The Effect Of Dopaminergic And Noradrenergic Receptor Blockade On Cocaine Self-Administration In Rats.

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ABSTRACT

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The present study used the paradigm of intravenous drug self-administration to investigate the catecholaminergic basis of cocaine reward. The first experiment investigated the effects of a dopaminergic receptor blocking agent, pimozide (.0625, .125, .25, and .5 mg/kg), on rate of cocaine self-administration in rats. A dose-dependent effect was observed. At the lowest dose, the rate increased above baseline response levels, indicating an attenuation in the reward value of the cocaine injections. At higher doses, an extinction-like effect was observed: an initial increase in rate, followed by a cessation of responding. In the second experiment central injections of the alpha-noradrenergic receptor blocker phentolamine (50 ug, 75 ug, 100 ug) were administered to rats self-administering cocaine. Phentolamine injections produced variable responding, with a tendency to reduce rates of barpressing. These results were taken to indicate a critical role for dopamine and not noradrenaline in the mediation of stimulant drug reinforcement.

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TABLE OF CONTENTS

LIST OF FIGURES

I Introduction

In recent years, considerable research has been directed towards the study of brain mechanisms underlying motivated behavior and in particular the neural processes which mediate reward. The most fruitful approach to this subject has proven to be the study of the reward which results from direct electrical stimulation of the brain. The behavior maintained by such reward resembles the behavior maintained by conventional reward in many respects, suggesting that brain stimulation reward and conventional rewards have some mechanisms in common. But brain stimulation reward, unlike conventional reward, lends itself conveniently to direct anatomical and pharmacological investigation, so that behavioral phenomena can be related more directly to neural function. A more complete knowledge of the mechanisms mediating self-stimulation might eventually provide some idea of the processes maintaining natural motivated behavior.

One of the findings from the study of neural mechanisms mediating self-stimulation is that the catecholamines, which are presumed

central neurotransmitters, seem to be critically involved in brain stimulation reward. There is an anatomical correlation between sites which support self-stimulation and areas which are rich in catecholamines. Furthermore, pharmacological agents which disrupt catecholamine function also disrupt self-stimulation. It has been hypothesized from these findings that the catecholamines mediate reward. Some of the experiments which generated this hypothesis will be discussed below.

The discovery that catecholamines are important to the mediation of brain stimulation reward has suggested the use of another experimental paradigm in the study of reward systems in the brain, that of stimulant self-administration. Stimulant drugs such as amphetamine and cocaine, which facilitate the synaptic actions of the catecholamines, are rewarding when injected intravenously. It is possible that the rewarding effect of stimulant drugs is a direct result of their action on the catecholamine system. They might pharmacologically activate the same systems that are electrically activated during self-stimulation.

Intravenously administered stimulant drugs are effective reinforcers of operant responses, and are capable of maintaining a stable rate of responding which can be used as a behavioral baseline upon which to test the effects of pharmacological agents. Some aspects of the behavior of animals responding for stimulant drugs, it will be argued, make this paradigm particularly useful for determining the nature of central reward mechanisms.

II Catecholaminergic involvement in self-stimulation

Several lines of evidence suggest that one or both of the central catecholamines, dopamine and noradrenaline, are critical in the mediation of brain stimulation reward. Anatomically, there is a correlation between areas rich in catecholamines and areas supporting self-stimulation. Catecholamine-containing neurons have been traced from their origins in several groups of cell bodies in the brainstem, along axons forming part of the medial forebrain bundle, and terminating in a number of limbic and cortical structures (Ungerstedt, 1971). The strongest correlation between self-stimulation sites and catecholamine concentration has been observed in the medial forebrain bundle;

it is one of the most reliable sites for self-stimulation, and contains the most dense convergence of catecholamine fibers. There is also some correlation between self-stimulation sites and catecholamine content in other areas of the brain (German and Bowden, 1974). Attempts to demonstrate that self-stimulation depends on the integrity of catecholamine systems by electrolytically lesioning catecholamine systems, however, have met with only limited success. It is difficult to electrolytically lesion specifically catecholamine and not other types of cells in the brain; catecholamine fiber tracts in the medial forebrain bundle lie close to other fiber systems, and catecholamine terminals are diffusely distributed throughout the forebrain. More progress has been made in the investigation of the role of catecholamines by examining the effect on self-stimulation of pharmacological agents which alter central catecholamine function. Drugs which disrupt catecholamine function have been found to decrease rates of responding for brain stimulation, and conversely, drugs which potentiate catecholaminergic action have been found to enhance self-stimulation.

One of the earliest studies which implicated catecholamines in brain stimulation reward was a demonstration by Stein in 1962, of a decrease in rate of self-stimulation after treatment with two drugs which interfered with noradrenergic function, namely chlorpromazine, which blocks noradrenaline receptor sites, thereby blocking noradrenergic action, and reserpine, which reduces noradrenergic action by depleting functional stores of the catecholamines in the pre-synaptic terminal. Stein further found that amphetamine, a stimulant which was thought to potentiate the effect of noradrenaline, or to serve as a noradrenaline substitute because of its structural similarity to this transmitter substance increases self-stimulation rates. All three of these (chlorpromazine, reserpine and amphetamine) have since been shown to act on dopaminergic as well as noradrenergic systems, but the findings remain significant insofar as they implicate catecholamines in brain stimulation reward. At about the same time Poschel and Ninteman (1963) showed that self-stimulation is facilitated by a drug treatment which increases functional levels of catecholamines (alpha-methyl-meta-tyrosine, which moves catecholamines

from storage to functional pools, plus monoamine oxidase inhibitors which prevent the metabolic breakdown of the catecholamines in the synapse). They further showed that a drug which blocks the synthesis of catecholamines (alpha-methyl-para-tyrosine) suppresses lateral hypothalamic self-stimulation (Poschel and Ninteman, 1966) again demonstrating the importance of intact catecholamine systems.

Since these studies were done, numerous other investigators have confirmed the finding that drugs which interfere with catecholamine function disrupt self-stimulation (Stein, 1971; German and Bowden, 1974). In addition to catecholamine blocking studies, several other experimental techniques have produced results implicating catecholamines in rewarding brain stimulation. Stein and Wise (1969) reported that radioactively labelled noradrenaline which had been taken up into catecholamine terminals was released as a consequence of rewarding, but not non-rewarding lateral hypothalamic stimulation. Arbuthnott, Crow, Fuxe, Olson, and Ungerstedt (1970) showed histologically that when new catecholamine synthesis was inhibited, rewarding brain stimulation resulted in a depletion of stored

catecholamines, not only at the point of stimulation but also along the catecholamine pathways which project past the stimulation sites. Finally, several studies have shown that injections of 6-hydroxydopamine, a chemical which selectively destroys dopaminergic or noradrenergic cells when given in appropriate doses, suppresses self-stimulation (Breese, Howard, and Leahy, 1971; Lippa, Antelman, Fisher, and Canfield, 1973).

Thus, there is considerable evidence from anatomical, pharmacological, and combined techniques, suggesting that catecholamines are important in the phenomenon of rewarding brain stimulation. Much less agreement has been reached regarding the specific roles of noradrenaline and dopamine in this behavior. It will be seen that methodological problems with the self-stimulation paradigm have hindered the resolution of this question.

A number of pharmacological agents have been used to selectively disrupt dopaminergic or noradrenergic function, including drugs which block receptors, inhibit synthesis of new neurotransmitter substance, and those which chemically lesion particular kinds of cells. The effects of these treatments on self-

stimulation have provided considerable information regarding the neurochemical processes underlying self-stimulation, although at the same time some aspects of self-stimulation as a baseline behavior for drug treatments have made this approach vulnerable to misinterpretation. Wise and Stein (1969) showed that disulfiram, a drug which inhibits the synthesis of noradrenaline but leaves dopamine intact, decreases the rate of self-stimulation; they concluded from this that noradrenaline was involved in the mediation of reward. Roll (1970) subsequently argued, however, that the decrease in responding after disulfiram was not necessarily a function of a specific reward deficit; she showed that disulfiram causes sedation which might have accounted for the suppressed performance. Franklin and Herberg (1975) have recently demonstrated a suppression of lateral hypothalamic self-stimulation with no apparent motor incapacity, after treatment with a noradrenaline synthesis inhibitor (FLA-63) but only after the reserve stores had been previously depleted by reserpine. Wise, Berger, and Stein (1973) demonstrated a disruption of medial forebrain bundle self-stimulation after administration of phentolamine,

a drug which blocks noradrenergic receptors. The dopaminergic receptor blocker pimozide, on the other hand, had only a negligible effect on medial forebrain bundle self-stimulation, and no effect when electrodes were in the locus coeruleus, an area containing almost exclusively noradrenergic cells (Ritter and Stein, 1973). These two findings were again seen to implicate noradrenaline in brain stimulation reward: a drug which blocks noradrenergic receptors disrupted the behavior, while one which presumably blocked dopaminergic receptors had no effect. In the case of phentolamine, however, the possibility that the disruption in responding was due to depressant effects of the drug rather than an effect on the reward value of the stimulation was not ruled out. In the case of pimozide, it was subsequently found that Ritter and Stein's methods of administration of the drug may have been ineffective; Corbett, Harley and Wise (1975) found a suppression of locus coeruleus self-stimulation after administration of the same dose of pimozide when it was injected in a suitable vehicle by a suitable route. Pimozide has also been shown to

decrease self-stimulation with other placements (Pantel, Yokel, and Wise, 1974; Liebman and Butcher, 1973). Other data also conflict with those of Wise and Stein. Lippa, Antelman, Fisher, and Canfield (1973) tested self-stimulation in rats after treatments which inhibited synthesis of noradrenaline (FLA-63), or blocked noradrenergic receptors (phentolamine) or dopaminergic receptors (haloperidol). FLA-63 inhibits the conversion of dopamine into noradrenaline by blocking the action of the enzyme dopamine-beta-hydroxylase. Noradrenergic receptor blocker phentolamine was administered either by itself or in combination with 6-hydroxydopamine (6-OHDA) at a dose which damaged both noradrenergic and dopaminergic cells. This combination was intended to maximally disrupt noradrenergic function, by decreasing functional catecholamine terminals and blocking any remaining noradrenaline from acting on the receptor. However, self-stimulation rates remained near normal for all treatments except haloperidol, which produced a significant reduction in self-stimulation. Thus, in the hands of these investigators, neither inhibition of noradrenaline synthesis nor blockade of noradrenergic receptors, even when catecholamines

had been depleted by 6-OHDA, appeared to affect self-stimulation rate, whereas blockade of dopaminergic receptors resulted in significantly decreased rates. Both assay data and an observed reduction in food intake were taken to indicate that the noradrenergic treatments did affect noradrenergic function, and a motor test indicated that the suppressant effect of haloperidol was not due to gross motor impairment. These authors argued for a significant role for dopamine and not noradrenaline in the mediation of brain stimulation reward. Rolls, Kelly, and Shaw (1974) studied the effects of a dopaminergic receptor blocker (spiroperidol), a noradrenergic receptor blocker (phentolamine) and a noradrenergic synthesis inhibitor (disulfiram) on lateral hypothalamic self-stimulation as well as on two tests of general arousal (rearing and locomotor activity). They found the greatest reduction in self-stimulation, and no significant arousal deficit after dopamine receptor blockade. Noradrenergic treatments reduced self-stimulation slightly but produced significantly lower scores on rearing and locomotor tests.

These and a number of other studies (Hastings

and Stutz, 1973; Fibiger and Phillips, 1975; Pantel, Yokel, and Wise, 1974) have shown that to some extent both noradrenergic and dopaminergic receptor blockers reduce rates of self-stimulation. However, the problem of determining whether such drugs cause specific reward deficits or rather produce some form of performance difficulty has proven to be a serious obstacle in resolving the question of the respective roles of noradrenaline and dopamine in the production of behavior.

III Catecholamines and stimulant self-administration

Stimulant drugs such as amphetamine and cocaine are known to act on catecholaminergic neurons by effectively increasing the level of transmitter substance in the synapse. Amphetamine is thought to act by several mechanisms: by causing the release of dopamine and noradrenaline from pre-synaptic terminals, by inhibiting monoamine oxidase, an enzyme which usually causes the metabolic breakdown of catecholamines, and by blocking the re-uptake of catecholamines into the pre-synaptic terminals (Randrup and Munkvad, 1966; Glowinski and Baldessarini, 1966; Carr and Moore, 1969). There are also indications that amphetamine has a direct stimulative action on

post-synaptic catecholaminoceptive neurons (Hoffer, Siggins, Bloom, 1971; Hoffer, Olson, Seiger, Bloom, 1975; Feltz and de Champlain, 1972). Cocaine is believed to have its action by only one of these mechanisms, by the blockade of re-uptake of transmitter substance into the pre-synaptic cell (Ross and Renyi, 1967; Heikkila, Orlansky, and Cohen, 1975).

These and other psychomotor stimulants are characterized by a number of distinctive behavioral effects: at low doses they increase locomotor activity and at higher doses produce stereotyped sniffing and head movements; they are anorexigenic; in large doses they produce euphoria in man, and they can act as effective reinforcers of operant behavior in animals when injected intravenously (Goodman and Gilman, 1975, pg.387). Considerable research has been directed at the question of which of these effects are mediated by catecholaminergic systems, and in particular whether they depend on dopaminergic or noradrenergic systems. There are at present indications that certain effects are primarily dopaminergically mediated (for example stereotypic behavior) or noradrenergically mediated (for example exploratory activity) (Costall, Naylor, and

Olley, 1972; Corrodi, Fuxe, Ljungdahl, and Ogren, 1970), and there may eventually be sufficient evidence to permit the use of one or more of these behavioral effects as reliable indicators of specific neuronal activity. Until such certainty is achieved, however, the neuropharmacological basis of each of the behavioral effects of stimulant drugs should be considered independently of other effects.

Intravenous injections of stimulant drugs can serve as effective reinforcers in an operant situation. When infusions of amphetamine or cocaine are made contingent on a desired response, animals readily learn and perform the response (Deneau and Yanagita, 1969; Dougherty and Pickens, 1973a); they maintain stable rates of responding on a continuous reinforcement schedule (Pickens and Harris, 1968; Dougherty and Pickens, 1973a); they exhibit typical patterns of responding on partial reinforcement schedules, such as fixed interval (Dougherty and Pickens, 1973b), fixed ratio (Pickens and Thompson, 1968; Pickens and Harris, 1968) and variable interval schedules (Iglauer and Woods, 1974); and they show a characteristic pattern of responding during extinction when

reinforcement is withheld (Yokel and Wise, 1975; Yokel and Pickens, 1976). There is one notable feature of the pattern of responding at the most effective doses of drug reinforcement, which is seen regardless of the schedule: that is, there typically is a long pause after the delivery of each drug infusion, before the next response is initiated. The duration of this post-infusion pause is very consistent, and is directly related to the dosage of drug per infusion: the larger the dose the longer the subsequent period of non-responding. Thus, on a continuous reinforcement schedule, the rate of responding is low (two to ten responses per hour, depending on the particular drug and drug dose used) and very regular. When the dosage per injection is increased, the rate of responding decreases, and conversely when the dose is decreased, the response rate increases. This inverse relationship between magnitude of reward and rate of responding is peculiar to drug reinforcers, and, as will be seen, it is this characteristic which makes drug self-administration a particularly suitable paradigm in reward mechanism research. It should be noted that this inverse dose-rate

relationship only holds for a limited range of doses per injection: doses that are too small or too large produce an erratic pattern of responding or an abrupt stop (Pickens and Thompson, 1968; Dougherty and Pickens, 1973a). Dougherty (1973) found that for rats self-administering cocaine this range fell between .4 and 2.56 mg/kg/injection of cocaine: response rates within this range varied linearly and inversely with injection dose.

The characteristic features of responding for drug injections, the long, stable post-infusion pause and the inverse relationship between reward magnitude and rate, can be understood in terms of prolonged drug satiation after a drug infusion reinforcement, which is terminated by the metabolic breakdown of the drug. Each infusion of a particular dose of stimulant raises the blood level of the drug by a fixed amount. With no further infusions this level will drop in a consistent and predictable manner as a result of the body's metabolic breakdown of the drug. It would appear that a certain minimum, or threshold blood level of drug is needed for the stimulant to be rewarding; thus when first

given drug access, animals show a burst of unregulated responding. Then, after a peak in blood level is reached, the animals' pattern of responding suggests that further increases do not result in further reward. That is, as long as the animal's blood level of drug is above this point, the animal is drug-satiated. As soon as the level falls below this point as a result of metabolism, the animal responds to restore the level. When larger doses per injection are used, they raise the blood level higher above the threshold level, and therefore a longer period of metabolism is needed before another response is needed. This account is supported by findings of Yokel and Pickens (1974), who measured blood level of amphetamine at the moment of responding in rats. They found that at the time of responding the blood level of drug was always near .18 µg/ml regardless of dose per injection (dose range tested was .25-1 mg/kg). These data directly support the view that animals respond to maintain a certain blood level of drug.

Two alternative explanations have been postulated for the occurrence of long periods of non-responding after a drug infusion (Wilson,

Hitomi, and Schuster, 1971). Firstly, it is possible that animals do not make further responses immediately after an infusion because higher blood levels of drug are aversive. This explanation seems unlikely since rats show no preference for several smaller doses over fewer larger doses when given a two-lever, two-dose choice (Yokel, 1975). If an aversive aspect of a high blood level of drug suppresses responding immediately after an infusion, animals should learn to avoid the higher dose when given a two-lever choice. The second hypothesis is that the animal is unable to respond immediately after a drug injection, due to stereotypic behavior or some other response conflict or interfering drug effect. This can be ruled out because animals are able to bar-press continuously throughout the inter-response interval, and will do so when a second lever is available for intracranial self-stimulation (Yokel and Wise, unpublished). Thus neither aversive nor debilitating effects of stimulants seem to adequately account for the regular pacing of drug intake. It seems more likely that the animals are drug satiated as long as their blood level of drug is above a certain point,

and that they become "drug-hungry" when it is metabolized below this point.

The self-administration paradigm provides a stable baseline behavior to use to study the reward system, and with some knowledge about the pharmacodynamics of responding for drug reinforcement, specific predictions can be made about the behavioral effects of alterations in reward mechanism function. A moderate dose of a drug believed to disrupt the reward system would be expected to reduce the reward efficacy of each stimulant injection, and a higher dose of such drug should block reward altogether. A reduction in reward efficacy should have a similar effect on rate of responding as a reduction in reward magnitude such as that seen when dose per injection is reduced, and a complete blockade of reward should produce a pattern of responding resembling that seen when reward is withdrawn completely. Thus in the self-administration paradigm a treatment drug which partly blocks the reward system should result in an increased rate of responding, just as dose-reductions produce an increase in response rate. Complete reward blockade should produce the typical extinction pattern, that is, an

initial increase in rate ("emotional" responding: Skinner, 1938, pg. 74) followed by response cessation. The increased response rate after partial reward system blockade can be understood in terms of the dynamics of the blood level of the stimulant drug. A treatment drug that partially blocks the rewarding effect of the stimulants would effectively raise the threshold level of the rewarding drug effect, so that more drug would be needed to achieve the same level of reward. This might occur neurally by some mechanism such as competition for receptor sites: more stimulant drug would be needed to compensate for the effect of a small amount of receptor blocking drug. If responding is initiated when blood levels reach an unusually high threshold, the total blood level of drug immediately after an infusion is proportionally higher. The rate at which the drug is metabolized, however, depends on the total amount of drug in the body. A constant percent of the total drug content is metabolized per unit time, so that the higher the blood level, the faster the rate of metabolism. This means that when the rewarding threshold is raised, the duration of effect of

the same dose of stimulant is shorter, because of faster metabolism. Thus to maintain a higher blood level of the stimulants, an animal must not only lever press more to initially achieve a higher level, but it must also press faster to maintain this level in face of faster catabolism.

Whereas a specific reward attenuating effect of a drug treatment is expected to increase the rate of response, at least initially, any other drug effects, such as sensory or motor deficits, or general malaise or sedation would be expected to decrease rate of responding. This differential effect of reward and performance blockers makes self-administration particularly well-suited to research on reward mechanisms. By contrast to this, in the self-stimulation paradigm, rate reductions due to reward deficits are indistinguishable, except by very careful analysis, (e.g. Fouriezos and Wise, 1976) from rate reductions due to other non reward-related deficits. Self-stimulation is particularly sensitive to other drug effects, because of the high response demands (one or two responses per second) in the self-stimulation paradigm. Self-administration response demands are trivial

in comparison (one response per ten to thirty minutes), so that it is unlikely that minimal debilitation will noticeably disrupt responding. Also, while with self-stimulation a ceiling effect of high response rates might mask any possible rate increases due to partial blockade or extinction, with self-administration there is clearly room for an increase in rate of responding.

As in the case of self-stimulation, the early experiments investigating the role of catecholamines in stimulant self-administration used pharmacological agents which affect both noradrenaline and dopamine. Pickens, Meisch, and Dougherty (1968) gave the catecholamine synthesis inhibitor alpha-methyl-para-tyrosine to rats self-administering amphetamine, and reported an extinction-like effect at high doses; that is, an initial increase in rate was followed by response termination. At low and intermediate doses, responding was accelerated in a dose-dependent fashion. Wilson and Schuster (1972) reported an increase in rate of self-administration of several different stimulant drugs in monkeys after treatment with a non-selective catecholamine receptor blocker

chlorpromazine (Goodman and Gilman, 1975, pg. 160). The increased rates were taken to indicate reward attenuation. Wilson and Schuster (1973b) pre-treated monkeys with the phenothiazine trifluoperazine before a cocaine self-administration session. Again, at low doses of the drug response rates increased by 50-100% and at higher doses rates transiently increased and then fell to zero. These results suggested a dose-dependent disruption of the reward mechanism. The same authors (Wilson and Schuster, 1974) studied the effects on cocaine self-administration in monkeys after potentiation of catecholaminergic function with a monoamine oxidase inhibitor, as well as after antagonism of catecholaminergic function with a synthesis inhibitor, (alpha-methyl-para-tyrosine) and a drug which depletes pre-synaptic stores (reserpine). The monoamine oxidase inhibitor (pargyline) decreased self-administration, possibly indicating a potentiation of reward due to increased synaptic levels of transmitter. This interpretation that reward potentiation rather than sedation caused the rate decrease was supported by the observation that the peripheral effects of cocaine also

appeared to be potentiated. Conversely, the catecholamine synthesis inhibitor, and, for the first 3-4 hours at least, the catecholamine depletor, produced increases in rate of lever-pressing, which seemed to indicate reward attenuation.

Davis and Smith (1972, 1973) demonstrated blockade of amphetamine reinforcement with alpha-methyl-para-tyrosine treatment in two other paradigms. In Experiment 1, rats were first trained to barpress using an intravenous injection of amphetamine as reinforcer. This acquisition session was followed by one extinction session, in which the amphetamine solution was replaced by a saline solution. On the test-day, re-acquisition of the barpress response for amphetamine was examined when experimental animals had been pre-treated with alpha-methyl-para-tyrosine. Re-acquisition was blocked in the alpha-methyl-para-tyrosine-treated animals (control animals readily relearned the response), suggesting that the amphetamine was no longer reinforcing under the AMPT condition. In Experiment 2, the sound of a buzzer was repeatedly paired with non-contingent intravenous amphetamine injections. Experimental animals were treated

with alpha-methyl-para-tyrosine. On a subsequent test day, the secondary reinforcing properties of the buzzer were tested. The drug-treated animals, unlike control animals, failed to barpress above operant rate for the buzzer alone. From this it was concluded that injections of amphetamine were not rewarding for animals pre-treated with AMPT. The failure to demonstrate the reinforcing properties of amphetamine after catecholamine synthesis inhibition in these experiments confirmed the conclusion from other paradigms that the catecholamines are necessary for amphetamine reinforcement.

Thus, interference with catecholaminergic function has been shown to attenuate intravenous stimulant reinforcement in a variety of paradigms. Complete blockade of catecholaminergic transmission has been seen to extinguish operant responding, and block learning in both classical and operant paradigms. Increased rates of self-administration were observed after more moderate applications of the same treatments in spite of the fact that in some cases the treatment was with tranquilizing drugs (such as chlorpromazine). From these studies it is clear that catecholamines play

an important role in the mediation of self-administration: it seems probable that the involvement is at the specific level of the reinforcement process.

The nature of the respective roles of noradrenaline and dopamine have been investigated in two studies using the conventional self-administration paradigm. Wilson and Schuster (1974) administered two noradrenergic receptor blocking agents, phentolamine and phenoxybenzamine, to monkeys self-administering cocaine. There was no change in rate of responding in either case, suggesting that normal noradrenergic transmission is not necessary for stimulant reinforcement. The authors qualified this conclusion by pointing out that the intramuscularly administered drugs may not actually have penetrated the central nervous system. Yokel and Wise (1975) used rats self-administering amphetamine to examine the effects of a dopamine receptor blocker (pimozide), an alpha-noradrenergic receptor blocker (phentolamine) and a beta-noradrenergic receptor blocker (propranolol). They found a dose-dependent increase in rate of responding after pimozide treatment at the three lowest doses,

(.0625, .125, and .25 mg/kg), and at the highest dose (.5 mg/kg) rats exhibited a typical extinction-like pattern of responding, an initial increase in responding followed by complete response cessation. Neither phentolamine nor propranolol had this effect on response pattern. Both noradrenergic blockers decreased rate, phentolamine did so in a dose-dependent manner, which suggested some deficit other than specific reward blockade. The results of their experiment thus support the hypothesis that dopamine plays a critical role in the mediation of stimulant reward, and confirm the observation of Wilson and Schuster (1974) regarding noradrenergic blockade.

Smith and Davis (Davis and Smith, 1975; Davis, Smith, and Khalsa, 1975; Smith and Davis, 1973; Davis and Smith, 1974) have done a series of experiments investigating the specific roles of dopamine and noradrenaline in drug reinforcement using their two experimental paradigms, testing the strength of Pavlovian conditioning, and the re-acquisition of an operant response. Their findings in both of these tests suggest that both noradrenaline and dopamine are involved

in amphetamine reinforcement. They found that noradrenaline synthesis inhibitors (dopamine-beta-hydroxylase inhibitors diethyldithiocarbamate and U14,624), as well as a dopaminergic receptor blocker (haloperidol) prevented both the Pavlovian conditioning (buzzer alone did not maintain responding after drug-buzzer pairings) and the re-acquisition of operant responding for intravenous amphetamine reinforcement (Davis and Smith, 1975; Davis, Smith, and Khalsa, 1975). Assuming that the synthesis inhibitors were as selective in their effect on noradrenaline as haloperidol on the dopamine system, this would seem to contradict the findings of Wilson and Schuster (1974) and Yokel and Wise (1975), suggesting, rather, that both transmitters are involved in stimulant reward.

The discrepancy between the findings of Wilson and Schuster (1974) and Yokel and Wise (1975) on the one hand, and Smith and Davis on the other is not yet understood. It may be that some difference in the two paradigms is involved. Alternatively, it may be that the noradrenergic blockers did not cross the blood-brain barrier and thus failed to cause central noradrenergic blockade. The present

study deals with this latter possibility.

In the first experiment it was confirmed that pimozide blocks the faster, more stable responding for cocaine, as well as responding for amphetamine. In the second experiment the cocaine self-administration paradigm was used to assess the effects of the noradrenergic blocker phentolamine, injected directly into the brain.

Experiment 1

The dose-dependent effects of specific dopaminergic receptor blockade on the reinforcing properties of stimulant drugs has as yet been demonstrated in only one self-administration study, which used amphetamine as the self-administered drug, and pimozide as the dopaminergic receptor blocking agent. The present experiment was conducted to determine if pimozide would have similar effects on cocaine self-administration. In view of the behavioral and pharmacological similarities of the two drugs, it was hypothesized that the effects of dopamine receptor blockade on cocaine self-administration would parallel the effect on amphetamine self-administration. At low doses of pimozide, responding should increase, and at higher doses an extinction-like pattern of responding should be seen.

Method

Subjects. Fourteen male Wistar rats from Bio Breeding Laboratories, Ottawa, weighing between 400 and 550 grams at the time of purchase, were subjects in this study. Large animals were used to allow for some weight loss during the experiment. Food and water were freely available except during barpress training.

stages, when rats were occasionally food-deprived. Eight of the rats were drug-naive for this experiment, three had had experience with amphetamine self-administration, and three had been subjects for Experiment 2 before they were tested in Experiment 1. It should be noted that for a variety of reasons not all animals prepared for self-administration reached an adequately stable response rate to be used in the experiment described. Some became ill or developed blocked catheters. Others did not learn to respond for cocaine reinforcement.

Surgery. An intravenous catheter, as described by Pickens and Thompson (1975) was implanted in each animal under sodium pentobarbital and chloral hydrate anaesthesia. The catheter passed subcutaneously from the jugular vein to the middle of the rat's back, where it was connected to a "back-pack" consisting of a subcutaneous anchor, a screw-type connector for the infusion tubing, and two externally-projecting stainless steel screws. Penicillin injections (3,000 IU) were given at time of surgery to minimize chances of infection. After surgery, catheters were flushed daily with .5-ml of a heparin solution (20 IU/ml in

saline) to protect against formation of embolisms in the vein. Some animals remained in the test chamber between experimental sessions; they received hourly intravenous injections of .13 ml of the heparinized saline. The regular diet of Purina Lab pellets was frequently supplemented by wet mash (water and powdered pellets) with vitamin drops and Terramycin powder. Animals were not allowed access to cocaine until at least 2 days after surgery, and then only if they had recovered their preoperative weight.

Apparatus. The test boxes were 20 x 20 cm operant chambers with fittings above the box to suspend a brass swivel and infusion tubing. Each box contained one or two levers each with a small stimulus light mounted above it, a house-light, food and water, and a sliding partition to make the lever inaccessible between sessions. Each box was enclosed in a ventilated, sound attenuating chamber. Infusion tubing which led from the rat's back pack to the brass swivel was enclosed in a coil of stainless steel wire which twisted the swivel as the animal moved, and afforded some protection to the plastic tubing. This coil of wire encasing the tubing was attached to

the screws in the back-pack and to the moving part of the swivel. Further tubing led from the swivel to an infusion pump outside the chamber. In the two-lever boxes, one lever served as a control lever for the determination of operant level of lever-pressing; depressions on this lever were counted and recorded on the event recorder but had no consequences for the animal other than the click of a relay. Each depression of the operative lever activated a counter and an event recorder, and started a timer which in turn activated the infusion pump for the number of seconds needed to deliver the appropriate volume of drug solution. The stimulus light over the operative lever was lighted for the duration of the infusion, and further bar presses during this time did not reset the timer and had no further experimental consequences. All bar presses and infusions were recorded on event-recorders and counters.

Only one concentration of cocaine hydrochloride solution (in physiological saline)

was used, and adjustments for dosages by weight were made by altering volume of infusion. To deliver a 1 mg/kg infusion dose of cocaine to a 500 gram rat, a volume of .125 ml of solution was injected over 13 seconds. The injection time (and hence volume) was adjusted appropriately for rats whose weights were below or above 500 grams. Pimozide was dissolved in tartaric acid solution, and a new solution was prepared on each day of testing.

Procedure. In an effort to facilitate subsequent acquisition of the barpress response for drug reinforcement six of the rats were trained to barpress for food reinforcement (Noyes pellets) before catheter implantation. The others were naive at the time of surgery. Following recovery from surgery, self-administration training was begun. Animals were placed in the chamber, infusion tubing was connected, and several non-contingent injections of cocaine were administered. From the first day and throughout all subsequent sessions, each barpress resulted in an infusion of 1 mg/kg cocaine hydrochloride. Rats which failed to make any barpresses in the first 24 hours were deprived of food for the

next 23 hours, and a food pellet was taped to the lever to increase the likelihood of initial lever depression. The food pellet was removed when typical, regularly spaced responding for drug was observed. Training sessions continued until stable responding was maintained for a full six-hour session. Even after animals had in an earlier session exhibited regular responding for drug, one or more non-contingent "priming" injections of drug were often used to prompt the animal to begin responding at the beginning of the session. Since all animals did not begin self-administration with short latency, the criterion for beginning an experimental test session was at least one hour of well-spaced responding.

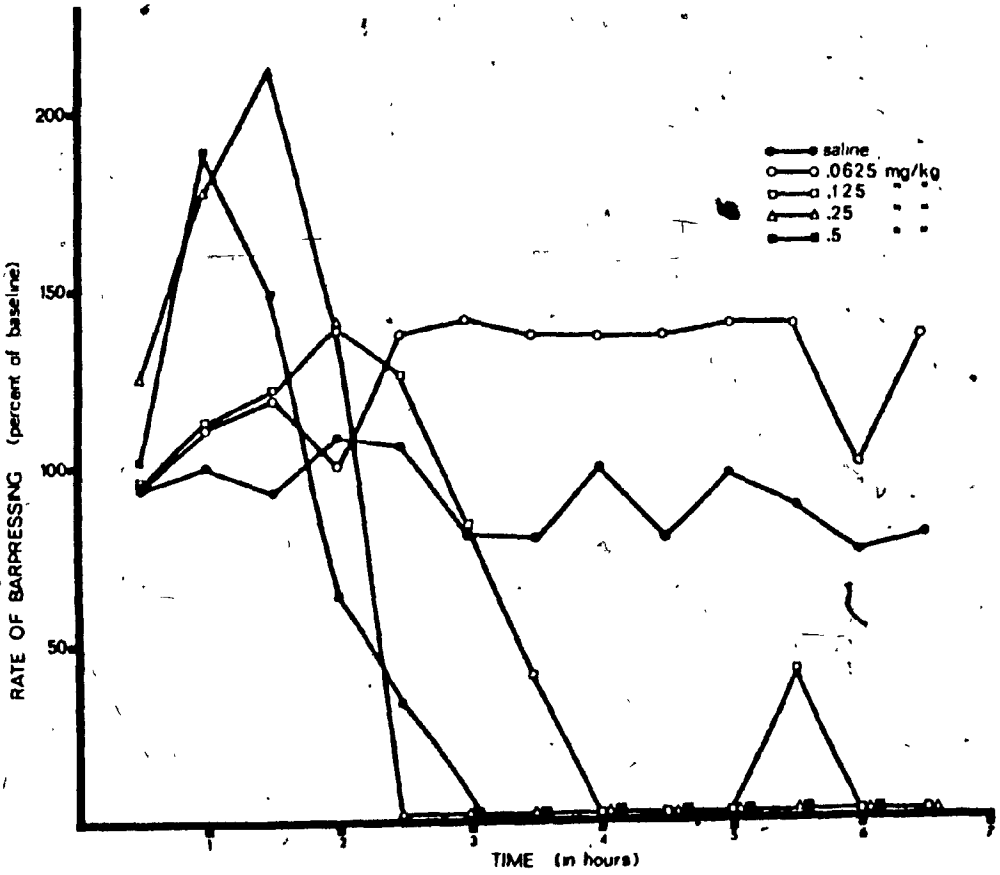
In experimental sessions animals received an intraperitoneal injection of either saline or pimozide (.0625, .125, .25, or .5 mg/kg) after at least one hour of stable responding. Sessions involving pimozide treatment were separated by at least 48 hours and were usually preceeded by a session during which saline was administered. This allowed for the assessment of the disruptive effects of the i.p. injection procedure. Sessions

continued for six hours after injection, after which either the animals were removed from the test box or the lever partitions were inserted. The order of administration of the four pimozide doses varied from animal to animal, and as many of the four doses as possible were tested with each animal.

Rats were weighed daily and not allowed access to cocaine if they had lost 10 grams or more from the previous day. Several animals died or had catheter failures during the course of the experiment.

Results

The rate of cocaine self-administration was affected by pimozide in a dose-dependent manner. The lowest dose of pimozide (.0625 mg/kg) increased rate of responding throughout the six hour session, while the higher doses (.125, .25, and .5 mg/kg) produced an extinction-like pattern of responding (Figure 1). The extinction-like pattern was characterized by an initial increase in rate lasting about two hours, followed by marked suppression or complete cessation of responding. There was some tendency for larger initial increases to be associated with the higher doses, and, in



Effects of pimozide (.0625, .125, .25 and .5 mg/kg) on rate of barpressing for intravenous cocaine infusions. Data points represent medians of percentage of pre-injection baseline rates per half hour, at each dose. A mean pre-injection rate was calculated for each animal on the basis of the hour of stable responding prior to treatment injection. These pre-injection rates varied little within animals from day to day, and were typically between 6 and 8 responses per hour.

Figure 1

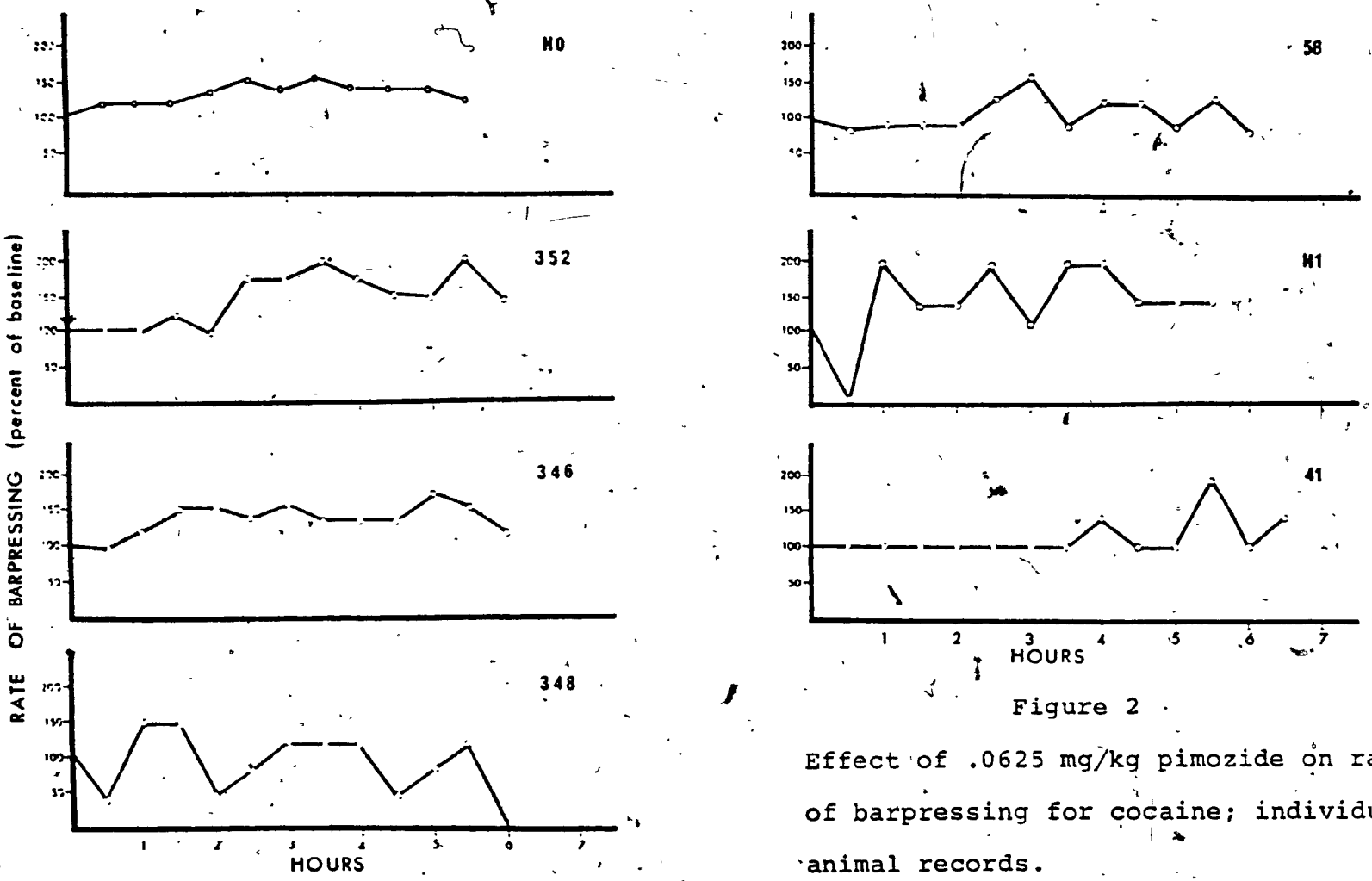


Figure 2

Effect of .0625 mg/kg pimozide on rate of barpressing for cocaine; individual animal records.

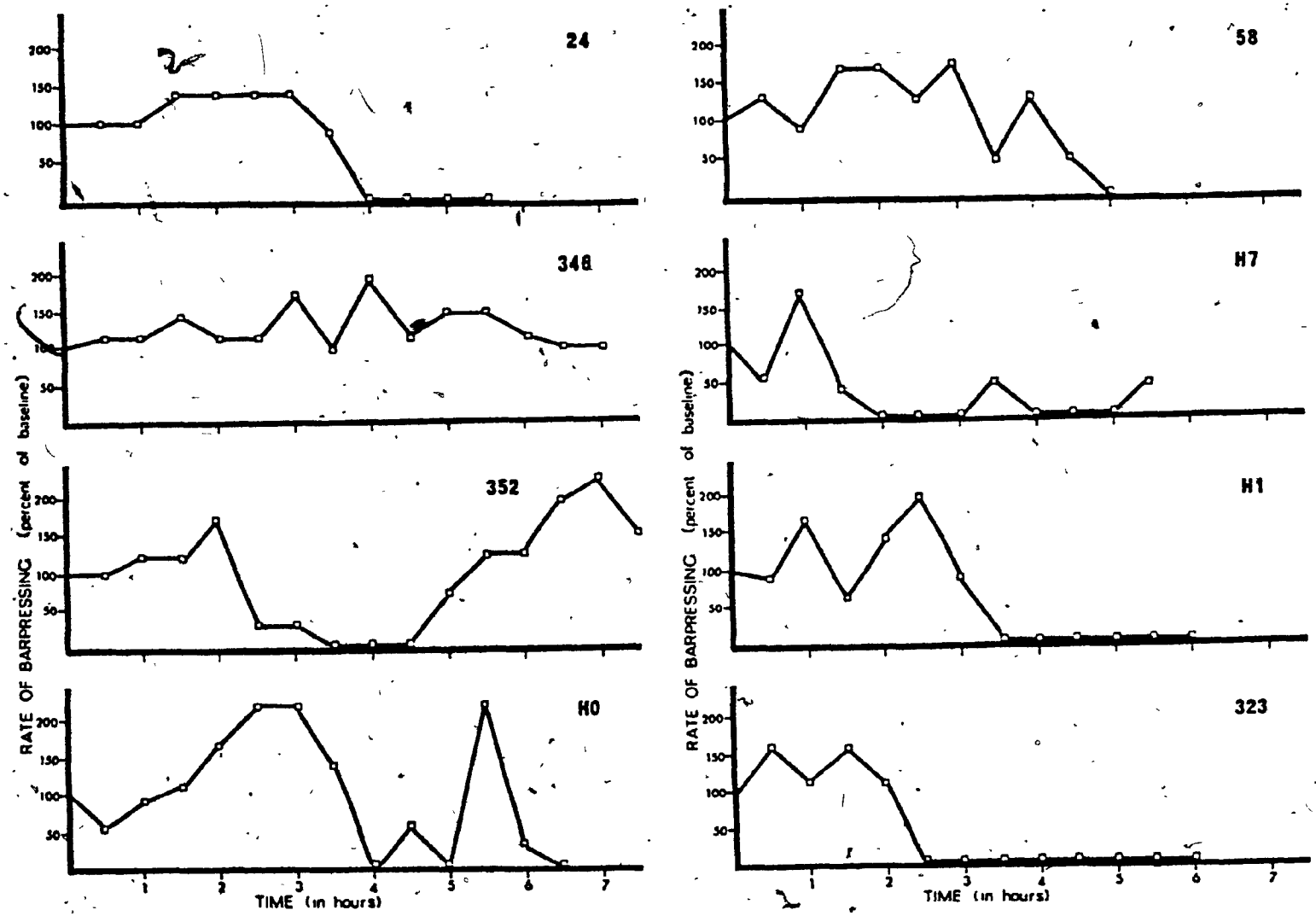


Figure 3
Effect of .125 mg/kg pimozide on rate of barpressing for cocaine; individual animal records.

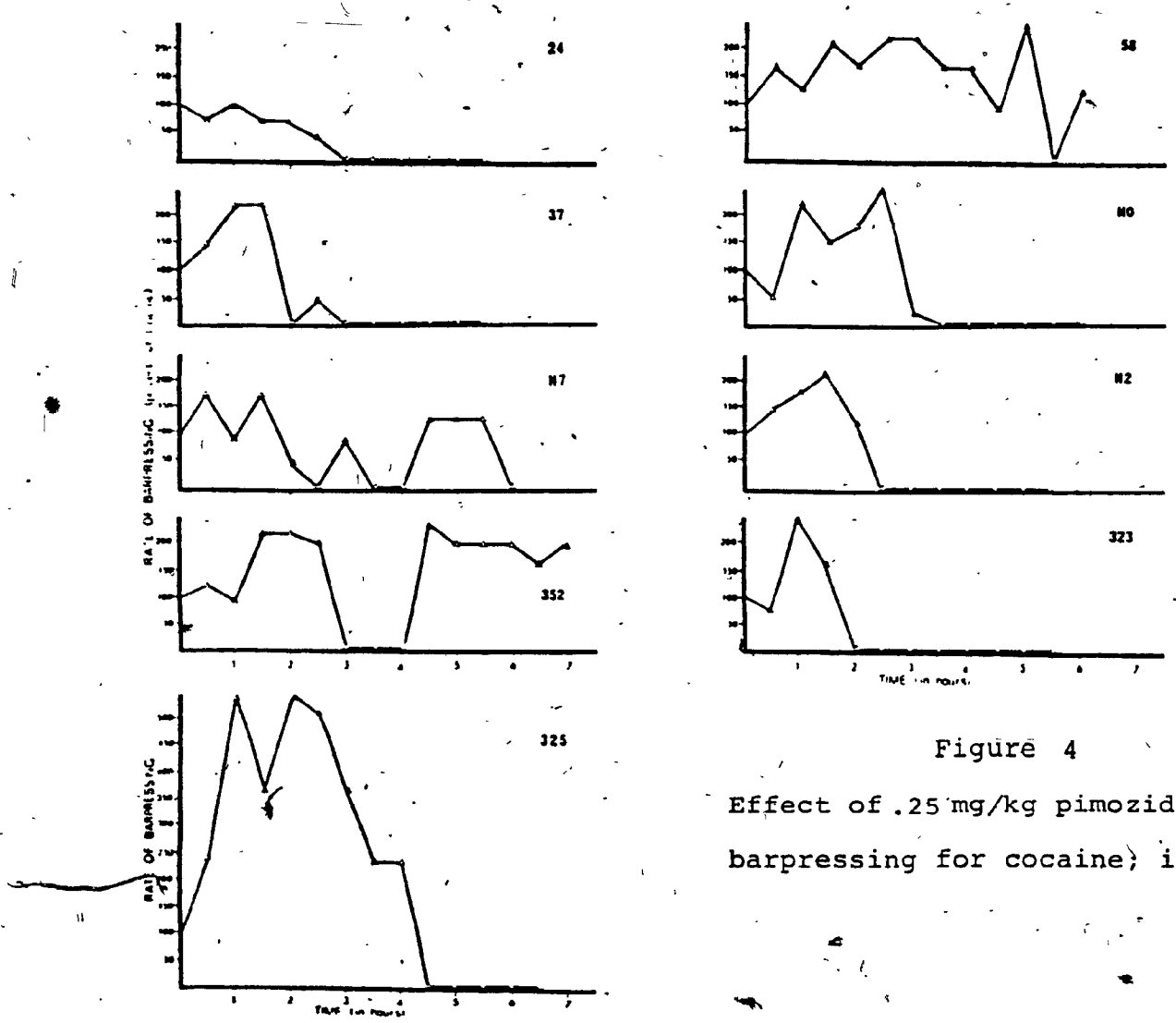


Figure 4

Effect of .25 mg/kg pimozide on rate of barpressing for cocaine; individual animal records.

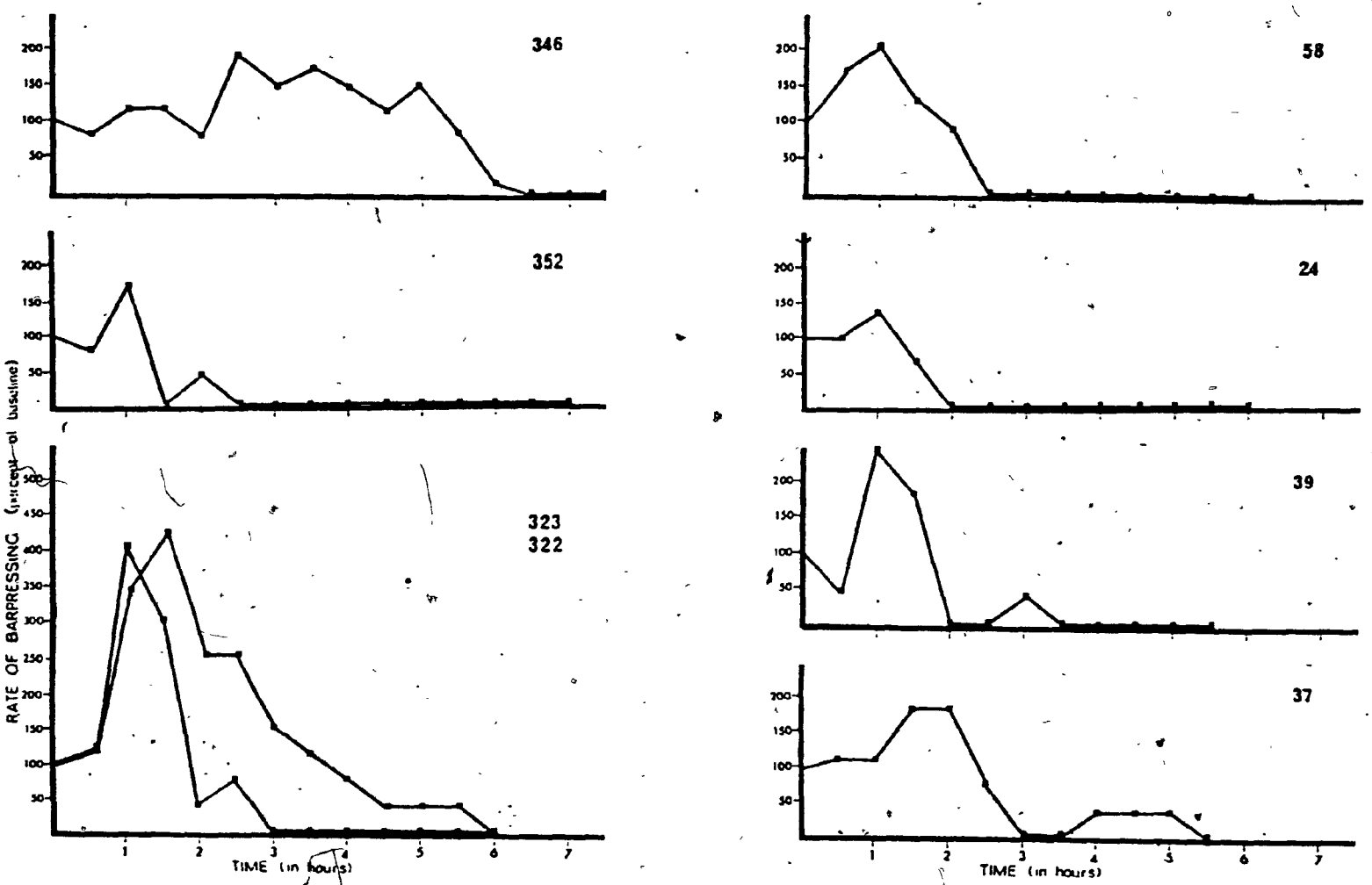


Figure 5

Effect of .5 mg/kg pimozide on rate of barpressing for cocaine; individual animal records.

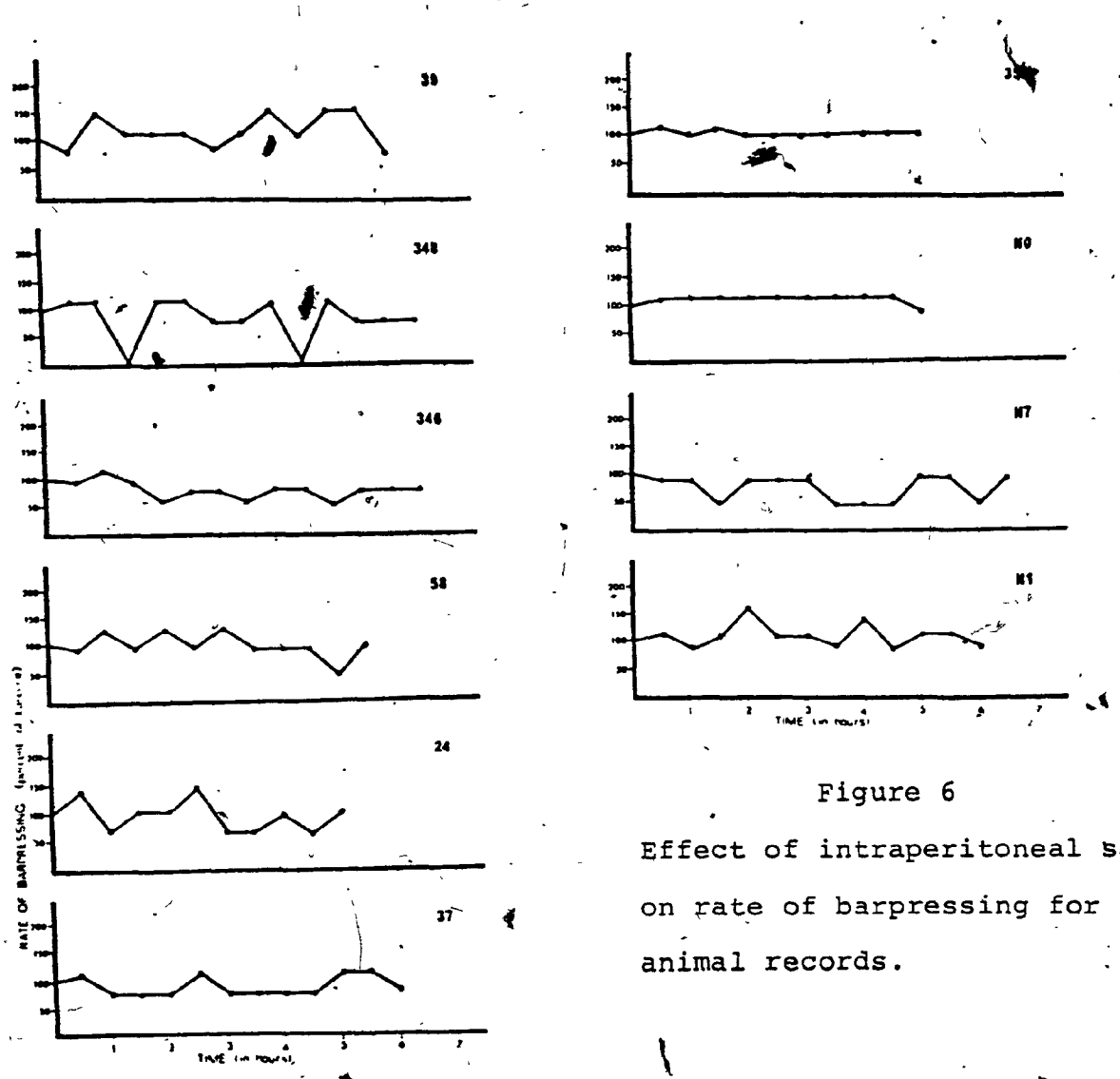


Figure 6

Effect of intraperitoneal saline injections on rate of barpressing for cocaine; individual animal records.

addition, the latency of onset of the pimozide effect decreased as the dose increased. Rate increases after the .0625 mg/kg dose did not peak until three hours after injection, whereas the peak effect for the two highest doses occurred within two hours after injection. The latency for the intermediate dose effect fell between these two. Rates for saline treated animals remained near the pre-injection baseline, decreasing only slightly over time.

The results from individual animals conform closely to those seen for the grouped data (Figures 2-6). At the smallest dose (.0625 mg/kg) only one of the seven animals failed to show a rate increase. Seven out of eight animals at the next highest dose (.125 mg/kg) showed the initial increase, and subsequent cessation of responding for at least one half hour. One animal (#348) showed only a slight increase and no reduction below baseline. Two of the rats which stopped responding subsequently recovered at rates which exceeded initial baseline rates. At the .25 mg/kg dose, eight out of the nine animals showed increased rates initially. Then all stopped responding for at least one half hour period; five animals ceased

responding altogether after the third hour. All animals tested at the .5 mg/kg dose stopped responding by the end of the session, and all showed an initial increase in rate. Individual animals differed in the magnitude of this increase. One animal (#348) at this dose continued to respond at an increased rate for 5 hours before responding stopped. It is interesting to note that this animal also showed an atypical pattern of responding when tested at .125 mg/kg.

Discussion

Low doses of the dopamine receptor blocker, pimozide, were seen to increase the rate of cocaine self-administration. Similar increases in rate of responding for cocaine have been reported when reward magnitude was reduced by lowering the dose of cocaine per injection (Pickens and Thompson, 1968). This similarity suggests that the higher rate obtained in the present experiment was caused by a reduction in reward value of the cocaine, brought about by the pimozide treatment. Such a reduction in reward after treatment with a dopamine blocking drug would support the hypothesis that the dopaminergic system of the brain is the primary substrate of cocaine's rewarding effect.

This interpretation is further supported by the findings with higher doses of pimozide. At the highest doses of pimozide, the rate of responding for cocaine increased initially, then dropped to zero. This pattern of responding is characteristic of extinction responding seen when reinforcement is withheld entirely, suggesting that maximal dopamine receptor blockade effectively blocks the reinforcing efficacy of cocaine. The extinction-like effect was most pronounced at the highest doses; the latency of onset of the increase was shorter, the magnitude of the increase was greater, and the cessation occurred sooner and was longer lasting at the .5 and .25 mg/kg doses than at the .125 mg/kg dose. These rapid extinction effects reflect reduced reinforcing efficacy and are consistent with the view that greater dopamine receptor blockade is associated with lower reward value.

These results agree generally with those of Yokel and Wise (1975), who studied the effect of dopamine receptor blockade on the reinforcing efficacy of amphetamine injection. They found increased rates of amphetamine self-administration at the lowest dose of

pimozide studied, and an extinction-like pattern after higher doses of pimozide. One notable difference between the present results for cocaine self-administration and those of Yokel and Wise for amphetamine self-administration is the time course and the severity of the disruptive effect of pimozide treatment on rate of self-administration. Maximal rate increases in cocaine self-administration occurred one hour after pimozide injection, while with amphetamine, peak response rates were reached four hours after injection. Furthermore, cocaine self-administration rates were eventually suppressed below baseline rate for all but the lowest dose of pimozide, while only the highest dose suppressed responding for amphetamine. Responding for cocaine seems to be disrupted more quickly and more severely than responding for amphetamine by the same dose of pimozide. This might in part be a function of the inter-response time differences between amphetamine and cocaine self-administration. Animals self-administering cocaine respond more frequently than do animals self-administering amphetamine. As a result they might experience reduced rewarding effects

sooner and more frequently after a pimozide injection than do animals self-administering amphetamine. It is unlikely, however, that this effect alone would account for the considerable differences in time course as large as those observed. The effectively non-reinforced responses should result in a rate increase within a few responses after pimozide had taken effect.

A more likely explanation for the difference in the course of effect is that cocaine-induced activation of the dopamine system is more easily disrupted by receptor blockade than amphetamine-induced activation because of some aspect of their dissimilar modes of action at the neuronal level. While amphetamine has its effect on the dopaminergic system by four possible different mechanisms (release of pre-synaptic transmitter substance, inhibition of MAO, inhibition of re-uptake, and possibly even direct stimulation of the receptors (Glowinski and Baldessarini, 1966; Stein, 1964; Carr and Moore, 1969; Randrupp and Munkvad, 1966) cocaine acts only by inhibiting re-uptake of transmitter into the pre-synaptic cell (Ross and Renyi, 1967). If amphetamine does act directly on the receptor,

as well as through these other mechanisms which all act to increase synaptic levels of transmitter, it seems reasonable to suppose that more receptor blocking substance might be needed to achieve the same effective blockade. Thus, responding for cocaine reinforcement might be more vulnerable to disruption by dopamine receptor blockade than amphetamine because of its single mechanism of stimulating the dopamine receptors.

The peaks of rate increases after pimozide (expressed as a percent of baseline response rate) were lower for cocaine self-administration than for amphetamine self-administration. The reason for this difference is not clear, although it may merely reflect the baseline rate differences in responding for the two drugs.

In spite of the differences in time course, dose-sensitivity and possibly magnitude of effect, the effects of pimozide on cocaine self-administration were essentially parallel to those reported for amphetamine self-administration, demonstrating an apparent attenuation of the reward value of stimulant drugs as a function of the extent of dopamine receptor blockade.

Experiment 2

Yokel and Wise (1975) found in their study with amphetamine self-administration that intraperitoneal injections of 2.5, 5, and 10 mg/kg of phentolamine, an alpha-noradrenergic receptor blocking agent, had only suppressant effects on responding, and produced no indications of attenuating the rewarding properties of amphetamine. However it is not clear that their treatment actually caused central noradrenergic blockade. Phentolamine is well-established as a peripheral alpha-noradrenergic receptor blocker (Nickerson and Hollenberg, 1967), but there is some reason to believe that it may not cross the blood-brain barrier. Andén and Strombom (1974) found that intraperitoneally administered phentolamine does not block the noradrenergically mediated flexor reflex in rats. Similarly, Kleinrok and Zebrowska-Lupina (1971) found that intravenous injections of phentolamine affect neither locomotor activity nor the excitatory effects of amphetamine. On the other hand, both of these behavioral effects were blocked

by phentolamine when it was administered intraventricularly (Kleinrok and Zebrowska-Lupina, 1971). Thus it is possible that phentolamine only exerts its blocking effect on central noradrenergic receptor sites when it is administered centrally. The failures to find a specific reward-blocking effect on self-administration after intraperitoneal injections of phentolamine (Yokel and Wise, 1975; Wilson and Schuster, 1974) may have been due only to inadequate distribution of the drug to the central nervous system. The present experiment tested this possibility by administering the phentolamine directly into the ventricle of the brain.

Method

Subjects. Eight male Wistar rats from Bio Breeding Laboratories, Ottawa, weighing between 400 and 550 grams were used in this experiment. All animals had been trained to barpress for 45 mg Noyes pellets in a separate apparatus before self-administration training, and none had participated in any other studies. Housing and deprivation conditions were as in Experiment 1.

Surgery. Animals were prepared with

catheters as described in Experiment 1; after self-administration training they were re-anaesthetized and stereotaxically implanted with intraventricular cannulae (Kreig co-ordinates: 1.4 mm posterior to Bregma; 3.6 mm ventral to the surface of the skull; and 3.2 mm lateral to the midline). As before, rats were not allowed access to cocaine until two days after surgery and then only if their weight was at least at pre-operative level.

Apparatus. The apparatus was as described for Experiment 1.

Procedure. The initial training to self-administer cocaine was carried out in the same way as in Experiment 1. Animals reaching stable rates were then prepared with the intraventricular cannulae. Stable rates of self-administration of cocaine were then re-established during at least one six-hour session. In the subsequent experimental test sessions animals received, after one hour of stable responding, 10-second intraventricular injections of either 50, 75, or 100 µg phentolamine HCl dissolved in 10 µl of Ringer's solution or the Ringer's solution alone. The order of the doses administered

differed from animal to animal. Six animals were tested at each dose. Phentolamine injections were always separated by at least 48 hours.

Results

Treatment with phentolamine resulted in a pattern of responding which was variable but consistently depressed below that of saline controls (Figure 7). variability in grouped data for the three doses of phentolamine reflects inconsistencies between animals as well as a tendency for the treatment to produce irregular responding within animals. In spite of these fluctuations in rate, there were few instances of increases in rate over baseline levels, or over the rates observed after saline treatment. The suppressant effect of the three doses of phentolamine appeared to be to some extent dose related.

Individual records show that after saline treatment animals maintained rates close to baseline (Figure 8). After the 50 µg dose of phentolamine four out of five animals showed no consistent deviation from baseline rate; only one animal (#39) showed a clearly decreased rate (Figure 9).

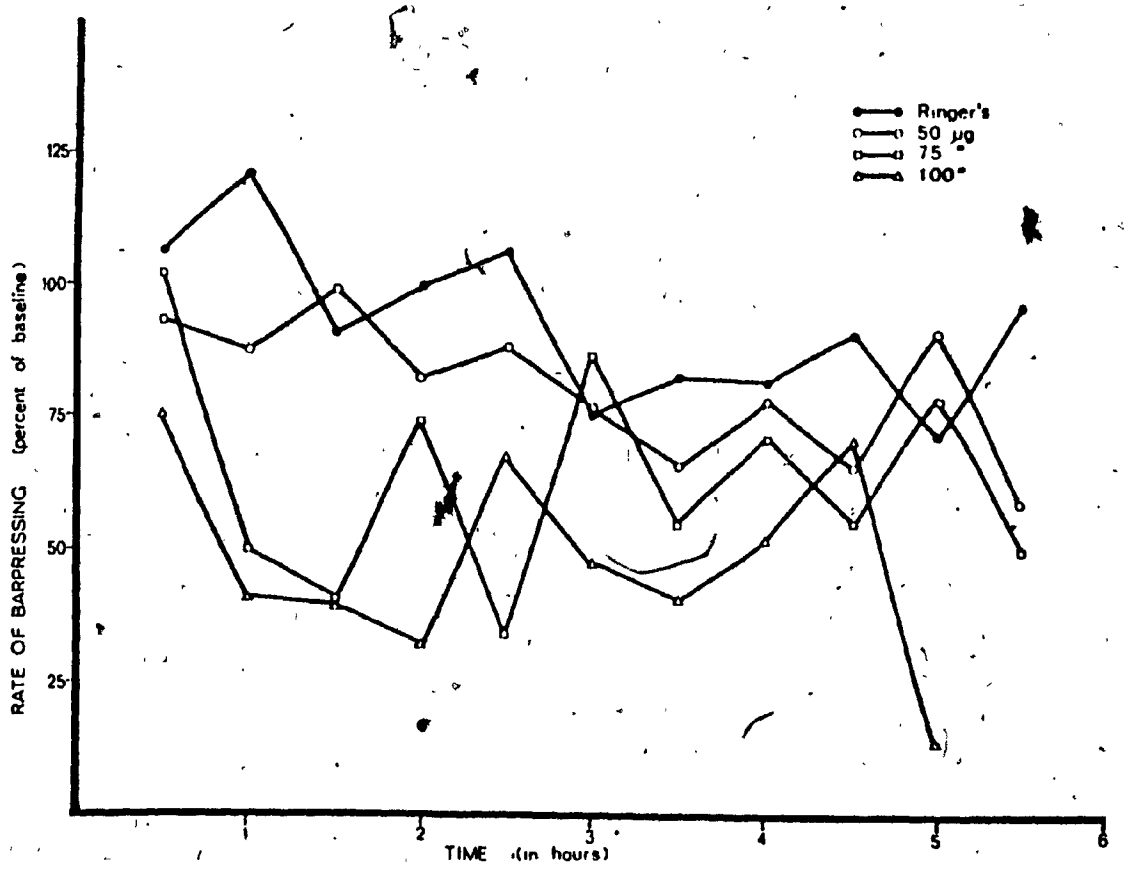


Figure 7

Effects of centrally injected phentolamine (50, 75, and 100 µg) on rate of barpressing for intravenous cocaine infusions. Data points represent medians of percentage of pre-injection baseline rates per half hour, at each dose.

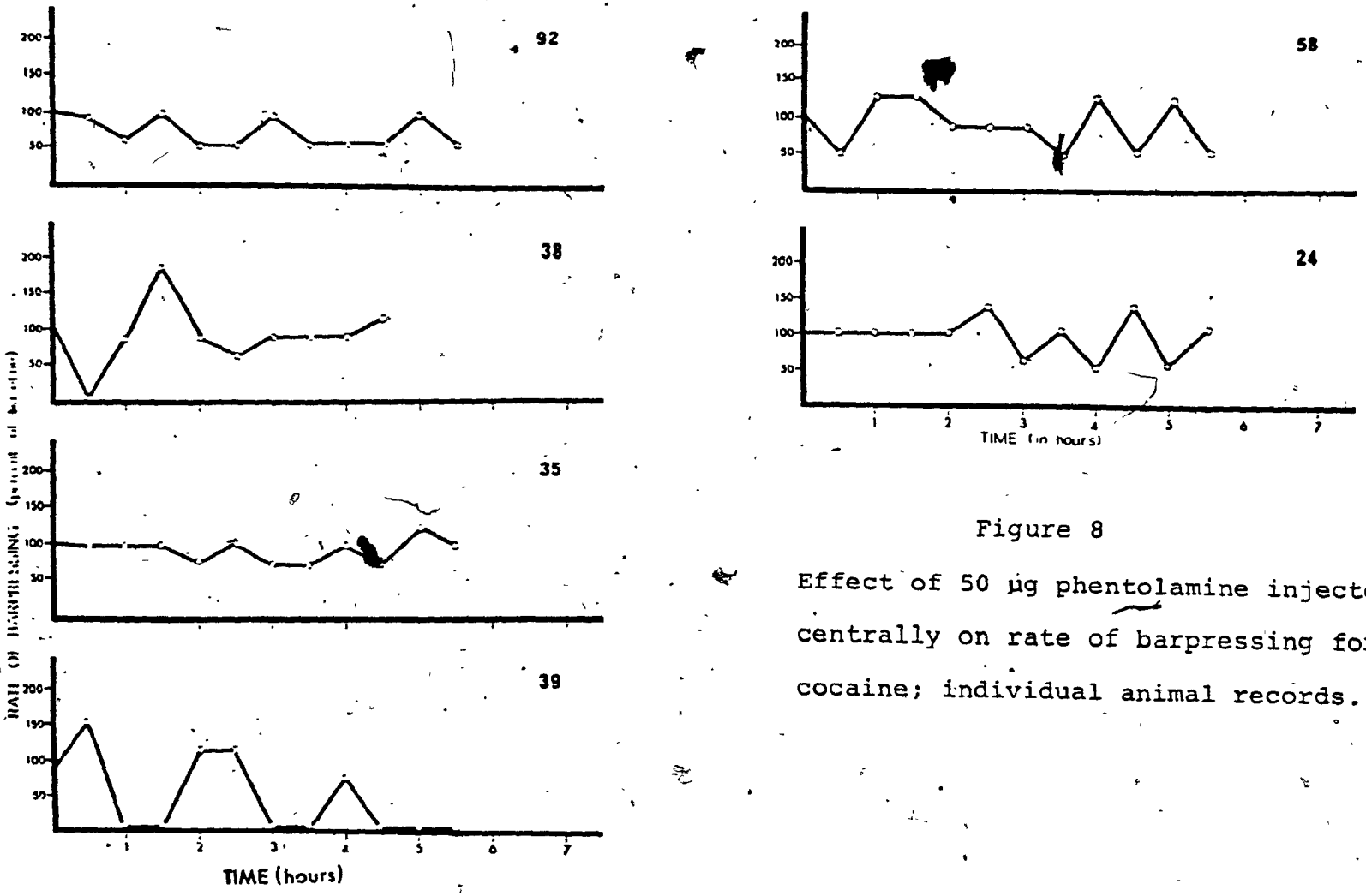


Figure 8

Effect of 50 µg phentolamine injected centrally on rate of barpressing for cocaine; individual animal records.

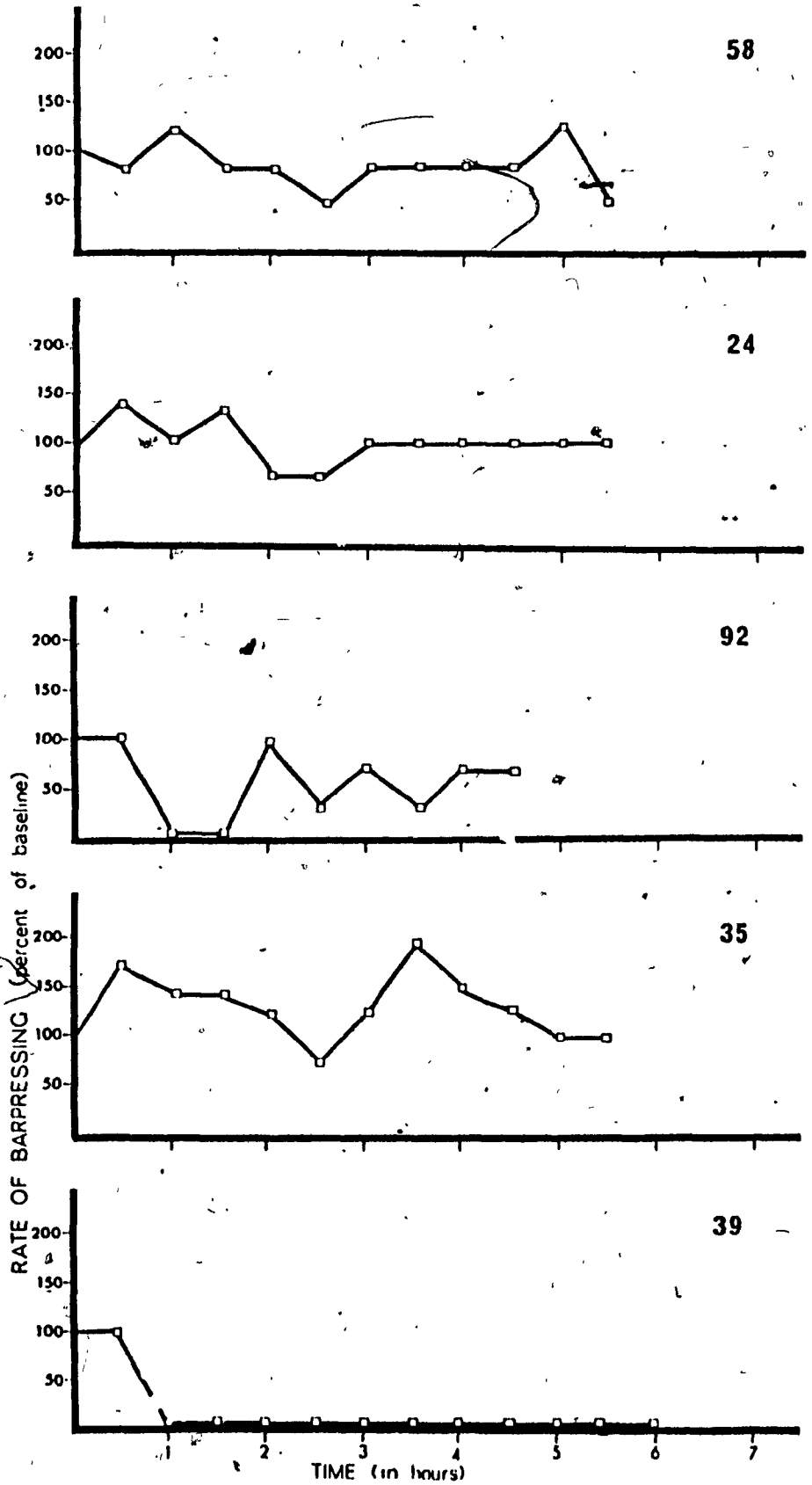
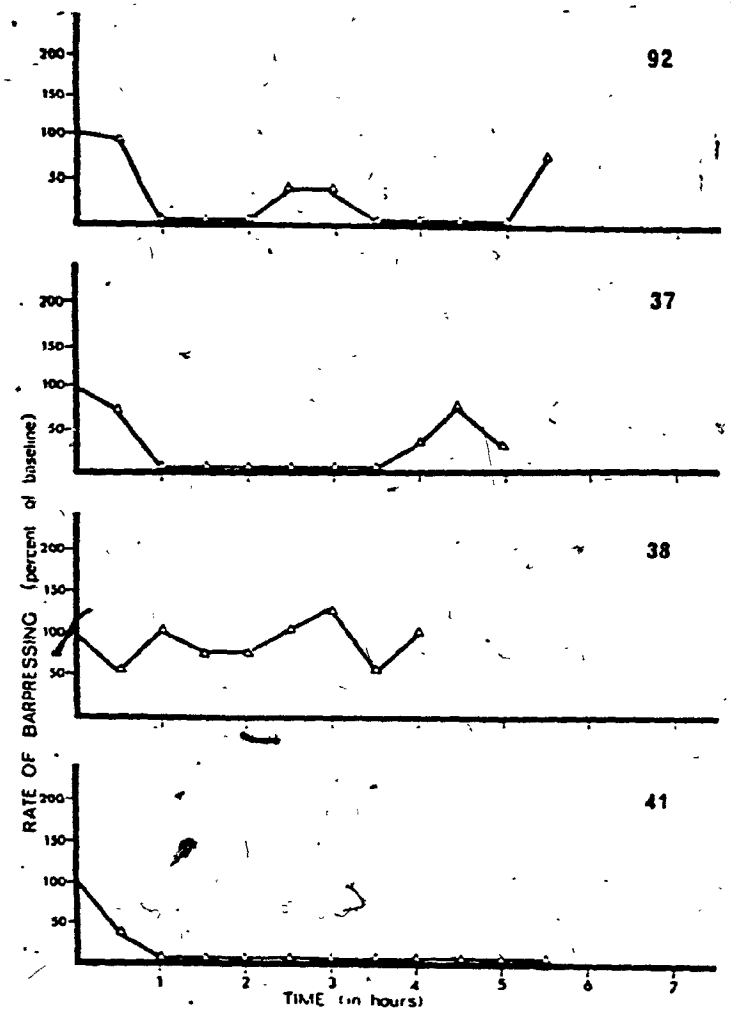


Figure 9

Effect of 75 µg phentolamine injected centrally on rate of barpressing for cocaine; individual animal records.



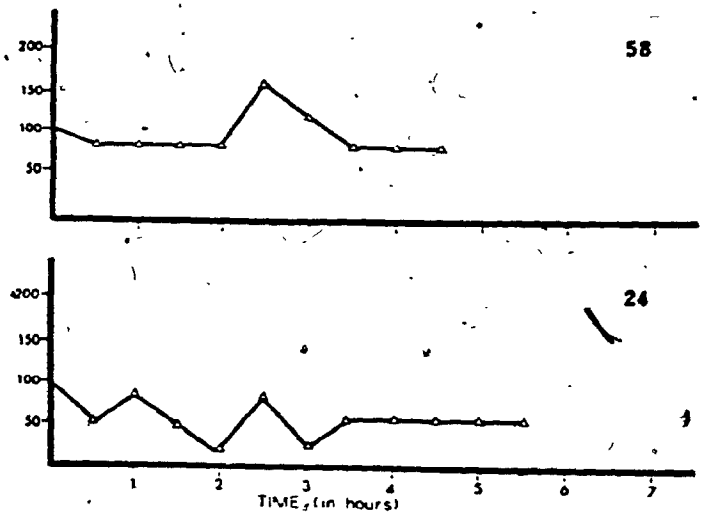
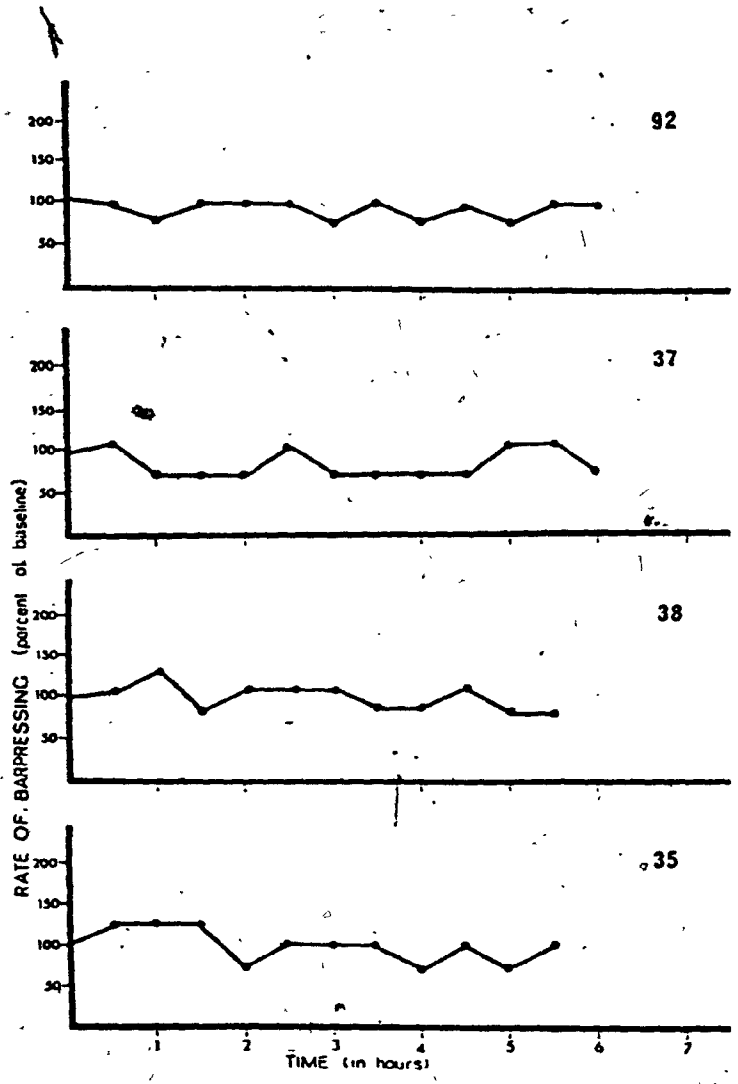


Figure 10

Effect of 100 µg phentolamine injected centrally on rate of barpressing for cocaine; individual animal records.



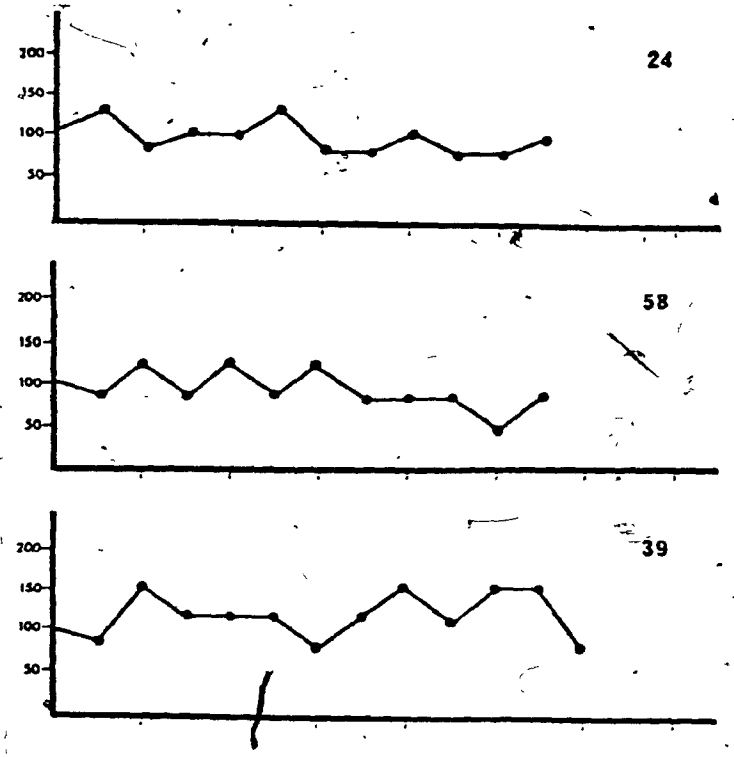


Figure 11

Effect of Ringer's solution injected centrally on rate of barpressing for cocaine; individual animal records.

At 75 µg, results were inconsistent. Two animals (#58, #24) remained relatively unaffected, one (#39) showed total suppression from the first hour, and one each showed decreased (#H92) and increased (#35) responding throughout the six-hour session (Figure 10). At the 100 µg dose three animals showed distinct suppression and three remained at normal or very slightly below normal rates (Figure 11).

A slight sedative effect was noted at high doses of phentolamine.

Discussion

Central injections of phentolamine resulted in reduced rates of cocaine self-administration. A dose-dependent decrease was observed which began within one half hour of injection and continued throughout the five-hour session; rate was halved at the highest dose and smaller doses reduced rates to a lesser extent. Similar results were found by Yokel and Wise (1975) when the effects of intraperitoneal injections of phentolamine were studied in the amphetamine self-administration paradigm. In the present

study there was considerable variability between animals in their response to phentolamine treatment, but compared to the effects of equivalent volumes of Ringer's solution the drug depressed responding.

It has been observed and argued above that when animals are self-administering drugs, a reduction in the magnitude or in efficacy of the reward should result in an increase in rate of responding. Intraventricular injections of phentolamine, believed to block central noradrenergic receptors, did not increase the rate of self-administration. Thus it would appear that this treatment did not specifically reduce the reward value of cocaine injections.

The decrease in rate of self-administration observed after phentolamine could have resulted from some general disrupting, or debilitating behavioral effects of the drug such as sedation brought about by central noradrenergic blockade. On the other hand it might be argued that the decreased rate of self-administration was caused by an enhancement of coaine's rewarding effects brought about by some action of the phentolamine. Human subjects have reported

enhanced amphetamine euphoria after the alpha-noradrenergic blocker phenoxybenzamine (Gunne, Anggard, and Jonsson, 1972), and Pickens and Thompson (1968) have shown that increases in reward magnitude decrease the rate of self-administration. It is conceivable that a direct or indirect effect of alpha-noradrenergic blockade or some other effect of phentolamine, could potentiate the reward value of cocaine injections. Vasodilation, an effect of peripheral alpha-noradrenergic receptor blockade (Goth, 1972, pg. 146) could, for example, allow more cocaine to be absorbed from the blood to exert a greater effect. Another possibility is that phentolamine simply slows the metabolism of the cocaine, thereby prolonging the effect of each cocaine injection. However, either reward enhancement interpretation of the rate decreases is speculative; one would want to eliminate all other possible causes of performance disruptions before concluding that reward potentiation was the source of the rate decrease.

A number of technical questions can be raised regarding the efficacy and site of action

of the alpha-noradrenergic blockade by central phentolamine injections in this experiment. Of the four animals for which cannula placements were determined, three were found to have cannula tips just lateral to the ventricle. In spite of this it is likely that most of the 10 ul volume of solution injected so near the ventricular wall actually diffused into the ventricle (Myers, 1974, pg. 74). The fact that some of the drug solution may have been injected into brain tissue is probably not critical because, even with well-placed intraventricular cannulae, some fluid is thought to reach brain tissue directly by seeping up along the cannula shaft (Myers, 1974, pg. 9). Several of the animals were given an intraventricular carbachol injection drinking test to verify cannulae placements. All animals tested responded positively by commencing to drink within 5 seconds of injection. It is possible that the variability in cannula placements accounts for some of the variability in the data, but this possibility is not verifiable due to incomplete histological data. In spite of these problems, the reduction in rate of self-administration observed after phentolamine injections, and not after control

injections, indicates that the injections were effective; only the exact dose and the exact locus of action cannot be determined.

The present study again failed to produce evidence for involvement of noradrenergic mechanisms in stimulant self-administration. Two recent experiments using a different alpha-noradrenergic receptor blocking agent produced similar results. In the first, phenoxybenzamine, an alpha-noradrenergic receptor blocking agent which does cross the blood-brain barrier (Andén and Strombom, 1974) was administered intraperitoneally in doses of 2.5, 5, and 10 mg/kg to rats self-administering amphetamine (Yokel and Wise, in press). There was no effect on rate of self-administration. In the second, Wilson and Schuster (1974) reported that phenoxybenzamine had no effect on rate of responding when given to rhesus monkeys self-administering cocaine. These findings taken with the present data, suggest that alpha-noradrenergic receptor blockade, central or peripheral, does not affect either stimulant reward efficacy or self-administration performance, and that the reductions in rate of self-administration of cocaine

and amphetamine seen after phentolamine treatment were the effect of some other action of this drug.

General Discussion

The results reported in this study of the effects of dopaminergic and noradrenergic receptor blocking drugs (pimozide and phentolamine) on cocaine self-administration agree with the results of Yokel and Wise (1975) with amphetamine self-administration. In both studies dopaminergic but not noradrenergic treatments resulted in response rate changes suggestive of an attenuation of the reward value of the self-administered drugs. This demonstration of dopaminergic involvement in stimulant drug reward provides an interesting parallel to recent findings implicating dopamine as a critical neurotransmitter in the mediation of brain stimulation reward. It is possible that both electrical brain stimulation and stimulant drugs have their rewarding effects via the same neurochemical system.

Some question has been raised regarding the specificity of the dopamine receptor blocking drug used in this and in Yokel and Wise's (1975) study. Evidence that pimozide acts not only on the dopaminergic system but possibly also on the noradrenergic system comes from a study by Blumberg, Taylor, and Sulser (1975). They found

that pimozide also inhibited the accumulation of noradrenaline-induced cyclic AMP in limbic forebrain tissue, using an in vitro preparation. It is not clear, however, whether the concentrations of pimozide which were effective on the isolated tissue are comparable to those effective in behavioral studies such as the present one, where the drug is distributed physiologically from the intraperitoneal cavity to the intended receptors. Although the concentration of the fluid injected intraperitoneally was within the range found to have an effect on noradrenaline-sensitive adenylate cyclase (.5 mg/kg/ml Ξ 10^{-7}M), it seems likely that the concentration actually reaching receptors in the central nervous system was significantly lower than this due to diffusion through the system and metabolic breakdown of the drug. Andén, Butcher, Corrodi, Fuxe, and Ungerstedt (1970) in their original investigation into the specificity of action of pimozide also reported an increase in turnover of noradrenaline, but only at doses 5 to 10 times greater than those needed to affect dopaminergic turnover. Although such biochemical data are essential in the determination of the actions of a particular drug,

of primary significance in the selection of a drug for behavioral tests are the data derived from other behavioral studies. Pimozide has been shown to block dopaminergically mediated behavioral responses while having little effect on noradrenergically mediated responses. Andén et al (1970) showed that pimozide at doses as low as .1 mg/kg blocks the turning response seen in animals with unilateral corpus striatum lesions, a response which is believed to be mediated by dopaminergic neurons on the intact side. These researchers found that doses of pimozide as high as 25 mg/kg were ineffective in blocking the noradrenergically-mediated flexor response induced by l-dopa. More recently, Settler (personal communication to R.A. Wise) found a similar absence of blocking effect of pimozide (until about 5 mg/kg). on a noradrenergically mediated flexor reflex. Furthermore, pimozide at .5 mg/kg has been shown to block behavioral effects of the dopamine agonist apomorphine (stereotypy (Janssen, Niemegeers, Schellekens, Dresse, Lenaerts, Pinchard, Schaper, Van Nueten, and Verbruggen, 1968) as well as its reinforcing effects (Baxter, Gluckman, Stein, and Scerni, 1974). For these reasons, it seems unlikely that the effects of pimozide on rate of cocaine self-administration were the

result of its effect on the noradrenergic system, but rather of its blocking effect on dopaminergic receptors.

The use of drug self-administration as a baseline behavior upon which to test the effect of possible reward-blocking drug treatments has proven to be a valuable technique in the study of neurochemical substrates of reward. There are general limitations of the technique, however, which must be considered in the interpretation of the results. There exist situations in which reward attenuation does not result in increased rates of self-administration, as in the case of very small injection doses, and there are also instances of increases in rate of responding which are not due to reward deficits.

At very small injection doses, which maintain blood level of drug below a satiating level, the relationship between rate of responding for drug and reward magnitude appears to be not inverse, but rather direct as it is with other reinforcers such as sucrose solution (Guttman, 1953). In such cases, response rate increases as a function of reward magnitude. Two recent studies have reported such an effect. Goldberg and Kelleher

(1976) showed that for doses of cocaine between 12 and 100 micrograms per kilogram per injection, the rate of barpressing in monkeys increases as a function of dose per injection on fixed ratio and fixed interval schedules. Llewellyn, Iglauer, and Woods (1976) reported that monkeys responding for doses of cocaine between .013 and .8 milligrams per kilogram per injection on a two-lever concurrent VI-1 VI-1 schedule also showed higher response rates for the higher dose. Thus, at these doses and on these schedules a decrease in reward magnitude or efficacy would be expected to decrease rather than increase response rates.

Several non reward-related effects of treatment drugs might also increase the rate of self-administration, in a manner indistinguishable from the effect of reward attenuation. As mentioned earlier, a drug which increases the rate of metabolism of the self-administered drug could increase the rate of responding by shortening the duration of effect of each drug injection (Dougherty and Pickens, 1974). With respect to the present study, pimozide has been shown not to increase the rate of metabolism of another stimulant, amphetamine (Soudijn and

Wijngaarten, 1972), but the possibility that it does alter cocaine metabolism should be tested.

Response rate might also be increased by a treatment which facilitates ongoing behaviors. Wilson and Schuster (1973a) reported that a centrally acting anti-cholinergic drug, atropine, resulted in increased rates of self-administration of cocaine in monkeys, and suggested that this effect may have been due to the release of a behaviorally inhibitory (cholinergic) mechanism. They argued that since other stimulant drug effects are not antagonized by anti-cholinergic agents, it is unlikely that the rewarding effect of cocaine was antagonized. They suggested that the atropine caused the increase in rate of responding for the drug just as it increases the frequency of any ongoing behavior.

Finally, another way in which self-administration rate might increase independently of reward value was also suggested by Wilson and Schuster (1973a) and involves the removal by

the treatment drug of possible aversive or debilitating effects of the self-administered drug. Although in a choice situation animals show no preference for smaller (presumably less aversive) doses (Yokel, 1975; Iglauer, 1973) the possibility remains that some combination of the rewarding, satiating, and aversive effects of each infusion controls the pattern of individual responses, and that an alteration of any of these might affect the rate of responding.

The above observations point to general limitations on the usefulness of rate as a measure of stimulant reward efficacy, and do not, in my view, present a serious problem for the present study. The complementary findings of increased rate at low doses, and extinction-like response pattern at higher doses strongly suggest that reward attenuation is the best interpretation of the present results. None of the above alternative explanations alone could adequately account for both these effects. The general problem of interpretation of rate measures does argue for a more serious consideration of alternative measures of reward value of stimulants such as the two used by Davis and Smith (1973).

In their first paradigm, non-response-contingent pairings of a buzzer and an intravenous infusion of a drug such as morphine or amphetamine are presented to animals, with or without pre-treatment with a putative reward blocking drug. On a subsequent test day, the effectiveness of the buzzer as a secondary reinforcer is determined by the extent to which it will establish and maintain operant responding for the buzzer alone. This technique has the advantage that the animals are tested for the effect of treatment drugs in a non-drug state, so that measurements on the test day are not contaminated with drug effects which might directly affect some aspect of performance not related to reward efficacy. In their second experimental paradigm, animals are first trained to lever press for drug infusion, then extinguished by replacing the drug with saline, then the re-acquisition of drug self-administration is tested under a treatment drug condition. Animals should not re-acquire the response if the treatment drug is blocking the rewarding aspect of the self-administered drug. This experimental design circumvents some of the problems with changes in rate of ongoing behavior, and tests for an

important indicator of reinforcer efficacy, that is its ability to establish a response. The Smith and Davis paradigms also have their own particular problems of interpretation. It is possible that non reward-related effects of a drug treatment such as general malaise might also interfere with the establishment of a conditioned reinforcer in the classical paradigm, or inhibit the reinstatement of responding in the re-acquisition paradigm. Some more specific aspects of the Davis and Smith paradigm also require further investigation. For example, at the very low dose range typically used, it is not clear whether increased responding during re-acquisition after a drug treatment indicates attenuation or enhancement of reward value. Conclusions about the neurochemical basis of stimulant reward using pharmacological treatments should be based on results from more than one experimental paradigm to rule out artifactual results such as those due to non reward-related effects of the treatment drugs.

It is interesting to note that the results obtained from human studies carried out to date agree in general with the results obtained with self-administration in laboratory animals.

Drugs which interfere with catecholamine function (AMPT), and with dopamine in particular (pimozide), are reported to reduce the euphoric effects of amphetamine in human users. Interestingly, the noradrenergic blocking agent phenoxybenzamine was found to slightly enhance amphetamine euphoria (Gunne, Anggard, and Jonsson, 1972). Subjective ratings and verbal reports might provide a useful alternative source of information regarding the reward-specific effects of catecholamine blocking agents.

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APPENDIX A

Raw Data For Experiment 1

.0625 mg/kg Pimozide

NUMBER OF BARPRESSES PER HALF HOUR

Hours From Treatment Injection

Animal	-2.5	-2	-1.5	-1	-.5	0	.5	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5
58	2	2	2	2		2	2	2	2	3	4	2	3	3	2	3	2	2		
HØ	4	3	4	3		4	4	4	5	6	5	6	5	5	5	4				
352		6	4	4		4	4	5	4	7	7	8	7	6	6	8	6			
346			6	4		5	6	8	8	7	8	7	7	7	9	8	6			
348		3	3	4		1	4	4	1	2	3	3	3	1	2	3	0	0		
H1	3	4	4	4		0	7	5	5	4	4	7	7	5	5	5				
41	3	3	3	4	2	3	3	3	3	3	3	3	4	3	3	6	3	4	3	

.125 mg/kg Pimozide

NUMBER OF BARPRESSES PER HALF HOUR

Hours From Treatment Injection

Animal	-2.5	-2	-1.5	-1	-.5	0	.5	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5
58		2	3	2	2	3	2	4	4	3	4	1	3	1	0	0	0			
24		3	3	3	2	3	3	4	4	4	4	2	0	0	0	0				
346		6	5	6	3	6	6	7	6	6	9	5	10	6	7	7	6	5	5	
352		3	4	4	4	4	5	5	7	1	1	0	0	0	3	5	5	8	9	
HØ		2	4	2	3	2	3	4	6	8	8	5	0	2	0	8	1	0	0	
H7				3	3	1	4	1	0	0	0	1	0	0	0	1	0	0		
H1		2	5	2	3	3	6	2	5	7	3	0	0	0	0	0	0	0		
323				3	3	4	3	4	3	0	0	0	0	0	0	0	0	0		

.25 mg/kg Pimozide

NUMBER OF BARPRESSES PER HALF HOUR

Hours From Treatment Injection

Animal	-2.5	-2	-1.5	-1	-.5	0	.5	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5
58				2	3		4	3	5	4	5	5	4	4	2	6	0	3	1	
24			4	4	3		2	3	2	2	1	0	0	0	0	0	0	0	0	
37			3	3	3		4	6	6	0	1	0	0	0	0	0	0	0	0	
H7			2	2	2		3	2	3	1	0	2	0	0	3	3	3	0	0	
352		4	5	3	5		5	4	9	9	8	0	0	0	12	8	8	8	7	
Hø	3	4	2	3	4		2	8	5	6	9	1	0	0	0	0	0	0	0	
H2	4	4	3	3	2		4	5	6	4	0	0	0	0	0	0	0	0	0	
325			1	2	1		5	12	8	13	11	8	5	5	0	0	0	0	0	

.5 mg/kg Pimozide

NUMBER OF BARPRESSES PER HALF HOUR

Hours From Treatment Injection

Animal	-2.5	-2	-1.5	-1	-.5	0	.5	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5
58			3	3	3	4	5	3	2	0	0	0	0	0	0	0	0	0	0	0
24			2	3	3	3	4	2	0	0	0	0	0	0	0	0	0	0	0	0
323				2	2	3	9	11	7	7	4	3	2	1	1	1	0	0	0	
39				4	2	1	8	5	0	0	1	0	0	0	0	0	0	0	0	
37			3	3	2	3	3	5	5	2	0	0	1	1	1	0	0	0	0	
322			3	3	2	3	11	8	1	2	0	0	0	0	0	0	0	0	0	
346				4	5	4	6	6	4	0	10	8	9	8	6	8	5	1	0	
352				5	6	3	7	0	2	0	0	0	0	0	0	0	0	0	0	

SALINE

NUMBER OF BARPRESSES PER HALF HOUR

Hours From Treatment Injection

Animal	-2.5	-2	-1.5	-1	-.5	0	.5	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5
346			7	6	7		5	6	5	3	4	4	3	4	4	3	4	4	4	6
352	4	3	6	4	2		4	3	4	3	3	3	3	3	3	3	2			
Hø				4	4		4	4	4	4	4	4	4	4	4	3				
H7				2	3		2	2	1	2	2	2	1	1	1	2	2	1	2	3
H1				3	4		4	3	4	6	4	4	3	5	3	4	4	3	4	5
58		4	2	3	3		2	3	2	3	2	3	2	2	2	1	1	2	2	1
24		3	3	3	3		4	2	3	3	4	2	2	3	2	2	3	2	3	
37			4	2	3		3	2	2	2	3	2	2	2	2	0	3	3	2	4
39				3	3		2	4	3	3	3	2	3	4	3	4	4	2		
348	4	1	2	1	4		3	3	0	3	3	2	2	3	0	3	2	2	2	2

APPENDIX B

Raw Data For Experiment 2

50 µg Phentolamine

NUMBER OF BARPRESSES PER HALF HOUR

Hours From Treatment Injection

Animal	-2.5	-2	-1.5	-1	-.5	0	.5	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5
58		3	2	2	2		1	3	3	2	2	2	1	3	1	3	1			
24		3	3	4	2		3	3	3	3	4	2	3	2	4	2	3			
H92		4	4	2	3		3	2	3	2	2	3	2	2	2	3	2			
35		5	4	4	3		4	4	4	3	4	3	3	4	3	5	4	4		
39				3	2		4	0	0	3	3	0	0	2	0	0	0	0		
38			4	4	4		0	3	7	3	2	3	3	3	4	3				

75 µg Phentolamine

NUMBER OF BARPRESSES PER HALF HOUR

Hours From Treatment Injection

Animal	-2.5	-2	-1.5	-1	-.5	0	.5	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5
35			6	6	4	7	6	6	5	3	5	7	6	5	4	4	4	3		
39	3	3	4	4	2	3	0	0	0	0	0	0	0	0	0	0	0	0		
58		2	2	3	1	2	3	2	2	1	2	2	2	2	3	1				
24		4	3	3	2	4	3	4	2	2	3	3	3	3	3	3	3			
H92		4	3	3	3	3	0	0	3	1	3	1	2	1	2	2	1			
37			3	3	3	0	0	0	0	0	0	0	0	0	0	0	0			

100 µg Phentolamine

NUMBER OF BARPRESSES PER HALF HOUR

Hours From Treatment Injection

Animal	-2.5	-2	-1.5	-1	-.5	0	.5	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5
58		3	2	3	3		2	2	2	2	4	3	2	2	2					
24		3	2	3	3		3	4	3	2	4	2	3	3	3	3	3			
H92		4	4	3	4		3	0	0	0	1	1	0	0	0	0	2			
38		5	4	3	4		2	4	3	3	4	5	2	4						
37		3	4	2	4		2	0	0	0	0	0	0	1	2	1	7	4		
41	4	4	4	3	3		1	0	0	0	0	0	0	0	0	0				

Intraventricular Saline

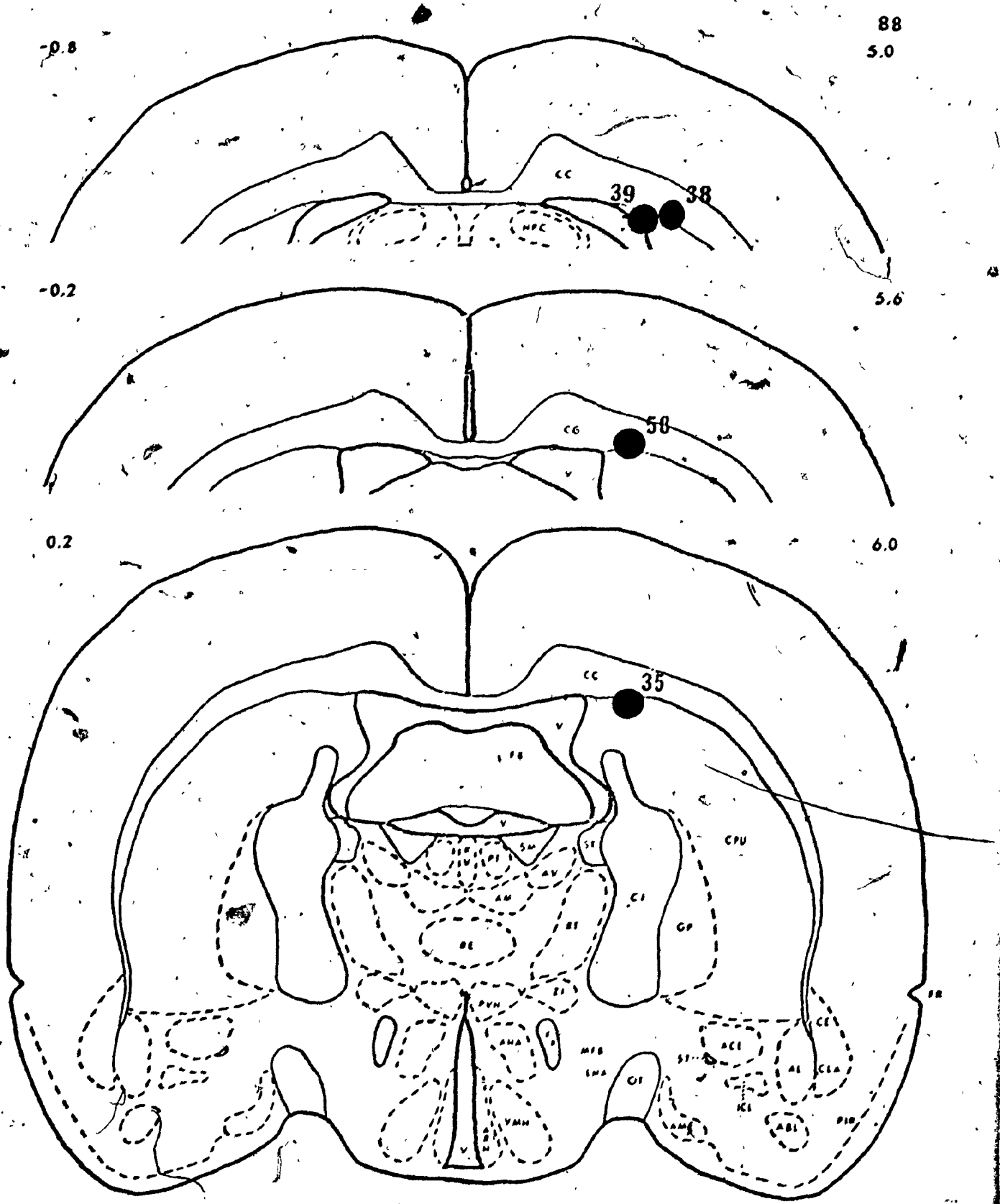
NUMBER OF BARPRESSES PER HALF HOUR

Hours From Treatment Injection

Animal	-2.5	-2	-1.5	-1	-.5	0	.5	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5
58		4	2	3	3		2	3	2	3	2	3	2	2	2	1	2	2	1	2
24		3	3	3	3		4	2	3	3	4	2	2	3	2	2	3	2	3	
H92	3	3	3	4	3		3	2	3	3	3	2	3							
37			4	2	3		3	2	2	2	3	2	2	2	2	3	3	2	4	
38				3	3		4	5	3	4	4	4	3	3	4	3	3	5		
35			6	4	4		5	5	5	3	4	4	4	3	4	3	4	4		
39				3	3		2	4	3	3	3	2	3	4	3	4	4	2		

APPENDIX C

Cannula Placements for Experiment 2


88
-0.8
5.0
CC
39
38
HPC
-0.2
5.6
CG
50
0.2
6.0
CC
35
V
LV
CPU
SM
SF
AM
AV
CI
GP
BE
BI
PVN
AHA
MFB
LHA
OT
VMH
ACI
AI
CLA
ICJ
ABL
PIR