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Effects of Repeated Signalled and Unsignalled Intravenous Infusions of Cocaine on Locomotor Activity in Female Rats

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ABSTRACT

Effects of Repeated Signalled and Unsignalled Intravenous Infusions of Cocaine on Locomotor Activity in Female Rats

Kira H. Leeb

While many drug effects become weaker with repeated injections, the dominant behavioral effects of psychomotor stimulants tend to become stronger (sensitization). This effect on behaviour has been linked to the ability of psychomotor stimulants to enhance synaptic levels of the neurotransmitter dopamine. Cocaine, a potent psychomotor stimulant, is less able to enhance synaptic dopamine levels than other psychomotor stimulants yet produces a similar effect. It is thus possible that cocaine is acting synergistically with something that also enhances synaptic dopamine levels to produce its locomotor effects. As cocaine-associated stimuli appear to cause arousal and thus activate dopamine systems, the effectiveness of repeated signalled or unsignalled infusions of cocaine were compared on the basis of their ability to induce locomotor sensitization. Female rats implanted with intravenous (i.v.) catheters were given five infusions of either cocaine (1.25 or 2.5 mg/kg) or saline at 48 hour intervals. Half the rats were aroused prior to the i.v. infusions by being handled and given intraperitoneal injections of saline (signalled). The other half were given i.v. infusions in the absence of any prior arousal (unsignalled). A test infusion of cocaine (1.25 mg/kg) given to all animals revealed a minimal effect of the signal given in conjunction with cocaine. Furthermore, each group of rats pretreated with cocaine was more active in response to the test infusion than were the groups pretreated with saline. Progressive increases in cocaine-induced locomotor activity were evident in two of the groups tested; this effect was not consistent with regard to dose of drug or type of infusion (signalled or unsignalled). The failure to observe progressive increases in locomotor activity in all groups treated with cocaine infusions, despite a clear indication of

sensitization (test infusion), suggests a possible dissociation between the behavioral response evident upon repeated administrations of the drug and that which is elicited by a test infusion given after a period of drug withdrawal.

ACKNOWLEDGEMENTS

This project would never have been realized without the continuous guidance of my supervisor, Dr. Roy Wise, from whom I have learned a great deal about science and, especially, about myself over the last two years. I am greatly indebted to my officemate, Bill Carlezon, who patiently read, re-read and provided invaluable comments on many portions of this work. I am also indebted to Phyllis Webster, Fay Guarraci, Pat Bauco, Dany Gitnick, Beth Noel, Margaret Forgie, Dic Charge, and probably a number of others, who provided support and understanding during the final stages of this project and whose continuous belief in me gave me the energy to carry on. I would also like to thank Dany Gitnick for patiently teaching me the surgical techniques necessary to carry out this study and Steve Cabilio for never being more than a stone's throw away when I ran into computer problems. Finally, there is really no way to describe the contribution my husband, Ian Gordon, has made to this project. I could not ask for a better partner in life.

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Cocaine is a potent psychomotor stimulant with similar behavioral consequences to those of amphetamine. The predominant behavioral consequences of either drug are locomotion with lower doses and focused behavioral stereotypies with higher doses. The phrase 'behavioral stereotypies' refers to restrictive and repetitive components of species-typical (Randrup and Munkvad, 1967) investigatory reflexes (Wise and Bozarth, 1987) such as licking, biting, and sniffing in the rat and repetitive head and eye movements in the cat. Locomotion and behavioral stereotypies are collectively termed the "psychomotor stimulant" properties of cocaine, amphetamine, and related compounds (Ayd, 1957; Cole et al., 1961). With repeated intermittent administrations of either cocaine or amphetamine, animals become sensitized to the drug's psychomotor stimulant properties. Sensitization is reflected either as an increase in level of behavioral response to a fixed dose, or as a decrease in the dose needed to produce a given level of behavioral activation (Robinson and Becker, 1986).

The psychomotor stimulant effects of cocaine and amphetamine and the sensitization that develops to these effects with repeated drug experience have largely been attributed to the fact that these drugs increase extracellular levels of the neurotransmitter dopamine in the caudate and nucleus accumbens (Zetterström et al., 1983; Church, Justice and Byrd, 1987; Sharp et al., 1987; Kalivas et al., 1988; Peris et al., 1990; Kalivas and Duffy, 1993a, 1993b). However, unlike amphetamine, cocaine does not cause dopamine release *per se* (Heikkila, Orlansky and Cohen, 1975); rather, cocaine only prolongs the effective life of dopamine that has been released as a result of spontaneous cell firing or through external activation of dopamine neurons. Thus the psychomotor stimulant effects of cocaine may, unlike the effects of amphetamine, depend critically on an interaction between the pharmacological actions of the drug and the activation of the dopamine system by stress or environmental stimuli. The present study explores this possibility.

1. Behavioral actions of cocaine and amphetamine.

Low to moderate doses of either cocaine or amphetamine induce low to moderate levels of locomotor activity (Segal and Mandell, 1974; Segal, 1975; Post and Rose, 1976; Stripling and Ellinwood, 1977b; Kilbey and Ellinwood, 1977; Short and Shuster, 1976, Shuster, Yu and Bates, 1977; Post et al., 1981). With higher doses, locomotion appears briefly but is replaced by behavioral stereotypies that dominate until much of the high dose is metabolized (Segal, 1975; Ellinwood and Kilbey, 1975; Ellinwood and Kilbey, 1977, Shuster, Yu and Bates, 1977).

For the rat, the behavioral stereotypies produced by cocaine and amphetamine have been well characterized. Rats given a high dose of cocaine or amphetamine, respond with repetitive head and forelimb movements as well as with periods of continuous sniffing (Scheel-Krüger et al., 1977). With a higher dose of amphetamine, the animal engages in even more intense and prolonged sniffing as well as biting and licking (Scheel-Krüger et al., 1977; Robinson and Becker, 1986). Rats engaged in behavioral stereotypies perform these behaviours to the exclusion of other behaviours such as grooming (Randrup and Munkvad, 1967), and their movements become confined in space (Scheel-Krüger et al., 1977). Interestingly, very high doses of cocaine do not appear to produce the same intensity of behavioral stereotypy as is seen with amphetamine (Scheel-Krüger et al., 1977). For example, high doses of cocaine induce stereotyped head and limb movements and periods of continuous sniffing; cocaine fails to induce biting and licking (Scheel-Krüger et al., 1977). This failure, however, may be related to cocaine's inherent side-effects (e.g., convulsions, Post, 1977; Post et al., 1981) rather than to differences in the stimulant properties of cocaine and amphetamine.

Sensitization to the psychomotor stimulant effects of cocaine or amphetamine occurs with repeated, intermittent treatment (Robinson and Becker, 1986). Progressive increases in the level of drug-induced locomotor activity and in the intensity of drug-induced behavioral stereotypies provide indices of the degree of sensitization produced by

the repeated drug administrations. For example, animals given repeated administrations of low doses show progressively higher levels of drug-induced locomotor activity (Segal and Mandell, 1974; Post and Rose, 1976). Behavioral stereotypies may also begin to emerge with sufficient repetitions of low dose treatments (Post and Rose, 1976). With repeated administrations of a higher dose locomotion becomes increasingly less evident as progressively more intense and prolonged periods of behavioral stereotypies come to dominate (Stripling and Ellinwood, 1977; Segal, 1975). As the drug is metabolized and the behavioral stereotypies begin to subside, the animals again show elevated levels of locomotor activity (Stripling and Ellinwood, 1977; Segal, 1975; Segal and Kuczenski, 1987). Another indication of sensitization is the enhanced behavioral responsiveness of a drug experienced animal to doses of drug that are ineffective or only mildly effective in drug-naive animals (Kalivas and Duffy, 1993a, 1993b; Kilbey and Ellinwood, 1977; Leith and Kuczenski, 1981).

2. Role of dopamine in cocaine- and amphetamine-induced locomotion and behavioral stereotypies

The psychomotor stimulant effects of cocaine and amphetamine appear to depend largely on the effect of these drugs on dopaminergic neurons (for review, see Wise and Bozarth, 1987 , but, see, Kuczenski and Segal, 1988). Consistent with this notion, amphetamine-induced locomotor activity is blocked by a systemic injection of the dopamine synthesis inhibitor (and thus noradrenaline inhibitor) alpha-methyl-para-tyrosine (Weissman, Koe and Tenen, 1966), but not when only the conversion of dopamine to noradrenaline is inhibited by dopamine-beta-hydroxylase inhibitors (Thronburg and Moore, 1973). Behavioral responses to systemic injections of cocaine or amphetamine are also blocked by selective 6-hydroxydopamine lesions of dopaminergic, but not noradrenergic, pathways (Creese and Iversen, 1975).

It has further been demonstrated that it is the increased levels of dopamine in the terminal regions of the mesolimbic dopaminergic pathway that are primarily associated with

amphetamine- or cocaine-induced locomotor activity. Increased levels of dopamine in the terminal regions of the nigrostriatal dopaminergic pathways have primarily been associated with cocaine- and amphetamine-induced behavioral stereotypies. The mesolimbic dopaminergic pathway originates in the midbrain region of the ventral tegmental area and projects to various target areas including the nucleus accumbens, amygdala and olfactory tubercle (Ungerstedt, 1971). The origins of the nigrostriatal dopaminergic pathway are also in the midbrain but are located in the compact region of the substantia nigra; included in the areas that receive projections from the substantia nigra are the caudate nucleus and putamen (Dahlstrom and Fuxe, 1964). With the development of *in vivo* microdialysis—a technique that enables the direct measurement of extracellular levels of dopamine—a strong correlation has been noted between increases in nucleus accumbens dopamine levels and locomotor activity and between increases in the striatal dopamine levels and behavioral stereotypies (Sharp et al., 1987). Further, infusions of dopamine and other dopamine agonists directly into the nucleus accumbens induce locomotor activity, whereas infusions of amphetamine directly into the caudate nucleus tend to induce behavioral stereotypies (Costall et al., 1977). Intra-accumbens injections of either amphetamine or dopamine, but not noradrenaline or serotonin, also produce increases in locomotor activity that are blocked by pretreatment with the dopamine antagonist haloperidol (Pijnenburg et al., 1976; Pijnenburg, Honig and Van Rossum, 1975). Conversely, injections of haloperidol directly into the nucleus accumbens blocks locomotor responding to a systemic injection of amphetamine (Pijnenburg, Honig and Van Rossum, 1975). Whereas dopamine-selective 6-hydroxydopamine lesions of the nucleus accumbens block the locomotor response to systemic injections of cocaine or amphetamine (Kelly, Seviour and Iversen, 1975; Kelly and Iversen, 1976; Joyce, Stinus and Iversen, 1983), similar lesions of the caudate nucleus block the behavioral stereotypies induced by high doses of amphetamine or cocaine (Creese and Iversen, 1974; Kelly, Seviour and Iversen, 1975).

Because behavioral stereotypies consistently require higher doses of drug than does locomotion, it was previously argued that locomotor activity was at the low end and behavioral stereotypies at the high end of a behavioral continuum controlled by dopaminergic activation (Segal and Mandell, 1974). However, given the evidence presented above, it appears likely that these two behaviours are not the respective consequences of lower and higher levels of activation of a common circuit. Rather, drug-induced locomotor activity and drug-induced stereotypies depend on the activation of separate dopaminergic pathways. The results of these behavioral studies and those of recent *in vivo* microdialysis studies (Di Chiara and Imperato, 1988) suggest that low doses of cocaine and amphetamine may preferentially increase extracellular levels of dopamine in the nucleus accumbens; higher doses of drug would thus be needed to sufficiently increase extracellular levels of dopamine in the nigrostriatal pathway to induce behavioral stereotypies.

3. Actions of cocaine and amphetamine on dopaminergic function.

Since the psychomotor stimulant properties of cocaine and amphetamine depend on the integrity of dopaminergic-containing neurons, it is the actions of these drugs on dopaminergic neurons that have received much experimental attention. While cocaine and amphetamine are each indirect dopamine agonists, they increase extracellular levels of dopamine by somewhat different actions.

Cocaine acts primarily to inhibit the reuptake, and thus prolong the synaptic activity, of released dopamine (Ross and Renyi, 1967; Harris and Baldessarini, 1973; Heikkila, Orlansky and Cohen, 1975). Thus, cocaine added to rat (Harris and Baldessarini, 1973) or rabbit (Ross and Renyi, 1967) striatal tissue preparations inhibits the reuptake but does not promote the release (Heikkila, Orlansky and Cohen, 1975) of tritiated (radio-actively labeled) dopamine. Blockade of dopamine reuptake and the concomitant increase in extracellular levels of dopamine also results in the inhibition of

dopamine cell firing (Einhorn, Johansen and White, 1988) and thus the inhibition of impulse-dependent dopamine release.

Whereas cocaine only blocks dopamine reuptake, amphetamine elevates extracellular levels of dopamine by two mechanisms. Like cocaine, amphetamine inhibits the reuptake of dopamine into striatal (Harris and Baldessarini, 1973; Holmes and Rutledge, 1976) and cortical (Heikkila, Orlansky and Cohen, 1975) tissue preparations. Unlike cocaine, however, amphetamine also causes dopamine release (Heikkila, Orlansky and Cohen, 1975; Raiteri et al., 1975; Arnold, Molinoff and Rutledge, 1977; Butcher et al., 1988). Amphetamine, like cocaine, inhibits cell-firing (Bunny et al., 1973; White and Wang, 1984) and thus impulse-dependent dopamine release. However, its effects on impulse flow notwithstanding, amphetamine causes profound impulse-independent dopamine release (Arnold, Molinoff and Rutledge, 1977; Hurd and Ungerstedt, 1989).

4. The effects of external stimuli on dopamine release and behaviour.

A variety of external stimuli increase dopamine cell firing which, in turn, elevates extracellular dopamine levels (Lindsay et al., 1981; Keller, Stricker and Zigmond, 1983; Louilot, LeMoal, and Simon, 1986; Schultz, 1992; Ljungberg, Apicella and Schultz, 1992). Single cell recordings from dopaminergic neurons of the mesolimbic and nigrostriatal pathways indicate that these neurons are activated when animals are exposed to a variety of novel (Chiodo et al., 1980; Ljungberg, Apicella and Schultz, 1992; Schultz, 1992) reward related (Ljungberg, Apicella and Schultz, 1992; Schultz, 1992), or stressful stimuli (Chiodo et al., 1979; Chiodo et al., 1980). The fact that the presentation of a variety of stimuli produces measurable elevations in extracellular dopamine levels has been confirmed by *in vivo* microdialysis and by *in vivo* voltammetry. Thus animals placed in an environment previously paired with drug administrations (Kalivas and Duffy, 1990) or exposed to tail or foot shock (Abercrombie et al., 1989; Sorg and Kalivas, 1991) have elevated nucleus accumbens extracellular dopamine levels as measured by microdialysis.

Interestingly, increases in the intensity of the stressful stimulus induce intensity-dependent levels of extracellular dopamine (Sorg and Kalivas, 1991) and more widespread activation of dopaminergic brain regions (Dunn, 1988; Roth et al., 1988). Elevated extracellular levels of dopamine in the substantia nigra or the nucleus accumbens have also been detected using *in vivo* voltammetry in animals exposed to novel olfactory or visual stimuli (Keller, Stricker and Zigmond, 1983; Mitchell and Gratton, 1992) and to a variety of stressful stimuli including fear evoking stimuli (Lindsay et al., 1981), tail pinch (Curzon, Hutson and Knott, 1979; Louilot, LeMoal and Simon, 1986; Doherty and Gratton, 1992), physical restraint (Curzon, Hutson and Knott, 1979; Doherty and Gratton, 1992), tail shock and cold water baths (Keller, Stricker and Zigmond, 1983).

Given that stressful external stimuli can increase the levels of extracellular dopamine in the mesolimbic and nigrostriatal dopamine pathways, it is not surprising that the presentation of these stimuli can also induce locomotion and components of behavioral stereotypies. Thus animals exposed to foot shock show increased locomotor activity (Leyton and Stewart, 1990) whereas prolonged exposure of animals to tail pinch stress can induce repetitive and restrictive biting and licking behaviours (Antelman et al., 1975). Interestingly, with repeated exposure to foot shock progressive increases in the level of stress-induced locomotor activity are seen (Leyton and Stewart, 1990). Thus repeated exposure to stress appears able to sensitize animals to the locomotor activating effects of a stressful stimulus (Leyton and Stewart, 1990).

Because repeated exposure to stress and repeated exposure to cocaine or amphetamine produce sensitization, it has been argued that drugs are merely stressors, and that sensitization is essentially a phenomenon of stress (Antelman and Chiodo, 1983). In support of the notion that stress- and drug-induced sensitization are inherently related, repeated exposure to stressful stimuli have been shown to sensitize animals to the stimulant properties of cocaine or amphetamine and vice-versa (Kalivas and Duffy, 1989; Antelman et al., 1980); a phenomenon known as cross-sensitization (Antelman et al., 1980). Cross-sensitization between drugs and stress has been demonstrated by a variety of studies: for example, rats repeatedly exposed to tail pinch have

enhanced behavioral responses to a subsequent administration of amphetamine; repeated administrations of amphetamine also enhance the behavioral responses elicited by a subsequent exposure to tail pinch (Antelman et al., 1980). Similarly, rats repeatedly exposed to foot shock have enhanced behavioral responses to a subsequent administration of cocaine or amphetamine (Kalivas and Duffy, 1989; Leyton and Stewart, 1990; Sorg and Kalivas, 1991); repeated administrations of cocaine also enhance the behavioral responses elicited by a subsequent exposure to foot shock (Kalivas and Duffy, 1989).

5. Present Investigation.

The purpose of the present investigation was to determine the contribution of the environmental manipulations of handling and injection to the behavioral activation and sensitization caused by cocaine injections. Female rats were given cocaine by remote intravenous (i.v.) infusion once every second day for 10 days. Half the rats were handled and given i.p. saline injections, thus receiving the combination of drug and handling that is typical of most cocaine sensitization studies. The remaining animals received the drug without handling and without any external cue as to when the drug was infused. Four to five days after completion of the repeated i.v. infusions each animal received a test infusion of cocaine to determine whether sensitization was evident after the repeated drug treatments had ceased.

METHODS

Subjects

Forty-eight female Sprague-Dawley rats (Charles River, Quebec, CA) weighing 280-330g at the start of the experiment served as subjects. They were housed one to a cage and had free access to food and water except during testing. The lights in the housing room were on a 12 hrs on/12 hrs off schedule (lights on at 08:00).

Surgery

At least one week after arrival, each animal was implanted with a chronic intravenous (i.v.) catheter. Each animal was first anesthetized with sodium pentobarbital (40 mg/kg, i.p.); it then received an injection of atropine sulfate (0.12 mg, s.c.) to minimize bronchial secretions and an injection of penicillin G (60 000 units, i.m.) to prevent infection. A small incision was made to the right of the midline of the neck and the external jugular vein was isolated and opened and a silastic i.v. catheter was inserted approximately 5 cm such that the tip of the catheter lay just over the heart. The other end of the catheter was fed subcutaneously around the right side of the neck to exit through a small opening at the back of the skull. A curved piece of 22 gauge stainless steel tubing was inserted into the end of the catheter and secured to the animal's skull with dental cement anchored by stainless steel screws to serve as a connector between the catheter and the infusing line. The catheter was flushed with heparinized saline and capped after surgery to prevent the clotting of blood. The catheter was similarly flushed the day before the experiment began and upon completion of testing each day.

Apparatus and Materials

Locomotor testing was done in covered 45 X 20 X 25 cm activity chambers with grid floors. Each chamber was equipped with two lights and photocells placed at equal intervals along the walls of the chamber. An i.v. infusion line was introduced through a slit in the top of each chamber in such a way as to allow the animal free movement during testing. Activity counts were determined by photobeam interruptions and were recorded by a microprocessor. During testing white noise (75 dB) was broadcast in the room. Room lighting was provided by a 40watt lamp.

The i.v. catheter was connected to a 20 ml syringe by a polyethylene infusion line and a fluid swivel (Lomar Co.). Intravenous delivery of the drug was controlled by a

microprocessor programmed to activate each syringe pump for 30 seconds delivering an infusion of 0.25 ml.

Drug

Cocaine hydrochloride was dissolved in physiological saline (and sterilized by filtration) to yield a dosage of either 1.25 or 2.5 mg/kg infusion for each rat.

Procedure

Repeated Infusions

The animals were given one week to recover from surgery and then drug testing began. Each animal was connected to an infusion line and placed in the activity chamber for three hours daily for 10 days; locomotor activity was recorded for each three hour period. Infusions were given every second day so that being placed in the activity chamber was not necessarily associated with an infusion; however, for half of the animals the infusions were deliberately signalled. Thus, each animal received five drug infusions and each drug infusion was separated by a day on which no infusion occurred.

Six groups of animals were tested, each receiving one of the following treatment assignments: 2.5 mg/kg cocaine, signalled (S2.5, n=8); 1.25 mg/kg cocaine, signalled (S1.25, n=10); saline, signalled (SS, n=6); 2.5 mg/kg cocaine, unsignalled (U2.5, n=7); 1.25 mg/kg cocaine, unsignalled (U1.25, n=10); saline unsignalled (US, n=7). On each drug treatment day, the first two hours the animals spent in the activity chamber constituted an habituation period. Each animal was then given an i.v. infusion of either cocaine (1.25 or 2.5 mg/kg) or saline. In the case of signalled infusions, the experimenter entered the room, removed the animal from the activity chamber, administered an i.p. saline injection and returned the animal to the activity chamber just prior to the remotely controlled i.v. infusion of drug or saline. In the case of unsignalled infusions, the i.v. infusion was given in the absence of any handling, i.p. injection, or even the disturbances associated with entry of the experimenter into the room. As the i.v. infusions for both the signalled and

unsignalled groups were controlled by a microprocessor preprogrammed to activate the syringe pumps at the end of the habituation period, the i.p. injections served to signal the onset of the i.v. infusions for the rats receiving signalled infusions. For the rats receiving unsignalled infusions, no intentional environmental disturbances occurred during or at the end of the 2 hour habituation period. On the alternating days, when no drug was given, the rats remained untouched in the activity chambers for the three hour period. At the end of every day each rat was removed from the activity chamber, its cannula was flushed with heparinized saline and recapped; each rat was then weighed and returned to its home cage. To ensure that the animals receiving unsignalled infusions were not disturbed prior to the onset of the infusions, animals receiving signalled infusions and animals receiving unsignalled infusions were not infused on the same day. Thus half of the animals in each of the six groups received infusions on days 1,3,5,7 and 9 of testing while the other half received infusions on days 2,4,6,8, and 10 of testing. Following the tenth day, each animal was kept in its home cage for four days; catheters were flushed once daily with heparinized saline during this period.

Test Infusion

To determine whether the treatment infusions had produced sensitization, the animals were tested with the low dose of cocaine five days after the end of the treatment period. Each animal was again connected to an i.v. infusion line, placed in an activity chamber for two hours (habituation) and then given an unsignalled i.v. infusion of cocaine (1.25 mg/kg over 15 sec). Activity was recorded during the habituation period and for one hour following the drug infusion.

Statistical Analysis

The time course of the effect of the first (Day 1) i.v. infusion of cocaine or saline on locomotor activity was evaluated using a three-way (dose X signal X time after infusion)

repeated measures analysis of variance (ANOVA). Saline was treated as a null dose for this and all subsequent analyses. A three-way (dose X signal X days) repeated measures ANOVA was used to evaluate whether, with the repeated drug infusions, locomotor activity increased progressively across the test days. The influence of the drug infusions on spontaneous locomotion (locomotion occurring in the absence of the drug) was evaluated in two separate analyses. First, a three-way (dose assignment X signal assignment X days) repeated measures ANOVA was used to determine whether the locomotor activity occurring 20 minutes prior to each i.v. infusion increased significantly across days. Second, the locomotor activity evident on the days when no infusion occurred was evaluated using a three-way (dose assignment X signal assignment X days) repeated measures ANOVA. This analysis was performed in an attempt to determine whether, with repeated pairings of the activity chamber with i.v. infusions, the animals became progressively more active when simply placed in the locomotor chambers but not infused. The effect of the test infusion on locomotor activity was evaluated using a three-way (previous dose assignment X prior signal assignment X time after infusion) repeated measures ANOVA. Because some of the i.v. catheters became blocked prior to the test infusion the analysis of these data is based on the following animals per group: S2.5, n=6; S1.25, n=10; SS, n=6; U2.5, n=6; U1.25, n=10; US, n=6. Finally, a close inspection of the data suggested the possibility that the differences in the counterbalanced initial conditions (i.e., drug or no drug on Day 1) may have inadvertently influenced the locomotor response to subsequent i.v. infusions. To test for this possible confound, the animals were regrouped according to their drug experience (drug or no drug) during the first exposure to the activity chambers and a post hoc three-way (dose assignment X first exposure X days) repeated measures ANOVA was performed.

Significant interactions were analyzed by simple effects analyses and post hoc comparisons according to Keppel (1991).

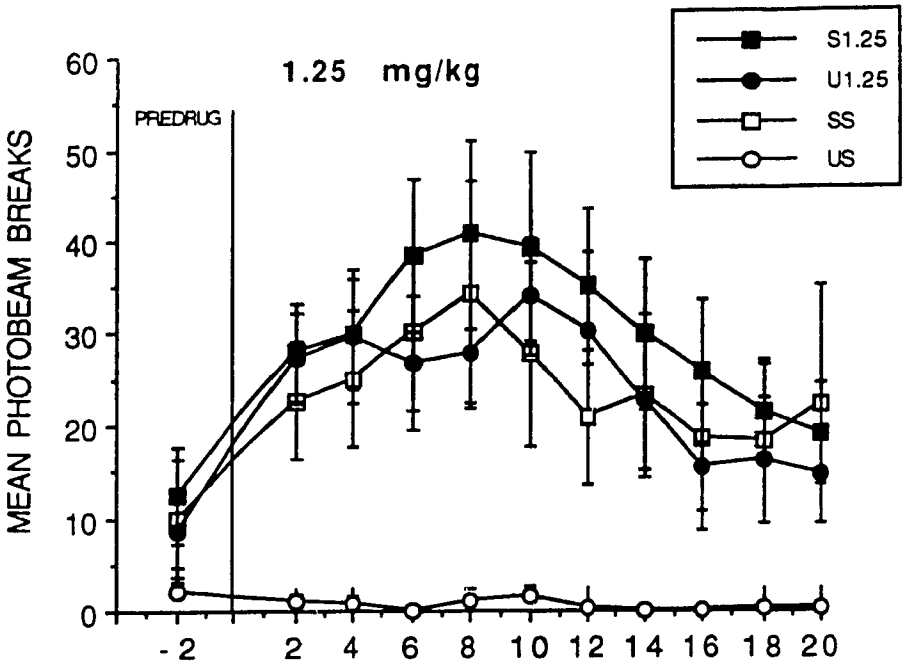
Day 1

On the first day of infusion, cocaine induced significantly more locomotor activity than did saline (Fig. 1); a dose X signal X time after infusion ANOVA (repeated measures) revealed a significant effect of dose ($F_{2,42}$=8.90, $p<0.001$). Animals receiving either 1.25 or 2.5 mg/kg were significantly more (multiple comparisons) active than were the animals receiving saline (p's<0.02). Furthermore, animals infused with cocaine or saline showed a transient increase in locomotion indicated by a significant effect of time after infusion ($F_{9,42}$=5.46, $p<0.0001$). Although the overall activity of the animals receiving signalled infusions was not greater than the activity of animals receiving unsignalled infusions, the signal influenced locomotor activity in some conditions; a significant interaction of dose X signal ($F_{2,42}$=3.55, $p<0.04$) was revealed in the analysis. Comparisons of the effect of the signal at each dose revealed that animals receiving signalled infusions of saline were more active than animals receiving unsignalled infusions of saline ($p<0.02$). There was no evidence on the first day of infusion to suggest that the signalling condition influenced the locomotor activity of the animals receiving cocaine.

Across Test Days

Cocaine induced dose-dependent locomotion across the treatment days; there was also a general trend toward progressive increases in locomotor activity with the repeated treatments (Fig. 2). The dose X signal X days ANOVA (repeated measures) revealed a significant effect of dose ($F_{2,42}$=35.23, $p<0.0001$) and of days ($F_{4,168}$=4.85, $p<0.001$). Although the analysis also revealed a significant interaction of dose X days ($F_{8,168}$=2.45,

Figure 1. Mean (+/- S.E.M.) activity counts (expressed as photobeam breaks) in 2 minute intervals for 2 minutes prior and 20 minutes following the first intravenous infusion of cocaine or saline. For clarity animals receiving 1.25 mg/kg and animals receiving 2.5 mg/kg are presented on separate graphs. The saline groups are the same for each graph.


1.25 mg/kg
PREDRUG
S1.25
U1.25
SS
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MEAN PHOTOBEAM BREAKS
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50
40
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18
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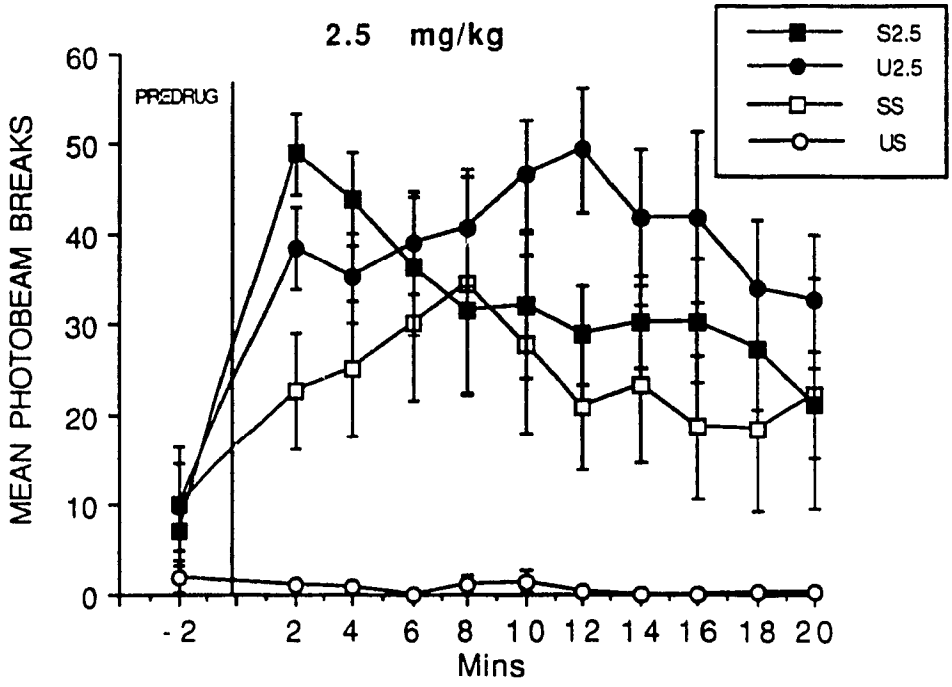
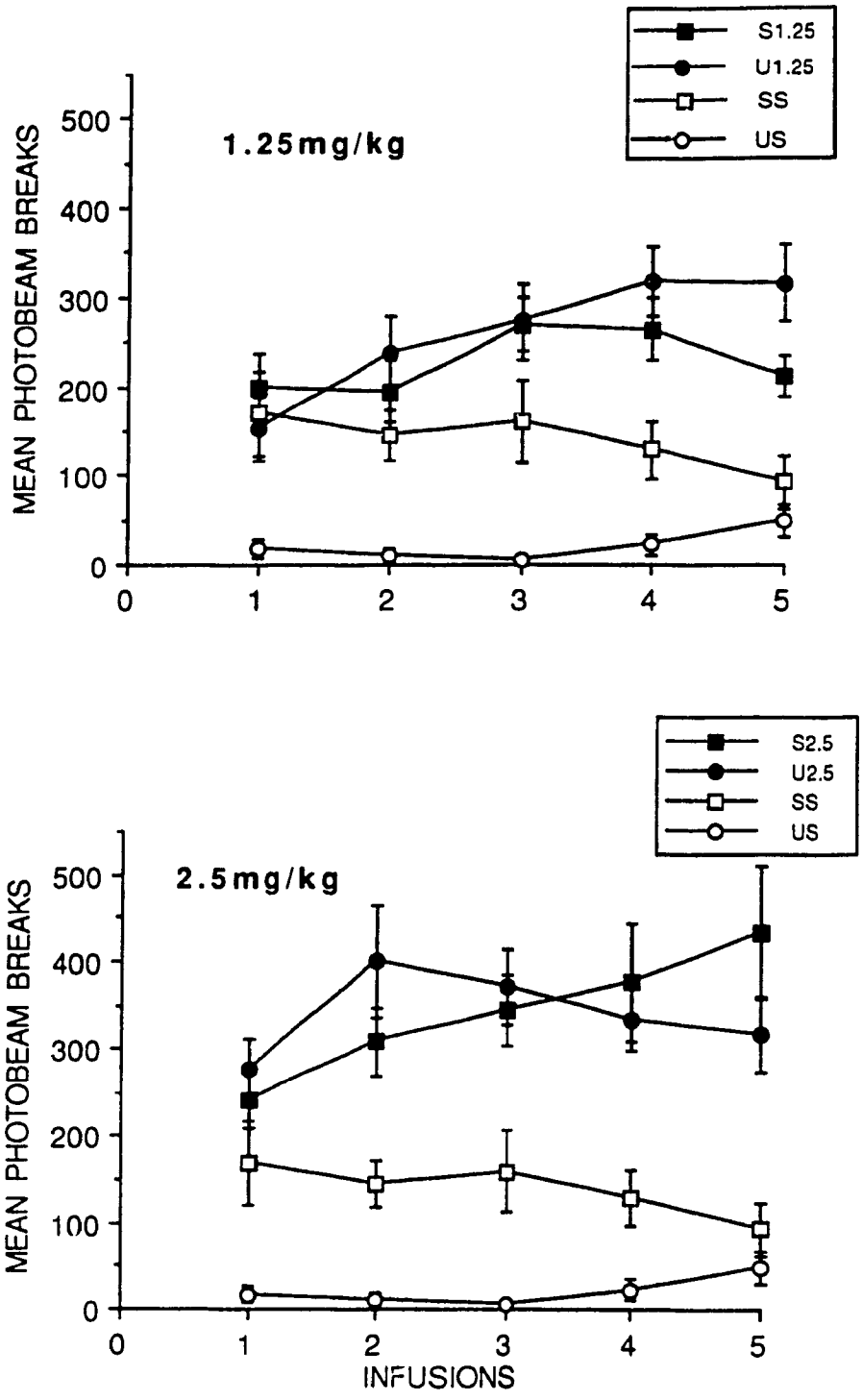

2.5 mg/kg
PREDRUG
S2.5
U2.5
SS
US
MEAN PHOTOBEAM BREAKS
60
50
40
30
20
10
0
-2
2
4
6
8
10
12
14
16
18
20
Mins

Figure 2. Mean (+/- S.E.M.) activity counts (expressed as photobeam breaks) in 15 minutes after each intravenous infusion of cocaine or saline for each day of testing. For clarity animals receiving 1.25 mg/kg and animals receiving 2.5 mg/kg are presented on separate graphs. The saline groups are the same for each graph.


S1.25
U1.25
SS
US
1.25mg/kg
MEAN PHOTOBEAM BREAKS
500
400
300
200
100
0
0
1
2
3
4
5
S2.5
U2.5
SS
US
2.5mg/kg
MEAN PHOTOBEAM BREAKS
500
400
300
200
100
0
0
1
2
3
4
5
INFUSIONS

$p<0.02$), there was a differential interaction of the signal with dose across days ($F_{8,168}=2.76$, $p<0.007$). Simple effects analyses of this three-way interaction revealed that the activity of the unsignalled animals receiving the low dose increased progressively with the repeated treatments, whereas the activity of the unsignalled animals receiving the high dose of cocaine or saline did not: a simple effects analysis of dose X days for only the animals receiving unsignalled infusions indicated a significant simple effect of days ($F_{4,168}=5.11$, $p<0.001$) only for the unsignalled animals receiving the low dose of cocaine. On the other hand, the activity of the signalled animals receiving the high dose of cocaine increased progressively with the repeated treatments, whereas the activity of the signalled animals receiving the low dose of cocaine or saline did not. Again, a simple effects analysis of dose X days for only the animals receiving signalled infusions revealed a simple effect of days ($F_{4,168}=5.62$, $p<0.0005$) for only the signalled animals receiving the high dose of cocaine. Finally, signalled animals receiving saline infusions showed significantly more (multiple comparisons) activity on the first three days of testing ($p's<0.05$) than the unsignalled animals receiving saline.

20 Minutes Prior to the Onset of Each Infusion

Activity levels 20 minutes prior to the scheduled infusion time varied as a function of treatment dose (Fig. 3); a dose assignment X signal assignment X days ANOVA (repeated measures) revealed only a significant effect of dose assignment ($F_{2,42}=3.77$, $p<0.04$). Animals receiving 1.25 mg/kg had higher levels (multiple comparisons) of activity than the animals receiving saline ($p<0.01$). The signalling condition did not influence the activity of the animals 20 minutes prior to the infusions.

Figure 3. Mean (+/- S.E.M.) activity counts (expressed as photobeam breaks) in 20 minutes prior to the onset of each intravenous infusion. Each dose contains the animals receiving signalled and the animals receiving unsignalled intravenous infusions of that dose.

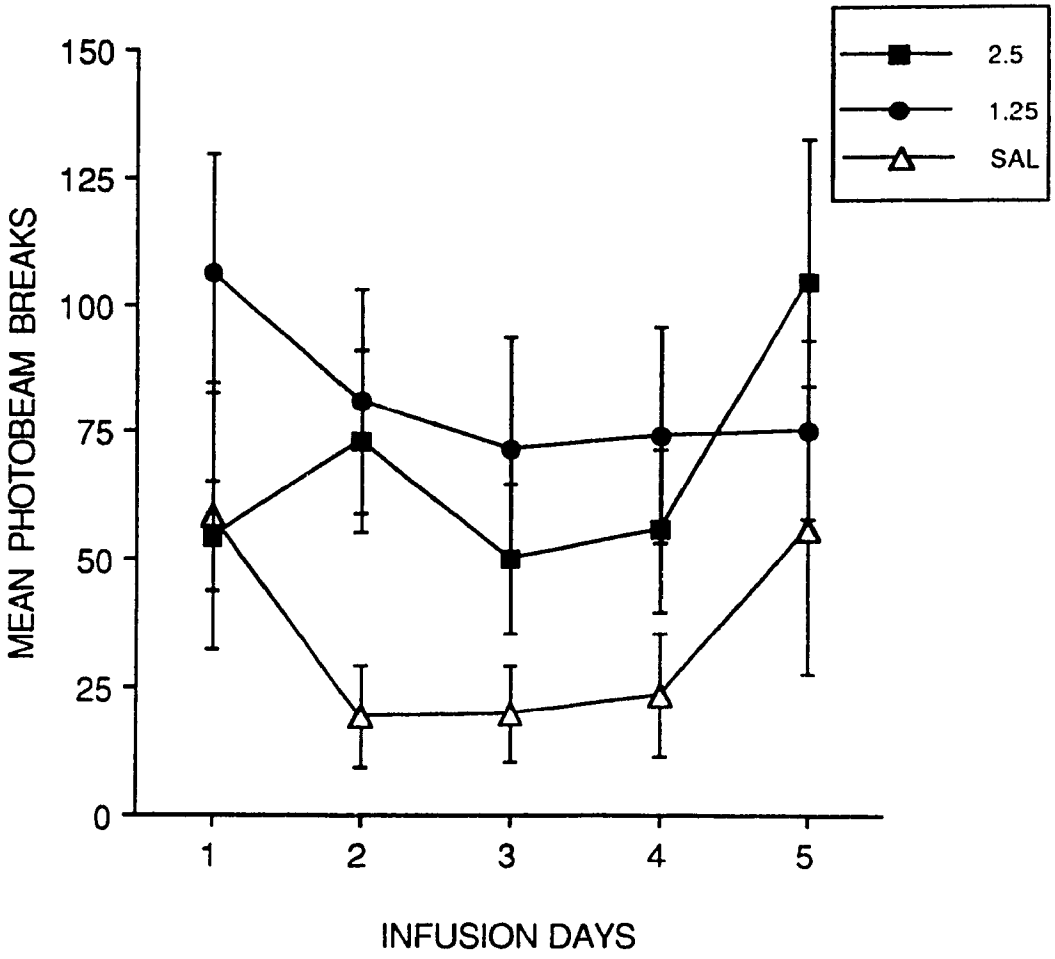
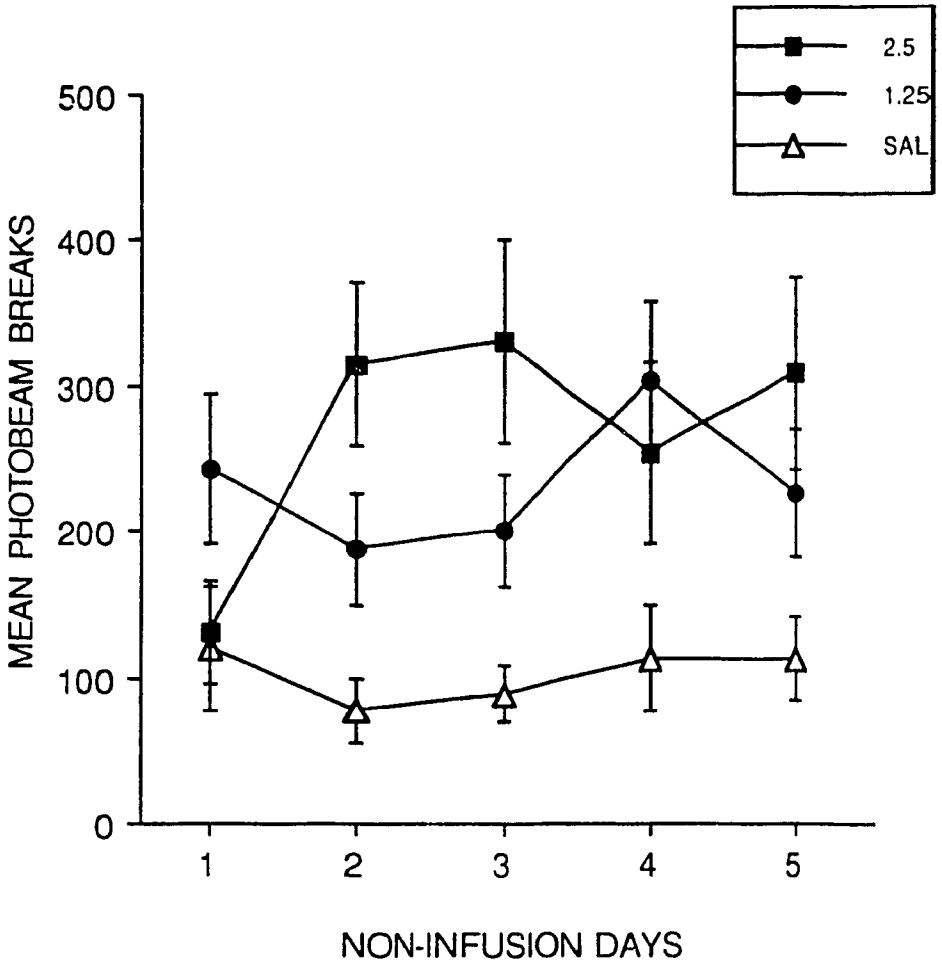

150
125
100
75
50
25
0
MEAN PHOTOBEAM BREAKS
1
2
3
4
5
INFUSION DAYS
2.5
1.25
SAL

Figure 4. Mean (+/- S.E.M.) activity counts (expressed as photobeam breaks) for the final 60 minutes the animals spent in the activity chambers on each of the non-infusion days. Each dose contains the animals assigned to receive signalled and the animals assigned to receive unsignalled infusions of that dose.


2.5
1.25
SAL
500
400
300
200
100
0
MEAN PHOTOBEAM BREAKS
1
2
3
4
5
NON-INFUSION DAYS

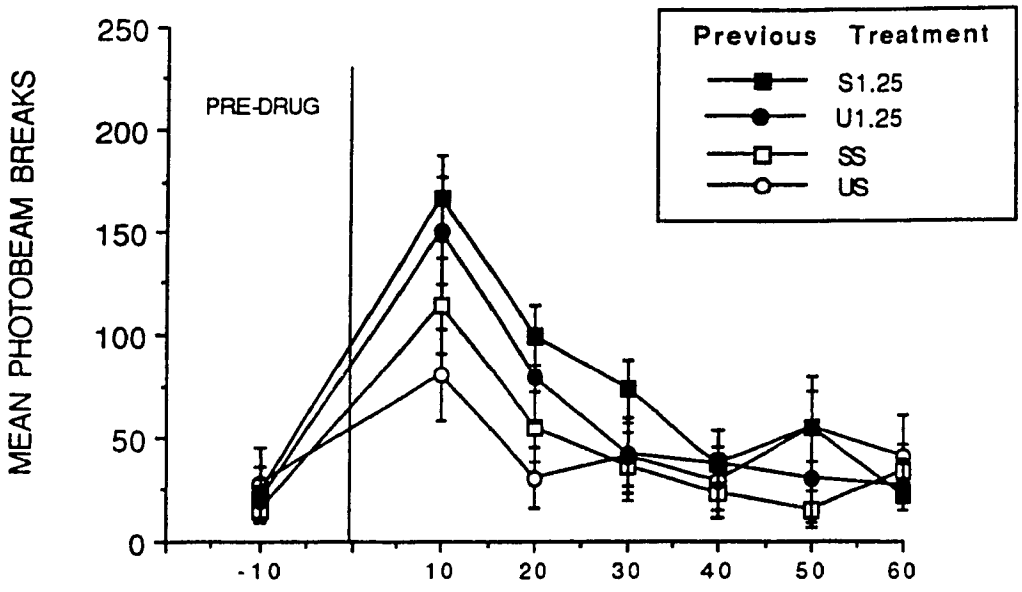
Locomotor Activity on Non-Drug Days

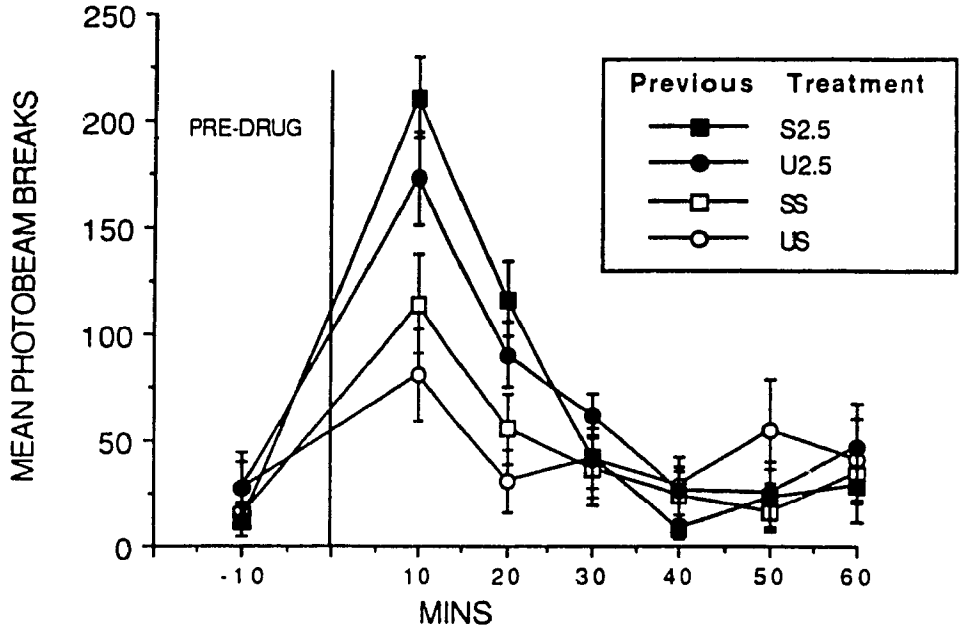
Activity levels on the days between drug infusion varied as a function of treatment dose; animals receiving dosages of 1.25 or 2.5 mg/kg showed higher activity on these intervening days than did animals receiving saline (Fig. 4). A dose assignment X days X signal assignment ANOVA revealed a significant effect of dose assignment ($F_{2,42}$=7.5, $p<0.002$) and comparisons indicated that animals in each of the cocaine-treated groups were more active than those in the saline-treated group (p's<0.008). This difference in activity relative to the saline-treated animals was consistent for the animals receiving the 1.25 mg/kg dosage but increased progressively across the non-infusion days with the animals receiving the 2.5 mg/kg dosage. This effect was indicated by the presence of a significant dose assignment X days interaction ($F_{8,168}$=2.24, $p<0.03$) and further characterization with simple effects analyses revealed only a significant effect of days ($F_{4,168}$=4.04, $p<0.004$) for the 2.5 mg/kg dosage groups. The signalling condition did not influence the activity of the animals on non-infusion days.

Test Infusion

All animals treated with the unsignalled test infusion of 1.25 mg/kg cocaine showed a transient increase in locomotor activity (Fig. 5); a prior dose assignment X prior signal assignment X time after infusion revealed a significant effect of time after infusion ($F_{5,190}$=63.58, $p<0.0001$). However, the activity in response to the test infusion also varied as a function of both prior treatment dose and signal assignment: the significant interaction of prior treatment dose X time after infusion ($F_{10,190}$=5.77, $p<0.0001$) indicated that animals previously treated with cocaine initially showed more locomotor activity in response to the test infusion than animals previously treated with saline. Comparisons between each dose within the first 10-min periods after the infusion indicated a prior dose treatment-dependent response to the test infusion: animals previously treated with the high dose of cocaine were more active than the animals previously treated

Figure 5. Mean (+/- S.E.M.) activity counts (expressed as photobeam breaks) in 10 minute intervals for 10 minutes prior and one hour after the test infusion of 1.25 mg/kg. Labels refer to group assignment during the repeated treatment phase of the experiment. For clarity animals previously treated with 1.25 mg/kg and animals previously treated with 2.5 mg/kg are presented on separate graphs. Animals previously treated with saline are represented on each graph.


MEAN PHOTOBEAM BREAKS
250
200
150
100
50
0
PRE-DRUG
Previous Treatment
S1.25
U1.25
SS
US
-10
10
20
30
40
50
60


MEAN PHOTOBEAM BREAKS
250
200
150
100
50
0
PRE-DRUG
Previous Treatment
S2.5
U2.5
SS
US
-10
10
20
30
40
50
60
MINS

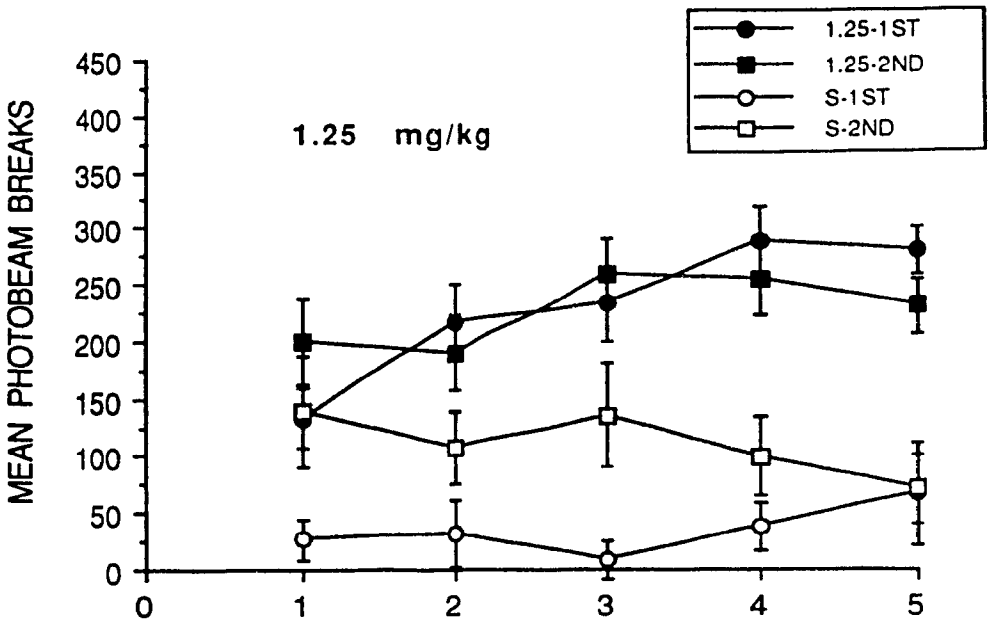
with either the low dose or saline (p's<0.05) for the first 10-min period, and were more active than the animals previously treated with saline for the second 10-min period (p<0.009). Similarly, animals previously treated with 1.25 mg/kg were more active for the first two time periods after the test infusion than animals previously treated with saline (p's<0.009).

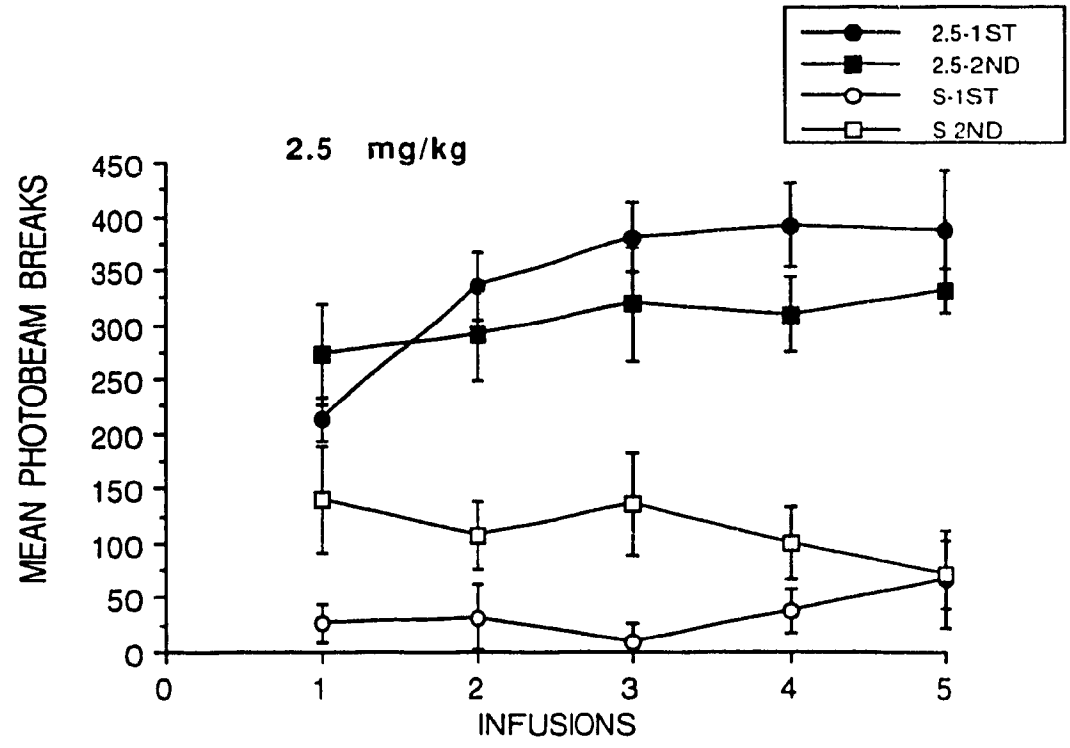
The animals that had previously been signalled with respect to the infusion in the treatment phase, regardless of whether they had received cocaine or saline, were more active than the animals unsignalled with respect to the infusion in the treatment phase; a significant interaction of previous signal assignment X time after infusion ($F_{5,190}$=2.41, p<0.04) was indicated by the analysis. Further analysis of this effect (multiple comparisons) revealed only a significant increase in the activity of the animals previously signalled above that of the animals previously unsignalled with respect to the infusions for the first time period after the infusion (p<0.05).

First Exposure

Half the animals received an infusion of cocaine or saline on the first day in the activity chambers and on subsequent odd-numbered days, while half the animals were not infused on the first day, receiving infusions on the second and subsequent even-numbered days. For those animals whose first cocaine or saline infusion was on their first day in the activity chamber, the infusion induced less activity than it did on subsequent days or than it did in animals that received their first infusion on their second day in the activity chambers (Fig. 6). The post hoc dose X first exposure X days ANOVA (repeated measures) revealed a significant interaction of first exposure X days ($F_{4,168}$=3.87, p<0.005). Comparisons of the effect of first exposure within each day of treatment revealed that animals infused on their first day in the activity chambers were less active relative to animals infused on their second in the activity chambers for only day 1 of the repeated

Figure 6. Mean (+/- S.E.M.) activity counts (expressed as photobeam breaks) in 15 minutes after each infusion of cocaine or saline for each of the test days. Animals have been regrouped on the basis of their first exposure to the activity chambers (see text for details). For clarity animals receiving 1.25 mg/kg and animals receiving 2.5 mg/kg are presented on separate graphs. The saline groups are the same for each group. Note: 1ST denotes animals that received the first infusion during their first exposure to the activity chambers, 2ND denotes animals that received the first infusion during their second exposure to the chambers.


1.25-1ST
1.25-2ND
S-1ST
S-2ND
1.25 mg/kg
MEAN PHOTOBEAM BREAKS
450
400
350
300
250
200
150
100
50
0
0
1
2
3
4
5


2.5-1ST
2.5-2ND
S-1ST
S 2ND
2.5 mg/kg
MEAN PHOTOBEAM BREAKS
450
400
350
300
250
200
150
100
50
0
0
1
2
3
4
5
INFUSIONS

treatments ($p<0.008$). This post hoc finding suggests one source of the complex interactions in the first days of the earlier across test days analysis. Not surprisingly, effects that were present in the previous analysis of the activity induced by each infusion (across test days analysis) were also present in this post hoc analysis. These effects were as follows: a significant effect of dose ($F_{2,42}=43.49$, $p<0.0001$), of days ($F_{4,168}=6.10$, $p<0.0002$) and an interaction of dose X days ($F_{8,168}=2.32$, $p<0.03$).

Discussion

Animals that had previously received repeated administrations of cocaine, whether signalled or unsignalled, subsequently showed greater locomotor activity in response to the test infusion (1.25 mg/kg) than did animals previously treated with repeated saline infusions (Fig. 5). Signalled infusions were somewhat more effective than unsignalled infusions in sensitizing the animals to the locomotor effects of the drug. The present investigation thus provides some degree of support for the hypothesis that cocaine given in conjunction with stressful or arousing environmental stimulation produces stronger effects than cocaine given without such stimulation. The present study fits with the *in vivo* microdialysis demonstration (Wilcox, Robinson and Becker, 1986) that even repeated i.p. injections of saline can enhance drug-induced dopamine release and perhaps facilitate the development of sensitization. Although it was not confirmed by independent measurements that the handling and injection treatment in the present experiment was stressful, this finding is also compatible with the suggestion of Antelman and colleagues (1980) that stress itself is a major factor in a variety of sensitization phenomena.

While the handling manipulation alone appeared to contribute to the development of sensitization (as reflected in the data from the test infusion) the magnitude of effect was minimal in relation to the strength of the locomotor response of the animals previously receiving unsignalled infusions. Moreover, there was little evidence of an effect of the signalling manipulation on the drug-induced locomotion of each group receiving cocaine in combination with the signalling manipulation (Fig. 2). Thus the signalling manipulation did not contribute as strongly as might have been expected to the development of cocaine-induced sensitization.

The lack of a substantial signalling effect in the present experiment does not, however, rule out the possibility that stress or arousal interacts importantly with the behavioral effects of cocaine. Despite the precautions taken to ensure that the animals were not aroused prior to the infusion there was some indication that the animals were in fact

aroused by non-pharmacological events. Various aspects of the way in which the animals were tested in the present investigation may have inadvertently produced arousal in the animals. In many studies of cocaine-induced sensitization animals are removed from their homecages, injected with the drug and placed in a test chamber. To eliminate the contribution of the activation initially present when animals are removed from their home cages and placed in test cages, and to eliminate a major predictor of the infusions, the animals were habituated to the activity chambers for two hours prior to receiving each infusion. Further, in order to minimize the contribution of conditioning (a factor reported to have a profound influence on cocaine-induced sensitization: Post et al., 1981; Post, Weiss and Pert, 1987; Weiss et al., 1989; Post et al., 1992; Hooks et al., 1993), animals received infusions only every second day; the infusion environment was thus associated equally with drug and non-drug experiences. By controlling for these possible sources of arousal and by employing a route of drug administration that allowed for minimal contact with some animals it was hoped that this investigation would provide a good measure of the contribution of handling and a subsequent i.p. injection to the psychomotor stimulant effects of cocaine and to the sensitization that develops to these effects with repeated drug treatments. However, it would seem from the elevated locomotor activity occurring 20 mins prior to each infusion that the animals were not in an 'unaroused state' at the time of infusion (Fig. 3). That the spontaneous locomotor activity of the animals being treated with cocaine was affected in some unanticipated way is further evident from the elevated locomotor activity exhibited by the cocaine-treated animals on non-infusion days (Fig. 4). It thus appears that some sources of arousal were present in this investigation despite attempts to eliminate them.

One source of the arousal seen in the cocaine-treated animals was almost certainly the stimulus properties of the drug solution. Cocaine hydrochloride dissolved in physiological saline has an acid pH. Infusions of the acidic solution appeared to be somewhat aversive to the animals; the animals became highly agitated and pawed at the

catheterized neck region within seconds of the cocaine infusion. Although the response was limited to the animals receiving cocaine the obvious agitation of the animals suggested that the reaction to the infusion was unrelated to the stimulant effects of the drug. Given the irritation caused by the infusion of cocaine it is clear that the delivery of the drug cannot be considered 'unsignalled' for any of the groups treated with cocaine. It is thus possible that the drug infusion itself produced sufficient arousal to render any further contribution of the handling manipulation to sensitization inconsequential.

Interestingly, although irrelevant to the initial hypothesis of the present experiment, all groups previously treated with cocaine showed sensitization to the test infusion but not all groups treated with cocaine showed progressive increases in drug-induced locomotor activity across drug treatments. Progressive increases in the level of drug-induced activity are thought to be characteristic of the development of sensitization (Robinson and Becker, 1986). It is thus difficult to understand why sensitization was evident when the animals were given the test infusion and not when given the repeated drug treatments. One possible explanation for this finding comes from work done with *in vitro* and *in vivo* tissue preparations. Enhanced drug-induced dopamine release following repeated treatments of cocaine or amphetamine is thought to be a neurochemical consequence of sensitization (Kolta et al., 1985; Robinson et al., 1988; Kolta, Shreve and Uretsky, 1989; Paulson, Camp and Robinson, 1991; Kalivas and Duffy, 1993a, 1993b; Keller et al., 1992). However, there is some evidence indicating that enhanced drug-induced levels of extracellular dopamine in striatal tissue preparations is evident two to four weeks after repeated drug treatments cease but is not evident after only a 1-3 day drug-free period (Kolta, Shreve and Uretsky, 1985; also see Kalivas and Duffy, 1993a, 1993b). It is then possible that the sensitization that develops in response to the repeated drug treatments is not always evident, either behaviorally or neurochemically, until after a period of drug withdrawal. Thus, the response to a test for sensitization performed after some period of

drug withdrawal may be a more clear indicator of sensitization than progressive increases in the level of drug-induced activation across drug treatments.

Finally, data from the present study indicate that progressive increases in drug-induced locomotion with repeated drug treatments do not necessarily reflect the development of progressively stronger responses to the drug. In the present investigation the two groups that appeared to have progressively stronger locomotor responses to cocaine actually responded less to the first drug infusion than did the groups that did not show progressive increases in locomotion. Thus, the progressive increases in locomotor activity seen with these two groups appear to have resulted from habituation to some form of response suppression that was not apparent in the other animals. The seemingly sensitizing animals were "catching up" to normal activity levels rather than going beyond them. Suppressed locomotion was also clearly evident in those animals that received their first drug infusion during their first exposure to the activity chambers (Fig. 6). While the results of a post hoc analysis must be viewed with some caution, it seems possible that when an animal initially receives a novel drug in a relatively novel environment their response is somewhat inhibited. As the animal receives more pairings of the drug with the environment their locomotor response gradually becomes disinhibited and thus gives the appearance of sensitization. It is possible that a number of studies of sensitization reflect a disinhibition of locomotor responding rather than the development of drug-induced sensitization.

In summary, the present study raises the possibility that "set and setting" variables that are important for a variety of drug effects can play a role, though perhaps a minor one, in the effects of cocaine. A stronger test of this hypothesis would require cocaine infusions that were more clearly devoid of sensory properties, particularly properties sufficient to cause stressful or arousal reactions in the animals.

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