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Effect on Core Temperature of Restraint after Peripherally and Centrally Injected Morphine in the Sprague-Dawley Rat

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MARTIN, G. E. AND N. L. PAPP. *Effect on core temperature of restraint after peripherally and centrally injected morphine in the Sprague-Dawley rat.* PHARMAC. BIOCHEM. BEHAV. 10(2) 313–315, 1979.—The changes in core temperature (T_c) evoked by morphine in the Sprague-Dawley rat were altered by restraining the rat. The T_c of the free-moving rat rose after the IP (5, 15, 30, 60 mg/kg) or intracerebral injection (10, 20, 50 μg) of morphine. In the restrained rat, however, identical doses of morphine evoked either a hyperthermia of lesser magnitude than in the free-moving rat or a drop in T_c. These findings reemphasize the importance of restraint in determinating the action of morphine on T_c and extend the finding to the Sprague-Dawley rat.

Morphine Sprague-Dawley strain Body temperature Restraint

THE ACTION of parenterally administered morphine on the core temperature (T_c) of the Wistar-derived rat can be altered by restraining the animal in a plastic holder during the extent of the drug's action [6]. As originally suggested by Myers [8], the restraint may interfere in some way with morphine's action on T_c. More recently, restraining the rat has been shown to attenuate the hyperthermic action of intrahypothalamically administered morphine in both the Wistar and Holtzman strains [5,10]. These findings are important in interpreting the physiological mechanism underlying the hypothermia observed following the intrahypothalamic or parenteral administration of morphine in the restrained Sprague-Dawley rat (see [3] for review). Since threshold differences exist between strains of mice for the analgesic and toxic actions of morphine [2] and since much of the previous work on this opiate and T_c was done using the Sprague-Dawley strain, it was crucial to determine whether restraint would modulate the T_c altering action of morphine in this strain. In the present experiment the T_c of the restrained or free-moving Sprague-Dawley rat was measured after morphine was administered either intracerebrally or parenterally.

METHOD

Male Sprague-Dawley rats (Blue Spruce Farms, Altamount, NY) weighing between 250–400 g were used.

Morphine sulfate (Merck Sharp and Dohme), dissolved in saline (0.9%), was administered (IP) in doses of 5, 15, 30 and 60 mg/kg. Each dose of M and the vehicle was given to 10 restrained and 10 free-moving rats. The concentration of morphine was adjusted so that a volume of 1.0 ml/kg was injected in each rat. All injections were made between 0900 and 1000 hr with the ambient temperature at 21–24°C. T_c was recorded for 6 hr after injection in the restrained rat as previously described [6]. All temperature readings were expressed as deviations from baseline T_c defined as the mean of three T_c readings taken 60 min, 30 min and immediately before the injections. In the free-moving rat, T_c was measured by inserting a YSI thermistor probe 6.5 cm into the rectum at selected time intervals.

Using methods and stereotaxic coordinates reported previously [5], a single 24 ga microinjection guide cannula was chronically implanted above a site in the preoptic or anterior hypothalamic (PoAH) in each of 24 rats. The T_c was measured as following the IP injections. Morphine, dissolved in an artificial CSF [7], was administered in doses of 10, 20 and 50 μg to 6 rats at each dose level. In addition, 0.5 μl of CSF was administered as a control to rats in each condition of restraint. The 50 μg dose level was administered in a volume of 1.0 μl, whereas all the other injections (n=6) were given in a volume of 0.5 μl. All microinjections were administered slowly by hand.

Each animal was given two microinjections, one during restraint in a plastic holder and one when the rat was free-moving. The two injections were separated by an interval of at least one week and the order in which the animals were either free-moving or restrained was counter balanced.

The deviations from baseline T_c associated with each rat formed the basic data for the statistical analysis. The changes from baseline T_c in the free-moving and restrained rats were compared using the Mann-Whitney U test ($p<0.05$).

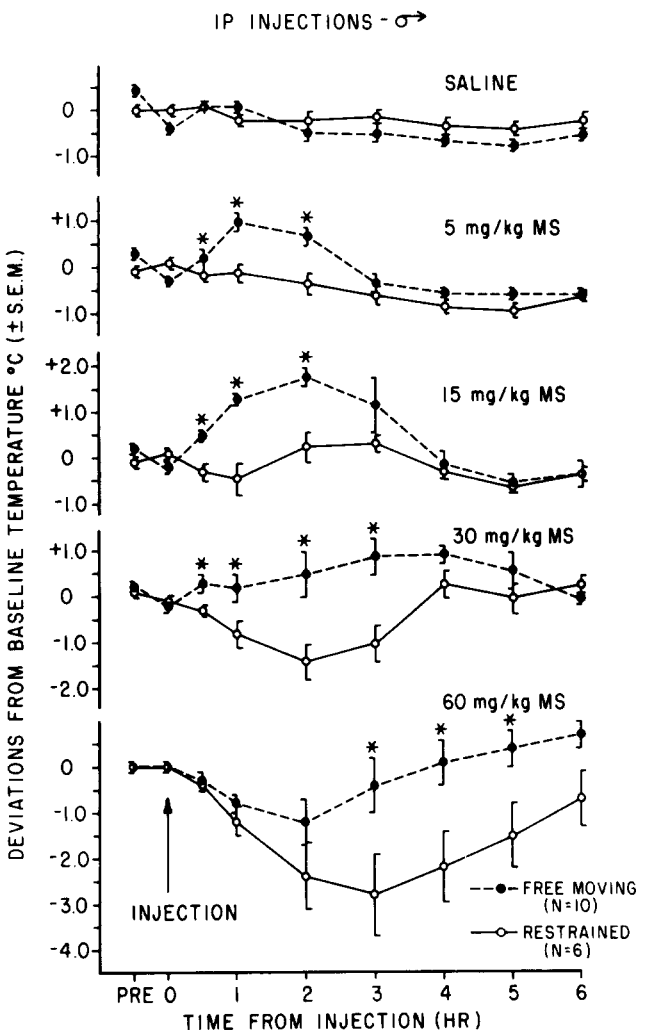

FIG. 1. The mean deviations from baseline temperature (± S.E.M.) following the intraperitoneal (IP) injection of morphine in the free-moving (- - - - ● - - - -) or restrained (———○———) rat. The asterisk (*) denotes a significant difference ($p<0.05$) between the two groups using the Mann-Whitney U test. The mean baseline T_c for the restrained rats was 37.0 ± 0.6°C (± S.D., n=30) and 37.5 ± 0.3°C (n=60) for the free-moving rats.

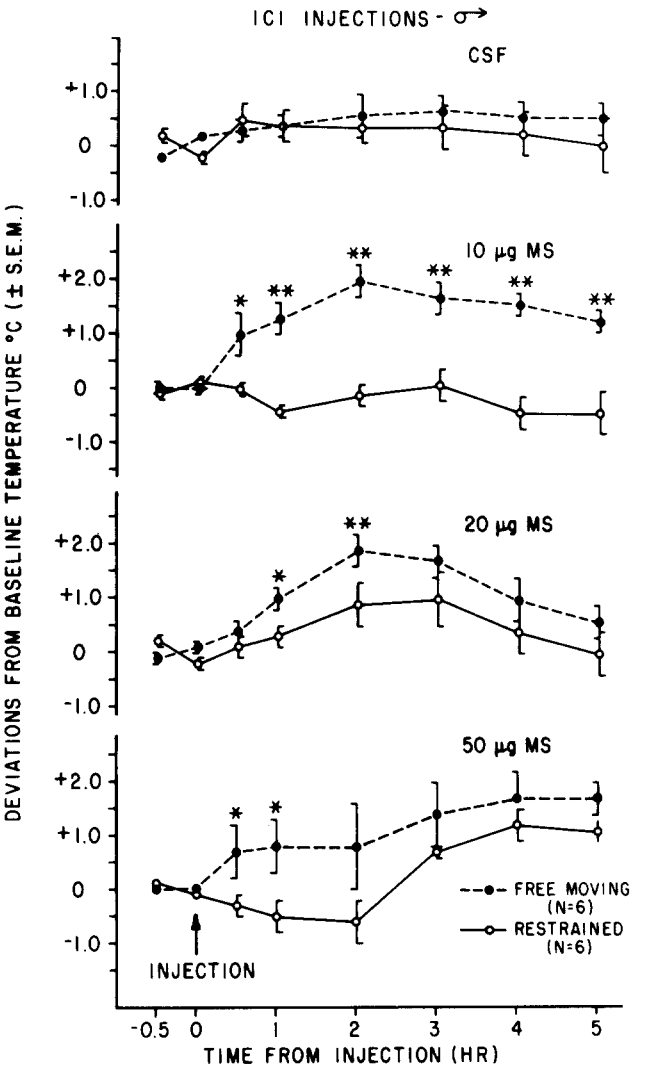

FIG. 2. The mean deviations from baseline T_c (± S.E.M.) observed following the intracranial (IC) microinjection of morphine in the indicated doses. The mean baseline T_c for the free-moving rats was 37.8 ± 0.4°C (± S.D., n=24) and 38.2 ± 0.7°C (n=24) for the restrained rats. The asterisks denote a significant difference between the two groups using the Mann-Whitney U test (*$p<0.05$; **$p<0.02$)

RESULTS

In the free-moving rat mild hyperthermic responses were elicited from the 5, 15 and 30 mg/kg injections of morphine, whereas a short-lived drop in T_c occurred after the 60 mg/kg dose. In the restrained rat, little or no change in T_c occurred after the 5 and 15 mg/kg injections, but a drop in T_c occurred after the 30 and 60 mg/kg injections. As shown in Fig. 1, there were statistically significant differences in the changes in T_c evoked by morphine between the free-moving and restrained rat after each dose of M. The saline injection exerted no marked effect on the T_c of either group.

The direct intracranial microinjection of morphine evoked an increase in T_c in the free-moving rats which, after each dose of the drug, rose significantly greater than the T_c of the restrained animal after the morphine injection as shown in Fig. 2. The anatomical location of the microinjection sites is depicted in Fig. 3. The difference between the free-moving and the restrained rats was most marked following the 10 μg injection, whereas there was no significant difference between the two groups in the T_c response following the microinjection of the CSF. The only drop in T_c occurred for 2 hr following the 50 μg injection of morphine in the restrained rat. At three hr after this injection, however, the response had changed into a slight increase in T_c above the baseline level.

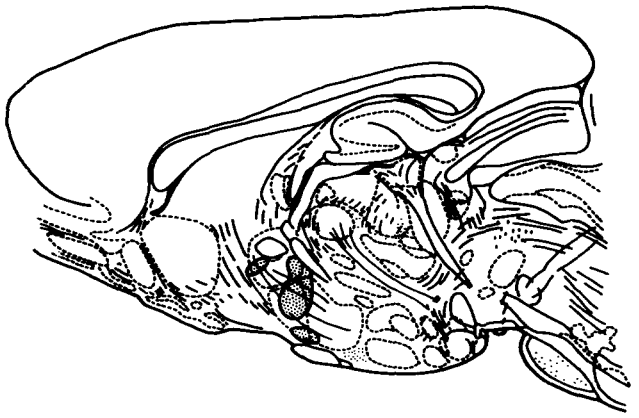

FIG. 3. The region in the forebrain at which the microinjections of morphine were made is depicted by the stipples.

DISCUSSION

The changes in T_c evoked by morphine in the Sprague-Dawley rat can be altered by restraining the animal. Specifically, the increase in T_c following low doses of the opiate are attenuated when the rat is restrained in a plastic holder, and the drop in T_c elicited by the larger doses of morphine is greater in duration or magnitude when the animal is restrained. This is true whether morphine is given peripherally or directly into the brain.

No significant fall in T_c was observed in the free-moving rat following the central microinjection of 50 μg morphine in agreement with previous reports for free-moving Wistar rats [5,9]. On the other hand, the drop in T_c observed following the 50 μg injection of morphine in the restrained Sprague-Dawley rat was not as marked as that previously reported by Lotti *et al.* [4]. It is not possible to explain this discrepancy on the basis of the anatomical loci of the microinjections nor on the ambient temperature since both factors were similar in the two studies. Perhaps, the restraint exerted in the earlier experiments [4] was more restrictive than in the present tests. In this regard, slight changes in restraint cage design have been shown to alter morphine's toxicity [11].

Paolino and Bernard [9] failed to elicit a significant drop in T_c when 50 mg/kg of morphine was administered IP to the free moving Wistar rat. Similarly, 60 mg/kg elicited only a short drop followed by a prolonged but mild increase in T_c in free-moving rats in a thermoneutral environment in this experiment. These results are in direct contrast to those reported for the restrained Sprague-Dawley rat by Lotti *et al.* [4]. In the restrained rat, Lotti *et al.* reported significant drops in T_c using doses as low as 15 mg/kg IV. The different routes of administration as well as the degree of restraint may have caused the observed differences in the T_c responses.

The rise in T_c observed following the injection of low doses of morphine may be linked to the increased motor activity evoked by this drug [1]. Restraint could have attenuated the rise in T_c by preventing this motor activity. The drop in T_c evoked by the higher doses of morphine may be due to a non-specific depression of all physiological functions caused by the opiate [8]. Whatever morphine's mechanism of action might be, these results reemphasize the importance of controlling for restraint in experiments in which an opiate's action on the rat's T_c is measured.

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