Pharmacology Biochemistry and Behavior, Vol. 46, pp. 561-567, 1993

0091-3057/93 $6.00 + .00

Behavior-Associated Changes in Blood Pressure During Heroin Self-Administration

EUGENE A. KIYATKIN*[1] AND ELLIOT A. STEIN*†

*Departments of *Psychiatry and †Pharmacology, Medical College of Wisconsin, 8701 Watertown Plank Road, MFRC-4026, Milwaukee, WI 53226*

Received 21 January 1993

KIYATKIN, E. A. AND E. A. STEIN. *Behavior-associated changes in blood pressure during heroin self-administration.* PHARMACOL BIOCHEM BEHAV **46**(3) 561-567, 1993.—Changes in arterial blood pressure (ABP) were studied in freely moving rats during the development and performance of operant IV heroin self-administration (SA) behavior (100 μg/kg/injection). Heroin SA was accompanied by bidirectional, phasic ABP fluctuations in the absence of significant alterations in long-term, basal ABP levels. In trained rats, ABP gradually increased starting 5 min before each lever-press for the drug, reached a peak at the moment of lever-press and abruptly decreased after heroin infusion. This biphasic pattern corresponded to a preresponding behavioral activation followed by a postheroin sedation. These ABP fluctuations were absent during the initial heroin self-injections in drug-naive rats and during the first self-injections of a session in trained rats. A slight hypo- and hypertension were seen in these cases, respectively. The postdrug ABP decrease became more pronounced after rats received a double dose of heroin. With training, nonreinforced lever-presses and sound stimulation previously associated with heroin self-injections also significantly decreased ABP. Thus, a gradual ABP increase appears to be an essential correlate of drug-seeking and -taking behavior, while a subsequent ABP decrease may be related to the alleviation of these behaviors by heroin and possibly correlate to its rewarding (euphorigenic) action.

Arterial blood pressure Heroin self-administration Drug-taking behavior Reinforcement

RATS rapidly learn to perform an operant task, such as lever-pressing, if the behavior is reinforced by an injection of one of several classes of drugs. With the exception of hallucinogens, all drugs that are abused by man will be self-administered by animals and thus the self-administration (SA) paradigm is generally considered an excellent animal model for human addictive behavior (22,23). In the case of opiate drugs, this behavior is characterized by cyclic alternations of drug searching (motivated behavior) and temporary drug-induced "satiety" correlated with the drug's rewarding (euphorigenic) action (7,11,23). Through a better understanding of the neuroanatomic sites and physiological mechanisms involved in this behavior, a better understanding of the human condition may be forthcoming.

Heroin SA behavior is a complex interaction between a drug's pharmacological properties and its physiological and behavioral consequences. As a goal-directed behavior, rats rapidly learn to associate an operant response with drug delivery. This response is a function of the amount of drug delivered, the amount and timing of drug previously received, and the state of the animal (i.e., dependent, withdrawal, food deprived) (6,22,23). Specific pharmacological effects of opiates upon ongoing ("spontaneous") behavior and various autonomic and central nervous system processes will be influenced by the repetitive, cyclic nature of the behavior. In humans, the intense euphoria and subsequent drug-induced relaxation associated with drug intake is finally transformed into an activational dysphoric state, which is only temporarily blocked by subsequent drug intake (6,11).

In our previous work (7), we demonstrated that together with the behavioral activation leading up to drug SA and the cessation of locomotion and other behaviors following drug delivery, parallel alterations in mesolimbic dopamine (DA) activity also occur. Using in vivo voltammetry, biphasic increases and decreases in nucleus accumbens DA-related signals were observed preceding and following each heroin self-injection.

The principal aim of the present study was to examine changes in arterial blood pressure (ABP), a strictly regulated homeostatic index, during the development and performance of heroin SA behavior, to trace how heroin's pharmacological effects on ABP become organized and regulated during drug-taking behavior, as well as to determine the interrelationship between SA behavior and an index of an organism's homeostatic state. We report herein that, as for mesolimbic DA, phasic changes in blood pressure develop during heroin self-injections with a slow increase in ABP leading up to the lever-press and a rapid decline immediately thereafter.

[1] To whom requests for reprints should be addressed.

METHOD

Animals and Surgery

Six adult, male Sprague–Dawley rats (Sasco, Madison, WI) weighing 440–530 g were individually housed under a 12 L : 12 D cycle (light off at 0730 h) with food and water freely available. Two chronic catheters were implanted under Chloropent anesthesia (2.5 ml/kg, IP, 10 min after 0.05 mg/kg, SC, atropine sulfate). One silastic catheter was implanted into the right jugular vein and fed under the skin to exit on the dorsal side of the animal's neck. The second polyethylene catheter (o.d. 0.5–0.6 mm) was implanted into the abdominal aorta 9–12 cm from its entry via the caudal tail artery (24). The caudal artery was isolated via a small (12–14 mm) cutaneous incision 15 mm from base of the tail, and the catheter (with a wire stylet) was quickly inserted through a small hole in the artery and threaded into the abdominal aorta. To prevent thrombosis, the catheter was filled with a 40% solution of polyvinylpirrolidon (PVP, Sigma Chemical Co., St. Louis, MO; molecular weight 40 000). This biologically inert polymer is highly viscous, thereby preventing diffusion of blood into the catheter's tip. The catheter was refilled after each daily recording session with PVP, which prolonged catheter patency and increased the number of SA sessions a rat experienced. The IV catheter was flushed daily with sterile saline. Rats were allowed 2–3 days recovery before experimentation.

Procedures and Equipment

All experiments took placed in a light- and sound-attenuated operant chamber (30 × 40 × 60 cm) illuminated with a red light (25 W) and equipped with a lever mounted on one side wall 5 cm from the cage floor. Rats were habituated to the chamber for 2 days prior to catheter implantation. On the day of experimentation, rats were connected to a pressure transducer (Statham P-23, Grass Instruments, Inc., Quincy, MA) via polyethylene tubing shielded with a stainless steel spring. Blood pressure and heart rate along with a self-injection marker were recorded on a polygraph (Model 7, Grass Instruments). The IV catheter was connected to an infusion pump (Razel) through a length of polyethylene tubing and a liquid swivel (Carnegie Medicine, Pittsburgh, PA). Depression of the lever resulted in the delivery of a single heroin infusion (100 μg/kg/injection) in a volume of between 0.165–0.203 ml. To maintain a fixed drug dose for each rat, the injection volume varied from 14.75 to 18.14 s. Each drug infusion was accompanied by a tone (4,500 Hz, 75 dB) delivered through an overhead speaker that sounded for the entire drug delivery interval.

At each experimental session, baseline physiological values were recorded for 20–30 min, during which time the rat was free to explore the chamber while access to the lever was prevented. Lever availability was signaled at the initiation of each session with an experimenter-delivered tone (4,500 Hz, 75 dB for 15 s). At no time did animals received any heroin "priming" injections, and all drug administrations were initiated by the animal. Two deviations from this scheme were used: a) To determine the dose–response nature of the ABP effect, most SA sessions included one double-dose injection of heroin (200 μg/kg) delivered randomly during the session; and b) the last lever-press of each session was nonreinforced with no heroin delivered following the response. SA sessions lasted from 4 to 8 h, with each rat subjected to one to four daily sessions depending upon the quality of ABP recording. No experimenter intervention occurred once an experimental session commenced. Rats were observed throughout each session and general behavioral patterns (e.g., locomotion, grooming, sleeping, etc.) coded on the polygraph.

Analysis

Slow changes in ABP accompanying SA behavior were determined based upon the absolute value of the mean ABP at the time of each voluntary lever-press. Rapid, phasic changes in ABP associated with drug self-injections and/or tone presentation were determined based upon relative changes in ABP with respect to these events. Each lever-press or tone presentation was assumed as zero both for time and ABP, and the mean pressure preceding and following the event were quantified with a bin width of 30 s. One-way analyses of variance (ANOVAs) with repeated measures were used to analyze data. Tests for simple effects (Scheffe or Mann–Whitney *U*-test) were performed as appropriate.

RESULTS

Self-Administration Behavior

In all six animals, stable heroin self-administration behavior was observed from the first experimental session and continued throughout each subsequent session. The mean interval between lever-presses for all sessions was 27.8 ± 1.5 min (range 8–87 min) with a mode of 15–25 min (40% of all lever-presses). After double-drug injections, the latency to the next lever-press increased to 45.5 ± 9.5 min while after non-reinforced lever-presses it decreased to 8.9 ± 1.4 min ($p < 0.001$ compared to regular self-injections; Student's *t*-test). In trained rats, the interval between tone stimulation signaling lever availability and the first lever-press varied from 5 to 87 min (mean 21.22 ± 8.8 min).

Biphasic changes in behavior were found to accompany all heroin self-injections with a decrease in locomotor and exploratory behavior seen immediately after heroin injections (latency 25–30 s) and slowly disappearing over an 8- to 14-min period. Rat activity level then increased beyond predrug levels and became most pronounced immediately preceding the next lever-press. Circular locomotion, washing, and grooming were

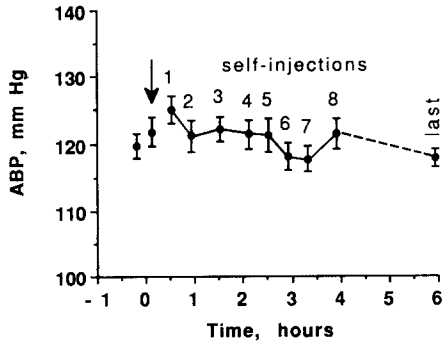

FIG. 1. Mean changes in arterial blood pressure (ABP, mm Hg) associated with heroin self-administration (SA) behavior in rats. Data represent mean (± SEM) ABP value at the beginning of each SA session (first point), at the moment of tone presentation that signaled drug availability (arrow), the first eight consecutive heroin self-injections, and the last SA of each session. Data were obtained from 6 rats over 13 sessions for a total of 127 self-injections.

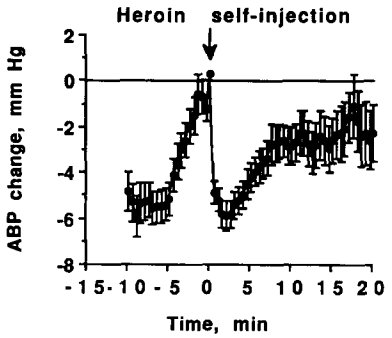

FIG. 2. Phasic changes in arterial blood pressure (ABP) preceding and immediately following heroin self-injections (6 rats, 55 self-injections). Each point represents the mean (± SEM) ABP in successive 30-s bins normalized to the moment of lever-press (arrow).

most often seen at this stage. Subsequent injections within a session resulted in an apparent tolerance to the drug-induced sedation while the postsedative activation was more pronounced and occurred earlier. The interresponse interval decreased slightly as a function of injections both within, $F(6, 90) = 3.91$, $p \leq 0.002$, and, to a lesser degree, across, $F(3, 199) = 3.03$, $p = 0.05$, sessions.

Changes in ABP Associated With Heroin SA Behavior

ANOVA revealed no effect of heroin SA on tonic changes in mean ABP across all SA sessions, $F(14, 181) = 1.11$, $p > 0.37$. As can be seen in Fig. 1, ABP levels were stable throughout the 6-h SA session with no trend to either increase or decrease.

To analyze the phasic changes associated with self-injections, the mean values of ABP preceding and following each self-injection were determined for all rats and across all sessions. All double-dose injections and nonreinforced lever-presses, as well as the first injection of each session, were analyzed separately and are discussed below. A few self-injections with short inter-injection intervals of < 5 min (6 of 55 self-injections) were also excluded.

As can be seen in Fig. 2, regular heroin self-injections were accompanied by significant biphasic changes in ABP. A one-way ANOVA with repeated measures revealed a powerful and highly significant effect of time, $F(19, 1,099) = 13.225$, $p < 0.001$. ABP gradually increased during the 5 min before the lever-press for heroin, abruptly decreased after heroin injections, and gradually increased again, reaching a peak at the moment of the next lever-press. Figure 3 shows several original polygraph tracings of ABP associated with heroin self-injections. Despite some between-injection and among-animal variability, biphasic ABP fluctuations, with transition at the moment of self-injections, were evident in almost all cases analyzed.

In several instances, when lever-pressing resulted in a double dose (200 μg/kg/injection) of heroin, the postinjection decrease in ABP became more pronounced (Fig. 4A). When the regular lever-press resulted in no drug delivery, a similar, "drug-like" decrease in ABP was seen immediately after the lever-press (Fig. 4B). In addition, a decrease in behavioral activation similar to that seen after heroin SA also ensued. However, this "sedation" quickly disappeared and, compared to heroin-reinforced self-injections, rats generally performed a subsequent lever-press earlier (6–8 min) with a concomitant ABP increase.

In contrast to the above, "atypical" ABP changes were seen both before and after the initial heroin self-injections in naive rats (Fig. 4C) and the first self-injections of each session (Fig. 4D). In both cases, the gradual prepressing ABP increase seen

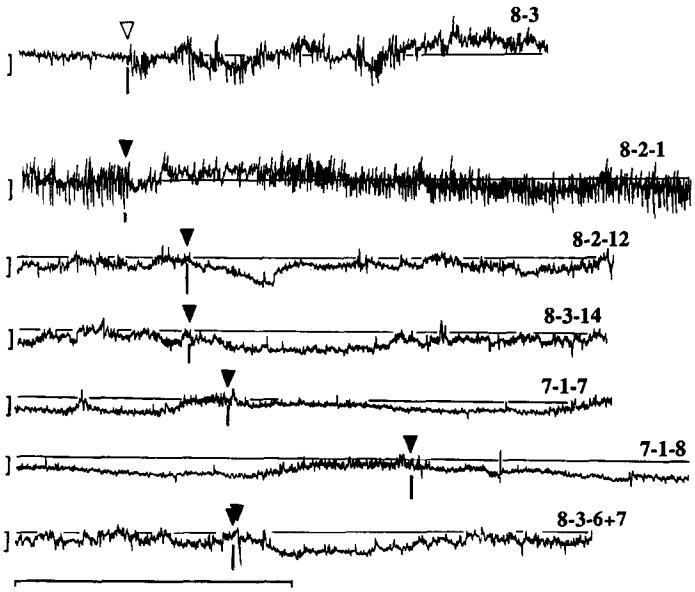

FIG. 3. Original polygraph records of mean arterial blood pressure (ABP) changes associated with tone presentation (△) and heroin self-injections (▲, 100-μg/kg/injection; ▲▲, 200-μg/kg/injection). Numbers represent rat, session, and self-injection number within the session, respectively. Calibration bars: time, 10 min; ABP, 10 mm Hg.

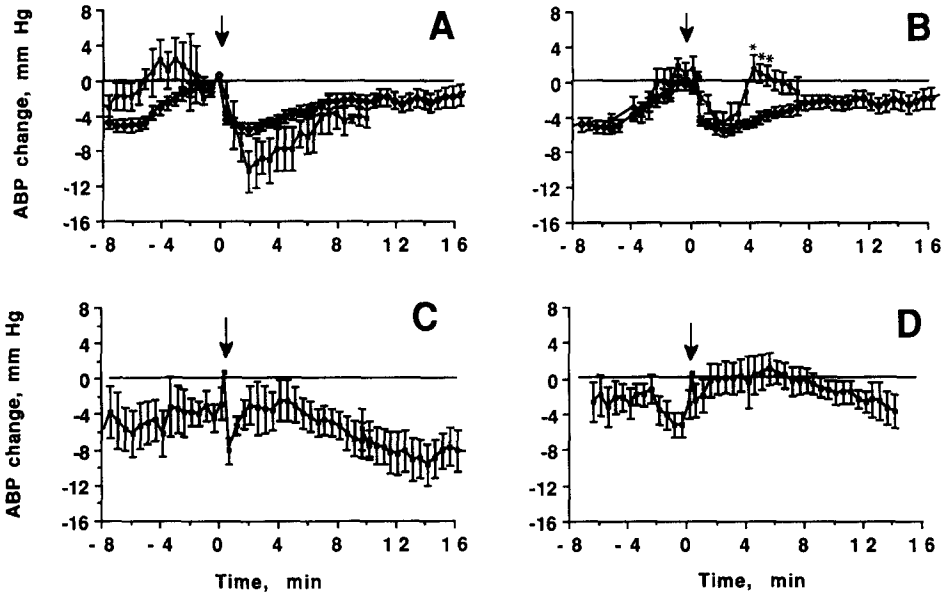

FIG. 4. Changes in mean (± SEM) arterial blood pressure (ABP) associated with: (A) double-dose (200 μg/kg) self-injections (●, 5 rats, 5 sessions), (B) nonreinforced lever-presses for heroin (4 rats, 8 sessions), (C) the initial heroin self-injection in drug-naive rats (6 rats), and (D) the first injections of a session in trained rats (5 rats, 8 sessions). The moment of lever-press was set to zero for both time and ABP levels and is indicated by an arrow. (○), ABP changes associated with regular heroin self-injections repeated from Fig. 2 for comparison. *Significant between-group differences ($p < 0.05$; Mann-Whitney U-test).

in trained animals and discussed above was absent. Rather, a small, brief increase in ABP was seen associated with a naive rat's first heroin self-injection, followed by a brief (25–40 s) decrease in pressure immediately after drug injection. These pressure changes were associated with pronounced alterations in heart rate (arrhythmia, acute bradycardia). In these cases, ABP levels remained relatively stable after drug delivery with only a gradual decrease in pressure occurring with a latency of 8–10 min. In contrast, a slight hypertension was observed in trained rats after the first heroin self-injection of a session. In some cases, the changes in ABP associated with the second and third drug self-injections were of a transitional type from a slight hypertensive response to the biphasic fluctuations commonly seen during the rest of the session and illustrated in Fig. 2.

Figure 5 shows the effects of tone alone on ABP as a function of drug conditioning. As can be seen, a significant effect of time was seen in drug-naive rats after the initial sound stimulation, with tone causing an increase in ABP [$n = 5$; $F(10, 54) = 2.23$, $p < 0.05$], while after training the same auditory stimulus elicited a small prolonged, nonsignificant ABP decrease [$n = 10$, $F(10, 109) = 1.81$; $p = 0.069$]. The differences between groups, however, were significant between 2.5 and 5 min ($p < 0.05$; Mann-Whitney U-test).

Figure 6 is a record of ABP (top) and heart rate (lower) changes associated with several natural behaviors recorded during the present experiment. As can be seen, large pronounced ABP and heart rate alterations occurred during such behaviors as washing, grooming, and locomotion but not during sleep-like quiescence.

DISCUSSION

The main finding of the present study is the strong relationship found between heroin SA behavior and phasic ABP changes. In trained rats, ABP gradually increased by about 5 mm Hg before each lever-press for drug, reached a peak at the moment of lever-press, and abruptly decreased after heroin self-injection. A slow increase in ABP then ensued, reaching a new peak at the moment of the next lever-press. These phasic pressure changes occurred concomitant with biphasic alterations in behavioral activity levels as a function of heroin SA. Drug-induced "sedation" was temporally linked with the decreases in ABP, while the subsequent behavioral activation corresponded to ABP increases. No tonic alterations in the "basal" or resting ABP levels accompanied these phasic changes as pressure was relatively stable during the entire 6-h

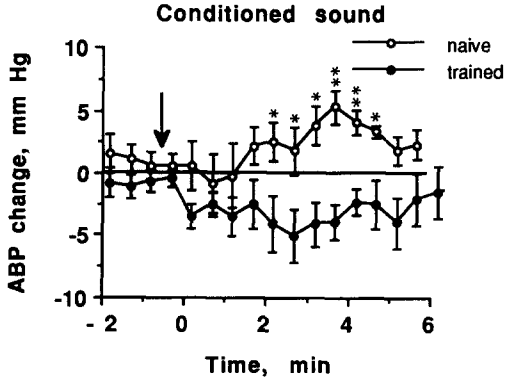

FIG. 5. Changes in arterial blood pressure (ABP) as a function of tone stimulation (presented at arrow) in drug-naive ($n = 5$; ○) and trained (5 rats, 10 sessions; ●) rats. *, **Significant between-group differences ($p < 0.05$ and $p < 0.01$, respectively; Mann-Whitney U-test).

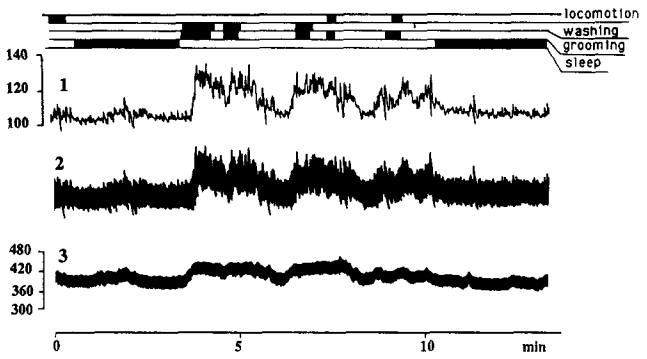

FIG. 6. Changes in (1) mean and (2) systolic/diastolic (mm Hg) blood pressure and (3) heart rate (beats/min) associated with various "natural" behaviors in a freely moving rat.

SA session. These data appear to be the first demonstration of cyclic, biphasic behavior-associated changes in an autonomic (ABP) function during the performance of a highly motivated, reinforced goal-directed behavior.

IV drug SA behavior combines pharmacological, physiological, and behavioral components. First, it is a prototypic learned, goal-directed behavior that quickly develops in drug-naive animals following the temporal association of an "accidental" motor act with a drug injection. There are both motivational and reinforced components to this behavior; trained animals respond on an intermittent, yet relatively regular schedule even when drug is continuously available. Drug delivery, acting as a reinforcer, terminates the previous behavioral cycle for the drug and triggers a new one. Second, drugs induce specific pharmacological actions on numerous ongoing behaviors and various homeostatic (physiological) indices. When a drug is self-administered by an animal, each lever-press for the drug is influenced by the previous drug effects and/or changes in the organism's association with these effects. Because there are repeated trials in a session, each of these individual pharmacological- or associative-induced alterations become superimposed and summate to drive the behavior. Finally, IV drug SA in animals is thought to model human addictive behavior, which is characterized by dramatic and bidirectional changes not only in physiological but also in emotional processes (6,11,13). In man, intense euphoria and relaxation associated with drug intake is gradually transformed into an activational, arousal state that is blocked (temporarily) by subsequent drug intake. Hence, drug SA is an integrative sequence of behaviors driven by pharmacological and physiological considerations.

Multiple factors likely also contribute to the relatively rapid, biphasic changes in ABP seen. The preinjection increase appears to correlate with various aspects of the rat's drug-seeking behavior, including grooming, washing, locomotion, and finally organization and performance of the drug-taking operant act. Except for the first response of a session, a previous drug injection occurred, in general, 20–25 min before a given lever-press. Thus, the observed ABP increase also depends, in part, upon the drug's previous pharmacological actions. That the preinjection ABP increase was absent before the first-in-life and first-in-session self-injections speaks to the influence of previous heroin effects on these changes.

The postinjection APB decrease developed quickly after heroin infusions and may be considered either as an effect of drug on specific blood pressure regulatory mechanisms or as a reflection of CNS processing of heroin's rewarding action. In should be noted that this pressure decrease also corresponded to a cessation of previous drug-seeking and drug-taking behavior and a profound drug-induced sedation. That this effect is not simply drug-induced, however, is suggested by the observation that the same ABP decrease and temporary "sedation" were also seen immediately after nonreinforced lever-pressing in trained rats. In addition, a brief, modest decrease in ABP was seen following presentation of tone alone (acting as a conditioned stimulus) at the beginning of a session in trained rats, suggesting a possible contribution of conditioning factors in the mediation of this effect. Thus, it is likely that at least three factors contributed to the bidirectional, phasic fluctuations in ABP seen during heroin SA: direct pharmacological action of heroin, the development of drug-associative behaviors, and learned, conditional drug properties.

Systemic opiate administration has been shown to induce acute cardiovascular depression in several species, which is both state-dependent and subject to tolerance development after repeated drug administration. In general agreement with the rapid hypotension seen in the present experiment, Thornhill et al. (21) found a transient but precipitous decrease in ABP and heart rate following a slow IV infusion of a relatively high dose of morphine (7.5 mg/kg) in drug-naive rats. This hypotensive response changed into a pressor effect after 3 days of twice-daily 5 mg/kg injections. Likewise, a pronounced bradycardia concurrent with a brief decrease followed by a rise in ABP was seen after an IV morphine injection (10 mg/kg) in awake rats (20). Significantly, smaller doses of IV morphine (20–500 μg/kg) have also been shown to transiently decrease heart rate along with the rapid formation of tolerance (18). Similar decreases in heart rate, along with hypotension, have also been seen following low doses of morphine (150 and 600 μg/kg) in monkeys (2) and dogs (1). In contrast, rabbits respond to IV morphine injections (3 mg/kg) with a profound bradycardia associated with transitory hypertension (12). The absence of any significant changes in ABP, pulse, and respiration in human addicts were noted after injections of large (1–2 g morphine IV over a period of 2.5 h) doses of opiates (5).

Numerous studies have demonstrated a positive correlation between changes in ABP and various natural behaviors. ABP increases have been noted during feeding (9,14), drinking (9,16), aggressive (10), and avoidance (8) behaviors. Because heroin SA is a cyclic behavior manifest as cycles of sedation and activation, behavior-associated changes in ABP therefore might also be expected to be cyclic, or bidirectional. A close correlation between various "spontaneous" behaviors (washing, grooming, rearing, locomotion, etc.) and ABP was noted in the present experiments. All of these behaviors have been shown to be accompanied by significant increases in ABP compared to the resting condition of quiet wakefulness (9) or sleep (3). The fact that locomotion, grooming, and washing behaviors also usually preceded lever-pressing for heroin suggests a close correlation between the prepressing gradual ABP increase with goal-directed, behavioral activation.

It is noteworthy that a comparable biphasic pattern to that observed herein for ABP has recently been reported in mesolimbic DA levels associated with heroin SA using in vivo voltammetry (7). Like ABP, DA-related signals were found to increase gradually before each lever-press for heroin and decrease abruptly after drug injections. This correlation may suggest an interrelationship between these two processes. It has been postulated that the gradual DA activation is associ-

ated with an opiate-induced disinhibition of DA cell firing that may mediate some motivational, activation components involved in searching for and obtaining the drug. Phasic increases in ABP may be one autonomic, homeostatic manifestation of this CNS activational state. In contrast, the abrupt decrease in mesolimbic DA levels may be the result of an opiate-induced overactivation of DA cells (leading to a depolarization blockade), which would induce a temporary inhibition of DA release. This cellular mechanism may be responsible for cessation of the preinjection activation (perhaps related to sedation in animals and euphoria in humans). The phasic ABP decrease may be a "nonspecific" component of this pharmacological state, which gradually transforms into accelerated activation preceding the next lever-press for the drug. Hence, if heroin SA is due to the unity of the drug's CNS effects, drug-associated behaviors and learning, our data suggests that this goal-directed behavior is accompanied by cyclic fluctuations in at least one index (ABP) of an organism's physiological, homeostatic state. It is not clear at this time whether the two phenomena—biphasic mesolimbic DA and ABP alterations—are causatively related or are correlated phenomena with no functional relationship. To address this issue, future studies should be directed at determining the cellular mechanisms of each.

That biphasic changes in ABP were manifest only following the development of drug-taking behavior appears to suggest an involvement of learning mechanisms in its mediation. In addition, both nonreinforced SA trials in trained rats as well as passive tone prior to a daily session also resulted in a cessation of behavioral activation and an abrupt ABP decrease following the lever-press. Such drug-induced conditional responses have been previously reported in man and lower animals [for review, see (4,15)] and are thought to either mimic the direct, pharmacological effects of the drug (19) or, if manifest in an opposite direction, "compensatory" physiological processes (17).

Hence, it appears that phasic increases in ABP are a correlate of drug-seeking and drug-taking behavior and may represent a manifestation of an internal drive state, while subsequent phasic decreases in ABP are associated with cessation of these behaviors and may reflect the rewarding action of heroin. If true, similar biphasic changes in ABP may accompany other types of learned goal-directed behaviors established by natural and drug reinforcers. Thus, phasic ABP increases may be an essential, general component in the organization and performance of all highly motivated behaviors related to the interaction of an organism with various biologically significant environmental stimuli.

ACKNOWLEDGEMENTS

This research was supported in part by NIDA Grant DA05012 to E.A.S. and a grant from the R.D. and Linda Peters Endowment to the Medical College of Wisconsin. Heroin was kindly donated by the Resource Technology Branch, NIDA.

REFERENCES

1. Agarwal, R. K.; Pandey, U. S.; Dixit, K. S.; Shukla, N.; Singh, S. K. Role of dopaminergic system in opioid-induced cardiovascular responses in dogs. Ind. J. Med.Sci. 43:323–328; 1989.
2. Cuthbert, B. N.; Holaday, J. W.; Meyerhoff, J.; Li, C. H. Intravenous beta-endorphin: Behavioral and physiological effects in conscious monkeys. Peptides 10:729–734; 1989.
3. Del Bo, A.; Ledoux, J. E.; Tucker, L. W.; Harshfield, G. A.; Reis, D. J. Arterial pressure and heart rate during natural sleep in rat. Physiol. Behav. 28:425–429; 1982.
4. Grabowski, J. C.; O'Brien, C. P. Conditioned factors in opiate use. In: Mello, N. K., ed. Advances in substance abuse. vol. 2. Greenwich, CT: JAI Press; 1980:34–46.
5. Jaffe, J. H. Drug addiction and drug abuse. In: Gilman, A. G.; Rall, T. W.; Nies, A.S.; Taylor, P., eds. The pharmacological basis of therapeutics. New York: Pergamon Press; 1990:522–573.
6. Johanson, C. E.; Fischman, M. W. The pharmacology of cocaine related to its abuse. Pharmacol. Rev. 41:3–52; 1989.
7. Kiyatkin, E. A.; Wise, R. A.; Gratton, A. Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous heroin self-administration in rats. Synapse 14: 60–72; 1993.
8. Kiyatkin, E. A.; Zhukov, V. N. Impulse activity of mesencephalic neurons on nociceptive stimulation. Neurosci. Behav. Physiol. 18:393–400; 1988.
9. Ledoux, J. E.; Tucker, L. W.; Del Bo, A.; Harshfield, G.; Green, L.; Talman, W. T.; Reis, D. J. A hierarchical organization of blood pressure during natural behavior in rat and the effects of central catecholamine neurons thereon. Clin. Sci. 59:271s–273s; 1980.
10. Mancia, G.; Zanchetti, A. Hypothalamic control of autonomic functions. In: Morgane, P. J.; Panksepp, J., eds. Handbook of hypothalamus. Behavioral studies of the hypothalamus. New York: Dekkers; 1981:147–202.
11. Mansky, P. A. Opiates: Human psychopharmacology. In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., eds. Handbook of psychopharmacology. vol. 18. New York: Plenum Press; 1978: 95–185.
12. May, C. N.; Whitehead, C. J.; Heslop, K. E.; Mathias, C. J. Evidence that intravenous morphine stimulates central opiate receptors to increase sympathoadrenal outflow and cause hypertension in conscious rabbits. Clin. Sci. 76:431–471; 1989.
13. Moore, K. E. Amphetamines: Biochemical and behavioral actions in animals. In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., eds. Handbook of psychopharmacology. vol. 11. New York: Plenum Press; 1978:41–97.
14. Myers, M. M.; Scalzo, F. M. Blood pressure and heart rate responses of SHR and WKY rat pups during feeding. Physiol. Behav. 44:75–83; 1988.
15. O'Brien, C. P.; Childress, A. R.; Mc Lennan, A. T.; Ehrman, R. A learning model of addiction. In: O'Brien, C. P.; Jaffe, J. H., eds. Addictive states. New York: Raven Press; 1992:157–177.
16. Shido, O.; Nagasaka, T. Metabolic and blood pressure response to feeding activity is enhanced in freely moving spontaneously hypertensive rats. Jpn. J. Physiol. 39:537–548;1989.
17. Siegel, S. The role of conditioning in drug tolerance and addiction. In: Keehn, J.D., eds. Psychopathology in animals: Research and treatment implications. New York: Academic Press; 1979:143–168.
18. Stein, E. A. Morphine effects on the cardiovascular system of awake, freely behaving rats. Arch. Int. Pharmacodyn. Ther. 223: 54–63; 1975.
19. Stewart, J.; de Wit, H.; Eikelboom, R. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. Psychol. Rev. 91:251–268;1984.
20. Suemaru, S.; Dallman, M. F.; Darlington, D. N.; Cascio, C. S.; Shinako, J. Role of alpha-adrenergic mechanisms in effects of morphine on the hypothalamo-pituitary-adrenocortical and cardiovascular systems in the rat. Neuroendocrinology 49:181–190; 1989.
21. Thornhill, J. A.; Townsend, C.; Gregor, L. Intravenous morphine infusion (IMF) to drug-naive, conscious rats evokes bradycardic, hypotensive effects, but pressor actions are elicited after IMF to rats previously given morphine. Can. J. Physiol. Pharmacol. 67:213–222; 1989.
22. Weeks, J. R.; Collins, R. J. Screening for drug reinforcement

using intravenous self-administration in the rat. In: Bozarth, M. A., ed. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987:35–43.
23. Wise, R. A. Intravenous drug self-administration: A special case of positive reinforcement. In: Bozarth, M. A., ed. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987:117–141.
24. Yumatov, E. A.; Kiyatkin, E. A. Cardiovascular reactions from hypothalamic self-stimulation in the rat. Acta Physiol. Acad. Sci. Hung. 60:107–120; 1982.