Pharmacology Biochemistry & Behavior, Vol. 31, pp. 561–566. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Tolerance and Sensitization to the Heart-Rate Effects of Morphine

KAREN S. SCHWARZ[1] AND CHRISTOPHER L. CUNNINGHAM

Department of Medical Psychology, The Oregon Health Sciences University, Portland, OR 97201

Received 12 November 1987

SCHWARZ, K. S. AND C. L. CUNNINGHAM. *Tolerance and sensitization to the heart-rate effects of morphine.* PHARMACOL BIOCHEM BEHAV **31**(3) 561–566, 1988.—The effect of daily exposure to one of several doses of morphine (0, 2.0, 4.0 and 8.0 mg/kg IV) on heart rate was assessed in restrained (R) and unrestrained (U) rats. Initially, morphine produced a biphasic heart-rate response; bradycardia followed by tachycardia. Tolerance to the bradycardic effect was established in the 4 and 8 mg/kg R groups and in the 2 and 4 mg/kg U groups. Sensitization developed to the tachycardic effect in the 2 and 4 mg/kg U groups but not in the 8 mg/kg U group or any of the R groups. After several exposures to morphine, mean preinfusion heart rate increased in the 4 and 8 mg/kg dose groups but not in the 0 and 2 mg/kg dose groups. These results are generally consistent with the other data suggesting that tolerance develops only to the depressant effects of morphine, and either no change or sensitization develops to its stimulant effects. The development of higher preinfusion heart rates in the higher dose groups may represent a learned anticipatory response.

Morphine Heart rate Stress Tolerance Sensitization Rats

MORPHINE produces both depressant and stimulant effects on the central nervous system which are characterized by time-dependent biphasic changes in the response to a single dose as well as biphasic dose-response functions. In the former case, the depressant effect usually precedes the stimulant effect. In rats, for example, morphine-induced hypothermia and hypoactivity are followed by hyperthermia and hyperactivity, respectively [e.g., (4,8)].

Although previous studies have suggested that morphine produces only a monophasic, depressant effect on heart rate (i.e., bradycardia), a recent study has shown a biphasic response. The initial bradycardia induced by morphine was gradually replaced by a dose-related tachycardia that lasted for several hours after intravenous (IV) infusion of 10 mg morphine/kg body weight (22). In addition, a comparison between restraint-stressed and freely moving rats indicated that restraint augmented the bradycardia and attenuated the tachycardia.

For drugs showing biphasic effects, it has often been noted that tolerance develops only to the depressant effects and not to stimulant effects (23). Although the literature is fairly consistent in showing tolerance to such morphine-induced depressant effects as hypoactivity (4, 7, 10, 15, 18, 20, 21, 30), hypothermia (5, 8, 17, 28) and bradycardia (9, 11, 27), there has been less agreement about the nature of changes in morphine-induced stimulant effects. Most investigators report either no change or sensitization to morphine hyperthermia and hyperactivity (4, 6, 8, 15–17, 20, 21, 24, 28, 29, 32). No study has yet examined the development of tolerance or sensitization to morphine's tachycardic effect, presumably because tachycardia has rarely been observed.

The present study was designed to assess the effect of repeated morphine exposure on the biphasic heart-rate response to morphine. Different groups of rats received one of four doses of morphine (0, 2, 4, or 8 mg/kg, IV) in 12 daily sessions and were then tested with all four doses for evidence of tolerance or sensitization. Because our previous research had shown that restraint-stress altered the relative magnitudes of bradycardia and tachycardia induced by morphine (22), and because restraint-stressed rats may differ from nonstressed rats with respect to tolerance or sensitization to the tachycardic effect (19,32), restraint was included as a factor in the design. Also, because of evidence suggesting that tolerance to the depressant phase of morphine-induced biphasic responses is mediated by a learned compensatory response (18), the procedure included a long preinfusion measurement period to permit observation of anticipatory learned changes in heart rate.

METHOD

Subjects

The subjects were 64 adult male albino rats (Holtzman Co., Madison, WI) weighing an average of 402 g at the start of testing. These rats were housed individually in a colony room on a normal 12-hr light/dark cycle. Food and water were available ad lib except during experimental sessions.

Surgical Preparation

Several days before the start of testing, each rat was fully anesthetized with halothane gas while two heart-rate electrodes and a jugular cannula were implanted under antiseptic

[1]Requests for reprints should be addressed to Karen S. Schwarz, Department of Medical Psychology, L470, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201.

conditions. Each heart-rate electrode consisted of a 36-cm length of 32-ga stainless steel suture wire loosely looped four times through the superficial muscle under a ventral and dorsal incision. The jugular cannula consisted of an intravascular portion of silastic tubing (31) (0.51 mm i.d. × 0.94 mm o.d.) and a subcutaneous portion of polyethylene tubing (Intramedic, PE10 and PE20). The external end of the cannula was attached to a blunt hypodermic needle which was plugged and clipped to a saddle that fit around the animal's chest and back (31). A detailed description of the surgical procedure can be found elsewhere (22).

Apparatus

Unrestrained rats were tested in a 21×21×23 cm cage with clear acrylic and aluminum walls, and a stainless steel grid floor; restrained rats were tested inside a cylindrical restrainer (7 cm diameter × 17 cm length) composed of wire rings mounted in Plexiglas rails at 1.2-cm intervals (2). These containers were placed inside ventilated, light- and sound-attenuating chambers (50×52×45 cm) and connected to ECG preamplifiers via a spring-covered wire "leash." A fluid swivel with electrical circuits (Ealing Corporation/Harvard Bioscience) was mounted above each cage, permitting direct attachment of freely-moving animals to the infusion/recording system. After amplification, heart-rate signals were fed into a peak detector (25) that converted each R-wave into a digital signal. A PDP8/F computer recorded interbeat intervals (20 msec resolution).

Procedure

After surgery, rats were assigned to four morphine dose groups: 0, 2, 4 and 8 mg/kg. Within each dose group there were both restrained (R) and unrestrained (U) rats matched in pairs by weight. Thus, there were eight groups with eight rats in each group. Sessions were 3 hr long and occurred at 24-hr intervals. The experiment required 19 sessions. After three apparatus-habituation sessions, all rats received 12 training sessions during which saline or morphine was injected after a 60-min baseline period. Morphine sulfate, dissolved in a 0.5-ml volume of sterile saline, was automatically infused through the jugular cannula by an infusion pump (Harvard Apparatus) at a rate of 1 ml/min. The training dose received corresponded to the dose group to which the subject belonged.

During the last four sessions (tolerance test phase), each rat received each dose of morphine to assess development of tolerance. The purpose of this test phase was to allow comparison of the response to morphine between drug-experienced rats (2, 4, 8 mg/kg groups) rats and drug-naive (0 mg groups) rats that had received equal amounts of handling and exposure to the apparatus. The test doses were administered in one of eight different orders and a different order was assigned to each rat in each group. Although subject attrition disrupted the intended counterbalancing within each group, each dose was given to roughly the same number of rats on each test day.

Data Analysis

The mean interbeat interval computed for each minute of the session was converted into mean heart rate (bpm). As a way of eliminating the contribution of electrical noise to these data, all intervals outside a range of 80–300 msec or different by more than 20 msec from the previous interval were excluded. If the total duration of acceptable intervals was less than 2 sec of any minute, data from the entire minute were discarded. For statistical analyses, an average score was computed from adjacent minutes and inserted in place of the discarded data. The data for each subject were averaged across 5-min sample periods, and during the training phase, data were averaged across 2-day blocks for analyses of variance (ANOVA). All p values less than 0.05 were considered significant. In instances where estimates of missing data were inserted, the degrees of freedom were properly adjusted (12).

RESULTS

The data from three subjects in the restraint-stressed group were discarded because of procedural problems, i.e., one rat's cannula became obstructed and two rats were removed due to problems with the restrainers. Two additional R rats died after their first exposure to the 8 mg/kg dose of morphine. Seven other rats died or were sacrificed because of poor health. Of these seven, four rats were restrained and three were unrestrained. Thus, groups sizes were 7, 6, 5, and 5 for the 0, 2, 4 and 8 mg/kg R dose groups, respectively, and 7, 8, 7 and 7 for the 0, 2, 4 and 8 mg/kg U dose groups, respectively. A Chi Square test performed on the relative proportion of survivors in Groups R and U (ignoring those removed from procedural problems) revealed no relationship between restraint and attrition, $\chi^2(1)=0.78$. Unweighted means analyses of variance were used to accommodate unequal cell sizes in all analyses described below.

During the preinfusion baseline hour, heart rate was higher in the R groups than in the U groups. There was no systematic effect of training dose on heart rate among the R and U groups, although the restraint effect varied somewhat across doses. The mean heart rates were 424, 407, 419 and 454 for the 0, 2, 4 and 8 mg/kg R groups, respectively, and 374, 394, 387 and 374 for the 0, 2, 4 and 8 mg/kg U groups, respectively. Generally, heart rate declined over the preinfusion hour. The decrease was greater in U groups (−67 bpm) relative to R groups (−46 bpm).

Figure 1 shows how preinfusion baseline heart rate changed over training days as a function of training dose (collapsed over restraint). During the first three blocks, baseline heart rate decreased in all groups, presumably because of habituation to the experimental procedure. However, during the last two blocks, baseline heart rate increased in the 4 and 8 mg/kg dose groups.

A four-way ANOVA (Restraint × Drug Exposure Dose × Blocks × Sample Periods) performed on the baseline data revealed significant Restraint × Blocks × Sample Periods, $F(55,2391)=1.52$, Restraint × Dose, $F(3,44)=3.37$, Restraint × Sample Periods, $F(11,484)=6.14$, and Dose × Blocks, $F(15,218)=3.17$, interactions. There were also significant main effects of Restraint, $F(1,44)=31.47$, Blocks, $F(5,218)=5.62$, and Sample Periods, $F(11,484)=208.15$. The Restraint × Blocks × Sample Periods interaction occurred because the U groups showed consistent changes in heart rate over blocks in each sample period, while the R groups showed greater differences between blocks during the first few sample periods than during the later sample periods. The Restraint × Sample Periods interaction is due to the greater decrease in heart rate over the preinfusion hour in U groups than in R groups.

The Dose × Blocks interaction supports the observations made from Fig. 1. Follow-up analyses revealed significant

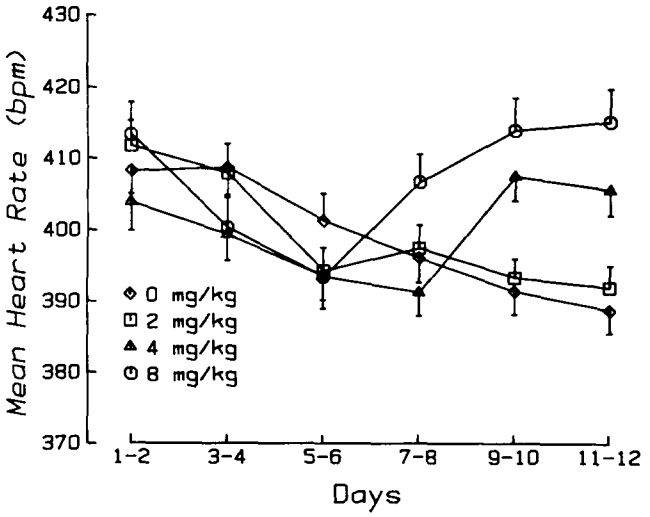

FIG. 1. Mean preinfusion heart rate (±SEM) over 2-day blocks of the training phase for each dose group. Each point represents a mean of both R and U groups for the entire preinfusion hour.

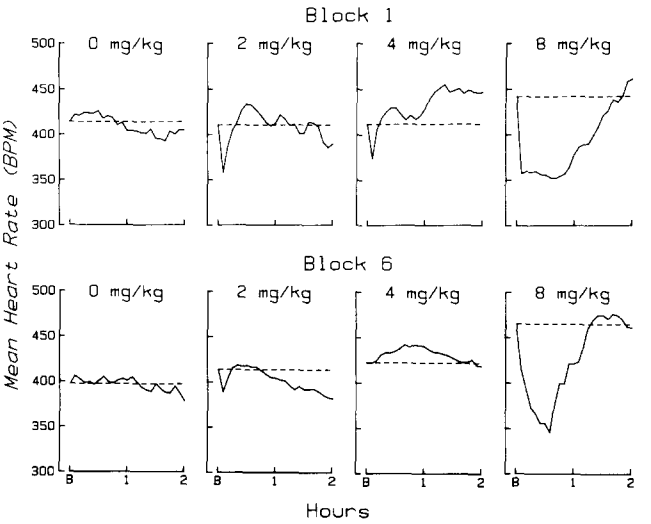

FIG. 2. Mean heart rate of the R groups during the 5-min period just before infusion (B) and for 2 hr after infusion. Each panel represents a different training dose group. The top row of panels depicts the response on Block 1 (Day 1–2) of the training phase, and the bottom panels depict the response on Block 6 (Day 11–12) of the training phase. The horizontal dashed line in each panel shows the preinfusion baseline heart rate.

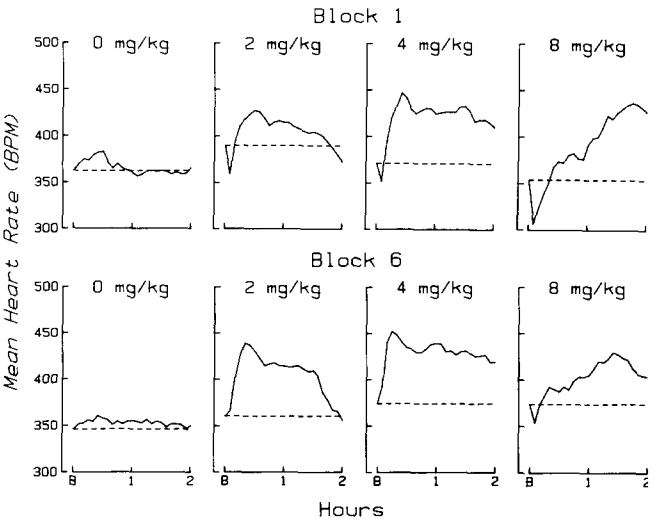

FIG. 3. Mean heart rate of the U groups during the 5-min period just before infusion (B) and for 2 hr after infusion. Each panel represents a different training dose group. The top panels depict the response on Block 1, and the bottom panels depict the response on Block 6 of the training phase.

effects of Dose during Blocks 5 and 6, $F(3,44)=3.08$ and 3.52, respectively, but not in Blocks 1 through 4. These data indicate that repeated administration of the higher doses of morphine (4 and 8 mg/kg) produced an elevation in baseline heart rate during sessions that occurred 24 hr after the previous drug administration.

Figure 2 shows mean heart rate calculated for the 5-min baseline period just before infusion (B) and for 2 hr following infusion in the R groups in Block 1 (top panels) and Block 6 (bottom panels) of the training phase. The horizontal dashed line represents baseline heart rate. Figure 3 shows mean heart rate in the U groups. The groups receiving saline showed little change over the 2-hr postinfusion period. In general, the acute effect (Block 1) of morphine was biphasic: an initial decrease in heart rate followed by an increase relative to preinfusion heart rate. By Block 6, the bradycardia in all groups had decreased in terms of magnitude and duration, suggesting tolerance to this effect. The tachycardia changed in terms of an increased magnitude with a shorter latency in the U groups suggesting sensitization.

Because some of the change observed in the drug response may be due to a general habituation to the experimental procedure, the results of the training phase are somewhat ambiguous. For this reason, a Tolerance Test phase was included in which all rats received all doses so that a direct comparison could be made between the drug naive rats (0 mg/kg) and each training dose group where all had received equal experience with the procedure.

For the tolerance test phase, dose-response curves of lowest and highest heart rate during the 1.5-hr period after infusion of each test dose are shown in Fig. 4 and 5, respectively. Given the time course of the cardiac response to morphine, these measures represent the maximum bradycardic and tachycardic responses, respectively. Figure 4 shows that the bradycardia response of the training dose groups varied with restraint, such that in the R groups (left panel), the two highest training dose groups (4 and 8 mg/kg) responded with the less bradycardia (i.e., a higher heart rate) to all test doses than the 0 and 2 mg/kg groups. In the U groups, differences between the training dose groups were less systematic, although the 0 mg/kg showed more bradycardia than the other groups. With respect to effects of test dose, the R groups showed a test dose related increase in bradycardia. There was no clear test dose relationship in the U groups.

In order to determine whether tolerance developed to the bradycardic effect, each morphine dose group was compared individually with the appropriate saline control group. In

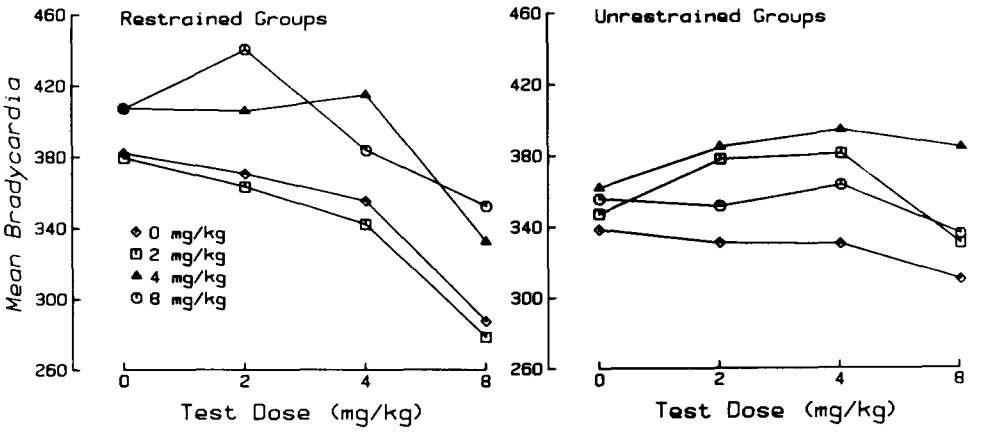

FIG. 4. Lowest heart rate within 1.5 hr after infusion of each morphine test dose. The data are plotted for each training dose group in both restrained (left panel) and unrestrained (right panel) rats.

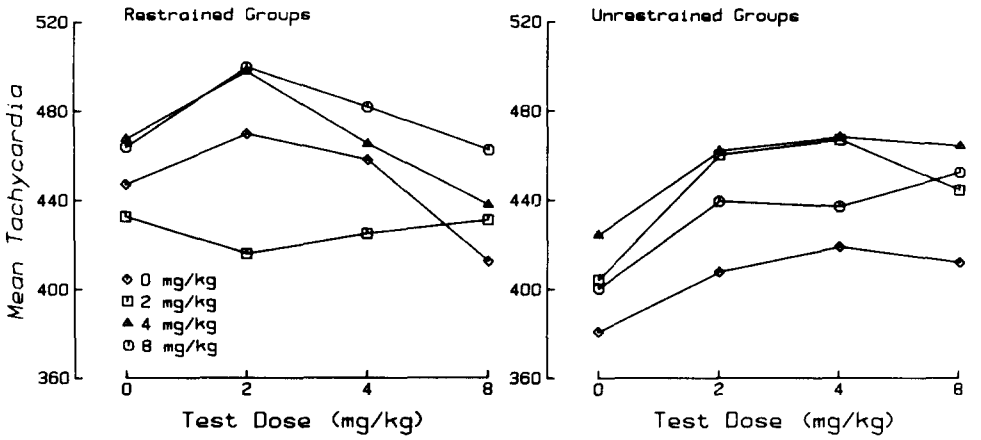

FIG. 5. Highest heart rate occurring within 1.5 hr after infusion of each morphine test dose. The data are plotted for each training dose group in both restrained (left panel) and unrestrained (right panel) rats.

other words, the test dose responses of each R morphine group were compared with those of the 0 mg/kg R group, and the responses of each U morphine group were compared with those of the 0 mg/kg U group. These analyses supported the foregoing observations. In the R groups, a significant difference was found when comparing the 0 versus 4 mg/kg dose groups, $F(1,10)=5.90$, and the 0 versus 8 mg/kg groups, $F(1,10)=5.94$. No difference was found between the 0 and 2 mg/kg groups. In the U groups, a significant difference was revealed when comparing the 0 versus 2 mg/kg groups, $F(1,13)=8.45$, and the 0 versus 4 mg/kg groups, $F(1,12)=34.37$, but not when comparing the 0 versus 8 mg/kg groups. These observations imply tolerance in the 4 and 8 mg/kg R groups and the 2 and 4 mg/kg U groups, but not in the 2 mg/kg R group or 8 mg/kg U group.

Figure 5 shows the highest heart rate after drug infusion for each group in response to each test dose. In the U groups, the magnitude of tachycardia was less in the saline group relative to the drug-experienced animals especially the 2 and 4 mg/kg training dose groups. With respect to test dose effects, the U groups showed a test dose-related increase in magnitude of tachycardia. The tachycardia remained the same or decreased a little at the higher doses in the R groups which could reflect the fact that bradycardia was the predominant response relative to tachycardia at the higher doses.

To determine whether sensitization occurred to the tachycardic effect, each morphine dose group was compared individually with the appropriate saline control group. These analyses supported the foregoing observations, in that a significant difference was found between the 0 versus 2 mg/kg, $F(1,13)=13.45$, and the 0 versus 4 mg/kg U groups, $F(1,12)=20.04$. None of the other two-group comparisons revealed a difference. These results suggest sensitization developed to the tachycardic effect of morphine only in the 2 and 4 mg/kg U groups.

DISCUSSION

In agreement with previous findings (22), morphine produced a biphasic heart-rate response: an initial bradycardia followed by tachycardia. The magnitude of bradycardia was greater in the R groups relative to the U groups, while the tachycardia was greater in the U groups relative to the R groups. Generally speaking, tolerance developed to bradycardia and sensitization developed to tachycardia. Table 1 summarizes the results of the overall

TABLE 1
SUMMARY OF THE RESULTS OF THE TOLERANCE TEST PHASE

	Heart Rate	
	↓HR*	↑HR
Group R2	—†	—
R4	tol	—
R8	tol	—
U2	tol	sens
U4	tol	sens
U8	—	—

Note. R=Restrained; U=Unrestrained.
The numbers correspond to Dose.
*↓HR=bradycardia; ↑HR=tachycardia.
†—=absence of tolerance or sensitization; tol=tolerance, sens=sensitization.

two-group comparisons between each training dose group and its appropriate saline control in the test phase. In the R groups, tolerance was evident in the higher dose groups (4 and 8 mg/kg), and no sensitization in the 2 and 4 mg/kg groups. The 8 mg/kg U group also showed a tendency toward reduced bradycardia and enhanced tachycardia during testing, although these effects were not statistically reliable. Overall, these results are consistent with the suggestion (23) that tolerance develops only to the depressant effects and not to the stimulant effects of drugs.

There are several possible reasons why the U groups showed both tolerance and sensitization while the R groups showed only tolerance. First, the elevated baseline produced by restraint may reduce the apparent response to morphine due to a "ceiling" effect, i.e., heart rate can only increase to a certain absolute level. Second, if the heart-rate response is secondary to the locomotor response to morphine, the inability of restrained rats to exhibit hyperactivity may have retarded the development of sensitization to the tachycardic effect of morphine. A third possibility is that habituation to stress-induced tachycardia in the R groups may have counteracted sensitization to morphine-induced tachycardia [e.g., (32)].

During the preinfusion periods of the training phase, the mean heart rate of the two high dose groups (4 and 8 mg/kg) was significantly higher than that of the low dose groups (0 and 2 mg/kg) in Blocks 5 and 6. This finding suggests some effect of previous days' exposure to morphine. A residual drug effect is one possibility for the increase in mean baseline heart rate in the two high dose groups. The residual drug effect could be due to changes in the autonomic nervous system. For example, after one week of daily treatment with two 10 mg/kg injections of morphine, increased adrenal medullary levels of catecholamines, tyrosine hydroxylase and dopamine β-hydroxylase were observed in rats 24 hr after the last morphine injection (3). This increase in catecholamines could lead to an increased heart rate if there was also an increase in release of catecholamines into the circulation. However, plasma levels of catecholamines were not reported.

Another possible explanation for the higher preinfusion heart rate in the high dose groups is learned anticipation of the current day's treatment based on repeated exposure to the same sequence of cues every day. The increase in preinfusion heart rate may serve as a conditioned compensatory response to the initial bradycardic response to morphine. This response may mediate the expression of tolerance to morphine-induced bradycardia [cf. (26)]. It may also mediate sensitization to morphine-induced tachycardia. There are two problems with this interpretation: the first is that the R groups should have shown a greater increase in preinfusion heart rate than the U groups because they showed a greater magnitude bradycardia; however, the increase in baseline heart rate in the 4 and 8 mg/kg dose groups did not vary with restraint. The second problem is that the 2 mg/kg U group evidenced both tolerance and sensitization even though it did not show an increase in preinfusion heart rate.

An alternative to the compensatory response hypothesis is that the increase in preinfusion baseline heart rate occurred as a result of direct conditioning of the stimulant effects of the drug. Another possibility is that the increased baseline heart rate simply reflected anticipation of the positive reinforcing properties of the drug. However, all of these conditioning hypotheses must be considered with caution because although the saline control group in this study allows conclusions to be drawn about the effect of repeated exposure to morphine, it does not permit a clear-cut distinction to be made between associative and nonassociative effects.

The results of the present study are generally consistent with those showing development of tolerance to morphine's depressant effects on heart rate, body temperature and locomotor activity (4, 8, 11). With respect to morphine's stimulant effects, most studies report either no change or sensitization to morphine hyperthermia and hyperactivity (4, 6, 8, 15–17, 20, 21, 24, 28, 29, 32). Although there are a few reports of tolerance to the hyperthermic effect of morphine (14, 19, 26), in one study the decrease in morphine hyperthermia occurred after repeated exposures to high doses (e.g., 200 mg/kg) (14). When tolerance has been observed within the dose range used in the present study, the decrease may have been due to habituation to stress produced by a large number of rectal probings (26,32) or restraint (19).

In summary, it is now clear that morphine produces biphasic effects on at least three response systems: heart rate, temperature and locomotor activity. Repeated administration of morphine produces tolerance to the depressant effects and produces either no change or sensitization to the excitatory effects. Furthermore, repeated exposure to drug may lead to development of a learned anticipatory response which can be observed during a preinfusion period.

ACKNOWLEDGEMENTS

This research was supported in part by grants from the National Institute on Drug Abuse (DA03608) and the National Heart Lung and Blood Institute (HL07332). These data were presented at the 16th annual meeting of the Society for Neuroscience, Washington, DC, November 9–14, 1986.

REFERENCES

1. Amir, S.; Brown, Z. W.; Amit, Z. The role of endorphins in stress: Evidence and speculations. Neurosci. Biobehav. Rev. 4:77–86; 1979.
2. Anderson, D. C.; Plant, C.; Paden, P. Conditioned suppression of a running response as related to competing responses, drive, and basal skin resistance level. J. Comp. Physiol. Psychol. 63:282–287; 1967.
3. Anderson, T. R.; Slotkin, T. A. Effects of morphine on the rat adrenal medulla. Biochem. Pharmacol. 24:671–679; 1975.
4. Babbini, M.; Davis, W. M. Time-dose relationships for locomotor activity effects of morphine after acute or repeated treatment. Br. J. Pharmacol. 46:213–224; 1972.
5. Cox, B.; Ary, M.; Chesarek, W.; Lomax, P. Morphine hyperthermia in the rat: An action on the central thermostats. Eur. J. Pharmacol. 36:33–39; 1976.
6. Eikelboom, R.; Stewart, J. Temporal and environmental cues in conditioned hypothermia and hyperthermia associated with morphine. Psychopharmacology (Berlin) 72:147–153; 1981.
7. Fanselow, M. S.; German, C. Explicitly unpaired delivery of morphine and the test situation: Extinction and retardation of tolerance to the suppressing effects of morphine on locomotor activity. Behav. Neural Biol. 35:231–241; 1982.
8. Gunne, L-M. The temperature response in rats during acute and chronic morphine administration: A study of morphine tolerance. Arch. Int. Pharmacodyn. Ther. 79:416–428; 1960.
9. Hine, B. Morphine and delta-9-tetrahydrocannabinol: Two-way cross tolerance for antinociceptive and heart-rate responses in the rat. Psychopharmacology (Berlin) 87:34–38; 1985.
10. Hinson, R. E.; Siegel, S. Anticipatory hyperexcitability and tolerance to the narcotizing effect of morphine in the rat. Behav. Neurosci. 97:759–767; 1983.
11. Kiang, J. G.; Dewey, W. L.; Wei, E. I. Tolerance to morphine bradycardia in the rat. J. Pharmacol. Exp. Ther. 226:187–191; 1983.
12. Linton, M.; Gallo, P. S. The practical statistician: Simplified handbook of statistics. Monterey, CA: Brooks/Cole Publishing Co.; 1975.
13. Mansfield, J. G.; Wenger, J. R.; Benedict, R. S.; Halter, J. B.; Woods, S. C. Sensitization to the hyperthermic and catecholamine-releasing effects of morphine. Life Sci. 29:1697–1704; 1981.
14. Mucha, R. F.; Kalant, H.; Kim, C. Tolerance to hyperthermia produced by morphine in rat. Psychopharmacology (Berlin) 91:452–458; 1987.
15. Mucha, R. F.; Kalant, H.; Linseman, M. A. Quantitative relationships among measures of morphine tolerance and physical dependence in the rat. Pharmacol. Biochem. Behav. 10:397–405; 1979.
16. Mucha, R. F.; Volkovskis, C.; Kalant, H. Conditioned increases in locomotor activity produced with morphine as an unconditioned stimulus, and the relation of conditioning to acute morphine effect and tolerance. J. Comp. Physiol. Psychol. 95:351–362; 1981.
17. Oka, T. M.; Nozaki, M.; Hosoya, E. Effects of p-chlorophenylalanine and cholinergic antagonists on body temperature changes induced by the administration of morphine to nontolerant and morphine-tolerant rats. J. Pharmacol. Exp. Ther. 180:136–143; 1972.
18. Paletta, M. S.; Wagner, A. R. Development of context-specific tolerance to morphine: Support for a dual-process interpretation. Behav. Neurosci. 100:611–623; 1986.
19. Rudy, T. A.; Yaksh, T. L. Hyperthermic effects of morphine: Set point manipulation by a direct spinal action. Br. J. Pharmacol. 61:91–96; 1977.
20. Schnur, P. Morphine tolerance and sensitization in the hamster. Pharmacol. Biochem. Behav. 22:157–158; 1985.
21. Schnur, P.; Bravo, F.; Trujillo, M. Tolerance and sensitization to the biphasic effects of low doses of morphine in the hamster. Pharmacol. Biochem. Behav. 19:435–439; 1983.
22. Schwarz, K. S.; Peris, J.; Cunningham, C. L. Effects of restraint and naltrexone on the biphasic heart-rate response to morphine in rats. Alcohol Drug Res. 7:327–329; 1987.
23. Seevers, M. H.; Deneau, G. A. Physiological aspects of tolerance and physical dependence. In: Root, W. S.; Hofmann, F. G., eds. Physiology and pharmacology. New York: Academic Press; 1963:565–641.
24. Sherman, J. E. The effects of conditioning and novelty on the rat's analgesic and pyretic responses to morphine. Learn. Motiv. 10:383–418; 1979.
25. Shimizu, H. Reliable and precise identification of R-waves in the EKG with a simple peak detector. Psychophysiology 15:499–501; 1978.
26. Siegel, S. Tolerance to the hyperthermic effect of morphine in the rat is a learned response. J. Comp. Physiol. Psychol. 92:1137–1149; 1978.
27. Stein, E. A. Morphine effects on the cardiovascular system of awake, freely behaving rats. Arch. Int. Pharmacodyn. Ther. 223:54–63; 1976.
28. Stewart, J.; Eikelboom, R. Interaction between the effects of stress and morphine on body temperature in rats. Life Sci. 28:1041–1045; 1981.
29. Thornhill, J. A.; Hirst, M.; Gowdy, C. W. Changes in the hyperthermic reponses of rats to daily injections of morphine and the antagonism of the acute response by naloxone. Can. J. Physiol. Pharmacol. 56:483–489; 1977.
30. Vasko, M. R.; Domino, E. F. Tolerance development to the biphasic effects of morphine on locomotor activity and brain acetylcholine in the rat. J. Pharmacol. Exp. Ther. 207:848–858; 1978.
31. Weeks, J. R. Long-term intravenous infusion. In: Myers, R. D., ed. Methods in psychobiology. vol. 2. London: Academic Press; 1972:155–168.
32. Zelman, D. C.; Tiffany, S. T.; Baker, T. B. Influence of stress on morphine-induced hyperthermia: Relevance to drug conditioning and tolerance development. Behav. Neurosci. 99:122–144; 1985.