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Characterization of the Synergistic Effects of Cocaine with Lateral Hypothalamic Brain Stimulation Reward

Pasqualino Bauco

A Thesis
in
The Department
of
Psychology

Presented in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy at
Concordia University
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ABSTRACT

Characterization of the Synergistic Effects of Cocaine with Lateral Hypothalamic Brain Stimulation Reward

Pasqualino Bauco, Ph.D.

Concordia University, 1998

Cocaine is powerfully rewarding in humans and lower animals. The brain stimulation reward paradigm offers an interesting tool with which to study the reward-relevant actions of cocaine. Cocaine potentiates the rewarding impact of brain stimulation; the stimulation is thought to exert its reward-relevant effects on neural circuitry that subsumes the rewarding effects of cocaine and natural rewards such as food.

In the present experiments the curve-shift rate-frequency variant of the brain stimulation reward paradigm was used to characterize the reward-potentiating actions of cocaine in rats lever-pressing for lateral hypothalamic brain stimulation. In Experiment 1 a dose-response curve of cocaine's potentiation of brain stimulation reward was determined and served as a reference for the dosages tested in subsequent experiments. In Experiment 2 repeated intermittent injections of cocaine failed to sensitize cocaine's ability to potentiate brain stimulation reward as would be predicted from the drug self-administration and conditioned place-preference literature. In Experiment 3, the widely held notion that tolerance to the rewarding

effects of cocaine contributes significantly to the cocaine habit was tested in the brain stimulation reward paradigm. The reward-potentiating effects of cocaine failed, however, to undergo tolerance with repeated high-dose drug administration. In Experiment 4 a dose of cocaine or amphetamine that causes a 0.3-log unit shift of the rate-frequency curve to the left canceled the effects of a dose of the dopamine antagonist pimozide that causes a 0.3-log unit shift to the right. These findings further suggest that cocaine and amphetamine act as synergists of brain stimulation reward and provide additional evidence of the importance of dopaminergic function in mediating the reward-relevant actions of cocaine and amphetamine. Fischer 344 and Lewis rat strains have been hypothesized to be differentially sensitive to the reward-relevant effects of cocaine. In Experiment 5, however, cocaine produced an equipotent potentiation of brain stimulation reward in the two rat strains. These results suggest that factors other than the reward-relevant effects of cocaine may account for previously reported differences between these two rat strains.

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TABLE OF CONTENTS

LIST OF FIGURES ix
LIST OF TABLES xii
1. General Introduction 1
1.1 Overview 1
1.2 Animal models of the habit-forming actions of cocaine 3
1.2.1 Drugs that serve as operant reinforcers establish self-administration response habits 4
1.2.2 Drugs that serve as operant reinforcers reinstate extinguished self-administration habits 6
1.2.3 Drugs that serve as operant reinforcers establish conditioned place preferences 8
1.2.4 Drugs that serve as operant reinforcers often potentiate the impact of other reinforcers 9
1.2.5 Drugs that serve as operant reinforcers often potentiate brain stimulation reward 10
1.2.6 Discovery of brain stimulation reward 10
1.2.7 Numerous sites maintain operant responding for rewarding brain stimulation 11
1.2.8 Action of various habit-forming drugs on response rate for rewarding brain stimulation 12
1.2.9 Paradigmatic considerations: Limitations of simple response rate as a dependent measure 14
1.2.10 Paradigmatic considerations: Alternatives to simple response rate as a dependent measure 15
1.2.11 Interaction of various habit-forming drugs with rewarding brain stimulation: Threshold measures 20
1.3 The mesolimbic dopamine and the reward-relevant actions of various drugs 23
1.3.1 Overview 23
1.3.2 Anatomy 23
1.3.3 Neurochemical consequences: Rewarding brain stimulation and various habit-forming drugs 24

1.3.4 The mechanisms of drug reward seem homologous with those of potentiation of rewarding brain stimulation.......... 25
1.3.4.1 *Ventral tegmental area*.......... 26
1.3.4.2 *Nucleus accumbens*.......... 28
1.3.4.3 *Frontal cortex*.......... 31
1.3.4.4 *Putative reward-relevant brain areas*.......... 33
1.3.5 Conclusions.......... 34
1.4 Advantages of brain stimulation reward and the curve-shift paradigm in the study of the rewarding actions of habit-forming drugs.......... 34
1.5 Present experiments.......... 36

2. Experiment 1 Potentiation of lateral hypothalamic brain stimulation reward by cocaine: An analysis using the curve-shift method.......... 37
2.1 Introduction.......... 37
2.2 Materials and methods.......... 38
2.3 Results.......... 42
2.4 Discussion.......... 54

3. Experiment 2 Potentiation of lateral hypothalamic brain stimulation reward by cocaine: An analysis of intermittent dosing.......... 56
3.1 Introduction.......... 56
3.2 Materials and methods.......... 57
3.3 Results.......... 59
3.4 Discussion.......... 67

4. Experiment 3 Potentiation of lateral hypothalamic brain stimulation reward by cocaine: An analysis of repeated high dose administration.......... 69
4.1 Introduction.......... 69
4.2 Materials and methods.......... 72
4.3 Results.......... 74
4.4 Discussion.......... 82

5. Experiment 4 Effects of pharmacological blockade of dopamine by pimozide on brain stimulation reward: Interaction with cocaine and amphetamine.......... 85
5.1 Introduction.......... 85

5.2 Materials and methods 86
5.3 Results 90
5.4 Discussion 114

6. **Experiment 5** Potentiation of lateral hypothalamic brain stimulation reward by cocaine: Comparison between Fischer 344 and Lewis rat strains 117
6.1 Introduction 117
6.2 Materials and methods 120
6.3 Results 122
6.4 Discussion 134

7. **General Discussion** 139

8. **References** 145

LIST OF FIGURES

Figure 1.1 Rate of lever pressing (per min) as a function of stimulation frequency prior to and after systemic cocaine.......... 18

Figure 2.1 Mean rate of lever-pressing prior to and after cocaine at various doses; Experiment 1.......... 44

Figure 2.2 Self-stimulation frequency thresholds and maximum rates as a function of cocaine dosage.......... 47

Figure 2.3 Pre-injection frequency thresholds (raw scores)...... 49

Figure 2.4 Self-stimulation frequency thresholds and maximum rates as a function of time after injection with various cocaine doses.......... 51

Figure 2.5 Histological reconstruction of electrode tips.......... 53

Figure 3.1 Self-stimulation frequency thresholds and maximum rates as a function of repeated saline or cocaine injections; Experiment 2.......... 61

Figure 3.2 Pre-injection frequency thresholds (raw scores)...... 64

Figure 3.3 Histological reconstruction of electrode tips.......... 66

Figure 4.1 Self-stimulation frequency thresholds and maximum rates as a function of a thrice-and once-daily cocaine or saline injection regimen; Experiment 3.......... 76

Figure 4.2 Pre-injection frequency thresholds (raw scores)...... 79

Figure 4.3 Histological reconstruction of electrode tips.......... 81

Figure 5.1 Rate of lever pressing (per min) as a function of stimulation frequency prior to and after pimozide injection; Experiment 4 Group 1.......... 92

Figure 5.2 Self-stimulation frequency thresholds and maximum rates as a function of time after injection with pimozide or its vehicle........ 94

Figure 5.3 Pre-injection frequency thresholds (raw scores)...... 97

Figure 5.4 Histological reconstruction of electrode tips............. 99

Figure 5.5 Rate of lever-pressing (per min) as a function of stimulation frequency during post-baseline assessment under various drug treatments; Experiment 4 Group 2........ 102

Figure 5.6 Self-stimulation frequency thresholds and maximum rates as a function of pimozide and cocaine or amphetamine co-administration........ 104

Figure 5.7 Self-stimulation frequency thresholds as a function of time after injection with pimozide and amphetamine or cocaine co-dministration........ 107

Figure 5.8 Self-stimulation maximum rates as a function of time after injection with pimozide and amphetamine or cocaine co-administration........ 109

Figure 5.9 Pre-injection frequency thresholds (raw scores)........ 111

Figure 5.10 Histological reconstruction of electrode tips......... 113

Figure 6.1 Rate of lever pressing (per min) as a function of stimulation frequency prior to and after various doses of cocaine in a Fischer 344 and a Lewis rat; Experiment 5............. 124

Figure 6.2 Self-stimulation frequency thresholds and maximum rates as a function of cocaine dosage in Fischer 344, Lewis, and Long-Evans rats........ 126

Figure 6.3 Self-stimulation frequency thresholds and maximum rates as a function of time after injection with various cocaine doses in Fischer 344 and Lewis rats........ 129

Figure 6.4 Pre-injection frequency thresholds (raw scores)........ 131

Figure 6.5 Histological reconstruction of electrode tips in Fischer 344 and Lewis rats.. 133

LIST OF TABLES

Table 1.1 Summary of treatment groups; Experiment 4.................. 88

Table 1.2 Summary of post-baseline injection protocol; Experiment 4.. 89

GENERAL INTRODUCTION

1.1 Overview

Cocaine is an alkaloid extracted from leaves of the coca plant (*Erythroxylon coca*). The drug has a long history of self-administration by humans (Siegel, 1985; Erickson *et al.*, 1987). Recent epidemiological data underscore cocaine's habit-forming potential. The most recent and comprehensive estimates of cocaine use available are for the United States. In 1995 an estimated 1.5 million Americans (aged 12 and older) were using cocaine. Approximately one third of users were classified as "frequent users"; frequent use was defined as using cocaine 51 or more days in the year. For the same year an estimated 2.5 million Americans used cocaine on 12 or fewer days (Substance Abuse and Mental Health Services Administration, 1996a). The number of people reporting crack use (the street name given to cocaine that has been processed from the salt, cocaine hydrochloride, to a free base for smoking) was estimated at 400,000 (Substance Abuse and Mental Health Services Administration, 1996a). During approximately the same period (1995) in the United States the number of cocaine-related emergency department "episodes" (seeking treatment related to cocaine use at a hospital emergency department) was at its highest level (142,900 episodes) since 1978 (3,400 episodes) when this statistic was first recorded (Substance Abuse and Mental Health

Services Administration, 1996b). The prevalence of cocaine use and the social concern over its use has contributed to the scientific investigation of the actions of cocaine that promote this drug's continued use.

As with other drugs, cocaine has multiple and complex actions in the central and peripheral nervous system. For example, because of its actions in the central nervous system, cocaine (at relatively low doses) improves motor coordination and suppresses REM sleep when sleep does occur in both humans (Watson *et al.*, 1992) and rats (Hill *et al.*, 1977). In humans the drug produces subjective feelings of "well-being" and alertness, magnifies normal pleasures, and decreases anxiety (Gawin & Ellinwood, 1988; Gawin, 1989; Ritchie & Greene, 1990). Moderate to high doses produce dose-related increases in heart rate and blood pressure (Fischman *et al.*, 1976; Resnick *et al.*, 1977; Isner *et al.*, 1986). The resulting changes in heart rate and blood pressure account for the drug's pyrogenic (fever), or heat producing effect, while its vasoconstrictive action contributes to the reduction of heat loss. Cocaine is a local anesthetic (Ritchie & Greene, 1990), and potentiates the function of the monoamines epinephrine, norepinephrine, dopamine and serotonin in the peripheral (Ritchie & Greene, 1990) and central (Knapp & Mandell, 1972; Friedman *et al.*, 1975; Heikkila *et al.*, 1975a; Calligaro & Eldefrawi, 1988) nervous systems. It is unlikely that all of these actions contribute to the cocaine habit and the task, therefore, has been to dissociate the actions relevant to the cocaine habit from those which are not. For example, it appears unlikely that cocaine's local anesthetic action contributes to the drug habit. A number of local anesthetics (lidocaine, procainamide and diethylaminoethanol) do not

reliably maintain response habits in animals initially trained to respond for intravenous cocaine (Woolverton & Balster, 1979). In those cases where local anesthetics do maintain response habits (Ford & Balster, 1977; Woolverton & Balster, 1979; Johanson, 1980), the drugs have no known habit-forming potential in humans (Fischman, 1984); the drugs only *maintain* already established response habits and do not establish or *initiate* response habits themselves. This evidence suggests that some action other than cocaine's local anesthetic action must account for this drug's habit-forming actions.

The use of animal models has contributed significantly to our understanding of the cocaine habit in humans (Schuster & Thompson, 1969; Johanson 1978; Schuster & Johanson, 1981; Brady, 1991). Of cocaine's various actions, the study of the drug's reinforcing actions and it's actions on endogenous dopaminergic function has significantly advanced our understanding of the cocaine habit. The present thesis extends the analysis of the behavioral pharmacology of cocaine's reinforcing and habit-forming actions.

1.2 Animal Models of the Habit-Forming Actions of Cocaine

The habit-forming actions of drugs and other stimuli and events are discussed in psychological theory under the rubric of "reinforcement". It is widely held (e.g. Schlosberg, 1937; Skinner, 1937; Mowrer, 1947; Rescorla & Solomon, 1967) that there are two fundamentally different forms of reinforcement: "operant"

reinforcement (Skinner, 1937), which involves the strengthening of associations between responses and their consequences, and "Pavlovian" reinforcement (Pavlov, 1903, cited in Pavlov 1928), which involves the strengthening of associations between stimuli.

Cocaine is reinforcing in the operant tradition because it maintains or strengthens a behavior upon which drug delivery is made contingent, as demonstrated in the drug self-administration paradigm (Weeks, 1962). Cocaine is also reinforcing in the Pavlovian sense because by being "paired" or "associated" with certain environmental stimuli it establishes a preference for those stimuli, such that they come to elicit conditioned approach reactions (Spragg, 1940; Beach, 1957a, 1957b; Schwartz & Marchok, 1974; Rossi & Reid, 1976).

1.2.1 Drugs that serve as operant reinforcers establish self-administration response habits

The most common route to establish drug self-administration in laboratory studies is by intravenous injection (Johanson, 1978; Pickens *et al.*, 1978). Drug self-administration can also be established, however, by inhalation of volatile fumes (Yanagita *et al.*, 1970; Wood *et al.*, 1977), and by means of oral (Meisch & Thompson, 1973; Meisch & Henningfield, 1977; Amit *et al.*, 1987), intragastric (Amit & Stern, 1969; Altshuler *et al.*, 1975; Götestam, 1973; Yanagita & Takahashi, 1973), intraperitoneal (Headlee *et al.*, 1955), intramuscular (Goldberg *et al.*, 1976), and intracranial route (Amit *et al.*, 1976; Bozarth & Wise, 1981a; Hoebel *et al.*, 1983; Goeders & Smith; 1983).

Oral drug self-administration in studies using laboratory animals is a preferred model when the primary route of drug intake in humans is oral as is the case for ethanol (Mello, 1973, 1976; Amit *et al.*, 1987; Stewart & Grupp, 1992; Meisch & Stewart, 1994). In the cases of cocaine and heroin self-administration, intravenous self-administration has been the preferred model.

The defining characteristic of operant reinforcement is that the reinforcer is administered or delivered to the animal in a response-contingent manner; the animal must earn the reinforcer, typically by pressing a lever. The pioneering work by Nichols *et al.*, (1956), Weeks (1962), Thompson and Schuster (1964), and Yanagita *et al.,* (1965) established that some drugs are capable of initiating and maintaining self-administration habits. Drugs that are commonly self-administered by humans are also self-administered by laboratory animals (Weeks, 1962; Schuster & Thompson, 1969; Schuster & Johanson, 1974; Woods, 1978; Griffiths *et al.*, 1979). Given this parallel between human and laboratory animals in drug self-administration, the intravenous drug self-administration paradigm has been proposed as a method to predict the "abuse liability" (Griffiths *et al.*, 1979, 1980; Collins *et al.*, 1984), or habit-forming potential of drugs.

Opiates (Weeks, 1962; Thompson & Schuster, 1964; Blakesley *et al.*, 1972) and amphetamine (Yokel & Pickens, 1973; Risner, 1975; Risner & Jones, 1975; Johanson *et al.*, 1976) reliably establish and maintain self-administration response habits. The first reports that laboratory animals will voluntarily work for intravenous infusions and regulate their intake of cocaine were by Pickens and Harris (1968) and

Pickens and Thompson (1968) in rats and by Deneau *et al.* (1969) in monkeys. Although in the laboratory the most practical and reliable method to study the habit-forming actions of drugs is with intravenous self-administration techniques, cocaine is also self-administered when oral (Meisch *et al.*, 1990), intragastric (Woolverton & Schuster, 1983), chewing, or smoking routes (Siegel *et al.*, 1976) are used. Furthermore, cocaine is reinforcing in a number of species of animals. The drug is reinforcing in humans (Fischman & Schuster, 1982; Paly *et al.*, 1982; Fischman, 1984; Henningfield *et al.*, 1987), squirrel monkeys (Goldberg, 1973; Katz, 1979), rhesus monkeys (Woods & Schuster, 1968; Wilson *et al.*, 1971), pigtail macaques (Young & Woods, 1980), baboons (Griffiths *et al.*, 1975), cats (Balster *et al.*, 1976), and dogs (Risner & Jones, 1975).

1.2.2 Drugs that serve as operant reinforcers reinstate extinguished self-administration habits

Drugs that serve as reinforcers also "prime" or reinstate previously extinguished self-administration habits. An example of a natural reinforcer that is familiar to most humans is the ability of tasting a single salted peanut or potato chip to prime further consumption. In humans, relapse to drug use is a central feature in formerly dependent drug users (Jaffe, 1990; Stitzer & Cox, 1996) and as little as a single drink, cigarette, or drug injection can often re-establish drug habits in detoxified ex-drug users (Stewart *et al.*, 1984; Wise, 1988). Indeed, environmental stimuli associated with the drug can also re-establish drug taking (O'Brien *et al.*, 1992). For example,

even after long periods of abstinence, exposure to alcohol (see Cohen *et al.*, 1971; Stockwell *et al.*, 1982.) increases the probability to seek out and self-administer the drug; priming injections of heroin (Meyer & Mirin, 1979), nicotine (Chornock *et al.*, 1992) and cocaine (Jaffe *et al.*, 1989; Preston *et al.*, 1992) all increase, in the detoxified ex-addict, the desire, craving or willingness to work for more drug.

In laboratory animals, priming or unearned drug injections reinstate behaviors previously established and maintained with the same or related drugs (Stewart & de Wit, 1987). To test the ability of a drug to reinstate responding, an animal is first trained to self-administer the drug. Responding is then extinguished by testing the animal under conditions where the previously trained behavior no longer produces drug injections. If a subsequent unearned injection of the drug reinitiates the trained response despite the continued absence of response-contingent drug delivery, the drug is said to "prime" or "reinstate" the previously extinguished self-administration habit.

Natural and drug reinforcement as well as reinforcing brain stimulation are capable of priming rats. Priming administration of food (Eiserer, 1978), heroin (de Wit & Stewart, 1983; Shaham *et al.*, 1994), morphine (Davis & Smith, 1976; Stewart & Wise, 1992), cocaine (Gerber & Stretch, 1975; de Wit & Stewart, 1981), amphetamine (Gerber & Stretch, 1975), or brain stimulation (Gallistel, 1973) all facilitate the initiation of responses previously associated with their delivery. Furthermore, injection of one reinforcing drug can reinstate responding that was established with another reinforcing drug when such drugs share some common physiological consequences. For

example, responding established by cocaine can be reinstated by heroin (de Wit & Stewart, 1981) and vice-versa (de Wit & Stewart, 1983).

1.2.3 Drugs that serve as operant reinforcers establish conditioned place preferences

Laboratory animals not only develop attachments to drugs that establish response habits, they also develop attachments to stimuli associated with the environments in which the reinforcing actions of a drug have been experienced. Several drugs known to serve as operant reinforcers can establish conditioned place preferences (Bozarth, 1987a; Wise & Bozarth, 1987; Carr *et al.*, 1989; Wise, 1989). To test this facet of drug reinforcement the drug is administered to the animal in a distinct portion of its environment or "place"; the animal will develop a learned preference for that portion of the environment that is revealed when it is tested in a "drug-free" state. The resultant "conditioned place preferences" are established by Pavlovian pairing of drug injections with environmental stimuli. Unlike the drug self-administration paradigm, in the conditioned place-preference paradigm there is no contingency between the behavior of the animal and the administration of the drug. The Pavlovian conditioning involved in the conditioned place-preference paradigm is thus held to be (Skinner, 1937, 1938, but see Bindra, 1972) fundamentally different from the operant conditioning involved in the self-administration paradigm. The place-preference paradigm has been proposed as a reliable method to study this facet of the reinforcing actions of drugs (van der Kooy, 1987; Carr *et al.*, 1989). Amphetamine (Sherman *et al.*, 1980; Reicher &

Holman, 1977; Spyraki *et al.*, 1982a; Asin *et al.*, 1985; Di Scala *et al.*, 1985; Carr *et al.*, 1988; Lett, 1989), and morphine (Beach, 1957a; Rossi & Reid, 1976; Katz & Gormezano, 1979; Bardo *et al.*, 1984; Mucha & Iversen, 1984; Barr *et al.*, 1985; Bardo & Neisewander, 1986) are clearly reinforcing when tested in this paradigm. The reinforcing action of cocaine has also been established in the conditioned place-preference paradigm (Mucha *et al.*, 1982; Spyraki *et al.*, 1982b; Mackey & van der Kooy, 1985; Bardo *et al.*, 1986; Morency & Beninger, 1986; Spyraki *et al.*, 1987; Nomikos & Spyraki, 1988).

1.2.4 Drugs that serve as operant reinforcers often potentiate the impact of other reinforcers

Habit-forming drugs often also potentiate the impact of other reinforcers such as food or sex. Feeding is facilitated by opiates (Jenck *et al.*, 1986; Mucha & Iversen, 1986; Noel & Wise, 1993, 1995), Δ^9-tetrahydrocannabinol (cannabis; Hollister, 1971; Glick & Milloy, 1972; Trojniar & Wise, 1991), and, under some circumstances, even by the appetite suppressant amphetamine (Blundell & Latham, 1976; Evans & Vaccarino, 1986; Colle & Wise, 1988a, 1989; Wise *et al.*, 1989). Acute administration of low doses of cocaine facilitates the sexual behavior of the male rat (Wilkins *et al.*, 1995; Ferrari & Giuliani, 1997; J.G. Pfaus, personal communication February 02, 1998), as do opiates (Mitchell & Stewart, 1990a) or stimuli that have been previously associated with opiate injections (Mitchell & Stewart, 1990b).

1.2.5 Drugs that serve as operant reinforcers often potentiate brain stimulation reward[1]

Opiate and psychostimulant drugs not only potentiate feeding and sexual behavior but also potentiate the habit-forming actions of brain stimulation reward (Wise, 1980; Wise & Rompré, 1989; Wise, 1996b).

1.2.6 Discovery of brain stimulation reward

The discovery of brain stimulation reward (Olds & Milner, 1954) derived from the observation that a short burst of direct septal stimulation guided or shaped a rat's behavior. The rat initially made approach responses and subsequently remained in the portion of the environment where the stimulation had been made available (Olds & Milner, 1954). With their original observations Olds and Milner had essentially demonstrated that the stimulation produced a learned place preference. The ability of brain stimulation to serve as a reinforcer has since been confirmed in a more traditional conditioned place-preference paradigm (Ettenberg & Duvauchelle, 1988).

---

[1] The terms "reward" and "reinforcement" are often used interchangeably and are differentially defined (if at all) by researchers. The terms have, however, long standing and distinct connotations (Wise, 1989). The term "reward" is used here to reflect the combined effects of reinforcement (of which there are two types; operant and Pavlovian) and of "priming" or "incentive motivation" which cannot be completely dissociated with the animal model used in the present thesis. The term "reward" is therefore used throughout the remainder of the thesis to reflect the combined effects of priming and reinforcement.

1.2.7 Numerous sites maintain operant responding for rewarding brain stimulation

While the most often studied sites in brain stimulation reward studies are sites in the medial forebrain bundle (lateral hypothalamus and ventral tegmental area; Liebman, 1989), sites that sustain self-stimulation extend from the telencephalon to the met- and mylencephalon. Some sites where stimulation is rewarding include frontal cortex (Mora, 1978; Prado-Alcala *et al.*, 1984), lateral septum (Prado-Alcala *et al.*, 1984), habenula, (Sutherland & Nakajima, 1981), mediodorsal thalamus (Clavier & Gerfen, 1982), nucleus accumbens (Jenkins *et al.*, 1983; Prado-Alcala & Wise, 1984), fornix (Brown & Winocur, 1973), substantia nigra (Crow, 1972), periaqueductal gray (Liebman *et al.*, 1973; Ackerman *et al.*, 1977), median and dorsal raphe (Miliaressis *et al.*, 1975; Rompré & Miliaressis, 1985), and trigeminal nucleus (van der Kooy & Phillips, 1979). Whether these sites are components of multiple reward circuits organized in parallel (Phillips, 1984) or represent components of a single reward circuitry connected in series (Wise & Bozarth, 1984) it is clear that the stimulation is powerfully rewarding (Wise, 1980). For example, rats will lever-press thousands of times per hour for rewarding lateral hypothalamic brain stimulation (Valenstein & Beer, 1964) and will withstand, following 24 hrs of food deprivation, higher levels of footshock to gain access to rewarding brain stimulation than they will withstand to gain access to food (Olds, 1958a). Animals otherwise denied food, when given access to food or to rewarding brain stimulation for 1 hr per day, will consistently opt for the brain stimulation to the point of self-

starvation (Routtenberg, 1964; Routtenberg & Lindy, 1965). Rats placed in a cold environment and given a choice between rewarding brain stimulation and heat opt for the brain stimulation to the point of immobility due to the cold (Carlisle & Snyder, 1970).

1.2.8 Action of various habit-forming drugs on response rate for rewarding brain stimulation

The early self-stimulation work relied on an analysis of "simple response rate" as the dependent measure from which changes in reward strength were inferred. This choice of dependent measure simply involves recording the animal's rate of response per given unit of time (e.g. every 5 min) prior to and following a manipulation.

Drugs that are rewarding in their own right (as assessed in the self-administration and conditioned place-preferences paradigms) generally increase the rate of responding for rewarding brain stimulation. For example, low and moderate systemic doses of amphetamine increase the rate of responding for brain stimulation (Stein, 1964; Olds & Travis, 1970; Domino & Olds, 1972; Robertson & Mogenson, 1979) as does cocaine (Crow, 1970; Wauquier & Niemegeers, 1974a). In the case of morphine moderate and high systemic doses have biphasic effects on self-stimulation rate. Self-stimulation rate is depressed for one to three hours after initial injections of moderate systemic doses (Olds & Travis, 1960; Jackler *et al.*, 1979) and this period is followed by a period of one or two hours of response acceleration (Lorens & Mitchell, 1973; Bush *et al.*, 1976; Lorens, 1976; Jackler *et al.*, 1979; Schaefer & Holtzman, 1979). This latter period of

increased responding results once the initial high dose of morphine is partially metabolized.

For several habit-forming drugs, their effects on responding for rewarding brain stimulation have been less consistent. In the case of ethanol, rate-dependent effects on self-stimulation have been reported. At equivalent doses systemic ethanol has, in a number of studies, been reported to increase rate of responding for self-stimulation (Lorens & Sainati, 1978; de Witte & Bada, 1983; Bain & Kornetsky, 1989; Lewis *et al.*, 1989) and, in other cases, to have no effect or to decrease response rates (Carlson & Lydic, 1976; Schaefer & Michael, 1987; Schaefer *et al.*, 1988). Low to moderate doses of nicotine increase responding for brain stimulation (Olds & Domino, 1969a, 1969b; Pradhan & Bowling, 1971; Newman, 1972). Moderate and high systemic doses of Δ^9-tetrahydrocannabinol (one of the psychoactive substances in marijuana) have biphasic effects on self-stimulation rate. Self-stimulation response rates are depressed in the first hour immediately following treatment and this period is followed by a one or two hour period of increased responding (Bailey & Pradhan, 1972; Bhattacharyya *et al.*, 1980). With repeated injections, tolerance rapidly develops to the initial response suppressive effects (Becker & Reid, 1977).

Low to moderate systemic doses of benzodiazepines have been reported to increase self-stimulation rates in some animals (Olds, 1966; Domino & Olds, 1972; Olds, 1976; Wauquier, 1976; Lorens & Sainati, 1978; Caudarella *et al.*, 1984; Ichitani *et al.*, 1985; Carden & Coons, 1989) and to be ineffective or decrease rates in other similarly treated animals (Caudarella *et al.*, 1982; Caudarella *et al.*, 1984; Panksepp *et al.*, 1970). The effect of benzodiazepines on rate of

responding for brain stimulation is also affected by the stimulation site chosen. Doses of diazepam that potentiate responding in animals with hippocampal electrodes reduce response rates in animals with hypothalamic stimulating electrodes (Caudarella *et al.*, 1982; Caudarella *et al.*, 1984).

Systemic injections of low to moderate doses of barbiturates such as pentobarbital increase the rate of responding for lateral hypothalamic brain stimulation while high doses depress responding (Mogenson, 1964; Reid *et al.*, 1964). As with benzodiazepines, the response increasing effects of barbiturates are not as robust as those of opiates and stimulant drugs (Wise, 1980). The low dose response potentiating effects of barbiturates, however, do suggest that compounds from the drug class may also function in a synergistic manner with brain stimulation to potentiate reward. Low systemic doses of caffeine increase the rate of responding for brain stimulation while high doses reduce response rates (Valdes *et al.*, 1982).

1.2.9 Paradigmatic considerations: Limitations of simple response rate as a dependent measure

It is not clear from experiments using simple-rate measures whether habit-forming drugs increase the rewarding impact of the stimulation or rather merely increase the performance capacity of the animal. The limitations of simple response rate measures are best characterized by data from "choice measure" experiments. Animals will often choose stimulation that sustains low rates of self-stimulation (such as the septum) over sites that sustain high rates

(Hodos & Valenstein, 1962; Ross, 1973). Animals responding for stimulation at parameters that all produce asymptotic or maximal response rates will, when given the choice between low and high levels of stimulation, consistently choose the high level over the low (Miliaressis & Malette, 1987; Waraczynski, *et al.*, 1987). Although simple response rate measures can be indicative of a change in reward strength they are insensitive to differences in reward strength that are clearly important to the animal when stimulation parameters that produce maximal response rates are tested.

1.2.10 Paradigmatic considerations: Alternatives to simple response rate as a dependent measure

One way to avoid the limitations of simple-rate studies is to focus on a minimal rather than a maximal level of responding. The minimum stimulation required to sustain reliable responding is termed the "threshold" level of stimulation, and it sustains responding at levels well below the demonstrated capacity of the animal. There are several ways to measure thresholds; each is designed to determine the minimal level of stimulation that is clearly rewarding. One commonly used method to estimate reward threshold is the "priming threshold" paradigm (Esposito & Kornetsky, 1977, 1978; Kornetsky & Esposito, 1979; Kornetsky & Esposito, 1981). In this method, the threshold for priming of rewarding electrical stimulation is estimated by successive approximation. Non-contingent brain stimulation is given at the beginning of each trial; if the animal lever-presses, an identical level of stimulation is delivered following the lever-press. If the animal

does not respond, a new trial is given at a higher level of current. Testing continues in this manner over a descending series of stimulation intensities until the animal does not lever-press, at which time an ascending series of intensities is tested. Reward threshold is operationally defined as the midpoint between the intensities where lever-pressing is initiated on ascending series and discontinued on descending series. Alterations in the reward threshold after drug treatment are manifested by changes in the intensity that sustains contingent responding.

Another approach is termed the “autotitration” method (Stein, & Ray, 1960; Schaefer & Holtzman, 1979; Nazzaro & Gardner, 1980; Gardner *et al.*, 1988a). This method measures the minimal stimulation required to maintain responding rather than the minimal stimulation required to elicit responding. The animal is tested under conditions where two operant levers are made available to the animal; when the animal presses the “primary” lever, rewarding stimulation is delivered. However, after a predetermined amount of responding the stimulation intensity is decreased by a small amount. A response on the “secondary” lever does not itself result in delivery of stimulation, but instead resets the stimulation level on the primary lever to its original intensity. Threshold is defined as the average current at which the animal makes a “reset response”, and any alteration of this threshold by psychoactive drugs is thought to reflect an interaction with the rewarding impact of the stimulation.

A self-stimulation paradigm that has emerged as the paradigm of choice by many investigators when both the reward strength of the stimulation and the performance capacity of the animal are to be

measured is the "curve-shift" paradigm. The curve-shift paradigm was first extensively discussed by Edmonds and Gallistel (1974) and has since been used by many self-stimulation researchers (Franklin, 1978; Fibiger & Phillips, 1981; Liebman, 1983; Yeomans *et al.*, 1985; Miliaressis *et al.*, 1986b; Gallistel & Freyd, 1987; Shizgal & Murray, 1989; Stellar & Rice, 1989; Wise, 1989; Wise & Rompré, 1989; Wise *et al.*, 1992; Wise, 1996b).

The curve-shift paradigm offers what is essentially a traditional "dose-response" analysis of brain stimulation reward (Liebman, 1983) in which leftward or rightward shifts are inferred to reflect treatments that increase or decrease, respectively, the rewarding potency of the stimulation. Upwards or downwards shifts are caused by changes in the response demands of the task or changes in the response capacity of the animal (Edmonds & Gallistel, 1974; Stellar & Neeley, 1982; Miliaressis *et al.*, 1986b) and thus reflect changes in the efficacy of the stimulation in the specific task presented (see Fig. 1.1).

It has been argued by several researchers in the psychophysics of brain stimulation reward (Gallistel *et al.,* 1974; Gallistel, 1978, Miliaressis *et al.,* 1986b; Gallistel, 1987; Gallistel & Freyd, 1987) that the most useful standard of measurement or metric of drug-induced changes in the rewarding potency of brain stimulation is the amount of stimulation that must be given to offset a given (drug) treatment and restore the level of an animal's performance to normal. The emerging consensus (Liebman 1983; Miliaressis *et al.,* 1986a, 1986b; Gallistel 1987; Gallistel & Freyd 1987; Wise & Rompré, 1989) as to the most useful stimulation parameter to vary in such determinations is the stimulation frequency (Yeomans, 1975); the number of stimulation

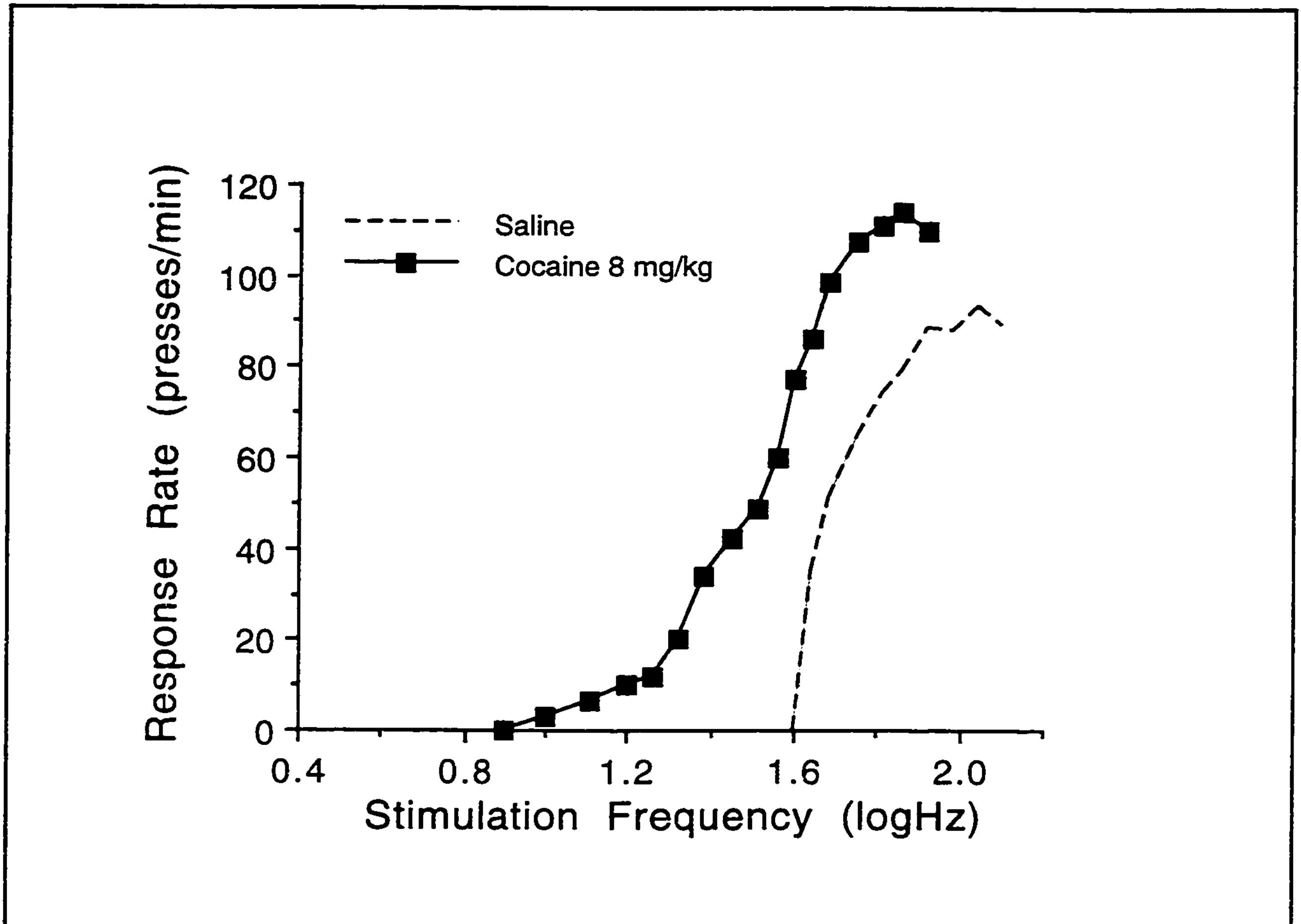

Figure 1.1: Rate of lever-pressing as a function of stimulation frequency in the first 15 min following injection. The amount of stimulation that sustains levels of responding following a saline injection is reduced after intraperitoneal administration of 8 mg/kg of cocaine, an effect reflected by a parallel leftward shift in the rate-frequency function. Such shifts are taken as evidence that drug potentiates the rewarding impact of the stimulation, and thus has reward-relevant properties of its own (modified from Experiment 1).

pulses per reward (with reward intensity, duration, and pulse width held constant). The reason to vary the stimulation frequency in preference to the stimulation intensity, train duration, or pulse width is that this parameter appears to vary most linearly with the strength of the reward signal (Gallistel, 1987). With pulse width held at 0.1 msec and with stimulation frequencies that do not encroach on the refractory periods of the target neurons, each stimulation pulse depolarizes local axons long enough to trigger one and only one action potential in each fiber sufficiently close to the electrode tip (Matthews, 1977, 1978); the number of rewarding action potentials, which contribute equally to the total rewarding impact of the stimulation (Gallistel *et al.*, 1981; Gallistel 1987), is thus directly proportional to the number of stimulation pulses per reward. Inasmuch as the number of rewarding pulses, and, hence, the number of reward-relevant action potentials necessary to offset a given drug treatment can be directly compared with the number necessary to offset a given antagonist (Gallistel & Freyd, 1987). Between-drug and between-dose comparisons of drug treatments affecting the rewarding potency of brain stimulation are possible when stimulation frequency is varied systematically. Other parameters of the stimulation, such as stimulation intensity or pulse width do not vary linearly with the number of action potentials they induce in the reward pathway (Gallistel, 1974; Yeomans, 1975; Gallistel, 1978, 1987); thus they are less useful for quantitative comparisons between drugs and between doses. Variations of stimulation intensity, for example, change the effective spread of current, adding to or subtracting from the population of reward-relevant neurons to which the stimulation

spreads; the effective spread of current varies as a power function of the distance from the electrode tip (Wise, 1972). Inasmuch as the actions of drugs on brain stimulation reward can vary with the location of the directly-activated reward-relevant fibers (Stephens & Herberg, 1975; Liebman & Segal, 1977), it is essential to activate the same population of fibers when quantitative drug- and dose-comparisons are being made. Variations in pulse width alter the number of action potentials generated by each stimulation pulse, but the degree of alteration is not linearly related to pulse width. For these reasons, systematic quantitative comparisons of the effectiveness of drug treatments in modifying the rewarding potency of electrical stimulation of the brain have generally come to involve rate-frequency determinations by investigators that have followed the "Gallistel" model (Miliaressis *et al.*, 1986b; Gallistel, 1987; Gallistel & Freyd, 1987).

1.2.11 Interaction of various habit-forming drugs with rewarding brain stimulation: Threshold measures

Systemic amphetamine injections lower the threshold for rewarding brain stimulation (Wauquier & Niemegeers, 1974b; Esposito *et al.*, 1980; Greenshaw *et al.*, 1985; Hubner *et al.*, 1987; Schaefer & Michael, 1988) as do systemic injections of cocaine (Esposito *et al.*, 1978; Kornetsky & Esposito, 1981). In the case of systemic morphine injections, self-stimulation thresholds are lowered even in the period when simple response rate is depressed (Esposito & Kornetsky, 1977; Kelley & Reid, 1977; Esposito *et al.*, 1979; Kornetsky *et al.*, 1979;

Marcus & Kornetsky, 1974; Nazarro *et al.*, 1981; van Wolfswinkel & van Ree, 1985; Hubner *et al.*, 1987). Ethanol has been reported to lower self-stimulation thresholds in some instances (Lewis & Phelps, 1987; Moolten & Kornetsky, 1990) and to have no effect on self-stimulation thresholds in others (Unterwald *et al.*, 1984; Unterwald & Kornetsky, 1985; Schaefer & Michael, 1987). Systemic Δ^9-tetrahydrocannabinol lowers the threshold for self-stimulation (Gardner *et al.*, 1988a, 1989b). These data suggest that Δ^9-tetrahydrocannabinol shares with amphetamine and morphine the ability to potentiate the rewarding impact of brain stimulation. Low doses of chlordiazepoxide (Stark *et al.*, 1969) lower the threshold for self-stimulation thereby suggesting that under certain conditions benzodiazepines can potentiate brain stimulation reward. Systemic low doses of caffeine had no effect on threshold while high doses raised the threshold for self-stimulation (Mumford *et al.*, 1988; Mumford & Holtzman, 1990) and pentobarbital lowers self-stimulation thresholds (Seeger *et al.*, 1981).

As when priming and autotitration threshold determinations are used, when tested in the “curve-shift” paradigm (Miliaressis *et al.*, 1986b; Frank *et al.*, 1987; Gallistel, 1987), systemic injections of a variety of drugs that are rewarding in their own right are seen to increase the potency of rewarding stimulation, shifting to the left the functions relating response rate to the frequency, intensity, or train length [factors contributing to the rewarding “dose” (Yeomans, 1975; Liebman, 1983; Frank *et al.*, 1987)] of brain stimulation given for each lever-press (Gallistel & Karras, 1984; Gallistel & Freyd, 1987; Frank *et al.*, 1992; Wise *et al.*, 1992).

Amphetamine (Colle & Wise, 1988b; Gallistel & Karras, 1984; Gallistel & Freyd, 1987; Wise & Munn, 1993), morphine (Glick *et al.*, 1982; Rompré & Wise, 1989; Carlezon & Wise, 1993a), nicotine (Wise *et al.*, 1992; Bauco & Wise, 1994; Wise *et al.*, 1998), phencyclidine (Carlezon & Wise, 1993b), cocaine (Frank *et al.*, 1988; Kokkinidis & McCarter, 1990; Corbett, 1991; Frank *et al.*, 1992; Wise *et al.*, 1992; Maldonado-Irizarry, 1994) and the "cocaine-like" compound GBR-12909[2] (Rompré & Bauco, 1990; Maldonado-Irizarry *et al.*, 1994) each cause leftward shifts in functions relating response rate to stimulation frequency, rate-train duration, or rate-intensity.

The effects of ethanol on rewarding brain stimulation using the curve-shift paradigm have only been reported for a single experiment. Intravenous ethanol did not produce a clear parallel leftward shift of the rate-frequency curve (Wise *et al., 1992*; Trojniar & Wise, unpublished observations). Ethanol's intoxicating effects, its relatively short duration of action, and methodological differences across ethanol self-stimulation studies have made the inconsistencies in these data difficult to interpret.

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[2] The GBR-12909 compound is relatively new and has not been demonstrated to have habit-forming properties in humans. GBR-12909 shares with cocaine the ability to increase extrasynaptic concentrations of the neurotransmitter dopamine (Andersen, 1989; Izenwasser *et al.*, 1990; Nomikos *et al.*, 1990) in the terminal regions of the mesolimbic dopamine system (see section 1.3.2 below). In laboratory experiments using monkeys (Wojnicki & Glowa, 1996) and rats (Roberts, 1993) with a history of cocaine self-administration, GBR-12909 maintains self-administration habits. GBR-12909 is not, however, very effective in initiating intravenous self-administration (Wojnicki & Glowa, 1996).

1.3 The Mesolimbic Dopamine System and the Reward-Relevant Actions of Various Drugs

1.3.1 Overview

Evidence from experiments involving lesions (Lippa *et al.*, 1973; Phillips & Fibiger, 1978; Fibiger *et al.*, 1987), anatomical mapping (Corbett & Wise, 1979, 1980), and pharmacological manipulations (Liebman & Butcher, 1974; Fouriezos & Wise, 1976; Franklin & McCoy, 1979; Zarevics & Setler, 1979; Gallistel & Davis, 1983; Wise & Rompré, 1989; Wise, 1996b) have implicated the mesolimbic dopamine system in the reward-relevant actions of various habit-forming drugs including cocaine.

While the exact function dopamine serves in mediating reward is not clear (Wise, 1982a; Wise & Rompré, 1989; Di Chiara, 1995), it is clear that a functional midbrain dopamine system is important in mediating the reward-relevant actions of cocaine and most other habit-forming drugs (Wise, 1978a; Wise & Bozarth, 1987; Fibiger & Phillips, 1988; Wise & Rompré, 1989; Di Chiara, 1995).

1.3.2 Anatomy

The midbrain dopamine system comprises two populations of dopamine neurons: the ventral tegmental area, or A10 neurons, with axons projecting primarily to cortical and limbic structures such as the nucleus accumbens, olfactory tubercle, hippocampus, septum, and

amygdala (Fallon & Moore, 1978; Domesick, 1988; Fallon, 1988); and the substantia nigra pars compacta, or A9 neurons, that send fibres primarily to the caudate-putamen and to a lesser degree to some cortical and limbic structures (Ungerstedt, 1971; Fallon & Moore, 1978; Lindvall & Björklund, 1983, 1984).

1.3.3 Neurochemical consequences: Rewarding brain stimulation and various habit-forming drugs

Increased dopaminergic neurotransmission is one action common to rewarding brain stimulation and several habit-forming drugs. Rewarding medial forebrain bundle stimulation is seen to potentiate mesolimbic dopamine neurotransmission in the nucleus accumbens as studied by *in vivo* electrochemical (Gratton *et al.*, 1988; Phillips *et al.*, 1989; Blaha & Phillips, 1990; Wightman & Garris, 1996) and *in vivo* neurochemical (Miliaressis *et al.*, 1991; Phillips *et al.*, 1992; Bauco *et al.*, 1993a; Bauco *et al.*, 1994) techniques.

Just as rewarding brain stimulation of the medial forebrain bundle augments mesolimbic dopamine neurotransmission in the nucleus accumbens, systemic injection with cocaine (Di Chiara & Imperato, 1988a; Hernandez & Hoebel, 1988; Carboni *et al.*, 1989), amphetamine (Di Chiara & Imperato, 1988a; Hernandez & Hoebel, 1988; Carboni *et al.*, 1989), morphine (Di Chiara & Imperato, 1988a, 1988b), nicotine (Imperato *et al.*, 1986; Di Chiara & Imperato, 1988a; Mifsud *et al.*, 1989), ethanol (Di Chiara & Imperato, 1985; Imperato & Di Chiara, 1986; Di Chiara & Imperato, 1988a), and Δ^9-tetrahydrocannabinol or

cannabis (Chen *et al.*, 1989; Gardner *et al.*, 1989b; Chen *et al.*, 1990) share this action. Microinjection of amphetamine (Hernandez *et al.*, 1987; Hoebel *et al.*, 1989) or morphine (Leone *et al.*, 1991) directly into respective reward-relevant brain areas (see below) also increases extrasynaptic dopamine concentrations in the nucleus accumbens as does intravenous self-administration of cocaine (Wise *et al.*, 1995a) or heroin (Wise *et al.*, 1995b). The ability to increase extrasynaptic concentrations of mesolimbic dopamine is hypothesized to mediate the habit-forming actions of cocaine and numerous other rewarding drugs as well as rewarding brain stimulation (Wise & Bozarth, 1987; Wise & Rompré, 1989; Koob, 1992; Woolverton & Johnson, 1992; Wise, 1996a, 1996b).

1.3.4 The mechanisms of drug reward seem homologous with those of potentiation of rewarding brain stimulation

The search for the substrates mediating the rewarding and reward-potentiating actions of various habit-forming drugs has centered along two research axes; each of these implicates the mesolimbic dopamine system in the habit-forming actions of opiate and psychomotor stimulant drugs. The first approach has been one based on pharmacological manipulations of the dopamine system by neuroleptic (dopamine antagonist) blockade and the consequences of such pharmacological manipulations on the reward-relevant effects of habit-forming drugs. The second approach has focused on the localization of the substrate mediating the habit-forming actions of

various drugs by mapping the brain areas where local drug infusion produces rewarding-relevant actions.

In the cases tested to date, the brain structures where a given drug is rewarding (as assessed in the self-administration, reinstatement or conditioned place-preference paradigms) have been found to be the same as the structures where that drug has the ability to potentiate brain-stimulation reward. The reward-relevant actions of various habit-forming drugs (see below) have been localized to either the dopamine cell body region of the ventral tegmental area and/or to the dopamine terminal region of the nucleus accumbens or frontal cortex. Several other putative brain regions have been suggested to mediate the rewarding actions of some drugs and are discussed separately below. To date amphetamine and morphine have been well-characterized in each of the reward-relevant paradigms and converging evidence suggests that the rewarding and reward-potentiating actions of cocaine are also mediated within the mesolimbic dopamine system.

1.3.4.1 Ventral tegmental area

The ventral tegmental area is one brain region where opiates have rewarding-relevant actions. Rats self-administer morphine (Bozarth & Wise, 1981a; Welzl *et al.*, 1989), the opioid fentanyl (van Ree & de Wied, 1980), and the selective mu and delta opioid agonists DAGO ([D-Ala^{2},N-Me-Phe^{4}-Gly^{5}-ol]-enkephalin) and DPDPE ([D-Pen^{2},D-Pen^{5}]-enkephalin; Devine & Wise, 1994) directly into the ventral tegmental

area but will not self-administer morphine into the caudate, lateral hypothalamus or periventricular gray (Bozarth & Wise, 1980). Microinjection of morphine into the ventral tegmental area also reinstates extinguished responding in rats previously trained to lever-press for intravenous heroin (Stewart, 1984). Neuroleptics reduce intravenous heroin self-administration and selective dopamine depletion by 6-hydroxydopamine lesions (lesions that destroy cells of origin) of the ventral tegmental area blocks the acquisition of intravenous opiate self-administration (Bozarth & Wise, 1986).

Morphine (Phillips & LePiane, 1980; van der Kooy *et al.*, 1982; Bozarth, 1987b) and the mu opioid agonist DAGO (Bals-Kubik *et al.*, 1990) microinjected into the ventral tegmental area establish conditioned place preferences, whereas morphine microinjections rostral, caudal and dorsal (Bozarth, 1987b) to the ventral tegmental area do not; the place-preference studies demonstrate that the rewarding effectiveness is lost when injections of opiates are made within a few tenths of a millimeter outside the region of dopamine-containing cell bodies of the ventral tegmental area (Phillips & LePiane, 1980, Bozarth, 1987b) and neuroleptics block opiate-induced conditioned place preferences (Bozarth & Wise, 1981b). Opiate microinjections into the ventral tegmental area also potentiate the rewarding impact of medial forebrain bundle brain stimulation (Broekkamp *et al.*, 1976; van Wolfswinkel & van Ree, 1985; Jenck *et al.*, 1987; Rompré & Wise, 1989; Bauco *et al.*, 1993b) whereas microinjections of morphine dorsal to the ventral tegmental area are ineffective (Rompré & Wise, 1989).

There is evidence that the ventral tegmental area may also mediate the rewarding actions of nicotine. The nicotinic agonist cytisine establishes conditioned place preferences when microinjected into the ventral tegmental area (Museo & Wise, 1994).

1.3.4.2 Nucleus accumbens

There is evidence that opiates are also rewarding when microinjected into the area of the nucleus accumbens. Rats self-administer morphine (Olds, 1982) or methionine enkephalin directly into the nucleus accumbens (Goeders *et al.*, 1984). 6-Hydroxydopamine lesions of the nucleus accumbens attenuate responding for intravenous morphine such that a doubling of the dose is required (post lesion) to maintain self-administration (Smith *et al.*, 1985) and the disruption of heroin self-administration correlates positively with the degree of nucleus accumbens destruction by kainic acid lesions (Zito *et al.*, 1985) which spare fibers of passage. Morphine microinjections into the nucleus accumbens (van der Kooy *et al.*, 1982) also establish conditioned place preferences; electrolytic (Kelsey *et al.*, 1989) and 6-hydroxydopamine lesions of the nucleus accumbens attenuate such conditioned preferences following systemic morphine (Schwartz & Marchok, 1974) or heroin (Spyraki *et al.*, 1983). In contrast, opiate injections into other brain regions such as the amygdala, caudate, and nucleus ambiguous are ineffective in establishing conditioned place preferences (van der Kooy *et al.*, 1982). Opioids microinjected into the nucleus accumbens increase lever pressing (Broekkamp *et al.*, 1976,

1979) and lower self-stimulation thresholds (West & Wise, 1988, 1989; Duvauchelle, *et al.*, 1997) for rewarding medial forebrain bundle stimulation; injections into the overlying caudate are ineffective (West & Wise, 1988, 1989).

The reward-relevant actions of amphetamine appear to be mediated by the mesolimbic dopamine system. Blockade of dopamine receptors with systemic injections of neuroleptics cause compensatory increases in lever-pressing for intravenous amphetamine (Yokel & Wise, 1975, 1976). The brain area identified with the reward-relevant actions of amphetamine is also the nucleus accumbens. Rats lever press for amphetamine microinjected directly into the nucleus accumbens (Lenard *et al.*, 1980; Monaco *et al.*, 1980; Hoebel *et al.*, 1983) as they do for dopamine itself (Guerin *et al.*, 1984) but not for amphetamine microinjections into the ventral accumbens (Hoebel *et al.*, 1983), or into the lateral ventricles (Monaco *et al.*, 1980). Amphetamine microinjections into the nucleus accumbens reinstate extinguished self-administration habits (Stewart & Vezina, 1988) and selective dopamine-depleting lesions of the nucleus accumbens attenuate the rewarding actions of intravenous amphetamine (Lyness *et al.*, 1979). Amphetamine establishes conditioned place preferences when microinjected into the nucleus accumbens (Aulisi & Hoebel, 1983; Carr & White, 1983,1986); microinjections into the amygdala, medial prefrontal cortex, area postrema (Carr & White, 1986), and caudate (Carr & White, 1983, 1986), however, are ineffective. Lesions of the nucleus accumbens abolish conditioned place preferences established with systemic amphetamine injections (Spyraki *et al.*, 1982a; Olmstead & Franklin, 1996) and dopamine antagonists block conditioned place

preferences established by amphetamine (Spyraki *et al.*, 1982a). The only area where amphetamine microinjections are known to potentiate the rewarding actions of brain stimulation is the nucleus accumbens. When microinjected into the nucleus accumbens, but not into the anterior hypothalamus nor into the ventricular system, amphetamine increases self-stimulation rates (Broekkamp *et al.*, 1975) and lowers self-stimulation thresholds as tested in the curve-shift paradigm (Colle & Wise, 1988b; Ranaldi & Beninger, 1994). When amphetamine is microinjected into the caudate, a dose four times that which produces a minimal effect in the nucleus accumbens is required to produce a (marginal) lowering in brain stimulation reward threshold (Colle & Wise, 1988b) providing further confirmation that the nucleus accumbens is the site of this reward-potentiating action of amphetamine.

The reward-relevant actions of cocaine also appear to be dopamine-dependent. Systemically administered dopamine antagonists cause compensatory increases in lever-pressing for intravenous cocaine (de Wit & Wise, 1977; Ettenberg *et al.*, 1982) While rats will not reliably work for cocaine injections directly into the nucleus accumbens (Goeders & Smith, 1983; Carlezon *et al.*, 1995), there is evidence that this terminal of the mesolimbic dopamine system mediates cocaine's reward-relevant actions. Rats will reliably self-administer the cocaine-like potent dopamine uptake inhibitor, nomifensine, directly into the nucleus accumbens (Carlezon *et al.*, 1995; Carlezon & Wise, 1996a); nomifensine also potentiates the rewarding impact of lateral hypothalamic brain stimulation reward when microinjected into the nucleus accumbens (Carlezon & Wise,

1996b). The importance of the nucleus accumbens in mediating the rewarding actions of cocaine is also reflected the finding that injections of the dopamine antagonist spiroperidol into the region of the nucleus accumbens (Phillips *et al.*, 1983) reduce the rewarding impact of intravenous cocaine. Moreover, kainic acid (Zito *et al.*, 1985) or 6-hydroxydopamine (Roberts *et al.*, 1977, 1980; Pettit *et al.*, 1984; Koob *et al.*, 1987) lesions of the nucleus accumbens disrupt intravenous self-administration of cocaine; 6-hydroxydopamine lesions of the ventral tegmental area which gives rise to dopamine terminals in the nucleus accumbens also disrupt intravenous cocaine self-administration (Roberts & Koob, 1982) in a manner similar to pharmacological blockade of the dopamine system. In contrast, injections of 6-hydroxydopamine into the caudate nucleus (Roberts & Zito, 1987) or the dorsal tegmentum (Roberts *et al.*, 1977) do not alter cocaine self-administration. There is also some evidence, although preliminary, indicating that microinjection of cocaine into the nucleus accumbens establishes conditioned place preferences (Aulisi & Hoebel, 1983) and pharmacological blockade of the dopamine system generally attenuates place preferences conditioned by cocaine (Morency & Beninger, 1986; Spyraki *et al.*, 1987; but see Spyraki *et al.*, 1982b).

1.3.4.3 Frontal cortex

The frontal cortex has been implicated in the reward-relevant actions of cocaine, and amphetamine. Amphetamine is self-administered into the dopamine-rich areas of orbitofrontal cortex by

rhesus monkeys (Phillips *et al.*, 1981). Rats will work for microinjections of cocaine into the prefrontal cortex (Goeders & Smith, 1983) and co-infusion of the dopaminergic antagonist sulpiride attenuates intracranial self-administration of cocaine into the prefrontal cortex (Goeders & Smith, 1983). Dopamine depletion by 6-hydroxydopamine of the prefrontal cortex disrupts intracranial self-administration into this same area; responding is reinstated when dopamine is substituted for cocaine (Goeders & Smith, 1986). While these data point to a dopaminergic mediation of the rewarding actions of cocaine in the prefrontal cortex there are data that are inconsistent with this hypothesis. Whereas Martin-Iversen *et al.* (1986) report that intravenous cocaine self-administration is not substantially affected following 6-hydroxydopamine lesions of the prefrontal cortex, Schenk *et al.* (1991) report that similarly lesioned rats become supersensitive to the rewarding actions of intravenous cocaine. Animals with lesions of the prefrontal cortex respond for marginal doses of the drug that are not self-administered by non-lesioned animals. Similarly, while 6-hydroxydopamine lesions of the prefrontal cortex (Hemby *et al.*, 1992) are reported not to block conditioned place preferences established with systemic cocaine injections, Issac *et al.* (1989) report that destruction of the prefrontal cortex by means of suction ablation blocks conditioned place preference established by systemic cocaine injection.

1.3.4.4 Putative reward-relevant brain areas

Rats have been reported to lever-press for lateral hypothalamic injections of morphine (Olds, 1979) and an enkephalin analogue (Olds & Williams, 1980); however, the doses and procedure that are effective with ventral tegmental injections (Bozarth & Wise, 1981a) have not been found effective with lateral hypothalamic injections (Bozarth & Wise, 1982). No dorsal or ventricular controls were tested in the case of lateral hypothalamic self-administration (Olds, 1979; Olds & Williams, 1980) and the possibility of diffusion from the site of injection cannot be ruled out. Kainic acid lesions of the lateral hypothalamus do not affect intravenous heroin self-administration (Britt & Wise, 1981).

Rats have been reported to self-administer the endogenous opiate dynorphin A directly into the CA3 region of the hippocampus (Stevens *et al.*, 1988, 1991); these findings have not been explored further by other investigators. Lateral hypothalamic (van der Kooy *et al.*, 1982) and hippocampal (Corrigall & Linseman, 1988) morphine injections have been reported to establish conditioned place preferences. Here, again, no anatomical (dorsal or other) controls were reported. The lateral hypothalamus and the hippocampus, therefore, do not appear to contribute significantly to the rewarding actions of opiates. Morphine injections into the periaqueductal gray have been reported to establish conditioned place preferences (van der Kooy *et al.*, 1982); the doses tested were higher than those needed to establish conditioned place preferences following injection into the ventral tegmental area and low doses (Bozarth, 1987b; Phillips & LePiane, 1980) that establish

conditioned place preferences when injected into the ventral tegmental area are ineffective when injected 2 mm dorsal to the ventral tegmental area close to the periaqueductal gray (Phillips & LePiane, 1980).

1.3.5 Conclusions

These reported experiments provide converging evidence consistent with the hypothesis that the reward-relevant actions of amphetamine, cocaine, and opiates are mediated by actions within the mesolimbic dopamine system. While the data reviewed in this section do not point to the exact nature of dopamine's function in mediating reward and while dopamine is certainly not the only reward neurotransmitter nor the final common path for all rewards (Wise & Rompré, 1989), what these data do suggest is that the functional integrity of this system is required in mediating the direct rewarding and reward-potentiating actions of at least several habit-forming drugs.

1.4 Advantages of Brain Stimulation Reward and The Curve-Shift Paradigm in The Study of The Rewarding Actions of Habit-Forming Drugs

The brain stimulation reward paradigm has a number of practical experimental advantages over the so-called "natural" rewards of food and sex. Brain stimulation reward is unaffected by satiety with the

stimulation parameters normally used in brain stimulation reward experiments and thus there is no need for animals to be in a state of deprivation such as in a feeding experiment. Animals can be tested for long periods of time with little or no decay in the reward strength of the stimulation necessary to maintain operant responding (Olds & Milner, 1954; Olds, 1958b; Valenstein & Beer, 1964). In a feeding experiment reward strength varies inversely with level of food deprivation and therefore curtails the test duration. Finally, the stimulation "dose" can be precisely measured and delivered to the animal to a much greater degree than can the rewards of food or sex.

The curve-shift rate-frequency brain stimulation reward paradigm offers several advantages over the self-administration and conditioned place-preference paradigms. One advantage of the curve-shift paradigm is the ability to dissociate reward-relevant from reward-irrelevant treatment effects. Second, each rate-frequency curve covers the full range of effective stimulation levels, rather than being based on arbitrary parameters that might be subject to floor or ceiling effects. Indeed, the curve-shift paradigm makes the experimenter aware of the floor and ceiling for the response rates of interest. Third and perhaps the most important advantage of the curve-shift paradigm involves the scaling of treatment effects. Lateral shifts in the rewarding impact of the stimulation can be quantified on a ratio scale (Gallistel *et al.*, 1981) when their magnitudes are expressed in terms of logarithmic (Log) units (Gallistel & Freyd, 1987; Wise & Rompré, 1989), thereby allowing for quantitative precision when assessing changes in reward strength.

1.5 Present Experiments

The present experiments were designed to more fully characterize the effects of systemic cocaine on brain stimulation reward using the rate-frequency curve-shift paradigm.

In Experiment 1 the ability of cocaine to potentiate brain stimulation reward across the full range of effective doses was quantified. In Experiments 2 and 3 the effects of repeated injections of cocaine on brain stimulation reward was assessed in tests for sensitization and tolerance to the drug's reward-potentiating action, respectively. In Experiment 4 the effect of blocking dopaminergic neurotransmission and its interaction with cocaine on brain stimulation reward was assessed. In Experiment 5 the ability of cocaine to potentiate the rewarding impact of brain stimulation was compared in Fischer 344 and Lewis rat strains; these two strains are thought to have differential sensitivity to the rewarding effects of cocaine.

EXPERIMENT 1

Potentiation of Lateral Hypothalamic Brain Stimulation Reward by Cocaine: An Analysis Using The Curve-Shift Method

2.1 INTRODUCTION

The rate-frequency variant of the curve-shift paradigm has been used to assess and quantify the reward-potentiating actions of systemic cocaine (Wise *et al.*, 1992; Maldonado-Irizarry *et al.*, 1994), amphetamine (Gallistel & Karras, 1984; Gallistel & Freyd, 1987; Colle & Wise, 1988b; Wise & Munn, 1993), morphine (Carlezon & Wise 1993a), nicotine (Bauco & Wise, 1994; Wise *et al.*, 1998), phencyclidine (Carlezon & Wise, 1993b) and cannabis (Lepore *et al.*, 1996). In each case the drug is seen to potentiate the rewarding potency of the stimulation. With one exception (Bauco & Wise, 1994), there has been no thorough dose-response analysis of the reward-potentiating actions of habit-forming drugs using the curve-shift paradigm. In Experiment 1 the entire dose range—from an ineffective to a maximally effective dose—of cocaine's reward-potentiating actions was determined and quantified. The results from Experiment 1 were used to determine the doses of cocaine tested in subsequent experiments.

2.2 MATERIALS AND METHODS

Subjects: Eight 300 to 350g male Long-Evans rats (Harlan Sprague Dawley, U.S.A.) were used. They were housed individually in polyethylene cages with wood chip bedding and free access to food and water. Lighting was maintained on a normal 12-h light/dark cycle; the animals were tested at the end of the dark phase.

Surgery: Under sodium pentobarbital anesthesia (65 mg/kg ip); atropine (0.6 mg/kg, ip) was administered 20 min prior to the anesthetic to minimize bronchial secretions. Each animal was implanted bilaterally with monopolar stainless steel electrodes (0.25-mm diameter) insulated with varnish (Formvar), except for the rounded tip. Flat-skull coordinates were 2.5 mm posterior to bregma, 1.7 mm lateral to the midline and 8.0 mm ventral to the skull surface. Four stainless-steel screws were used to anchor each electrode; the screws were wrapped with uninsulated wire that served as an anode. The electrode and screw assembly was embedded in dental cement.

Apparatus: A microprocessor-based system controlled delivery of stimulation via a constant current generator (Mundl, 1980) connected to each animal by flexible leads through a mercury commutator that allowed the animal free movement. Each animal was tested in a 26 X 26-cm cage with an operant lever protruding 2.5 cm from the rear wall at a height of 7.5 cm from the floor. The operant lever controlled a microswitch connected to the current generator. Each test cage was

enclosed within a larger wooden chamber that reduced external noise and visual distractions.

Procedure: Self-stimulation testing began 7 days after surgery. The animals were placed in test boxes and allowed to explore without experimenter-administered stimulation. Each initially investigatory depression of the operant lever resulted in delivery of a 200-ms train of 0.1-ms rectangular cathodal pulses to the selected electrode. Each stimulation train was followed by an 800-ms "time-out" period when responding was not reinforced; the purpose of the time-out was to allow significant decay (Black *et al.*, 1985; Fouriezos, 1995) of proactive post-pulse "priming" effects of earned stimulation (Gallistel *et al.*, 1974), thus increasing the sensitivity of the paradigm to changes in drug-induced response-reinforcement *per se* (see general discussion). Initial stimulation frequency was 72 Hz, and initial current intensity was 100 μA (a low level). If the animal did not learn to lever-press for stimulation at this intensity the current was increased daily in 50-μA increments until the animal learned to lever press reliably or until the current intensity reached an upper limit of 800 μA. Once a current level that established steady responding at a minimum rate of 30 lever presses per min was reached, the current was fixed and the animal was allowed to lever press freely for 1 hr/day on 3 consecutive days. If the animal did not continue lever-pressing or if the stimulation produced aversive side-effects (*e.g.*, gross head or body movements to one side, spinning, retreating to a corner of the test cage, vocalization, or jumping) the animal was retested using the contralateral electrode. One or two test sessions

were sufficient to produce reliable lever-pressing in each of the animals reported in the present experiments.

Following the initial screening phase the animals were acclimatized to the rate-frequency paradigm. Here, testing began with high frequency stimulation that sustained responding at maximal levels and progressed, incrementally, to low frequency stimulation that would not sustain responding. Each tested frequency was available for 50 s; a sample of 5 "priming" trains (1 per s) was administered at each new frequency. Test trials were separated by 5 s with the pulse frequency decreased by 0.05 log units (approximately 12%) between trials. Response rate was determined for each 50-s trial; each rate-frequency determination covered 12-15 stimulation frequencies and took 12-15 min. For each animal the initial (highest) pulse frequency tested was 0.05 log units greater than the pulse frequency at which maximal (asymptotic) responding had been recorded on the previous test day; the frequency was decreased until the animal failed to respond at two consecutive frequencies.

Nine rate-frequency determinations were made each day. Following the first few days of rate-frequency determinations, current intensity was adjusted such that the "threshold" stimulation frequency (see below) was between 30 and 40 Hz. Once responding for a given animal was stable in this range, stimulation intensity was fixed for that animal for the remainder of the experiment. Drug testing began when mean daily self-stimulation thresholds varied by less than 10% across 3 consecutive days of testing.

Each animal received a single injection of each dose of cocaine (0.5, 1, 2, 4, 8, 16, and 32 mg/kg ip) in ascending order on alternate

days; on the intervening days the animals were tested following injections of vehicle (saline). Each drug or vehicle test consisted of a baseline assessment in which three rate-frequency functions were determined prior to the injection (the first of these was treated as a "warm-up" period and the data were not used for subsequent statistical comparisons) and a post-injection assessment. The duration of the post-injection determinations involved assessing two rate-frequency determinations per hour for five hours. Lever-pressing was not reinforced or recorded during the remainder of each hour.

The effects of drug and vehicle treatments on self-stimulation thresholds (see below) and maximum rates of responding were evaluated statistically with two-way, Treatment (dosage) X Time (hour), analyses of variance.

Confirmation of electrode placements: At the end of testing each animal was anesthetized and a 1.5-mA anodal current was passed for 15 s through the stimulating electrode. The animals were then perfused with physiological saline followed by 10% formaldehyde. Next, the brains were immersed for 15 min in a formalin-cyanide solution (10% formaldehyde, 3% potassium ferrocyanide, 3% potassium ferricyanide, and 0.5% trichloroacetic acid). This solution forms a blue reaction product with iron particles that have been expelled by the anodal current into the tissue around the electrode tip. Following storage for at least one week in 10% formaldehyde the brains were frozen, sliced in 40-μm sections, and stained with thionin for determination of electrode placements relative to the drawings and coordinates of Swanson (1992).

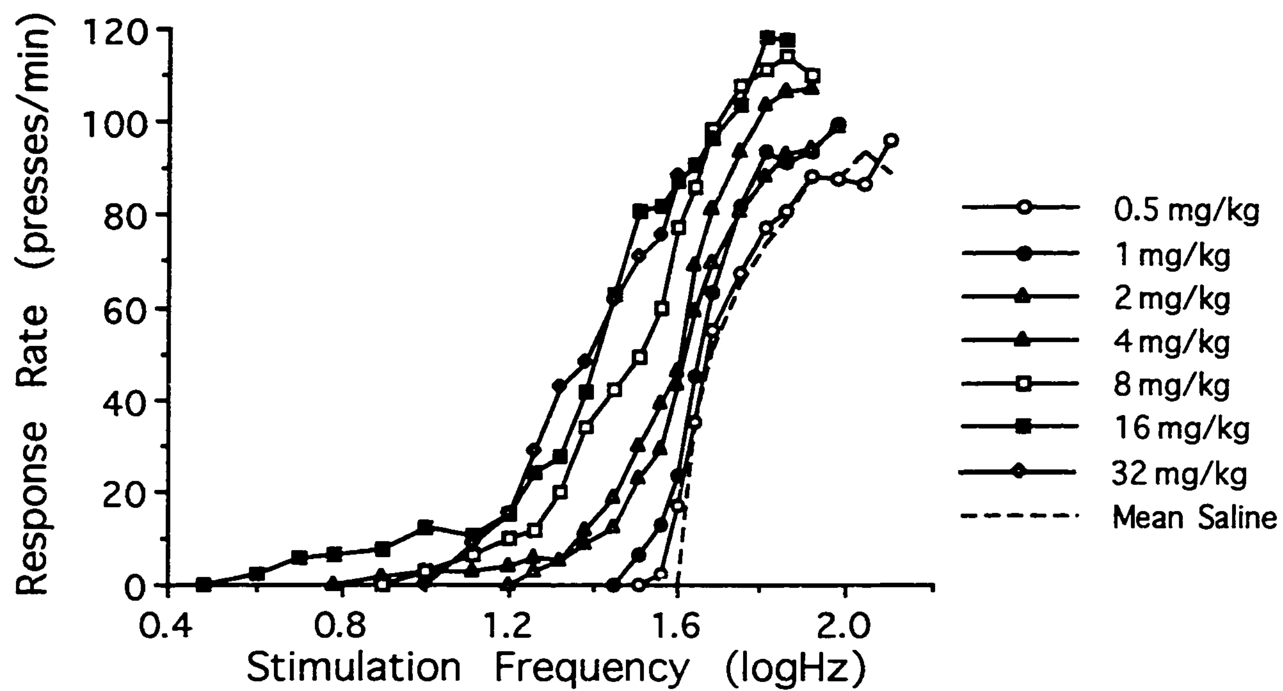
Estimation of self-stimulation threshold: Self-stimulation frequency thresholds were defined as the minimum stimulation frequency required to sustain lever pressing at greater than chance rates. Due to the greater variability of responding at stimulation frequencies near threshold levels, threshold estimates involved extrapolation and curve fitting based on the more reliable range of stimulation frequencies. A regression line was fitted to the data points for the frequencies estimated, by interpolation, to sustain responding at 20%, 30%, 40%, 50%, and 60% of maximum, and threshold was estimated as the point at which this regression line crossed the abscissa (Miliaressis *et al.*, 1986b).

Drug: Cocaine hydrochloride (BDH Chemicals, Toronto, Canada) was dissolved in sterile physiological saline and administered ip (1 ml/kg); dosage is expressed as the salt.

2.3 RESULTS

Cocaine caused leftward and upward shifts of the functions relating the logarithm of stimulation frequency (stimulation "dose"; Yeomans, 1975) to response rate. The leftward and the upward shifts were each dose-orderly (Fig. 2.1). There were no significant differences ($F_{7,49}$=.84, p>0.55) in the slopes of the rising portions of the curves (estimated for each animal prior to averaging by computer algorithm from the threshold estimating procedure). A tendency to perseverate when receiving low stimulation frequencies, well

Figure 2.1: Mean lever-pressing rate during the first 15 min after cocaine injection as a function of stimulation frequency and cocaine dosage. Frequency data were transformed to log difference-from-baseline values for each animal before averaging in order that the slope of the mean rate-frequency functions not be contaminated by between-animal differences in threshold.



Response Rate (presses/min)
120
100
80
60
40
20
0
0.4
0.8
1.2
1.6
2.0
Stimulation Frequency (logHz)
0.5 mg/kg
1 mg/kg
2 mg/kg
4 mg/kg
8 mg/kg
16 mg/kg
32 mg/kg
Mean Saline

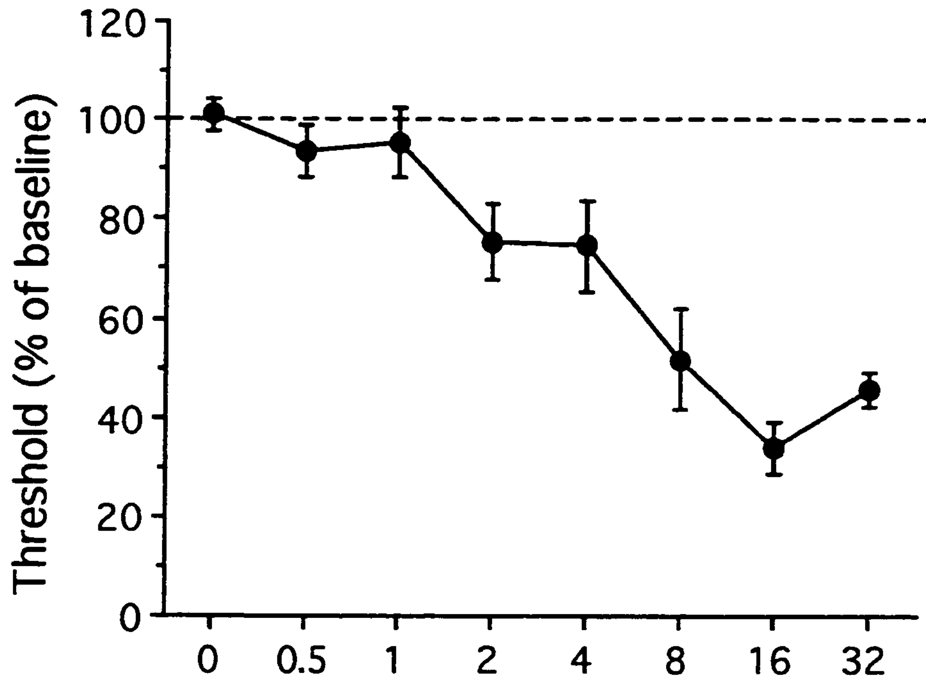
characterized in the case of amphetamine (Olds & Travis, 1970), was seen with the higher cocaine dosages. The leftward shifts in the curves were reflected by a significant decrease in threshold as a function of cocaine dosage (Fig. 2.2 top panel; $F_{7,49}= 12.92$, $p<0.01$); the upward shifts were reflected by a significant increase in maximum rate as a function of dosage (Fig. 2.2 bottom panel; $F_{7,49}= 7.10$, $p<0.01$). At the 16 mg/kg dose (the dose producing the largest average decrease in threshold) cocaine reduced the threshold frequency by 0.47 log units, which represents a 3.1-fold increase in the rewarding potency of the stimulation.

There were no significant day-to-day changes in pre-drug (baseline) responding Fig. 2.3 ($F_{13,91}= 1.13$, $p>0.05$).

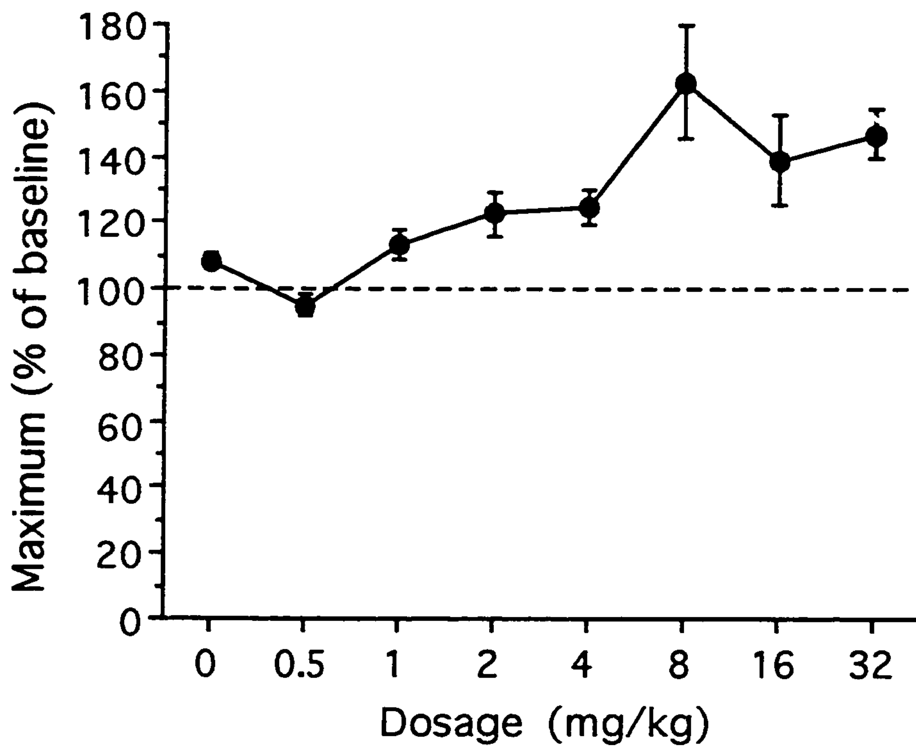
Time-courses of the effects of cocaine at various dosages are shown in Fig. 2.4. Thresholds were significantly decreased (Fig. 2.4 top panel; $F_{7,56}= 2.19$, $p<0.05$) and maximum response rates significantly increased (Fig. 2.4 bottom panel; $F_{7,56}= 7.05$, $p<0.01$) for one to two hours with the lower doses and for three hours with the higher doses.

All electrode tips were within the boundaries of the medial forebrain bundle at the level of the lateral hypothalamus (Fig. 2.5).

Figure 2.2: Mean (±SEM) self-stimulation frequency threshold (top) and maximum response rates (bottom), expressed as a percent of baseline, as a function of cocaine at different doses. All values are means from the first threshold determination (15 min) in the first hour after injection. For this and subsequent figures, each reference (baseline) value is the mean from the two threshold determinations taken just prior to the respective test.



Threshold (% of baseline)
120
100
80
60
40
20
0
0
0.5
1
2
4
8
16
32



Maximum (% of baseline)
180
160
140
120
100
80
60
40
20
0
0
0.5
1
2
4
8
16
32
Dosage (mg/kg)

Figure 2.3: Mean (±SEM) pre-injection self-stimulation frequency threshold (raw scores) on saline (odd numbered) and cocaine (even numbered) test days.

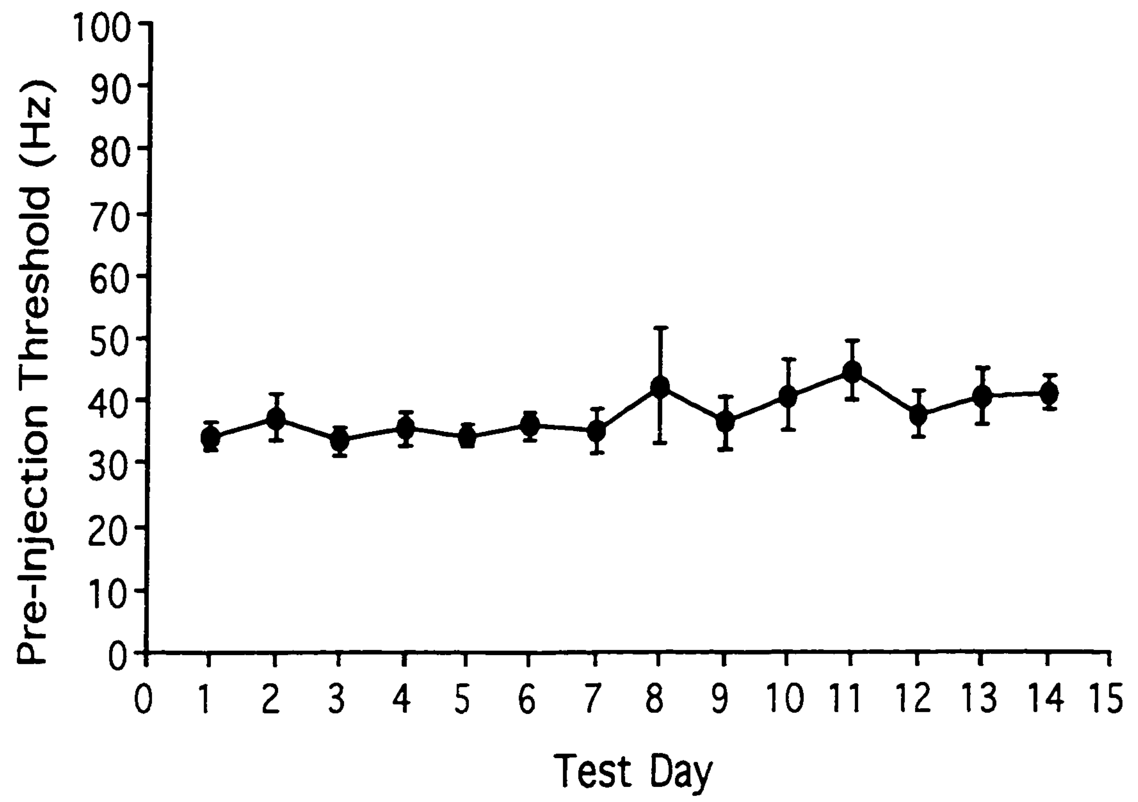
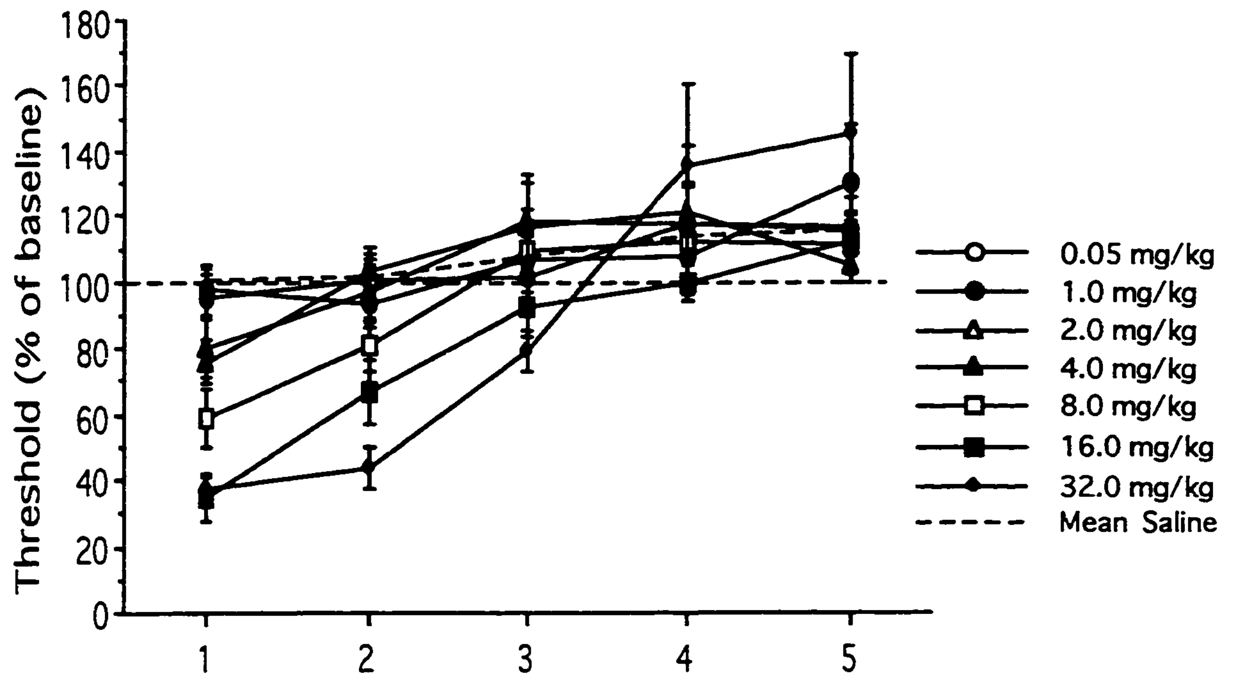

Pre-Injection Threshold (Hz)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Test Day

Figure 2.4: Mean (±SEM) self-stimulation frequency threshold (top) and maximum response rates (bottom) as a function of time after injection with cocaine at different doses. The animals were tested after injections of the cocaine vehicle (saline) on the days preceding each of the seven drug tests; saline values are the means across these seven vehicle tests.


Threshold (% of baseline)
0
20
40
60
80
100
120
140
160
180
1
2
3
4
5
0.05 mg/kg
1.0 mg/kg
2.0 mg/kg
4.0 mg/kg
8.0 mg/kg
16.0 mg/kg
32.0 mg/kg
Mean Saline

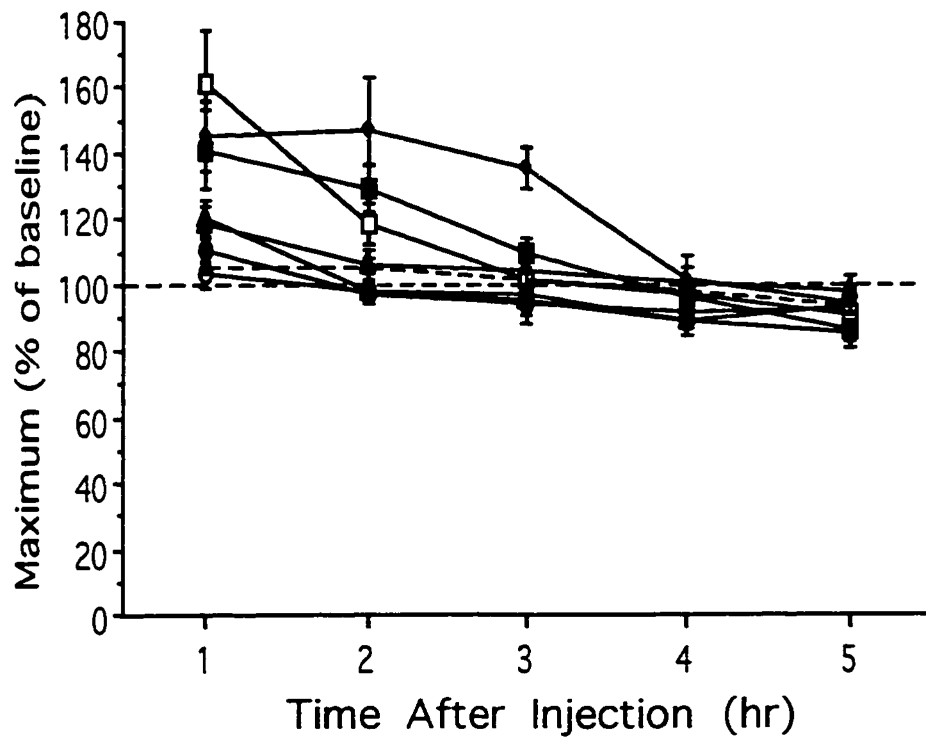
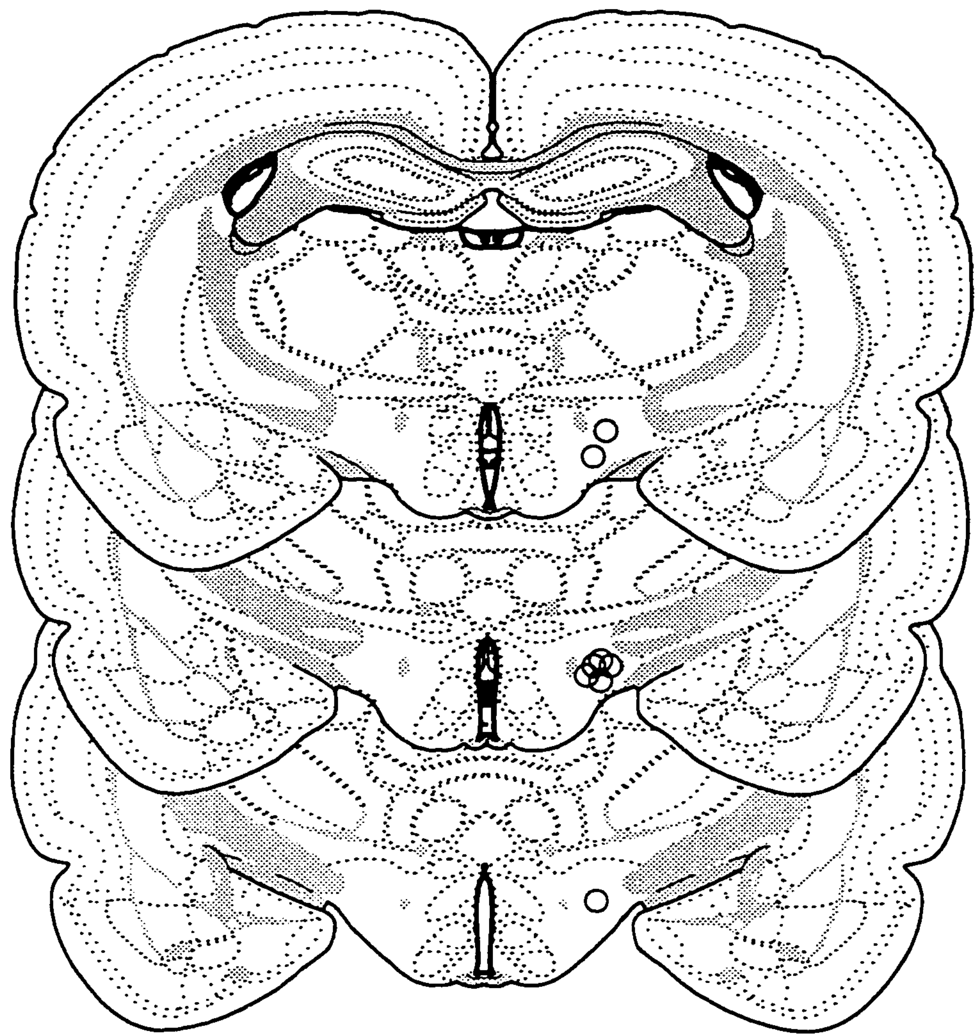

Maximum (% of baseline)
0
20
40
60
80
100
120
140
160
180
1
2
3
4
5
Time After Injection (hr)

Figure 2.5: Histological localization of stimulating electrode tips. The number beside each brain slice represents the distance from the bregma. Reconstructions are based on the stereotaxic atlas of Swanson (1992). To facilitate comparisons all electrode tips are shown in the left hemisphere.



-2.3

-2.5

-2.8

2.4 DISCUSSION

As has been found with several other reinforcing or habit-forming drugs such as morphine (Schenk *et al.*, 1981; Bauco *et al.*, 1993b; Carlezon & Wise, 1993a), amphetamine (Gallistel & Karras, 1984; Gallistel & Freyd, 1987; Wise & Munn; 1993), nicotine (Bauco & Wise, 1994; Wise *et al.*, 1998), phencyclidine (Carlezon & Wise, 1993b), and cannabis (Lepore *et al.*, 1996), cocaine decreased brain stimulation reward thresholds (in each of the animals), by causing leftward shifts in the functions relating response rate to stimulation frequency. These findings are consistent with findings from rate-train duration (Frank *et al.*, 1988, 1992) and rate-intensity (Kokkinidis & McCarter, 1990) paradigms and extend earlier studies to characterize the full range of reward-potentiating cocaine dosages. Inasmuch as the stimulation frequency determines the "dose" of rewarding stimulation per lever-press (Yeomans, 1975), the leftward shifts in the rate-frequency functions can be considered equivalent to leftward shifts in the brain stimulation reward "dose-effect" function (Liebman, 1983; Wise, 1996b). Cocaine can be seen to increase the rewarding potency of the stimulation and not mereley the response capacity (Edmonds & Gallistel, 1974; Stellar & Neeley, 1982) of the animals. The drug reduced the dose of stimulation necessary to sustain responding at a given criterion level, thus in some sense substituting for a portion of the rewarding stimulation. In essence, there was summation between the effects of cocaine and the rewarding action of lateral hypothalamic stimulation, suggestive of a common mechanism of cocaine reward and brain stimulation reward (Wise *et al.*, 1992; Wise, 1996b).

The present findings suggest that the threshold dose of cocaine for potentiating brain stimulation reward is approximately 2 mg/kg. This dose produced noticeable but marginally significant results in the first half-hour after injection. Maximal effectiveness was seen with the 16 mg/kg dose; this dose produced an average 65% reduction in the stimulation frequency required to sustain minimal responding. The 32 mg/kg dose produced longer-lasting potentiation but did not appear to produce a greater magnitude of potentiation.

In Experiment 2 the ability of cocaine to potentiate the rewarding impact was assessed following repeated drug tests. The aim was to determine whether there are any progressive changes in the threshold lowering effects of cocaine following repeated intermittent drug injections.

EXPERIMENT 2

Potentiation of Lateral Hypothalamic Brain Stimulation Reward by Cocaine: An Analysis of Intermittent Dosing

3.1 INTRODUCTION

Psychomotor-stimulant sensitization involves a progressive increase in the behavioral responses to repeated drug administration. In contrast, psychomotor-stimulant tolerance involves a progressive decrease in the behavioral responses to repeated drug administration. While it has been widely held that the development of tolerance and resulting escalation of drug dosage constitute the hallmarks of drug dependence in humans (Jaffe, 1990) the opposite has more recently been argued. There clearly is tolerance to some actions of abused drugs (see introduction to Experiment 3). There appears, however, to be sensitization or "reverse" tolerance to the specific actions of several habit-forming drugs such as amphetamine (Piazza *et al.*, 1990a) and cocaine (Horger *et al.*, 1990, 1992) that make them rewarding as reflected in self-administration (Horger *et al.*, 1990; Piazza *et al.*, 1990a; Horger *et al.*, 1992) and conditioned place-preference (Lett, 1989; Shippenberg & Heidbreder, 1995, Shippenberg *et al.*, 1996) paradigms. While it is difficult to quantify progressive changes in the rewarding efficacy of drugs in drug self-administration (see, e.g. Gerber & Wise, 1989; Winger *et al.*, 1989) and conditioned place-

preference (Bozarth, 1987a) paradigms, the capacities of drugs to augment the rewarding actions of brain stimulation are usually predictive of the ability of those drugs to serve as rewards in their own right (Wise, 1996b) and are reliably quantified and compared in the curve-shift paradigm (Miliaressis *et al.*, 1986b; Gallistel, 1987; Gallistel & Freyd, 1987). Studies of the effects of cocaine using simple rate (Kokkinidis & McCarter, 1990) or rate-train duration measures (Frank *et al.*, 1988) suggest that there is little if any sensitization of the reward-enhancing actions of medial forebrain bundle electrical stimulation. Experiment 2, therefore, was designed to examine whether there is sensitization to the reward-potentiating actions of medial forebrain bundle electrical stimulation by cocaine using the curve-shift rate frequency brain stimulation paradigm.

3.2 MATERIALS AND METHODS

Subjects: Twenty-two 300 to 350g male Long-Evans rats (Harlan Sprague Dawley, U.S.A.) were used. They were housed individually in polyethylene cages with wood chip bedding and free access to food and water. Lighting was maintained on a normal 12-h light/dark cycle; the animals were tested at the end of the dark phase.

Surgery: The surgical procedure was the same as that used in Experiment 1.

Apparatus: The apparatus was the same as that used in Experiment 1.

Procedure: The self-stimulation screening and training procedures were the same as those used in Experiment 1.

Two independent groups of animals were tested five times, at 48-hr intervals following injection of 4 mg/kg (n=8) or 16 mg/kg (n=6) of cocaine; these animals were tested following vehicle (saline) injections on the intervening days. Eight additional animals were similarly tested five times, at 48-hr intervals, following ip injections of 16 mg/kg of cocaine; however, these animals were maintained in their home cages, without testing, on days intervening cocaine tests.

Each drug or vehicle test consisted of a baseline assessment in which three rate-frequency functions were determined prior to the injection (the first of these was treated as a "warm-up" period and the data were not used for subsequent statistical comparisons) and a post-injection assessment. The duration of the post-injection assessment was 2 hrs (4 mg/kg group) or 5 hrs (16 mg/kg groups); two rate-frequency determinations per hour were recorded. Lever-pressing was not reinforced or recorded during the remainder of each hour.

The effects of drug and vehicle treatments on self-stimulation thresholds (see below) and maximum response rates were evaluated statistically with two-way, Treatment (dosage) X Time (hour or day), analyses of variance.

Confirmation of electrode placements: The procedure to confirm the placement of electrodes was the same as that used in Experiment 1.

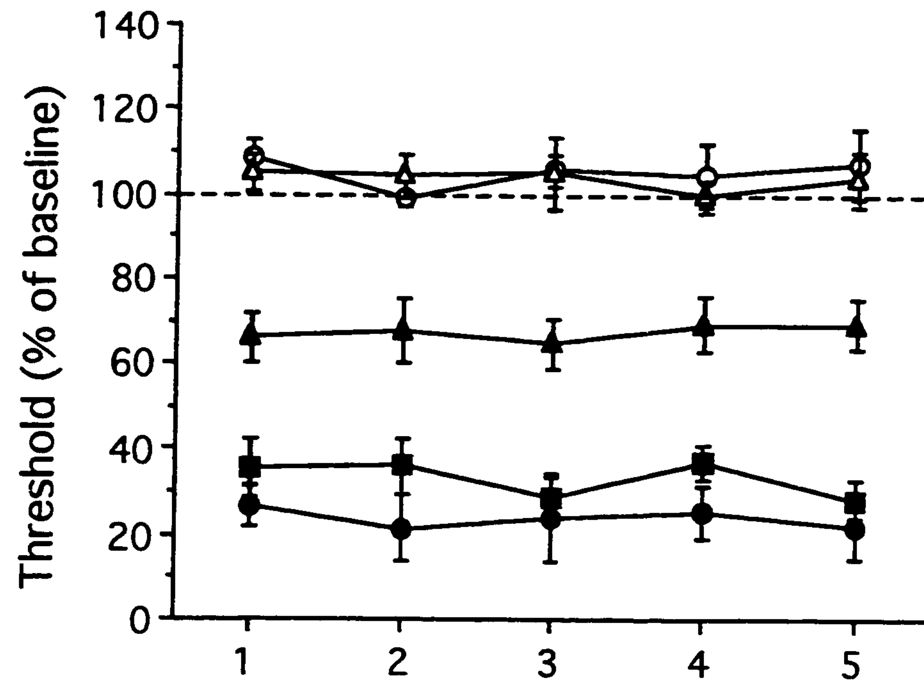
Estimation of self-stimulation threshold: The procedure to estimate self-stimulation threshold was the same as that used in Experiment 1. *Drug:* The drug and vehicle were the same as those used in Experiment 1.

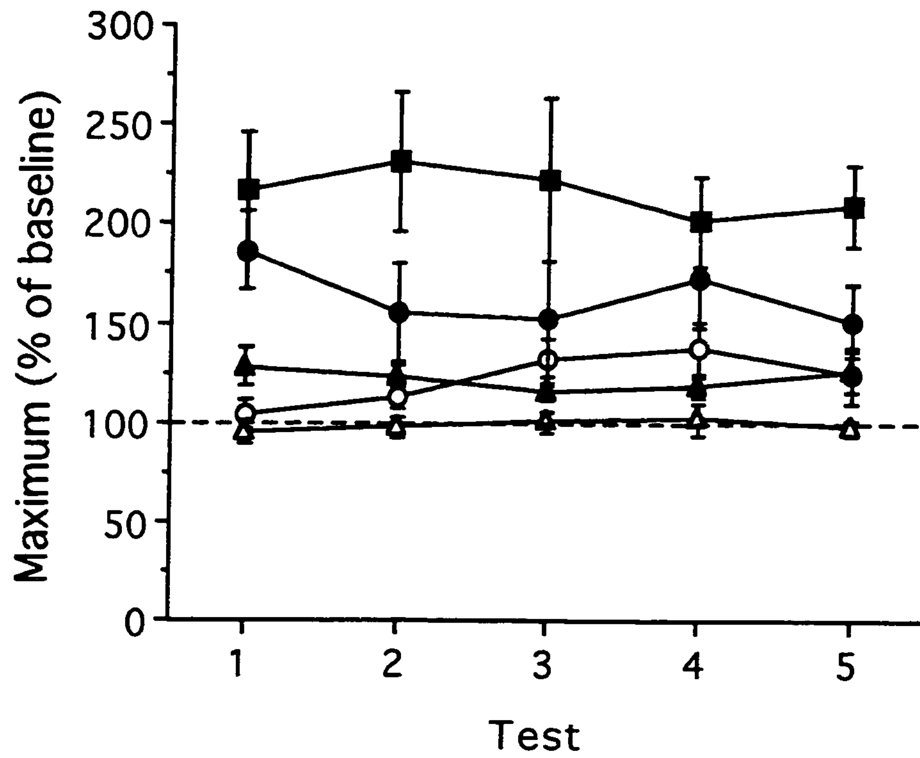
3.3 RESULTS

As in Experiment 1 cocaine caused leftward and upward shifts of the functions relating the logarithm of stimulation frequency (stimulation "dose"; Yeomans, 1975) to response rate in each of the animals (rate-frequency curves not shown).

The mean thresholds for the first two determinations (first hour after injection) were also used to compare cocaine effects (4 or 16 mg/kg) across days. There were no significant differences in the effects of cocaine on self-stimulation thresholds across days (Fig. 3.1 top panel; $F_{4,76}= 0.44$, $p>0.05$) or maximum response rates (Fig. 3.1 bottom panel, $F_{4,76}= 0.59$, $p>0.05$). Moreover, thresholds were significantly lowered ($F_{2,19}= 42.21$, $p<0.01$), and maximum response rates significantly elevated ($F_{2,19}= 6.28$, $p<0.01$) in the two groups of animals injected with the 16 mg/kg compared to the group injected with 4 mg/kg cocaine.

Figure 3.1: Mean (±SEM) self-stimulation frequency threshold (top) and maximum response rate (bottom), expressed as a percent of baseline, on successive days of testing for the first hour following repeated cocaine at 4 or 16 mg/kg. Circles (16 mg/kg group) and triangles (4 mg/kg group) indicate data for animals tested with saline (open symbols) on days intervening drug tests; squares indicate data for animals kept in home cages on days intervening drug tests. Cocaine caused significant decreases ($p<0.01$) in threshold and significant increases in maximum rates; there were no statistically significant Treatment X Days interactions.


Threshold (% of baseline)
140
120
100
80
60
40
20
0
1
2
3
4
5


Maximum (% of baseline)
300
250
200
150
100
50
0
1
2
3
4
5
Test

There were no significant day-to-day changes in pre-drug (baseline) responding (Fig. 3.2) in any of the three groups of animals (4 mg/kg saline intervening group $F_{9,63}$= 1.26, p>0.05; 16 mg/kg saline intervening group $F_{9,45}$= 1.59, p>0.05; 16 mg/kg no saline intervening group $F_{4,28}$= 1.20, p>0.05).

All electrode tips were within the boundaries of the medial forebrain bundle at the level of the lateral hypothalamus (Fig. 3.3).

Figure 3.2: Mean (±SEM) pre-injection self-stimulation frequency threshold (raw scores) on saline (odd numbered) and cocaine (even numbered) treatment days.

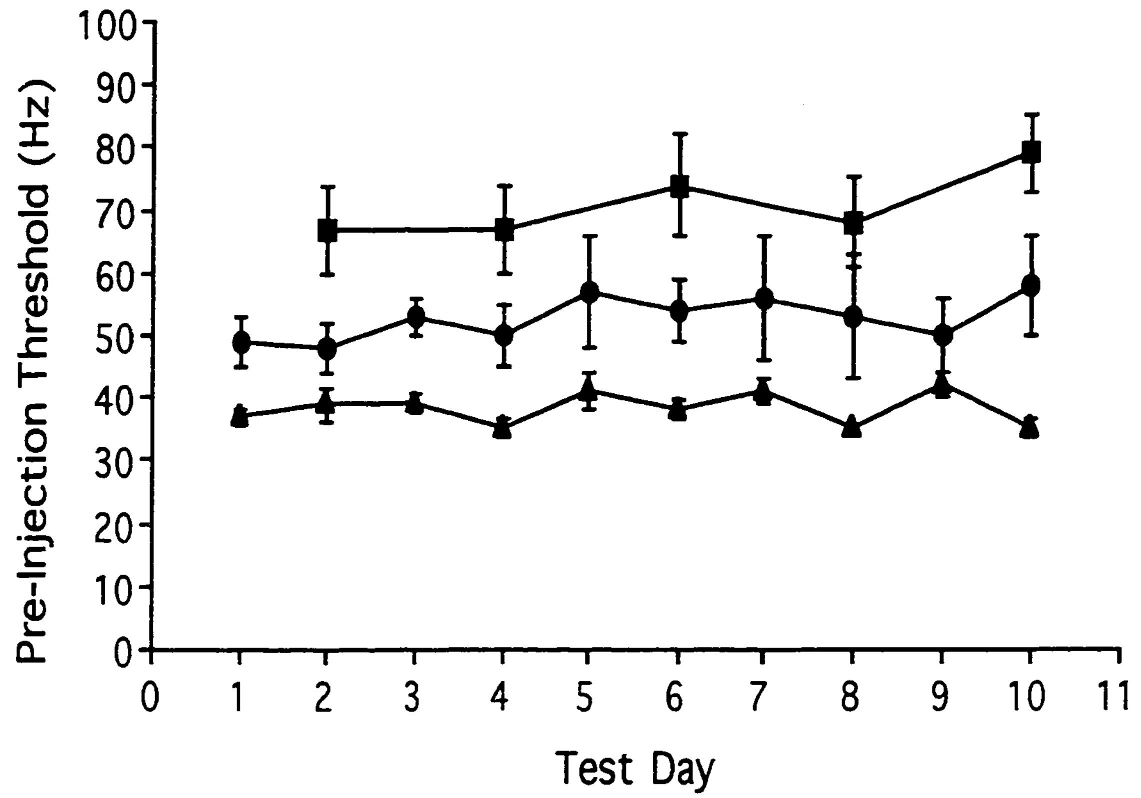
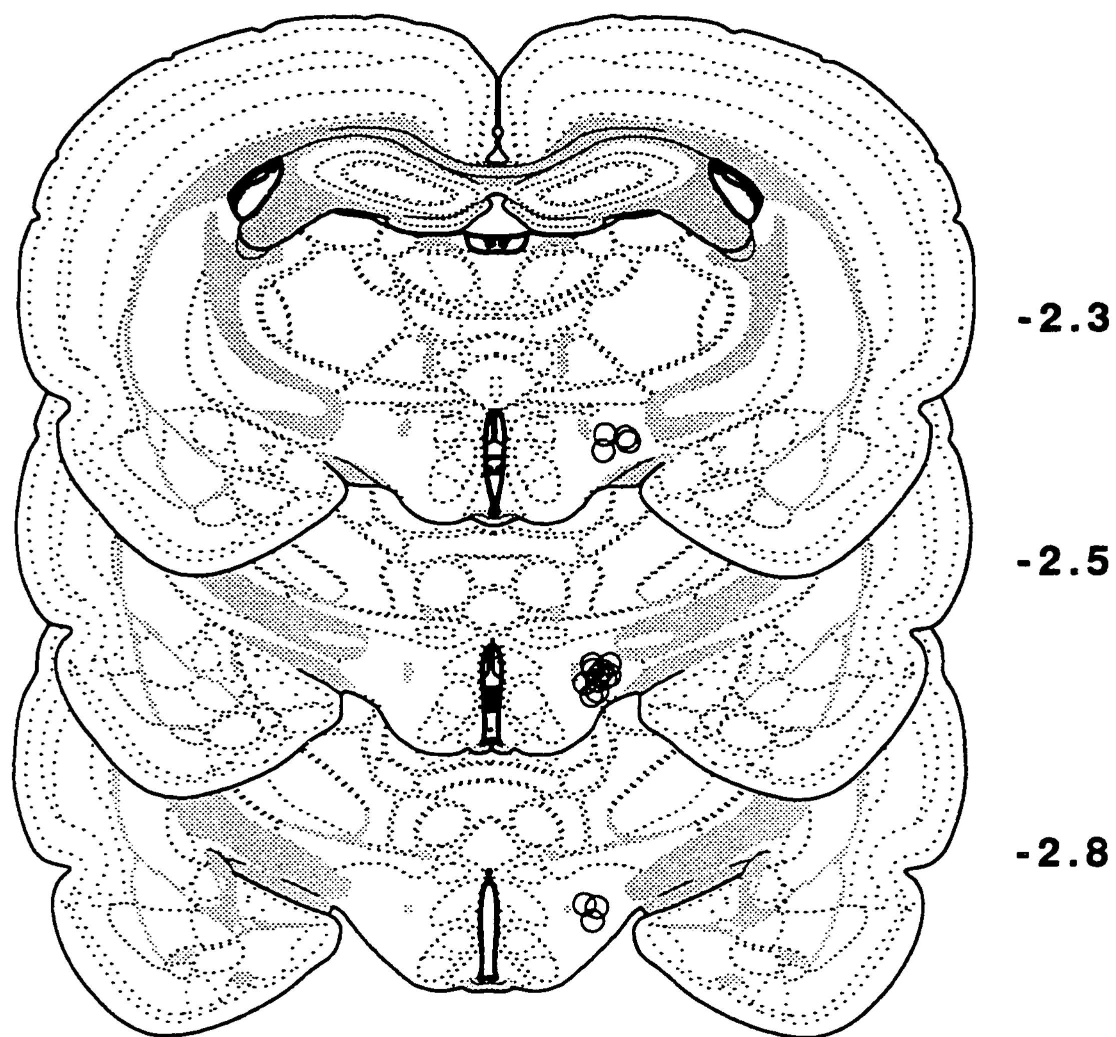

Pre-Injection Threshold (Hz)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
Test Day

Figure 3.3: Histological localization of stimulating electrode tips. The number beside each brain slice represents the distance from the bregma. Reconstructions are based on the stereotaxic atlas of Swanson (1992). To facilitate comparisons all electrode tips are shown in the left hemisphere.


-2.3
-2.5
-2.8

3.4 DISCUSSION

The hypothesized common denominator of incentive-motivation and reinforcement involves the brain mechanisms of forward locomotion, the common response to all positive reinforcers (Schneirla, 1959; Glickman & Schiff, 1967; Perkins, 1968; Bindra, 1972; Wise & Bozarth, 1987). However, the effects of cocaine and other psychomotor stimulants (including, at appropriate doses and by appropriate routes of administration, opiates: Wise & Bozarth, 1987) show sensitization or "reverse-tolerance" with repeated administration (Babbini & Davis, 1972; Post & Rose, 1976; Stripling & Ellinwood, 1976), while the reward-potentiating effects of cocaine in the present experiment clearly did not. This finding is consistent with most previous reports of the effects of repeated treatment with cocaine (Frank, *et al.*, 1988, 1992), amphetamine (but see Predy & Kokkinidis, 1984; Wise & Munn, 1993) morphine (Schenk *et al.*, 1981; Bauco *et al.*, 1993b), nicotine (Bauco & Wise, 1994) and phencyclidine (Carlezon & Wise, 1993b) on brain stimulation reward. These findings would appear to falsify the hypothesis (Wise & Bozarth, 1987) that the brain mechanisms of forward locomotion are homologous with the brain mechanisms of drug-potentiation of brain stimulation reward. Against this view are the findings that rewarding medial forebrain bundle electrical stimulation and stimulation-induced exploratory locomotion along the same fiber bundle may be mediated by different neural substrates (Rompré & Miliaressis, 1980; Durivage & Miliaressis, 1987). Also inconsistent with the hypothesis that the reward-potentiating and direct rewarding effects of cocaine are homologous is the finding that

the direct rewarding effects of cocaine *do* undergo sensitization with repeated injections (Horger *et al.*, 1990). Insofar as the mechanisms of forward locomotion and of reward appear to have dopaminergic modulation and the region of the nucleus accumbens in common, and insofar as dopamine modulates multiple sets of parallel circuits in this part of the brain (Alexander & Crutcher, 1990), the present data suggest that it may be different subsets of cortico-striatal-thalamo-cortical sub-circuitry that play roles in the two closely associated phenomena.

It is difficult to reconcile the finding that maximum response rates during intoxication with 16 mg/kg of cocaine differed depending on whether the animals were given saline tests on the days intervening cocaine or were left in their home cage without testing on the intervening days. These findings suggest that response maxima may be a function of more than simple motoric capacity but do not suggest what other factors might be involved. The fact that cocaine-induced threshold shifts were not affected by whatever actions differentially altered cocaine-induced maximum response rates, however, adds to the evidence that left-right and up-down shifts in rate-frequency functions are independent of one another (Edmonds & Gallistel, 1974; Stellar & Neeley, 1982; Rompré & Wise, 1989).

In Experiment 3 the question of whether tolerance develops to the reward-potentiating actions of medial forebrain bundle electrical stimulation by cocaine was experimentally addressed.

EXPERIMENT 3

Potentiation of Lateral Hypothalamic Brain Stimulation Reward by Cocaine: An Analysis of Repeated High Dose Administration

4.1 INTRODUCTION

Whereas sensitization reflects a progressive increase in behavioral responses to repeated drug injections (Stewart & Badiani, 1993; Wise & Leeb, 1993; Emmett-Oglesby, 1995), tolerance reflects the progressive decrease of the original response to repeated drug injections or drug exposure (Jaffe, 1990; Stewart & Badiani, 1993; Emmett-Oglesby, 1995). Though many factors may contribute to the development of sensitization or tolerance to the effects of drugs, it is clear that the dosing regimen is important. Whereas repeated intermittent drug injections have been reported to result in sensitized behavioral responses (see introduction Experiment 2), the development of tolerance to the actions of drugs is thought to require nearly continuous drug delivery (e.g. by means of subcutaneous drug reservoirs) or injection regimens that produce prolonged periods of high circulating blood levels of the drug (Stewart & Badiani, 1993; Schenk & Partridge, 1997). The behavioral consequences are thus determined in part by the dosing protocol and the same drug effect may undergo sensitization with intermittent exposure or tolerance with continuous exposure (Post, 1980; Giknis & Damjanov, 1984). For

example, sensitized locomotor activity is observed when morphine is administered to mice at intervals of several days whereas tolerance to the locomotor-stimulant actions of morphine are observed when similar injections are given twice daily (Shuster *et al.*, 1975).

Tolerance develops, for example, to the hyperthermic (Harrison *et al.*, 1952; Götestam, 1976), anorexigenic (Tormey & Lasagna, 1960; Kosman & Unna, 1968; Costa & Garattini, 1970; Götestam, 1976), cardiovascular (Fischman *et al.*, 1985; Foltin & Fischman, 1991), and toxic effects of psychostimulant drugs (Lewander, 1968). Tolerance also develops to the analgesic, motor inhibiting, and depressant actions of opiates (Di Chiara & North, 1992). With the exception of "acute" or "within-session" tolerance (LeBlanc *et al.*, 1975; Fischman *et al.*, 1985; Emmett-Oglesby & Lane, 1992; Emmett-Oglesby *et al.*, 1993;) there is no clear evidence from animal models that *long-lasting* tolerance develops to the rewarding actions of habit-forming drugs. While acute tolerance to the rewarding or euphoric actions of psychostimulants may account for the progressive increase in consumption or drug dose (Fischman *et al.*, 1985; Gawin & Ellinwood, 1988), this tolerance dissipates during drug withdrawal (Kalivas *et al.*, 1993). In studies using lower animals it is not clear whether tolerance develops to the rewarding actions of drugs.
Both tolerance (Shippenberg *et al.*, 1988) and lack of tolerance (Bechara & van der Kooy, 1992; Contarino *et al.*, 1997) has been reported to develop to systemic injections of opiates when tested in the conditioned place-preference paradigm. The rate-increasing effect of amphetamine in the brain stimulation reward paradigm appears to undergo tolerance in some instances (Leith & Barrett, 1976; Anderson

et al., 1978) yet fails to do so in others (Miller *et al.*, 1976). There also appears to be no tolerance to the rate-increasing (Bush *et al.*, 1976) or threshold lowering (Kelley & Reid, 1977) effect of systemic morphine injections when tested in the brain stimulation reward paradigm. Tolerance has been reported to develop to the rewarding actions of cocaine (Emmett-Oglesby & Lane, 1992; Li *et al.*, 1994) and amphetamine (McCown & Barrett, 1980) in rats and to cocaine in primates (Yanagita, 1973) when each drug is self-administered intravenously. In contrast, studies of the effects of cocaine using simple rate (Kokkinidis & McCarter, 1990) or rate-train duration measures (Frank *et al.*, 1988) suggest that there is little tolerance to the reward-potentiating actions of medial forebrain bundle electrical stimulation.

Whereas Experiment 2 was designed to determine whether sensitization develops to the reward-potentiating actions of cocaine (intermittent injections), Experiment 3 was designed to determine whether tolerance develops to cocaine's reward-potentiating actions on lateral hypothalamic electrical stimulation. The drug injection protocol was adapted from protocols that have been reported to produce within-session tolerance to self-administered (Emmett-Oglesby & Lane, 1992) and to the reward-potentiating actions (Frank *et al.*, 1988) of cocaine.

4.2 MATERIALS AND METHODS

Subjects: Fifteen 300 to 350g male Long-Evans rats (Harlan Sprague Dawley, U.S.A.) were used. They were housed individually in polyethylene cages with wood chip bedding and free access to food and water. Lighting was maintained on a normal 12-h light/dark cycle; the animals were tested at the end of the dark phase.

Surgery: The surgical procedure was the same as that used in Experiments 1 and 2.

Apparatus: The apparatus was the same as that used in Experiments 1 and 2.

Procedure: The self-stimulation screening and training procedures were the same as those used in Experiments 1 and 2.

Two groups of animals were compared during a thrice-daily, followed by a once-daily, injection regimen. The thrice-daily injection regimen was designed to induce *acute* or *within-session* (LeBlanc *et al.*, 1975; Kalant, 1977) tolerance to the rewarding effects of cocaine; it was adapted from the protocols of Emmett-Oglesby and Lane (1992) and of Frank *et al.* (1988). During the thrice-daily regimen the animals in one group (n=7) received injections of cocaine every 8 hrs (5:00 a.m., 1:00 p.m., and 9:00 p.m.); the other group (n=8) received saline on the same schedule. On each day of the thrice-daily regimen the animals received their first injection in their test cage and the subsequent two injections in their home cage. Self-stimulation was assessed prior to

and following the 5:00 a.m. injection on days 1, 2, 3, 5, 6, and 7 of the thrice-daily regimen. On Day 1 for the 5:00 a.m. injection animals were administered cocaine 10 mg/kg or saline; the subsequent two injections (home cage) were 20 mg/kg cocaine or saline. On Day 2 animals were administered cocaine 20 mg/kg or saline for each of the 3 injections. On Day 3 animals were administered cocaine 20 mg/kg or saline for the 5:00 a.m. injection. Due to deaths of three of these animals, subsequent thrice-daily cocaine injections were given at the dosage of 10 mg/kg. Following the thrice-daily cocaine and saline treatment regimens, the two groups were tested for baseline brain stimulation reward thresholds and responses to 10 mg/kg of cocaine. These tests occurred 1,2,3,6,9,12, and 15 days after the last thrice-daily treatment injection.

As in Experiments 1 and 2 each drug or vehicle test consisted of a baseline assessment in which three rate-frequency functions were determined prior to the injection (the first of these was treated as a "warm-up" period and the data were not used for subsequent statistical comparisons) and a post-injection assessment. Three rate-frequency curves, each lasting approximately 15 min, were determined following the injection.

The effects of drug and vehicle treatments on self-stimulation thresholds (see below) and maximum response rates were evaluated statistically with two-way, Treatment (Group) X Day, analyses of variance.

Confirmation of electrode placements: The procedure to confirm the placement of electrodes was the same as that used in Experiments 1 and 2.

Estimation of self-stimulation threshold: The procedure to confirm the placement of electrodes was the same as that used in Experiments 1 and 2.

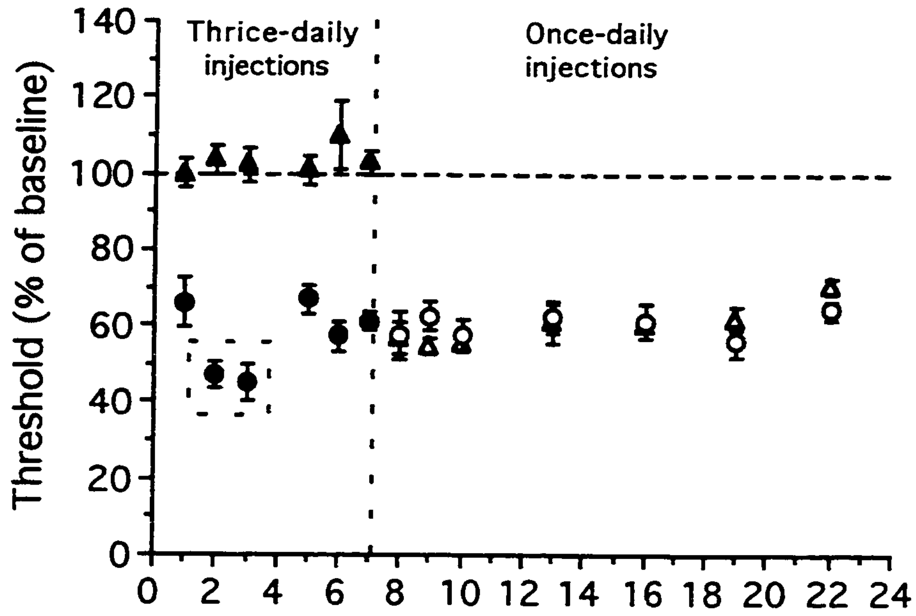
Drug: The drug and vehicle were the same as those used in Experiments 1 and 2.

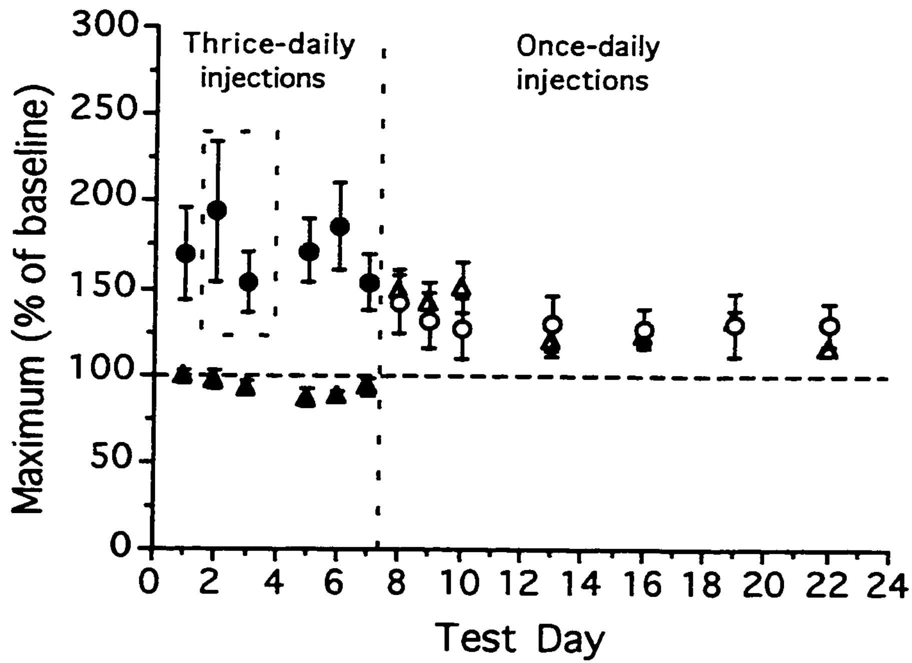
4.3 Results

As in Experiments 1 and 2 cocaine caused leftward and upward shifts of the functions relating reponse rate to the logaritm of stimulation frequency (stimulation "dose": Yeomans, 1975) in each of the animals (rate-frequency curves not shown).

There were no significant differences in the threshold lowering effects of 10 mg/kg cocaine when Days 2 and 3 (20 mg/kg dose) are excluded from the analysis; Fig. 4.1 top panel; $F_{10,60} = 0.79$, $p>0.05$. While maximum response rates were significantly elevated in the cocaine group throughout the thrice-daily injection regimen this effect decreased markedly with once-daily injections (Fig. 4.1 bottom panel; $F_{10,60} = 2.98$, $p<0.01$). The means of three threshold determinations were used for the comparisons across days. Moreover, there were no significant differences between groups during the once-daily injection

Figure 4.1: Mean (±SEM) self-stimulation frequency threshold (top) and maximum response rate (bottom) on successive days of testing for the first 45 min during a thrice-daily (filled symbols) and once-daily (open symbols) injection regimen. Values are means from the first three threshold determinations (45 min) after injection. Each reference (baseline) value is the mean from the two threshold determinations taken just prior to the respective test. Cocaine [circles, 10 mg/kg (and 20 mg/kg, dashed box)] caused significant decreases in threshold and increases in maximum response rates ($P < .01$). The effect of 10 mg/kg cocaine on threshold did not vary significantly across the treatment days.


Threshold (% of baseline)
Thrice-daily
injections
Once-daily
injections
140
120
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20 22 24


Maximum (% of baseline)
Thrice-daily
injections
Once-daily
injections
300
250
200
150
100
50
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Test Day

regimen in the threshold lowering effect of 10 mg/kg cocaine ($F_{1,6}$ = 0.00, $p>0.05$) nor in the ability of cocaine to increase maximum response rates ($F_{1,6} = 0.02$, $p>0.05$).

There were no significant day-to-day changes in pre-drug (baseline) responding (Fig. 4.2) between the two groups of animals ($F_{1,13} = 0.00$, $p>0.05$) or across the treatment days ($F_{12,156} = 1.69$, $p>0.05$).

All electrode tips were within the boundaries of the medial forebrain bundle at the level of the lateral hypothalamus (Fig. 4.3).

Figure 4.2: Mean (±SEM) pre-injection self-stimulation frequency threshold (raw scores) on successive treatment days. Circles are data from animals injected with cocaine during the thrice daily injection regimen (Days 1,2,3,5,6 & 7) and triangles from animals injected with saline during the thrice daily injection regimen (Days 1,2,3,5,6 & 7).

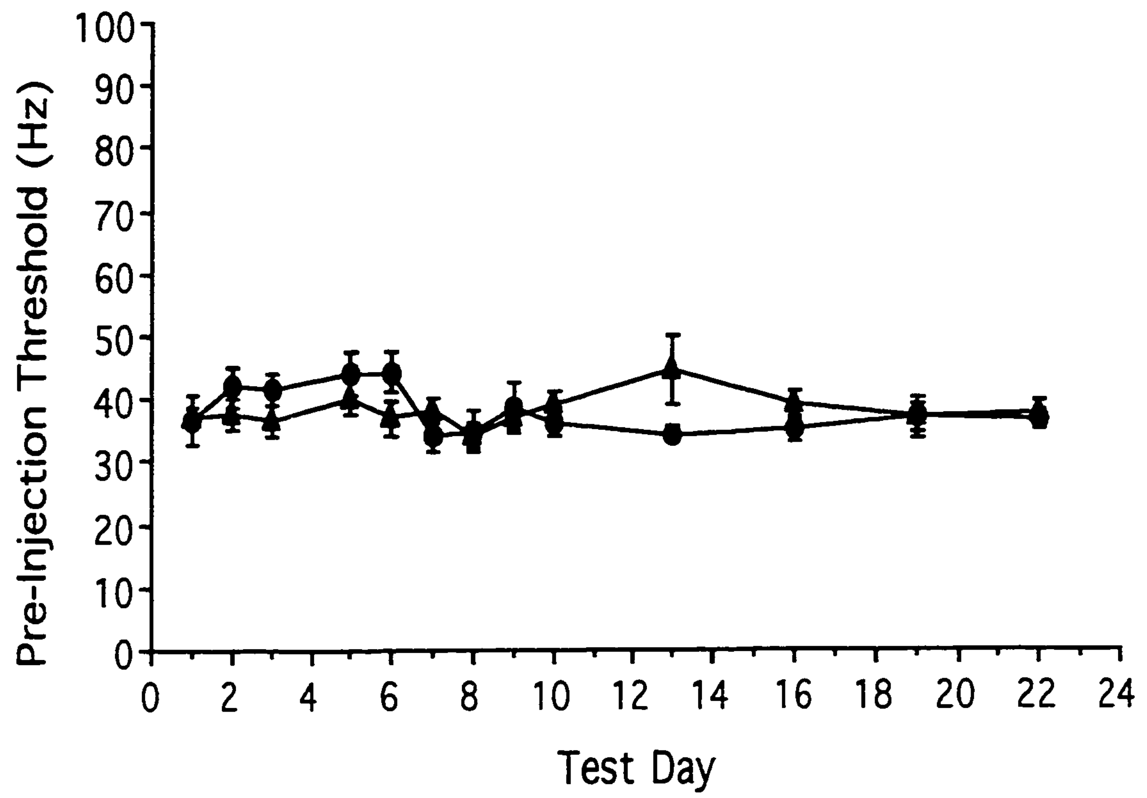
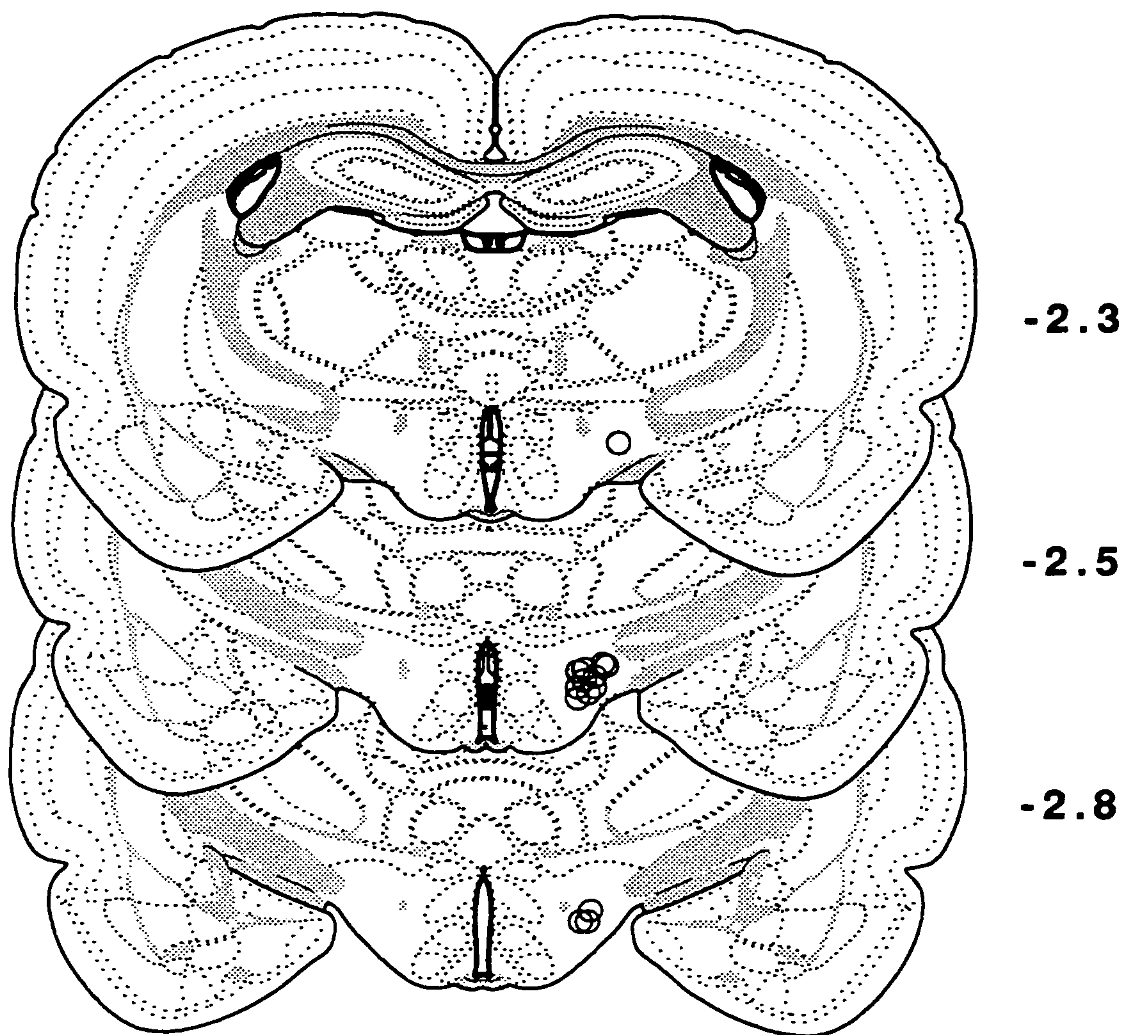

Pre-Injection Threshold (Hz)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Test Day

Figure 4.3: Histological localization of stimulating electrode tips. The number beside each brain slice represents the distance from the bregma. Reconstructions are based on the stereotaxic atlas of Swanson (1992). All electrode tips are shown in the left hemisphere to facilitate comparisons.


-2.3
-2.5
-2.8

4.4 DISCUSSION

The present data are inconsistent with the commonly held notion that there is necessarily profound and long-lasting tolerance to the habit-forming actions of drugs of abuse. With the exception of acute or "within-session" tolerance in humans (Fischman *et al.*, 1985; Ambre *et al.*, 1988) and lower animals (LeBlanc *et al.*, 1975)—where tolerance to the rewarding effects of cocaine have been clearly demonstrated (Fischman *et al.*, 1985; Emmett-Oglesby & Lane, 1992; Emmett-Oglesby *et al.*, 1993)—recent evidence generally goes against the assumption of tolerance to the specific rewarding actions of both psychomotor stimulants and opiates. Prior experience with amphetamine (Piazza *et al.*, 1990a) or cocaine (Horger *et al.*, 1990) is reported to increase rather than decrease the rewarding effectiveness of subsequent amphetamine or cocaine, reducing the threshold dose to establish an operant response habit or reducing the amount of training necessary to establish stable operant performance. Moreover, amphetamine and nicotine are reported to cross-sensitize rats to the reinforcing effects of cocaine (Horger *et al.*, 1992). Prior amphetamine or morphine experience has also been reported to sensitize animals to the ability of amphetamine, morphine, or cocaine to establish conditioned place preferences (Lett, 1989). The present data fail to offer any support for the suggestion that there is between-session tolerance to these effects.

It is somewhat surprising that the present data also fail to offer any evidence for acute tolerance to the reward-enhancing effects of cocaine, inasmuch as acute tolerance has been shown for the direct

rewarding effects. The direct rewarding and reward-enhancing effects of cocaine have been argued to involve a common reward mechanism in the brain (Wise & Bozarth, 1987; Wise, 1996b); an obvious factor is dosage. The treatment regimen in which acute tolerance has been shown in rats (Emmett-Oglesby & Lane, 1992; Emmett-Oglesby *et al.*, 1993) is 20 mg/kg, thrice daily for seven days. This dosage regimen proved fatal for some of the animals, perhaps because the first dose each day was given during sessions of intracranial self-stimulation. The failure in the present experiment to observe acute tolerance involved half the dosing regimen of Emmett-Oglesby *et al.* (1993). Still, when their animals were tested at several time points after the final injection, Frank *et al.* (1988, 1992) found no evidence of acute tolerance in animals treated with 25 or 30 mg/kg thrice daily for three days. Tolerance is generally assumed to reflect drug-opposite neuroadaptations and dopamine depletion (Dackis & Gold, 1985) and elevated brain stimulation reward thresholds (Leith & Barrett, 1976) have been suggested as reward-relevant consequences of such neuroadaptations. Evidence of elevated self-stimulation thresholds has been found when animals are allowed to self-administer cocaine (Markou & Koob, 1991) and in this case the animals received approximately the same daily dose of cocaine (on average, 27 mg/kg/day) as was given in the present study. In Markou and Koob's study, however, the drug was given intravenously every few minutes rather than intraperitoneally every 8 hours as in the present study. Thus the Markou and Koob regimen involved more continuous intoxication. Interestingly, Markou and Koob saw an immediate elevation of brain stimulation reward thresholds after as little as six

hours of cocaine self-administration, when their animals were still intoxicated with satiating levels of cocaine. This is surprising given that the acute effect of intoxicating doses of cocaine is a *decrease* in brain stimulation reward threshold and given the assumption that increased reward thresholds are a rebound consequence of drug intoxication (Solomon & Corbitt, 1973), to be expected only after the drug is metabolized and the drug effect wears off. The other known opponent-process neuroadaptation to cocaine, extracellular dopamine depletion (Parsons *et al.*, 1991; Robertson *et al.*, 1991), has been reported ten days after termination of a cocaine-treatment regimen of 20 mg/kg once-daily for 10 days (Parsons *et al.*, 1991), and 7 days after termination of a regimen of 30 mg/kg once-daily for 18 days (Robertson *et al.*, 1991). Relative to those of the present study, these treatment regimens involve less daily cocaine in the first case and less chronic intoxication in both cases. Thus it would appear that while acute tolerance to cocaine can occur with high-dose and chronic-treatment regimens, it seems not to be a simple consequence of the dopamine depletion reported with dosing regimens more modest than that used in the present study.

In Experiment 4 the interaction between pharmacological blockade of the dopamine system and cocaine on brain stimulation reward was assessed.

EXPERIMENT 4
Effects of Pharmacological Blockade of Dopamine by Pimozide on Brain Stimulation Reward: Interaction With Cocaine and Amphetamine

5.1 INTRODUCTION

Strong evidence of dopaminergic mediation of brain stimulation reward comes from experiments involving pharmacological manipulations of the dopamine system. Pharmacological blockade of the dopamine system by dopaminergic antagonists (neuroleptics) decrease self-stimulation rate (Olds & Travis, 1960; Wauquier & Niemegeers, 1972; Atalay & Wise, 1983) and attenuate the rewarding impact of brain stimulation (Fouriezos & Wise, 1976; Fouriezos *et al.*, 1978; Franklin, 1978; Gallistel & Davis, 1983; Stellar *et al.*, 1983; Lynch & Wise, 1985; Miliaressis *et al.*, 1986a; Bird & Kornetsky, 1990). Gallistel and his co-workers (Gallistel & Karras, 1984; Gallistel & Freyd, 1987) have used the curve-shift rate-frequency paradigm to quantify the effects of dopaminergic blockade by the relatively selective dopamine D_2-like receptor antagonist pimozide (Creese *et al.*, 1976; Leysen *et al.,* 1978; Seeman, 1981) and its interaction with amphetamine on brain stimulation reward. When amphetamine and pimozide were co-administered at a dose that produced an equipotent (0.3-log units) but opposing shift of the rate-frequency curves, the effect of each drug alone was eliminated and the resulting behavior was like that of a normal non-treated animal (Gallistel & Karras, 1984;

Gallistel & Freyd, 1987). Similar findings have been reported in the case of opiates. Morphine antagonizes the rightward shift caused by pimozide in the rate-frequency curve-shift paradigm (Rompré & Wise, 1989). These results provide evidence of dopaminergic mediation of reward function and that pimozide and amphetamine or morphine exert their effects on reward potency on a common set of mesolimbic dopaminergic synapses (Wise & Rompré, 1989).

The aim of the present experiment was to replicate the findings by Gallistel and his co-workers (Gallistel & Karras, 1984; Gallistel & Freyd, 1987) of the interaction of amphetamine and pimozide on the rewarding impact of brain stimulation reward and to extend the analysis to cocaine in the same animals.

5.2 MATERIALS AND METHODS

Subjects: Sixteen 300 to 350g male Long-Evans rats (Harlan Sprague Dawley, U.S.A.) were used. They were housed individually in polyethylene cages with wood chip bedding and free access to food and water. Lighting was maintained on a normal 12-h light/dark cycle; the animals were tested at the end of the dark phase.

Surgery: The surgical procedure was the same as that used in Experiments 1, 2, and 3.

Apparatus: The apparatus was the same as that used in Experiments 1, 2, and 3.

Procedure: The self-stimulation screening and training procedures were the same as those used in Experiments 1, 2, and 3.

Two independent groups of animals were tested (see Table 1.1). Group 1 was tested in order to obtain a time-course of the effects of pimozide (0.3 mg/kg ip) and its vehicle tartaric acid (0.3%) on brain stimulation reward thresholds and maximum response rates. Although the time-course for pimozide's effects on brain stimulation reward has already been characterized by others it was important to determine the time-course under the conditions of the present experiment given the addition of the 800-msec time-out period following each stimulation train. These animals were tested once with pimozide and once with its vehicle at a 48-h interval; half the animals were injected with the vehicle first and half with pimozide and the injection order was reversed for the second test.

Each drug or vehicle test consisted of a baseline assessment in which three rate-frequency functions were determined prior to the injection (the first of these was treated as a "warm-up" period and the data were not used for subsequent statistical comparisons) and a post-injection assessment. In Group 1 the post-injection determinations started immediately following injection and involved assessing two rate-frequency determinations per hour for six hours. Lever-pressing was not reinforced or recorded during the remainder of each hour and animals remained in their test cages.

Table 1.1: Summary of treatment groups

Group	*n*	Treatment
1	8	Two tests at 48-h intervals; half the animals tested with pimozide first and half with vehicle first
2	8	*1st -- 2nd injection*
		Test 1: Tartaric acid -- Saline
		Test 2 & 3: Tartaric acid -- Amphetamine or Cocaine
		Test 4: Pimozide -- Saline
		Test 5 & 6: Pimozide -- Amphetamine or Cocaine
		Test 7: Pimozide -- Saline
		Test 8: Tartaric acid -- Saline

The second group of animals (Group 2) were tested at 48-h intervals for a total of 8 tests (see Table 1.1). Each test consisted of a baseline assessment in which three rate-frequency functions were determined prior to injection (the first of these was treated as a "warm-up" period and the data were not used for subsequent statistical comparisons). Animals were then removed from their test cages and injected either with the tartaric acid (0.3%) vehicle or pimozide (0.3 mg/kg) and returned to their home cages for 4 h (see Table 1.2). The 4-h interval between the post-baseline injection and post-baseline assessment was chosen based on the time-course of pimozide's effects on self-stimulation thresholds (see results section for Group 1) and is consistent with previous reports of the time-course of pimozide's actions on brain stimulation reward thresholds (Franklin 1978; Gallistel & Karras, 1984). Prior to the post-baseline assessment

animals received a second injection (see Table 1.2). The second injection occurred 30 min prior to the post-baseline assessment when animals were injected with amphetamine (2 mg/kg, ip) and 5 min prior to the post-baseline assessment when injected with cocaine (8 mg/kg, ip); in all tests with amphetamine or cocaine (Days 2, 3, 5, and 6) the order of drug testing was counterbalanced such that half the animals were injected with amphetamine and half with cocaine for the second injection prior to the post-baseline assessment of brain stimulation reward. In all cases six additional rate-frequency determinations were assessed (15 min per determination) beginning 4 h after animals received their first injection of tartaric acid or pimozide.

Table 1.2: Summary of post-baseline injection protocol

Drug (ip)	Time of injection prior to post-baseline assessment
Saline	5 min
Tartaric Acid (0.3%)	4 h
Pimozide (0.3 mg/kg)	4 h
Amphetamine (2 mg/kg)	30 min
Cocaine (8 mg/kg)	5 min

The effects of drug and vehicle treatments on self-stimulation thresholds (see below) and maximum response rates were evaluated statistically with a *t*-test for related samples (Group 1) and by two-way, Treatment (drug combination) X Time analyses of variance (Groups 1 and 2).

Confirmation of electrode placements: The procedure to confirm the placement of electrodes was the same as that used in Experiments 1, 2, and 3.

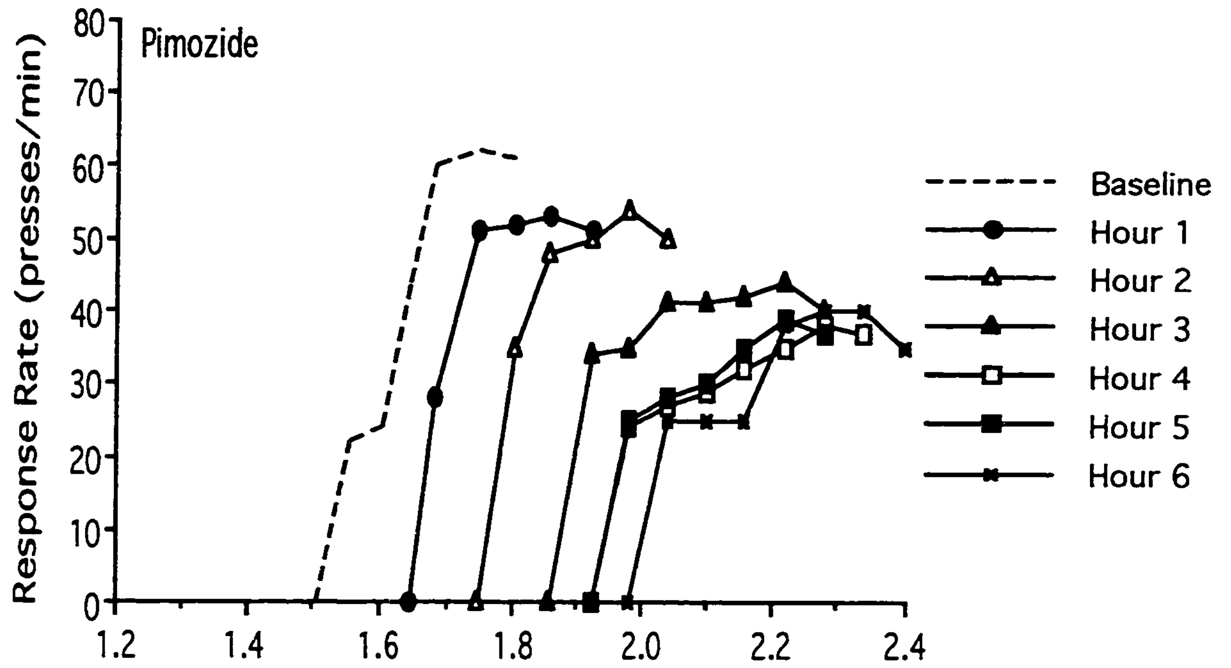
Estimation of self-stimulation threshold: The procedure to estimate self-stimulation threshold was the same as that used in Experiments 1, 2, and 3.

Drugs: Cocaine hydrochloride (BDH Chemicals, Toronto) and *d*-amphetamine sulphate (Sigma Chemical Company, St. Louis, MO) were each dissolved in sterile physiological saline and administered ip (1 ml/kg); dosage is expressed as the salt. Pimozide (Research Biochemicals, Natick, MA) was dissolved in a 0.3% solution of tartaric acid and administered ip (1 ml/kg).

5.3 RESULTS

Group 1: Pimozide caused rightward and downward shifts of the functions relating the logarithm of stimulation frequency to response rate in each of the animals tested (Fig 5.1 top panel); injection with the pimozide vehicle (tartaric acid) did not produce significant shifts in the rate-frequency curves (Fig 5.1 bottom panel). The magnitude of the rightward shifts increased as a function of time after injection. The rightward shifts in the curves were reflected by a significant increase in threshold following injection with pimozide (Fig. 5.2 top panel; $F_{1,7}$= 224.27, p<0.01); the downward shifts were reflected by a

Figure 5.1: Rate of lever-pressing (per min) as a function of stimulation frequency prior to (Baseline) and after (Hour 1-6) injection with Pimozide (top panel) or its vehicle tartaric acid (bottom panel). Each post-injection rate-frequency curve represents the lever-press rate of the second rate-frequency determination assessed for each of the six hours; baseline represents the rate-frequency determination assessed immediately prior to injection. Data in both panels are from the same representative animal.


Pimozide
Response Rate (presses/min)
0
10
20
30
40
50
60
70
80
1.2
1.4
1.6
1.8
2.0
2.2
2.4
Baseline
Hour 1
Hour 2
Hour 3
Hour 4
Hour 5
Hour 6

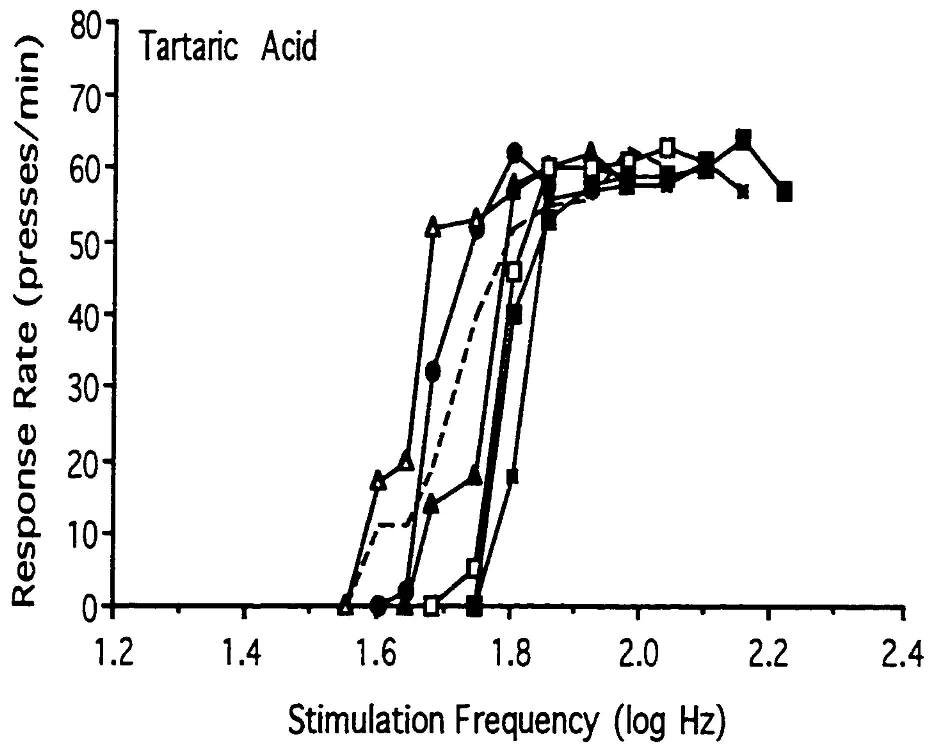
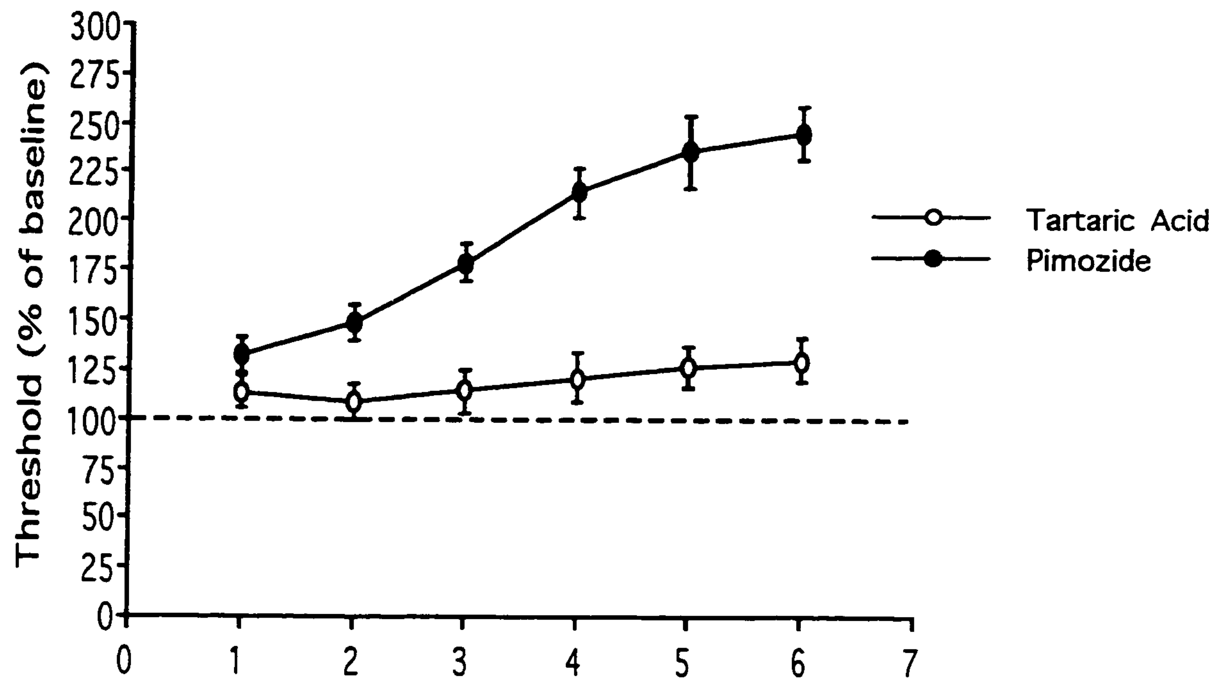
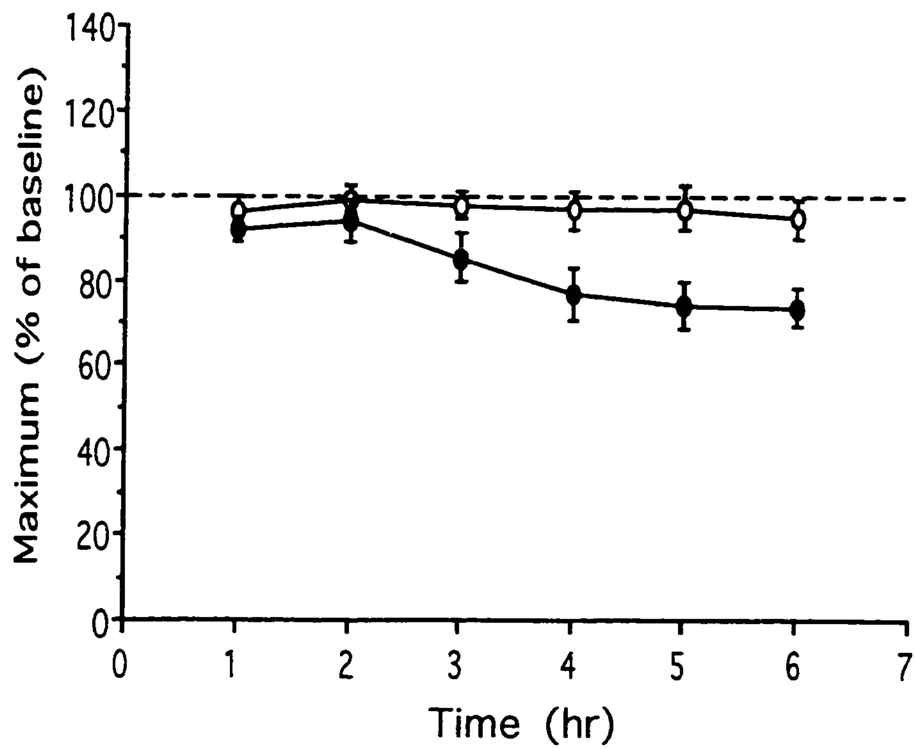

Tartaric Acid
Response Rate (presses/min)
0
10
20
30
40
50
60
70
80
1.2
1.4
1.6
1.8
2.0
2.2
2.4
Stimulation Frequency (log Hz)

Figure 5.2: Mean (±SEM) self-stimulation frequency threshold (top) and response maximum (bottom) expressed as a percent of baseline as a function of pimozide (0.3 mg/kg) or vehicle and time after injection. Values are means from the two threshold determinations assessed each hour after injection. Pimozide caused significant elevations in threshold (top) in the second hour onwards and significant decreases in response maximum in the third hour onwards (bottom). For this and subsequent figures the reference (baseline) value is the mean from the two determinations of threshold and response maximum taken just prior to the respective test.


Threshold (% of baseline)
300
275
250
225
200
175
150
125
100
75
50
25
0
0
1
2
3
4
5
6
7
Tartaric Acid
Pimozide


Maximum (% of baseline)
140
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Time (hr)

significant decrease in maximum rate as a function of pimozide injection (Fig. 5.2 bottom panel; $F_{1,7}$= 13.59, p<0.01). The effects of pimozide on threshold ($F_{1,42}$= 21.06, p<0.01) differed significantly from those of tartaric acid in the second hour after injection and onwards and in the third hour after injection and onwards for maximum rate ($F_{1,42}$= 16.12, p<0.05); the time-course data were used to determine the injection protocol for testing in Group 2.

There were no significant changes in pre-injection (baseline) responding between the two test days (Fig. 5.3; $t(7) = 1.72$, p>0.05). All electrode tips were within the boundaries of the medial forebrain bundle at the level of the lateral hypothalamus (Fig. 5.4).

Figure 5.3: Mean (±SEM) pre-injection self-stimulation frequency threshold (raw scores) as a function of test day.

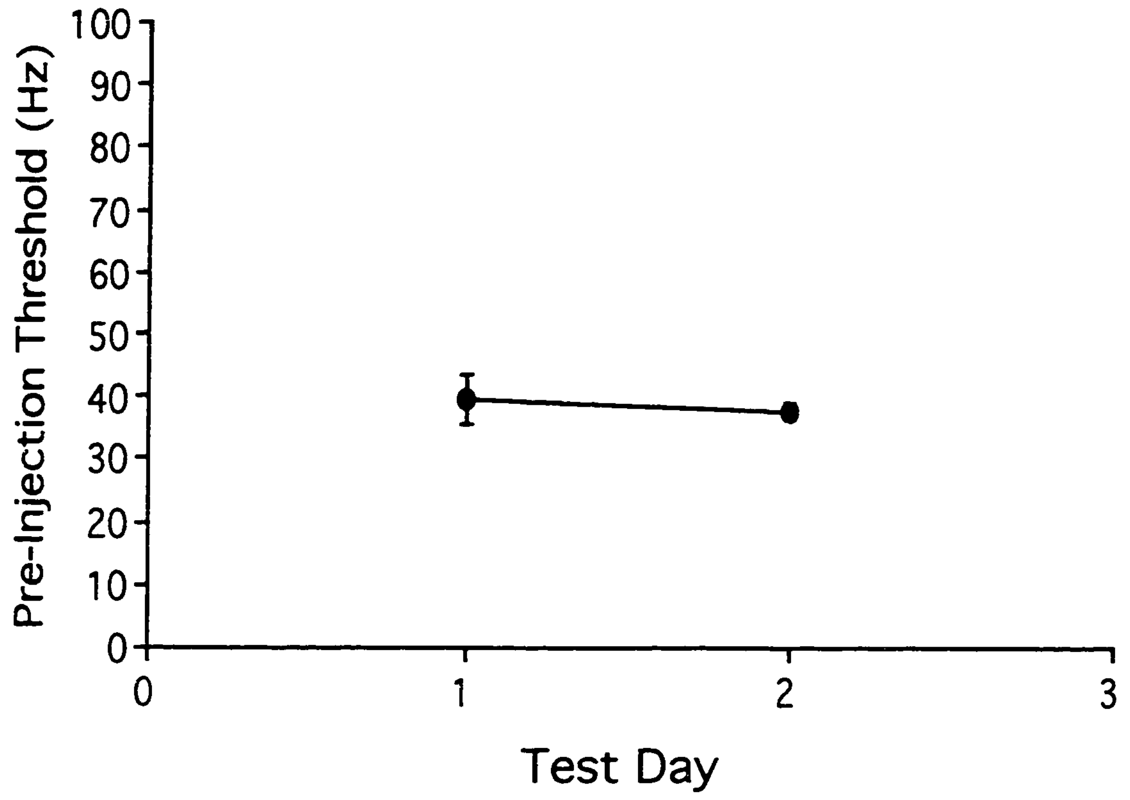
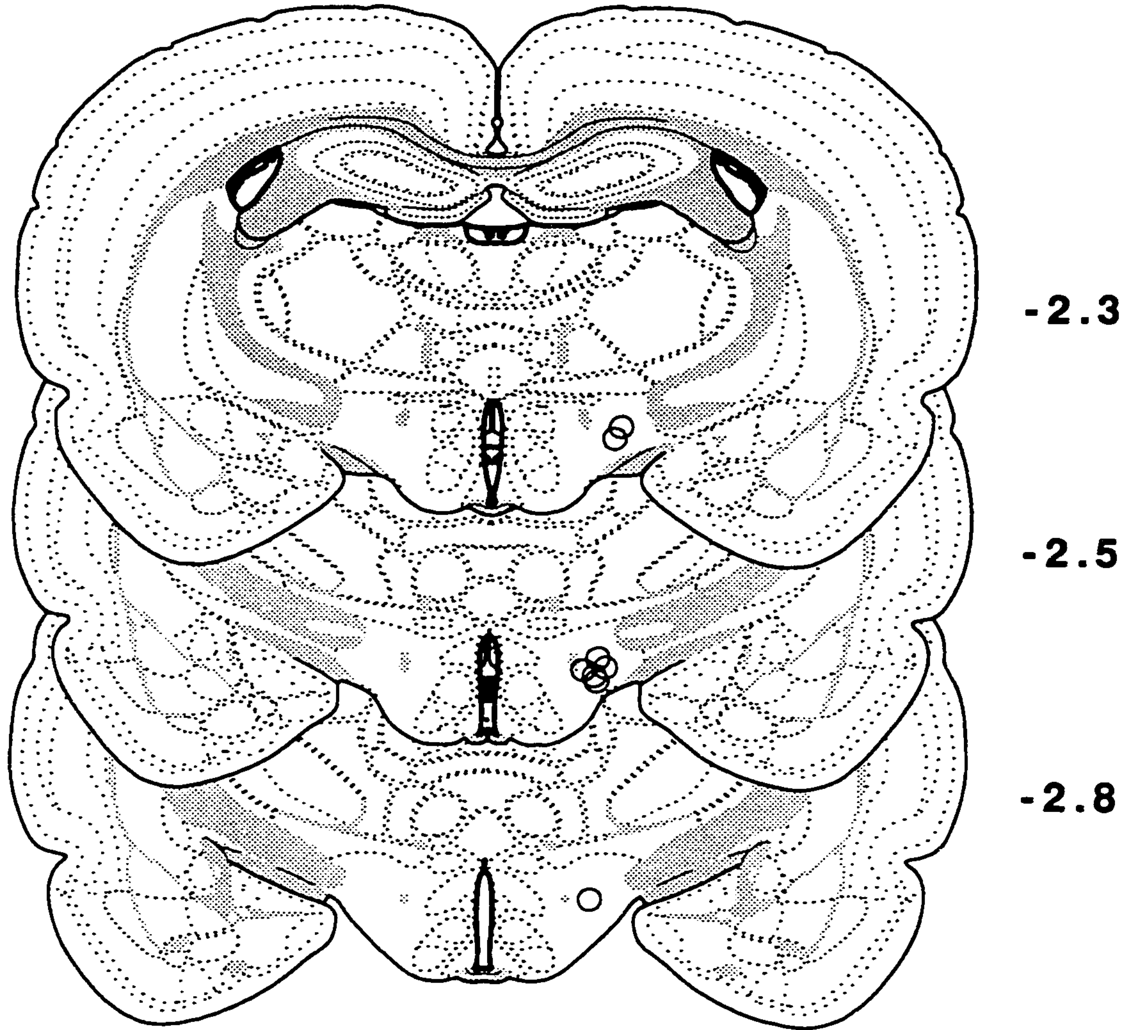

Pre-Injection Threshold (Hz)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
Test Day

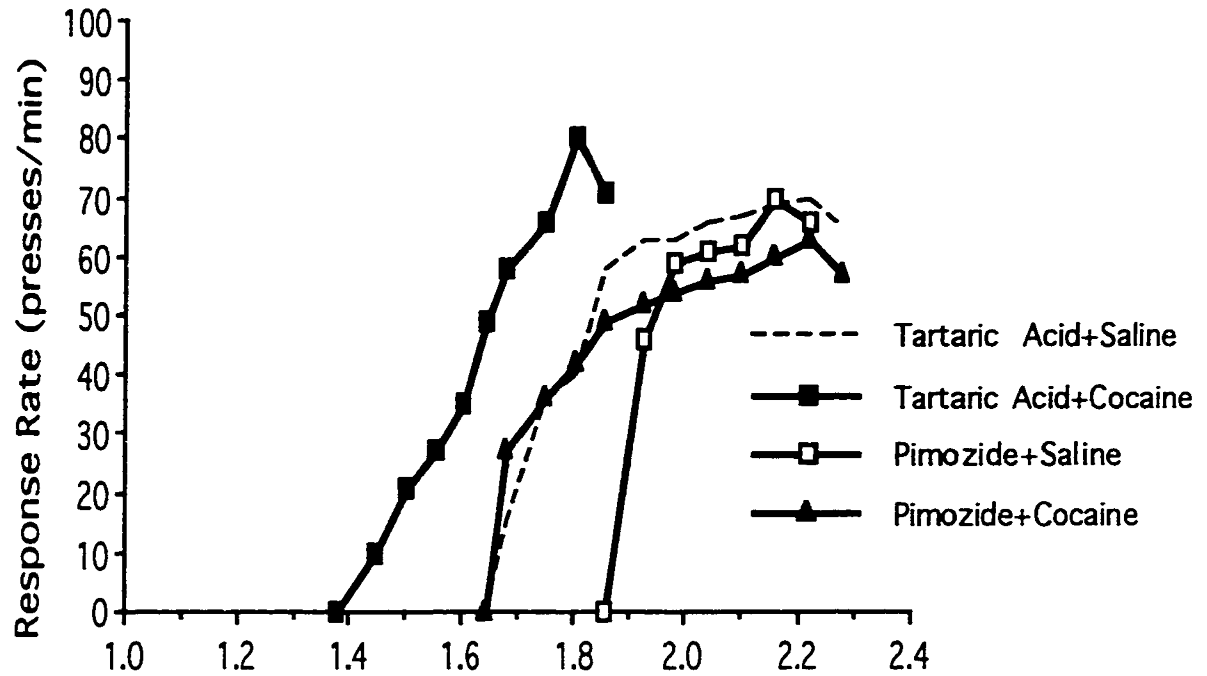
Figure 5.4: Histological localization of stimulating electrode tips. The number beside each brain slice represents the distance from the bregma. Reconstructions are based on the stereotaxic atlas of Swanson (1992). To facilitate comparisons all electrode tips are shown in the left hemisphere.


-2.3
-2.5
-2.8

Group 2: As in Group 1 pimozide (0.3 mg/kg) caused rightward and only marginal downward shifts of the functions relating the logarithm of stimulation frequency to response rate in each of the animals tested (Fig. 5.5, top and bottom panels). Cocaine (8 mg/kg; Fig. 5.5 top panel) and amphetamine (2 mg/kg; bottom panel) each caused leftward and upward shifts in the rate-frequency functions. The rate-frequency functions for the drug combination tests pimozide + cocaine and pimozide + amphetamine were not significantly different from that of the tartaric acid + saline combination. The tartaric acid + saline combination tested on Day 1 and 8 (threshold $F_{1,7}$= 2.83, p>0.05; maximum rate $F_{1,7}$= 2.46, p>0.05) as well as the pimozide + saline combination tested on Day 4 and 7 (threshold $F_{1,7}$= 1.08, p>0.05; maximum rate $F_{1,7}$= 2.83, p>0.05), respectively, did not statistically differ from each other and therefore the data for test Day 1 and 8 were pooled as were the data for test Day 4 and 7 for the purpose of statistical analysis.

The shifts in the rate-frequency functions were reflected by a significant overall increase or decrease in threshold (Fig. 5.6 top panel; $F_{5,35}$= 25.89, p<0.01) and maximum rate (Fig. 5.6 bottom panel; $F_{5,35}$= 3.48, p<0.01) as a function of drug treatment for the second rate-frequency determination (30 min). The second rate-frequency determination was chosen based on time-course data (see Fig. 5.7) showing that cocaine and amphetamine produced their greatest decrease in threshold 30 min after the start of the post-baseline assessment.

Figure 5.5: Rate of lever-pressing (per min) 30 min (second rate-frequency function) after the start of the post-baseline assessment as a function of stimulation frequency and drug treatment (cocaine combinations top panel; amphetamine combinations bottom panel). Tests were conducted at 48-h intervals. Each panel represents data from a single representative animal respectively.


Response Rate (presses/min)
100
90
80
70
60
50
40
30
20
10
0
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
Tartaric Acid+Saline
Tartaric Acid+Cocaine
Pimozide+Saline
Pimozide+Cocaine

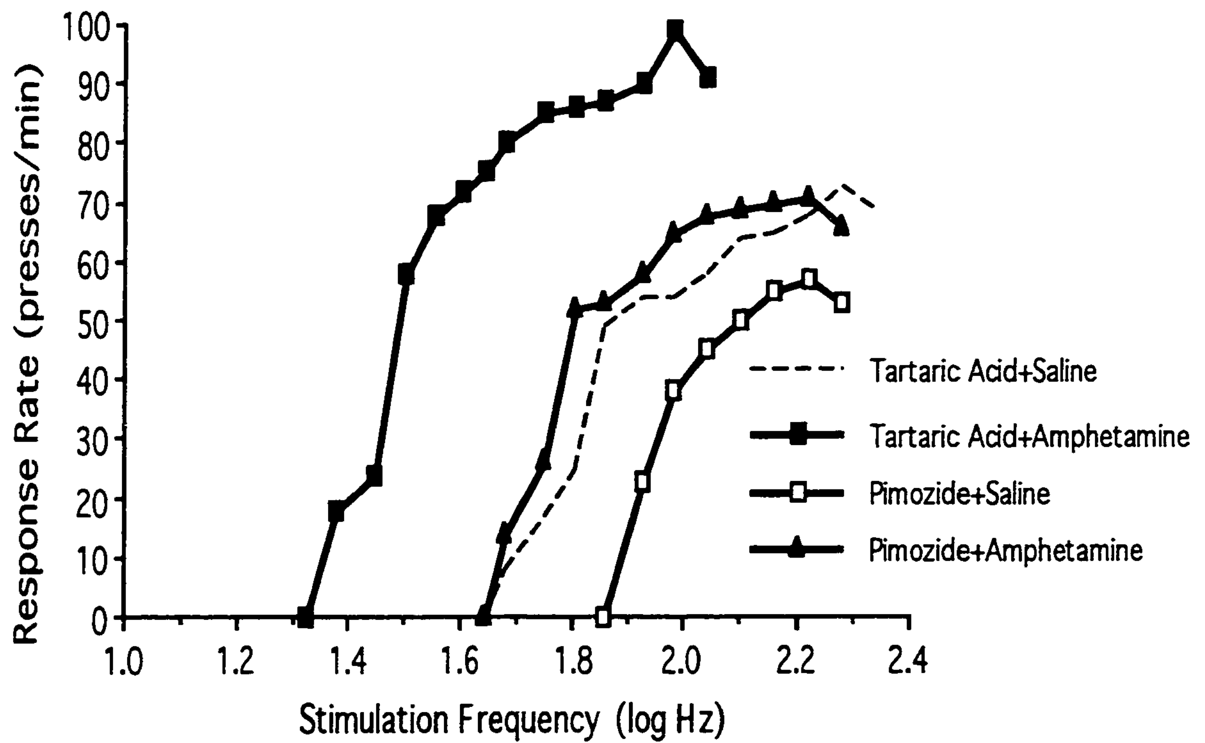
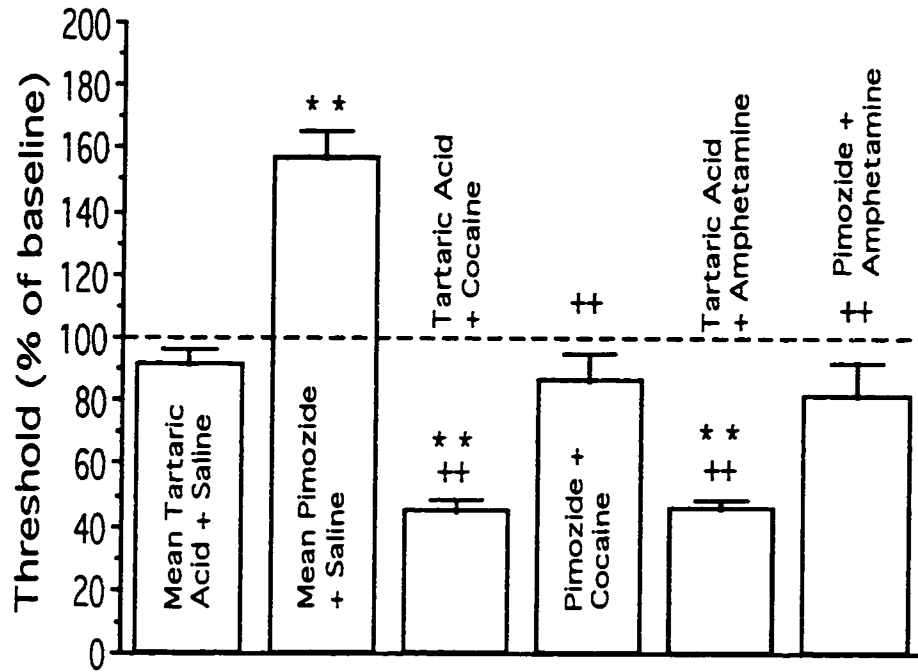
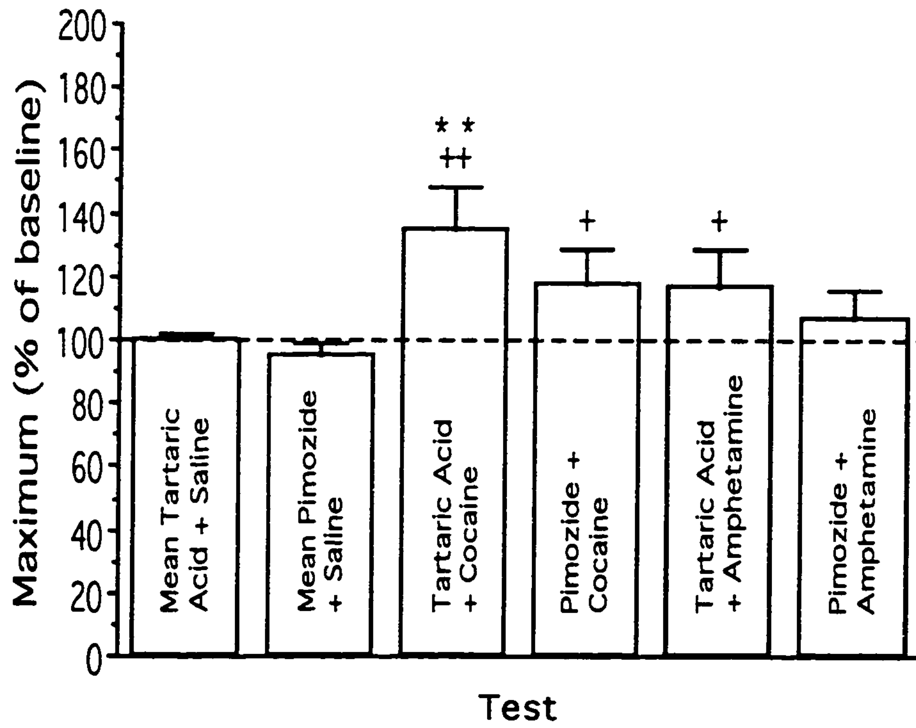

Response Rate (presses/min)
100
90
80
70
60
50
40
30
20
10
0
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
Stimulation Frequency (log Hz)
Tartaric Acid+Saline
Tartaric Acid+Amphetamine
Pimozide+Saline
Pimozide+Amphetamine

Figure 5.6: Mean (±SEM) self-stimulation frequency threshold (top) and maximum rates (bottom), expressed as a percent of baseline, as a function of pimozide and cocaine or amphetamine co-administration. All values are means from the second determination (30 min) after the start of the post-baseline assessment.

Significant differences from Mean Tartaric acid + Saline are depicted as ** $p<0.01$ and significant differences from Mean Pimozide + Saline as ++ $p<0.01$; + $p<0.05$.


Threshold (% of baseline)
200
180
160
140
120
100
80
60
40
20
0
Mean Tartaric Acid + Saline
Mean Pimozide + Saline
* *
Tartaric Acid + Cocaine
* *
++
Pimozide + Cocaine
++
Tartaric Acid + Amphetamine
* *
++
Pimozide + Amphetamine
++

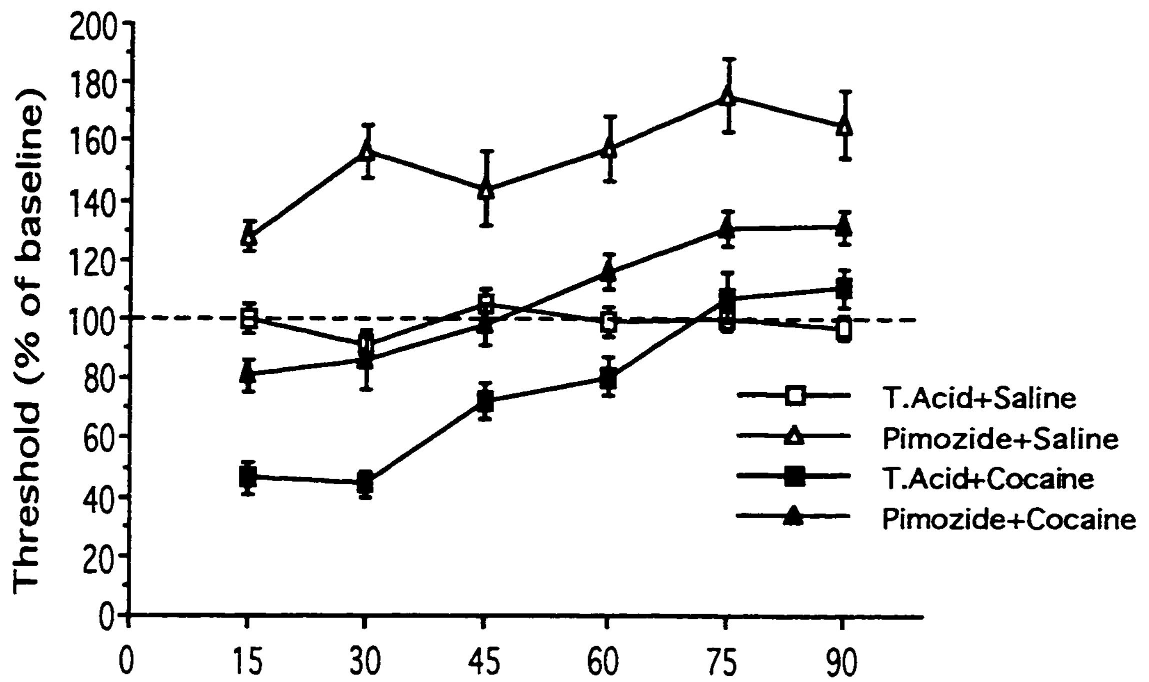

Maximum (% of baseline)
200
180
160
140
120
100
80
60
40
20
0
Mean Tartaric Acid + Saline
Mean Pimozide + Saline
Tartaric Acid + Cocaine
* *
++
Pimozide + Cocaine
+
Tartaric Acid + Amphetamine
+
Pimozide + Amphetamine
Test

Time-courses of the effects of the various drug treatments are shown in Fig. 5.7. The shifts in the rate-frequency functions were reflected by significant overall increases or decreases in threshold when the effects of pimozide and cocaine (Fig. 5.7 top panel; $F_{3,21}$= 48.27, $p<0.01$) and the effects of pimozide and amphetamine (Fig. 5.7 bottom panel; $F_{3,21}$= 39.97, $p<0.01$) were compared to the mean tartaric acid + saline combination. The upward and downward shifts in the rate-frequency functions were reflected by significant overall changes in maximum rate when the effects of pimozide and cocaine (Fig. 5.8 top panel; $F_{3,21}$= 3.32, $p<0.05$) and the effects of pimozide and amphetamine (Fig. 5.8 bottom panel; $F_{3,21}$= 3.73, $p<0.05$) were compared to the mean tartaric acid + saline combination. The drug combination tests pimozide + cocaine and pimozide + amphetamine did not differ significantly from the mean tartaric acid + saline combinations for threshold or maximum rate.

There were no significant changes in pre-injection (baseline) responding between the two test days (Fig. 5.9; $F_{7,49}$= 0.78, $p>0.05$).

All electrode tips were within the boundaries of the medial forebrain bundle at the level of the lateral hypothalamus (Fig. 5.10)

Figure 5.7: Mean (±SEM) self-stimulation frequency threshold expressed as a percent of baseline as a function of drug treatment and of time after the start of the post-baseline assessment. Presented in the top panel are data for the pimozide (0.3 mg/kg) and cocaine (8 mg/kg) treatment combinations and in the bottom panel the data for the pimozide (0.3 mg/kg) and amphetamine (2 mg/kg) treatment combinations; note that the tartaric acid+Saline (T.Acid+Saline) and Pimozide+Saline treatment data are the same in both panels and are duplicated only to facilitate comparisons between treatments.


200
180
160
140
120
100
80
60
40
20
0
Threshold (% of baseline)
0
15
30
45
60
75
90
T.Acid+Saline
Pimozide+Saline
T.Acid+Cocaine
Pimozide+Cocaine

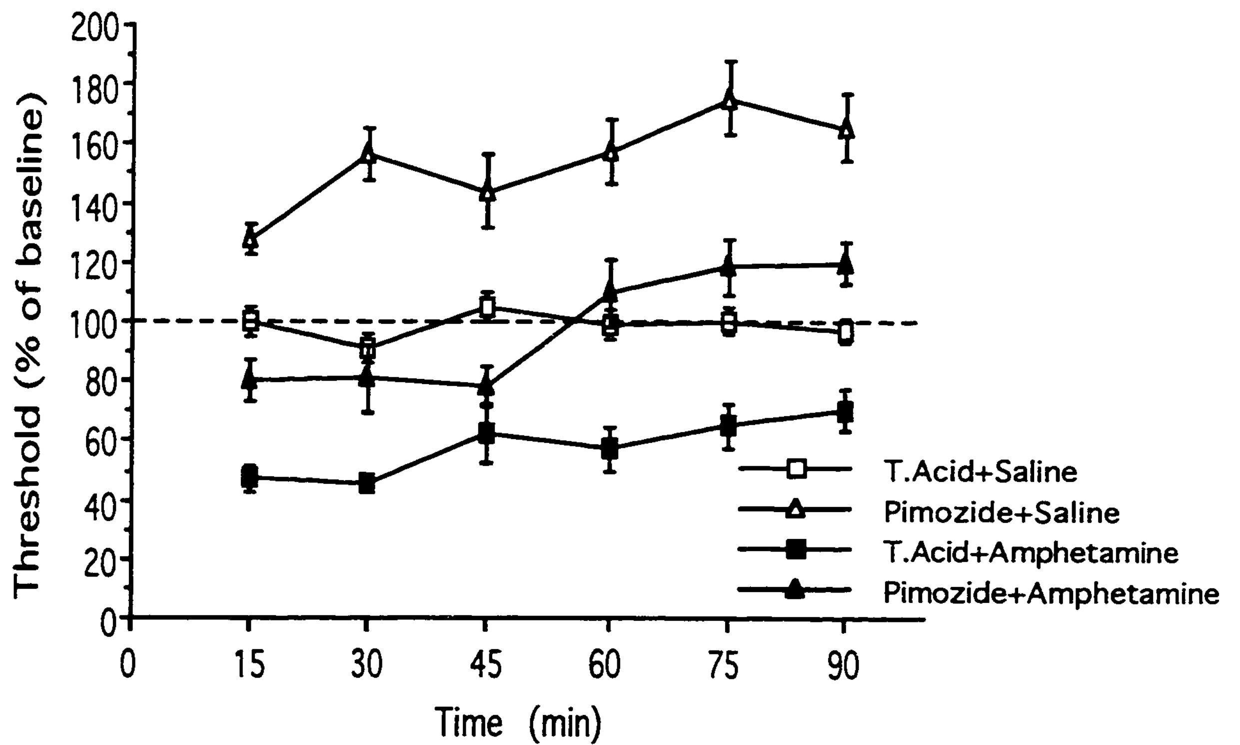
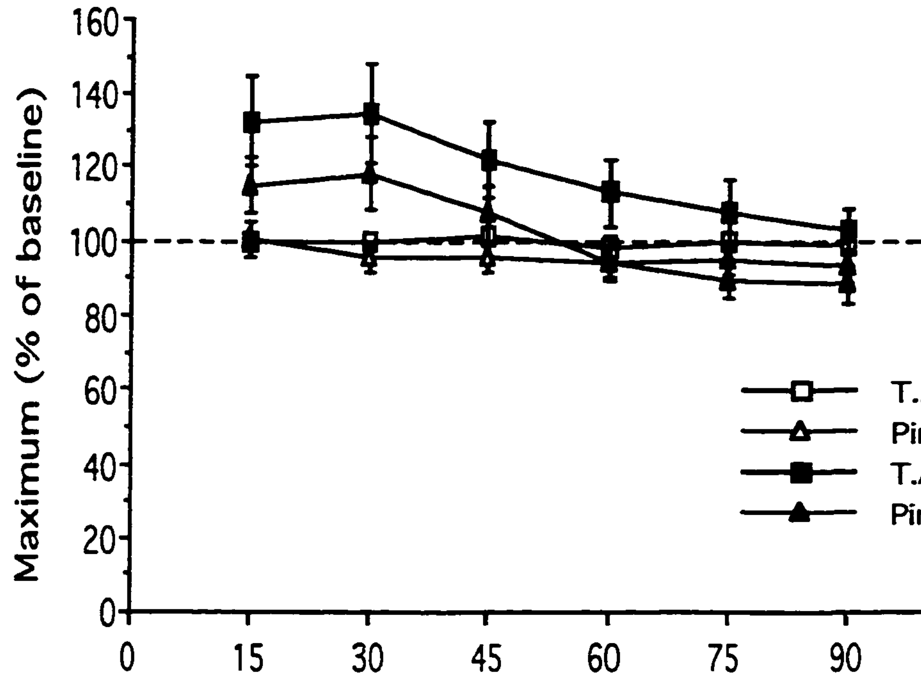

200
180
160
140
120
100
80
60
40
20
0
Threshold (% of baseline)
0
15
30
45
60
75
90
Time (min)
T.Acid+Saline
Pimozide+Saline
T.Acid+Amphetamine
Pimozide+Amphetamine

Figure 5.8: Mean (±SEM) self-stimulation maximum response rates expressed as a percent of baseline as a function of drug treatment and of time after the start of the post-baseline assessment. Data are for the pimozide (0.3 mg/kg) and cocaine (8 mg/kg) treatment combinations (top panel) and for the pimozide (0.3 mg/kg) and amphetamine (2 mg/kg) treatment combinations (top panel); note that the tartaric acid+Saline (T.Acid+Saline) and Pimozide+Saline treatment data are the same in both panels and are duplicated only to facilitate comparisons between treatments.


160
140
120
100
80
60
40
20
0
Maximum (% of baseline)
0
15
30
45
60
75
90
T.Acid+Saline
Pimozide+Saline
T.Acid+Cocaine
Pimozide+Cocaine

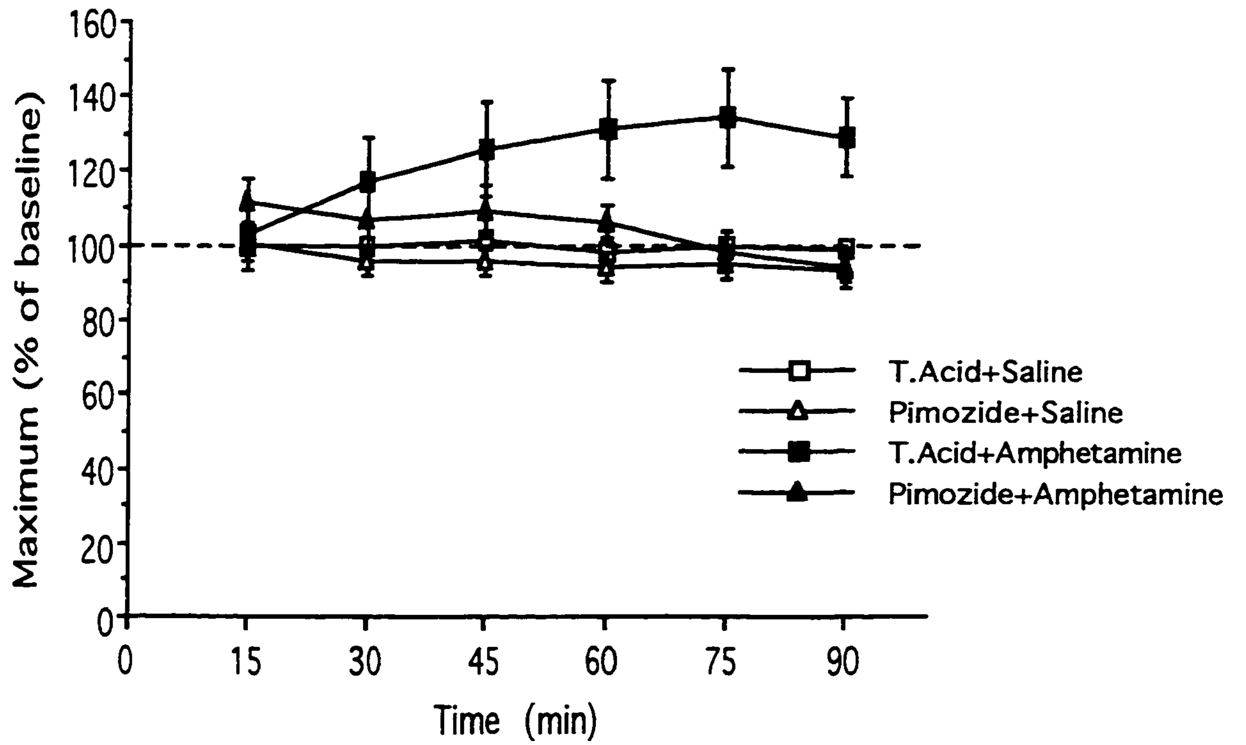

160
140
120
100
80
60
40
20
0
Maximum (% of baseline)
0
15
30
45
60
75
90
Time (min)
T.Acid+Saline
Pimozide+Saline
T.Acid+Amphetamine
Pimozide+Amphetamine

Figure 5.9: Mean (±SEM) pre-injection self-stimulation frequency threshold (raw scores) as a function of test day.

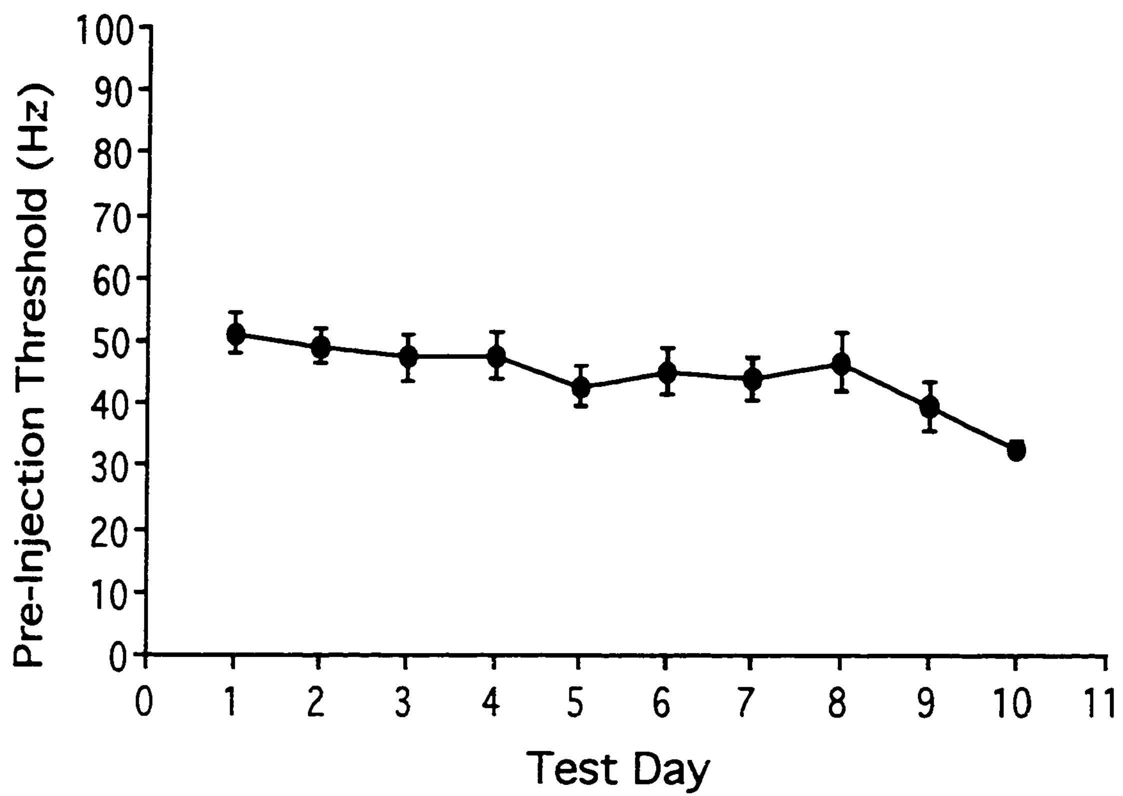
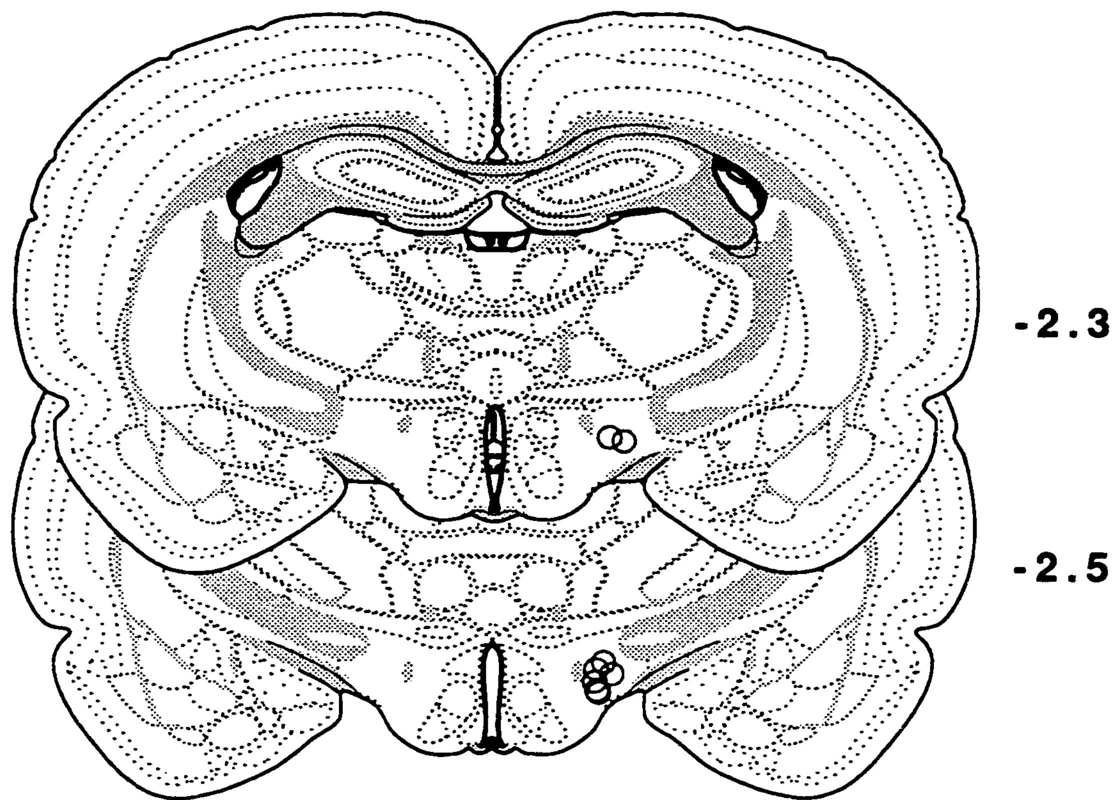

Pre-Injection Threshold (Hz)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
Test Day

Figure 5.10: Histological localization of stimulating electrode tips. The number beside each brain slice represents the distance from the bregma. Reconstructions are based on the stereotaxic atlas of Swanson (1992). To facilitate comparisons all electrode tips are shown in the left hemisphere.


-2.3
-2.5

5.4 DISCUSSION

In the present experiment a 0.3 mg/kg dose of pimozide (Group 1 and 2) produced significant shifts to the right of the rate-frequency functions as reflected by the increases in threshold but produced only marginal decreases in maximum rate as reflected by shifts downward in the rate-frequency functions. The present results are consistent with other studies of pimozide's effects on brain stimulation reward (Fouriezos & Wise, 1976; Fouriezos *et al.*, 1978; Franklin, 1978; Gallistel & Davis, 1983; Stellar *et al.*, 1983; Gallistel & Karras, 1984; Gallistel & Freyd, 1987; Lynch & Wise, 1985; Miliaressis *et al.*, 1986a; Bird & Kornetsky, 1990) as well as with the only other known study where a fixed-interval schedule of reinforcement for brain stimulation was used to assess the effects of pimozide (Boye & Rompré, 1996). Data from Group 2 showed that a dose of cocaine and amphetamine that shifted the rate-frequency curve to the left by 0.3-log units cancels the 0.3-log unit shift to the right produced by pimozide. These findings are consistent with previous results with amphetamine (Gallistel & Karras, 1984; Gallistel & Freyd, 1987) and morphine (Rompré & Wise, 1989) and now extend to cocaine. Thus, cocaine and amphetamine acted as synergists of brain stimulation reward by reducing the level of stimulation required to produce a given level of responding and by canceling the effects of a reward antagonist that has the opposite effect on brain stimulation reward thresholds.

The present results are also consistent with the findings that doses of pimozide below 0.5 mg/kg do not significantly impair lever-press rate (Franklin & McCoy, 1979; Wise, 1982b; Lynch & Wise, 1985;

Miliaressis *et al.*, 1986a; Gallistel & Freyd, 1987). This factor is important in light of the long-standing debate of whether neuroleptics reduce reward value or merely produce performance deficits (Fouriezos & Wise, 1976; Franklin, 1978; Wise, 1978b; Phillips & Fibiger, 1979; Gallistel *et al.*, 1982; Hamilton *et al.*, 1985; Ettenberg, 1989). In the present experiment the use of a dose of pimozide below that which significantly impairs motoric capacity and the ability of the rate-frequency curve-shift paradigm to dissociate between treatment-induced changes in reward and performance (Miliaressis *et al.*, 1986b; Gallistel, 1987) further establishes that pimozide alters the rewarding-impact of the stimulation.

Pimozide is a relatively selective dopamine D_2-like receptor antagonist (Creese *et al.*, 1976; Leysen *et al.*, 1978; Seeman, 1981) and neuroleptic capacity to block reward is highly correlated with its *in vitro* affinity for the D_2-like receptor (Gallistel & Davis, 1983). In contrast, amphetamine and cocaine are thought to exert their reward-relevant effects due to their ability to potentiate dopaminergic function (Wise & Bozarth, 1987; Wise & Rompré, 1989; Kuhar *et al.*, 1991; Gardner, 1992; Di Chiara, 1995). For example, both amphetamine and cocaine increase dopamine function as assessed by *in vivo* microdialysis (Di Chiara & Imperato, 1988a; Hernandez & Hoebel, 1988) and *in vivo* voltammetric electrochemistry (Gazzara *et al.*, 1986; Hughes & Pottinger, 1986; Gerhardt *et al.*, 1988; Gono, 1988; Stamford *et al.*, 1988,1989) techniques and thus function as dopamineomimetics.

Given the near complete cancellation of the leftward and rightward shifts when pimozide is co-administered with amphetamine or cocaine, compared to when each drug is injected alone, the present

results confirm the hypothesis that pimozide, amphetamine and cocaine exert their effects on reward potency on the same subset of dopaminergic synapses and further underscore the importance of the D_2-like receptor in mediating reward function.

In Experiment 5 the quantitative precision of the curve-shift paradigm was used to compare the reward-potentiating actions of cocaine in two rat strains hypothesized to be differentially sensitive to the rewarding actions of several habit-forming drugs.

EXPERIMENT 5

Potentiation of Lateral Hypothalamic Brain Stimulation Reward by Cocaine: Comparison Between Fischer 344 and Lewis Rat Strains

6.1 INTRODUCTION

The contribution of genetic factors to the establishment and maintenance of drug habits has traditionally been associated with the study of susceptibility to alcoholism in humans (Goodwin, 1979; Cloninger, 1987). The laboratory study of genetic contributions to the habit-forming actions of drugs has, more recently, been advanced by the use of inbred rat strains; unlike outbred strains, these provide a stable genotype by which to study differences in responses to habit-forming drugs (George & Goldberg, 1989; Crabbe & Belknap, 1992). Two inbred rat strains that differ anatomically in the reward-relevant circuitry of the mesolimbic dopamine system and behaviorally in their responses to some habit-forming drugs are Fischer 344 and Lewis rats.

Fischer 344 and Lewis rats are structurally and functionally different in the neural circuitry that comprises the mesolimbic dopamine system. Structurally, as assessed by blot immunolabeling, compared to Lewis rats, Fischer 344 rats have a lower density of tyrosine hydroxylase (the rate-limiting enzyme in dopamine synthesis) in the ventral tegmental area but a higher density in the nucleus accumbens (Beitner-Johnson *et al.*, 1991). In contrast, using

immunohistochemical analysis, Lewis rats express half the density and number of tyrosine hydroxylase-positive ventral tegmental area dopamine neurons (Harris & Nestler, 1996) compared to Fischer 344 rats. Lewis rats have lower levels of some neurofilament proteins in the ventral tegmental area (Guitart *et al.*, 1992), have higher levels of adenylate cyclase and cyclic AMP-dependent protein kinase activity in the nucleus accumbens, but have lower levels of $G_{i\alpha}$ and G_{β} in the same nucleus (Guitart *et al.*, 1993). These structural differences are thought to account for the functional differences in the mesolimbic dopamine system of these two strains as demonstrated by microdialysis and electrophysiological experiments.

Functionally, as measured by microdialysis, compared to Fischer 344, Lewis rats have lower basal levels of dopamine metabolites in the nucleus accumbens but no difference in dopamine (Camp *et al.*, 1994; Strecker *et al.*, 1995). Similarly, acute injections of cocaine elevate dopamine levels in the nucleus accumbens of both strains (Camp *et al.*, 1994; Strecker *et al.*, 1995) with a more prolonged elevation in Lewis rats (Strecker *et al.*, 1995). Moreover, as measured by electrophysiology, Lewis rats have lower numbers of spontaneously active dopamine neurons in the ventral tegmental area; more of these neurons exhibit a burst firing pattern (Minabe *et al.*, 1995). It has been hypothesized that this burst firing pattern may help maintain dopamine levels despite the relatively low numbers of spontaneously active cells in Lewis rats (Minabe *et al.*, 1995).

Behaviorally, in novel environments (Chaouloff *et al.*, 1995) Fischer 344 rats have been reported to show greater levels of locomotor activity compared to Lewis rats; however, when animals

have been surgically implanted with an intravenous catheter for subsequent testing of drug self-administration, Fischer 344 rats have been reported to show lower levels of locomotor activity compared to Lewis rats when placed in a novel environment (Ambrosio *et al.*, 1995). In contrast, compared to Fischer 344 rats, Lewis rats show greater levels of locomotor activity following injections of amphetamine (Camp *et al.*, 1994) and cocaine (George & Goldberg, 1988; Camp *et al.*, 1994).

Lewis and Fischer 344 rats have a differential willingness to self-administer a number of habit-forming drugs. Lewis rats more readily self-administer ethanol (Suzuki *et al.*, 1988a), opiates (Suzuki *et al.*, 1988b, 1992), and cocaine (George & Goldberg, 1988; Bell *et al.*, 1993,1995) self-administration by the oral route. Lewis rats more readily acquire morphine (Ambrosio *et al.*, 1995) and cocaine (Kosten *et al.*, 1997) habits by means of intravenous self-administration. Neither Fischer nor Lewis rats, however, have been reported to acquire intravenous nicotine self-administration (Shoaib *et al.*, 1997). In contrast to this finding nicotine does establish a conditioned place preference in Lewis rats but Fischer 344 rats show no preference for the drug-paired compartment after 5 drug pairings and show conditioned place aversion after 10 drug pairings of 0.4 mg/kg s.c. nicotine (Horan *et al.*, 1997). Morphine (Suzuki *et al.*, 1988b) and cocaine (Kosten *et al.*, 1994) each establish conditioned place preferences to a greater degree in Lewis rats; relatively low doses of cocaine (7.5-15 mg/kg) do not produce a significant place preference in Fischer 344 rats while a relatively high dose of cocaine (30 mg/kg) which produces a significant place preference in Lewis rats produces a

conditioned place aversion in Fischer 344 rats. Lastly, cannabis potentiates the impact of rewarding brain stimulation in Lewis but not Fischer 344 rats (Gardner *et al.*, 1988b, 1988c, 1989a; Lepore *et al.*, 1996).

The structural, functional, and behavioral differences between Lewis and Fischer 344 rat strains have been hypothesized to reflect genetic differences in the rewarding actions of some habit-forming drugs; ethanol, morphine, and cocaine have been the best characterized thus far. To date there has been no direct comparison of the relative ability of cocaine to potentiate the rewarding impact of electrical brain stimulation in these two strains. In Experiment 5 the curve-shift rate-frequency brain stimulation reward paradigm was used to determine whether cocaine differentially potentiates the rewarding impact of lateral hypothalamic electrical stimulation in Lewis and Fischer 344 rats. The results were compared to those obtained in Experiment 1 in which Long-Evans rats were tested.

6.2 MATERIALS AND METHODS

Subjects: Nine male Fischer 344 and nine male Lewis strain rats weighing 300 to 350g (Harlan Sprague Dawley, U.S.A.) were used. They were housed individually in polyethylene cages with wood chip bedding and free access to food and water. Lighting was maintained on a normal 12-h light/dark cycle; the animals were tested at the end of the dark phase.

Surgery: The surgical procedure was the same as that used in Experiments 1, 2, 3, and 4.

Apparatus: The apparatus was the same as that used in Experiments 1, 2, 3, and 4.

Procedure: The self-stimulation screening and training procedures were the same as those used in Experiments 1, 2, 3, and 4.

Each test consisted of a baseline assessment in which three rate-frequency functions were determined prior to cocaine or saline injection (the first of these rate-frequency functions was treated as a "warm-up" and the data were not used for subsequent statistical comparisons) and a one-hour post-injection assessment where four additional rate-frequency functions were determined. Animals were tested at 24-hour intervals. During the first (Day 1) and last test (Day 6) animals were injected with saline (control). On Days 2 to 5 animals received a single injection of cocaine in ascending dose order (2, 4, 8, and 16 mg/kg).

The effects of cocaine and vehicle treatments on self-stimulation thresholds (see below) and maximum rates of responding were evaluated statistically with two-way, Treatment (dosage) X Time, analyses of variance.

Confirmation of electrode placements: The procedure to confirm the placement of electrodes was the same as that used in Experiments 1, 2, 3, and 4.

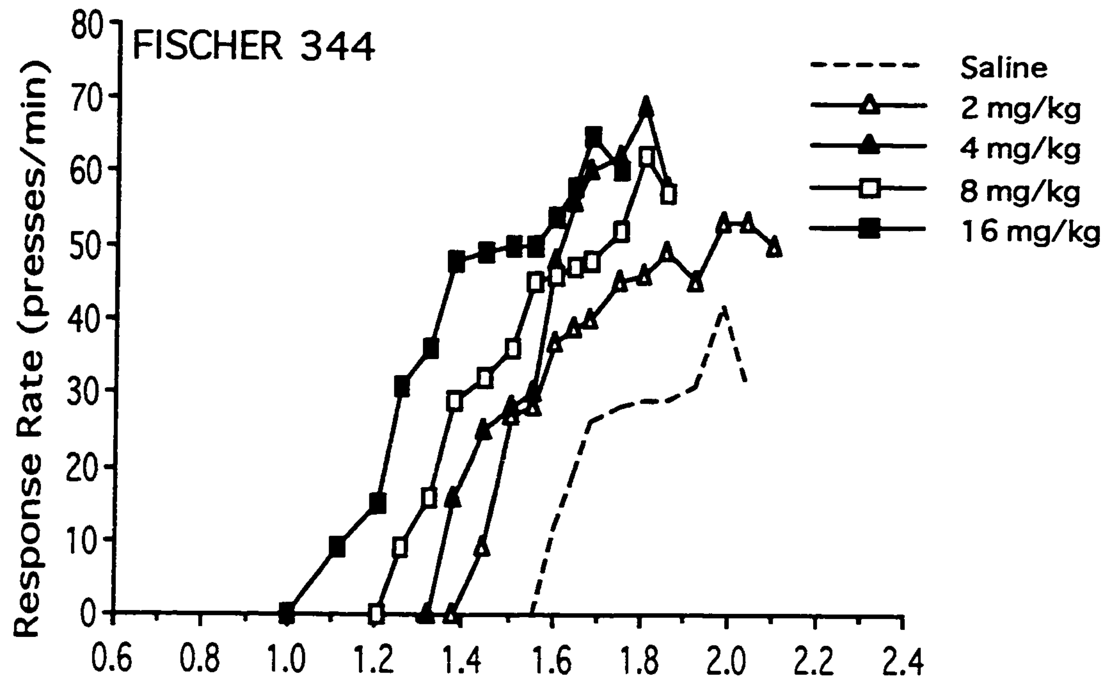
Estimation of self-stimulation threshold: The procedure to estimate self-stimulation threshold was the same as that used in Experiments 1, 2, 3, and 4.

Drug: The drug and vehicle were the same as those used in Experiments 1, 2, and 3.

6.3 RESULTS

Cocaine caused leftward and upward shifts of the functions relating the logarithm of stimulation frequency (stimulation "dose": Yeomans, 1975) to response rate in each of the Fischer 344 and Lewis rats tested. The leftward and upward shifts were dose-orderly in both Fischer 344 (Fig. 6.1 top panel) and Lewis (Fig. 6.1 bottom panel) rats. The leftward shifts in the curves were reflected by a significant decrease in threshold as a function of cocaine dosage in Lewis and Fischer 344 rats (Fig. 6.2 top panel; $F_{4,64} = 47.87$, $p<0.01$) and the upward shifts in a significant increase in maximum response rate (Fig. 6.2 bottom panel; $F_{4,64} = 4.39$, $p<0.01$). There was no significant difference, however, between Lewis, Fischer 344, and Long-Evans (data from Experiment 1) rats for threshold (Fig. 6.2 top panel; $F_{2,23} = 0.16$, $p>0.05$) or maximum rate (Fig. 6.2 bottom panel; $F_{2,23} = 2.03$, $p>0.05$). At the 16 mg/kg dose (the highest dose tested and the dose producing the largest average decrease in threshold) cocaine reduced the threshold frequency by an average 0.42 log units in Lewis rats and 0.44 log units in Fischer 344 rats, which represents an average 2.9-fold

Figure 6.1: Rate of lever-pressing (responses per min) as a function of stimulation frequency. Each plot represents data from a single animal in Fischer 344 (top) and Lewis (bottom) rat strains during the first 15 min following an injection of saline (Day 1) and ascending doses of cocaine (Days 2-5).


FISCHER 344
Response Rate (presses/min)
80
70
60
50
40
30
20
10
0
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
Saline
2 mg/kg
4 mg/kg
8 mg/kg
16 mg/kg

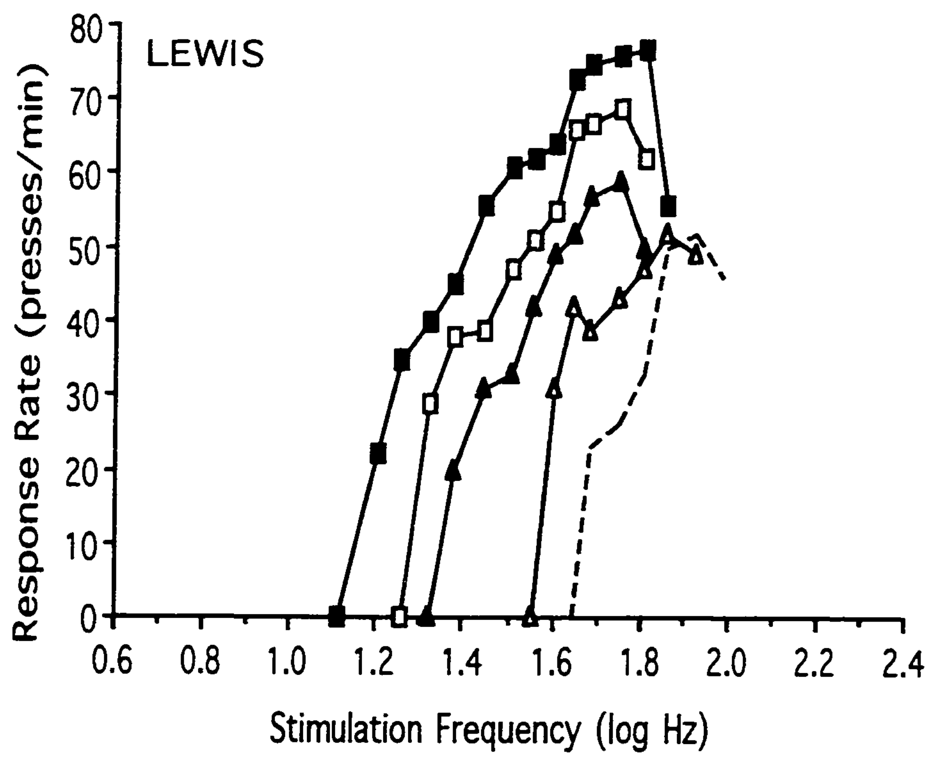
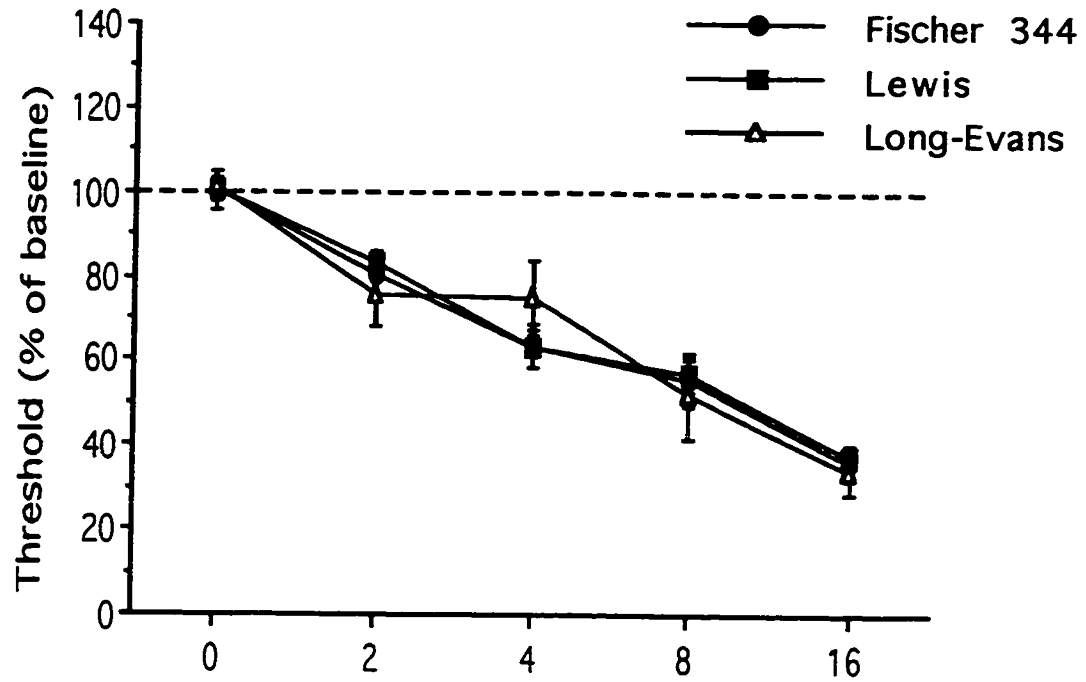
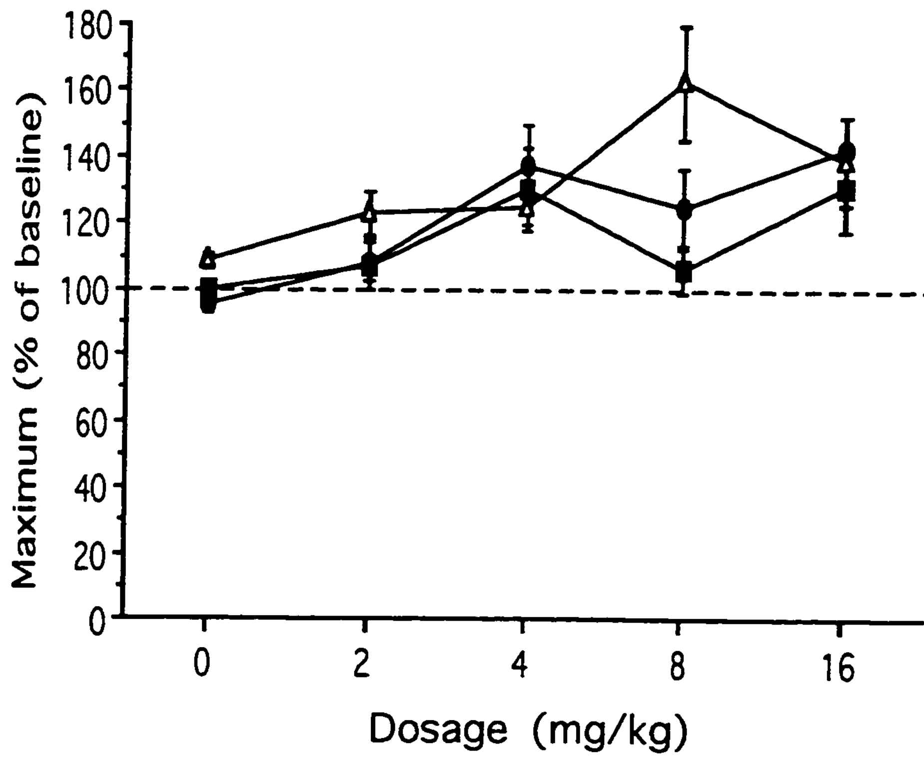

LEWIS
Response Rate (presses/min)
80
70
60
50
40
30
20
10
0
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
Stimulation Frequency (log Hz)

Figure 6.2: Mean (±SEM) self-stimulation frequency threshold (top) and response maximum (bottom) expressed as a percent of baseline as a function of cocaine dosage in Fischer 344 (n=9), Lewis (n=9), and Long-Evans (n=8; data from Experiment 1) rat strains. Values are means from the first threshold determination (15 min) after injection. Saline values represent averages of saline tests in each respective group. For this and subsequent figures, each reference (baseline) value is the mean from the two determinations of threshold and response maximum taken just prior to the respective drug test.


Fischer 344
Lewis
Long-Evans
Threshold (% of baseline)
140
120
100
80
60
40
20
0
0
2
4
8
16


Maximum (% of baseline)
180
160
140
120
100
80
60
40
20
0
0
2
4
8
16
Dosage (mg/kg)

increase in the rewarding potency of the stimulation. This is in the range of average increase in rewarding potency of lateral hypothalamic stimulation following an injection of 16 mg/kg cocaine reported for Long-Evans rats (0.47 log units, Experiment 1).

Time courses of the effects of cocaine at various dosages on threshold and maximum response rate in Fischer 344 and Lewis rats are shown in Fig. 6.3. Thresholds (Fig. 6.3 top) were significantly decreased ($F_{3,48} = 123.95$, $p<0.01$) and maximum response rates (Fig. 6.3 bottom) significantly increased ($F_{3,48} = 15.94$, $p<0.01$) for the first 15-30 min after injection and returned towards pre-injection levels thereafter.

There were no significant day-to-day changes in pre-injection (baseline) responding in either Fischer 344 ($F_{5,40} = 0.26$, $p>0.01$) or Lewis ($F_{5,40} = 1.66$, $p>0.01$) rats (Fig. 6.4); pre-injection responding did not differ significantly between the strains ($F_{1,48} = 0.07$, $p>0.01$).

All electrode tips were within the boundaries of the medial forebrain bundle at the level of the lateral hypothalamus (Fig. 6.5).

Figure 6.3: Mean (±SEM) self-stimulation frequency threshold (top) and response maximum (bottom) as a function of time after injection with cocaine at different doses in Fischer 344 and Lewis rat strains. Saline values are means of the two vehicle tests (Day 1 and 6).

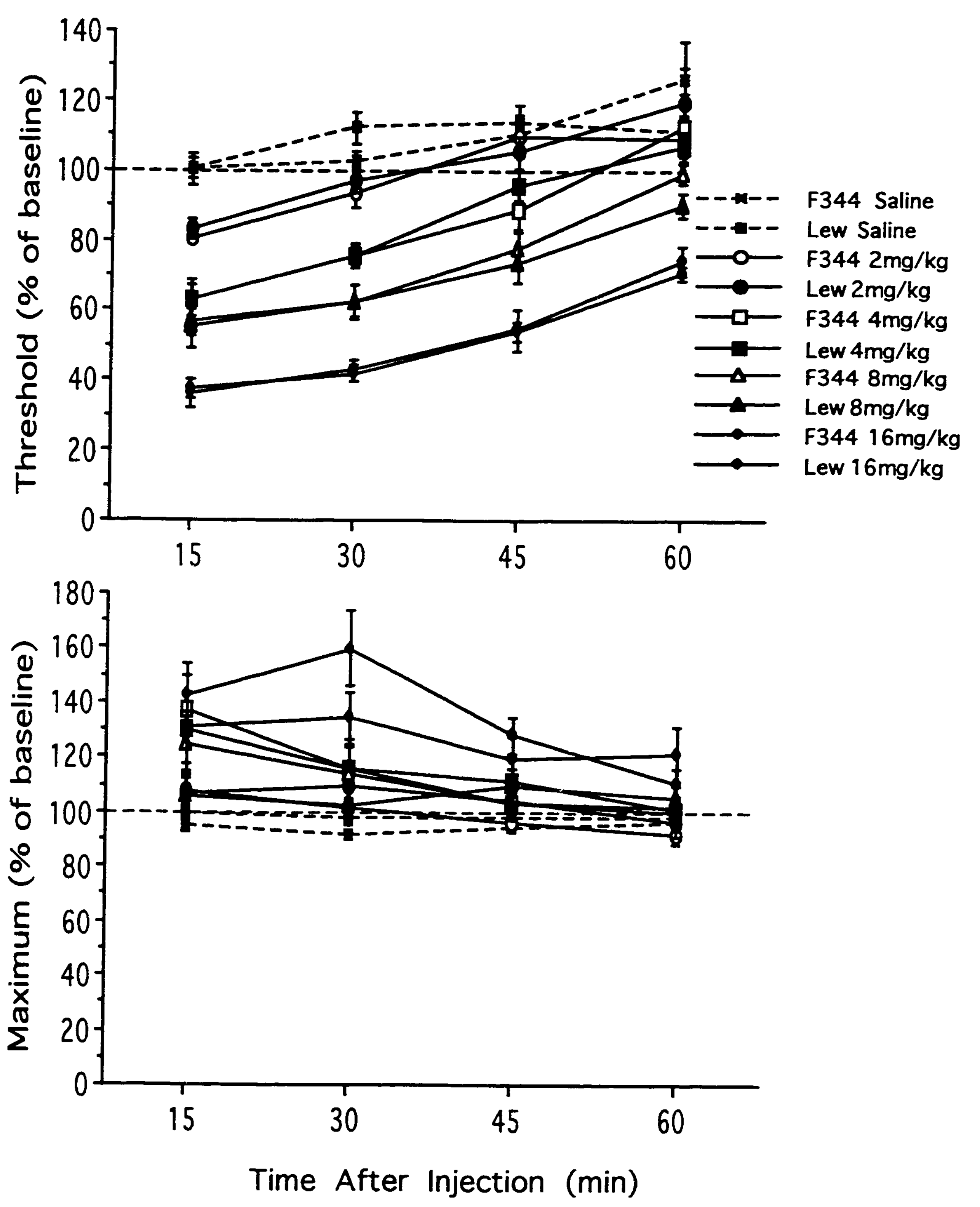
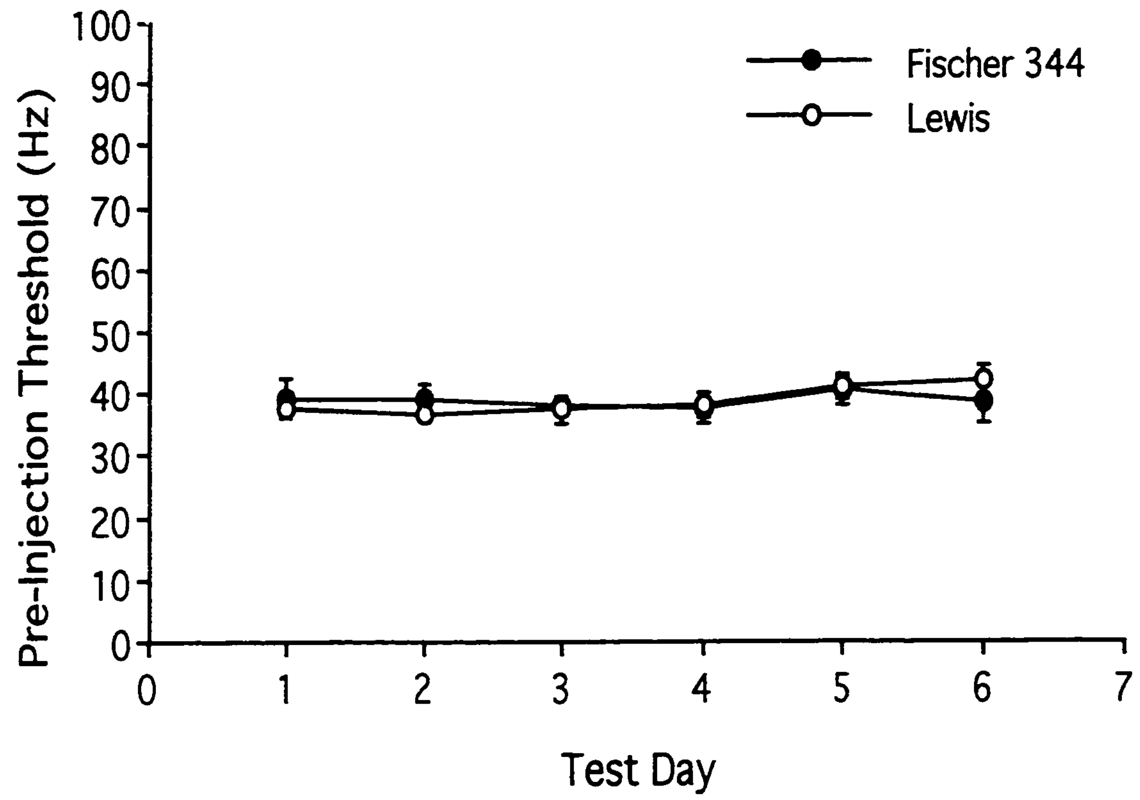

Threshold (% of baseline)
140
120
100
80
60
40
20
0
15
30
45
60
F344 Saline
Lew Saline
F344 2mg/kg
Lew 2mg/kg
F344 4mg/kg
Lew 4mg/kg
F344 8mg/kg
Lew 8mg/kg
F344 16mg/kg
Lew 16mg/kg
Maximum (% of baseline)
180
160
140
120
100
80
60
40
20
0
15
30
45
60
Time After Injection (min)

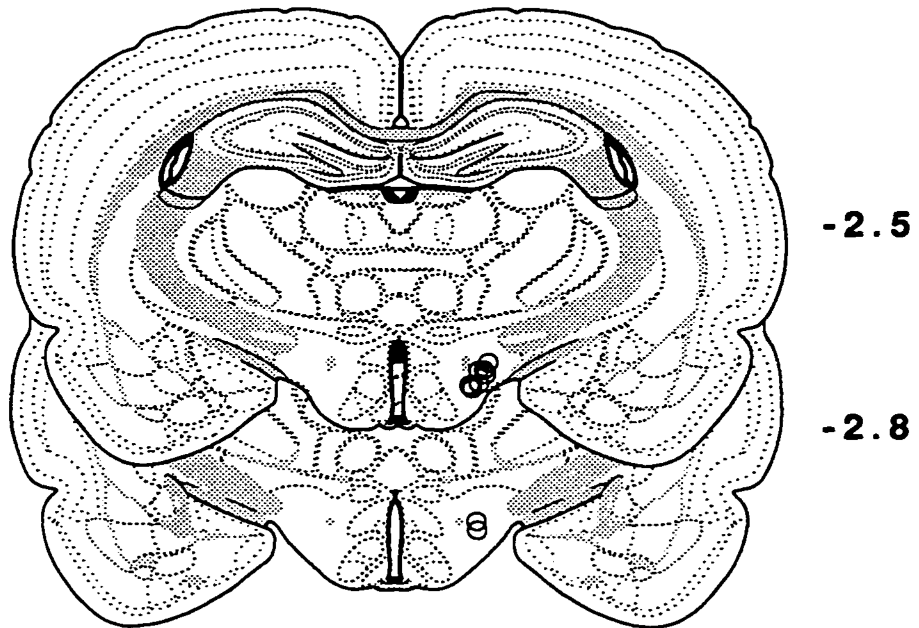
Figure 6.4: Mean (±SEM) pre-injection self-stimulation frequency threshold (raw scores) on saline (Day 1 and 6) and cocaine (Days 2-5) test days.



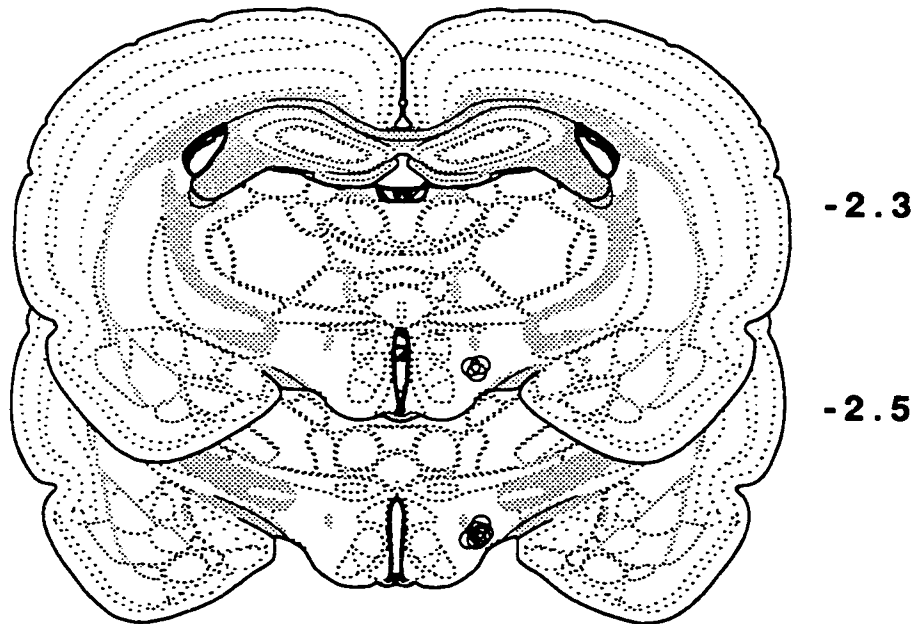
Pre-Injection Threshold (Hz)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
Test Day
Fischer 344
Lewis

Figure 6.5: Histological localization of stimulating electrode tips for Fischer 344 (top panel) and Lewis (bottom panel) rats. The number beside each brain plate represents the distance from the bregma. Reconstructions are based on the stereotaxic atlas of Swanson (1992). Electrodes were implanted in the left and right hemispheres but for the purpose of comparison are all shown in the left hemisphere.

FISCHER 344



LEWIS



6.4 DISCUSSION

The present data show that cocaine potentiated the rewarding impact of brain stimulation in Fischer 344 and Lewis rats and are consistent with previous reports of cocaine's threshold lowering (Esposito *et al.*, 1978; Kornetsky & Esposito, 1981) and curve-shifting (Frank *et al.*, 1988; Corbett, 1991; Wise *et al.*, 1992) effects on brain stimulation reward. In the present experiment cocaine produced a dose orderly potentiation of brain stimulation reward and the magnitude of the reward potentiation was not statistically different between Fischer 344, Lewis, and Long-Evans (Experiment 1) rats. For example, the highest dose of cocaine (16 mg/kg) tested in Fischer 344, Lewis rats and also tested in Long-Evans rats in Experiment 1 produced equipotent shifts to the left (decrease in threshold) of the rate-frequency curves. The 16 mg/kg dose of cocaine shifted the rate-frequency curves to the left by an average 0.44-log units which represents a 2.9-fold increase in the rewarding potency of the stimulation.

The present findings are inconsistent, however, with reports of differential sensitivities to the reward-relevant actions of cocaine in Fischer 344 and Lewis rats. Lewis rats have been reported to acquire cocaine self-administration more readily than Fischer 344 rats (George & Goldberg, 1988; Bell *et al.*, 1993,1995; Kosten *et al.*, 1997). Cocaine more readily establishes conditioned place preferences in Lewis rats but is ineffective or produces a conditioned place aversion in Fischer 344 rats (Kosten *et al.*, 1994). This differential sensitivity extends to morphine (Ambrosio *et al.*, 1995) and ethanol (Suzuki *et al.*, 1988a)

self-administration as well as to the establishment of conditioned place preferences by morphine (Suzuki *et al.*, 1988b) and nicotine; nicotine does not establish a conditioned place preference in Fischer 344 rats but rather produces a conditioned place aversion after 10 drug pairings (Horan *et al.*, 1997). While these findings suggest that Fischer 344 and Lewis rats are differentially sensitive to the reward-relevant actions of several habit-forming drugs they are inconsistent with the findings of the present experiment in the case of cocaine.

One important distinction between the self-administration and conditioned place-preference paradigms on the one hand and the brain stimulation reward paradigm on the other relates to the issue of acquisition versus maintenance. Fischer 344 and Lewis rats differ in their acquisition of drug self-administration and in their acquisition of conditioned place preferences (or place aversion, see paragraph above). In the only published data comparing Fischer 344 and Lewis rats for both acquisition and maintenance of intravenous drug self-administration, Fischer 344 rats take longer to acquire intravenous cocaine, but not for heroin (Leeb & Wise, 1993), self-administration compared to Lewis rats, both as a function of number of training trials and drug dose (Kosten *et al.*, 1997). Once the self-administration habit is acquired, however, the self-administration profiles of Fischer 344 and Lewis rats do not differ for cocaine (Kosten *et al.*, 1997) or heroin (Leeb & Wise, 1993). In the brain stimulation reward paradigm, drug effects are assessed once the self-stimulation behavior has been acquired and self-stimulation thresholds do not vary significantly from one day to the next (maintenance phase). As such, the lack of strain difference in the reward-potentiating effects of cocaine in Experiment

5 are consistent with the lack of strain difference during maintenance of intravenous cocaine self-administration in Fischer 344 and Lewis rats by Kosten *et al.*, (1997).

Reported differences between Fischer 344 and Lewis rats in the reward-potentiating effects of cannabis (Lepore *et al.*, 1996) appear to be inconsistent with the present findings. A dose of 1 mg/kg cannabis potentiates the rewarding impact of brain stimulation in Lewis rats but was ineffective in Fischer 344 rats. Unfortunately the conclusions of the Lepore *et al.* study rest on results of a single dose of cannabis tested (1 mg/kg) and the lack of effect in Fischer 344 rats makes the data difficult to interpret. It is not clear from these results whether the 1 mg/kg dose of cannabis was ineffective because it was too low to be rewarding in Fischer 344 rats or whether this dose was marginally aversive (too high) and thus had no significant effect on brain stimulation reward thresholds.

The reported strain differences in the acquisition of drug self-administration habits are generally thought to reflect inherent differences in the initial rewarding effects of drugs. While the present data do not address "acquisition" findings directly they do raise the question of whether Fischer 344 and Lewis strain differences in acquisition of drug self-administration are truly differences in the initial rewarding effects of the drugs or whether other factors may account for the differences.

Fischer 344 and Lewis strain differences in acquisition of intravenous cocaine self-administration are not likely due to strain differences in cocaine pharmacokinetics. Plasma cocaine levels are not significantly different between Fischer 344 and Lewis rats up to 30

min following intravenous (1 mg/kg; Kosten *et al.*, 1997) or 60 min following systemic injection with cocaine (Guitart *et al.*, 1992) or morphine (Guitart *et al.*, 1992). However, Camp *et al.* (1994) report greater plasma and brain levels of cocaine in Lewis compared to Fischer 344 rats with systemic drug injection.

Locomotor activity in a novel environment (Piazza *et al.*, 1989; 1990b; Deroche *et al.*, 1993) or in response to psychostimulants (Piazza *et al.*, 1989; Hooks *et al.*, 1991) are two predictors of rate of acquisition of drug self-administration habits. Given the differential rate of acquisition of drug self-administration in Fischer 344 and Lewis rats, it would be predicted that locomotor activity in a novel environment and locomotor activity in response to psychostimulants should also be differentially affected in these two rat strains; Lewis rats should locomote more when placed in a novel environment and in response to injections of psychostimulants. Indeed, locomotor activity in a novel environment has been reported to be higher in Lewis rats (Camp *et al.*, 1994; Ambrosio *et al.*, 1995; but see Chaouloff *et al.*, 1995) and Lewis rats locomote more in response to systemic injections of cocaine (George & Goldberg, 1988; Camp *et al.*, 1994; Kosten *et al.*, 1994) or amphetamine (Camp *et al.*, 1994) and thus support the hypothesis that these two strains of rats differ in their sensitivity to the rewarding effects of habit-forming drugs.

In contrast, Fischer 344 and Lewis rats exhibit differential stress response profiles that may account for differences in acquisition of drug self-administration. Fischer 344 rats do exhibit greater behavioral (Rosecrans *et al.*, 1986; Armario *et al.*, 1995; Sondern *et al.*, 1996; but see Chaouloff *et al.*, 1995) and neuroendocrine

(Rosecrans *et al.*, 1986; Dhabhar *et al.*, 1993,1997; Armario *et al.*, 1995; Dhabhar *et al.*, 1997; Grota *et al.*, 1997) responses to stress compared to Lewis rats. Fischer 344 rats may be more "timid" and thus less likely to explore novel environments or to perform an operant task to "get a taste" for the drug. If Fischer 344 rats are less likely to sample the drug due to their "timidity" it follows that their rate of acquisition should be slower than that of the less timid and less stressed Lewis rat.

While it is not clear that differential rewarding effects of habit-forming drugs solely account for the observed differences in the acquisition of self-administration habits in Fischer 344 and Lewis rats, it is clear in the case of cocaine, at least, that once behavior has been acquired there are no strain differences in the intravenous self-administration or potentiation of brain stimulation reward profiles between these two rat strains.

GENERAL DISCUSSION

The aim of the present thesis was to further characterize the effects of cocaine on brain stimulation reward. Towards this end, the rate-frequency variant of the curve-shift paradigm was used to quantify the reward-potentiating actions of cocaine on lateral hypothalamic brain stimulation reward.

In Experiment 1 the effective-dose range of potentiation of brain stimulation reward by cocaine was determined. As shown with several other habit-forming drugs (Wise, 1996b) cocaine decreased brain stimulation reward thresholds by producing parallel leftward shifts in the rate-frequency functions. The results of this experiment suggest that the threshold dose of cocaine for potentiating brain stimulation reward is approximately 2 mg/kg and that the maximally effective dose for potentiating brain stimulation reward is 16 mg/kg. The 16 mg/kg produced an average 0.47 log unit reduction in threshold frequency. The finding from this experiment reflects a summation between the rewarding effects of cocaine and the rewarding action of the stimulation (Wise *et al.*, 1992; Wise, 1996b).

In the present experiments an 800-ms "time-out" was given after each 200-ms train of rewarding stimulation; this corresponds to a fixed interval (1-s) schedule of reinforcement and was used to minimize the proactive "priming" effects of each earned stimulation train. There are at least two sets of consequences of stimulation that contribute to the control of rate of responding: the *priming effect* (Deutsch & Howarth, 1963; Gallistel, 1969; Reid *et al.*, 1973; Gallistel *et al.*, 1974) and the *reinforcing effects* (Deutsch & Howarth, 1963;

Gallistel *et al.*, 1974); it is for this reason that brain stimulation reward specialists tend to use the term "reward"—implying the sum of the two factors—rather than the term "reinforcement"—which suggests irrelevance of (or reflects lack of awareness of) the incentive-motivational contribution (Wise, 1989). The priming effect is a proactive effect; priming refers to the post-stimulation arousal or activation that is associated with more avid performance of the next response (Deutsch & Howarth, 1963). Some brain stimulation reward paradigms reflect *only* the post-stimulation priming effects of stimulation (e.g., Esposito *et al.*, 1978; the reinforcement-constant condition of Gallistel *et al.*, 1974). Priming effects are inherent in any brain stimulation reward study where the next stimulation is given within seconds or perhaps even minutes (Gallistel, 1969; Reid *et al.*, 1973; Gallistel *et al.*, 1974) of the last stimulation, and priming (which might be termed the "salted peanut" effect) almost certainly accompanies drug reward (Gerber & Stretch, 1975; de Wit & Stewart, 1981, 1983; Wise *et al.*, 1990) and more conventional rewards as well as brain stimulation reward (Wise, 1989). The reinforcing effects of stimulation are two: the stimulation confers both Pavlovian (Stein, 1958; Robbins & Koob, 1978; Ettenberg & Duvauchelle, 1988) and operant (Olds & Milner, 1954) reinforcement. Both forms of reinforcement are retroactive in the sense that they "reinforce" (Pavlov, 1928) or "stamp in" (Thorndike, 1898) stimulus (Pavlov, 1928) or response (Thorndike, 1898; Skinner, 1937) associations that were established or activated prior to the reinforcing event but whose traces are presumed active in the nervous system at the time the

reinforcement signal arrives (Thorndike, 1898; Pavlov, 1928; Olds & Olds, 1965; Landauer, 1969).

It is not clear whether cocaine augmented the rewarding effects of the stimulation by summating with the priming effect or one of the reinforcing effects of the stimulation. Cocaine clearly *can* augment the priming effect of stimulation (Esposito *et al.,* 1978). The priming, (Esposito *et al.*, 1979; see also Wasserman *et al.*, 1982 Ettenberg & Duvauchelle, 1988)[3], and the reinforcing (operant: Fouriezos & Wise, 1976; Franklin, 1978; Pavlovian: Ettenberg & Duvauchelle, 1988) effects of stimulation are attenuated by dopamine antagonists, as are both the incentive-motivational (Spyraki *et al.*, 1987) and reinforcing (operant: de Wit & Wise, 1977; Pavlovian: Spyraki *et al.*, 1987) effects of cocaine. Inasmuch as cocaine was given independent of the behavior of the animal, it did not, by definition, qualify as an operant reinforcer (Skinner, 1937). Inasmuch as its effects were pro-active (they were reflected in behavior that occurred *after* drug administration and absorption), it may seem most reasonable to assume that it was the incentive-motivational (priming) effect of cocaine that summated with the rewarding effect of the stimulation. That the priming effects of cocaine should summate with rewarding stimulation that was biased

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3 The failure suggested in the title of Wasserman *et al.*, (1982) is reflected in only the first few trials of each session. The decay of this "spared" priming effect undergoes a rapid extinction-like process that suggests it to be a memory-dependent holdover from prior reinforcement (see Skinner, 1933). The robust component of the priming effect is memory-independent (Gallistel *et al.*, 1974) and should thus not undergo extinction; it is absent in the neuroleptic-treated animals of this experiment. Wasserman *et al.* did not see a sustained priming effect in neuroleptic-treated animals and Esposito *et al.*, (1979) —whose paradigm offers an uncontaminated measure of priming effects —saw neuroleptic-induced loss of stimulation effectiveness. Thus while there may be a memory-dependent contribution to the priming effect that is not dopamine-dependent for its expression (it almost certainly is dopamine-dependent for its development; Beninger and Phillips, 1980; Beninger and Hahn, 1983), the robust effect of priming is lost in neuroleptic-treated animals.

toward reinforcement and away from priming by the 800-ms time-out (given the rapid decay of the priming effect of brain stimulation) is not surprising, since the neural substrates of incentive motivation and operant reinforcement are sufficiently similar as to have been hypothesized to be homologous (Bindra, 1972; Wise & Bozarth, 1987; Wise, 1989). However, despite the fact that the cocaine injection was not response-contingent and was thus not, by definition, reinforcing in its own right, cocaine may amplify the sensitivity of the reward system and thus amplify the reinforcing effects of the response-contingent brain stimulation. Thus, the drug may have contributed to the priming effect, one of the reinforcing effects of the stimulation or to any combination of the three.

In Experiments 2 and 3 the ability of the reward-potentiating actions of cocaine to undergo sensitization or tolerance, respectively, was tested. The hypothesized common denominator of incentive-motivation and reinforcement involves the brain mechanisms of forward locomotion (the common response to all positive reinforcers; Schneirla, 1959; Glickman & Schiff, 1967; Perkins, 1968; Wise & Bozarth, 1987). The effects of cocaine and other psychostimulants show sensitization with repeated administration (Babbini & Davis, 1972; Post & Rose, 1976; Stripling & Ellinwood, 1976). In Experiment 2, repeated intermittent injections of cocaine failed, however, to undergo sensitization to the drug's reward-potentiating action. Indeed, the present data suggest that there may some fundamental differences in the hypothesized common denominator of forward locomotion between incentive-motivation and reinforcement. The present data do not address however what that difference might be. For example, Wise

and Munn (1993) have shown sensitization to the locomotor-stimulating effects of amphetamine in the same animals and in response to the same amphetamine injections that potentiate brain stimulation reward but that failed to show sensitization to the reward-potentiating action. In Experiment 3 repeated high-dose injections of cocaine failed to undergo tolerance in this paradigm. These findings suggest that there is no profound between-session tolerance to the reward-potentiating action of cocaine.

In Experiment 4 a dose of cocaine or amphetamine and the dopamine D_2-like antagonist pimozide that produce equal but opposite shifts in the rate-frequency curves when each drug is injected alone canceled each other when co-administered thus the resulting behavior profile was like that of a normal non-treated animal. These results further implicate dopaminergic function in the reward-potentiating action of cocaine and amphetamine and of brain stimulation reward. These results also provide further evidence that cocaine and amphetamine function as synergists with brain stimulation reward.

In Experiment 5 the reward-potentiating effects of cocaine on brain stimulation reward were compared in Fischer 344 and Lewis rats strains. These two strains of rats have been hypothesized to be differentially sensitive to the rewarding effects of cocaine and several other habit-forming drugs such as opiates and ethanol based on their self-administration profiles of these drugs. In the present study, however, cocaine potentiated brain stimulation reward equipotently in both strains. Moreover, there were no strain differences when the results from Experiment 1 are compared to the results of Experiment 5. Cocaine produced equipotent potentiation of brain stimulation reward

in Long-Evans, Fischer 344 and Lewis rats at all doses tested. These findings suggest that factors other than merely the reward-relevant actions of cocaine may account for previously reported differences in Fischer 344 and Lewis rats.

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