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Assessment of Motivational Aspects Involved in Initiation of Cocaine and Heroin Self-Administration in Rats

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GERRITS, M. A. F. M. AND J. M. VAN REE. *Assessment of motivational aspects involved in initiation of cocaine and heroin self-administration in rats.* PHARMACOL BIOCHEM BEHAV 52(1) 35–42, 1995.—A behavioral paradigm was explored to assess the motivational aspects involved in drug-taking behavior during initiation of drug self-administration. In separate saline-controlled experiments, naive animals were allowed to self-administer either cocaine or heroin (0.16 and 0.32 mg/kg per infusion) during five consecutive daily 3-h sessions by pressing one of two levers present in the test cage. During 15 min preceding the last four self-administration sessions, the animals had access to the levers but pressing the reinforcement lever did not result in a drug infusion. The animals properly self-administered both doses of cocaine and heroin, because the amount of self-infusions was higher than their saline control groups. Animals self-administering the high dose of cocaine and either dose of heroin performed lever-press behavior during the preceding period in a similar fashion as during the self-administration sessions, suggesting that this behavior is reinforcement-related. Because the lever-press behavior during the preceding period was performed in the absence of the primary reinforcer, this behavior likely reflects the motivational state of animals to obtain the drug reinforcer, and thus may serve as a measure of the motivational aspects involved in the initiation of drug self-administration.

Cocaine Heroin Self-administration Initiation phase Motivational aspects

IT HAS become clear that laboratory animals can become dependent on a variety of drugs that are abused by humans. Animals readily self-administer stimulant drugs such as cocaine and amphetamine (20,21) as well as opiate drugs such as heroin and morphine (29,32). Over the years different theories have been proposed to explain what exactly causes psychoactive drugs to initiate and maintain drug self-administration (11,18,24,25,27,28,34).

With respect to initiation of drug self-administration, behavior during this phase is thought to be mainly determined by the positive reinforcing effects of the drug (27). In addition, drugs are able to confer their positive motivational properties to environmental cues, which in turn, by facilitating successful contact with the drug stimulus, could contribute to the initiation of drug self-administration (incentive-motivational stimuli) (4,5,6,8,25). During maintenance of drug self-administration the behavior is presumably maintained by both these positive motivational aspects and by the negative motivational (aversive) properties of dependence [i.e., the need for continued exposure to a drug to avoid a withdrawal syndrome when the drug is withdrawn (18,24)].

In animal studies evaluation of motivational aspects involved in drug-taking behavior is complicated. In the currently used self-administration procedures it is difficult to make a distinction between the primary reinforcing effects of the drug and other aspects that motivate the animal to obtain the drug reinforcer. In the present study we explored a behavioral paradigm to assess the motivational aspects involved in drug-taking behavior. To circumvent the negative motivational properties related to withdrawal, we focused on the initiation phase of self-administration (29). During five consecutive self-administration sessions, drug- and lever responding-naive animals were allowed to self-administer either cocaine or heroin (0.16 and 0.32 mg/kg per infusion) by pressing a lever. During

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a short period preceding the last four self-administration sessions the animals had access to this lever, but pressing it did not result in a drug-infusion. A procedural characteristic of this behavioral paradigm is that during the preceding period behavior of the animal is performed in absence of the delivery of the drug infusion. We investigated whether the behavior of animals during the drug-free preceding period could serve as an measure of the motivational state of the animal to obtain the drug reinforcer.

METHOD

Animals and Surgery

Animals were male Wistar rats bred from our own live stock, weighing 210–270 g at the time of surgery. Before surgery the animals were group housed, received food and water ad lib, and were maintained under a 12 L : 12 D cycle with lights on between 0700 and 1900 h. At the time of surgery the animals were anaesthetized with Hypnorm [0.08 ml/mg, intramuscularly (IM)] and a cannula was inserted into the jugular vein [for details see (29)]. The cannula was guided subcutaneously up to the skull, where it was fixed to a curved metal tube that was secured onto the skull with screws and dental acrylic cement. After surgery the animals were placed in individual home cages and allowed to recover from the operation for 5–7 days before testing was started. During testing food and water (ad lib) were available in the home cages, except in the experiments in which cocaine was offered. In these experiments the food supply was restricted to reduce body weights by 20%, which has been shown to facilitate initiation of cocaine self-administration (9). The day–night cycle was reversed (lights on between 1900 and 0700 h) 3 days before testing.

Procedure

Details of the procedure have been reported previously (12). Testing was done in standard operant conditioning cages placed in sound-attenuated rooms. The test cages were equipped with two levers, one of which was marked by a red light placed just above the lever. The IV cannulae of the animals were connected to an infusion pump. Depression of the lever marked by the red light [reinforcement lever (RL)] resulted in an IV infusion of 0.25 ml fluid during 13 s on a continuous reinforcement schedule. The red light went off during the infusion and pressing the lever during this time did not result in an infusion. Depression of the other lever [nonreinforcement lever (NRL)] had no consequences. Drug-naive animals were placed in the test cages and allowed to IV self-administer a (drug) solution for 3 h a day (starting at 1000 h). Testing took place during five consecutive daily sessions. From days 2–5, the described standard self-administration procedure was extended with a test period directly preceding the self-administration session. The animals were placed in the test cages and had access to both levers (RL and NRL) for 15 min. During the preceding test period, depression of the RL did not result in an infusion of the (drug) solution, nor did the stimulus light above the RL go off.

Experimental Design

In separate experiments groups of drug- and lever responding-naive animals were allowed to initiate IV drug self-administration with 2-U doses of cocaine or heroin (0.16 and 0.32 mg/kg per infusion). Lever-press behavior was measured during IV self-administration sessions and the period preceding the self-administration sessions. Each experiment was vehicle (saline) controlled. The number of animals per treatment group varied between five and eight.

Drugs

Hypnorm (0.2 mg fentanyl and 10 mg fluanison/ml) was manufactured by Janssen Pharmaceutica (Tilburg, The Netherlands). Heroin (diacetylmorphine-HCl; OPG, Utrecht, The Netherlands) and cocaine (cocaine-HCl; OPG) were dissolved in saline. The pH of drug solutions and saline prepared for self-administration was adjusted to 7.30 ± 0.05.

Statistical Analysis

The data are presented as the mean ± SEM. The data obtained during the self-administration sessions and the period preceding the self-administration sessions were analyzed per unit dose experiment with either cocaine or heroin, using two-way analysis of variance (ANOVA) with repeated measurements (MANOVA). Treatment (drug vs. saline) and time (five sessions) were grouping variables and number of self-infusions (SI), number of responses on the RL, and number of responses on the NRL were the dependent variables. The level of significance was set at $p < 0.05$.

RESULTS

Both doses of cocaine were tested twice. Statistical ANOVA showed no effect of replication of experiments on any of the parameters tested. The data of initiation of drug self-administration and lever-press behavior during the period preceding the self-administration sessions will be discussed separately.

Initiation of Drug Self-Administration

The number of SI in the cocaine and heroin experiments is shown in Fig. 1. Two-way ANOVA per unit dose of cocaine and heroin [0.16 mg/kg per infusion (low) and 0.32 mg/kg per infusion (high)] revealed a significant interaction between treatment and time in the experiment with the high-unit dose of cocaine [$F(4, 92) = 9.7$, $p < 0.01$] and in both experiments with heroin [low $F(4, 36) = 4.7$, $p < 0.01$; high $F(4, 40) = 4.9$, $p < 0.01$]. The interaction did not reach a significant level in the case of the low-unit dose experiment with cocaine [$F(4, 84) = 2.1$, $p = 0.08$], which might be attributed to an incidental decrease in the number of self-infusions during Session 3. In addition, a significant main treatment (drug vs. saline) effect was found in all experiments with cocaine and heroin [cocaine: low $F(1, 21) = 6.2$, $p < 0.05$; high $F(1, 23) = 26.1$, $p < 0.01$; heroin: low $F(1, 9) = 20.4$, $p \leq 0.01$; high $F(1, 10) = 6.5$, $p < 0.05$]. A significant main time effect was present in experiment with the high-dose cocaine [$F(4, 92) = 2.7$, $p < 0.05$] and low-dose heroin [$F(4, 36) = 2.8$, $p < 0.01$]. Thus, all animals showed proper initiation of self-administration in that the self-administration rate of the drugs was significantly different from that of saline. In addition, all animals showed significantly increased drug intake over time, with the exception of the low dose of cocaine.

Responding on the RL is presented in Figs. 2 and 3 (main figures). A significant interaction between treatment and time was present in the experiment with the high dose of cocaine [cocaine: low $F(4, 84) = 0.8$, NS; high $F(4, 92) = 6.9$, $p < 0.01$; heroin: low $F(4, 36) = 2.5$, $p = 0.06$; high $F(4, 40) = 1.8$, NS]. A significant main treatment effect (drug vs. saline) was found in all experiments with cocaine and heroin [cocaine:

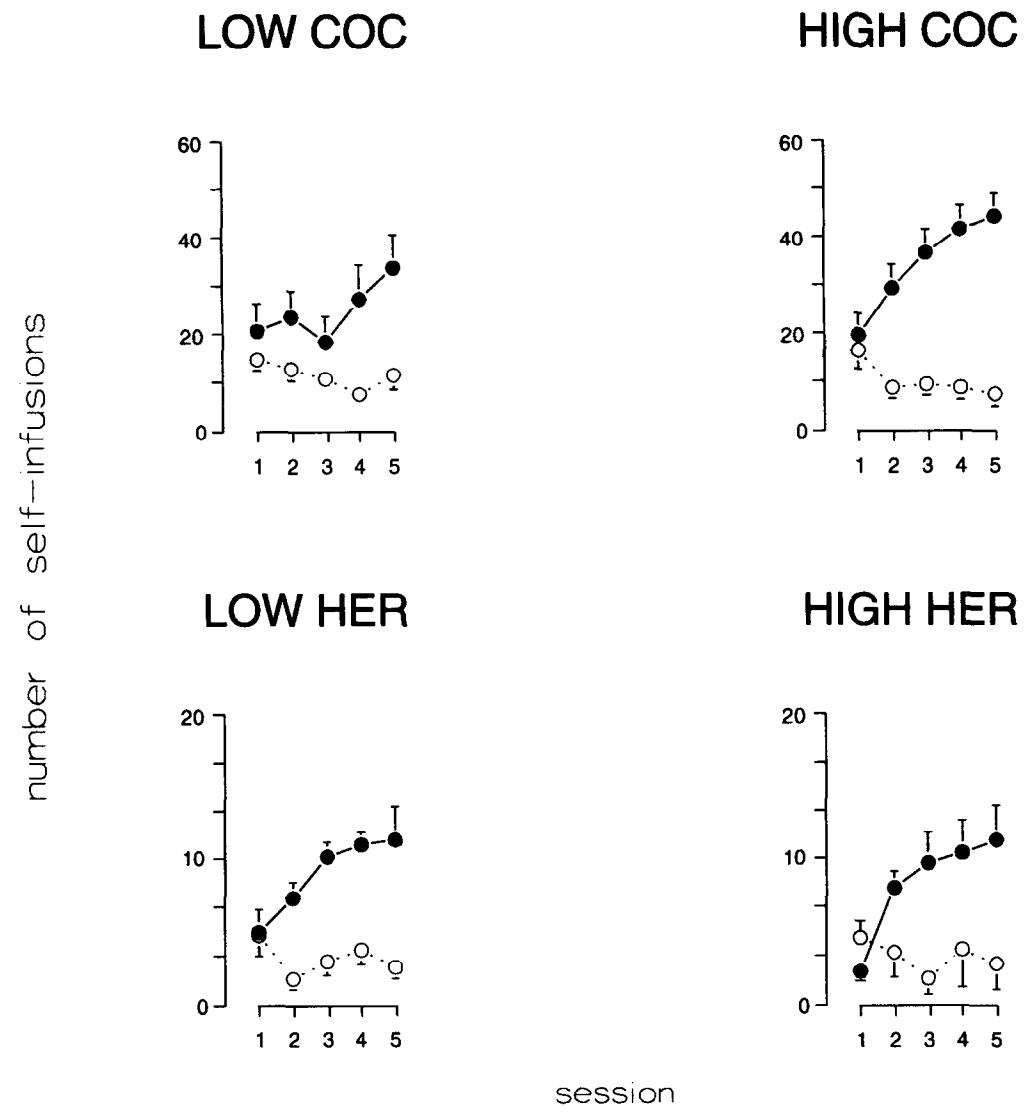

FIG. 1. Initiation of IV cocaine and heroin self-administration. Drug-naive animals were allowed to self-administer saline (○) or 2-U doses of a drug solution (●) composed of either cocaine (LOW COC, 0.16 mg/kg per infusion; or HIGH COC, 0.32 mg/kg per infusion) or heroin (LOW HER, 0.16 mg/kg per infusion; or HIGH HER, 0.32 mg/kg per infusion). Animals were tested during five consecutive daily 3-h sessions. The mean number of self-infusions (SI) are plotted vs. the day of testing. Vertical bars represent SEM (see text for statistics).

low $F(1, 21) = 4.2$, $p \leq 0.05$; high $F(1, 23) = 12.9$, $p < 0.01$; heroin: low $F(1, 9) = 10.5$, $p \leq 0.01$; high $F(1, 10) = 4.7$, $p \leq 0.05$]. A significant time effect was absent in all experiments. In general, responding on the RL was comparable with the data from the SI parameter.

Responding on the NRL was different from that on the RL. In the experiments with the cocaine unit doses, there was no significant treatment × time effect [low $F(4, 84) = 1.2$, NS; high $F(4, 92) = 0.4$, NS] or significant effect of treatment or time (Fig. 2, main figures). Responding on the NRL with heroin was different from that of cocaine, in that there was a significant treatment × time effect in the high-unit dose experiment [$F(4, 40) = 3.4$, $p < 0.05$] and significant effect of treatment (drug vs. saline) on NRL responding in both unit dose experiments [low $F(1, 9) = 9.9$, $p < 0.05$; high $F(1, 10) = 6.8$, $p < 0.05$]. No significant time effects were found (Fig. 3, main figures). Thus, in animals self-administering cocaine NRL responding did not differ from animals self-administering saline, whereas in animals self-administering heroin, the response rate on this lever was higher than that for saline animals.

Examples of typical response records are shown for two rats, one self-administering cocaine and the other heroin (Fig. 4). Over five consecutive sessions the responses on RL and NRL during each 3-h session are shown. Each mark represents a single response on either lever. Over the five consecutive sessions the animal self-administering cocaine increased the number of responses on RL, until it reached a regular pattern in RL responding, with similar time intervals throughout the session. Responding on the NRL of this animal decreased over

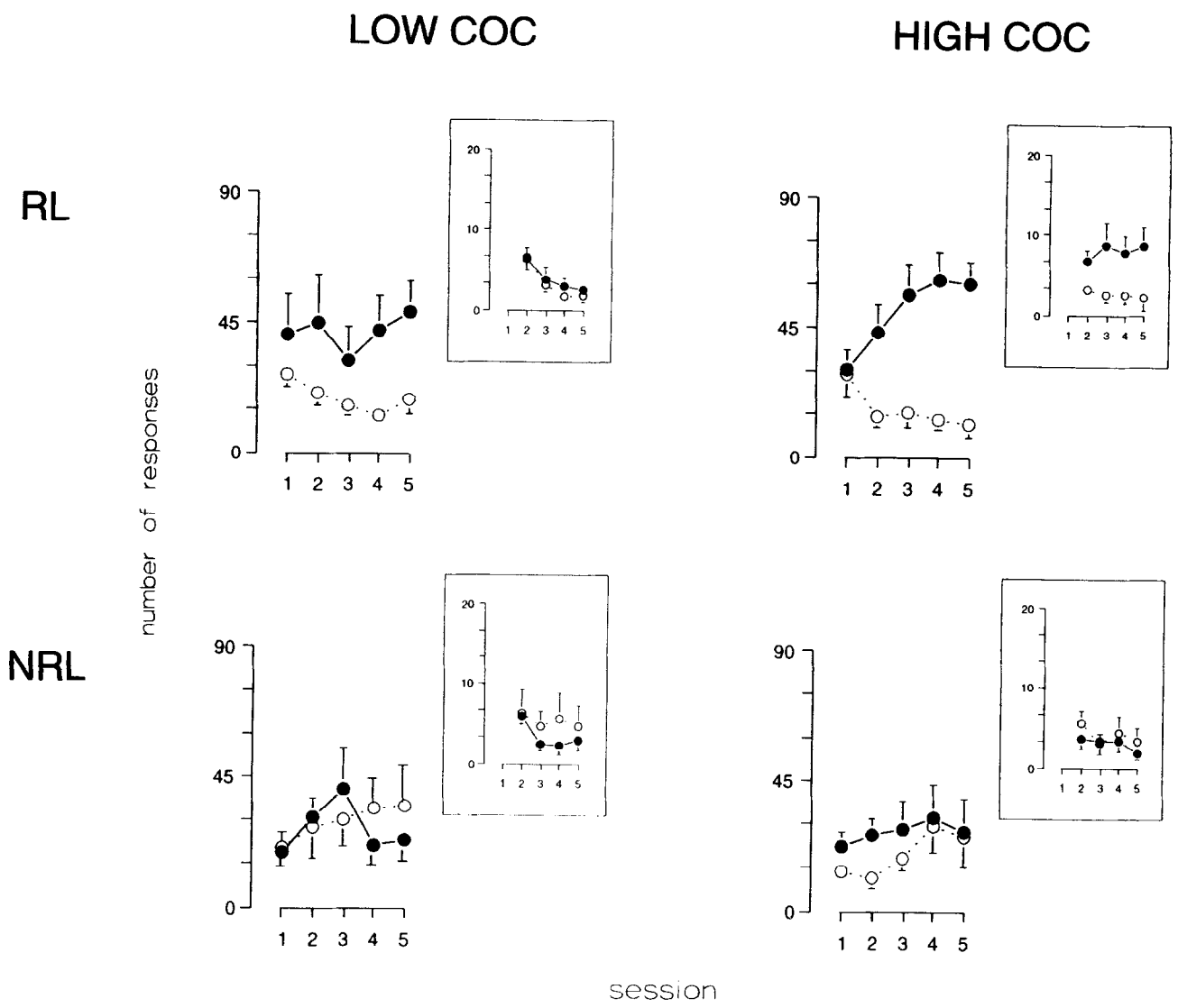

FIG. 2. Responding on reinforcement (RL) and nonreinforcement (NRL) lever during the self-administration sessions (main figures) and during the period preceding the self-administration sessions (insets) of animals self-administering saline (○) or two doses of cocaine (●) composed of LOW COC (0.16 mg/kg per infusion) and HIGH COC (0.32 mg/kg per infusion). The animals were tested for drug self-administration during five consecutive daily 3-h sessions. The preceding period consisted of daily 15-min sessions preceding the last four self-administration sessions. The mean number of responses on RL and NRL are plotted vs. the day of testing. Vertical bars represent SEM (see text for statistics).

the five sessions. The animal self-administering heroin also slowly increased responding on the RL over the five sessions. Responding on the NRL of the heroin animal differed from cocaine animals in that the NRL responding was higher and increased over sessions.

Lever-Press Behavior During the Period Preceding Self-Administration Sessions

The lever-press behavior of the animals during the preceding period is shown in Figs. 2 and 3 (insets). Two-way ANOVA of RL data revealed no significant interaction between treatment and time [cocaine: low $F(3, 63) = 4.2$, NS; high $F(3, 69) = 0.4$, NS; heroin: low $F(3, 27) = 0.2$, NS; high $F(3, 30) = 1.3$, NS]. Except for the low dose of cocaine [$F(1, 21) = 0.3$, NS] there was a significant treatment (drug vs. saline) effect [cocaine: high $F(1, 23) = 7.8, p \leq 0.01$; heroin: low $F(1, 9) = 6.5, p < 0.05$; high $F(1, 10) = 13.5, p < 0.01$]. A significant time effect was only present in the experiment with the low dose of cocaine [$F(3, 63) = 7.9, p < 0.01$], reflecting a decrease in RL responding over time. Thus, responding on the RL during the period preceding the self-administration sessions was increased in animals self-administering cocaine and heroin, except in the case of the low dose of cocaine. Animals self-administering saline showed no RL responding during the preceding period.

With regard to responding on the NRL during the preceding period, no significant treatment × time interactions were

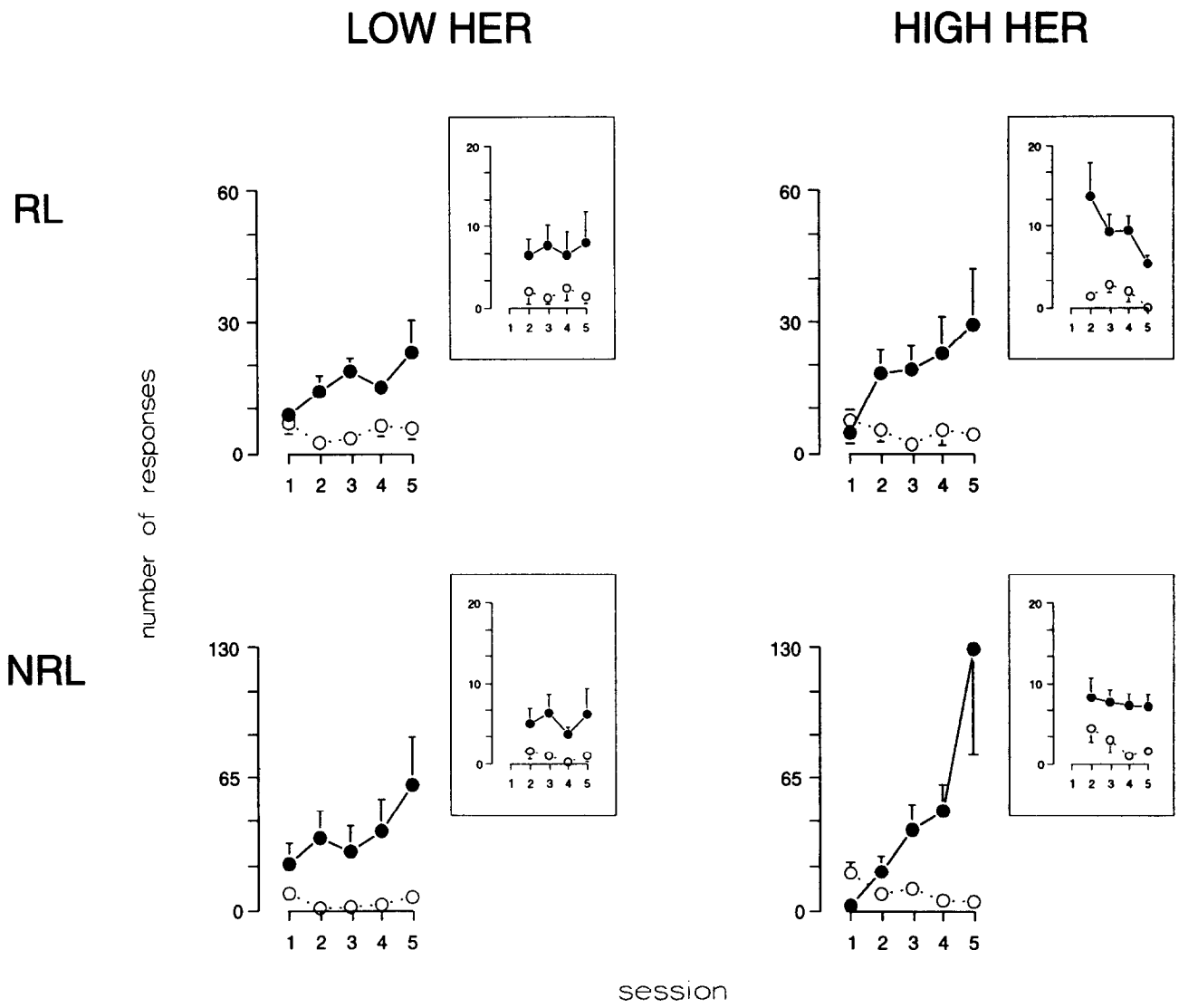

FIG. 3. Responding on reinforcement (RL) and nonreinforcement (NRL) lever during the self-administration sessions (main figures) and during the period preceding the self-administration sessions (insets) of animals self-administering saline (○) or two doses of heroin (●), composed of LOW HER (0.16 mg/kg per infusion) and HIGH HER (0.32 mg/kg per infusion). Animals were tested for drug self-administration during five consecutive daily 3-h sessions. The preceding period consisted of daily 15-min sessions preceding the last four self-administration sessions. The mean number responses on RL and NRL are plotted vs. the day of testing. Vertical bars represent SEM (see text for statistics).

observed [cocaine: low $F(3, 63) = 0.6$, NS; high $F(3, 69) = 0.3$, NS; heroin: low $F(3, 27) = 0.3$, NS; high $F(3, 30) = 0.2$, NS]. No main treatment and time effects were found in experiments with cocaine unit doses [treatment: low $F(1, 21) = 1.5$, NS; high $F(1, 23) = 1.5$, NS; time: low $F(3, 63) = 2.1$, NS; high $F(3, 69) = 1.1$, NS]. In the experiments with heroin there were no significant time effects, but a significant treatment effect was present in the high-unit dose experiment [$F(1, 10) = 20.9$, $p < 0.01$] and a tendency to a significant effect in case of the low-unit dose of heroin [$F(1, 9) = 4.8$, $p = 0.06$]. These data indicate that animals self-administering cocaine and saline during the self-administration period did not display responding on NRL lever during the preceding period. Animals self-administering heroin showed higher responding on the NRL during the preceding period compared to saline controls.

DISCUSSION

The present study was designed to explore a behavioral paradigm, based on the self-administration model, to access the motivational aspects involved in drug-taking behavior during initiation of drug self-administration. Lever-press behavior of animals was determined before and during self-administration sessions. Behavior during the self-administration sessions is mainly determined by the positive reinforcing effects of the drug (27). Additional motivational aspects are suggested to facilitate self-administration behavior (4,5,8,25).

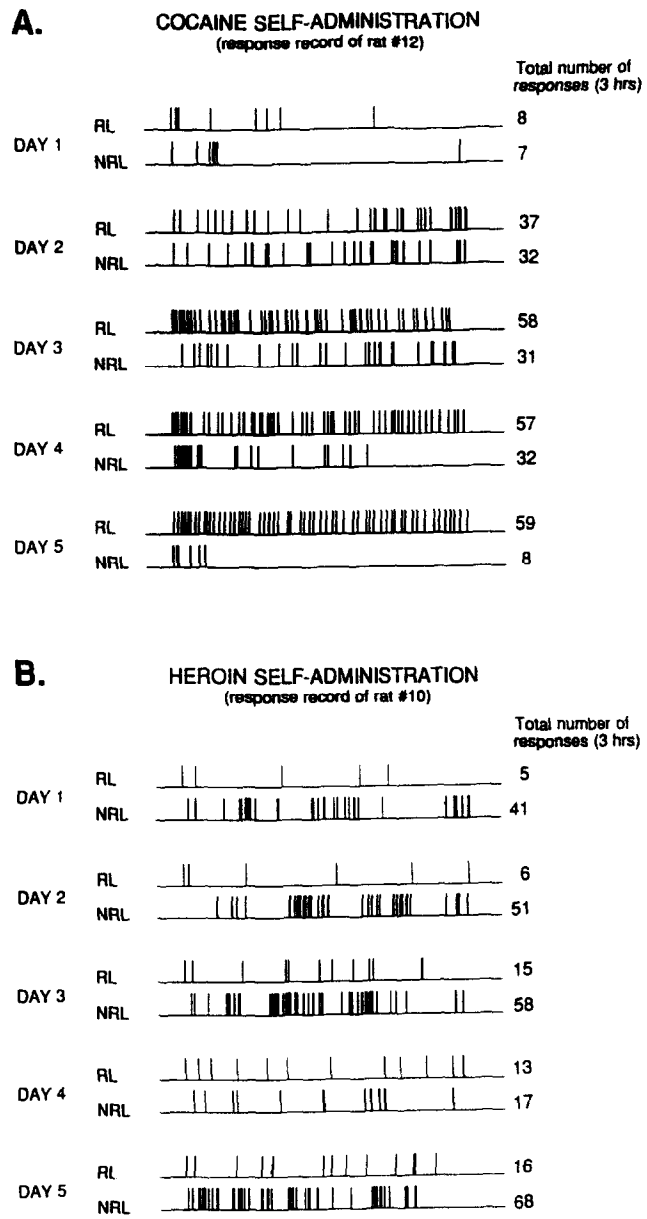

FIG. 4. Representative response records for two self-administering animals. (A) Animal self-administering cocaine; (B) animal self-administering heroin. Responses on RL and NRL over five consecutive daily 3-h sessions are shown. Each mark represents a single response on either lever.

During the period preceding the self-administration sessions, lever-press behavior is performed in the absence of the drug infusions, and therefore, probably an index of an animal's motivation to obtain the drug reinforcer. In the following section this suggestion will be discussed more extensively in relation to the data obtained in this study.

Initiation of Drug Self-Administration

Animals allowed to self-administer both unit doses of either cocaine or heroin (0.16 and 0.32 mg/kg per infusion) showed proper self-administration, because the number of self-infusions was higher than that in animals given the opportunity to self-administer saline. During initiation of drug self-administration the relationship between unit dose of the drug and rate of self-administration (i.e., number of SI) tends to be an inverted U-shape curve. However, the amount of drug taken appears to be a linear function of the unit dose delivered. It has been postulated that the unit dose is a major determinant governing the reinforcing efficacy of drugs during initiation of drug self-administration (29). Hence, an increase in unit dose results in increased total drug intake, and thus in reinforcing efficacy (7,9,29,32). The present findings are in agreement with this hypothesis, because an increase in unit dose of cocaine and heroin caused an increase in the average total intake [mean (± SEM) total drug intake in milligrams per kilogram: cocaine: low 4.0 ± 0.5; high 11.0 ± 1.6; heroin: low 1.4 ± 0.2; high 2.7 ± 0.6]. Animals allowed to self-administer saline showed a higher number of self-infusions in the experiments with cocaine as compared to experiments with heroin. Because animals in the cocaine experiments were food deprived to facilitate initiation of self-administration, the increase in saline intake is probably indirectly due to weight loss-induced general activity (9).

Animals allowed to self-administer both cocaine and heroin showed increased responding on the RL as compared to their saline controls, but differed in their responding on the NRL. In the self-administration model as used in the present study, responding on the RL is dependent on the SI rate, and thus related to reinforcing properties of the infused drug. Responding on the NRL, on the other hand, is thought to be independent of the SI rate and more a reflection of nonspecific behavior (23). In the present study, animals self-administering cocaine showed increased responding on the RL, whereas responding on the NRL was not different from the saline animals. This suggests that the behavior of the animals is directed to obtain the rewarding cocaine infusions. Animals self-administering heroin exhibited higher responding on the NRL, which even increased over time in the case of the higher unit dose. This increased NRL responding has also been noticed in a previous study with initiation of heroin self-administration (12). The nature of this behavior has not yet been elucidated. Several reports have demonstrated that systemically administered opiates have biphasic effects on locomotor behavior. Repeated administration of opiates results in the development of tolerance to the motor-depressing effects and an enhancement of the motor-stimulating component (behavioral sensitization) (1,3,30,31). Furthermore, it has been established that opiate-induced hyperactivity can be conditioned in classical conditioning paradigms; thus, a distinct environment can potentiate the motor-stimulant effect of opiates (14,17,19). Although the present results do not exclude a role of these and other nonspecific behavioral phenomena in enhanced NRL responding during heroin self-administration (e.g., behavioral stereotypy), it has been demonstrated that cocaine can also induce enhanced motor activity as well as conditioned hyperactivity and stereotypy (2,15,16,22,26). Because in the present experiments NRL responding was not enhanced during cocaine self-administration, the observed NRL responding during heroin self-administration may not be due only to drug-induced activation or a conditioned response. Increased NRL responding during heroin self-administration could also imply that the animals did not learn fully to discriminate the source of a rewarding drug infusion (23). However, despite high responding on the NRL, animals showed a proper and stable increase in responding on the RL, the lever directly related to the rewarding heroin infusions. Moreover, responding on the NRL was considerably higher than responding on the RL. When the animals were not able to discriminate between the

two levers for the source of drug infusion, the responding on both levers was expected to be proportionally high and increase with the same rate. Thus, the data suggest that the behavior of the animals was directed toward obtaining the rewarding drug infusion, despite increased NRL responding. Furthermore, it is likely that responding on this lever in the case of heroin but not cocaine is somehow related to the reinforcing effects of heroin. This suggestion fits well with the observed responding on the NRL in the period preceding the self-administration sessions (see subsequent discussion).

Lever-Press Behavior During the Period Preceding Self-Administration Sessions

Animals allowed to self-administer cocaine and heroin showed increased lever-press behavior during the period preceding the self-administration sessions. With regard to responding on the RL, animals self-administering the high-unit dose of cocaine or either unit dose of heroin exhibited increased responding on this lever. Animals given the opportunity to self-administer the low cocaine unit dose did not differ in responding on the RL from their saline controls during this period. In this period, responding on the NRL was similar in cocaine and saline animals, but higher in the heroin animals as compared to saline controls. Thus, animals offered cocaine, heroin, or saline during self-administration sessions performed lever-specific behavior during the preceding period in a fashion corresponding to that during the self-administration sessions, suggesting that this behavior is related to the reinforcing effects of the drug. Furthermore, because lever-press behavior during the preceding period was performed in absence of the primary reinforcer the behavior probably reflected a motivational state of the animals to obtain the drug reinforcer. It has been suggested recently that drug reward, like natural rewards, possesses incentive as well as consummatory properties (11,25). The incentive properties of reward stimuli are thought to be essential in the learning of a behavioral response directed toward approaching the reward. In the case of natural rewards, the incentive aspect was provided by distinctive sensory properties of the reward stimulus, for example (e.g., smell, colour, shape, or taste). However, these properties were less likely to be involved in the IV self-administration procedure. Drug reward may depend more heavily on incentive motivational learning—that is, the ability of drugs of abuse to confer their positive motivational properties to environmental cues. Neutral environmental cues after repeated association with the primary reinforcing effects of the drug become reliable predictors of the rewarding stimulus and, as such, gain incentive value. In time, the presence of the so-called conditioned (incentive) motivational stimuli is sufficient to initiate and maintain goal-directed behavior (e.g., lever-press behavior) in the absence of the primary rewarding stimulus (4,5,8,10,25). In view of this hypothesis, the lever-press behavior during the preceding period in this study probably depends on the motivational properties of drug-associated stimuli in the test cage. In the present study, cocaine animals were food deprived to facilitate initiation of cocaine self-administration (9), whereas heroin animals were not. Because both cocaine and heroin animals showed increased responding on the RL during the preceding period, food deprivation itself probably does not generate or affect the motivational state of the animal for obtaining the drug. Furthermore, it was found that the increased responding on the RL in cocaine and heroin animals during the preceding period was stable over the four sessions. This indicates that the reinforcement-related behavior is not subjected to extinction or sensitization. Thus, although the self-administration rate of animals increased over the five sessions, the motivation of animals to obtain the drug may have remained constant over time.

Animals self-administering the low dose of cocaine did not respond on the RL during the period preceding the self-administration sessions. It has been established that the unit dose of a drug is the major determinant governing its reinforcing efficacy (13,29). The low dose of cocaine has primary reinforcing effects, as drug intake is increased during the self-administration sessions. However, the reinforcement efficacy of this dose of cocaine is probably not high enough to give incentive value to environmental cues, because the animals did not perform RL responding during the preceding period.

Responding on the NRL during the preceding periods resembled responding during the self-administration sessions. In the case of cocaine, responding was not different from that of saline in both periods, indicating that neither reinforcement nor other motivational aspects were involved. In the case of heroin, responding on the NRL exceeded that of saline in both periods. This responding is probably related to the reinforcing and/or motivational properties of heroin. However, more experimentation is needed to elucidate the exact nature of this responding.

In summary, we found that animals self-administering a high dose of cocaine or either dose of heroin during self-administration performed lever-press behavior during the period preceding the self-administration sessions indicative of reinforcement-related behavior. Because the lever-press behavior during this period was performed in absence of the primary reinforcer, we propose that this behavior reflects the motivation of animals to obtain the drug. Thus, lever-press behavior during the drug-free preceding period may serve as a measure of the motivational aspects involved in the initiation of drug self-administration.

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