PIPRADROL ENHANCES THE EFFECT OF CONDITIONED STIMULI ON BEHAVIOUR

by

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B.A., The University of Cambridge, 1978

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF ARTS

in

THE FACULTY OF GRADUATE STUDIES

(Department of Psychology)

We accept this thesis as conforming

to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

May 1980

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ABSTRACT

This thesis examined the effects of the stimulant drug pipradrol on operant responding in the presence of stimuli paired previously with food or shock. The first series of studies replicated previous findings of enhanced acquisition of responding with conditioned reinforcement after treatment with pipradrol, using a different test paradigm. The experiment began with a pre-exposure phase to determine the operant rate of pressing two levers, one of which produced a three second tone; during a conditioning phase, the same three second tone was paired with the delivery of food pellets; in a final test phase, the rates of pressing the two levers were determined again. Conditioned reinforcement was defined as a relative increase in pressing the lever that produced the tone. Pipradrol was shown to produce a dose-dependent enhancement of this effect on lever preference. Subsequent experiments examined the possible role of non-specific stimulus change, feeding in the test environment and prior exposure to the conditioned stimulus, in producing this enhancement. The data suggested that associations involving environmental stimuli may play a role in mediating this effect; animals pre-exposed to the tone stimulus and subsequently fed in the same environment as pre-exposure and test showed evidence of "conditioned reinforcement". Disrupting the relationship between tones in the pre-exposure phase and environmental stimuli paired with food prevented

this pattern of responding in drugged animals. Sensory preconditioning was suggested as a possible mechanism for these associations and data were collected that were consistent with this hypothesis. Pipradrol also was shown to enhance "conditioned suppression". In this situation, animals were tested for suppression of ongoing licking behaviour to a stimulus that had been previously classically conditioned to shock. An effect of explicit sensory preconditioning training was demonstrated in this paradigm, however, pipradrol could not be shown to enhance this effect. Implications for current theories of stimulant drug action are discussed.

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CHAPTER 1: GENERAL INTRODUCTION

Psychomotor stimulant drugs include cocaine, pipradrol, d-amphetamine and methylphenidate. All these drugs have striking behavioural effects in both animals and man. At low doses these drugs produce a general increase in motor activity while at higher doses, a selective facilitation of some components of behaviour and an inhibition of others is seen (Randrup & Munkvad, 1967).

One aspect of the effects of these drugs on behaviour is their ability to produce "stereotyped behaviours". This is the repetition of behaviour with little variation (Randrup & Munkvad, 1966); in extreme cases a single activity or sequence of activities is performed continuously and dominates the subject's behaviour, e.g. continuous sniffing, biting and licking in the rat (Ernst & Smelik, 1966). The factors determining the pattern of responding under these drugs is one aspect of the studies described here.

Stereotyped behaviour is produced by all the amphetamines (and derivatives) at appropriate doses (Randrup & Munkvad, 1970) and by a few stimulants chemically unrelated to amphetamine, such as cocaine. Some stimulants, e.g., caffeine (Fog, 1969) do not produce stereotyped behaviour at any dose. Furthermore, stereotyped behaviour can be produced by amphetamines in many (probably all) mammalian and avian species, but not in lower vertebrates e.g., lampreys, eels and lizards (Nilakantan & Randrup, 1969). In rodents, such as the

rat, sniffing together with gnawing and licking is the predominant stereotyped behaviour. In non-human primates, such as the rhesus monkey, typical stereotyped behaviours are persistant visual staring and grooming (Ellinwood, 1970).

The production of stereotyped activity across species seems to be a basic property of the psychomotor stimulants, with the dominant behaviour depending on the species. In man, chronic amphetamine or cocaine usage also can lead to stereotyped behaviour patterns; often, these stereotyped behaviours are manipulative in nature, (Randrup & Munkvad, 1967) sometimes taking the form of repeated patterns of self-grooming to the point of producing skin lesions. This is strikingly similar to the stereotyped grooming behaviour seen in monkeys treated with amphetamine (Ellinwood, 1970).

The dramatic effects on motor behaviour associated with these drugs are not surprising from a pharmacological point of view; these drugs interact with the catecholaminergic neurones in the brain (Creese & Iversen, 1973; Scheel-Kruger, 1971) and the catecholamines, especially dopamine (DA), are involved in the control of motor behaviours (Kelly, 1975). Amphetamine's effects on behaviour seem to depend primarily on dopaminergic neurones (Thornberg & Moore, 1973). It seems also that the mechanisms that produce increased general locomotor activity may differ from those producing stereotyped behaviour (Sahakian, Robbins, & Morgan, 1975) and even may have a different neural substrate (Kelly, Seviour, & Iversen, 1975).

Investigations of the neuronal mechanisms underlying the

effects of amphetamine have used selective lesions of forebrain dopamine and noradrenalin systems in animals and observed the effects of these lesions on the response to amphetamine. Kelly, Seviour, & Iversen (1975) produced selective chemical lesions of the terminal regions of the "mesolimbic" and "nigrostriatal" dopamine systems, the nucleus accumbens and corpus striatum, respectively. Lesions of the nucleus accumbens abolished the characteristic locomotor stimulation seen in response to low doses of amphetamine. Striatal lesions, however, abolished the stereotyped behaviour seen at higher doses of amphetamine but failed to abolish the locomotor effect of the drug. Reviewing this and other studies, Cole (1978) concluded that the data support a role for both dopaminergic (nigrostriatal and mesolimbic) and noradrenergic systems in mediating the locomotor effects of amphetamine but a "rather exclusive" involvement of the dopaminergic nigrostriatal system in mediating the production of stereotyped behaviour by amphetamine.

There is evidence that the effects of psychomotor stimulants may not be solely on a system controlling motor performance of behaviour. Pipradrol has been used to elevate mood and improve attention deficits in depressive patients (Hill, 1970). Studies also have shown amphetamine to increase rates of intracranial self-stimulation in rats (Stein & Wise, 1970). In this procedure, a response by the subject is followed by low-level electrical stimulation of a region of the brain. In certain regions of the brain such stimulation is

positively reinforcing : the response is made at increased rate. Amphetamine administration can facilitate self-stimulation by either increasing response rates (Phillips & Fibiger, 1973) or by changing the reinforcing properties of the stimulation, for example, lowering current threshold (Stein & Ray, 1959). A large literature suggests that biochemical manipulations of catecholaminergic neurones, such as is produced by amphetamine administration, affect processes of reward or reinforcement (Beninger & Phillips, 1980; Stein & Wise, 1970) as well as motor performance of behaviour.

Psychomotor stimulants including pipradrol, d-amphetamine, cocaine and methylphenidate also have been found to support intravenous self-administration (Wilson, Hitomi, & Schuster, 1971). In this procedure a response is followed by injections of a drug via an intravenous catheter. Studies using this paradigm suggest also that the catecholaminergic neurones affected by these drugs, especially dopamine, are involved in reward processes (Yokel & Wise, 1975). Yokel & Wise, for example, found that the dopamine receptor blocker pimozide affected responding in a manner best compared to that resulting from "loss of reward" from the injections and in the opposite direction from that predicted on the basis of pimozide's usual motor effects.

These data, suggesting effects on processes of reinforcement or reward, are interesting when compared to clinical data. Chronic stimulant use by human addicts can produce a syndrome known as "amphetamine psychosis" (Randrup &

Munkvad, 1970). Stereotyped behaviour is one aspect of this syndrome. Also, the behaviour and apparent mental state of the addict can so resemble some forms of schizophrenia that misdiagnosis has occurred (Randrup & Munkvad, 1967). Furthermore, stereotyped behaviour has been described as "one of the most striking external manifestations of schizophrenia" (Bleuler, 1950). Thus, understanding the basis of the stereotype-producing action of these drugs might provide insight into basic psychological disorders. This idea is supported by the fact that disorders of the catecholaminergic systems affected by these drugs have been implicated in the etiology of schizophrenia (see Iversen, 1979; Snyder, 1974).

A current theory to account for the effects of stimulants on behaviour is that they enhance the effects of reinforcing stimuli on behaviour (Stein, 1964). In particular, recent studies have examined the effects of these drugs on the acquisition of responses reinforced by "conditioned reinforcers"; these are stimuli that have few or no reinforcing properties themselves, but acquire them by virtue of previous association with an unconditioned reinforcer such as food, water or certain types of brain stimulation (Mackintosh, 1970). A variety of recent experiments have found psychomotor stimulants, particularly the drug pipradrol, to enhance responding for conditioned reinforcement greatly (Hill, 1970; Robbins, 1972, 1976; Robbins & Koob, 1978). Robbins (1976) found water-deprived rats treated with pipradrol responded for a stimulus previously paired with

water much more than saline-treated animals. Responding for the same stimulus after it had been randomly correlated with water presentations was not enhanced by the drug. Robbins (1972, 1976) has demonstrated that learned responses producing conditioned reinforcers can be part of the pattern of stereotyped responses seen under stimulant treatment. He suggests also that a general action of stimulants may be to cause increased repetition of responding, with response-selection being determined by prior contingencies of reinforcement as reflected by the establishment of conditioned reinforcement (see Lyon & Robbins, 1975 and Robbins, 1976).

The studies described in the present thesis used different paradigms to extend the range of observations on the effect of stimulants on responding for conditioned reinforcement. The first study examined the effect of pipradrol in a "conditioned reinforcement" paradigm (Beninger & Phillips, 1980). Rats were pre-exposed to a chamber with two levers, one of which produced a tone. Following determination of the rate of pressing of each lever, the tone was paired with food in the absence of the levers. A subsequent test session measured any change in proportion of total responses made on the tone lever. "Conditioned reinforcement" was defined as a relative increase in total responding on the tone lever. The second study examined whether a factor other than conditioned reinforcement, such as non-associative effects of feeding or stimulus change could account for the pattern of responding seen in drugged animals. Finally, the effect of

pipradrol on "conditioned suppression" was observed. This study sought to determine whether pipradrol enhanced the suppressive effect of a conditioned stimulus on behaviour, in contrast to the usual excitatory effect of the drug. Also, a prediction from the previous studies about the effect of the drug on sensory preconditioning was tested. A further review of the relevant literature is provided at the start of each section.

CHAPTER 2

EXPERIMENT 1. THE ACQUISITION OF RESPONDING WITH CONDITIONED REINFORCEMENT: THE EFFECTS OF PIPRADROL.

Introduction

This study observed the effect of various doses of pipradrol on responding for conditioned reinforcement in the paradigm of Beninger and Phillips (1980). This determined whether pipradrol has the same effect in this particular paradigm as compared to other conditioned reinforcement paradigms (Hill, 1970; Robbins, 1972, 1976, 1978).

METHOD

Subjects

Twenty-eight male albino rats of the Wistar strain were housed individually in a climatically controlled colony room maintained on a twelve hour light/dark cycle. The rats weighed from 225 to 315g and were maintained at 80% of these *ad libitum* weights throughout the experiment.

Apparatus

Four similar Plexiglas chambers (30.0 x 21.5 x 46.5 cm high) contained within ventilated sound-attenuating boxes with overhead illumination served as experimental environments throughout these studies. Two chambers had wax paper covered wooden floors and two had grid floors. Each chamber had two removable levers (7.7 x 4.4 cm), one located in each of the 21.5 cm walls. A force of approximately 0.10 N was required for lever closure. At the centre of one side was a feeder cup at a height of 1.5 cm above the floor. A 2900 Hz tone generator (Sonalert) was mounted inside each sound-attenuating box. Environmental contingencies and data collection were controlled by a Data General Nova 3 computer for three chambers and solid state switching and timing devices (BRS/LVE) for the remaining one.

Drugs

The drug pipradrol was dissolved as pipradrol hydrochloride (Merrel G) in sterile distilled water and injected intraperitoneally (i.p.) ten min prior to the Test at a volume of 1 ml/kg.

Procedure

All animals were exposed to identical behavioural training and testing procedures. This consisted of three phases, referred to as the Pre-exposure, Conditioning and Test phases. The Pre-exposure phase consisted of six 40-min exposures to the chamber with the two levers present. One session per day was given for three days, then two days in the home cage, followed by the remaining three sesions over the next three days. During all these sessions, depressions of one of the levers (the tone lever) resulted in a 3-sec presentation of a tone while depression of the other (the no-tone lever) had no programmed consequences. Previous studies (Beninger & Phillips, 1980) have shown that almost all rats showed a preference for the same side. The tone lever was put on the non-preferred side. Dependent variables were the number of responses on each lever.

The conditioning phase consisted of four 60-min sessions. One session per day was given for the two days immediately following the Pre-exposure phase, then two days in the home cage followed by the two remaining daily sessions. Throughout all the Conditioning sessions both levers were removed, the resulting apertures being covered by sliding Plexiglas plates. During each session the 3-sec tone was presented 80 times on a random time (45-sec) schedule. Thus, tones were presented with an average inter-tone interval of 45 sec. Throughout the first Conditioning session each tone presentation terminated with

the delivery of one 45 mg Noyes Precision Food pellet. During the remaining 3 sessions pellet delivery occurred only after a random 33% of the tone presentations. Partial pairing was employed to produce more durable conditioned reinforcement when measured in extinction (Knott & Clayton, 1966; Mackintosh, 1970). The Test phase consisted of one 40-min session on the day following the last Conditioning session. Prior to the Test session animals were given one of the following treatments: four groups were injected with either 0 mg/kg (saline), 5.0 mg/kg, 10 mg/kg or 15 mg/kg of pipradrol. Group sizes were 8, 6, 8, 6, respectively.

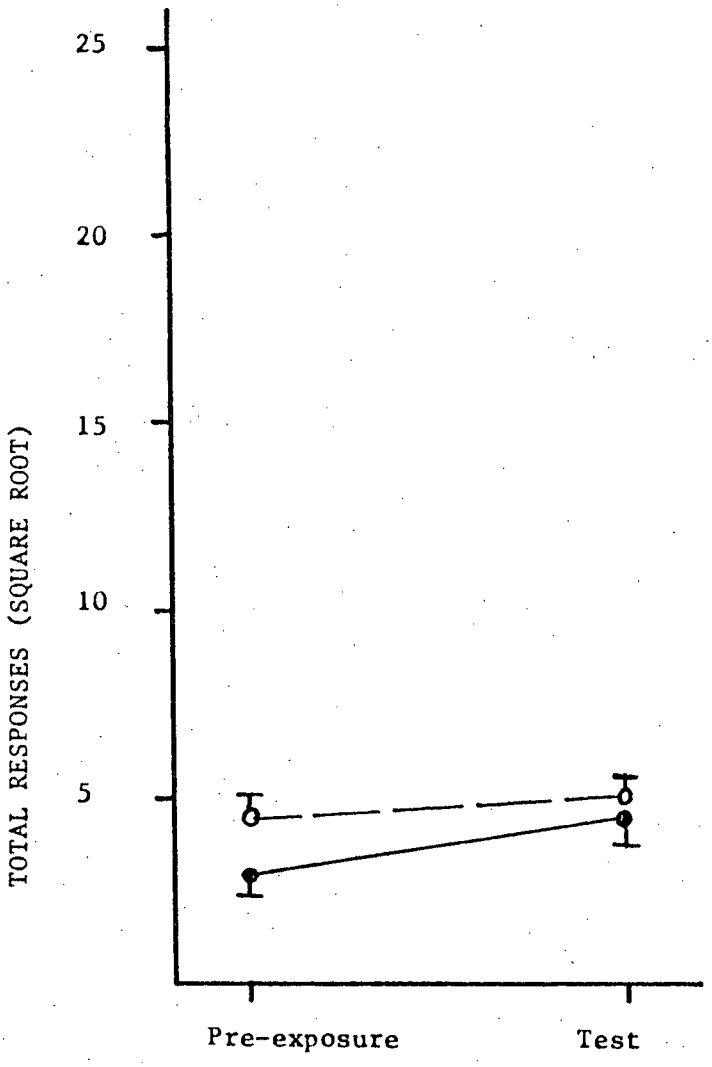
RESULTS

Results from the Pre-exposure phase enabled the rate of pressing on the tone and no-tone levers to be determined prior to conditioning. These rates (presses/session) were calculated as the mean for both levers over the last three sessions of this phase. In the Test phase, lever presses for the one Test session were recorded. Thus data consisted of two pairs of numbers for each rat, its operant rate on each of the two levers before and after conditioning.

The group receiving saline served as a control group. The results for this group are shown in Figure 1. The data suggest that the increase in responding on the tone lever from Pre-exposure to Test was greater than for the no-tone lever. This greater relative increase in responding is indicative of the

Figure 1: Mean number (+SEM) of responses (square root) on the tone (closed circles) and no-tone (open circles) levers in the Pre-exposure and Test phases for the saline injected group. The increase in responding on the tone lever was greater than on the no-tone lever.

CONTROL



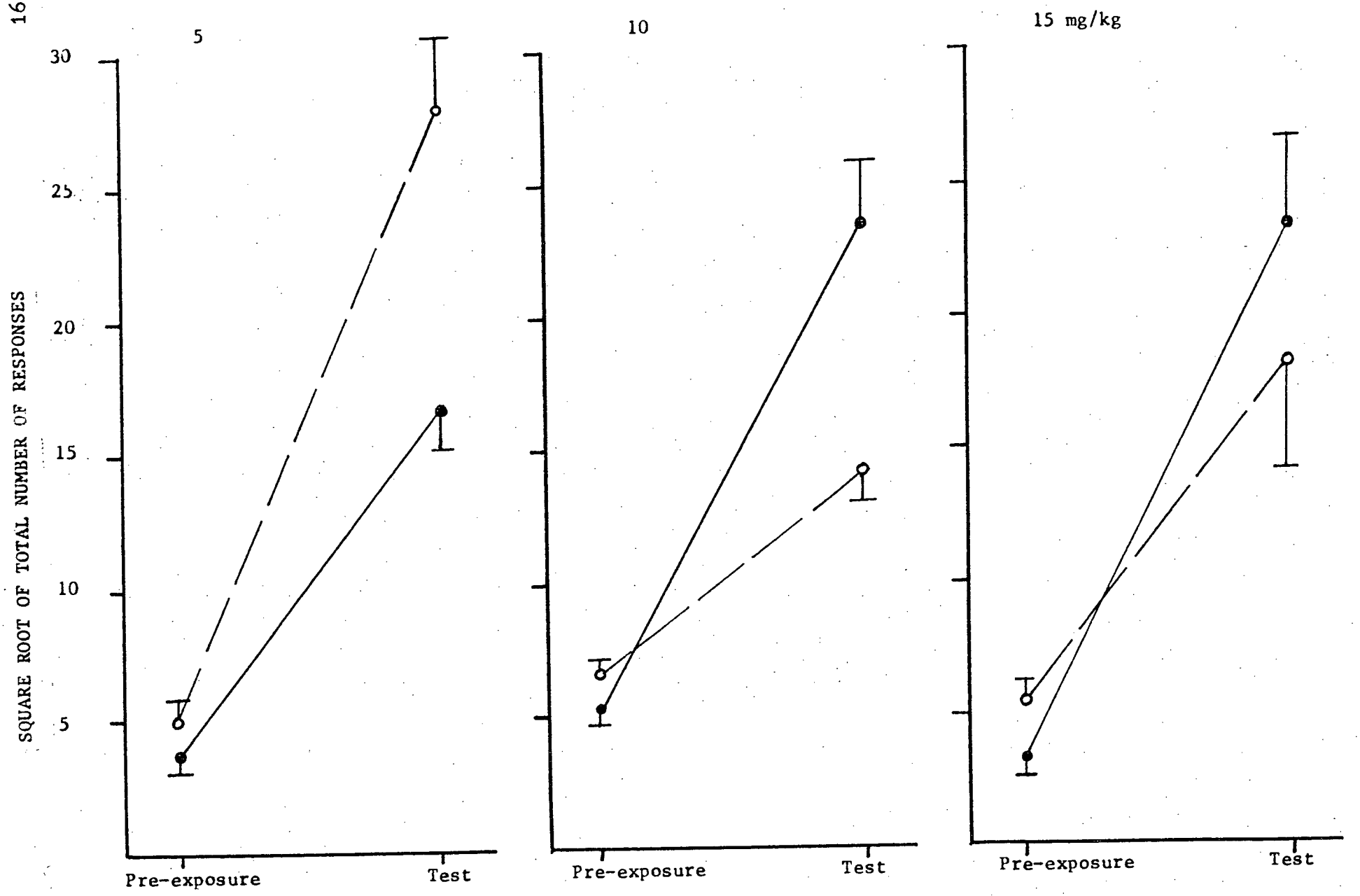
tone having become a conditioned reinforcer. Statistical analysis supported this description but with only a marginally significant effect. Two-way analysis of variance with repeated measures on both variables (levers and phases) was performed on the square roots of the data; square root transformations were done throughout all these studies to reduce the difference in the variances of the two samples. Thus, a significant lever by phase interaction would reveal that the difference in rate of responding on the two levers had changed from the Pre-exposure to Test phase. This interaction was only marginally significant ($F=3.89$, $df=1,5$, $.05<p<.1$). Thus non-drugged animals showed a small change in preference for the tone lever over the no-tone lever after exposure to the tone paired with food.

The results for the pipradrol groups (5,10, and 15 mg/kg) are shown in Figure 2. All the groups showed an overall increase in responding on the two levers from Pre-exposure to Test. However, whereas the groups receiving doses of 10 and 15 mg/kg changed their preference to favour the tone lever in the Test the 5 mg/kg group did not.

Two-way analysis of variance was performed on the data for each group, variables analysed were levers and phases. All the groups showed a significant effect of phase, reflecting the increased overall level of responding seen in the Test phase ($F=158.4$; 92.93; 56.22; $df=1,5$; 1,7; 1,5; $p<.01$ for the 5, 10 and 15 mg/kg groups respectively). Phase by lever interaction was not significant for the 15 mg/kg group ($F<1$,

Figure 2: Mean number (+SEM) of responses (square root) on the tone (closed circles) and no-tone (open circles) levers in the Pre-exposure and Test phases for the pipradrol-injected groups. All the groups showed a significant overall increase in responding on both levers; the relative increase in responding on the tone lever was greater than for the no-tone lever at the 10 mg/kg dose only.

PIPRADROL


5
10
15 mg/kg
SQUARE ROOT OF TOTAL NUMBER OF RESPONSES
30
25
20
15
10
5
Pre-exposure
Test
Pre-exposure
Test
Pre-exposure
Test

df=1,5, p>0.2) but significant for the 5 and 10 mg/kg groups (F=6.74; 22.73; df=1,5; 1,7; p<.05 for each group, respectively). However, the change in lever preference reflected by these interactions was clearly in opposite directions in these two groups, only the 10 mg/kg group showing enhanced responding on the tone-lever during the Test.

Three-way analyses of variance were carried out for each group together with the saline control group. Measures analysed were phase, lever and group. This allows a comparison of the magnitude of the phase by lever interaction in each drug group (our measure of conditioned reinforcement) to that of the saline-treated animals. A significant three-way interaction of phase, lever and group would show a different phase by lever interaction in the drug group as compared to the controls. This interaction was significant at the 5 and 10 mg/kg doses (F=8.57; 11.92; df=1,10; 1,12; p<.05 respectively) but not at the 15 mg/kg dose (F<1, df=1,10 p>.05). In the 5 mg/kg group this reflects the fact that the increased responding was shown on the "no-tone" lever rather than on the tone lever. This demonstrates also that the 10 mg/kg group showed a greater increase in responding for conditioned reinforcement than the saline controls.

DISCUSSION

In summary, there appear to be at least two effects of pipradrol in the present experimental situation. Firstly, there is an effect on overall responding on both levers during the Test. The levers project 4.5 cm into the chamber from both sides and are depressed by the animals during the course of normal locomotor activity. Thus, this effect is probably due to hyperactivity in the Test causing the animals to depress both levers indiscriminatively at higher rate. Such hyperactivity usually is observed following administration of these drugs (Kelly, 1975). It is interesting to note that the locomotor stimulant effcts of these drugs seem to predominate at the lower doses (Scheel-Kruger, 1971). In the group receiving the lowest dose of pipradrol (5 mg/kg) a strong locomotor stimulant effect may have obscured any effect of the tone stimulus on rates of bar-pressing as it is clear that any effects of conditioned reinforcement must be seen over and above this general stimulation of bar-pressing.

The measure of conditioned reinforcement used here is the relative enhancement of total responding on the tone lever. Using this measure, the results of treatment with pipradrol parallel many previous studies (Hill, 1970; Robbins, 1975, 1976 & 1978; Robbins & Koob, 1978). The group that received 10 mg/kg of pipradrol showed a clear increase in responding for the conditioned stimulus and this was significantly enhanced relative to saline-treated controls. The group that

received 5 mg/kg showed increased responding on the "no stimulus" lever. This apparent enhancement of an established spatial preference may have been seen in this paradigm because of the large effect of motor stimulation on bar-pressing as described earlier.

The measure of conditioned reinforcement defined above may, in fact, result in an exaggerated assessment of responding for the tone stimulus; responses made during the tone are included and not only those responses actually producing tones. This meaure was suggested from the work of Stein (1958) and in Experiment 1 the effects of pipradrol on this measure parallel the results of other studies (e.g., Hill, 1972; Robbins, 1976, 1978). The effect of the drug on this particular measure shall be examined further in CHAPTER 3.

The group that received 15 mg/kg of pipradrol failed to show significant evidence of conditioned reinforcement. The small change in preference for the tone lever seen in this group parallels Robbins and Koob's (1978) observation of little enhancement of conditioned reinforcement by this dose of the drug. This lack of increase in responding on the tone lever might have been due to the fact that 15 mg/kg of pipradrol produces very intense and constricted stereotyped behaviour which probably interfered with lever responding by response incompatability (Lyon & Robbins, 1975). Thus, in this paradigm, 10 mg/kg is the optimally-effective dose of pipradrol to produce increased responding for the conditioned

stimulus. In the light of recent studies on the effects of pipradrol (Robbins, 1976, 1978; Robbins & Koob, 1978) further studies in the present thesis concentrate on the enhancement of the effects of conditioned stimuli that is usually produced by 10 mg/kg of this drug. Possible effects of the other doses used in Experiment 1 are not investigated further.

CHAPTER 3. THE EFFECTS OF PIPRADROL ON RESPONDING FOR CONDITIONED REINFORCEMENT AND CONTROL PROCEDURES.

Introduction

The first section assessed the effects of three doses of pipradrol on the performance of a response reinforced by a conditioned reinforcer (see CHAPTER 2). These data demonstrated using a new experimental procedure that 10 mg/kg of pipradrol produces the most consistent facilitation of responding for a conditioned reinforcer. It is assumed that this effect represents an effect of pipradrol on conditioned reinforcement, additional studies will be required to rule out some other possible interpretations in the present context.

Early studies used the ability of a stimulus to maintain responding in extinction as a measure of conditioned reinforcement. For example, rats trained to bar-press for food pellets respond at higher rates in extinction if bar presses produce the "click" of the pellet dispenser but no food, as compared to animals extinguished without this stimulus (Bugelski, 1938; Hill, 1970). However, this procedure confounds possible reinforcing effects of the stimulus with "generalisation decrement" occuring from training to extinction conditions (see Mackintosh, 1974, pp. 234-235). The present procedure avoids this problem, by using the establishment of a new response reinforced by the stimulus to

measure its reinforcing properties.

Previous work by Robbins and others has examined the issue of whether or not the enhancement of responding for conditioned reinforcers seen in animals given psychomotor stimulants can be accounted for on the basis of other effects of the stimuli or the drugs. For example, the general increase in locomotor activity produced by these stimulants cannot account for the relative increase in responding seen on one of two levers (Robbins, 1975; see also Experiment 1). Stimulants also can enhance responding for stimulus change (Kiernan, 1965) but this is not sufficient to account for the effects on conditioned reinforcers; Robbins (1976) found pipradrol to enhance responding for a light stimulus only slightly as compared to responding for the same stimulus paired with reinforcement. Similarly, enhancement of responding for a novel stimulus is insufficient to account for the effect of pipradrol on responding for conditioned reinforcement (Robbins, 1978). Robbins and Koob (1978) also have ruled out enhancement of spatial preference by counterbalancing the lever providing conditioned reinforcment across a previously measured two-lever spatial preference. On the basis of control data such as these, it has been suggested that pipradrol selectively enhances responding for conditioned reinforcement.

Earlier work with the paradigm used in this thesis showed that pipradrol failed to enhance responding for a tone whose presentation was correlated negatively with food (Beninger & Phillips, 1980). Contingencies were arranged so that food

pellets were not presented within 3 sec of any tone during the Conditioning phase. This was expected, as stimuli negatively correlated with reinforcement do not normally acquire reinforcing properties (see Mackintosh, 1974). However, enhancement of responding for tones was seen after random occurrences of tones and food (Beninger & Phillips, 1979). It was proposed that the tone acquired reinforcing properties due to chance pairings with food (see Beninger & Phillips, 1979). One test of this hypothesis would be to incorporate a control group fed in the absence of tones and tested subsequently with pipradrol.

The studies described in this section were designed to assess the effects of the relationship between tones and food in more detail by presenting food pellets paired with tones or in the absence of tones. Pilot data had indicated that environmental variables may mediate an association of tones with food reward. Further manipulations of the relationship between tones, food and other (environmental) stimuli would allow for a closer examination of the associational basis of conditioned reinforcement in this paradigm. Pharmacological parameters were constant throughout all the following studies with animals receiving either injections of saline or an optimally-effective dose of pipradrol (10 mg/kg:- see CHAPTER 2)

GENERAL METHOD

Subjects

Sixty-eight male albino rats of the Wistar strain were housed individually in a climatically controlled colony room maintained on a twelve hour light/dark cycle. Rats weighed from 305 to 420g and were maintained at 80% of these *ad libitum* feeding weights throughout the experiment.

Apparatus

As described in CHAPTER 2 (METHOD).

Procedure

This study consisted of five experiments. All of the eight groups were tested with the same basic experimental design; this design followed that described in CHAPTER 2, consisting of the same three phases of Pre-exposure, Conditioning, and Test. Any variations from the exact procedure described in CHAPTER 2 are stated for each experiment. Each experiment is described separately, together with its results and a brief discussion. A general discussion of CHAPTER 3 follows this.

EXPERIMENT 2

This experiment represents a replication of the basic conditioning proceedure in undrugged animals and compares the effect to that seen in animals given 10 mg/kg pipradrol.

Procedure

Twenty rats were randomly assigned to the Control (n=8) or Pipradrol (n=12) groups. The training of both groups was identical to that described in CHAPTER 2. Animals in the Control group received injections of saline (i.p.) 15 min prior to the Test session. The pipradrol group received i.p. injections of pipradrol (10 mg/kg) 15 min before the Test session.

RESULTS

Figure 3 shows the mean number of responses (+SEM) on the tone and no-tone levers in the Pre-exposure and Test phases for the Control and Pipradrol groups. The Control group showed a greater increase in responding on the tone as compared to the no-tone lever after conditioning, demonstrating that the tone had acquired reinforcing properties. The Pipradrol group showed increased responding on both levers but a far greater increase in responding on the tone lever than on the no-tone lever. Thus, the drug produced an enhancement on our measure of conditioned reinforcement.

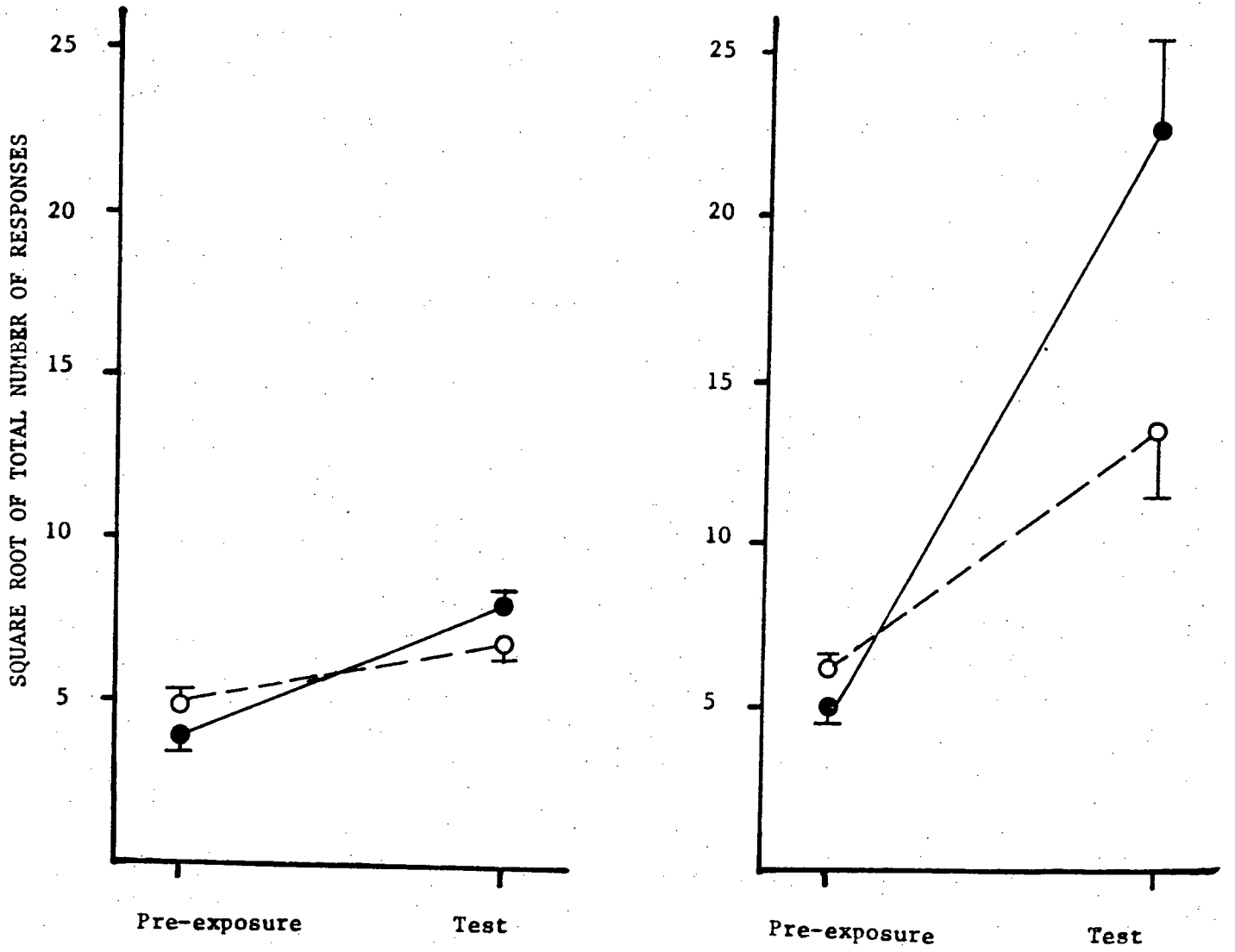
Figure 3: Mean number (+SEM) of responses (square root) on the tone (closed circles) and the no-tone (open circles) levers in the Pre-exposure and Test phases for the Control (A) and the Pipradrol (B) groups in Experiment 2. Both groups showed a greater increase in responding on the tone lever than on the no-tone lever showing the tone had acquired reinforcing properties.

A CONTROL

Pre-ex: TONE
Cond: TONE & FOOD
Test: VEHICLE

B PIPRADROL

Pre-ex: TONE
Cond: TONE & FOOD
Test: PIPRADROL (10 mg/kg)



This interpretation was confirmed by statistical analysis. Analysis of variance for the Control group revealed a significant lever by phase interaction ($F=5.76$, $df=1,7$, $p<.05$) showing a clear effect of conditioned reinforcement. This interaction also was significant for the pipradrol group ($F=21.97$, $df=1,11$, $p<.001$) as was the increase in overall responding from Pre-exposure to Test phase ($F=45.16$, $df=1,11$, $p<.001$).

The magnitude of the conditioned reinforcement effect was compared between the two groups by performing a three-way analysis of variance. The variables analysed were groups, phases and levers, the latter two with repeated measures. The three-way interaction was significant ($F=8.98$, $df=1,18$, $p<.008$) indicating that the two-way interaction of phases and levers differed for the two groups. This confirms that pipradrol (at 10 mg/kg) enhanced conditioned reinforcement in this experimental situation.

DISCUSSION

This observation of enhanced responding for conditioned reinforcement by 10 mg/kg pipradrol is in agreement with a number of other reports (Hill, 1970; Robbins, 1975, 1976, 1978; Robbins & Koob, 1978).

EXPERIMENT 3

This experiment examined whether pipradrol might produce enhanced responding for stimulus change in this paradigm. As a test of this possibility, a group receiving no tones and no food in the Conditioning phase and pipradrol prior to test was included in Experiment 3. Pipradrol might produce such enhancement of stimulus change only after feeding in the experimental environment. Therefore a second group received food but no tones in the Conditioning phase and pipradrol prior to Test.

Procedure

Sixteen rats were assigned randomly to one of two groups: the No-tone, no-food group (n=8) and the Food-alone group (n=8). Both groups received the usual three phases of training. During the Pre-exposure phase both groups were exposed to the tone and no-tone levers as previously described. For the first group, no tones or pellets were given during the four sessions of the Conditioning phase. The second group received food pellets during the Conditioning phase in the same fashion as the Control group but no tones occured. Both groups received injections of pipradrol (10 mg/kg i.p.) 15 min prior to the Test session.

RESULTS

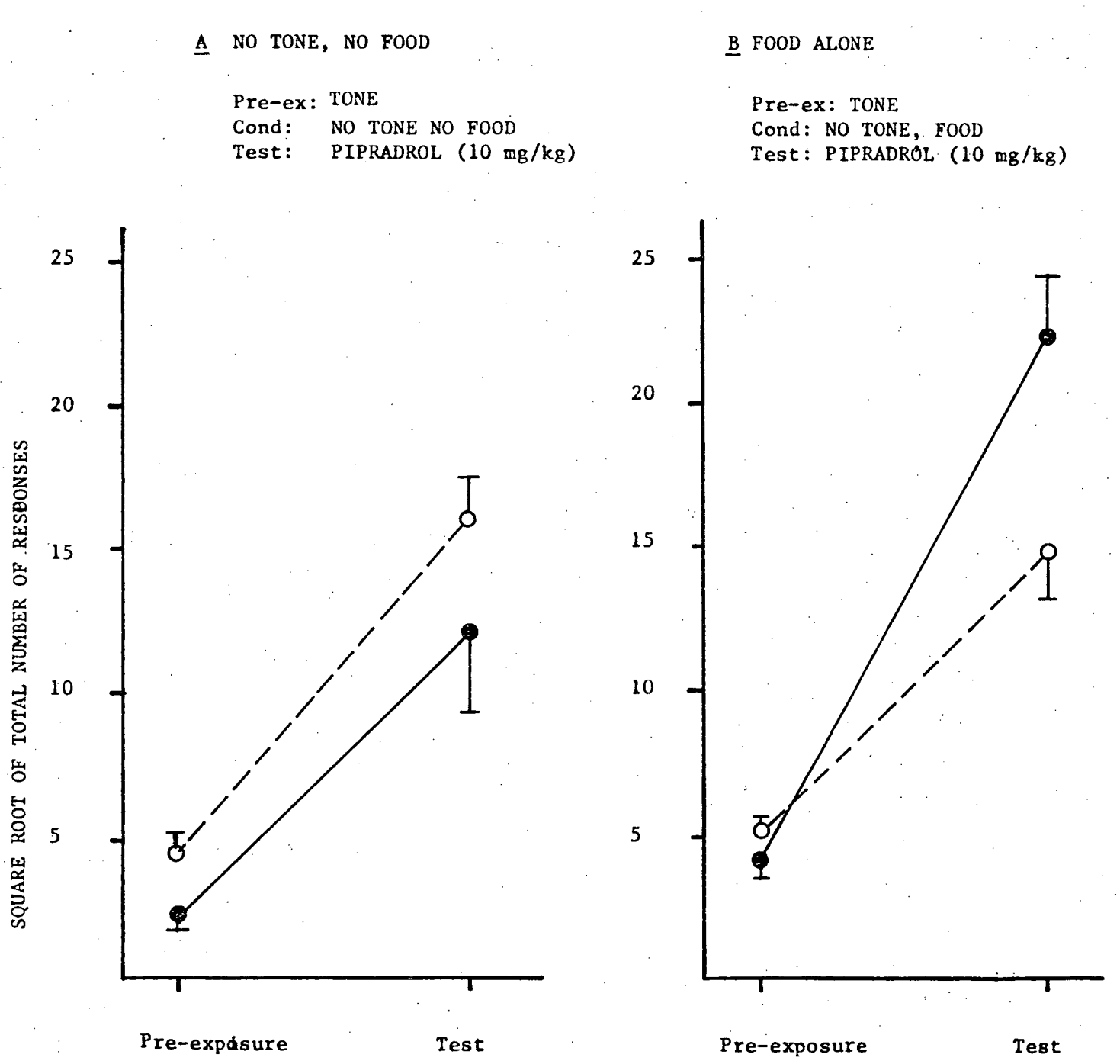
Mean number of responses in each phase for the No-tone, no-food and Food-alone groups are shown in Figure 4. Both groups showed an overall increase in responding from Pre-exposure to Test phase but, whereas the No-tone, no-food group showed no relative change in response rate on the two levers, the Food-alone group showed a relatively greater increase in depressing the tone lever.

Two-way analysis of variance was performed for each group with repeated measures on both variables (levers and phase). Both groups showed an overall increase in responding from Pre-exposure to Test ($F=18.85$, $df=1,7$, $p<.003$ for No-tone, no food group and $F=195.08$, $df=1,7$, $p<.001$ for Food-alone). Phase by lever interaction, indicating a change in relative preference for the tone lever from Pre-exposure to Test, was significant for the Food-alone group ($F=9.05$, $df=1,7$, $p<.02$) but not for the No-tone, no-food group ($F=0.65$, $df=1,7$, $p>.05$).

DISCUSSION

The results of Experiment 3 indicated that the enhanced responding on the tone lever after treatment with pipradrol was observed even in the absence of any direct pairing of tones and food in the Conditioning phase (Food-alone group). This observation calls into question the need for pairing the tones with food during the Conditioning phase. This in turn raises the question of whether or not the apparent enhancement

Figure 4: Mean number (+SEM) of responses (square root) on the tone (closed circles) and no-tone (open circles) levers in the Pre-exposure and Test phases for the No-tone, no-food (A) and Food-alone (B) groups in Experiment 3. Both groups received pipradrol prior to test (10 mg/kg). There was no difference in the amount of increase in responding on the two levers for (A); for (B) the increase was significantly greater on the tone lever than on the no-tone lever.


A NO TONE, NO FOOD
Pre-ex: TONE
Cond: NO TONE NO FOOD
Test: PIPRADROL (10 mg/kg)
B FOOD ALONE
Pre-ex: TONE
Cond: NO TONE, FOOD
Test: PIPRADROL (10 mg/kg)
SQUARE ROOT OF TOTAL NUMBER OF RESPONSES
25
20
15
10
5
Pre-exposure
Test
Pre-exposure
Test

of "conditioned reinforcement" by pipradrol has its basis in any tone-food "association". Such a basis is required if this effect is to be regarded as an enhancement of conditioned reinforcement. The failure of the No-tone, no-food group to show any enhancement of responding for the tone shows that enhanced responding for stimulus change per se cannot account for the effects of pipradrol in this paradigm. It shows also that the enhancement of responding for tones produced by pipradrol was seen only if the animals were fed in the Test environment. The remaining experiments examine the precise nature of this effect of feeding.

EXPERIMENT 4

Previous studies have demonstrated that pipradrol increases responding for conditioned reinforcment by enhancing a conditioning effect produced by prior behavioural training (Lyon & Robbins, 1975; Robbins, 1976). That is, training produces some increase in responding for the stimulus that can be seen in undrugged animals. This raises the possibility that animals given training similar to the Food-alone group in Experiment 3 would show increased responding on the tone lever during a test in the absence of pipradrol. If this result was obtained then one interpretation of the previous results could be that training produced a small conditioning effect that is enhanced by the drug.

Procedure

Eight rats were assigned to the Food-alone control group. This group received the same training as described for the Food-alone group in Experiment 3. These animals received an injection of saline 15 min prior to the Test session.

RESULTS

The mean number of responses on each lever in each phase is shown in Figure 5. The data indicate a relative increase in responding on the tone lever from Pre-exposure to Test. Analysis of variance revealed that the Food-alone control group showed a significant phase by lever interaction ($F=10.77$, $df=1,7$, $p<.05$) confirming the occurrence of a clear shift in preference to the tone lever in the Test session.

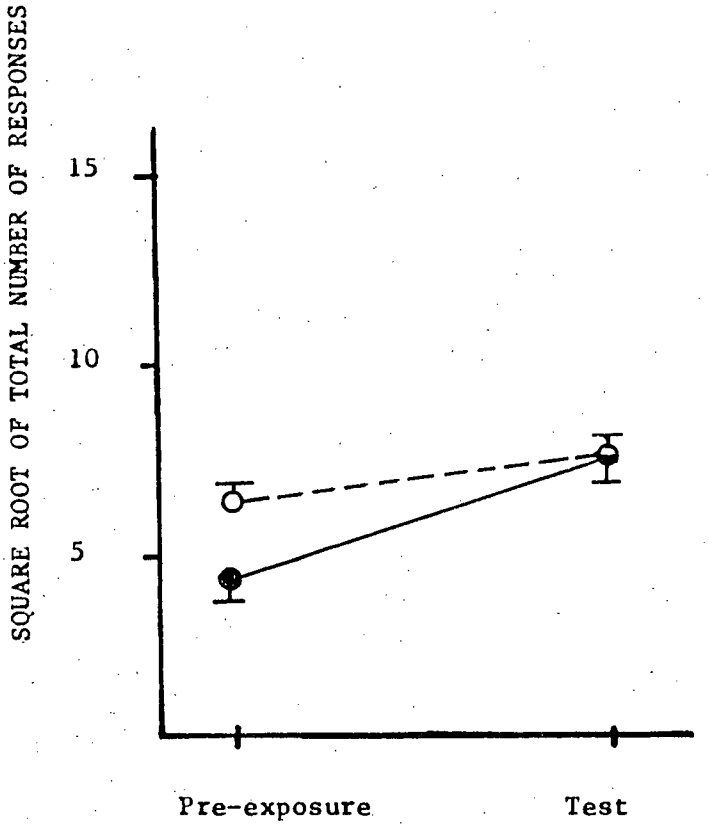
DISCUSSION

The results of Experiment 4 demonstrated that animals exposed to tones in a Pre-exposure phase and food pellets alone during conditioning showed increased responding for tones in the Test, even in an undrugged state. The fact that increased reponding for tones was seen in these undrugged animals shows that feeding animals in the same environment in which they previously received exposure to tones enabled the tone to acquire reinforcing properties. Thus, the previous results of the Food-alone group given pipradrol can be

Figure 5: Mean number (+SEM) of responses (square root) on the tone (closed circles) and no-tone (open circles) levers in the Pre-exposure and Test phases for the Food alone Control group in Experiment 4. The increase in responding on the tone lever was greater than on the no-tone lever.

FOOD ALONE CONTROL GROUP

Pre-ex: TONE
Cond: NO-TONE, FOOD
Test: VEHICLE



interpreted as as an enhancement of a small change in lever preference comparable to that seen in the Food-alone control group of the present experiment.

Sensory preconditioning (SPC) might provide one explanation for the data described above. This procedure (Brogden, 1939; see reviews by Siedel, 1959 and Thompson, 1972) involves a pre-exposure phase where one stimulus is presented (e.g., a light) immediately before a second stimulus (e.g., a tone). This is followed by a phase where the second stimulus is paired with an "unconditioned stimulus" such as food or electric shock. Finally, the first stimulus is tested for increased generalisation of the conditioning to the second stimulus relative to control subjects.

In one example of SPC, Adamacek and Melzack (1970) gave animals pre-exposure to either paired or unpaired tones and clicks. Following this, the food-deprived animals were trained with one stimulus as a conditioned stimulus (CS) for milk presentation. In a generalisation test the animals that had received the paired pre-exposure showed greater transfer of the condtioned response to the other stimulus than those that had received unpaired presentations. In the Pre-exposure phase of the present paradigm, intermittent tones produced by the lever presses could have been associated with environmental stimuli such as floor texture, odours, general level of illumination, etc. During the Conditioning phase food would have been associated with the same environmental stimuli. Therefore, if sensory preconditioning was established in the

present paradigm, tones would acquire the capacity to reinforce lever-pressing because of their association with stimuli that signalled food. The following experiments examined this possibility.

EXPERIMENT 5

If sensory preconditioning produced the effect seen in the Food-alone group then the effect should be disrupted by removing the association of food with the environmental stimuli present in the Test session. The present experiment involved two groups in which the environmental stimuli present in the Conditioning phase differed from those of the Pre-exposure and Test phases. Floor texture and level of illumination were altered from the first to second phase of the experiment. One group was given food pellets but no tones during the Conditioning phase, ensuring that tones and food could be associated only with completely different sets of environmental stimuli and thus eliminating a role for sensory preconditioning. For this group, the tones should not acquire reinforcing properties. The second group received tone-food pairings in the changed environment (CE) during Conditioning. This would determine if an explicit contingency between tones and food was sufficient to provide evidence of conditioned reinforcement in the absence of sensory preconditioning.

Procedure

Sixteen rats were assigned randomly to one of two groups: the CE-Pairings group (n=8) and the CE-Food-alone group (n=8). Both groups received the Pre-exposure and Test phases in the ususal manner. During the Conditioning phase the environment for each group was changed. Four rats in each group had undergone Pre-exposure in a chamber with wooden floors and four in a chamber with grid floor. All rats received the Conditioning phase in the second environment and the house lights that were on throughout Pre-exposure and Test were turned off to provide a further difference. The CE-Pairings group received the Conditioning phase in this changed environment and received tone-pellet presentations in the usual manner (see METHOD, CHAPTER 2). The CE-Food-alone group were given the Conditioning phase in the changed environment but received only food and no tones, on the same schedule as the other group. Test sessions were in the original environment and all animals were injected with pipradrol (10 mg/kg) prior to the Test.

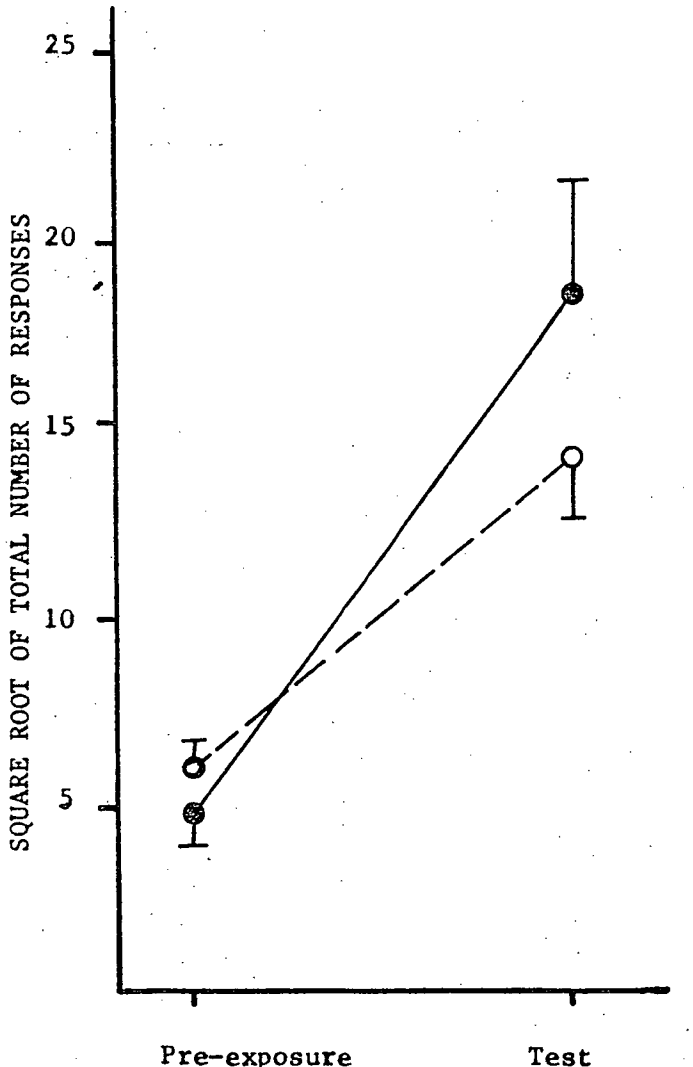
Results

Mean number of responses on each lever in both phases for the CE-Pairings and CE-Food-alone groups are shown in Figure 6. Both groups increased their overall responding from Pre-exposure to Test. The CE-Food-alone group showed no relative increase in responding on the tone lever but the CE-

Figure 6: Mean number (+SEM) of responses (square root) on the tone (closed circles) and no-tone (open circles) lever in the Pre-exposure and Test phases for the CE-Pairing (A) and CE-Food-alone (B) groups in Experiment 5. Both groups received pipradrol prior to test (10 mg/kg). The increase in responding on the tone lever was marginally greater than on the no-tone lever for A; there was no significant difference in the amount of increase in responding on the two levers for B.

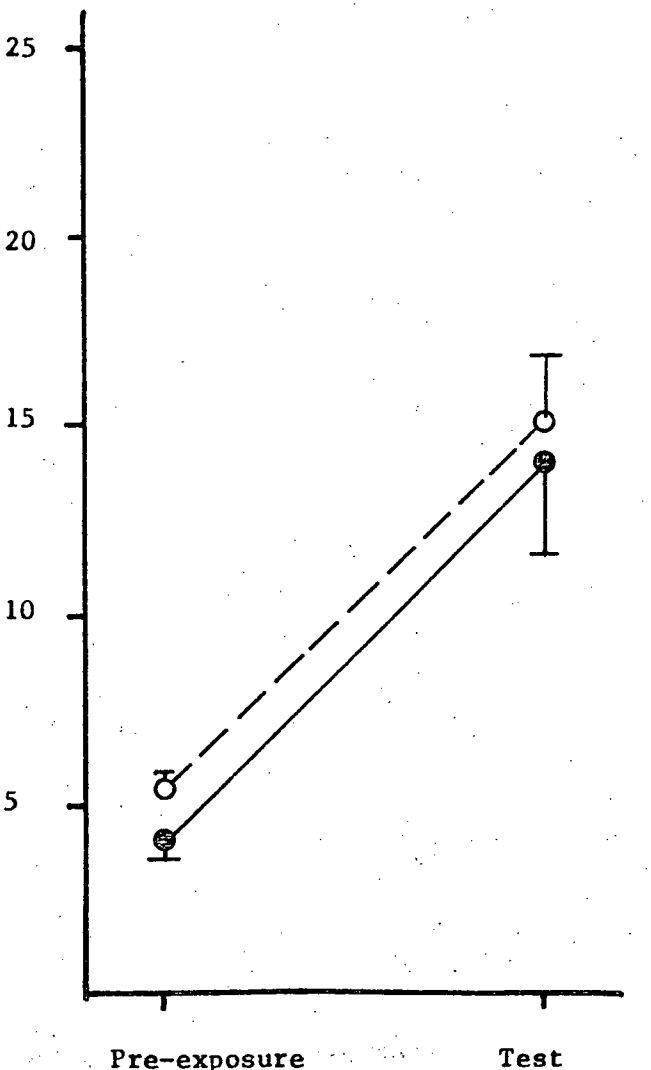
A CE PAIRING

Pre-ex: TONE
Cond: TONE & FOOD
CHANGED ENVIRONMENT
Test: PIPRADROL (10 mg/kg)



B CE FOOD ALONE

Pre-ex: TONE
Cond: NO TONE, FOOD
CHANGED ENVIRONMENT
Test: PIPRADROL (10 mg/kg)



Pairings group increased their response rates more on the tone lever than on the no tone lever.

Two-way analysis of variance revealed a significant increase in overall responding on both levers from Pre-exposure to Test ($F=23.12$, $df=1,7$, $p<.002$ for CE-Pairings group; $F=58.46$, $df=1,7$, $p<.001$ for the CE-Food-alone group). Phase by lever interaction for the CE-Pairings approached significance ($F=3.79$, $df=1,7$, $.05<p<.10$) while this interaction was far from significance for the CE-Food-alone group ($F<1$, $df=1,7$, $p>>.05$). Examining the scores of the individual animals supported this interpretation of the data; four of the animals in the CE-pairings group changed their preference somewhat while similar change was seen with only one animal from the other group.

DISCUSSION

These results demonstrated that the increase in responding on the tone lever after feeding alone during the Conditioning phase (Experiment 3) was lost if the feeding occurred in a different environment (the CE-Food-alone group). In the CE-Food-alone group, sensory preconditioning arising from pairing of tones to environmental stimuli and food to the same environmental stimuli could not occur; tones and food could be associated only with different sets of environmental stimuli. Thus, these results can be used to support indirectly the role of an associational mechanism such as sensory

preconditioning. An enhancement of responding for tones was obtained when pellets and tones were presented together in the changed environment. This showed that tone-food pairings can produce conditioned reinforcement in the absence of sensory preconditioning.

EXPERIMENT 6

As in Experiment 5, this study was designed to prevent the association between tones and the environmental stimuli that were present during the Conditioning phase. In Experiment 5 this was achieved by changing the environmental cues, thus preventing any association mediated by common environmental stimuli. In the current experiment, the tone was ommitted from the Pre-exposure phase and the animals were given food alone in the Conditioning phase. Therefore, the environmental stimuli remain constant from Pre-exposure to Test but their role in sensory preconditioning was precluded by the fact that the tones and environmental stimuli never occurred together prior to the Test phase. In both cases, if the sensory preconditioning hypothesis is correct, no tone-food association should be formed. Thus, the tone should not acquire conditioned reinforcing properties.

Procedure

Eight rats were assigned to the No-tone-pre-exposure, Food-alone group. During the Pre-exposure phase, depression of either lever had no programmed consequences, i.e., no tones were presented. In the Conditioning phase, food pellets (no tones) were delivered according to the usual random time schedule. All the rats received injections of pipradrol (i.p. 10 mg/kg) 15 min prior to test.

RESULTS

Figure 7 shows the responses on each lever in both phases for the No-tone-pre-exposure, Food-alone group. There was an overall increase in responding from Pre-exposure to Test but no significant evidence of a relative increase in responding on the tone lever from Pre-exposure to Test. Analysis of variance revealed an overall effect of phases ($F=26.99$, $df=1,7$, $p<.001$) whereas the phase by lever interaction was insignificant ($F<1.0$, $df=1,7$, $p>.05$).

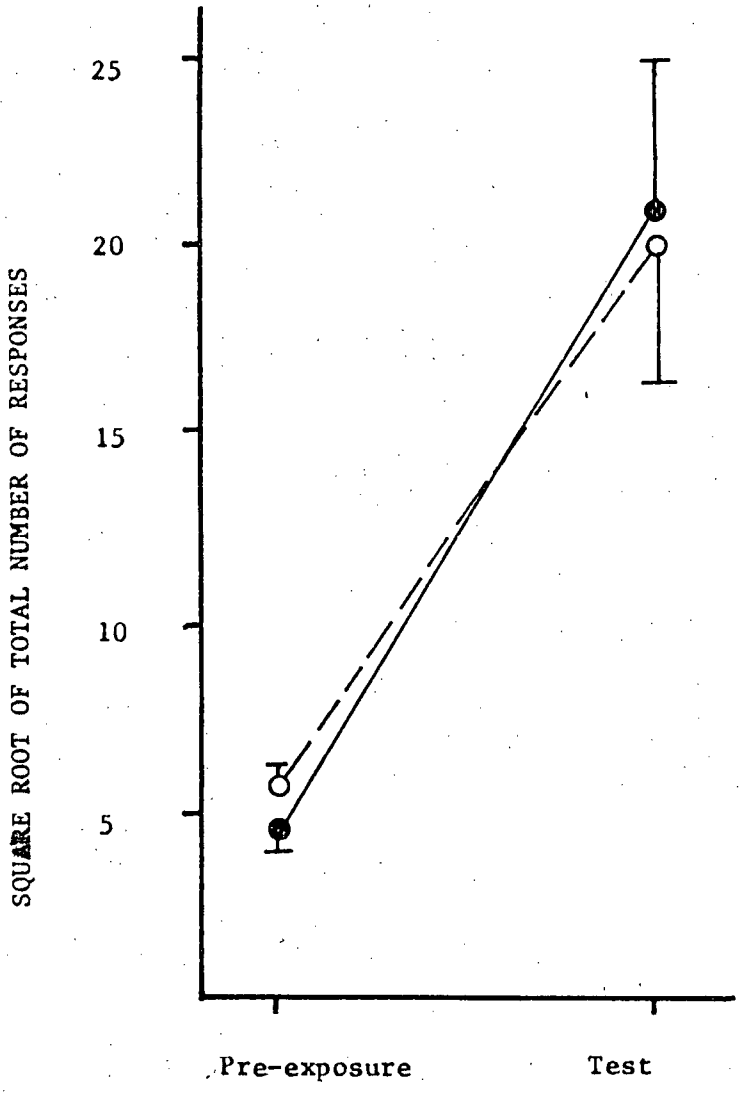
DISCUSSION

The results of Experiment 6 are in good agreement with those from the CE-Food-alone group of Experiment 5. It seems that feeding alone in the Conditioning phase only results in increased responding for the tones if tones and the environmental stimuli present during the Test phase have been associated previously. This is consistent with the hypothesis

Figure 7: Mean number (+SEM) of responses (square root) on the tone (closed circles) and no-tone (open circles) levers in the Pre-exposure and Test phases for the No-tone-pre-exposure, Food-alone group of Experiment 6. 10 mg/kg of pipradrol was injected prior to Test. There was no significant difference in the increase in responding on the two levers.

NO TONE PRE-EXPOSURE, FOOD ALONE

Pre-ex: NO TONE
Cond: NO TONE, FOOD
Test: PIPRADROL (10 mg/kg)



that the effect is mediated by sensory preconditioning.

DISCUSSION OF CHAPTER 3

It appears that pipradrol increases responding for conditioned reinforcement (Control, Pipradrol, Food-alone-control and CE-Pairings groups) but not for stimulus change (the No-food and No-tone-Pre-exposure groups) relative to responding on a "no stimulus" lever. Clearly, this cannot be due to any enhancement of lever-pressing in general. This is in complete agreement with the existing literature with one proviso; in the present paradigm, conditioned reinforcement can be established not only by direct pairings of tones and food (e.g., the Control group) but also by feeding in the presence of environmental stimuli common to Pre-exposure, Conditioning and Test phases (Food-alone and Food-alone control groups as compared to the CE-Food-alone group). Feeding alone will not produce this effect in certain circumstances, as shown by the No-tone-Pre-exposure and CE-Food-alone groups, thus ruling out an explanation of this effect in terms of "sensitisation" by feeding or "pseudoconditioning". As stated earlier, sensory preconditioning may provide a possible mechanism for this indirect association.

The establishment of conditioned reinforcement by sensory preconditioning provides a possible explanation for the previous observation of a conditioning effect in a group of animals that received random pairings of tones and food during Conditioning (Beninger & Phillips, 1980). The mechanism of

sensory preconditioning proposed here would account for this result. The mediation of conditioned reinforcement would be similar to that hypothesised to occur in the Food-alone groups. During Pre-exposure, tones would be associated with environmental stimuli and during conditioning, the animals would be fed in the presence of the same environmental stimuli. Some direct pairings of tones and food would be expected to occur on a random basis (see Beninger & Phillips, 1980) and would act to enhance further the association of tones and food. This hypothesis would, then, predict that the tones would acquire reinforcing properties due to their occurence in the presence of environmental stimuli which signalled food. It is interesting to note that in the same study when food pellets were presented explicitly unpaired with tones no conditioning effect was observed during Test. This agrees with the finding in the CE-pairings group that explicit contingency between tones and food during Conditioning can override some effects of sensory preconditioning. These data suggest also that, in some circumstances, a predictive relationship between stimuli is not necessary for the formation of association between them (e.g., Food-alone control group). This suggests that factors other than contingency (Rescorla, 1967; Rescorla & Wagner, 1972) can have a major effect on the formation of associations. This seems to be true at least when one stimulus is a transient event (such as a tone or food pellet presentation) and the other continuously present (such as

background illumination or floor texture). In these cases, occurrence together seemed a sufficient condition for association. For a further discussion, see: GENERAL DISCUSSION.

CHAPTER 4: EFFECTS OF PIPRADROL ON "CONDITIONED SUPRESSION" TO CLASSICALLY CONDITIONED AND SENSORY PRECONDITIONED STIMULI IN THE RAT

Introduction

In CHAPTER 3 of the present thesis it was proposed that sensory preconditioning (SPC) played a role in determining some of the behavioural effects of pipradrol. This proposal will be evaluated further in the present section.

The experimental paradigm used in CHAPTERS 2 and 3 was not designed to demonstrate SPC. It was suggested, however, that SPC occurred and that its effects on behaviour were enhanced by 10 mg/kg of pipradrol. This is to be evaluated by employing a procedure developed to display the effects of SPC and then observing the effects of pipradrol. This will permit a direct examination of the SPC process that was invoked previously on the basis of indirect evidence.

SPC has been shown to occur in appetitive situations (Adamacek & Melzack, 1970; Brown, Urmer, & Carr, 1958) but has been studied most frequently with aversive procedures (see, Thompson, 1972). "Conditioned supression"(Kamin, 1965) of licking in the rat has been used to demonstrate SPC (Prewitt, 1967; Tait, Maquis, Williams, Weinstein, & Suboski, 1969; Tait, Black, & Katz, 1972) and seems to provide clear, reliable demonstrations of SPC. This procedure measures the

disruptive effect of a stimulus on an ongoing behaviour. First, a tone stimulus is paired with electric shock "off baseline" (i.e., while the animal is not engaged in the response that is to be measured later). This pairing can be done by direct, classical conditioning or SPC; these procedures will be described later. Secondly, the effect of noncontingent presentations of this stimulus on the licking behaviour of water-deprived rats is observed relative to controls. Control animals have equal exposure to shock and tones but never in any paired fashion.

The first experiment examined the effects of pipradrol on supression produced by a stimulus classically conditioned to shock. This determined the suitability of the basic lick-supression measure as an index of the behavioural effects of pipradrol. Incidentally, this also allowed an examination of whether the effects of pipradrol are dependent on a given motivational state; in this section stimuli were paired with shock, as compared to stimuli paired with food in the previous sections.

The second experiment attempted to establish SPC in this paradigm in undrugged animals. The tone stimulus was paired indirectly with shock by means of SPC and the effects of this stimulus on ongoing behaviour was observed relative to controls. Thirdly, the effects of pipradrol administered prior to testing were observed in a separate group of animals given SPC training.

Following the description of the GENERAL METHOD of this

section there is an account of the procedure and results of experiments 7 to 9 followed by a general discussion.

GENERAL METHOD

Subjects

Eighty-four male albino rats of the Wistar strain were housed individually in a climatically-controlled colony room kept on a twelve hour light/dark cycle. Rats weighed from 180 to 275g at the start of the experiment. Food was available in the home cage at all times.

Apparatus

Two Plexiglas chambers (20cm x 18cm x 16cm) with grid floors contained within ventilated, sound-attenuating chests served as Training and Testing environments. Each chamber contained a drinking spout connected to a "drinkometer" circuit and a lever, depressions of which had no programmed consequences. A 4500 Hz tone generator (Sonalert) and a 5.5 W light were mounted near the drinking spout. A third, similar Plexiglas chamber housed in a small darkened room served as the environment for Conditioning. The grid floor of this chamber could be electrified by means of a direct current shocker. All data collection was performed by a Data General Nova 3 computer.

Procedure

Before the commencement of an experiment animals were handled for three min per day for four consecutive days. Prior to Training, animals were accustomed to a water-deprivation schedule; for one day, subjects had 20 min of access to water in the home cage. On the following day, they were given 15 min of access to water and on the third day, 10 min of access. Animals were maintained on 10 min access to water per day, either in the home cage or experimental chambers, throughout the remainder of each experiment.

All experiments consisted of three phases: Training, Conditioning and Test. During training animals were placed in the experimental chambers for 10 min with the water spouts present and water freely available. The licks of each animal at the water spout were recorded via the "drinkometer" circuit during 10-sec intervals throughout the 10 min session. Unless an animal failed to drink for five min or more of the session, no access tc water was given between sessions; animals drinking for less than five min were given water for an additional 5 min in the home cage 30 min after the end of the sesssion.

After four days of Training, animals received the conditioning trial. Details of individual Conditioning phases are given in the METHOD section of each experiment.

Test trials took place on the day following conditioning. Animals were returned to the Training chambers with the water

spouts present and water freely available. After the animal had made an initial 150 licks the test trials could begin. Presentation of the 4500 Hz tone stimulus (i.e., a test trial) was controlled by an "on-line" computer system. Contingencies were arranged so that tone presentations were made only during stable periods of the baseline (licking) behaviour. The criterion of stability was set so that an animal needed first to have made at least 40 licks during a 10-sec period (the "pre-CS" period) and at least three licks during the last second of this period. On fulfillment of these conditions the tone was presented. The minimum inter-trial interval was set at 150 licks. Thus, following a Test trial at least 150 licks needed to be made before the next pre-CS period would occur. After initiation of the first trial failure to make any licks during any 5 min period resulted in the termination of the Test session.

The time to complete the first 150 licks was recorded for each animal, as was the time taken to initiate the first trial. Dependent variables were the number of licks made during each 10-sec period and the number of licks made during each tone presentation. A suppression ratio for each animal on each trial was obtained by dividing the number of licks made during the tone presentation by the total number of licks made during the tone presentation and during the pre-CS period.

EXPERIMENT 7

This experiment examined the effect of pipradrol on "conditioned suppression". Previous studies have shown significant "conditioned suppression" following a single tone-shock conditioning trial (Lubow & Siebert, 1969) and a similar procedure is followed here. Comparing the behaviour of the "experimental" and "control" group subjects that received saline prior to test allows for a demonstration of significant suppression produced by this training. Comparing the effects of the drug in these two groups allows an assessment of pipradrol's effect on "conditioned suppression". If pipradrol enhances the disruptive effect of a stimulus on ongoing behaviour primarily on the basis of a previously established association with shock, increased suppression should be seen in animals treated with pipradrol in the group that received tone-shock pairing but not in the other (control) group.

Procedure

Twenty-four rats were assigned randomly to one of two groups, the "experimental" (n=12) and "control" (n=12) groups. All rats received an identical history of handling and water deprivation. The Training phase was identical for all rats and was carried out as described in the GENERAL METHOD.

For the rats in the "experimental" group, Conditioning consisted of being placed in the Conditioning chamber for 10 min; after 2 min animals received a single presentation of a

10-sec 4500HZ tone the termination of which coincided with the presentation of a 0.5-sec 2 mA shock to the feet. For the "control" group, Conditioning was similar except that the shock occurred 120 sec after the termination of the tone.

All animals received 10 min of access to water in the home cage approximately 30 min following Conditioning. This replaced the 10 minutes of access to water that was given in the Training chambers on the previous days.

On the next day the Test phase took place. Animals were returned to the Training chamber with the water spout present and water freely available. Tones were presented as described in the GENERAL METHOD above. Six animals in the "experimental" group and six in the "control" group received i.p. injections of 10 mg/kg pipradrol 15 min prior to Test (drug preparation was described in CHAPTER 2). The remaining animals in both groups received injections of saline 15 min prior to the Test.

RESULTS

Training

During the Training phase all animals learned rapidly to drink from the water spout in the Training chambers. Usually, by the second day, animals would lick for the entire ten min period apart from a brief bout of exploratory behaviour when first placed in the chamber. Average lick rates ranged from 3

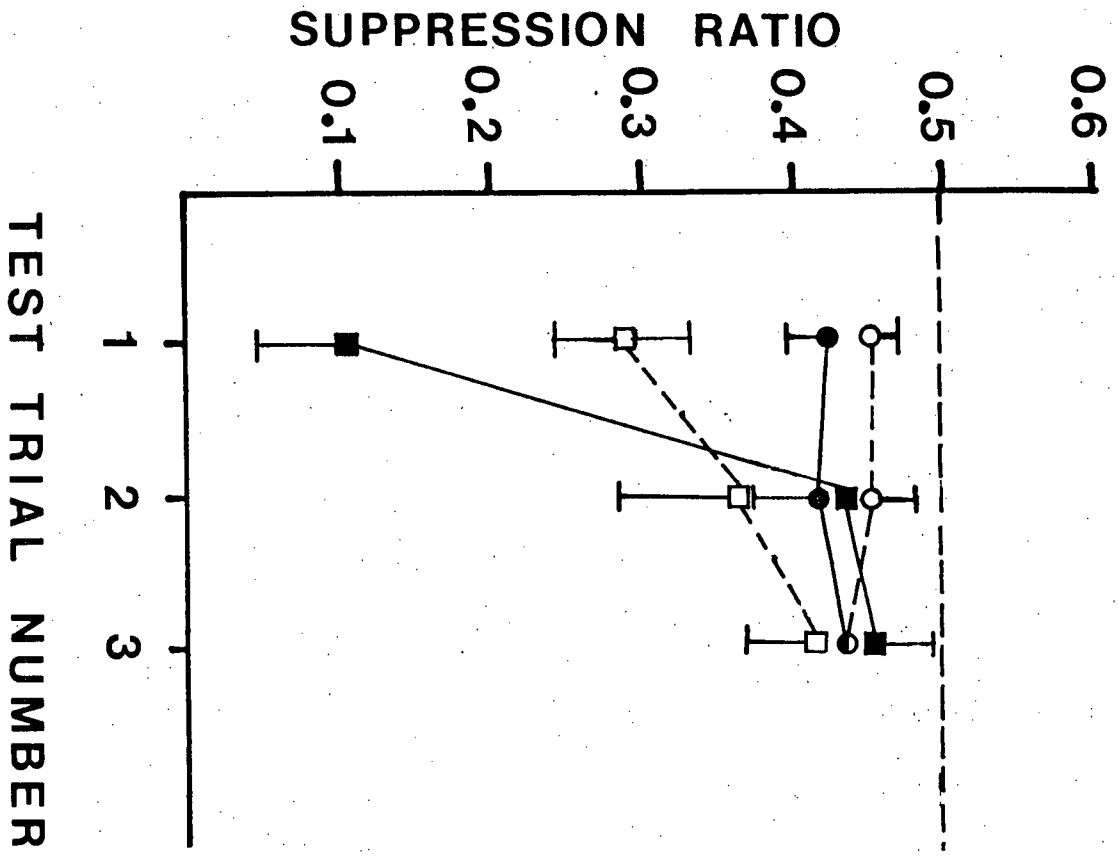
to 5 per second over the ten minutes and varied little for any particular animal.

Test

Suppression ratios were calculated as described above for each animal on each trial. Figure 8 shows these data for the "experimental" and "control" groups. For the "experimental" group, the animals given pipradrol prior to test show increased suppression as reflected by decreased ratios relative to saline-treated animals. This difference decreases after the first trial as both groups approach the level reflecting no suppression to the stimulus (a ratio of 0.5). For the "control" group, treatment with pipradrol produced no large or consistent effects.

The data for the first trial were subjected to statistical analysis. A oneway analysis of variance revealed a significant effect of groups ($F=16.4$, $df=3,19$ $p<.001$). Multiple comparisons among the means were carried out according to the procedures of Duncan and Newman-Keuls. Comparisons revealed that the mean of the pipradrol-treated "experimental" group animals differed significantly ($p<.05$) from all the other group means. This was true also for the mean of the saline-treated "experimental" group. The means of the saline-treated and pipradrol-treated "control" groups failed to differ from one another, but differed from the other two means. Thus, the saline-treated "experimental" animals

Figure 8. Mean suppression ratios (+SEM) for the animals of Experiment 7. Groups are represented as follows:
Experimental group: saline-injected; open circles.
Experimental group: pipradrol-injected (10 mg/kg); closed circles.
Control group: saline-injected; open squares.
Control group: pipradrol-injected (10 mg/kg); closed squares.


SUPPRESSION RATIO
0.1
0.2
0.3
0.4
0.5
0.6
TEST TRIAL NUMBER
1
2
3

showed increased suppression relative to controls, i.e., showed significant "conditioned suppression". Pipradrol treatment prior to test significantly enhanced the suppression shown by the "experimental" group animals. In the "control" group, this enhancement was not seen. Pipradrol, then, enhanced "conditioned suppression".

It is important to note, also, that 10 mg/kg of pipradrol had no generally disruptive effect on licking. The average time to complete the inter-trial interval of 150 licks (a measure of licking in general) did not differ significantly for the two groups, with a mean of 60.5 sec for the saline-treated animals and a mean of 61 sec for the pipradrol-treated animals. This is confirmed by the finding of no significant effect of the drug in the "control" group, or in any of the groups after the first trial. Thus, the effect of pipradrol seems be an enhancement of the disruptive properties of the CS for shock on ongoing behaviour.

In summary, it appears that 10 mg/kg pipradrol enhanced conditioned suppression in this paradigm on the first trial. This enhancement was not seen in the "control" group. This is seen most clearly by comparing the first trial to later trials for the "experimental" group; the later trials show the reduced enhancement of suppression that would be expected to accompany "extinction" of the tone-shock association over the Test trials.

EXPERIMENT 8

This experiment was designed to demonstrate SPC in the same paradigm that was used in Experiment 7. Such a demonstration would parallel the results of Prewitt (1967) and others who have found clear evidence for SPC using a lick-suppression measure.

In this experiment, animals underwent Training as described for Experiment 7 but the Conditioning phase differed. During Conditioning animals received one of three patterns of exposure to conditioning stimuli: animals in the SPC "experimental" group received paired light-tone presentations followed by the presentation of a light paired with shock. This procedure should establish an association between the tone and shock by means of SPC. "Control" animals received similar presentations, but with either (a) the tones and lights presented in an unpaired fashion or (b) with the light and the shock unpaired. These procedures should control for the tone-shock association produced by SPC in the "experimentals" (see, Rizley & Rescorla, 1972). Greater suppression of licking in the presence of the tone during Test by the "experimental" group compared to the "controls" would provide a demonstration of SPC.

Procedure

Eighteen rats were assigned randomly to either the SPC "experimental" group or one of two "control" groups. All the rats received an identical history of handling and water-deprivation. The Training phase was identical for all rats and was carried out as described in the GENERAL METHOD.

During Conditioning, all rats first received 10 min of access to water in the Training chamber. At the end of this period animals were exposed to light and tone stimuli. The six "experimentals" received four presentations of a 10-sec tone stimulus the termination of which coincided with the onset of a 10-sec 5.5 W light stimulus. One "control" group (n=6) received identical presentations of the same light and tone. The other "controls" received presentations of these stimuli individually and separated by 45 sec. After this exposure, the animals were transferred to the Conditioning chamber. The "experimentals" received one presentation of a 5.5 W light followed immediately by a 0.5-sec 2mA shock to the feet. The "control" animals that had received the unpaired presentations of lights and tones received the same light-shock pairing. The other "control" animals recieved a presentation of the light followed by the shock 120 sec after its termination.

On the next day, the Test took place. No injections were given prior to Test.

RESULTS

Training

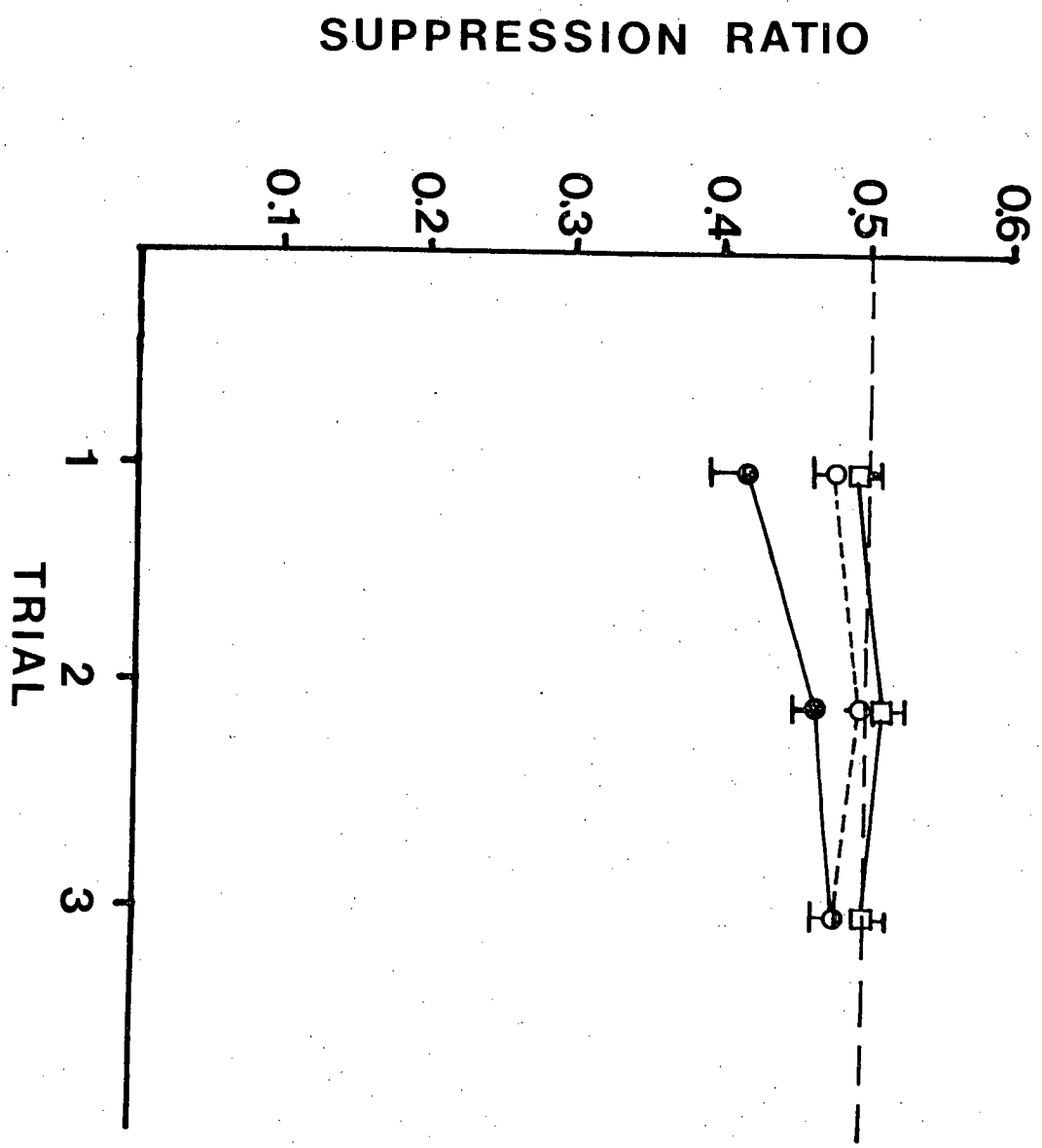
As in the previous experiments all animals learned rapidly to drink from the water spout in the Training chamber.

Test

Suppression ratios for the animals in experiment 8 are presented in Figure 9. The SPC "experimental" animals showed greater suppression of licking upon presentation of the tone than the "control" animals.

Statistical analysis was performed on the data for these animals: the two "control" group means failed to differ ($F<1$, $df=1,11$ $p>.1$) and were almost identical; all the "control" animals were combined into one "control" group for the purpose of analysis. A oneway analysis of variance with groups ("experimental" vs "control") and trials as variables and repeated measures on trials was carried out. This revealed a significant effect of group ($F=7.1$, $df=1,16$ $p<0.05$), trial ($F=8.9$, $df=2,32$ $p<0.05$) and a significant interaction of group by trial ($F=3.4$, $df=2,32$ $p<0.05$). Thus, the SPC "experimentals" showed greater overall suppression than the "controls", the amount of suppression decreased over trials and the group difference was not the same on all trials (giving rise to the significant interaction). Post hoc tests

Figure 9: Mean suppression ratios (+SEM) for the animals of Experiment 8. Data for SPC experimentals are represented by the closed circles. Open squares are data for the control animals that received random exposure to lights and tones in conditioning. Open circles show data for the controls that received the light and shock in unpaired fashion.


SUPPRESSION RATIO
0.1
0.2
0.3
0.4
0.5
0.6
TRIAL
1
2
3

revealed a significant effect of groups on trials one and two ($F=5.8$, $df=1,16$ $p<0.05$; $F=5.0$, $df=1,16$ $p<0.05$, respectively) but not on trial three ($F=1.2$, $df=1,16$ $p>0.05$). Thus, the SPC "experimentals" showed increased suppression to the tone relative to "controls" on the first two trials of the Test session. This provides a demonstration of SPC in this experimental situation.

EXPERIMENT 9

This experiment examines the effect of pipradrol on SPC. Animals receiving the same conditioning procedure given to either SPC "experimentals" or "controls" in Experiment 8 were treated with pipradrol or saline prior to test. Comparing the effects of pipradrol in the two groups reveals the effect of pipradrol on SPC in this paradigm.

Procedure

Twenty-four rats were assigned randomly to either an SPC "experimental" group or an SPC "control" group. All animals received an identical history of handling and water-deprivation. Training was identical for all rats and was carried out as described previously.

During the conditioning phase, animals in the "experimental" group received the same exposure as described in Experiment 8 for "experimental" group animals. The "control" animals received the procedure of paired lights and

tones but unpaired light and shock described in Experiment 8.

Six animals in the "experimental" group and six in the "control" group received i.p. injections of pipradrol (10 mg/kg) 15 min prior to Test. The remaining animals received injections of saline prior to Test.

RESULTS

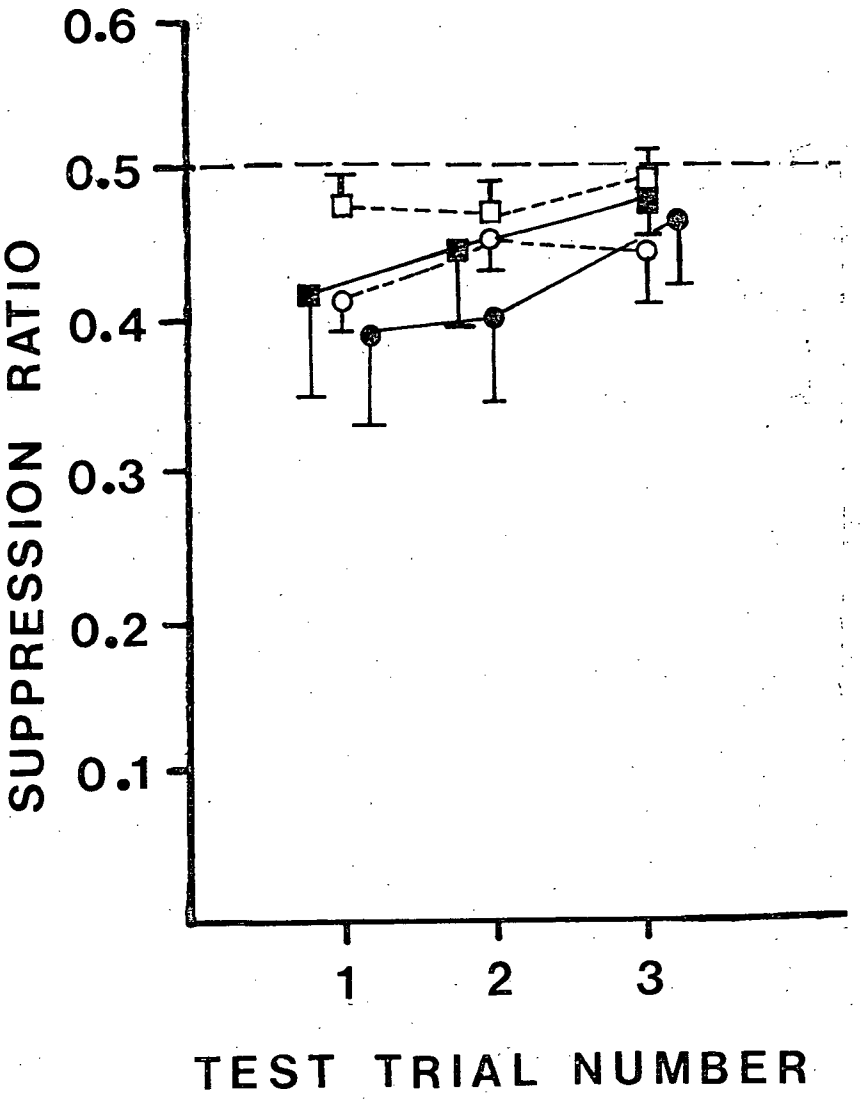
Training

As in the previous experiments all the animals learned readily to drink from the water spouts in the Training chambers.

Test

Supression ratios for the animals in Experiment 9 are presented in Figure 10. Oneway analysis of variance revealed an effect of group on the first trial only ($F=3.3$, $df=1,19$ $p<.05$). Multiple comparisons were carried out according to the procedure of Duncan. The only significant differences ($p<.05$) among the means were between the saline-treated "controls" and both groups of "experimentals". Thus pipradrol did not enhance the effect of SPC in this experiment.

Figure 10. Mean suppression ratios (+SEM) for the animals of Experiment 9. Groups are represented as follows:
SPC "experimental" group: saline-injected; open squares.
SPC "experimental" group: pipradrol-injected (10 mg/kg); closed squares.
Control group: saline-injected; open circles.
Control group: pipradrol-injected (10 mg/kg); closed circles.


0.6
0.5
0.4
0.3
0.2
0.1
SUPPRESSION RATIO
1
2
3
TEST TRIAL NUMBER

DISCUSSION

The results of this series of experiments show that pipradrol (at 10 mg/kg) enhanced behavioural suppression during the presentation of a stimulus paired previously with shock in a classical conditioning procedure. However, this enhancement was not seen if the suppression was produced by a stimulus paired previously with shock by SPC.

These data provide the first evidence of pipradrol enhancing a suppressive effect of a stimulus on behaviour. This finding parallels earler reports of d-amphetamine enhancing "conditioned suppression" (e.g., Miczek & Lutginger, 1978). Such suppression paradigms have the advantage over many appetitive procedures in that the observed drug effect is in the opposite direction to the general stimulant effect of the drug. The failure to see enhanced SPC-produced suppression could be due to a number of factors. Dose-dependency of the effect may account for this. 10 mg/kg of pipradrol is, however, found generally to be an optimally-effective dose of the drug (see, earler in this thesis; Robbins, 1978). For further elaboration, see GENERAL DISCUSSION.

CHAPTER 5: GENERAL DISCUSSION

It is well established that pipradrol enhances the effects of conditioned reinforcing stimuli on behaviour (Hill, 1970; Robbins, 1972, 1976 & 1978; Robbins & Koob, 1978). The present data provide further confirmation of this effect and extend the understanding of it in a number of important respects: firstly, pipradrol was observed to enhance responding for conditioned stimuli paired previously with food. Earlier studies employed water (Robbins, 1976), milk (Hill, 1970) or brain stimulation reward (Robbins & Koob, 1978). Secondly, there was the unexpected observation of enhanced responding for stimuli associated indirectly with reward, possibly by SPC. In a third series of experiments, pipradrol was shown to enhance conditioned suppression of drinking to a stimulus paired previously with shock. This demonstrated that the stimulant pipradrol can not only increase rates of responding but also increase behavioural inhibition.

The lick-suppression paradigm used in this thesis provides the first evidence of pipradrol enhancing the suppressive effects of a conditioned stimulus on behaviour. However, this is consistent with earlier studies in which other stimulants were shown to enhance "conditioned suppression" to a stimulus signalling shock (Appel, 1963; Lauener, 1963; Miczeck and Luttinger, 1978; Tenen, 1967). This effect has been observed in guinea pigs, as amphetamine

enhanced freezing behaviour that occurred normally when the experimenter entered the testing area (Randrup & Munkvad, 1967).

The paradigm used to demonstrate the effect of pipradrol on "conditioned reinforcement" was derived from an earlier study by Beninger and Phillips (1980). In this paradigm, the measure of conditioned reinforcement was an increase in total responses made on a lever providing the conditioned stimulus as compared to responses on a "no stimulus" lever. This paradigm was developed from those of Stein (1958) and Knott and Clayton (1966), using their operational definition of conditioned reinforcement. It could be argued that this measure might result in an exaggerated assessment of responding for conditioned reinforcement as it includes all responses made on the tone lever, not just those producing the tone stimulus. Furthermore, the lack of a stimulus on the second lever may have allowed responding for stimulus change to affect the results. This could have been controlled for by having a second stimulus, itself uncorrelated with reward, produced by the other lever. Beninger (unpublished data) has, however, observed a good relationship between the increase in this response-measure of conditioned reinforcement and the number of tone stimuli received by the animals in pilot data. Thus, though this measure is not as precise as it could have been, it has been previously accepted as an index of conditioned reinforcement and the results obtained parallel those from other paradigms. This demonstrates the generality

of this effect of pipradrol across experimental situations.

The enhancement of behavioural suppression by stimulants has implications for theories of their action. It has been hypothesised that these stimulants enhance the "motivational" properties of stimuli, either unconditioned (Stein, 1964) or conditioned (Hill, 1972). Other theories have attempted to account for the effects of these drugs on behaviour in terms of motor stimulant action per se (Dews, 1958; Lyon & Robbins, 1975). Dews, for example, hypothesised that low doses of amphetamine enhanced low (<20 responses per min) rates of responding preferentially and that high doses increased rates of responses that could be repeated rapidly and were of short duration. An extension of this hypothesis was proposed by Lyon and Robbins (1975). They proposed that psychomotor stimulants act to excite behaviour, but within only certain categories. At low doses, it was proposed that stimulants excite behaviours within a large number of categories. This could account for the increased general locomotor activity. At higher doses, excitation was thought to occur only within restricted categories of behaviour. The behavioural categories would be determined by the presence of stimuli of established motivational significance and include responses with short duration and lack of complexity (see, Lyon & Robbins, 1975). Thus, the stereotyped behaviours seen at high doses of these drugs were proposed to arise from maximal excitement occurring within very restricted categories of behaviour. Licking and biting would predominate among unconditioned behaviours in the

rat because they are of short duration, can be repeated rapidly and do not include a complex sequence of responses. Also, they occur frequently when members of this species are in the undrugged state. According to this theory, two factors would account for the present observation of increased responding on the lever providing the conditioned stimulus. First, the tone stimulus would increase the probability of a particular category of behaviour, i.e., barpressing on a specific lever and, secondly, the drug would increase responding within this category, preferentially. The apparent enhancement of responding for conditioned reinforcement would be attributed to the same excitatory mechanism thought to be responsible for the production of stereotyped behaviour.

On the one hand, the enhancement of conditioned suppression by pipradrol would appear to support Hill's (1970) contention that stimulants enhance the "motivational" properties of conditioned stimuli. However, Lyon and Robbins' proposal could account for these data by assuming that in the presence of the conditioned stimulus a specific class of freezing behaviour has a high probability of occurrence. Thus, in the presence of the stimulus, the stimulant effect of the drug would be seen primarily within this class of behaviour, resulting in increased suppression of ongoing drinking behaviour.

Evidence against the Lyon and Robbins' theory can be found in a study by Miczeck and Luttinger (1978). This study examined the effect of amphetamine on suppression of

barpressing for food to a stimulus paired either with shock or food. Presentation of a stimulus paired previously with shock results usually in suppression of operant responding for food (the "conditioned emotional response" or "conditioned suppression"); similar suppression of barpressing has been observed during the presentation of a stimulus paired previously with a high incentive food reward, such as sweetened milk ("positive conditioned suppression"; Azrin & Hake, 1969). Amphetamine enhanced suppression to the "pre-shock" stimulus but increased responding during the "pre-food" stimulus. According to the Lyon and Robbins theory, both stimuli would be signals for decreased bar-pressing and, therefore, suppression should be enhanced to both stimuli irrespective of their associations with different unconditioned stimuli. It must be noted, however, that in this study it proved impossible to equate completely the amount of supression to the conditioned stimuli in both cases; the "pre-shock" stimulus always elicited greater suppression than the "pre-food"stimulus. Drug treatment may have differentially affected the suppressive effects of the stimuli due to this difference in level of suppression, rather than because of the difference in association with unconditioned stimuli.

Data from Robbins' laboratory supports the Lyon and Robbins (1975) theory. In this study (Robbins, 1976), animals first had to press one lever, then a second, to obtain a conditioned reinforcer. Pipradrol increased the level of responding but primarily on the second lever. This reduced the

total number of conditioned reinforcers obtained, compared to saline controls. This suggests that the increased responding was maintained, at least in part, by perseverative rather than "reward-enhancing" effects. It appears that the stimulant effects of stimulant drugs may have multiple determinants and only careful analysis of responses made in a number of situations will allow an assessment of the relative importance of these factors.

Although the present thesis did not address directly the pharmacological issues relating to these studies, there are some important points that should be noted briefly. It has been shown (Scheel-Kruger, 1971) that all biochemical and behavioural actions of pipradrol and methylphenidate are blocked completely by reserpine but not by alpha methyltyrosine. The converse is true for amphetamine, its effects being blocked by alpha methyltyrosine and not by reserpine. Reserpine is believed to deplete a "storage pool" of catecholamines, unlike alpha mehtyltyrosine which interacts with a "newly-synthesised pool" of catecholamines (Iversen & Iversen, 1975). This pattern of reserpine-sensitivity is reflected by the fact that pipradrol and methylphenidate produced a dose-dependent enhancement of responding for conditioned reinforcement, unlike d-amphetamine in the same paradigm (Robbins, 1978). The stereotyped behaviours produced by all these drugs are, however, very similar (Braestrup, Nielson, Golembiowska, & Mogilnecka, 1972; Kuczenski & Segal, 1978). As stated earlier, it has been suggested that the

effects of these drugs in "conditioned reinforcement" paradigms and their ability to produce stereotyped behaviours share a common basis (Lyon & Robbins, 1975; Robbins, 1976). The ability of these drugs to produce stereotyped behaviour does not seem to depend on an interaction with the "storage pool" of catcholamines, as it occurs across the range of these drugs; however, the nature of their interaction with responding for conditioned reinforcement does appear to differ (Robbins, 1978). This is evidence against these two behavioural effects sharing a single underlying pharmacological mechanism. This suggests also that caution should be exercised when attempts are made to generalise about these drugs.

This discussion has concentrated on the fact that pipradrol (at 10 mg/kg) enhances the effect on behaviour of stimuli paired directly with reward. However, it should also be noted that similar effects were observed with stimuli paired indirectly with food. This conclusion is supported by the pattern of increased responding for tones observed in the conditioned reinforcement paradigm when tones had occurred in the the same environment in which feeding had taken place. Such results are consistent with an indirect association between tones and food due to SPC, the effect of which is enhanced by the stimulant. Another possible explanation of of these data is that the drug enhanced the effects of a "non-associative" effect of feeding on responding for the tone stimulus, such as "sensitisation". Two results make this

unlikely. Firstly, the group of animals fed in a different environment from that of Pre-exposure and Test phases failed to show a similar pattern of enhanced responding for tones in the drugged state. This rules out a direct effect of feeding per se. Secondly, again in drugged animals, feeding failed to produce enhanced responding for tones in the absence of prior exposure to tones.

It should be asked, however, whether the indirect association proposed to account for the present data has been observed in other studies of the effect of pipradrol on responding for conditioned reinforcement? Earlier studies using pipradrol have observed its effect on responding for the test stimulus in animals never exposed to the unconditioned stimulus (Robbins, 1978; Robbins & Koob, 1978) or on responding on a "no stimulus" lever (Robbins, 1975) as controls for the effects of the conditioned reinforcer. In neither of these control conditions would an indirect association, as hypothesised above, be expected to influence the pattern of responding. In one study (Robbins, 1976) the effect of pipradrol on responding for a stimulus paired previously with reward was compared to that on responding for the same stimulus whose presentation was randomly correlated with reward. In this situation, some indirect association would be expected in the randomly-exposed group. Responding for the uncorrelated stimulus was slightly enhanced by the drug on first two test trials, despite very low overall levels of responding. Numerous procedural differences such as the use

of repeated drug testing, water as the reinforcer and differing amounts of training and preexposure to the stimuli could account for the failure to see clear evidence of any indirect association, such as that seen in the present study.

Thus, an effect of SPC was inferred on the basis of indirect evidence from a paradigm not designed to display such effects. To further evaluate this possibility, the effect of pipradrol was observed in a lick suppression paradigm that had been used by others previously to demonstrate SPC (e.g., Prewitt, 1967). However, pipradrol failed to enhance explicit SPC effects in the lick-suppression paradigm. This occurred despite the previous demonstration of enhanced suppression to a stimulus paired directly with shock in the same paradigm. Failure to observe enhancement of SPC in the suppression paradigm does not allow for any firm conclusion regarding the possible effects of pipradrol on SPC in the appetitive paradigm used in this thesis. Enhancement of SPC might be seen only in appetitive paradigms and not in the suppression situation. Also, the effect on behaviour of association of continuous events such as floor texture, general illumination or odours and food or tones may be enhanced more readily than effects of association of transient lights and tones. This could be due to relative salience, duration or complexity of the stimuli.

A final matter for consideration concerns the question of indirect associations which may have been present in our experimental paradigm. The term "indirect association" refers

to the association of a stimulus with reward by virtue of its direct association with other stimuli, themselves associated directly with reward. If such associations were formed, it suggests that discrete events such as tones and the presentation of food pellets can be associated with continuous events such as overall level of illumination, floor texture or odours. This could occur as a result of the simple physical and temporal contiguity of the stimuli, and does not neccessarily imply the need for any "predictive" relationship or contingency between them (see, e.g., Rescorla & Wagner, 1972). However, there is clearly a "global contingency" between, for example, the food pellets and floor texture; the experimental chamber is the only place that the animal experiences these particular environmental stimuli together with tones or food pellet presentations. Such an overall predictive relationship might provide the basis for such an association, without having to invoke effects of contiguity alone. If it can be confirmed that pipradrol enhances the effect on behaviour of indirect associations between stimuili and reward through a process such as SPC, this would increase the generality of any theory attempting to account for the drug's effect on responding for conditioned reinforcement.

REFERENCES

Adamec, R. & Melzack, R. The role of motivation and orientation in sensory preconditioning. Canadian Journal of Psychology, 1970, 24, 231-239.

Appel, J.B., Drugs, shock intensity and the CER. Psychopharmacology, 1963, 4, 148-153.

Azrin, N.H., & Hake, D.F. "Positive conditioned suppression": Conditioned suppression using positive reinforcers as the unconditioned stimuli. Journal of the Experimental Analysis of Behaviour, 1969, 12, 167-173.

Beninger, R.J., & Phillips, A.G. The effect of pimozide on the establishment of conditioned reinforcement. Psychopharmacology, 1980 (in press).

Bleuler, E. Dementia Praecox. International Universities, New York, 1950.

Brown, W.L., Urmer, A.H., & Carr, R.M. The facilitative effect of sensory preconditioning on instrumental learning in the rhesus monkey. Journal of Comparative and Physiological Psychology, 1958, 51, 461-463.

Bugelski, B.R. Extinction with and without sub-goal reinforcement. Journal of Comparative and Physiological Psychology, 1938, 26, 121-134.

Cole, S.O. Brain mechanisms of amphetamine-induced anorexia, locomotion and stereotypy: a review. Neuroscience and Biobehavioural Reviews, 1978, 2, 89-100.

Creese, I., & Iversen, S.D. Blocking of amphetamine-induced motor stimulation and stereotypy in the adult rat following neonatal treatment with 6-hydroxydopamine. Brain Research, 1973, 55, 369-382.

Ellinwood, E.H. Amphetamine intoxication in non-human primates and man. In: E.H. Ellinwood (Ed.). Current concepts on amphetamine abuse, proceedings of a workshop, Dalhousie University Medical Centre. 1970.

Ernst, A.M., & Smelik, P. Site of action of dopamine and apomorphine in compulsive gnawing behaviour in rats. Experientia, 1966, 22, 837.

Hill, R.T. Facilitation of conditioned reinforcement as a mechanism of psychomotor stimulation. In Costa, E., & Garratini, L. (Eds.) Amphetamines and related compounds New york, Raven Press. 1970.

Iversen, L.I. The chemistry of the brain. Scientific American, 1978, 241. 134-149.

Kamin, L.J. Temporal and Intensity Characteristics of the Conditioned Stimulus. In: Prokasy, W.F. (Ed) Classical Conditioning: A Symposium. New York, Appleton-Century-Crofts. 1965.

Kelly, P.H. Drug induced changes in motor behaviour. In: Iversen, L.I., Iversen, S.D., & Snyder, S.H. (Eds.). Handbook of Psychopharmacology Volume 8. New York, Plenum Press. 1975

Kelly, P.H., Seviour, P.W., & Iversen, S.D. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Research, 1975, 94, 507-522.

Kiernan, C.C. Modification of the effect of d-amphetamine sulphate by past experience in the hooded rat. Psychopharmacology, 1965, 8, 23-31.

Knott, P.D., & Clayton, K.N. Durable secondary reinforcement using brain stimulation as the primary reinforcer. Journal of Comparative and Physiological Psychology, 1966, 61, 151-153.

Kuczenski, R., & Segal, D.S. Differential effects of d- and l-amphetamine and methylphenidate on rat striatal dopamine biosynthesis. European Journal of Pharmacology, 1975, 30, 244-251.

Lauener, H. Conditioned suppression in rats and the effects of pharmacological agents thereon. Psychopharmacology, 1963, 4, 311-325.

Lubow, R.E., & Siebert, L. Latent Inhibition within the CER Paradigm. Journal of Comparative and Physiological Psychology, 1969, 68, 136-138.

Lyon, M., & Robbins, T.W. The action of central nervous stimulant drugs: A general theory concerning amphetamine effects. In: Current developments in psychopharmacology Volume 2, 1975, Spectrum Publications, Inc.

Mackintosh, N.J. The Psychology of Animal Learning. New York, Academic Press. 1974.

Miczek, K.A., & Luttinger, D. Differential attenuation of two kinds of conditioned suppression by d-amphetamine and amobarbital. Journal of Pharmacology and Experimental Theraputics. 1978, 205, 282-290.

Nilakantan, B., & Randrup, A. Phylogenetic approach to the study of brain mechanisms involved in the action of amphetamine and other drugs. In: Proceedings of the Sixth International Congress of Neuropharmacology, 1968, Amsterdam.

Phillips, A.G., & Fibiger, H.C. Dopaminergic and noradrenergic substrates of positive reinforcement: differential effects of d- and l-amphetamine. Science, 1973, 159, 575-577.

Prewitt, E.P. Number of preconditioning trials in sensory preconditioning using CER training. Journal of Comparative and Physiological Psychology, 1967, 64, 360-362.

Randrup, A., & Munkvad, I. Dopa and other naturally occuring substances as causes of seereotypy and rage in rats. Acta psychiatrica Scandica Supplement, 1966, 191, 193-199.

Randrup, A., & Munkvad, I. Stereotyped activities produced by amphetamine in several animal species and man. Psychopharmacology, 1967, 11, 300-310.

Randrup, A., & Munkvad, I. Biochemical, anatomical and physiological investigations of stereotyped behaviours induced by amphetamines. In Costa, E., & Garratini, L. (Eds.) Amphetamines and related compounds New york, Raven Press. 1970.

Rizley, R.C., & Rescorla, R.A. Second order CR and sensory preconditioning. Journal of Comparative and Physiological Psychology, 1972, 78, 1-11.

Rescorla, R. A. Pavlovian Conditioning and its proper control proceedures. Psychological Review, 1967, 74, 71-80.

Rescorla, R.A., & Wagner, A.R. A theory of Pavlovian Conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In: Black, D., & Prokasy, W.F. (Eds.). Classical Conditioning II. 1972.

Robbins, T.W. The potentiation of conditioned reinforcement by psychomotor stimulant drugs. A test of Hill's hypothesis. Psychopharmacology, 1975, 45, 103-114.

Robbins, T.W. Relationships between the reward-enhancing and stereotypical effects of psychomotor stimulant drugs. Nature, 1976, 264, 57-59.

Robbins, T.W. The acquisition of responding with conditioned reinforcement: effects of pipradrol, d-amphetamine, methylphenidate and nomifensine. Psychopharmacology, 1978, 58, 79-87.

Robbins, T.W., & Koob, G.F. Piprdrol enhances reinforcing properties of stimuli paired with brain stimulation. Pharmacology, Biochemistry & Behaviour, 1978, 8, 219-222.

Sahakian, B.J., Robbins, T.W., & Morgan, M.J. The effects of psychomotor stimulants on stereotypy and locomotor activity in socially-deprived and control rats. Brain Research, 1975, 84, 195-205.

Scheel-Kruger, J. Comparative studies of various amphetamine analogues demonstrating different interactions with the metabolism of catecholamines in the brain. European Journal of Pharmacology, 1971, 14, 47-59.

Siedel, R.J. A review of sensory preconditioning. Psychological Bulletin, 1959, 56, 58-79.

Snyder, S.H. Madness and the Brain. New York, McGraw-Hill. 1974.

Stein, L. Secondary reinforcement with subcortical stimulation. Science, 1958, 127, 466-467.

Stein, L. Amphetamine and neural reward systems. In: Steinburg, H., & Knight, S.V. (Eds). Animal Behaviour and Drug Action. London: Churchill, 1964. 91-118.

Stein, L., & Ray, O.S. Self-regulation of brain stimulation current intensity in the rat. Science, 1959, 130, 570-572.

Tait, R.W., Black, J., & Katz, M. Sensory preconditioning using the CER. Canadian Journal of Psychology, 1972, 26, 201-205.

Tait, R.W., Marquis, H.A., Weinstein, L., & Suboski, M.D. Extinction of sensory preconditioning using CER training. Journal of Comparative and Physiological Psychology, 1969, 69, 170-172.

Tenen, S.S. Recovery time as a measure of CER strength: effects of benzodiazepines, amobarbitol, chlorpromazine and amphetamine. Psychopharmacology, 1967, 12, 1-7.

Thompson, R.F. Sensory preconditioning. In: Thompson, R.F., & Voss, J.F. (Eds) Topics in Learning and Performance. New York, Academic Press. 1972.

Thornberg, T.E., & Moore, K.E. The relative importance of dopaminergic and noradrenergic neurones for the stimulation of locomotor activity induced by amphetamine and other drugs. Neuropharmacology, 1973, 12, 85 3-866.

Yokel, R.A., & Wise, R.A. Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. Science, 1975 , 187, 5 47-5 48.

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