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Differential Effects of an Early Housing Manipulation on Cocaine-Induced Activity and Self-Administration in Laboratory Rats.

Alan E. Boyle

A Thesis
in
The Department
of
Psychology

Presented in Partial Fulfillment of the Requirements
for the Degree of Master of Arts at
Concordia University
Montreal, Quebec, Canada

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Abstract

Differential Effects of an Early Housing Manipulation on Cocaine Induced Activity and Self-Administration in Laboratory Rats.

Alan E. Boyle

Previous research has suggested that environmental influences as reflected by the social housing conditions of the rat may play a role in the expression of individual differences in drug self-administration. The experimental evidence available has indicated that the effects of early housing manipulations on cocaine-induced behavioral responding is limited and equivocal. The experiments in the present thesis were performed to further examine the effects of early housing manipulations on cocaine-induced behavioral responding. In the first study, it was found that the early housing manipulation of grouped-housed animals produced a significantly greater increase in cocaine-induced locomotor behavior than was observed in isolation-housed animals. Experiments 2 and 3 examined the effects of these housing manipulations on the self-administration of cocaine under a continuous and a progressive ratio schedule of reinforcement, respectively. There was no differential pattern of self-administration observed between the two housing groups suggesting that the housing manipulations failed to effect the reinforcing efficacy of cocaine. Experiment 4 examined the influence of housing manipulations on the strength of conditioned learning within the self-administration paradigm, as measured by the extinction to cocaine self-administration. Consistent with the findings of experiments 2 and 3, housing manipulations failed to produce differential patterns of responding in extinction. The results of the present investigation suggest that early housing manipulations do not appear to play a role in the expression of individual differences in the liability to self-administer cocaine in rats.

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The problem of illicit drug use has been at the forefront of the consciousness of the North American public for quite some time. There are statistics to indicate that 50 million individuals have used drugs at least once in the previous year (National Household Survey on Drug Abuse: population estimates 1985). However, the statistics reflect a very heterogeneous pattern of drug use. For example, only 16 % of cocaine users (Johanson & Fishman, 1988) may be characterized as chronic or dependent users. An understanding of the mechanisms that mediate the expression of individual differences in the pattern of drug use may hold some potential for improved treatment or prevention strategies.

Over the past 40 years, research has provided data to suggest that an animal model may provide a valid method for the study of the processes which mediate the reinforcement properties of drugs in both animals and humans (Deneau, Yanagita & Seevers, 1969; Balster & Lukas, 1985; Falk, 1983). The substantial between subject variability frequently observed in the drug-seeking behavior of non-human species is consistent with the heterogeneous pattern of human drug use. For example, Deneau et al., (1969) demonstrated that monkeys exhibit individual differences in the acquisition of cocaine and morphine self-administration. Similarly, oral ethanol (Blanchard, Hori, Tom & Blanchard, 1987) and opiate (Alexander Coambs & Hadawy, 1978) self-administration studies have also demonstrated individual differences in the magnitude of drug self-selection.

POTENTIAL INFLUENCES OF ENVIRONMENT

Jaffe (1980) has suggested that the differences in the pattern of human drug use represented an individual predisposition or vulnerability for the abuse of drugs. While the variability in the pattern of drug use did, in all probability, involve an interaction between behavioral, biological, psychosocial and cultural influences (Crowley & Goebel, 1988), one line of research has attempted to demonstrate a role for specific environmental influences in the expression of individual differences in drug self-selection (Schenk, Lacelle, Gorman, & Amit , 1987; Bozarth, Murray & Wise, 1989; Nurco 1979).

In animals, the role of environmental influences have been examined, through the manipulation of the social housing conditions. Investigations examining the effects of housing conditions on animal behavior and physiology have typically incorporated designs which have manipulated the relative degree of physical interaction permitted between subjects. The most common have employed designs which contrasted the effects of being housed in isolation with those being housed in groups of varying sizes (Walsh, 1980). Isolation within the context of these studies has been defined as a physical separation, inasmuch as olfactory, auditory, and in some cases visual communication, remains intact (Brain & Benton, 1979). The finding of Gentsch, Lichtsteiner, Frischknecht, Feer & Siegfried, (1988) that some of the effects of housing manipulations, including hyperactivity and hypoalgesia, may be blocked or reversed by prior handling or by resocialization of the isolates supports the proposed role of physical separation in the mediation of behavioral changes produced by such housing manipulations.

It has also been proposed, that the magnitude of the effects of housing manipulations may be dependent upon the age of the animal at the onset of the manipulation (Einon & Morgan, 1976). Einon & Morgan, (1976) have suggested that, in rats, there is a critical period lasting for about three weeks following weaning. During this period, isolated rats were described as being most susceptible to maladaptive physiological and behavioral changes. Consistent with these findings Schenk, Ellison, Hunt, & Amit , (1985) suggested that differential effects of housing manipulations on performance, as measured in a heroin conditioned place preference paradigm, were evident in young but not mature rats.

EFFECTS OF DIFFERENTIAL HOUSING ON PHYSIOLOGY

Some studies have provided data which suggested that the environment, in the form of housing manipulations, can have profound and diverse effects upon the physiological development of the rat (Brain et al., 1979). Other studies, however, have suggested that the effects of the housing manipulations may not be consistent across species (Valzelli 1981; Brain et al., 1979).

Among the effects that have been reported to be affected by isolation housing is alteration of the structural development of the brain. Specifically, decreases in neural tissue density and mass have been observed, which were suggested to be reflective of reduction in dendritic branching, synaptic connections, and amount of supporting glial cells (Holloway, 1966; Volkmar & Greenough, 1972; Brain et al., 1979). In addition, Schenk, Britt, Atalay and Charleson (1982) have demonstrated that isolation housing produced decreases in the number of opiate binding sites in the neural tissue of rats. This finding relates well to the increased levels of analgesia, as assessed through tail flick latency (Gentsch et al., 1988; Kostowski, Czlonkowski, Remerski & Piechock, 1977) and the decreased morphine withdrawal severity, observed in isolates (Adler, Bendotti, Ghezzi, Samanin & Valzelli, 1975; Marks-Kaufman & Lewis, 1984).

In addition, Blanc, Herve, Simon, Lisoprawski, Glowinski and Taasin, (1980) have suggested that housing manipulations modify the rats basic response to stress. Blanc et al., (1980) found that isolated rats exhibited a more pronounced stress induced physiological response of the meso-limbic-cortical dopamine system, compared with group-housed subjects. These changes were associated with an increased incidence of freezing behavior (Blanc et al., 1980).

THE EFFECTS OF DIFFERENTIAL HOUSING ON BEHAVIOR

Considering the broad effects of early isolation housing on neural development and physiology, it is not surprising that housing manipulations have been found to influence the behavioral responding of the rat. Since Hebb's, (1949) early work examining differential effects of housing on "intelligence", several attempts have been made to specify more quantitatively the effects of this manipulation on behavior. Valzelli, (1981) has suggested that isolates, as opposed to group-housed subjects, demonstrated greater levels of aggressive behavior. In addition, isolation housed rats have been shown to exhibit greater locomotor activity in various open-field tests (Morgan, 1973; Morgan, Einon & Nicholas, 1975; Gentsch, Lichtsteiner & Feer, 1981; Gentsch et al., 1988). Gentsch et al., (1981) has suggested that the increased levels of activity reflect an enhanced reactivity by isolates to novel environments as opposed to simply an enhanced level of spontaneous locomotor activity. Gentsch et al., (1981) suggested that the hyperreactive response of the isolates is a reflection of a decreased sensitivity to novelty of environmental stimuli (Gentsch et al., 1988).

Morgan, (1973) and Morgan et al., (1975) have reported that housing manipulations have effects on learning tasks. Morgan et al., (1975) demonstrated that social isolation inhibited the acquisition of an operant response by rats under a alternate choice lever paradigm. Furthermore, isolation inhibited the ability of animals to abandon a previously successful response in order to accommodate changes in task requirements (Morgan et al., 1975).

It has been suggested (Morgan et al., 1973; Morgan et al., 1975) that the behavioral deficits observed in isolates may reflect a deviation in the functioning of normal inhibitory processes. This hypothesis was consistent with the findings that isolated rats habituated (Einon, Morgan & Sahakian, 1975; Einon, Humphreys, Chivers, Fields & Naylor, 1981) and extinguished behaviors more slowly (Lovely, Pagano & Paolina, 1972) than group-housed subjects.

Such effects of housing on operant learning in rats have provided a rationale for a further examination of the effects of housing manipulations on self-selection of drugs, such as cocaine (Hill & Powell, 1976) and by implication, the processes mediating drug reinforcement.

EFFECTS OF DIFFERENTIAL HOUSING ON DRUG INDUCED BEHAVIORS

Hill et al., (1976), examining the effects of housing manipulations on oral cocaine self-administration in a free choice paradigm, found that isolated subjects consumed less cocaine than grouped subjects. In the same study, however, no effects were found on oral morphine self-administration. Hill et al., (1976) attributed the failure to observe effects on morphine intake to the very low levels of self-administration obtained. On the basis of the effects on cocaine self-administration they concluded that group housing influenced the emotionality and learning capabilities of the subjects.

In contrast to the effects on both cocaine and morphine seen by Hill et al., (1975), Alexander et al., (1978) and Alexander, Beyerstein, Hadaway and Coambs, (1981) reported increased oral consumption of morphine in isolates. Using an oral self-administration procedure, these authors demonstrated that isolated subjects when given a free choice between morphine and water, consumed significantly greater quantities of a morphine solution. They concluded that grouped subjects were less sensitive to the reinforcing properties of morphine than were isolates. The interpretation of these results is in direct contradiction to those of recent studies in which group-housed subjects were more sensitive to the effects of opiates than were isolates, as measured by place preference (Schenk, Ellison, Hunt & Amit, 1985), conditioned taste aversion (Schenk, Hunt, Malovechko, Robertson, Klukowski, & Amit , 1986) and the severity of withdrawal from morphine (Marks-Kaufman et al., 1984; Adler et al., 1975).

These contradictory findings with morphine (Alexander et al., 1978; Alexander et al., 1981) combined with the earlier findings of the effects of housing on oral cocaine self-administration (Hill et al., 1976) make it difficult to draw any conclusion about the effects of housing manipulations on reinforcement processes. One of the problems may be that these results are based almost exclusively on oral self-administration studies. Both Schuster et al., (1969) and Cicero, (1979) have suggested that the assessment of the reinforcing efficacy of drugs by this method may be confounded by factors such as the influence of the palatability of the drug solution itself or of the additives used to mask the aversive properties of these agents (Schuster & Thompson, 1969; Cicero, 1979).

In an attempt to avoid the limitations inherent in the use of oral self-administration, intravenous (IV) self-administration procedures have been employed (Schenk, Robinson, & Amit , 1988; Schenk et al., 1987; Bozarth et al., 1989). This latter method has several advantages over oral self-administration methods. It enabled one to eliminate confounds related to palatability of drugs and provided for precise regulation of drug administration parameters such as dose and onset of action. In addition, IV self-administration provided immediate reinforcement, due to the short latency period between the performance of an operant response and the initiation of the central pharmacological actions of the drug.

HOUSING MANIPULATIONS AND I.V. DRUG SELF-ADMINISTRATION

Schenk et al., (1988) found that housing manipulations failed to affect the acquisition of amphetamine self-administration in rats. Furthermore, although isolates did respond more frequently than grouped-housed subjects at all doses, the peak response rate for both groups occurred at the same dose. The results suggested that housing manipulations did not alter the sensitivity of rats to the reinforcing properties of amphetamine. Consistent with these results, Schenk et al., (1986) found that early housing manipulations failed to produce any significant differences in the magnitude of a conditioned place preference based on amphetamine. Similarly, Sahakian, Robbins, Morgan, & Iversen, (1975) and Schenk et al., (1988) found using an open-field apparatus that although isolated animals were different in measures of locomotor activity, the early housing manipulation failed to alter amphetamine induced locomotion.

In contrast to the absence of effects of housing on amphetamine related behaviors, the literature, regarding the effects of housing on cocaine I.V. self-administration and cocaine induced behavior is equivocal.

Schenk et al., (1987) reported that early housing manipulations altered the propensity of rats to self-administer cocaine intravenously. In this study, grouped subjects failed to reliably self-administer cocaine and as a result were described as being insensitive to the reinforcing properties of cocaine. Isolated subjects, on the other hand, exhibited robust self-administration of this drug. As a result, the authors concluded that housing manipulations play a major role in mediating the expression of individual differences in the expression of self-administration, and by implication, cocaine reinforcement.

The notion of enhanced sensitivity of isolates to the effects of cocaine (Schenk et al., 1987) was not supported, however, by research using conditioned place preference. Schenk et al., (1986) demonstrated that group-housed subjects exhibited a place preference induced by cocaine while isolates were shown to be relatively insensitive to the effects of the drug. Thus, the finding, using IV cocaine self-administration, that isolates are more sensitive to cocaine than are group-housed subjects (Schenk et al., 1987), was unique. The results (Schenk et al., 1987) stand in contrast to findings suggesting a greater sensitivity to cocaine in group-housed subjects, as measured by both oral cocaine self-administration (Hill et al., 1975) and conditioned place preference (Schenk et al., 1986).

Recently, Bozarth et al., (1989) reported an attempt to assess the extent to which housing manipulations influenced the propensity of animals to self-administer cocaine as well as other drugs of abuse. Results indicated that both isolated and group-housed subjects readily acquired the operant response to self-administer cocaine. Furthermore, they found that housing manipulations also failed to produces differences in the optimal rates of heroin self-administration. They concluded that isolation housing was not necessary for the expression of IV cocaine self-administration and further, that the underlying reinforcement mechanisms were not influenced by environmental conditions (Bozarth et al., 1989).

Although this latter study (Bozarth et al., 1989) was consistent with the findings reported by Schenk et al., (1988) on the effects of housing on amphetamine self-administration, interpretation of the Bozarth et al., (1989) results, must be subject to qualification. First, Bozarth et al., (1989) used subjects which were considerably older (63 to 91 days of age) at the onset of the housing manipulation, compared to those typically (21 days of age) used in studies of this nature (Alexander et al., 1981; Schenk et al., 1986; Schenk et al., 1987; Schenk et al., 1988). Einon et al., (1976) suggested that the magnitude of the housing effects were dependent upon their implementation during a critical period following weaning. Therefore, the failure of Bozarth et al., (1989) to find an effect, for housing, may reflect the use of older rats, less susceptible to the effects of the housing manipulations. Secondly, the Bozarth et al., (1989) study also differed in that the housing manipulation was of relatively short duration (approximately 18 days). Thus, the use of mature rats and a manipulation of relatively short duration must be considered when interpreting the negative results.

In summary, the literature suggests that while housing manipulations fail to effect amphetamine induced behavioral responding, the literature for cocaine remains contradictory. Housing manipulations have, as a function of the particular study or paradigm utilized, been demonstrated to be effective as well as ineffective in producing a differential sensitivity to the reinforcing effects of cocaine, as reflected by the propensity to self-administer or exhibit a place preference for cocaine.

THE PRESENT STUDY

The experiments of the present study were performed to further examine the extent to which early housing manipulations can effect cocaine-induced behaviors. An attempt was made to overcome the difficulty in evaluating the effects of housing on cocaine related behaviors found in previous studies, by applying a consistent manipulation of housing and testing the animals in several behavioral situations. The effects of early housing manipulations on the sensitivity of rats to the locomotor activating properties of cocaine were assessed through the use of an open-field paradigm. In order to determine the extent to which early housing manipulations alter the propensity to self-administer cocaine, a progressive ratio method was used in addition to the continuous reinforcement method normally used. In addition, the influence of housing on the strength of the conditioned responding was assessed through the use of an extinction paradigm.

EXPERIMENT 1

Numerous studies have reported that differential housing conditions (isolated or grouped) during rearing can influence the nature of the behavioral responses of rats to their environment. An example of such an influence is social isolation which has been demonstrated to enhance the levels of reactivity in an open-field (Morgan 1973; Sahakian et al., 1975; Gentsch et al., 1981; Gentsch et al., 1988).

Additional research has attempted to examine the extent to which housing manipulations affected stimulant induced locomotion. Sahakian et al., (1975) have reported that housing manipulations failed to generate a differential sensitivity to the locomotor activating effects of amphetamine. Schenk et al., (1988) have reported comparable findings. However, a brief survey of the literature indicated that the failure of housing manipulations to produce a differential sensitivity to the locomotor activating effects of amphetamine may not be generalizable to other psychomotor stimulants.

Research utilizing the place preference (Schenk et al., 1986) and self-administration paradigms (Bozarth et al., 1989) suggested that the differential effects of housing manipulations may be specific to certain drugs or classes of drugs. The present experiment was intended to assess the extent to which the observed effects of early housing manipulations on the stimulant effects of amphetamine, could be generalized to cocaine induced locomotor activation and stereotypy.

EXPERIMENT 1A

In experiment 1A the effects of early housing manipulations on the sensitivity to cocaine induced locomotor activation was investigated.

METHOD

Subjects

60 male Long Evans rats (Charles River Canada) obtained at weaning (21 days of age) were used. The subjects were housed in hanging stainless steel cages either in isolation (cage size = 20 x 25 x 18 cm) or in groups of four (cage size = 41 x 25 x 18 cm) for six weeks post weaning. Food and water were freely available at all time except during testing. Subjects were maintained in a colony under reverse cycle lighting (off at 0900, on at 2100). All testing occurred within four hours of the onset of the dark cycle.

Apparatus

Open-field boxes (45.7 x 45.7 x 39.4 cm) were used to assess horizontal locomotor activity. Each open-field box was painted black and illuminated with dim red lighting. There were four sets of light sources and photocells located 3.8 cm above the chamber floor. The light sources were arranged such that one pair of light beams crossed the other pair perpendicularly, dividing the chamber into 9 equal sectors. Interruptions of the light beams were automatically registered in an adjacent laboratory.

Procedure

Following the termination of the six week housing period, subjects (63 days of age) were placed in the open-field chambers for a 50 minute habituation session on the day before drug testing. They were then randomly assigned to one of five drug conditions. During test sessions, all animals were placed in the boxes for a 50-minute recording of baseline activity. Following this, they were removed, given an intraperitoneal (IP) injection of cocaine HCl (0, 2.5, 5, 10 or 20 mg/kg dissolved in a constant volume of physiological saline) and returned to their chambers for an additional 50 minute period. Locomotor scores were recorded at 10 minute intervals for the duration of the pre and post injection periods.

RESULTS

A two-way ANOVA (group and dose) conducted on the baseline activity scores revealed a significant main effect for housing [F(1,70)= 8.19, $p<0.006$]. The isolated subjects exhibited significantly higher levels of baseline locomotor activity. The baseline activity score for isolation-housed subjects was 213.2, whereas group-housed subjects exhibited a baseline score of 163.75. Therefore, because of the initial differences in activity, all later analyses were based on the transformation of the data to a percent change from baseline. The percent change in activity was calculated using the cumulative activity scores for the 50 minute period prior to and following drug treatment.

Figure 1 shows the percent change from baseline activity scores for grouped and isolated subjects following cocaine injections. A two-way ANOVA (with the factors, housing and dose) of the transformed data yielded a significant 2-way interaction between housing and dose [F(4,70)=2.94, $p<0.04$]. An analysis of simple main effects revealed that the grouped subjects exhibited a significantly greater increase in locomotion in response to cocaine at the 10 mg/kg [F(1,70)= 10.93, $p<0.002$] and 20 mg/kg [F(1,70)=8.89, $p<0.004$] dose. The differences between the two groups at the 0, 2.5 and 5 mg/kg doses were not significant.

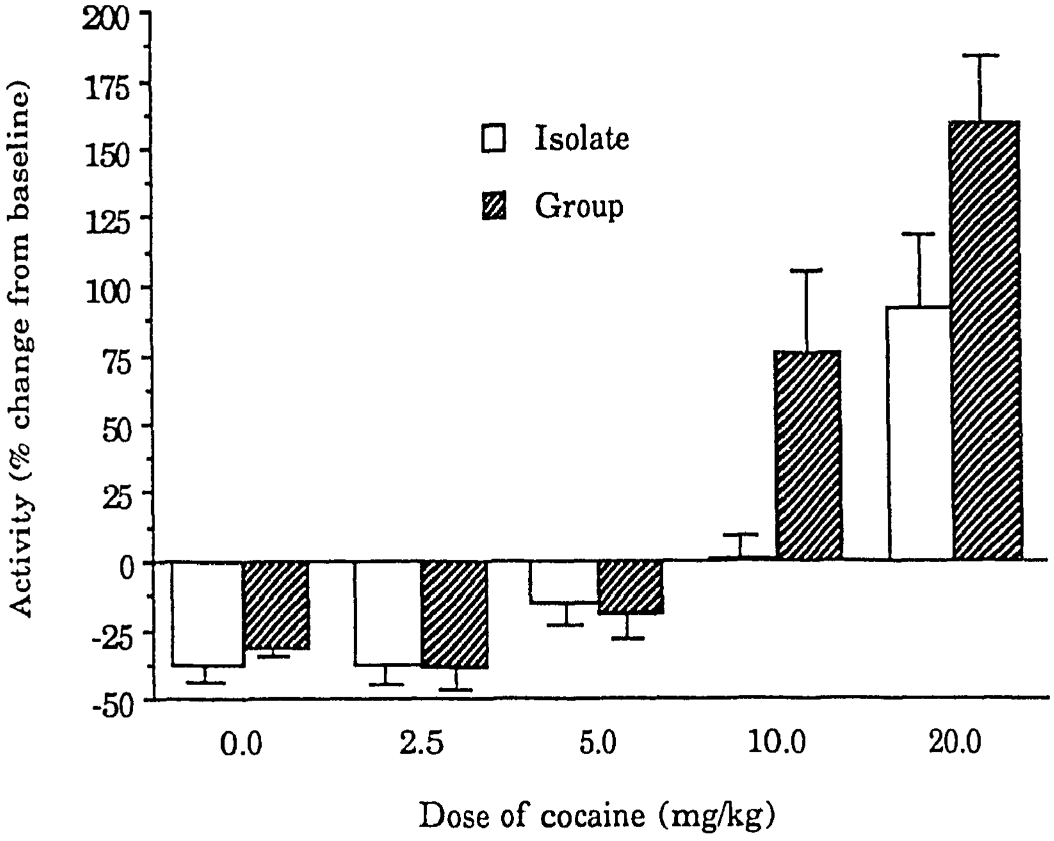

Figure 1. The effect of differential housing on cocaine-induced locomotor activation as represented by percent change from baseline activity for isolated and grouped housed subjects (n = 6/group). Vertical lines represent the S.E.M.

EXPERIMENT 1B

Experiment 1B studied the effects of housing on cocaine induced stereotypy as expressed in differentially housed subjects. Furthermore the influence of stereotypy on the differential levels of locomotor activation observed in experiment 1A was examined.

METHOD

Subjects

Twenty male Long Evans rats (Charles Rivers Laboratory Inc.) obtained at weaning (21 days of age) were used as subjects. The subjects were housed in hanging stainless steel cages either in isolation (cage size = 20 x 25 x 18 cm) or in groups of four (cage size = 41 x 25 x 18 cm) for six weeks post weaning. Subjects were maintained in a colony under reverse cycle lighting conditions (off at 900; on at 2100). Food and water were freely available except for test periods. All testing occurred within four hours of the onset of the dark cycle.

Apparatus

Subjects were tested for locomotion and stereotypy in Plexiglass open-field observation boxes (40 X 40 X 35 cm). The behavioral responses of the rats were recorded using an 8 mm video camcorder. Lighting conditions throughout the testing period consisted of the minimum level of white light necessary for the video recording. The videos were later used for analysis.

Procedure

Following the six-weeks housing period, the subjects (63 days of age) were placed in open-field chambers for a 50 minute habituation session on the day before drug testing. On the day of drug testing, subjects were placed in the open-field boxes for 20 minutes.

Following this interval, the subjects were removed, given an injection (IP) of 10 or 20 mg/kg of cocaine HCL and placed back into the chambers for an additional 20 minutes. Video recordings were made of both pre and post injection periods. The duration of the test period was selected on the basis of the observation, in experiment 1A, that the expression of locomotor activation was limited to the initial 20 minute time period.

The video tapes were scored with respect to the cumulative number of line crossings for the 20 minute sessions and the incidence of stereotypy. Stereotypic behavior was assessed, using a time sampling technique, by observing the subjects for a 1 minute period every 10 minutes during the 20 minute sessions. Stereotypy was rated on a scale from 0 to 6: 0- asleep or stationary, 1- actively locomoting, 2- predominantly active with bursts of stereotyped sniffing or rearing, 3- stereotyped sniffing along a fixed path, 4- stereotyped sniffing or rearing in one location, 5- stereotyped behavior in one location with bursts of gnawing or licking, 6- continual gnawing or licking in one location (Creese & Iversen, 1973).

RESULTS

The baseline activity scores for the isolated and grouped subjects were analyzed. The results showed as in Experiment 1A that there were significant differences [$F(1,56)=18.74$, $p<0.01$] in baseline activity rates between grouped and isolated subjects for the 20 minute period prior to injection. All subsequent analyses were based upon the transformation of scores to a percent change from baseline.

The percent change from baseline locomotion scores for the 20 minute (post injection) sessions are presented in Figure 2. A two-way analysis of variance with repeated measures yielded a significant main effects for housing [F(1,16)= 12.04, p<0.004] and dose [F(1,16)= 17.27, p<0.0008]. The results indicated that grouped subjects exhibited significantly greater changes in locomotor activity at both doses tested. These data are consistent with that observed in experiment 1A. The interaction between housing and dose was not significant.

Stereotypy ratings for the isolated and grouped subjects are presented in Table 1. There were no significant differences between the two groups.

DISCUSSION

The findings of the present experiment suggested that manipulations of early environmental housing influence the sensitivity of rats to the locomotor activating effects of cocaine. Group-housed subjects exhibited significantly greater levels of locomotor activation following cocaine treatment than did subjects housed under isolation conditions.

In addition, the results suggested that there were no significant group differences in the expression of cocaine-induced stereotypy. Therefore, the differential levels of activation observed in the two groups were not a function of enhanced stereotypy.

The results of the present study are inconsistent with the findings of Sahakian et al., (1975) and of Schenk et al., (1988) who reported the absence of an interaction between housing conditions and amphetamine induced locomotion. In the present study, the analysis of baseline

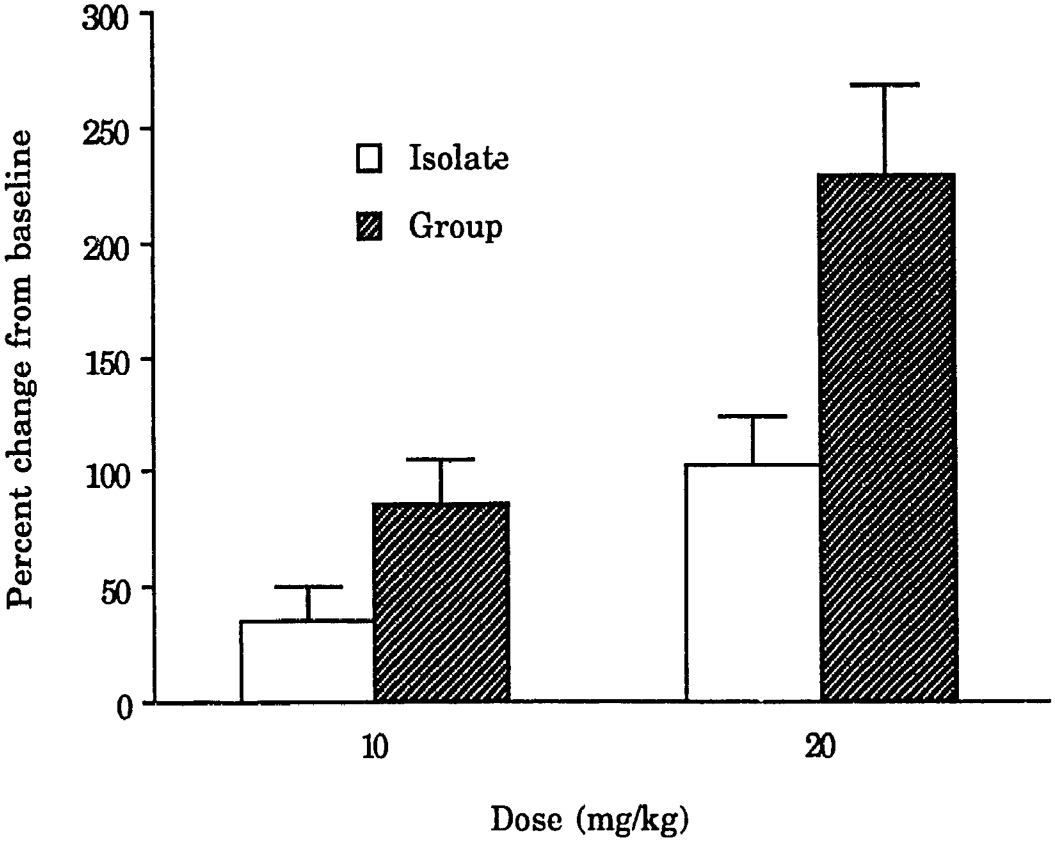

Figure 2. The percent change from baseline locomotion scores for the 20 minute (post injection) session following cocaine treatment (n = 5/group). Vertical lines represent the S.E.M.

Table 1. Effects of housing on cocaine induced stereotopy. Stereotypy was rated on a scale from 0 to 6: 0- asleep or stationary, 3- stereotyped sniffing along a fixed path, 6- continual gnawing or licking in one location

		Baseline		Test	
	Dose	10	20	10	20
Isolates	10	1	1	1	1
	20	1	1	2.6	1.2
Group	10	1	1	2	1.2
	20	1	1	2.4	1.4

activity scores suggested a significant effect due to housing. As a result, the locomotor activating effects of cocaine were assessed in terms of a percent change from baseline activity. In this manner. it was possible to disassociate the effects of housing induced environmental reactivity from its effect on cocaine activation. Therefore, the absence of a significant housing effect in previous studies, may reflect the failure to incorporate initial differences in activity into subsequent analyses of cocaine activation.

Alternatively, the inconsistency between the effects of housing manipulations on cocaine and amphetamine may be interpreted as support for the proposal that the effects of housing manipulations are specific for certain drugs or classes of drugs (Bozarth et al., 1989; Schenk et al., 1986). The differential effects of housing, observed on cocaine and amphetamine induced locomotor activation suggested that differential mechanisms may mediate the effects of the two drugs.

EXPERIMENT 2

The intravenous (IV) self-administration technique has been directly applied to the study of drug reinforcement. Pickens and Thompson (1968) demonstrated that rats equipped with an indwelling catheter will learn to press a lever, if the response was followed by an injection of cocaine. A biphasic relationship was found to exist between the dose of cocaine and the rate of responding. The dose response curve for cocaine self-administration indicates that an increase in the rate of self-administration is associated with the lower doses of the drug, while higher doses have been associated with decreases in responding (Wise 1987). Deviations in the rate of self-administration have been used to assess the extent to which manipulations alter the rewarding efficacy of cocaine.

Self-administration techniques utilizing a continuous reinforcement schedule, have been used to examine the effects of early housing manipulations on the reinforcing value of psychomotor stimulants. Schenk et al., (1988) reported that early housing manipulations failed to influence the dose response curve for amphetamine self-administration. This finding appears consistent with the failure to observe housing alterations in amphetamine induced locomotion (Schenk et al., 1988).

Equivocal results have been reported on the effects of housing on cocaine IV self-administration. Bozarth et al., (1989) reported that housing manipulations were ineffective in altering the efficacy of cocaine reinforcement as measured by I.V. self-administration. However, this study is problematic due to the short duration of the pretesting housing manipulation and the large variability in the age of the subjects at the onset of the housing manipulation.

Schenk et al., (1987) reported that housing manipulations influenced the subjects sensitivity to the reinforcing properties of cocaine. The failure to demonstrate self-administration by grouped-housed subjects was interpreted to mean that these animals were less sensitive to cocaine's positively reinforcing properties. This idea, however, is not supported by the results of experiment 1 in which it was found that grouped subjects demonstrated a heightened sensitivity to the locomotor activating effects of cocaine.

It was suggested, therefore, that the failure of grouped subjects to demonstrate self-administration was not due to a diminished sensitivity to the reinforcing properties of cocaine but rather to an attenuation of the subject's ability to acquire an operant response as suggested by Bozarth et al., (1989). In the experiment by Schenk et al., (1987), subjects self-administered cocaine, with the dose being systematically decreased every five days. The present authors proposed that the initiation of drug testing with the maximum dose of cocaine, disrupted the ability of the group-housed subjects to acquire the operant response due to the enhanced sensitivity of the grouped subjects to the locomotor stimulant effects of cocaine, as seen in experiment 1.

The present experiment examined the effects of early housing manipulations on the self-administration of cocaine. In contrast to the procedure used by Schenk et al., (1987) an ascending sequence of doses was used in this experiment. The intended purpose was to maximize the potential for acquisition of the operant response, in both grouped and isolated subjects.

METHOD

Subjects

Thirty two male Long Evans rats (Charles Rivers Canada) obtained at weaning (21 days of age) were used as subjects. The subjects were housed in hanging stainless steel cages either in isolation (cage size = 20 x 25 x 18 cm) or in groups of four (cage size = 41 x 25 x 18 cm) for six weeks post weaning. Subjects were maintained in a colony under reverse cycle lighting conditions (off at 9:00; on at 21:00). Food and water were freely available except for those periods during which testing occurred.

Apparatus

Ralph Gerbrands company Model C operant conditioning chambers equipped with a lever mounted 6 cm from the floor were used. Suspended above each box was a polyethylene tube attached to a flow through swivel (Brown, Amit & Weeks 1976) which served to connect the animal to a syringe mounted in a pump (model A, type 17, 1 RPM motor from Razel Scientific Instruments Inc.). Each depression of the lever activated, both, a cue light and the pump which delivered 0.1 mls of a cocaine HCL solution (prepared daily in a 0.9% saline solution) or saline control solution (0.9%). All operant responses were recorded on a paper strip recorder.

Procedure

Each rat was implanted with a chronically indwelling catheter. A modified version of Weeks (1962) catheter (Dow silastic ID=0.020; D=0.037) was implanted into the jugular vein of the rat. The catheter was passed subcutaneously to the skull where it was secured with stainless steel screws and dental acrylic. Subjects recovered over a five day period during which they received daily infusions through the catheter (1 ml) of a saline/penicillin solution. The daily infusions were performed in order to maintain the patency of the catheter and minimize the loss of subjects due to infection.

Following the recovery period the subjects were randomly assigned to either drug or saline conditions, following which testing in the self-administration chambers was initiated. Testing occurred during daily three hour sessions within the first four hours following the onset of the dark cycle. Each session was initiated with a noncontingent administration of a priming infusion of cocaine or saline solution. The subjects receiving infusions of drug, initially received .04 mg/kg/infusion of cocaine solution for 5 consecutive days. Subjects were subsequently exposed to doses of 0.08, 0.16, 0.32, and 0.64 mg/kg/infusion. Each dose was presented for a period of five days.

RESULTS

One subject was withdrawn from the study due to a leak in the catheter. Thirty one subjects completed the study. Figure 3 shows the mean number of responses for grouped and isolated subjects self-administering cocaine or saline. The data are expressed as the mean cumulative number of responses for the 5 trials at each individual dose.

An analysis of variance (with repeated measures) yielded a significant three-way interaction for the housing, dose and drug (cocaine or saline) [$F(4,108)=2.5$, $p<0.04$]. The main effect for the housing variable was not significant.

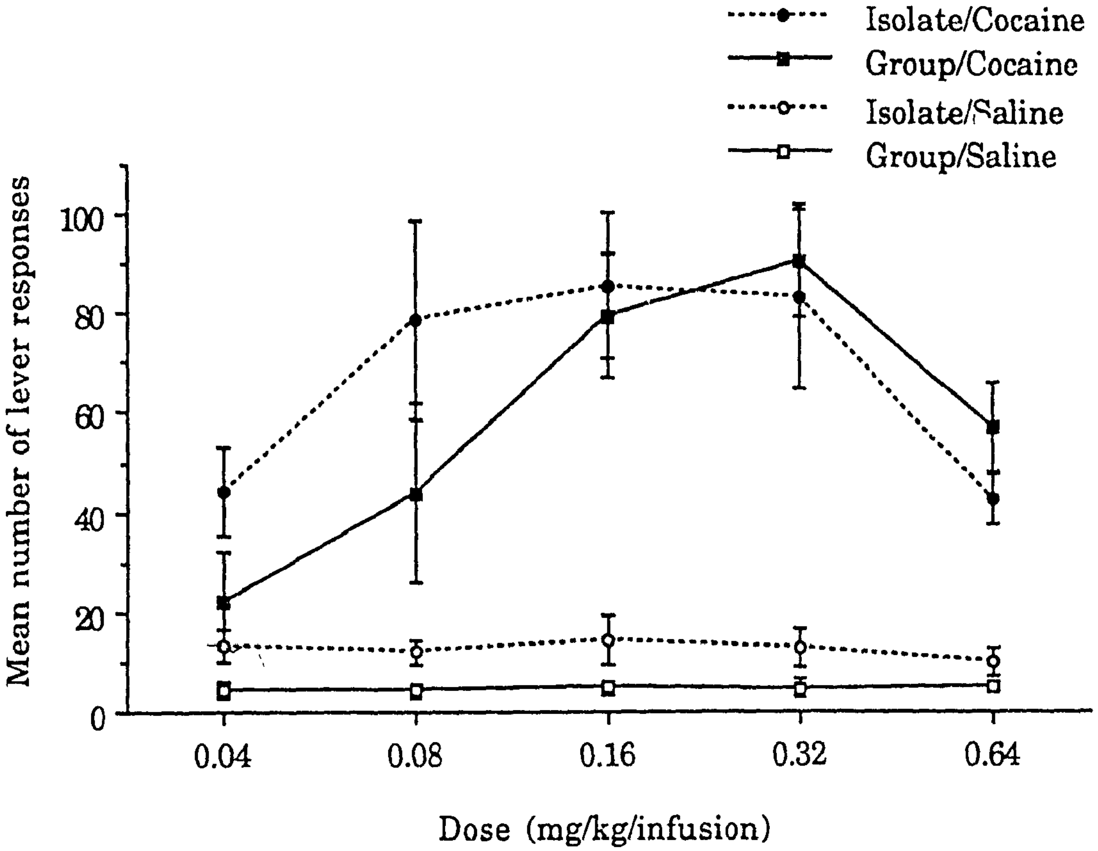

Figure 3. The mean number of responses for grouped and isolated subjects self-administering cocaine or saline under continuous reinforcement (n = 8/group). The data are expressed as the mean cumulative number of responses for the 5 trials at each individual dose. Vertical lines represent the S.E.M.

Post hoc analysis (Tukey) of the marginal means indicated that both the grouped and isolated subjects self-administering cocaine maintained operant rates significantly greater ($p<0.01$) than those subjects self-administering saline.

An examination of the simple main effects (drug held constant) suggested that there was a dose-dependent effect of cocaine on self-administration behavior [$F(4,108)=5.21$, $p<0.0007$]. Post hoc (Tukey) analysis indicated that both grouped and isolated animals significantly increased responding as the dose of cocaine was incrementally raised to 0.16 mg/kg/infusion ($P<0.05$). The number of responses did not increase further as the dose was further increased to 0.32 mg/kg/infusion. Additionally, the largest dose tested (0.64 mg/kg/infusion) resulted in a significant decrease ($p<0.05$) in the rates of responding for both groups. Saline controls maintained consistent operant rates over the 5 trial periods.

Simple main effects (dose held constant) suggested that the two groups did not differ significantly in their rates of self-administration across the doses between 0.08 and 0.64 mg/kg/infusion. Significant differences between housing groups were obtained only for the lowest dose tested (0.04 mg/kg/infusion) [$F(1,27)= 5.65$, $p<0.03$]. Post hoc analysis (Tukey) suggested that at the 0.04 dose, isolates exhibited significantly greater rates of cocaine self-administration ($p<0.05$) than did the grouped subjects.

DISCUSSION

The present experiment demonstrated that social isolation was not a necessary condition for the expression of cocaine IV self-administration. The results suggested that both grouped and isolated subjects self-administered cocaine in a dose dependent fashion. The results are in contrast to a previous report indicating that group-housed subjects failed to self-administer cocaine (Schenk et al., 1987).

The pattern of responding suggested that grouped subjects exhibited significantly lower rates of cocaine self-administration at the lowest dose tested. This would suggest that the acquisition of cocaine self-administration by the grouped animals was attenuated by this manipulation in comparison to the isolated animals. The results of experiment 1 suggested that there may be a differential reactivity to the locomotor stimulant effects of cocaine produced by exposure to different housing conditions. It was shown that grouped animals were more reactive to cocaine than isolated animals. It is possible that the enhanced sensitivity to the locomotor stimulant properties of cocaine may have attenuated the acquisition of the self-administration behavior of the grouped subjects. However, the nature of this proposed attenuation was clearly not of sufficient magnitude to affect acquisition over an extended period of time.

The results of the present experiment suggested that the early housing manipulation did not influence the animals sensitivity to the reinforcing properties of cocaine. Comparable rates of self-administration were observed for both isolated and grouped subjects in the present study. This finding was in contrast to the previous observation that grouped subjects display enhanced sensitivity to the locomotor activating effects of cocaine (Experiment 1). However, a growing consensus in the self-administration field has suggested that traditional measures of rate and drug intake may not be reliable indicators of a drug's reinforcing properties or of the motivation to self-administer a particular agent (Roberts, 1988; Roberts, Bennett & Vickers, 1989; Wise, 1987). The following experiment was conducted to address this issue.

EXPERIMENT 3

The previous experiment suggested that housing manipulations failed to influence the sensitivity of subjects to the reinforcing properties of cocaine. This conclusion was based upon the observation that the housing manipulation employed did not produce differences in the rates of responding between the groups. However, it has been suggested that changes in reinforcement efficacy may not be accurately reflected in the expression of operant rates under a continuous reinforcement schedule.

Reports have indicated that the effects of cocaine injections contingent on an operant response may not be limited to its reinforcing properties (Roberts, Loh, & Vickers 1989). For example, cocaine can when self-administered or experimenter injected disrupt ongoing behavior (Johanson, 1988). Thus, the use of a measure of rate to assess cocaine reinforcement may be problematic in that operant rates may be subject to the interaction between rate-decreasing and reinforcing effects (Johanson, 1988).

In order to circumvent this possible confound and obtain a potentially more accurate assessment of reinforcement, the use of the progressive ratio (PR) paradigm has been advocated (Hodos, 1961; Roberts et al., 1989). PR schedules quantify reinforcers in terms of their ability to maintain responding as the amount of work required to obtain an infusion (response cost) increases and not on the actual rate of responding.

The present study further examined the influence of early housing manipulations on the sensitivity to the reinforcing properties of cocaine as measured by a PR schedule of reinforcement. The modified PR technique described by Roberts et al., (1989) was used.

METHOD

Subjects

Ten male Long Evans rats (Charles Rivers Canada) obtained at weaning (21 days of age) were used as subjects. All subject were housed in conditions identical to those described in experiment 2.

Apparatus

The self-administration (continuous reinforcement) apparatus consisted of Ralph Gerbrands Company Model C operant conditioning chambers equipped with a lever positioned 6 cm from the floor. Suspended above each box was a polyethylene tube attached to a flow through swivel (Brown et al., 1976) which served to connect the animal to a syringe mounted in a pump (model A, type 17, 1 RPM motor from Razel Scientific Instruments Inc.). Each depression of the lever activated, both, a cue light and the pump which delivered 0.1 ml of cocaine HCL (prepared daily in a 0.9% saline solution).

Self-administration under a progressive ratio (PR) schedule of reinforcement was assessed using operant boxes and delivery systems identical to those used under the FR1 schedule. In addition, the PR system incorporated circuitry which systematically increased the number of lever responses required to receive an infusion of drug. Each infusion resulted in an progressive increase in the response requirements for each subsequent infusion. The response requirements for each infusion were based upon the following series: 2, 3, 5, 7, 9, 12, 15, 18, 23, 28, 33, 41, 49, 57, 70, 83, 96, 117, 138, 156, 200, 225, 275, 300, 325, 350, 375, 425 (Roberts 1988). Digital counters registered the cumulative lever responses for any given session. A paper strip recorder registered the number and pattern of infusions earned by the subjects.

Procedure

Each rat was implanted with a chronically indwelling catheter. The surgical procedure was identical to that described in experiment 2. Following the recovery period, testing was conducted during daily, 2 hour sessions carried out within the first four hours following the onset of the dark cycle. Each session was initiated with the presentation of a noncontingent priming infusion of cocaine solution. The subjects initially self-administered (FR1) a dose of .08 mg/kg/infusion of cocaine for a period of 5 days. The dose was increased to .16 and subsequently to .32 mg/kg/infusion. Each dose of drug was presented over 5 consecutive days. Following the fifth day at the .32 dose, all subjects, which exhibited stable rates of self-administration, were tested under a progressive ratio (PR) schedule of reinforcement. The dose of .32 mg/kg/infusion was determined to be an optimal dose for both housing groups, based upon the findings of experiment 2.

Testing under the PR schedule was repeated over a four day period. Each session was initiated with the noncontingent presentation of a priming infusion of cocaine. All subsequent infusions were earned on the basis of the PR schedule of reinforcement presented earlier. The sessions continued until all subjects had demonstrated extinction, defined as the failure to earn an infusion within a period of one hour. Subjects were evaluated on the basis of their breaking points which were defined as the final ratio at which an infusion was earned. In addition, differences between groups in the number of infusions earned per hour over a single session was examined.

RESULTS

Two subjects (1 grouped and 1 isolated) were eliminated from the study due to their failure to exhibit self-administration behavior under a FR1 schedule of reinforcement. Figure 4 shows the mean breaking points for the isolated and grouped subjects over the four day test period. An analysis of variance (with the factors group and days) indicated there were no significant differences between the housing groups.

The number of injections/hour earned by each group, over the four day period is shown in Figure 5. Similarly, an analysis of variance (with the factors group and days) suggested there were no significant differences between the two housing groups on this measure.

DISCUSSION

In the present study, the effects of early housing manipulations on cocaine self-administration under a progressive ratio schedule was examined. The results suggested that early housing manipulations were not effective in influencing the incentive value of cocaine reinforcement. Subjects from the two housing groups exhibited comparable breaking points derived from the PR schedule of reinforcement. The findings of this experiment supported those obtained in Experiment 2 in that early housing manipulations did not appear to alter the self-administration liability of cocaine.

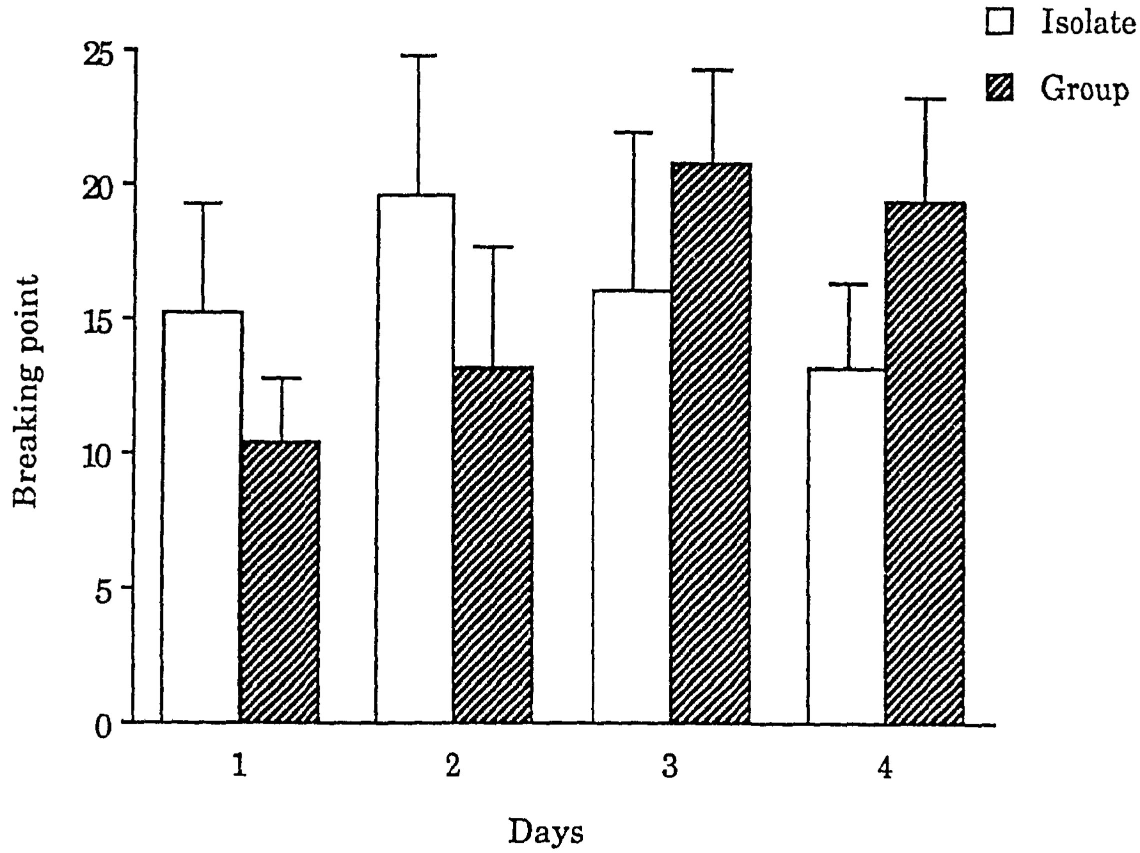

Figure 4. The mean breaking points for isolated and grouped subjects (n = 5/group) self-administrating cocaine (0.32 mg/kg/inf) over the four day test period under a prgressive ratio schedule of reinforcement. Vertical lines represent the S.E.M.

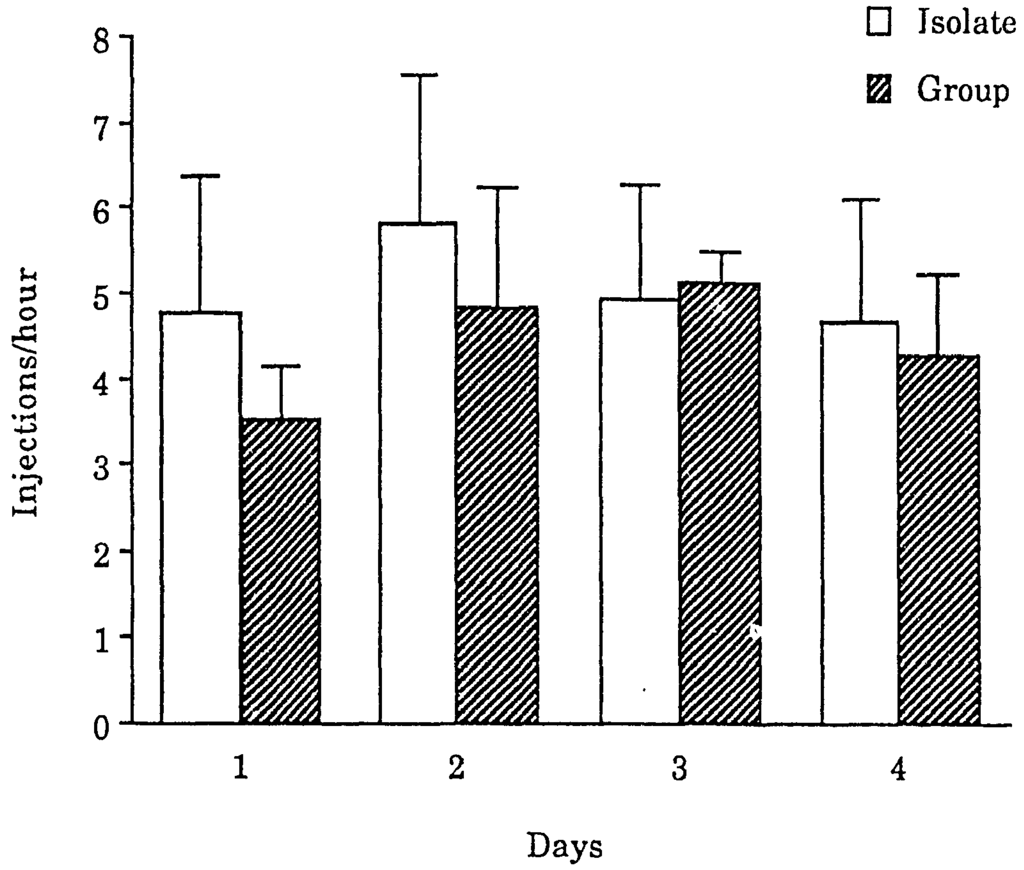

Figure 5. The mean number of injections per hour for isolated and grouped subjects (n = 5/group) self-administrating cocaine (0.32 mg/kg/inf) over the four day test period under a prgressive ratio schedule of reinforcement. Vertical lines represent the S.E.M.

EXPERIMENT 4

Reports in the literature (Einon et al., 1976; Einon et al., 1981; Lovely et al., 1972; Morgan 1973; Morgan et al., 1975) suggested that early housing manipulations influenced learning in rats. Morgan et al., (1975) demonstrated that social isolation inhibited both the acquisition of an operant response under an alternate lever schedule of food reinforcement and the ability to abandon a previously successful response in order to accommodate changes in task requirements (Morgan et al., 1975). It has been suggested (Morgan et al., 1973; Morgan et al., 1975) that learning deficits observed in isolates may be a reflection of a deviation in the functioning of normal inhibitory processes.

In light of the reported effects of housing on learning in the rat, the present study examined the extent to which an early housing manipulation influenced learning in an operant paradigm by measuring the observed resistance to extinction. It was expected that if the housing manipulations altered the strength of the operant conditioning, differences in the pattern of responding would be observed when responses were no longer reinforced with cocaine.

METHOD

Subjects

Twelve male Long Evans rats (Charles Rivers Laboratory Inc.) obtained at weaning (21 days of age) were used as subjects. The housing conditions were identical to those described in experiments 2 and 3.

Apparatus

Ralph Gerbrands company Model C operant conditioning chambers were utilized. Each chamber was equipped with a lever 6 cm from the floor of the cage. Suspended above each box was a tube attached to a swivel joint which permitted free movement by the subjects. The tube and swivel joint served to connect the subject to a syringe mounted upon a syringe pump (model A, type 17, 1 RPM motor from Razel Scientific Instruments Inc.). The subjects depression of the lever activated both a cue light and a pump which in turn delivered 0.1 ml of cocaine HCL (delivered in a 0.9% saline solution prepared daily). All operant responses were recorded on a paper strip recorder.

Procedure

Each rat was implanted with a chronically indwelling catheter. The surgical procedure utilized was identical to that described in experiments 2 and 3.

Following the recovery period, testing was initiated. Testing occurred during daily 2 hour sessions within the first four hours following the initiation of the subjects dark cycle. Each session began with a noncontingent presentation of a priming dose of a cocaine solution. The subjects initially self-administered a dose of .08 mg/kg/infusion of cocaine for a period of 5 days. The dose was increased to .16 and subsequently to .32 mg/kg/infusion. Similarly, each dose was maintained for a period of 5 days. After having self-administered .32 mg/kg/infusion cocaine for 5 days, saline (.9%) was substituted in place of the cocaine solution. All subjects were maintained on saline for an additional 5 day period. Cumulative self-administration rates were obtained for every 15 minute period throughout the 2 hour session and subsequently served as the foundation for further analysis. The responses of subjects on the final day at 0.32 mg/kg/infusion served as a baseline. The final dose of cocaine administered was determined to be the optimal dose for self-administration based upon the results of experiment 2.

RESULTS

The results were analyzed using an analysis of variance (with repeated measures) containing the factors housing, days and time. The analysis revealed that there were significant main effects for time [F97,81)= 11.10, $p<0.002$] and days [F(4,56)= 9.04, $p<0.0001$]. No significant main effects or interactions involving housing were obtained. The results suggest that the decreases in the rates of responding were comparable for both groups over the five extinction sessions. The mean operant rates for isolated and grouped subjects, collapsed over the 5 day extinction period, are presented in Figure 6.

DISCUSSION

The results of the present experiment suggested that an early housing manipulation failed to influence the pattern of resistance to extinction. These data suggested that the housing did not alter the strength of the instrumental conditioning induced by cocaine reinforcement in this self-administration paradigm.

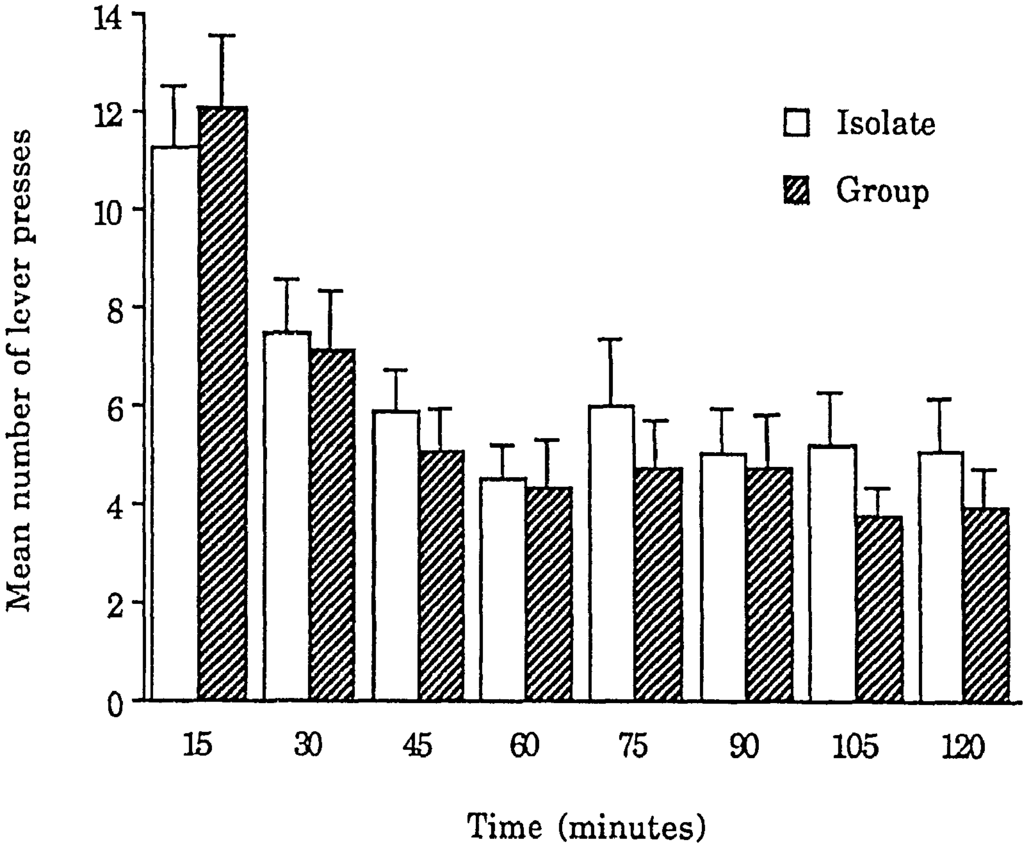

Figure 6. The mean number of lever presses for isolated and grouped subjects (n = 6/group) for each session time block collapsed over the 5 day extinction period. Vertical lines represent the S.E.M.

GENERAL DISCUSSION

The present series of experiments examined the extent to which an early housing manipulation influenced cocaine induced behavioral responding. In experiment 1, it was shown that rats who were housed in groups following weaning exhibited significantly greater cocaine induced locomotor activation, relative to isolation housed subjects. The increased sensitivity of group subjects to the activating effects of cocaine were inconsistent with the reports indicating that housing manipulations failed to influence amphetamine induced locomotion (Sahakian et al., 1975; Schenk et al., 1988). It was suggested that this discrepancy may reflect a failure on the part of earlier studies to include baseline activity levels in the assessment of drug induced activation. Consideration of the baseline levels of activity is justified on the basis of results described in the present study and others which suggested that group-housed subjects (Gentsch et al., 1988; Paivarinta 1990) exhibited significantly lower baseline rates of locomotor activity in open-field paradigms.

The differential effects of housing on cocaine and amphetamine induced locomotion, however, may also be interpreted as indicating that the effects of the present housing manipulation may be specific for cocaine. This would potentially suggest that the mechanisms which may mediate the expression of cocaine and amphetamine induced motor stimulation may be different. Further support for the concept of housing specificity is provided by the report that housing manipulations differentially influenced place preference for cocaine and amphetamine (Schenk et al., 1986).

In contrast to the findings of experiment 1, this early housing manipulation failed to alter the expression of cocaine self-administration in rats. The results of experiment 2 indicated that both isolation and group-housed subjects readily self-administered cocaine in a dose dependent manner. Furthermore, the maximum rate of responding attained for cocaine was comparable for both groups. The results of experiment 2 were consistent with the findings that housing manipulations failed to alter the development of I.V. cocaine, heroin (Bozarth et al., 1989) and amphetamine (Schenk et al, 1988) self-administration in rats. The acquisition of cocaine self-administration by both grouped and isolates in experiment 2 were interpreted as indicating that early housing manipulations failed to alter the reinforcing efficacy of cocaine.

While the reinforcing properties of cocaine, as measured in experiments 2 were not influenced by housing manipulations, it was found that the acquisition of self-administration in grouped subjects was inhibited. This finding is consistent with a previous report in the literature (Bozarth et al., 1989). It was demonstrated in experiment 2 that grouped subjects were slower than isolates in acquiring self-administration, as measured by the rate of responding during the first 5 days of testing. The grouped subjects did, however, exhibit equivalent rates for all subsequent doses tested. It was suggested that the enhanced sensitivity of grouped subjects to the locomotor activating effects of cocaine (experiment 1) may have interacted with the novelty of the environment to inhibit the acquisition of the operant response.

A previous report (Schenk et al., 1987) suggested that group-housed rats, are insensitive to the reinforcing effects of cocaine as evidenced by their failure to self-administer cocaine. This conclusion conflicts with the results obtained within the present study. It is suggested that the reported failure to observe self-administration (Schenk et al., 1987) in grouped subjects may be a result of an inhibited process of acquisition, as opposed to a reflection of differential effects upon motivational processes. The subjects in the study by Schenk et al., (1987) were initially presented with a large dose of cocaine and subsequently presented with doses of descending concentration. The findings of the present study suggested that the acquisition of self-administration by the grouped subjects may have been inhibited due to the stimulant effects of cocaine. Therefore, the presentation of a large initial dose of cocaine (Schenk et al., 1987) to grouped subjects which were naive with respect to the operant paradigm, may act to potentiate this inhibition and would necessitate a longer period for the acquisition of cocaine self-administration to become evident.

The self-administration studies (FR1 schedules), discussed above assessed reinforcement on the basis of changes in measures of rate. In consideration of the interpretive difficulties which measures of rate pose for the assessment of reinforcement, experiment 3 examined the effects of housing on cocaine self-administration tested with a progressive ratio schedule of reinforcement. Results of this experiment indicated that housing manipulations failed to produce differential patterns of responding as the work (response requirements) needed to earn an injection was systematically increased. Thus the finding supported the previous results (experiment 2), in that an early housing manipulation failed to produce differences in the efficacy of cocaine reinforcement.

Experiment 4 indicated that the housing manipulation failed to influence the strength of conditioned learning within the self-administration paradigm in rats. The strength of the conditioning was measured by the behavioral extinction patterns observed within sessions and over days. These findings are consistent with those of the other self-administration experiments (2 & 3) reported in the present investigation as there was no differential responding between the two housing groups.

The series of results obtained from the present investigation demonstrated that early housing manipulations influenced the sensitivity of rats to the locomotor activating effects of cocaine while failing to affect its rewarding properties as measured by the expression of self-administration. Not withstanding some possible methodological issues, these dichotomous results obtained in the present thesis, are not consistent with the suggestion that the stimulant and reinforcing properties of cocaine are homologous and are mediated by a common substrate (Wise and Bozarth, 1987). By contrast, the results of the present thesis suggest that the differential effects of early housing manipulations on the stimulant effects of cocaine failed to predict changes in the expression of I.V. cocaine self-administration. Therefore, the findings suggested that the substrates which mediate the stimulant properties of cocaine, may be distinct from those which mediate the reinforcing properties of cocaine, as assessed by self-administration.

The early housing manipulation used in the present series of experiments , did not appear to play a role in the expression of individual differences in the liability to self-administer cocaine I.V. in rats. Furthermore, it is evident from the literature (Einon et al., 1981;

Paivarinta, 1990; Valzelli, 1981) that the previous reports of the influence of early housing manipulations on drug induced behavioral responses are inconsistent across species and paradigms. It would appear, therefore, that an early housing manipulation which involves the simple comparison of grouped versus isolated subjects may not be an appropriate model for the investigation of the effects of environmental influences on drug induced behavioral responding.

In contrast to the above, reports have suggested that experimental manipulations involving rats in more naturalistic housing conditions may provide a more promising model for the study of environmental influences on human drug use (Blanchard et al., 1987). These reports argued that grouped housing in a more naturalized setting resulted in the expression of significant individual differences in the behavioral responding of animals (Crowley, 1988). Significant intragroup differences in oral ethanol consumption have also been reported for rats housed in grouped conditions but not for those housed in isolated conditions (Ellison, 1981). It has been suggested (Blanchard et al., 1987) that the variability observed within group-housed rats may be a reflection of the relative position within the social hierarchy of the group or colony. Blanchard et al., (1987) demonstrated that subordinate rats consumed significantly more ethanol than dominant rats when tested in an oral self-administration paradigm. It is possible that the social interactions which develop within groups may be a relevant determining factor for the expression of environmental influences. It would seem that any future investigation of the contribution of environmental influences on drug induced responding should focus upon the social dynamics involved in the interactions of rats within groups.

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