom,F.E. (1987) Positive reinforcement properties of drugs: search for neural substrates. In: Engel,J. and Oreland, L. (Eds.) Brain Reward Systems and Abuse Raven Press. New York

LaCosta,S and Roberts, D.C.S. (1993) MDL 72222, Ketanserin, and Methysergide pretreatments fail to alter breaking points on a progressive ratio schedule reinforced by intravenous cocaine. Pharmacology Biochemistry and Behavior, **44**:161-165

Loh,E.A.,and Roberts,D.C.S (1992) Break points on a progressive ratio schedule reinforced by intravenous cocaine following depletion of forebrain serotonin. Psychopharmacology, **101**:262-266

Loh,E.A., Fitch,T., Vickers,G., and Roberts,D.C.S (1992) Clozapine increases breaking points on a progressive ratio schedule reinforced by intravenous cocaine. Pharmacology Biochemistry and Behavior, **42**: 559-562

McGregor,A., Lacosta,S., and Roberts,D.C.S. (1993) L-Tryptophan decreases the break point under a progressive ratio schedule of intravenous cocaine reinforcement in the rat. Pharmacology, Biochemistry and Behavior,**44**:651-655

McMillen,B.A., Jones,E.A., Hill,L.J., Williams,H.L., Bjork,A. and Myers,R.D. (1993) Amperozide,a 5-HT antagonist, attenuates craving for cocaine by rats. Pharmacology, Biochemistry and Behavior, **46**:125-129

- Meltzer, H.Y. and Stahl, S.M. (1976) The dopamine hypothesis of schizophrenia: a review. Schizophrenia Bulletin, 2:19-76
- Meltzer, H.Y., Sommers, A.A. and Luchin, D.J. (1986) The effect of neuroleptics and other psychotropic drugs on negative symptoms in schizophrenia. Journal of Clinical Psychopharmacology, 6:329-338
- Meltzer, H.Y. (1989) Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis. Psychopharmacology, 99: S18-S27
- Meltzer, H.Y., Matsubara, S. and Lee, J.C. (1989) Classification of typical and atypical antipsychotic drugs in the basis of D-1, D-2 and serotonin₂ pKi values. Journal of Pharmacology and Experimental Therapeutics, 251:238-246
- Meltzer, H.Y. and Nasr, J.F. (1991) VII. Effects of antipsychotic drugs on serotonin receptors. Pharmacological Reviews, 43(4):587-604
- Pehek, E.A., Meltzer, H.Y. and Yamamoto, B.K. (1993) The atypical antipsychotic drug amperozide enhances rat cortical and striatal dopamine efflux. European Journal of Pharmacology, 240:107-109

Petterson,G., Johannessen,K., Hulthe,P. and Enge,J.A. (1990) Effect of amperozide on the synthesis and turnover of monoamines in rat brain. Pharmacology and Toxicology, 66(Suppl.1):40-44

Pettit,H.O., Ettenberg,A., Bloom,F.E. and Koob,G.F. (1984) destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology, 84:167-173

Richardson,N.R. and Roberts,D.C.S. (1991) Fluoxetine pretreatment reduces breaking points on a progressive ratio schedule reinforced by intravenous cocaine self-administration in the rat. Life Sciences, 49:833-840

Richardson,N.R., Piercey,M.F., Svensson,K., Collins,R.J., Myers,J.E. and Roberts,D.C.S. (1993) Antagonism of cocaine self-administration by the preferential dopamine autoreceptor antagonist, (+)-AJ 76. Brain Research 619: 15-21

Richardson,N.R., Smith,A.M. and Roberts,D.C.S. (in press) A single injection of either flupenthixol decaonate or haloperidol decaonate produces long term changes in cocaine self-administration. Drug and alcohol Dependence.

Roberts,D.C.S., Corcoran,M.E. and Fibiger,H.C. (1977) On the role of ascending catecholamine systems in intravenous self-administration of cocaine.

Pharmacology Biochemistry and Behavior,6:615-620

Roberts,D.C.S., Koob,G.F., Klonoff,P. and Fibiger,H.C. (1980) Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. Pharmacology Biochemistry and Behavior,12:781-787

Roberts,D.C.S. and Vickers,G.J. (1984) Atypical neuroleptics increase self-administration of cocaine: An evaluation of a behavioral screen for antipsychotic activity. Psychopharmacology, 82:135-139

Roberts,D.C.S. and Vickers,G.J. (1987) The effect of haloperidol on cocaine self-administration is augmented with repeated administrations.

Psychopharmacology,93:526-528

Roberts,D.C.S. and Goeders,N. (1987) Drug Self-administration: Experimental methods and determinants. In: Boulton, A.A., Baker, G.B. and Greenshaw, A.J. (Eds.) Neuromethods. Humana Press, Clifton. NJ.

Roberts,D.C.S. and Zito,K.A. (1987) Interpretation of lesion effects on stimulant self-administration. In: Bozarth, M.A., Ed.Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer-Verlag, New York.

Roberts,D.C.S., Loh,E.A. and Vickers,G.J. (1989b) Self-administration on a progressive ratio schedule in rats: Dose response relationship and effect of haloperidol pretreatment. Psychopharmacology,**97**:535-538

Roberts,D.C.S. (1989) Breaking Point on a progressive ratio schedule reinforced by intravenous apomorphine increase daily following 6-hydroxydopamine lesions of the nucleus accumbens. Pharmacology Biochemistry and Behavior,**32**:43-47

Roberts,D.C.S. (1992) Neural substrates mediating cocaine reinforcement: The role of monoamine systems. In: Lakoski, J.M., Galloway, M.P. and White, F.J.(Eds.) Cocaine,CRC Press, Boca Raton, London.

Spealman,R.D., Bergman,J., Madras,B.K.,Kamien,J.B. and Melia,K.F. (1992) Role of D1 and D2 dopamine receptor agonists in the behavioral effects of cocaine. Neurochem. Int. **20**(Suppl.):147S-152S

- Svartengren, J. and Simonsson, P. (1990) Receptor binding properties of amperozide. Pharmacology and Toxicology, **66**(Suppl.1):8-11
- Swerdlow, N.R., Vaccarino, F.J., Amalric, M. and Koob, G.F. (1986) The neural substrates for the motor-activating properties of psychostimulants: A review of recent findings. Pharmacology, Biochemistry and Behavior, **25**:233-248
- Tennant, F.S. and Sagherian, A.A. (1987) Double-blind comparison of amantadine and bromocriptine for ambulatory withdrawal from cocaine dependence. Archives of Internal Medicine **147**:109-112
- Ugedo, L., Grenhoff, J. and Svensson, T.H. (1989) Ritanserin, a 5-HT₂ receptor antagonist, activates midbrain dopamine neurons by blocking serotonergic inhibition. Psychopharmacology, **98**:45-50
- Waters, N., Pettersson, G., Carlsson, A. and Svensson, K. (1989) The putatively antipsychotic agent amperozide produces behavioral stimulation in the rat. Naunyn-Schmiedeberg's Archives of Pharmacology, **340**:161-169
- Wilson, M.C. and Schuster, C.R. (1971) The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. Psychopharmacology, **26**:115

Wilson, M.C. and Schuster, C.R. (1973) The effects of stimulant and depressants on cocaine self-administration by rhesus monkey. Psychopharmacology, 31:291-304

Wilson, M.C., Nitomi, M. Schuster, C.R. (1971) Psychomotor stimulant self-administration as a function of dosage per injection in the rhesus monkey. Psychopharmacologia, 22: 271-281

Woolverton, W.L., Goldberg, L.I. and Ginos, J.Z. (1984) Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. Journal of Pharmacology and Experimental Therapeutics 230:678-683

Yamamoto, B.K. and Meltzer, H.Y. (1992) The effect of atypical antipsychotic drug, amperozide, on carrier-mediated striatal dopamine release measured in vivo. The Journal of Pharmacology and Experimental Therapeutics, 263(1):180-185

Yokel, R.A. and Wise, R.A. (1975) Increased lever pressing for amphetamine after pimozide in rats: Implication for the dopamine theory of reward. Science, 187:547-549

Yokel, R.A. and Wise, R.A. (1976) Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. Psychopharmacology, 48:311-318

END

1 0-1 1-94

FIN