1 of/de 1

PM-1 3½"x4" PHOTOGRAPHIC MICROCOPY TARGET
NBS 1010a ANSI/ISO #2 EQUIVALENT

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

Your file - Votre référence

Our file - Notre référence

NOTICE

AVIS

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30, and subsequent amendments.

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.

THE PERIODICITY OF CHRONIC COCAINE SELF-ADMINISTRATION

by

THOMAS E. FITCH

**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, Ontario
1992**

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

Your file / Votre référence

Your file / Votre référence

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 0-315-79847-5

Canada

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

"THE PERIODICITY OF CHRONIC COCAINE SELF-ADMINISTRATION"

submitted by Thomas E. Fitch, B.A.
in partial fulfillment of the requirements for
the degree of Master of Science

Thesis Supervisor

Chair, Department of _____

Carleton University
September, 1992

ABSTRACT

Human cocaine self-administration (SA) has been reported to occur in episodic periods of prolonged high intake or 'binges', alternating with periods of abstinence and recuperation (Gawin, 1991). Animals, given chronic, unlimited access to cocaine will also show a pattern of prolonged, erratic intake which is reported to compromise the health of the subject, and, often results in overdose. Because of these overdose effects, animal models of cocaine SA which address the factors which lead to a reinitiation of a period of cocaine SA, are lacking. The present series of experiments have been undertaken in an attempt to address this issue.

In experiment 1, rats were given the opportunity to self-administer a single infusion of cocaine at various time intervals following a three hour period of free access to the drug. The results showed that the tendency to respond to this access trial followed the time course of the sleep/activity cycle, wherein rats were more likely to respond for the drug at times when they are normally active and not at times when normally asleep.

Experiments 2 and 3 were conducted in order to better characterize the parameters that regulate the periodicity of cocaine self-administration. Rats were given chronic, 7-10 day access to cocaine under various dose and frequency of access restrictions. Results suggest that when access is restricted to four access trials per hour, or to a median dose range (0.5 mg/kg/inj.), rats will self-administer cocaine in a cyclical manner over extended, infradian periodicities. This contrasts with previous studies where chronic unlimited access

schedules has resulted in subject overdose. The self-administration patterns seen in the present study are similar to the patterns of alternate 'binging' and abstinence found in human cocaine abuse. It is suggested that dose and frequency-of-access restrictions may be employed in order to develop new animal models of cocaine self-administration which examine the factors underlying the reinitiation of a cocaine 'binge' and which better model the present day clinical course of cocaine abuse.

ACKNOWLEDGEMENTS

I would like to express my appreciation and thanks to my advisor, Dr. D.C.S. Roberts for his guidance and teaching throughout the completion of this thesis. I would further like to thank the members of my committee, Dr Merali, Dr. Moffitt, and Dr. Anisman for their thoughtful comments and suggestions which added much perspective to the project. Finally, I would like to thank Dr. Roseanne Armitage for all her help, both with statistics and personal support.

TABLE OF CONTENTS

Introduction.....	1
A. Periodicity.....	3
B. Animal Models of Cocaine Self-Administration.....	4
C. Periodicity in Animal Cocaine Self-Administration..	6
General Methods.....	9
Experiment 1.....	10
A. Introduction.....	10
B. Methods.....	10
C. Results.....	12
D. Discussion.....	14
Experiment 2.....	16
A. Introduction.....	16
B. Methods.....	17
C. Results.....	18
D. Discussion.....	22
Experiment 3.....	28
A. Introduction.....	28
B. Methods.....	28
C. Results.....	29
D. Discussion.....	38
General Discussion.....	41
References.....	45
List of Tables.....	48

INTRODUCTION

Cocaine was first isolated in the 1860's by Niemann Lossen (1865) and is the principle alkaloid of the shrubs *Erythroxylon coca* and *erythroxylon Novogranatense*, species of the genus *erythroxylon* (Evans, 1981). The use of this plant has been traced back to as early as the 6th century AD (Peterson, 1977) when it was used as a stimulant by the Highland Indians of Peru. In 19th century Europe, following its isolation from the coca plant, cocaine was endorsed by leading scientists as a local anesthetic, and as a treatment for digestive disorders, asthma, and morphine addiction. Medical use of cocaine spread to America where it became commercially attainable in "Coca-Cola" and soon became a substance of abuse. Early 20th century legal restrictions on the use and sale of cocaine reduced its popularity and it was not until the 1970's that it again resurfaced as a drug of widespread abuse.

By the 1980's, cocaine use had become a prevalent social concern. A 1985 survey found that at least 22 million Americans had tried cocaine and, that 5.8 million had used it in the past 30 days (Adams et al., 1987). Another report found that 4% of the American population had used cocaine in 1989 (NIDA, 1989). Others report substantial increases in the number of people seeking help for cocaine related problems (Kozel and Adams, 1985), and increases in the number of cocaine related emergency room and treatment admissions (Adams et.al. 1987). In Canada, increases in the number of those seeking treatment for cocaine- related problems have also been reported (Firth, 1988). The 1987 "Ontario Household Survey" found that 6.1% of those surveyed had used cocaine and that 1.8% had used it in the last 12 months (Smart and Adlaf, 1987).

The primary psychological effect of cocaine is to produce feelings of profound well-being and euphoria in the user (Gawin, 1991). Cocaine has been reported to enhance emotions and sexual feelings, increase self-confidence, facilitate interpersonal communication, and, to reduce social inhibitions. Upon cessation of a period of high intensity cocaine use, a 'crash' phenomena has been reported to occur, characterized by depression, agitation, anxiety and, in some cases suspiciousness, and paranoia. This 'crash' syndrome may last from one- four hours and is followed by a period of intense hypersomnolence that can last up to several days before mood normalizes.

The administration of cocaine has been shown to produce a number of physiological effects including increases in heart rate and blood pressure (Fishman et al., 1977), and potent hyperthermic effects (Ritchie et al., 1971). Centrally, cocaine has been shown to influence monoamine systems by blocking the reuptake of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) at the neuronal synapse (see Roberts, 1992). Blocking the reuptake of DA has been shown to increase extracellular DA content in the nucleus accumbens septi (NAS) and other forebrain areas. By contrast, blocking the reuptake of 5-HT systems has been shown to potentiate autoreceptor activity of Raphe cells which consequently reduces extracellular 5-HT content in the forebrain (Broderick, 1991). Cocaine induced increases in the interaction of DA and 5-HT in the forebrain and, in particular, the NAS, are thought to be particularly relevant in mediating the rewarding effects of this drug.

Dopaminergic, noradrenergic, and serotonergic neurotransmitter systems have all been shown to display significant circadian variation

in their receptor binding characteristics, see Wirz-Justice, 1986. Given that cocaine administration alters the functioning of these neurotransmitter systems, chronic cocaine administration might be expected to alter the rhythmicity of these systems. It may be likely that the behavioral effects which follow a period of high-intensity cocaine self-administration, such as anxiety, depression, and hypersomnolence, as described above, are in part, due to cocaine induced disruptions of rhythmicity in neuronal regulation of such processes as sleep/activity cycles.

Periodicity

Cocaine use in humans has been reported to occur in episodic binges in which high intensity cocaine use is spaced by periods of recuperation and abstinence (Siegel, 1982, Gawin and Kleber, 1985). These binges are characterized by gradual decreases in sensitivity to cocaine's euphoric effects, states of paranoia and anxiety, disruption of sleep, and reports of intense craving with increased drug seeking behavior (Gawin and Kleber, 1986). Upon cessation of a binge, this increase in cocaine craving and drug seeking behavior is followed by a period of abstinence referred to as a "crash". This "crash" phenomenon has been widely documented and is characterized by a gradual reduction in cocaine craving with the user becoming increasingly dysphoric, depressed, fatigued, anhedonic, and less alert. Gawin and Kleber (1986) report that these episodes frequently meet clinical criteria for major depressive disorder and then gradually evolve into a state of dysphoric lethargy and hypersomnolence, devoid of cocaine craving. They also describe a 'withdrawal' phase wherein normal sleep/wake cycles return, mood is euthymic and subjects report 'being in control' of cravings.

Over a period of one-half to four days, however, cocaine craving returns, paralleled by 'distressing anhedonia', anxiety, and irritability, and characterized by resumed cocaine-seeking behavior.

Animal Models of Cocaine Self-Administration

In order to better understand the nature of cocaine self-administration (SA) and the parameters which govern these behaviors in humans, researchers have commonly employed animal models of drug SA. These procedures are based on the observation of a high correlation between drugs which are abused by humans and those which function as reinforcers in laboratory animals (Schuster and Thompson, 1969). Variables which have been found to influence drug SA in these animals, such as dosage, drug availability, response cost, and the animal's past history, have also been found to have similar and consistent effects across species (Griffiths et al., 1980; Johanson and Schuster, 1981).

Periodicity in Animal Cocaine SA

Animal models of drug SA have been employed in order to investigate the cyclic nature of cocaine and other psychomotor-stimulant drug SA. When allowed unlimited access to psychomotor stimulants, laboratory animals will self-administer these drugs in a cyclic manner (Johanson et al., 1976; Risner and Jones, 1976; Deneau et al., 1969;). Bozarth and Wise (1985) report that rats given unlimited access to intravenous cocaine will develop patterns of episodic drug self-administration with alternating periods of excessive intake and abstinence. The authors report a pronounced deterioration in the health of these animals with a mortality rate of 90% over 30 days.

Experimentation with animal models of cocaine SA has documented the

cyclic nature of cocaine SA, characterized by states of cocaine binging and of cocaine withdrawal, across a variety of species. Despite these findings, the bulk of work done on cocaine SA has restricted access to the drug, either by controlling the length of the test session, or by using discrete trials in which only a limited number of injections are available. Restricting drug access in these ways reveals a much different cocaine SA profile. Wilson et al. (1971) found that when access to cocaine was limited to daily, four hour sessions, monkeys would stabilize their cocaine intake to constant daily amounts. If dosage was increased or decreased under this schedule, subjects would alter their rate of intake accordingly, in order to maintain this constant level of drug intake. Furthermore, cocaine infusions were evenly spaced in time across the four hour experimental session.

Others have been able to control drug-intake by manipulating the dosage per infusion, rather than by limiting the length of the test session. Carroll and Lac (1987) and Carroll et al. (1989) allowed unlimited access to cocaine at a relatively low 0.2 mg/kg/infusion dose, and have reported long-term stability in daily cocaine intake with no health deterioration or high subject mortality rates.

Virtually all cocaine SA studies have attempted to restrict drug access by employing various reinforcement schedules, thereby limiting the variability of the data so that other research questions may be addressed (reviewed in Spealman and Goldberg, 1978). In order to assess the reinforcing properties of cocaine, many authors have examined alterations in the rate of drug SA over 3 to 5 hour testing sessions on an FR1 schedule of reinforcement. Experimental manipulations which cause increases in the rate of cocaine SA are typically interpreted to

reflect a decrease in the reinforcing efficacy of the drug, and vice versa (Roberts & Zito, 1987). It is believed that these manipulations induce alterations in the motivation to SA cocaine. Progressive ratio schedules have also been employed in order to assess the reinforcing properties of cocaine. Under this schedule, response requirements are progressively increased following each successive reinforcement. The ordinal value of the final ratio completed is used as the dependant measure and is termed the 'breaking point'. Experimental manipulations which induce variation in breaking point, as with rate measures, are interpreted to reflect alterations in the motivation to SA cocaine.

Dependant measures such as rate and breaking point may, however, be somewhat limited in terms of assessing the dynamic components underlying the motivation to self-administer cocaine. Both measures obtain data points from animals in which brain levels of cocaine are already high. These measures can be seen as assessments of the motivation to continue self-administering cocaine. They say little about the motivational factors which underlie the initiation of a period of cocaine SA. Researchers who employ these schedules, in fact, typically report the need to 'prime' an animal with a non-operant reinforcement in order to initiate operant responding (Roberts and Zito, 1987). Furthermore, because these schedules restrict access to the drug to limited time frames, they do not address the motivational factors which underlie the development of the SA profiles which characterize schedules of unlimited access to cocaine.

Few studies to date have examined variations in the periodicity of cocaine self-administration based on 24 hr access to drug, through

systematic manipulation of variables shown to influence these behaviors. Very little research has been directed towards the understanding of factors which initiate, maintain, and terminate an extended cocaine 'binge'. Further, no definitive animal models exist, at present, which may be used to investigate the motivational factors which underlie the initiation of such binges. Such models are required in order to examine the effects of pharmacologic and neurotoxic intervention on chronic cocaine SA.

Experimental intervention on animal models where response patterns are developed on less restricted, drug-access schedules may better model the present day human course of abuse. Epidemiological data has shown the 'typical' cocaine abuser to be unmarried, uneducated, and unemployed, see Johanson and Fischman, 1989. This, coupled with the increasing prevalence of the more addictive and less expensive, free base or 'crack cocaine' route of administration, indicates that cocaine SA in humans has become increasingly less restricted. Animal models of chronic, less restricted cocaine SA may have greater use in assessing interventions which could disrupt the cyclicity of human SA patterns and reduce the intensity of drug 'craving' that presumably plays an integral part in the reinitiation and maintenance of cocaine taking behavior.

Gawin (1991) states that:

...the cocaine disease process could be precisely reconstructed in animals, ...but animal models designed to mimic human cocaine administration have not been used. For example, potential pharmacotherapies targeted at conditioned cocaine craving have not appeared in clinical or preclinical research. Such treatments are nonetheless plausible and could be screened by assessment of the effect of pharmacological agents on cocaine-seeking behavior that has been linked to

conditioned cues in animals treated with cocaine
for long periods of time in a binge pattern like
that seen in humans. pp.1582

The following experiments were undertaken in order to develop a better understanding of the cyclic nature of cocaine self-administration and the motivational factors which underlie these behavioral processes. These experiments addressed the following three questions: 1.) What is the time course of cocaine craving, and how does it co-vary with circadian light/dark cycles; 2.) How do frequency of access restrictions effect the periodicity of chronic cocaine SA; and, 3.) How does unit dose impact on the periodicity of chronic cocaine SA.

General Methods

Male Wistar rats (Charles River Farms, Quebec) weighing 275-300g at the start of the experiment served as subjects. One week following their arrival from the supplier, rats were food deprived for 24 hours then trained to press a lever for food reinforcement on a FR1 schedule. Thereafter food was available ad libitum. Once trained to press a lever for reinforcement, each rat was implanted with a chronic, indwelling sytastic, jugular cannula which exited from the back at the mid-scapular region (Roberts & Goeders, 1987). Following cannulation, the rats were singly housed in 50 cm X 50 cm X 40 cm (h) operant testing apparatus. The cannula was mounted on a counterbalanced swivel apparatus, allowing free movement in the operant chamber.

EXPERIMENT 1

Human cocaine SA has been found to occur in cyclic 'binges', which alternate with periods of abstinence or 'crash'. See introduction. This crash is characterized by a cessation of cocaine SA and accompanied by states of dysphoria and anhedonia (Gawin, 1991). Similarly, laboratory animals, given unlimited access to cocaine, will continue to self-administer over a period of days thereby disrupting sleep/activity cycles. Animal models of cocaine induced anhedonia have also been proposed, wherein post-cocaine elevations in intracranial self-stimulation thresholds are taken to reflect a cocaine-withdrawal syndrome in these animals (Markou & Koob, 1991). Despite the documentation of cyclic patterns of cocaine SA in animals characterized by 'binging' and a 'crash'/withdrawal syndrome, the precise relationship between the time course of the development of cocaine withdrawal and 'craving', sleep/activity cycles, and the role these factors play in the reinitiation of cocaine SA in animals, remain to be fully characterized. A period of cocaine binging, followed by a period of post-cocaine anhedonia should be disruptive to normal behavioral processes which show circadian variation in animals. It is therefore hypothesized that, following a period of unlimited access to cocaine, a craving for additional drug will develop which will lead to the reinitiation of cocaine SA, and that this behavior will show variance over time and be disruptive to normal sleep/activity cycles.

Methods

Once cannulated, rats were allowed access to a response lever for a five hour period each day. Each lever response activated an injection pump delivering 0.1 ml of saline solution containing 0.6 mg/ml of

cocaine HCL over a 5 sec. period. Concurrent with the start of the injection, a stimulus light was activated which signaled a 20 sec. post-infusion time-cut period during which responding produced no programmed consequence. Once subjects had displayed acquisition of a regular pattern of responding on an FR1 schedule of reinforcement, their response requirements were incremented to an FR3 and then an FR5 schedule. When subjects had displayed consistent response patterns on this schedule they would be allowed a three hour period of unrestricted, free access to cocaine on an FR5 schedule. This was intended to simulate a cocaine 'binge'. Access to cocaine was then withdrawn in order to allow a post binge 'craving' to develop. At given post 'binge' time intervals, the cocaine lever was then reintroduced for a ten minute discrete trial, so that animals could be given the opportunity to self-administer a single additional injection. Responding on the post binge trial was reinforced on an FR 5 schedule, at post binge time intervals of 1, 2, 4, 6, 8, 10, 12, 18, 21, 36, and 45 hours. Each subject was tested at each post binge time interval. Subjects were tested within three different interval range groupings: 1.) 1, 2, 4, 6, and 8 hours post binge; 2.) 10, 12, and 18 hours post binge; and 3.) 21, 36, and 45 hours post binge. The order of testing was counterbalanced within each interval range, and order of interval range was also counterbalanced. It was felt that these intervals would be sensitive in elucidating the time course of both short and long term cocaine 'craving': intervals "1" through "8" would test the tendency to reinitiate responding during the active phase of the rats diurnal cycle, intervals "10" through "18" would chart this behavior across the first sleep phase of cocaine

abstinence, the "21" hour interval represents the same time of day as binge initiation on the previous day, "36" would test responding in the middle of the sleep phase 2 days following binge initiation, and, finally, the "45" hour post binge interval would test the response of rats two days following the initial binge at the same time of day as that binge. Given that several of these time intervals would allow post binge access to cocaine at times when rats typically sleep, correct responses at these times would indicate a craving induced disruption of normal sleeping behavior.

Results

Figure 1 shows the percent of animals (n=11) that self-administered a single cocaine infusion when allowed access to response levers at the various 'post-binge' time intervals specified. It was found that a very high proportion of rats tested (between 75 and 88%) would self-administer cocaine at the 1 to 8 hour time intervals but that fewer (55% and 25%) would do so at the 10, and 12 hour intervals with fewer still (18%) at the 18 hour post binge interval. At the 21 hour interval, a time which corresponds to the time of day when the initial 'binge' was begun and the time at which the normal activity cycle again begins, the percent of animals self-administering rose to 76%. This percentage then decreased again (30%) at 33 hours 'post-binge', a time at which sleep normally occurs. Finally, at 45 hours post binge, a time which corresponds again to the time of binge initiation, the percent of animals responding rose to 66%.

These results show that, following a three hour binge period of unrestricted, free access to cocaine, rats will self-administer an additional single dose of cocaine throughout their natural activity

FIGURE 1: Percent of rats self-administering cocaine at various time intervals, following a three hour period of free access to drug.

cycle, regardless of post-binge time length. Once rats enter the time frame of their normal sleep cycle, however, fewer rats will self-administer, reaching a low at 18 hours 'post binge'. This cyclic effect appears consistent across both one- and two-day post-binge time intervals.

Discussion

The present results indicate that the time course of 'post-binge' cocaine SA in rats is cyclical and would appear to fit the pattern of the light/dark cycle. Rats typically sleep during the light cycle and are active during darkness. It would appear from the present results that the cocaine craving which develops following a three hour period of unlimited access to cocaine does not disrupt the periodicity of rest/activity cycles. Clinical studies which have examined the periodicity of cocaine SA typically report profound disruptions in the patterns of sleep and wakefulness, where subjects avoid sleep for periods of up to several days and then enter into a period of hypersomnolence (Gawin and Kleber, 1986; Gawin, 1991). In rats, however, rest cycles would appear to override the tendency to self-administer cocaine as post-binge time intervals extend into light periods. It is possible that, in rats, these circadian cycles are more strongly entrained and, thereby more resistant to the disruptive effects of cocaine 'craving'.

Clinical studies of human cocaine taking behavior report that when a binge period of cocaine self-administration is followed by a drug-free interval, a 'crash' phase, characterized by drug abstinence, typically occurs (Gawin and Kleber, 1986; Gawin, 1991). It is

interesting to note that, in the present study, the percentage of animals that responded for post-binge cocaine did not drop off after the two hour time interval, but in fact remained high until the onset of light, 10 hours later. These data indicate that, when response requirements are relatively low (FR 5), rats will frequently reinitiate cocaine SA despite long drug-free intervals.

A number of factors may mediate the variation in the present data, such as response requirements, duration of drug access during the 'binge' period, 'binge' initiation times, and the duration of lever presentation at a post binge trial. Systematic examination of the effects of each of these variables on the periodicity of cocaine SA behavior would greatly expand understanding of the motivational factors involved in the reinitiation of cocaine SA and the cyclicity of this behavior. A clearer understanding of these factors would be useful in developing animal models of drug self-administration which could further explore drug taking characteristics such as 'binging' and 'craving' and be useful in testing the efficacy of various behavioral and pharmacological interventions. Some of these factors were explored in the following study.

It has been shown that limiting access to cocaine by restricting the length of the testing session will result in a stable, daily, drug-intake profile (Wilson et al., 1971). The causal factors involved in mediating this effect, however, remain unclear. It is possible that the length of the test session may be inadequate to allow blood cocaine levels to become sufficiently high to induce a need for a period of recuperation. Alternately, the introduction of daily, limited-time-frame, drug access schedules, may enforce a periodicity of cocaine SA which is self-perpetuating and which supercedes the tendency to develop the cyclic SA patterns which characterize unlimited access schedules. The results from Experiment 1 indicated that the time course of cocaine craving in rats is cyclical and that this craving may also serve a modulatory role in regulating the periodicity of cocaine SA.

Daily cocaine intake could be controlled by restricting the frequency of access to cocaine over continuous, 24 hour per day, access periods. In this way, cyclicity in chronic cocaine SA could be examined while maintaining controls over the maximum daily drug intake. It is hypothesized that, as the frequency of access to cocaine is reduced, the periodicity of self-administration would develop a more stable daily pattern of intake and that the longer cycles of alternating binging and abstinence would cease.

The following experiment has been undertaken in order to explore the notion that frequency-of-access restrictions will induce variation in the cyclicity of cocaine self-administration. Rats trained to press a lever for cocaine were given discrete, 10 minute drug access trials at fixed frequency intervals for continuous periods of 7-10 days. Subjects

were allowed a single injection per 10 minute access period with reinforcement on an FR 5 schedule. This experiment attempted to determine the effects of restricted drug access on cocaine 'binging' behavior by examining the intake profile and periodicity of cocaine SA as a function of various frequency-of-access restrictions.

Methods

Procedure. Male wistar rats (n=19), implanted with chronic, indwelling silastic jugular cannulae, were trained to respond for cocaine on an FR 5 schedule of reinforcement, 1.5 mg/kg per infusion. Subjects were then given 10 minute drug access trials, maximum 1 infusion/trial, at one of three frequency rates: one, two, or four, equally spaced, drug access trials/hour. A light stimulus was paired with lever presentation to signal availability of the drug. Completion of an FR 5 resulted in a cocaine infusion (1.5 mg/kg) which was signalled by the illumination of a stimulus light for 20 sec. Upon receiving the infusion, or if 10 minutes had elapsed, the trial was terminated and the lever retracted from the cage. Responding was recorded over 7-10 day time intervals. All subjects were tested in each frequency of access condition; order of testing was counterbalanced. Upon completion of each frequency of access condition, subjects were given access to cocaine for a period sufficient to demonstrate the patency of the cannula. Subjects whose cannulae were determined to be malfunctioning were removed from the analysis.

Data Analysis. For each hour, data were expressed as a percentage of the number of cocaine injections self-administered divided by the number of cocaine lever presentations in that hour. Time series were constructed for each animal over the 7-10 day period for each frequency

of access condition and subjected to power spectral analyses. Power spectral analysis, also known as fast-Fourier transforms, is a statistical algorithm used detect underlying rhythms in temporally distributed data. It is a frequency-domain, sine-wave model fitting technique that produces power estimates (area under the sine-wave curve) for each sine-wave fit. Successive sine-waves are applied to the time series reiteratively, until all variance is described (Gottman, 1981; Dixon, 1983). The frequency with the largest power value represents the period of the dominant rhythm in the time series. This statistical procedure has been used to describe rhythmicity in sleep EEG, task performance in wakefulness, and a variety of physiological processes (See Armitage et al., 1992). In this study, power spectral analyses were conducted using BMDP-1T subroutines (Dixon, 1983).

Results

Figure 2 shows the pattern of cocaine self-administration for a representative animal during the periods when access to cocaine was restricted to 1, 2 or 4 trials/hour. During the 1 trial/hour condition, this subject demonstrated cocaine self-administration behavior that was almost exclusively restricted to the dark period. In general, responding was likely to occur during 6-8 consecutive trials beginning a few hours into the dark phase. When given 2 trials/hour, cocaine SA would continue into time periods which begin to impinge on the light/inactive phase of the animals natural sleep/activity cycle. In the 4 trials/hr condition, the subject responded during consecutive trials which continued over periods unrelated to the circadian cycle. The animal collected the cocaine injections at almost every opportunity for periods of up to 18

animal : m746

1 trial / hour

animal : m746

2 trial / hour

animal : m746

4 trial / hour

FIGURE 2: Time series for a representative animal at each of the three access conditions tested. Scores represent the percentage of available injections taken each hour of a ten day test session. Access was restricted to 1, 2 or 4 trials for top, middle, and bottom panels respectively. Bars across the top of each diagram represent the time of the dark (active) phase.

hours.

Power spectral analyses of the time series data were generated for each subject ($n=16$) at each frequency-of-access condition. Figure 3 shows the mean power spectra calculated from the individual power spectral values at each frequency of access condition. The dominant frequency for the 1 and 2 trials/hour conditions was about 24 hours (circadian), whereas greater than 24 hour (infradian) peak periodicities predominate in the 4 trials/hour access condition.

Analysis of variance (ANOVA) was performed on each group's mean power values, treating period as a 48-level within-group variable. This analysis revealed significant within-group differences for the one-per-hour access condition ($F = 8.31$, $df = 47, 97$; $p < .0001$), the two-per-hour access condition ($F = 13.55$, $df = 47, 376$; $p < .0001$), and the four per hour access condition ($F = 14.34$, $df = 47, 282$; $p < .0001$), indicating significant rhythmicity at at least one frequency in each of these conditions. Significance testing for power spectral data is somewhat controversial, with little agreement over the choice of statistic to determine whether a given peak in the power spectrum is significantly different from neighboring periodicities (Armitage, 1986). The statistical procedure followed here employed multiple, within-group t-tests to compare mean power at the dominant period with power at adjacent frequencies. These results are shown in Table 1. For the one-per-hour frequency-of-access condition a peak periodicity of 24 hours is significantly different from neighboring periodicities of 30 and 21.82 hours. Significant power spectral peaks occur at 24 hours in the two-per-hour access condition, and at 48 hours in the four-per-hour frequency-of-access condition.

FIGURE 3: Frequency of access alters the periodicity of self-administration patterns. Lines represent the mean power spectral values for each of three groups given 1, 2 or 4 self-administration trials per hour for 10 days. The 1 and 2 trials per hour conditions generated a significant peak at 24 hours (i.e. circadian), whereas the 4 trials per hour condition produced a significant peak at the 48 hour rhythm.

ANOVA's were also performed on the group mean power spectral data, treating frequency-of-access as a three-level-between groups variable, to evaluate the influence of access condition on the distribution of rhythmic components in percent-reinforcement. A significant period X access interaction was obtained ($F = 7.85$, $df = 2, 94$; $p < .0001$), indicating that the periodicity of cocaine SA varied significantly as a function of access condition. Significant period X access differences were found to span a range of time periods. Of particular relevance to the present results were those obtained at the 48 hour period. Power at the peak periodicity of 48 hours in the four-per-hour access condition was revealed to be significantly different from power values at the 48 hour period in both the one and two-per-hour access conditions.

Discussion

Significant interactions in the present experiment indicate that restricting the frequency of access to cocaine will significantly alter the periodicity of cocaine self-administration. Dominant circadian rhythms with small, secondary ultradian peaks, were evident in the group power spectra for the one-per-hour frequency-of-access condition. Dominant circadian rhythms were evident at the two-per-hour frequency-of-access condition, while the four-per-hour frequency-of-access condition resulted in infradian patterns of cocaine SA. These results suggest that despite having 24 hour access to cocaine, rats will continue to show stable daily intake of drug when frequency-of-access is restricted to one or two times per hour. These animals continue to show circadian rhythmicity in their drug intake profile. As frequency of

access is increased however, drug intake profiles become less stable and regular circadian patterns of drug intake become disrupted. Animals begin to show self-administration profiles characteristic of cocaine 'binging' with extended infradian cocaine SA behavior patterns. They display alternating periods of prolonged high intake interspersed with periods of abstinence as seen with unlimited access schedules.

Previous investigators have shown that laboratory animals, when given continuous, unlimited 24 hour access to cocaine, will self-administer this compound in erratic 'binges', over prolonged time periods which often supercede the normal physiological processes of sleep and food consumption in these animals (Johanson et al., 1976; Risner and Jones, 1976; Deneau et al., 1969; Bozarth and Wise, 1985). By contrast, others have affected restrictions on cocaine intake by limiting the daily time frames of drug access. These restrictions typically induce an individual stability in the subjects daily intake pattern. The present results suggest that a similar drug intake stability may be achieved by restricting the frequency of access to cocaine to one or two discrete access trials per hour.

Several possible explanations for these phenomena are tenable. By restricting the daily time-frames of drug access, drug intake stability may occur as a result of an imposed periodicity of access which becomes self-perpetuating once established. Circadian zeitgebers (environmental cues which function to entrain the rhythmicity in physiological processes) may act as drug-associated cues that are paired with the drug SA response on a circadian basis. The circadian periodicity of these cues, then, would function to entrain drug SA behaviors to a similar circadian periodicity. Although these processes

may contribute, to some extent, towards establishing drug SA stability, the present results suggest that they are not a necessary component for establishing stable circadian cycles of cocaine SA. With frequency-of-access restrictions, a stable circadian pattern of behavior was established despite the continuous, 7-10 day, chronic, drug-access schedule.

The establishment of circadian rhythmicity in cocaine self-administration may depend more upon the interrelatedness of temporal and quantitative variables related to drug intake such as the frequency and duration of drug access and the amount of drug ingested. Restricting the frequency-of-access to cocaine to the one-per-hour access schedule in the present study may have prevented the establishment of brain cocaine levels which were high enough to induce the extension of cocaine SA behavior into time periods that disrupt regular circadian behavior and physiology. Alternatively, when the frequency of drug access was increased to four drug trials per hour, cocaine SA could occur at a rate sufficient to produce brain cocaine levels that may have crossed some form of threshold. This may have induced a physiological state, centrally, that was conducive to a continuation of drug SA response patterns and that disrupted the regular circadian regulation of such processes as sleep/wake cycles and digestive rhythms. Following the cessation of cocaine SA, an extended period of recuperation may be required, perhaps reestablishing the synchronization of these rhythms.

Studies which have restricted the length of daily, drug-access time-frames, then, may have prevented the establishment of brain cocaine levels high enough to induce the need for an extended period of drug

recuperation. It is conceivable that extending the time-frames of drug access under these designs would permit a disruption of the circadian drug intake patterns and extend these behaviors into greater than 24 hour periods.

Previous studies where 24 hour, continuous access to cocaine has been scheduled are consistent with the above explanation, wherein cocaine SA patterns are found to be infradian in nature and disruptive to a number of behavioral and physiological processes. These studies also suggest that that a ceiling effect may be reached where the length and frequency of access are increased to a degree which allows drug SA to occur at periodicities that permit brain cocaine levels to reach overdose levels. Alternatively, narrowing the daily time-frames of drug access, or further reducing the frequency-of-access to cocaine, may restrict drug brain cocaine levels to a point where continued cocaine SA ceases to be reinforcing, a floor effect is reached, and drug SA behavior does not continue. Further study is required to determine the relationship between frequency and length of daily access to cocaine, and by extension, drug brain-blood and brain tissue levels, and the periodicity of cocaine SA. Such study may prove fruitful in establishing the degree of co-linearity and co-dependence of these variables and possible threshold levels of cocaine intake required to disrupt circadian cycles of drug intake and abstinence found under particular access schedules.

The mechanisms which underlie the shifts in the pattern of cocaine SA due to alterations in drug restrictions might involve cocaine-induced alterations in the biological systems that control circadian sleep/activity cycles and and their regulation of sleep and wakefulness.

Cocaine has been shown to act as an indirect agonist at monoamine synapses, blocking the reuptake of norepinephrine (NE), dopamine (DA), and serotonin (5-HT), thus increasing the synaptic efficacy of these neurotransmitters. The intravenous route of administration employed here would induce global brain variation in these synaptic effects, causing widespread alterations in brain functioning. Of particular interest for the present results are the effects of cocaine on brainstem, diencephalon, and forebrain regulation of sleep/activity states. Serotonergic raphe neurons, and noradrenergic neurons of the locus ceruleus have both been implicated in the regulation of sleep and, in particular, REM sleep. See Siegel (1990). These cell nuclei have widespread innervation to midbrain and forebrain regions including the anterior hypothalamus, felt to be crucial in the regulation of circadian timing mechanisms, thermoregulation, and neuropeptide regulation (Holsboer, 1989). Chronic cocaine SA, then, would be expected to disrupt the homeostatic balance of this complex neuronal environment, resulting in dysregulation of circadian timing of biological and behavioral states. Future research should attempt to delineate the effects of chronic cocaine on these brain centers, with the intent of establishing the parameters necessary to induce this dysregulation.

The establishment of stable, daily drug-intake patterns has afforded researchers the opportunity to introduce other experimental manipulations and investigate their effects on drug intake. Restricting cocaine access to daily, four or five hour time periods has provided a powerful research tool for testing manipulations which alter the rate or stability of a previously established, baseline pattern of intake. A

manipulation which induces alterations in this baseline pattern, then, could be taken as an indication that the ongoing motivation to self-administer the drug has been altered. This paradigm may help identify variables variables that effect the motivation to continue self-administration but it does not, however, address the motivational factors which underlie the tendency to reinitiate a period of cocaine-intake. Drug access schedules that affect intake by restricting frequency-of-access while permitting availability over continuous, 24 hour periods may prove useful in exploring the motivational characteristics underlying chronic cocaine SA. Experimental manipulations which consistently induce alterations in pre-established, baseline periodicities of cocaine SA at one or more frequency-of-access conditions, may be considered for its causal role in altering the motivational factors underlying the reinitiation of cocaine SA behavior.

Experiment 3

With unlimited access to cocaine, a number of studies have reported high subject mortality rates, rapidly deteriorating health conditions, and low food intake (Deneau et al., 1969; Johanson et al., 1975; Bozarth and Wise, 1985). These studies have typically employed relatively high unit doses of cocaine. By contrast, others have used comparatively lower unit doses, under similar access schedules, and report no such ill health effects (Carroll and Lac, 1987; Carroll et al., 1989). It would appear that variations in dose per infusion alter the typical profile of unlimited access to cocaine. It is possible, however, that certain methodological inconsistencies among different studies and laboratories may be partially responsible for this discrepancy. No studies exist, to our knowledge, that have systematically tested the effects of various doses on long term, unlimited access schedules of cocaine self-administration.

In order to test the effects of dose of cocaine on the periodicity of cocaine SA, rats trained to self-administer cocaine were randomly assigned to one of three unit-dose subject groups. These rats were then given unlimited access to cocaine, reinforced on an FR 5 schedule, for 10 days. The purpose of this study was to compare the effects of unit dose on the duration and periodicity of cocaine 'binging' behavior.

Methods

Procedure Male wistar rats were implanted with chronic, indwelling, silastic, jugular cannulae and were trained to press a lever for cocaine on an FR 5 schedule of reinforcement over 5 hour SA sessions. Subjects were then allowed unlimited access to cocaine, reinforced on an FR 5

schedule, at one of three doses: 1.5 mg/kg/infusion (n=4), 0.5 mg/kg/infusion (n=5), 0.2 mg/kg/infusion (n=5). Two levers were continuously available, an active drug lever and an inactive control. Responses on the inactive lever were recorded but had no other programmed consequence. Subject assignment to groups was done on a random basis.

Data Analysis. Time of drug infusion was recorded for each subject, at each cocaine dose level, over the duration of the ten day test session. These data were then tabulated as number-of-infusions per hour for each hour of the experiment. Time series were constructed from the infusions-per-hour scores for each subject. The time series data were then analyzed by power spectral analysis in order to detect the underlying rhythmicity in the cocaine SA behavior at the three drug doses.

Results

The time series for three representative animals, tested at three different dose per injection levels, are shown in figure 4. It can be seen that, at the highest dose tested (1.5 mg/kg/inj), the animal shows almost continuous, high levels of intake. Marked deterioration in the health of this animal prevented the continuation of the experiment past the 70 hour time point. At the 0.5 mg/kg/inj dose, the animal displayed cyclical patterns of self-administration characterized by extended periods of high level responding alternating with extended periods of voluntary abstinence. The lowest dose tested (0.2 mg/kg/inj) maintained only minimal levels of cocaine self-administration in the animal shown. The self-administration behavior is found to occur exclusively in the active phase of the sleep/activity cycle.

FIGURE 4: Time series for representative animals tested at 3 different unit doses of cocaine. Scores represent the number of injections self-administered at 0.2, 0.5 and 1.5 mg/kg/inj doses for the top, middle and bottom panels respectively.

Power spectral analysis was performed on the time series data for each subject and the individual subjects' power spectral values were averaged across each dose level to form group mean power spectra (Figure 5). An examination of the mean power spectra at each dose level reveals peak power that differs as a function of dose. Peak power in the 0.2 mg/kg/inj group occurs at a periodicity of 26.7 hours with a smaller peak at 60 hours. The group which received infusion doses of 0.5 mg/kg/inj shows peak power spectral values at 60 hours. The 1.5 mg/kg/inj group shows peak power at 70 hours, a period equal to the duration of testing. Although dominant peaks were revealed in this analysis, spectral power was relatively low, suggesting weak rhythmicity. High, within-group variability, coupled with a small sample size, precludes the necessity to perform further statistical analysis on the power spectral data as statistical power was too low (Stevens, 1986).

Individual subject's data for each dose group are presented as a function of mean number-of-infusions per hour by time of day. Figure 6 shows these data for individual subjects at the 0.2 mg/kg/inj dose. One subject at this dose displayed high levels of responding which peak at the end of the dark (active) phase of the circadian sleep/wake cycle and then decline gradually throughout the remainder of the light (inactive) phase. The remaining subjects in this group, however, maintained only low rates of responding during the dark (active) phase of the cycle and little or no self-administration behavior during the light (inactive) phase. The peak power spectral value at a periodicity of 26.7 hours is consistent with

FIGURE 5: The effect of changes in unit injection dose on periodicity of cocaine self-administration. Lines represent the mean power spectra for each of three unit doses tested.

UNLIMITED ACCESS

0.2 MG/KG/INJ

FIGURE 6: Hourly intake of cocaine self-administration on an unlimited access schedule (0.2 mg/kg/inj). Points represent the intake for each hour of the day averaged across a 10 day session. Each line represents an individual animal. Note that four of the five animals maintained relatively low levels of responding only during the dark phase, whereas one animal displayed higher cocaine intake which was disruptive to the normal sleep/activity cycle.

the data shown in Figure 5, where four of the five animals did not SA drug during light (inactive) phases, showing circadian cyclicity in their intake profiles. Response rates were relatively low at this dose, but occurred at a ratio of at least 20:1 in comparison to inactive control lever responding.

At the 0.5 mg/kg/inj dose (Figure 7), a high degree of variability was evident in the response patterns, although the majority of subjects responded throughout the circadian dark (active) cycle, and continued into the light (inactive) cycle, tapering off to low levels at the end of the light phase. The mean spectral peak of 60 hours in the 0.5 mg/kg/inj group indicates a cyclicity in drug self-administration over the 10 day test period that is not reflected in the mean infusions-per-hour data. This cyclicity occurs over time periods greater than 24 hours, and therefore indicates infradian variation in the profiles characterized by the infusions-per-hour data. The mean power peak at 60 hours suggests that periods of drug intake alternate with periods of non-responding and that this rhythmicity in cocaine self-administration does not follow the day/night cycle exclusively, but rather occurs over extended, infradian periodicities.

Subjects in the 1.5 mg/kg/inj dose group (Figure 8) were withdrawn from testing at day 4 of the experiment due to rapidly deteriorating health. These subjects showed reduced intake of food and water, piloerection, rapid weight loss, and convulsions. Responding continued consistently throughout the light (inactive) phase showing little if any relationship to the light/dark cycle. The mean peak power value of 70 hours, equal to the total length of the test session,

coupled with the consistent levels of responding across the 24 hour period shown in Figure 8, indicates that these response levels were maintained with relative consistency throughout the duration of the experiment. Consistent alteration between periods of high intake and abstinence did not occur.

UNLIMITED ACCESS

0.5 MG/KG/INJ

FIGURE 7: Hourly intake of cocaine self-administration on an unlimited access schedule (0.5 mg/kg/inj). Points represent the intake for each hour of the day averaged across a 10-day session. Each line represents an individual animal. Apart from one animal that maintained low levels of responding exclusive to the dark phase, the remaining animals showed cocaine self-administration patterns which intruded into the light (inactive) phase.

UNLIMITED ACCESS

1.5 MG/KG/INJ

FIGURE 8: Hourly intake of cocaine self-administration on an unlimited access schedule (1.5 mg/kg/inj). Points represent the intake for each hour of the day averaged across a 10-day session. Each line represents an individual animal. All subjects showed self-administration patterns which continued throughout the 24 hour cycle.

Discussion

The periodicity of cocaine SA was found to vary as a function of cocaine dose per infusion. Although the results showed high inter-subject variability in response profiles at a given cocaine dose, it was found that the periodicity of cocaine SA increased to infradian time periods as the cocaine unit dose is increased. At the highest dose tested, animals continued to self-administer cocaine at such a high rate that the experiment was terminated prematurely, prior to any period of voluntary abstinence. At the midrange cocaine dose, most animals showed infradian rhythmicity in their self-administration behavior, characterized by extended periods of cocaine 'binging' that was disruptive to normal circadian sleep-wake cycles but caused no visible signs of severe health impairment. The lowest cocaine dose tested was found to maintain only minimal levels of responding in the majority of subjects. Responding which did occur at this dose level was limited almost exclusively to the active phase of the light/dark cycle. The majority of subjects tested at this dose, then, showed a circadian stability in their self-administration patterns.

The results of the present experiment are consistent with those of Carroll et al. (1989) where animals received long-term continuous access to cocaine while maintaining a stable daily-intake profiles. This is in direct contrast to the results of others (Johanson et al., 1976; Risner and Jones, 1976; Deneau et al., 1969; Bozarth and Wise, 1985) where long-term, continuous access to cocaine has resulted in binge-like SA profiles. The present results suggest that this discrepancy may be explained by differences in the unit dose employed. Varying the unit dose in chronic cocaine SA paradigms may have significant impact on

response profiles and should, therefore, be given careful consideration in future research where long-term access to cocaine is scheduled.

Varying the unit dose of cocaine in experimental paradigms that allow unlimited access to cocaine, induces alterations in the relationship between response cost and reinforcement (Bickel *et al.*, 1990). With increasingly lower drug dose, the maintenance of equivalent cocaine brain-blood levels requires increasingly higher response levels. In addition, the reinforcement efficacy of a given cocaine infusion would be expected to vary as a function of dose. The relationship between cocaine unit dose and efficacy of reinforcement remains unclear, see Johansson & Fischman, 1989. Although it is generally assumed that efficacy of reinforcement increases with dose, the precise nature of this relationship has not been quantified. The present results may be explained by the effects of either one or a combination of the variables. A given change in unit dose of cocaine may induce alterations in the efficacy of reinforcement per infusion and/or a change in the behavioral cost of maintaining a reinforcing brain-blood level of drug. Furthermore, the role of these variables in mediating periodicity in cocaine SA may be dynamic across time, and vary in their degree of influence over time. The precise contribution of behavioral cost and reinforcement per unit dose of cocaine in mediating the results of Experiment 3, remains unclear. Further experimentation is required in order to delineate the role of these variables in contributing to the periodicity of chronic cocaine SA.

The results of Experiment 3 suggest that manipulating cocaine unit dose may prove useful in developing research strategies where the

behavioral effects of continuous and unlimited access to cocaine are of interest. The notion that giving animals long-term, unlimited access to cocaine will necessarily result in a disruption of the ongoing health of the subject, appears false. The application of dose restrictions would appear to be a useful tool in developing experimental paradigms which investigate variations in chronic cocaine SA in animals and, perhaps, humans.

GENERAL DISCUSSION

The three experiments which have been described in the present paper have been conducted in an attempt to assess the time course and periodicity of cocaine SA and cocaine craving in rats. This was undertaken as a necessary step toward the development of new animal models based on chronic, unlimited access to cocaine. The need for a clearer understanding of the factors which contribute to the variability in chronic cocaine SA in rats was made apparent by the results of Experiment 1. It was hypothesized that, following a period of unlimited access to cocaine, animals would show a pattern of cocaine withdrawal and reinitiation similar to that noted by Gawin in humans. This pattern is described as a sharp decline in the desire to continue drug SA, lasting for several days, followed by a return of drug craving which results in a reinitiation of high level, extended drug SA. The rats in Experiment 1, however, responded to 'post binge' lever presentations in circadian fashion, responding at high rates during the active phase of the light-dark cycle but not during the inactive phase. These rats where, however, allowed only a three hour period of unlimited access during the 'binge' period. The results of Experiments 2 and 3, suggest that cocaine SA will vary according to access and dose restrictions. Further, SA patterns appear to follow a circadian periodicity when these restrictions do not allow cocaine intake to reach critical thresholds that disrupt circadian sleep/activity cycles. It is likely, therefore, tha. the three hour period of unlimited access given in Experiment 1 was of insufficient duration to allow rats to reach this critical level and induce infradian trends in the pattern of cocaine SA.

Animal models of cocaine SA, to date, have generally been based on paradigms where a regular, daily, baseline drug intake is established. This is followed by the manipulation of variables that may induce measureable changes in baseline intake. This daily, baseline pattern is generally established by introducing restrictions on the daily time frames of drug intake within a given test session. These designs are based on the logic that inducing a regular daily pattern of drug intake establishes control over drug intake variability, thus allowing a confound free estimate of the effects of the independent variable.

Although these designs have provided a useful tool for the investigation of the effects of a variety of agents and behavioral parameters on a period of ongoing cocaine SA, recent clinical data has suggested that these designs may not always be appropriate in modelling present cocaine abuse in humans. Gawin & Kleber (1986), have identified a subset of cocaine abusers whose pattern of use is long-term and is characterized by periods of high-dose, long-duration binging, separated by periods of several days abstinence. Those who show this pattern of cocaine SA have also been described as those who are most likely to seek treatment (Gawin & Kleber, 1985). It is suggested that a state of cocaine withdrawal which occurs near the end of this period of abstinence is the significant factor in the reinitiation of cocaine SA and is, therefore, highly significant in maintaining long-term cocaine abuse in humans (Gawin & Kleber, 1986; Gawin, 1991). These authors also suggest that this withdrawal phase may be a crucial focus for treatment, wherein pharmacotherapeutic intervention and elimination of access to cocaine may prove most efficacious. Given these factors, experimental paradigms which allow long-term, continuous access to cocaine and that

test manipulations which affect the tendency to reinitiate a period of cocaine SA, may prove to be more appropriate and useful models of present day cocaine abuse.

The results of the present studies suggest that a number of factors may induce variation in chronic cocaine SA and that these must be taken into consideration in order to develop concise animal models of cocaine abuse. Two variables which have been examined here, unit dose and frequency of access, were shown to induce significant variation in the periodicity of chronic cocaine SA. A number of other factors may similarly induce variation in the patterns of chronic cocaine SA. Future research should, therefore, investigate the effects of such factors as duration of access, time of day of access, differences among animal strains and species, and differences in response requirements. Once the role of these variables are more clearly understood, animal models may be developed that control for the variability induced by these factors.

Experiment 1 in the present paper was conducted in an attempt to assess the time course of the development of craving for cocaine in rats. Previous research has indicated that allowing long-term, continuous access to cocaine would result in health risks to the subject, see Introduction. Because of this, Experiment 1 allowed only three hours of continuous access in order to simulate a cocaine 'binge'. The experiment was limited, then, in that it did not schedule the pre-conditions necessary to allow for the development of chronic cocaine intake patterns. A modification to Experiment 1 is hereby proposed, wherein a post-binge access trial could be preceded by an

extended period of cocaine availability. Control over drug intake during this period could be achieved, then, by restricting the frequency of drug access to four trials per hour. This would serve to control for variability in pre-test, baseline drug intake as well as reduce the risk of overdose and health dangers in the test subject. Various 'post-binge test intervals' could then be evaluated under controlled experimental conditions and compared to behavior at baseline 'post binge test intervals'. The efficacy of this proposed model awaits experimental verification which should only be undertaken upon replication of the present results. Should the present results prove robust, they will have strong implications for the development of future animal models of cocaine abuse which test the factors which mediate the reinitiation of cocaine SA.

REFERENCES

- Adams, E.H., Groerer, J.C., Rouse, B.A., and Kozel, N.J. Trends in prevalence and consequences of cocaine use. In: M.S. Gold, M. Galanter, and B. Stimmel (eds.) Cocaine Pharmacology, Addiction, and Therapy, (1987).pp. 49-71, Haworth Press, New York.
- Armitage, R., Ultradian Rhythms in EEG and Performance: An of individual differences in the basic rest activity cycle. (1986).PhD thesis, Carleton University.
- Armitage, R., Roffwarg, H.P., Rush, A.J., Calhoun, J.S., Purdy, D.G., Giles, D.E., Digital period analysis of sleep EEG in depression. Biological Psychiatry, (1992), 31:52-68.
- Bickel, W.K., DeGrandpre, R.J., Higgins, S.T., Hughes, J.R., Behavioral economics of drug self-administration. Life Sciences (1990), 47:1501-1510.
- Broderick, P.A. Cocaine: On-line analysis of an accumbens amine neural basis for psychomotor behavior. Pharmacology Biochemistry and Behavior, (1991), 40: 959-968.
- Bozarth, M.A., Wise, R.A., Toxicity associated with long term intravenous heroin and cocaine self-administration in the rat. Journal of the American Medical Association, (1985) 254:81-83.
- Carroll, M.E., & Lac, S.T., Cocaine withdrawal produces behavioral disruptions in rat. Life Sciences, (1987), 40:2183-2190.
- Carroll, M.E., Lac, T.L., Nygaard, S.L., A concurrently available nondrug reinforcer prevents the acquisition or decreases the maintenance of cocaine-reinforced behavior. Psychopharmacology, (1989), 97:23-29.
- Dackis, C.A., & Gold, M.S., New concepts in cocaine addiction: the dopamine depletion hypothesis. Neuroscience and Biobehavioral Reviews, (1985), 9:469-477.
- Dackis, C.A., & Gold, M.S., Neurotransmitter and neuroendocrine abnormalities associated with cocaine use. Psychiatric Medicine, (1987), 3:461-483.
- Dackis, C.A., Dackis, M.A., Pottash, A.L.C., Martin, D., & Gold, M.S., Platelet serotonin transporter in cocaine patients. National Association of Drug Addiction Monograph, (1984), 55:164-169.
- Deneau, G.W., Yanagita, T., Seavers, M.H., Self-administration of psychoactive substances by the monkey: A measure of psychological dependence. Psychopharmacology, (1969), 16:30-48.
- Evans, W.C., The comparative phytochemistry of the genus *Erythroxylon*. J. Ethnopharmacol., (1981), 3:265-277.

Firth, J., Registrations with cocaine as the major problem substance, July 1983 - December, 1987. Unpublished data. (1988) Toronto: Clinical Institute, Addiction Research Foundation.

Fischman, M.W., Schuster, C.R., & Krasnegor, N.A., Physiological and behavioral effects of intravenous cocaine in man. In E.H. Ellinwood, Jr., & M.M. Kilbey (Eds), Cocaine and Other Stimulants, (1977). London: Plenum.

Gawin, F.H., & Kleber, H.D., Cocaine abuse in a treatment population: Patterns and diagnostic distinctions. NIDA Research Monograph Series 61. (1985) Washington DC, National Institute on Drug Abuse, pp 182-193.

Gawin, F.H., Cocaine addiction: Psychology and neurophysiology. Science, (1991) 251:1580.

Gawin, F.H., & Kleber, H.D., Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Archives of General Psychiatry, (1986), 43:107-113.

Gottman, J.M., Time Series Analysis, (1981). Cambridge:Cambridge University Press.

Griffiths, R.R., Bigelow, G.E., Henningfield, J.E., Similarities in animal and human drug taking behavior. In: N.K. Mello(ed.) Advances in Substance Abuse, Vol. 1, , (1980) pp. 1-90. JAI Press, Inc. Greenwich, Conn.

Holsboer, F., Psychiatric implications of altered limbic-hypothalamic-pituitary-adrenocortical activity. European Archives of Psychiatric Neurological Sciences, (1989), 238:302-322.

Johanson, C.E., Balster, R.L., Bonese, K., Self-administration of psychomotor Stimulant drugs: the effects of unlimited access. Pharmacology, Biochemistry & Behavior, (1976), 4:45-51.

Johanson, C.E., & Fischman, M.W., The pharmacology of cocaine related to its abuse. Pharmacological Reviews, (1989), 41:3-52.

Johanson, C.E., & Schuster, C.R., A comparison of the behavioral effects of l- and d-cathinone and d-amphetamine. Journal of Pharmacology and Experimental Therapeutics, (1981), 219:355.

Knapp, S. & Mandell, A.J., Narcotic drugs: Effects of cocaine on serotonin biosynthetic systems of the brain. Science, (1972), 177:1209-1211.

Kozel, N.J. and Adams, E.H., Cocaine use in America: Summary of discussions and recommendations. In: N.J. Kozel and Adams (Eds.) Cocaine Use in America: Epidemiologic and Clinical Perspectives, (1985) (Research Monograph No. 61, pp. 221-226). Rockville, MD: National Institute on Drug Abuse.

Lossen, w., Uber das Cocain. Annalen der Chemie und Pharmacie, (1865), 133:351-371.

Markou, A., Koob, G.F., Postcocaine anhedonia: An animal model of cocaine withdrawal. Neuropsychopharmacology, (1991), 3:17.

National Institute on Drug Abuse, National Household Survey on Drug Abuse [Department of Health and Human Services Publ.] (1989)(ADM) 89-1638, Government Printing Office, Washington, DC.

Petersen, R.C., Cocaine: an overview. In: R.C. Petersen and R.C. Stillman (eds.), Cocaine pp. 17-34, NIDA Monograph # 13, (1977), U.S. Government Printing Office, Washington DC.

Risner, M.E., & Jones, B.E., Characteristics of unlimited access to self-administered stimulant infusions in dogs. Biological Psychiatry, (1976), 11:625-634.

Ritchie, J.M., Cohen, P.J., & Dripps, R.D., Cocaine, procaine and other synthetic local anesthetics. In: L.S. Goodman & A. Gilman (Eds), The Pharmacological Basis of Therapeutics (4th ed.). (1971), New York: MacMillan.

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

Roberts, D.C.S., & Zito, K.A., In: M.A. Bozarth (ed), Methods of Assessing the Reinforcing Properties of Abused Drugs, (1987), 87-103, Springer-Verlag:New York.

Scheel-Kruger, J., Behavioral and biochemical comparison of amphetamine derivatives, cocaine, benztropine, and tricyclic antidepressant drugs. European Journal of Pharmacology, (1972), 18:63.

Schuster, C.R., & Thompson, T. Self-administration of and behavioral dependence on drugs. Annual Review of Pharmacology, (1969), 9:483-502.

Siegel, R.K., Cocaine smoking. Journal of Psychoactive Drugs, (1982), 14, 321-337.

Siegel, J.M., Mechanisms of sleep control. Journal of Clinical Neurophysiology, (1990), 7(1):49-65.

Smart, R.G., & Adlaf, E.M., Alcohol and Other Drug Use Among Ontario Adults 1977-1987, (1987). Toronto: Addiction Research Foundation.

Spealman, R.D., & Goldberg, S.R., Drug self-administration by laboratory animals: Control by schedules of reinforcement. Annual Review of Pharmacology and Toxicology, (1978), 18:319-39.

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

Wirz-Justice, A. (1986). Circadian rhythms in mammalian neurotransmitter receptors. Progress in Neurobiology, (1986), 29:219- 259.

TABLE 1

WITHIN GROUPS MULTIPLE COMPARISONS

Within Frequency of Access Groups

** - Comparisons significant at the 0.05 level

*** - Comparisons significant at the 0.01 level

Freq of Access = 1

Period 30 - 24*
Period 24 - 21.82*

Freq of Access = 2

Period 30 - 24 **
Period 24 - 20 **

Freq of Access = 4

Period 240 - 48*
Period 48 - 21.82*

TABLE 2

BETWEEN GROUPS MULTIPLE COMPARISONS
Access Schedule by Periodicity

Comparisons Significant at the 0.05 level

<u>One/hr - two/hr</u>	<u>One/hr - Four/hr</u>	<u>Two/hr - Four/hr</u>
	120	120
	80	80
	60	60
	48	48
	40	40
	34.29	34.29
	18.46	18.46
	17.14	17.14
8.57	8.57	
8.28	8.28	
8	8	
7.74	7.74	
7.5	7.5	
	7.27	
7.06	7.06	
6.86	6.86	
	6.67	
	6.49	
6.32	6.32	
6.15	6.15	
	6	
	5.85	
5.71	5.71	
5.58	5.58	
5.46	5.46	
5.33	5.33	
	5.22	
	5.11	

END

2|5 0|5 |93

FIN