Pharmacology Biochemistry & Behavior, Vol. 7, pp. 463–469.

Restraint Alters the Effects of Morphine and Heroin on Core Temperature in the Rat

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(Received 2 March 1977)

MARTIN, G. E., A. T. PRYZBYLIK AND N. H. SPECTOR. *Restraint alters the effects of morphine and heroin on core temperature in the rat.* PHARMAC. BIOCHEM. BEHAV. 7(5) 463–469, 1977. – The importance of restraint in determining the magnitude of alteration in the rat's core temperature (T_c) after the administration of morphine sulphate (M) and heroin hydrochloride (H) was investigated. M, in doses of 5, 15 and 30 mg/kg, or H, in doses of 0.1, 1 and 5 mg/kg, was administered IP to either the restrained or free-moving rats as T_c was measured. After the administration of 5 mg/kg of H or 30 mg/kg of M to the restrained rat, a marked hypothermia was observed which reached a maximum mean depth of 3.1 and 4.5°C below the baseline T_c, respectively. Conversely, a mean increase in T_c of 1.5 and 1.9°C occurred following the administration of these same doses of M and H in the unrestrained animal. Furthermore, the hypothermic effect of the highest dose of M was not observed when the third of 3 consecutive injections of M, administered at 48-hr intervals, was administered to the restrained rat. On the other hand, when M was repeatedly administered to the free-moving rat, the hyperthermic response was consistently observed. Pretreatment with naloxone hydrochloride (5 mg/kg IP) effectively blocked the opiate-induced hypothermia in the restrained animal, but a total dose of 10 mg/kg was necessary to completely block the hyperthermic response in the free-moving rat. Although the factor of restraint itself did not alter the rat's T_c, it did dramatically alter the action of M and H on the body temperature of the rat.

Restraint Morphine Body temperature Heroin Naloxone Tolerance Restraint stress

ALTHOUGH morphine-induced alterations in core temperature (T_c) occur in several species, the predominant effect of this opium alkaloid on mammalian thermoregulatory processes remains unclear. A marked drop in T_c has been reported following the parenteral administration of morphine (M) in the dog [21], rabbit [2] or guinea pig [3]. On the other hand, hyperthermia has been evoked by M in the cat [7,19] and in horses and cattle [10].

The rat is a special case since M could induce either a hyperthermia or a hypothermia in this species depending on the dose of the drug administered [11]. Following a parenterally administered dose of M of approximately 30 mg/kg or greater, a hypothermic episode was more probable, while a rise in T_c was elicited by lower doses of the drug [6, 8, 12]. Tolerance, however, developed rapidly to the hypothermic action of the high doses of M. In fact, the drug induced a hyperthermia when the injection was repeated in the restrained animal [14].

During many experiments in which a high dose of parenterally administered M induced hypothermia, the rat was restrained in a plastic holder [6, 12, 13]. On the other hand, the T_c of the free moving rodent either rose following the injection of M [8,21] or remained unchanged when the injections were made at normal ambient temperatures [15]. Perhaps the physiological concomitants of restraint could be interacting with the pharmacological actions of the opiate to alter the rat's thermoregulatory response. If this were true, hypothermia might result following the administration of certain doses of M in the restrained rat whereas hyperthermia should occur in the free-moving animal treated with the same dose of M. In this regard, Grant [5] has previously shown that restraint alone could elicit a hypothermic response in the rabbit. Therefore, the purpose of this study was to examine whether restraint alters the rat's thermal response following the IP injection of M and heroin (H), another potent opiate which has been shown to alter the rat's T_c [20]. In addition, the effect of repeated injections of M on the rat's T_c response was examined in both the free-moving and restrained animals. Heretofore, Lotti and his colleagues have reported that tolerance rapidly develops to the hypothermia evoked by M in the rat that is restrained [14], but no one has examined this effect of the narcotic in the free-moving rat. Finally, an attempt to block the T_c altering effects of the opiates was made using the narcotic antagonist, naloxone, which has been shown to have no effect on the T_c of the rat when administered in moderate doses [4].

GENERAL METHOD

Animals

Overall, 114 male albino rats of the Walter Reed Wistar strain, weighing between 300–500 g, were used. Each animal was housed individually and maintained on a 12-hr

light-dark cycle with light onset at 0700 hr. Food and water were available ad lib, except during restraint when there was no access to either food or water. The free-moving animals were maintained in operant chambers in which they could depress a lever to obtain either a food pellet or a 0.05 ml drop of water. Each free-moving rat's rate of responding on these levers was recorded on an Esterline Angus Event recorder and in a PDP–8 computer. Room temperature was maintained at 22 ± 1°C. All injections were made between 0900 and 1200 hr.

General Procedures

Measuring core temperature. The T_c of the restrained rat was measured by a temperature probe (Yellow Springs Instrument, YSI type 402) which was inserted 6–8 cm into the rectum. The lead wire was taped to the base of the rat's tail. Each rat was placed in a plastic restraining device (Arthur C. Thomas Co., Philadelphia) and the probe was connected to a YSI telethermometer (Model 43 TF or 43 TG) and a strip-chart recorder (Heath Schlumberger, model SR–255B). T_c was measured for a minimum of 1 hr before and for at least 6 hr after each injection. Each dose of the drug was administered to 10 restrained rats.

In the free-moving rat, however, a specially fabricated thermistor (YSI type 44033), implanted within the peritoneum, was used to measure T_c. The lead wires from this thermistor, externalized via a miniature connector cemented to the rat's skull, were connected to the telethermometer and recorder via a special swivel device which permitted the animal freedom of movement within its home cage as the temperature was recorded. For 7 days following surgery, 30,000 units of Crystacillin (Squibb, Sterile procaine penicillin G) were administered IM daily, and no animal was tested during this period. Both thermistors render similar estimates of the rat's T_c [16].

Calculation of baseline T_c. Although the T_c was recorded continuously during the course of the experiment, a baseline T_c was established for each animal based on the mean of T_c readings taken at 45, 30 and 15 min before the injection and at the time of drug administration. No injection was made unless a stable T_c was observed for at least 30 min prior to the injection. The T_c was considered to be stable if it had not changed more than 0.5°C in a half-hour period. The T_c of each animal was expressed as a deviation in °C from its baseline T_c at 30 min intervals after the injection. These deviation scores were the data used in the statistical analyses.

EXPERIMENT 1: REPEATED INJECTIONS OF MORPHINE

METHOD

When the animal is restrained, the hypothermic action of M changes to a hyperthermic effect when the drug is readministered to the same rat [14]. Hence, it is necessary to carefully control for this successive injection effect by using the restrained rat for only one injection of M. In the free-moving rat, however, preliminary indications from our pilot studies indicated that successive doses of M do not alter the direction of the free-moving rat's change in T_c following the drug's administration. Hence we planned to use the free-moving animals to receive more than one dose of the opiates in these experiments. To systematically determine whether it would be possible to utilize such a procedure, the effect of repeated administrations of M on temperature regulation in the free-moving and restrained animals was ascertained. M (30 mg/kg IP) was administered in three injections spaced at 48-hr intervals to both free-moving (n = 6) and restrained (n = 6) rats as T_c was measured as described above. Furthermore, an attempt was made to determine whether the alteration in the T_c response of the restrained rat to repeated injections of the drug was due to acclimation to the restraint apparatus or tolerance to the action of the drug.

To determine whether this alteration in the T_c response was due to acclimation to the restraint, 4 animals were placed in the restraint tube for two 8-hr periods separated by an interval of 48 hr, as rectal temperature was recorded. Only during a third session of restraint, however, was M (30 mg/kg) injected.

To determine the role of acquired tolerance to M, three injections of M (30 mg/kg) spaced at 48-hr intervals, were administered to each of 4 rats in another group. Only following the last injection, however, were these animals restrained and was the T_c recorded.

Statistics

The changes from baseline T_c in the free-moving and restrained rats were analyzed in two ways. First, the changes in T_c following the second and third injections of M were compared with the changes in T_c evoked by the first injection of M. These comparisons were drawn within both the free-moving and restrained groups at the half-hour intervals after the drug injection using the Mann-Whitney U test [18]. Second, a direct comparison of the mean changes in T_c between the free-moving and the restrained rats was made at half-hour intervals following the first, second and third injections of M also using the Mann-Whitney U test. The differences were considered significant if the p-value associated with the U score was equal to or less than 0.05.

RESULTS AND DISCUSSION

Morphine consistently evoked a hyperthermic response from the free-moving rat whereas the hypothermia which was evoked following the first and second injection of M in the restrained rat became a hyperthermia after the third drug treatment. There was no statistical significance in the pattern of changes in T_c following the first and second injections within either group. The mean baseline T_c for the free-moving group was 36.7 ± 0.1°C, whereas that of the restrained group was 37.1 ± 0.1°C. However, when the deviations from baseline T_c in the first and third injections were compared for the restrained animal group, a marked difference in the T_c response was noted. The hypothermia evoked following the first and second injections of M did not evolve following the third injection. In fact, there was a hyperthermic response. When compared statistically, the mean changes in T_c following the third M injection were signifiantly different from that following the first injection during the period from 1 to 4.5 hr after the injection.

On the other hand, the direction of the change in T_c remained constant after each successive dose of M in the free-moving rat. Pyrexia was observed after each injection. When the changes in T_c were statistically compared, the first and third injections differed but only in the magnitude of the fever in readings taken at 4 and 4.5 hr after the injection. The fever was slightly greater in the third injection at these time points. Unlike the restrained rats,

the magnitude of the T_c response was significantly different from the first injection at only two points following the third injection of M in the free-moving animals.

A between group comparison of the T_c response to M revealed a marked difference between the free-moving and the restrained rats following the first two injections of the drug. Although there were still significant differences in the pattern of the drug response after the third injection, the differences were in the magnitude of the hyperthermia not in the direction of T_c movement as shown in Fig. 1. These findings for the restrained rat corroborate those of Lotti *et al.* [14]. However, the findings for the free-moving rat are novel. Following the first two injections, hyperthermia results in the free-moving rat at this dose of the drug, whereas hypothermia occurred in the restrained rat. The hyperthermia initially observed in the free-moving rat did not diminish with the repeated injection of M; in fact, it increased slightly. The hypothermia observed in the restrained rat following the first two injections of the drug, was not present following the third injection of the drug. In fact, a hyperthermic response occurred.

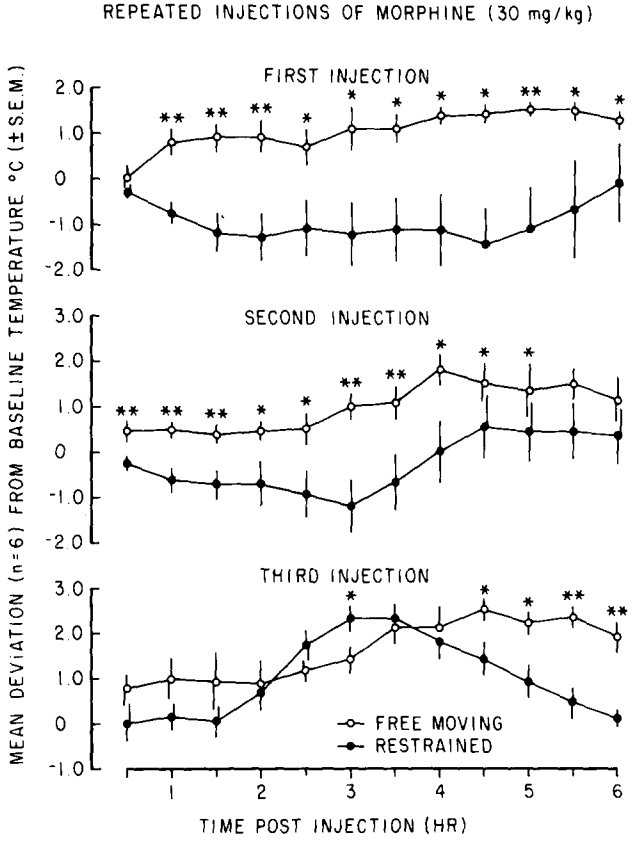

FIG. 1. The mean change in baseline T_c (± SEM) evoked by the repeated injection of M (30 mg/kg IP) in the free-moving (n = 6) and restrained (n = 6) rat. The asterisks denote a significant difference between groups at the $p<0.05$ (*) or $p<0.01$ (**) levels of significance using the Mann-Whitney U test.

Although the T_c response of the free-moving animals was somewhat greater at two points after the third administration of the drug than after the initial drug treatment, we felt that the overall profile of the T_c response was sufficiently unchanged with repeated injections of M to permit the use of free-moving animals in the administration of successive doses of M or H without drastically altering the shape of the T_c response. Since the T_c of the restrained rat either dropped or rose depending on the number of previous injections, the restrained rat would be used only for one injection in subsequent experiments.

Following the injection of the drug in the rats that had been restrained twice previously, but administered the M only during the third period of restraint, severe hypothermic episodes were observed in each of the four rats. Two animals succumbed following the administration of M, and the other two exhibited severe drops in T_c of 3.8 and 2.3°C, respectively. The mean baseline T_c in this group was 36.6 ± 0.4°C. In the other group, in which M was administered 3 times but only on the last occasion under the conditions of restraint, an increase in T_c occurred after a latency of 2 hr and 15 min. The mean maximum increase in T_c was 1.5°C. The mean baseline T_c in this group was 37.0 ± 0.1°C. Hence, it would seem that the increase in T_c seen after the third injection of the drug would more likely be due to tolerance to the drug's hypothermic action rather than to acclimation to the conditions of restraint.

EXPERIMENT 2: EFFECT OF DOSE LEVEL ON THE T_c RESPONSE EVOKED BY MORPHINE AND HEROIN IN THE FREE–MOVING AND RESTRAINED RAT

METHOD

To determine the dose-response relationship between changes in T_c for both M and H, each drug was administered at three dose levels to both the free-moving and the restrained rat. M was administered IP in doses of 5, 15 and 30 mg/kg. The more potent opiate, H, was administered IP in doses of 0.1, 1 and 5 mg/kg. Each drug was dissolved in a solution of sterile 0.9% saline and the concentration of drug was adjusted so that 1.0 ml/kg was the volume of injection at each dose level.

Restrained Animals

Each dose of M and H was administered to 10 drug-naive animals. As a control, 11 other animals were placed in the restraint tube and their temperature was recorded for a 7-hr period but they were given no drug. Of the control animals, 5 were administered the 0.9% saline solution as an injected control and 6 others were given no injections at all as a simple restraint control. Since the T_c records from these two control groups were similar, the data were combined and are reported as one control group containing 11 animals. Overall, 71 animals were used in the restraint experiments.

Free-Moving Animals

Since the data from Experiment 1 indicated that the repeated injection of M did not appreciably alter the T_c response of the free-moving rat, each of 12 animals prepared with an implanted thermistor was scheduled to receive each dose of M and H. To control for the slight order effect observed in Experiment 1, the order in which the dose of each drug was administered to each animal was determined by a Latin square design. Consecutive drug injections in each animal were separated by an interval of at

least 3 days. Although 12 animals were prepared for this portion of the experiment, the implanted thermistor did not remain intact in all animals for the completion of all six drug injections. As a result, M was administered at each dose to 8 animals and H was administered to 11 animals. A total of 10 saline control injections was performed.

Statistics

Once again, the deviations from baseline T_c formed the raw data for the statistical analyses. The deviation scores observed after each drug administration were compared with those obtained following the control animals at half-hour intervals from the time of injection using the Mann-Whitney U test. The drug responses of the free-moving animals were compared with the free-moving animal control responses. The restrained animals drug responses were compared with the restrained animal control responses.

RESULTS AND DISCUSSION

Restrained Animals

Morphine injections. Following the 30 mg/kg dose of M, a marked hypothermia was observed which reached a mean maximum depth of 4.5 ± 1.0°C below the baseline level. As indicated in Fig. 2, the drop in T_c was significantly below the control response from 30 min following the injection until at least 330 min later. A significant drop in T_c was measured for 90 min after the 15 mg/kg dose of M which reached a mean maximum depth of 1.4 ± 0.4°C below the baseline. However, a significant rebound hyperthermia occurred during the period from 270 to 300 min after the injection. The lowest dose of M elicited a short-lived hypothermia lasting 30 min. The T_c subsequently returned to baseline and continued to rise to become a statistically significant hyperthermia from 120 to 300 min after the injection. The mean baseline T_c for the 41 animals used in this experiment was 36.8 ± 0.1°C.

Heroin injections. Once again, the highest dose of the opiate evoked a dramatic fall in T_c. The 5 mg/kg dose of H elicited a significant fall in the mean T_c from 60 to 180 min after the injection as shown in Fig. 3. At the 0.1 mg/kg dose level, H had no significant effect on the T_c of the restrained rat. However, at the 1 mg/kg dose level, a significant rise in the mean T_c response was noted from 30 to 90 min after the injection. The mean baseline T_c for the 30 animals restrained and administered H in these experiments was 36.8 ± 0.1°C. Of the 10 restrained animals given the highest dose of H, 1 animal actually exhibited an increase in T_c of 1.3°C. One other animal showed almost no change from baseline at this dose level. Nonetheless, the maximum mean drop in T_c was 3.1 ± 0.7°C. The saline control data depicted in Fig. 3 are the same as those depicted in Fig. 2.

Free-Moving Animals

Morphine injections. The duration of the pyrexia induced by M in the free-moving rat was dose-dependent. The curves shown in Fig. 4 depict the mean deviation from baseline T_c for the 8 animals receiving each of the doses of the drug and for the 10 saline-injected control rats. The maximum mean rise in temperature following each dose level was: 1.6 ± 0.3°C; 2.2 ± 0.2°C; and 1.8 ± 0.2°C for the

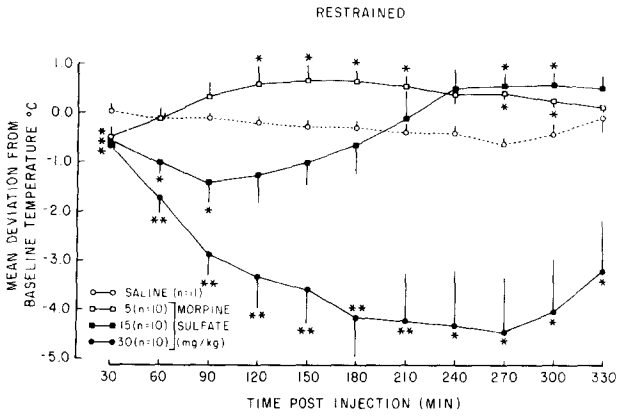

FIG. 2. The mean changes in T_c (+ or − SEM) evoked by the injection of M (IP) at the indicated dose levels in the restrained rat. The asterisks denote a statistically different response than that of the control group at the $p<0.05$ (*) or $p<0.01$ (**) levels of significance using the Mann-Whitney U test.

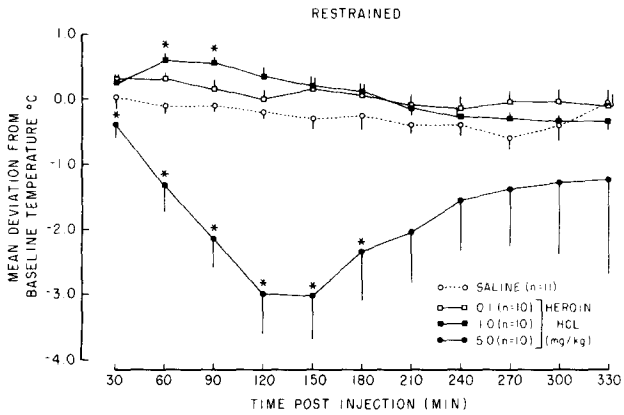

FIG. 3. The mean changes in T_c (+ or − SEM) following the injection of the indicated dose of H in the restrained rat. The asterisks denote statistical difference from the control response as previously noted.

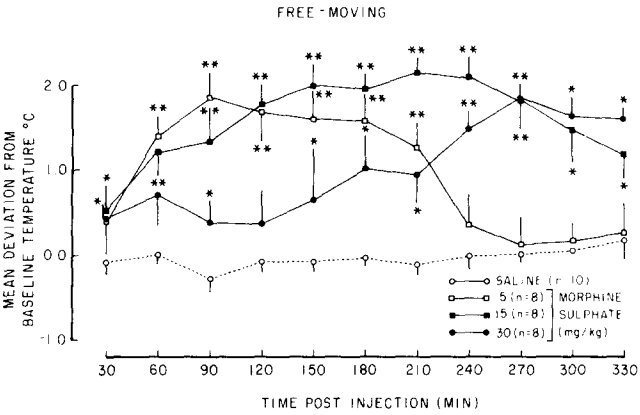

FIG. 4. The mean changes in T_c (+ or − SEM) evoked by the injection of M (IP) in the indicated doses in the free-moving rat. The asterisks denote a statistical significance from the control at the levels indicated in previous figures.

5, 15 and 30 mg/kg doses, respectively. A statistically significant hyperthermic response was observed during the periods: (1) 60 to 210 min after the 5 mg/kg injection; (2) 30 to 330 min after the 15 mg/kg injection; and (3) at 30 and 90 min after, and from 150 to 330 min following the 30 mg/kg injection. The hyperthermia following the highest dose of the drug required the longest time to evolve, but it lasted the longest. Although not shown in Fig. 4, the significant hyperthermia persisted to 450 min following the injection of the 30 mg/kg dose of M. As shown in Fig. 4, the fever lasted about 210 min following the lowest dose of the drug, but had not yet returned to normal at the end of the 330-min period following the two higher doses of M. The mean starting baseline T_c based on 34 experiments done on 10 animals was 36.9 ± 0.1°C.

Following the 30 mg/kg injection of M, a transient hypothermia was observed in 2 of the 8 free-moving animals. This slight tendency to a hypothermic response was markedly different than the prolonged deep hypothermia observed in the restrained animal, since the hypothermia in the free-moving animals was of short duration and was followed by a vigorous hyperthermia. No single instance of a significant long-lasting hypothermia was noted in the free-moving rat.

Heroin injections. Similar to the response elicited by M in the free-moving rat, T_c rose in a dose-related fashion following the IP injections of H. The mean deviations from baseline T_c following each dose level of the drug are depicted in Fig. 5. The mean starting baseline T_c for the 33 drug injections, derived from 11 animals, was 36.6 ± 0.1°C. The saline control data are the same as those depicted in Fig. 4. No hypothermic episode was observed following any dose of H in the free-moving animals. The 1 mg/kg dose of H induced the fastest rise in T_c, but a longer time was required for the subsidence of the fever elicited by the 5 mg/kg dose. The maximum mean alterations in T_c after the H injections were +0.7 ± 0.2°C, +1.7 ± 0.2°C and +1.5 ± 0.5°C for the 3 increasing doses. In marked contrast, the same doses of H evoked the following mean maximum changes in T_c in the restrained rat: +0.3 ± 0.1°C; +0.6 ± 0.1°C and −3.1 ± 0.7°C, respectively, for the increasing doses of H.

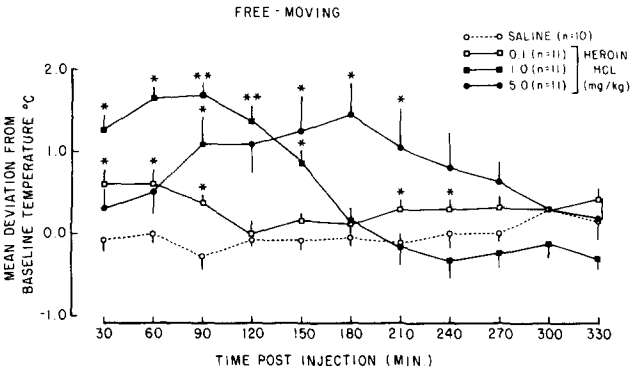

FIG. 5. The mean changes in T_c (+ or − SEM) evoked by the injection of H (IP) in the indicated doses in the free-moving rat. An asterisk denotes statistical difference from the control response at the levels noted in the previous figures.

The T_c rose significantly above the saline-injected control T_c during the periods: (1) 30 to 90 min after the 0.1 mg/kg injection; (2) 30 to 150 min after the 1 mg/kg injection, and (3) 90 to 210 min after the 5 mg/kg injection. As seen with M, the rise in T_c following the lower doses of H was higher in the free-moving than in the restrained rat. Furthermore, whereas fever was evoked by the high dose of H in the free-moving rat, the same dose of H elicited a fall in T_c in the restrained rat. It seems that by restraining the rat in the plastic holder, the pyrexic effects of H are somehow attenuated.

Neither M nor H exerted an obvious effect on the food intake pattern of the free-moving rat for the 7 hr period following drug administration. The period of T_c measurement ranged from 0800 to 1900 which corresponds to the daylight hours during which the rat normally consumes very little food. Hence, the possibility exists that food intake may have been depressed during this period, but it was difficult to detect such a difference since the baseline for comparison was so low. The effect of the opiates on T_c did not seem to be mediated via any activity related to feeding.

EXPERIMENT 3: PHARMACOLOGICAL ANTAGONISM OF THE EFFECT OF THE OPIATES ON T_c

METHOD

In this experiment, 8 restrained and 3 free-moving animals were used. All animals were drug-naive. In a group of 4 restrained animals, naloxone hydrochloride (5 mg/kg) was administered IP 10 min prior to the injection of M (30 mg/kg IP). In a second group of 4 restrained rats, naloxone hydrochloride was injected in a similar dose 10 min prior to the injection of H (5 mg/kg IP). Deviations from baseline T_c were computed as described above. The mean group T_c response was compared statistically with either the mean response evoked by the 30 mg/kg injection of M or that induced by the 5 mg/kg injection of H both of which were recorded in the restrained rat in Experiment 2.

In the 3 free-moving rats, 30 mg/kg of M was first administered alone. Three days later, following pretreatment with 5 mg/kg of naloxone 10 min earlier, the 30 mg/kg dose of M was readministered. When this dose of naloxone proved to be only partially effective in antagonizing the effect of M, the experiment was repeated 2 days later in the same 3 animals. On the third test day, each animal was again pretreated with naloxone (5 mg/kg IP) 10 min before the administration of M (30 mg/kg). However, when the antagonistic action of this dose of naloxone diminished, as indicated by the beginning of a pyrexic response, a second equipotent injection of naloxone was administered. In the free-moving animal, the T_c responses at the half-hour intervals after the injection of M alone were compared with the deviations from baseline T_c observed following the pretreatment with the opiate antagonist using the Mann-Whitney U test. The doses of naloxone utilized in this experiment have been shown to exert no effect on the T_c of the rat [4].

RESULTS AND DISCUSSION

Naloxone (5 mg/kg) completely prevented the hypothermia normally evoked the IP administration of either M or H to the restrained rat as shown in Fig. 6. When

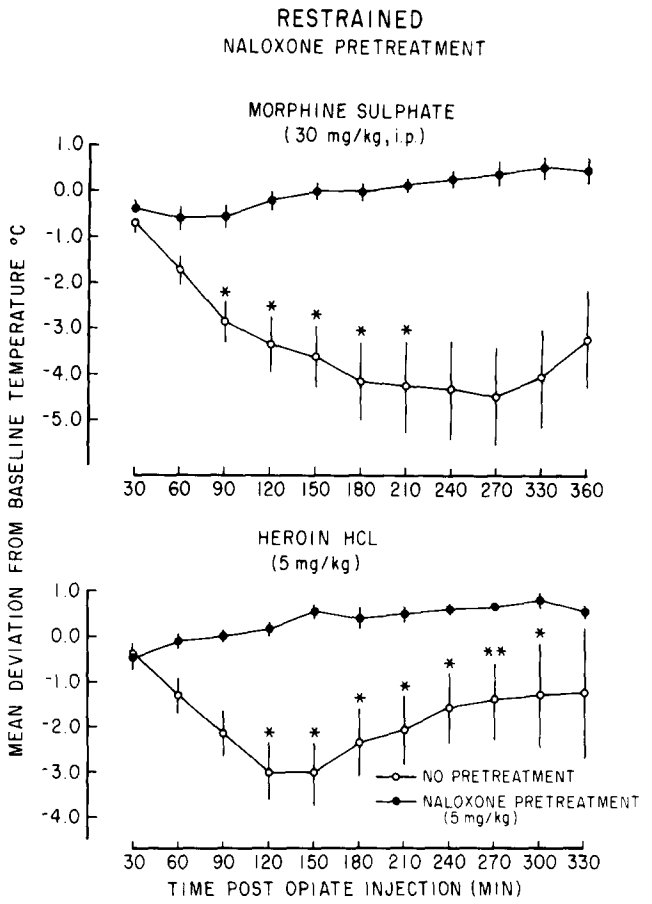

FIG. 6. The effect of naloxone pretreatment (5 mg/kg IP) 10 min prior to the injection of either M (30 mg/kg) or H (5 mg/kg) in the restrained rat. Each opiate antagonist was administered to 4 animals and the mean T_c responses (+ SEM) were compared with the mean T_cs recorded from the restrained rats which received either M (n = 10) or H (n = 10) in Experiment 2. The asterisks denote the levels of significance as in the previous figures.

compared with the drops in T_c recorded in Experiment 2, the drop in T_c was significantly greater in the animals which received no naloxone pretreatment as indicated in Fig. 6. When the M or H was preceded by pretreatment with the opiate antagonist, the mean T_c did not drastically change from its baseline level in the restrained rat. The mean baseline T_c for naloxone-pretreated rats which then received M was 37.1 ± 0.2°C; for those that received H it was 37.4 ± 0.1°C. The mean baseline T_c for the respective control groups were 36.5 ± 0.3°C and 36.6 ± 0.3°C.

In the free-moving animal, naloxone also blocked the T_c altering effect of M as shown in Fig. 7. Pretreatment with 5 mg/kg of naloxone antagonized the effect of M at the 60- and 90-min readings. However, the T_c began to increase after 90 min until it became similar to and then actually surpassed the fever evoked following the first injection of M. Nonetheless, when these free-moving rats were pretreated again with naloxone, and then administered a second dose of the opiate antagonist 120 min after the injection of M, the pyrexic response was blocked. The mean T_c response of the three rats was significantly below the pyrexic response evoked following the first injection of M

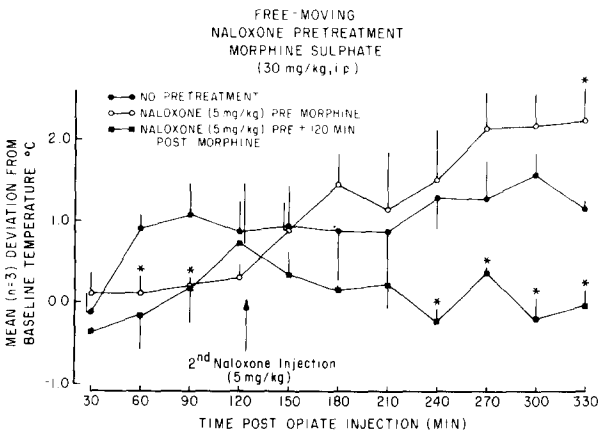

FIG. 7. The mean T_c responses of 3 free-moving rats given three injections of M, administered at 48-hr intervals. Naloxone hydrochloride (5 mg/kg) was administered 10 min prior to the second injection of M (———o———). Before the third injection of M (———■———), a pretreatment with naloxone was administered and a second injection of the opiate antagonist was administered at the time indicated by the arrow. The asterisks signify a statistical significance in the T_c response when compared to the first injection of M.

during the period from 240 to 330 min after the injection of M. The mean baseline T_c recorded prior to each M injection were: 36.8 ± 0.1°C, 36.5 ± 0.3°C, and 36.6 ± 0.1°C. The greater dose of naloxone may have been required in these free-moving animals because of the small tendency for the T_c to increase slightly more with the repeated injections of M.

GENERAL DISCUSSION

Restraint dramatically altered the direction of the change in T_c elicited from the rat following the IP administration of 30 mg/kg of M as shown in the first experiment. The hypothermia which this dose of M evokes in the restrained animal disappears when the injection of M is repeated. As a result, a hyperthermia, somewhat similar to that evoked in the free-moving animal, results after a third administration of the compound to the restrained animal. Furthermore, it seems that the reversal of M's effect on the restrained rat's T_c seems to be due to tolerance to the drug's effect. Similar data have been reported by Lotti *et al.* [14] regarding tolerance to the drug's hypothermic action. However, these data demonstrate for the first time that restraint can alter the direction of the animal's T_c response to M. With repeated injections, however, the restraint effect seems to diminish as shown in Experiment 1.

The second experiment indicated that restraint may attenuate the hyperthermic responses induced in the rat by doses of M lower than 30 mg/kg. Furthermore, the findings with regard to restraint's influence on T_c were extended to the more potent opiate, heroin. At a high dose of H, the restrained rat exhibited a drop in T_c whereas the free-moving animal developed a fever. The 5 mg/kg dose of H has previously been reported to evoke pyrexia in the free-moving rat [20]. The dampening effect of restraint on the pyrexia elicited by the lower doses of H was analogous

to that exerted on M-induced pyrexia. Hence, the restraint effect is not restricted to M, but may apply to other opiates and drugs as well.

The naloxone blockade of the hypothermia elicited by M or H demonstrates that the drop in T_c is a specific narcotic effect. We can only speculate as to the specific cause of the diminution of pyrexia caused by restraint at the lower doses of the opiates, and the reversal of pyrexia resulting in a deep hypothermia in the restrained rat after greater doses of M. Perhaps M's effect is exerted via an arousal mechanism or by interacting with restraint stress [9] rather than via a specific effect on thermoregulatory processes. M, at doses greater than 30 mg/kg, causes hypothermia even in free-moving animals [6,8]. This may be due to the general depressive effects of M on all physiological processes at high doses. With repeated injections, tolerance to these depressive effects may occur. On the other hand, M can produce excitation and increased motor activity at lower doses which might lead to an increase in T_c [1,17]. We are presently testing the hypothesis that the changes in T_c may be due to changes in activity levels in our laboratory.

In summary, by restraining the rat, the thermal response to the IP administration of M and H was markedly altered. Although the physiological mechanisms whereby this effect is exerted remain to be elucidated, it is clear that the degree of restraint must be controlled and should be considered as an important variable in studies of thermoregulation in the rat.

ACKNOWLEDGEMENTS

A preliminary report of these data was presented at the Meeting of the Federation of American Societies for Experimental Biology at Anaheim, California, in April 1976. G.E. Martin was a Research Associate of the National Research Council. His present address is Merck Institute for Therapeutic Research, West Point, PA 19486. N. H. Spector's present address is National Science Foundation, 1800 G. Street, N.W., Washington, D. C. 10006. In conducting this research, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," DHEW Publication No. (NIH) 73–23 as prepared by the Institute of Laboratory Animal Resources, National Research Council.

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