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Components of the Opioid Withdrawal Syndrome in Mice Are Thermoregulatory Responses

J. K. BELKNAP[1]

Research Service (151W), VA Medical Center, and Department of Medical Psychology
Oregon Health Sciences University, Portland, OR 97201
and Departments of Pharmacology and Neuroscience, University of North Dakota, Grand Forks, ND 58202

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BELKNAP, J. K. *Components of the opioid withdrawal syndrome in mice are thermoregulatory responses.* PHARMACOL BIOCHEM BEHAV **34**(2) 241–245, 1989.—C57BL/6J mice were rendered physically dependent on morphine by giving them ad lib access to a drinking fluid containing 0.2% saccharin and morphine for 14 days at 20–22°C. Core body temperatures were monitored by radio telemetry, which obviated the need for restraint, handling, or otherwise disturbing the animals. Consistent hyperthermia was present throughout the morphine intoxication phase, followed by hypothermia after the withdrawal syndrome had been precipitated by naloxone challenge (2.0 mg/kg, IP) at 22.5°C. The hypothermia could be blocked by exposing the animals to a 34.5°C ambient temperature, which also prevented the occurrence of tremor and "wet dog shakes." In contrast, the other withdrawal signs monitored were not significantly affected. In a second experiment, mice were given the same morphine-saccharin drinking fluid as before, except that a choice was provided between two interconnected home cages (23°C vs. 35°C) throughout the experiment. A marked preference for the 35°C cage was seen during intoxication, which served to enhance the hyperthermia due to morphine. Following withdrawal, when hypothermia is evident, the preference for the 35°C cage declined to control levels. These results suggest that hypothermia is both a consequence and a contributor to the opioid withdrawal syndrome.

Thermoregulation Morphine Opioids C57BL/6J mice Withdrawal syndrome Physical dependence
Body temperature by radio telemetry Hypothermia

MORPHINE and other opioids have long been known to cause thermoregulatory dysfunctions under acute dose conditions, and also following opioid withdrawal in physically dependent organisms, however, the pattern of effects appears to be complex (1, 4–6, 10). After acute administration of morphine to rats, hyperthermia is often seen after small doses, especially when no restraint is used, while hypothermia frequently develops after larger doses, or when the animals are under restraint [reviewed in (1, 4–6)]. Morphine-induced hyperthermia in rats appears to involve thermogenesis due to increased skeletal muscle activity (15), while hypothermia appears to involve decreases in aerobic metabolism (11). When hypothermia results, it is enhanced at low ambient temperatures and is eliminated by higher ones, leading to the suggestion that morphine-induced hypothermia is more related to impairment of thermoregulatory control (poikilothermia) than to changes in set point of the "central thermostat" in rats. In contrast, when hyperthermia is seen due to small, acute doses of morphine, changes in ambient temperature have relatively little effect, suggesting that set point is altered in an upward direction with little or no impairment of thermoregulatory control [reviewed in (4,5)]. With chronic administration by means of morphine pellet implants, hyperthermia is typically seen in rats during the intoxication phase, while hypothermia rapidly develops when these physically dependent animals are challenged with naloxone (2,7).

Studies using the laboratory mouse are scant compared to the rat, but the available data suggest considerable similarity between these two rodent species. Like the rat, small acute doses cause hyperthermia in mice, and larger doses cause hypothermia. These changes are highly ambient temperature-dependent in CD-1 mice (17), perhaps to a greater extent than in rats. Chronic morphine administration by serial IP injections resulted in initial hypothermia after each injection, which was gradually replaced by hyperthermia over several weeks of twice-daily treatment at 20°C or 25°C (18). Roughly similar results have been reported in the rat (16,21).

Behavior is an important aspect of thermoregulation, as well as a useful tool in assessing the mechanisms underlying drug-induced changes in thermoregulation. For example, if the behavior of the organism acts to change body temperature in the same direction as a drug-induced change, this often implies a drug-induced change in set point, and behavior would then be one of several mecha-

[1]Requests for reprints should be addressed to Dr. J. K. Belknap, Research Service (151W), VA Medical Center, Portland, OR 97201.

nisms brought into play to change body temperature toward the new set point. Should the opposite occur, namely that behavior acts to oppose a drug-induced change in body temperature, then drug-induced changes in heat gain or heat loss mechanisms are likely to be the dominant mechanism rather than changes in set point (4,8). For example, morphine pellet-implanted rats show persistent hyperthermia. At these times, the animals show a reduced avoidance of a usually noxious radiant heat source, which serves to enhance the hyperthermia due to morphine. An upward setting of the set point is thus indicated (2,7). However, when these physically dependent rats were challenged with naloxone, a fall in body temperature was seen as the withdrawal syndrome developed. At this time, the rats more strongly avoided the radiant heat source compared to controls, thus their behavior served to enhance the naloxone-precipitated hypothermia, indicating a change in set point as the primary effect of precipitated abstinence (2,7).

The purpose of the present studies was to assess thermoregulatory dysfunctions as a result of chronic morphine exposure in the C57BL/6J inbred mouse, and to explore the possibility advanced by Wei *et al.* (22) that some of the withdrawal signs are thermoregulatory in origin. These investigators noted that some of the morphine withdrawal signs are similar to thermoregulatory behavior in rats and in man. They hypothesized that changes in the "error signal" following chronic morphine exposure in rats may account for the appearance of some of the withdrawal signs such as "wet dog shakes" and escape jumping. Morphine pellet-implanted rats challenged with naloxone showed a high incidence of wet dog shakes at low ambient temperatures (6–10°C), while this behavior was completely suppressed at high ambient temperatures (34–37°C). In contrast, escape jumping following naloxone administration was most frequent at the high ambient temperature, and was much reduced at the low temperature. These workers hypothesized that wet dog shakes and escape jumping are normal response to abnormally low or high ambient temperatures, respectively, and precipitated withdrawal simply altered the threshold at which these behaviors would occur.

METHOD

Experiment 1

Eight C57BL/6J male mice, 5 months old, were made physically dependent on morphine by a modification of the method of Horowitz (9). A control group of the same strain (N = 8) was treated identically except that no morphine was administered. These animals were originally obtained from the Jackson Laboratories, Bar Harbor, ME. An aqueous 0.2% saccharin solution, containing varying concentrations of morphine sulfate, was given as the sole fluid source. The morphine sulfate concentration was 0.3 mg/ml on days 0–4, 0.5 mg/ml on days 5–10, and 0.75 mg/ml on days 11–14. This inbred strain readily consumes very large (and sometimes lethal) amounts of morphine with this procedure, which is not the case with most other inbred strains (9).

Core body temperature was monitored by radio telemetry (3) in all of the animals at zero to one hour after light onset. A surgically implanted AM band transmitter housed with a thermistor (Minimitter models X and XL, Sun River, OR) allowed core body temperature to be monitored in each animal without handling, restraining or disturbing the animals. Ambient temperature throughout these experiments was maintained at 20–22°C except where noted.

At the time of light onset on Day 12 of the intoxication phase, and again on Day 14, both control and morphine-treated mice were challenged with a 2.0 mg/kg IP dose of naloxone HCl. Following the injection, half of the animals were promptly taken to one of two "walk-in" chambers, one at 22.5°C and the other at 34.5°C. These animals were monitored for the presence or absence of withdrawal signs at 5-min intervals beginning at 10 min after injection, and continuing for five more observations. Following the last observation at 35 min after injection, the animals were returned to their home cages (room temperature) and the appropriate drinking fluid given as before. Two days later, the above procedure was repeated following a second naloxone challenge, except that the animals previously exposed to one temperature (either 22.5 or 34.5°C) were now exposed to the other temperature condition. Thus, each animal was challenged twice with naloxone two days apart, and promptly exposed to each of the two ambient temperatures for 35 min.

Scoring for withdrawal signs was accomplished by placing each mouse on a small platform (10 × 10 cm) suspended 32 cm above a table top, and observing it for a one-min period. The presence or absence of the following withdrawal signs was recorded: tremor, gross tremulousness of the entire body; diarrhea, watery stools; jumping, leaping off the small platform; lacrimation, teary eyes. If an animal jumped, it was returned to the platform for the remainder of that one min observation period. The suspended platform virtually eliminated any jumping seen in control mice. Body temperature was monitored 10 min prior to injection and again just prior to the 20-minute postinjection test period, when hypothermia is close to its peak based on pilot work in our laboratory. While it is possible that the differing ambient temperatures caused significant differences in the disposition of naloxone, we consider this to be unlikely, since Wei *et al.* (22) found no difference in brain naloxone concentrations in rats as a result of even larger ambient temperature differences than used in the present study.

Experiment 2

Separate groups of morphine-treated C57BL/6J mice (N = 8) were chronically treated with morphine as in Experiment 1, except that they were continuously allowed a choice between two interconnecting home cages, one maintained at 23°C and the other at 35°C. The warmer temperature was maintained by an infrared lamp. The rod dominated retina of mice is virtually insensitive to red and infrared light. A group of control mice (N = 8) without access to morphine was run concurrently. Food and fluids were given as in Experiment 1, and were freely provided in both cages (morphine in the morphine group; only the vehicle for the controls). A 6 cm length of 5 cm i.d. plastic tubing interconnected the two standard Maryland Plastics shoebox mouse cages, as described previously (3). Morphine consumption in the morphine group was similar to that seen in Experiment 1. Mean daily consumption averaged 82 mg/kg for Days 0–4, 152 mg/kg on Days 5–10, and 245 mg/kg on Days 11–14 of the intoxication phase. Since these mice did not have telemetry implants, rectal probe measurements (20 mm depth) were made at 3 hr after light onset on the last day of intoxication, and again 24 hours later at 10 hr after withdrawal. Withdrawal-induced hypothermia without naloxone is close to its maximum at this time (unpublished observations). Body temperatures were taken 5–8 min after removing each mouse from its home cage (22°C ambient).

On days 3, 8, 11 and 13 of the intoxication phase, and on the first day after morphine withdrawal, the cage in which the animal was found was recorded one hour after light onset, and again at hourly intervals for two more observations (intoxication) or three more observations (withdrawal). The vast majority of mice (80–90%) were found to be asleep at these times, thus ambient temperature preference primarily reflects sleeping site preference in these studies. Following each observation day, the cages were cleaned and the position of the infrared lamp was alternated to

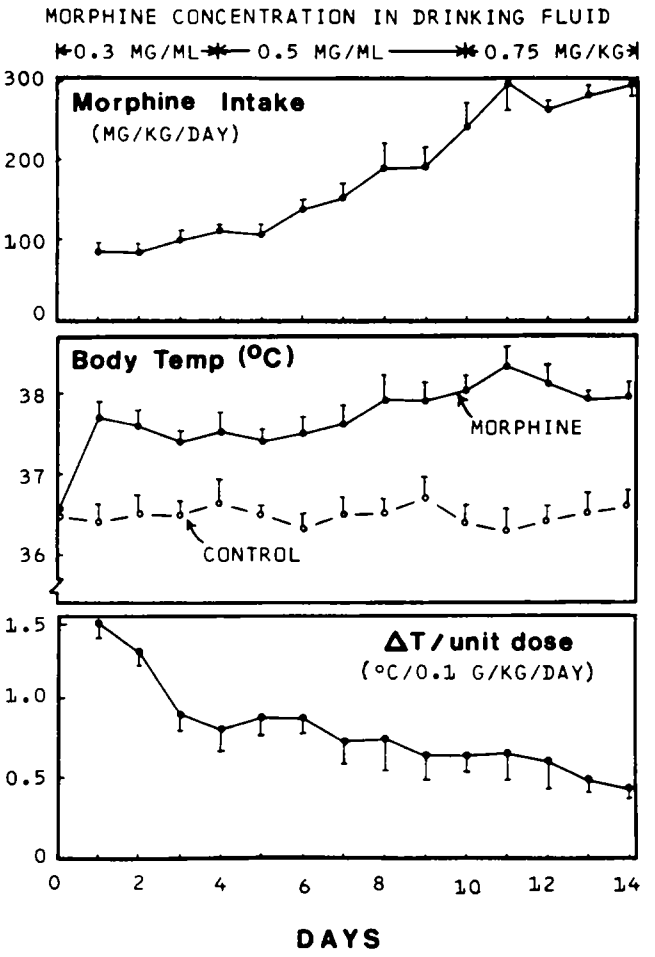

FIG. 1. Morphine sulfate intake (mg/kg/day) and body temperatures (°C) monitored by radio telemetry during the 14-day intoxication phase (Experiment 1). Morphine sulfate was administered to eight mice in the drinking fluid (0.2% saccharin) in the escalating concentrations shown at the top of the figure. The controls (N = 8) were given equivalent volumes of the saccharin fluid alone (mean of 11 ml/day). All animals had thermistor implants (Mini-mitter model X and XL), which allowed the determination of body temperature without handling or disturbing the animals. The change in body temperature (relative to controls) per unit morphine dose is also shown in the lower panel, which serves as an index of tolerance development.

prevent position preference effects.

RESULTS

In Experiment 1, morphine ingestion gradually increased over the 14 days of chronic drug exposure, reaching a mean of about 300 mg/kg/day at the end of this period (Fig. 1). Hyperthermia was consistently evident, averaging about +1.5°C compared to control values ($p<0.001$, two-tailed t-test). Tolerance gradually developed to the hyperthermic effect as indexed by the body temperature increase per unit dose (Fig. 1, lower panel), although disposition vs. functional components cannot be differentiated. The majority of the morphine mice and none of the controls showed Straub tail, a sign of skeletal muscle hypertonia associated with morphine intoxication. When the mice were challenged with 2.0 mg/kg naloxone, and the ensuing withdrawal syndrome

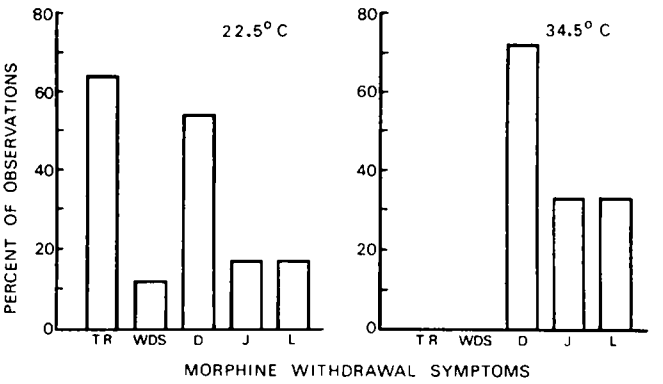

FIG. 2. Frequency of withdrawal signs in groups of morphine-dependent mice exposed to either a 22.5°C or a 34.5°C ambient environment following 2.0 mg/kg IP naloxone challenge on Day 12 and again on Day 14 of the intoxication phase (Experiment 1). The results are expressed in terms of the percent of the total number of observations (N = 48) in which a particular withdrawal sign occurred among the 8 mice. TR, tremor; WDS, "wet dog shakes"; D, diarrhea or soft stool; J, jumping; L, lacrimation. The 34.5°C environment resulted in the total elimination of hypothermia as well as TR and WDS, while the other withdrawal signs were not significantly affected by the warm ambient temperature ($p = 0.07$, Chi-Square, for J and L).

monitored over the next 35 min, pronounced tremor and "wet dog shakes" were clearly evident at the 22.5°C ambient temperature in the morphine group, but these two withdrawal signs were conspicuously absent at 34.5°C (Fig. 2). At 22.5°C ambient, 4 of the 8 mice showed wet dog shakes and 6 of 8 showed tremor, while none of the 8 mice at 35°C showed either sign (Fisher exact probability tests, $ps<0.05$). The hypothermia usually seen at 22.5°C ambient temperature was also eliminated at 34.5°C (Table 1). In contrast, the other withdrawal signs were not significantly affected by ambient temperature, although jumping and lacrimation tended to be more frequent at the higher temperature ($p = 0.07$, Chi-Square). The control group challenged with naloxone showed none of these signs. These results are shown on Fig. 2. Table 1 shows the body temperatures for the morphine and control groups before and after naloxone challenge at either 22.5°C or 34.5°C ambient temperatures. In the control group, a small but significant increase in body temperature was seen at either ambient temperature. This was apparently due to the effects of handling, the mild stress of injection, and exposure to a novel environment. In the morphine group, hypothermia developed at 22.5°C ambient in comparison to the control group ($p<0.05$, two-tailed t-test), but not at 34.5°C.

TABLE 1

BODY TEMPERATURES OF CHRONIC MORPHINE-TREATED VS. CONTROL MICE BEFORE AND AFTER NALOXONE CHALLENGE AT 22.5°C VS. 34.5°C AMBIENT TEMPERATURES

	Morphine Group	Control Group
Prior to injection at 22°C:	37.9 ± 0.4*	36.6 ± 0.3
20 min postinjection at 22.5°C:	35.2 ± 0.5*	37.1 ± 0.2
20 min postinjection at 34.5°C:	37.1 ± 0.3	37.5 ± 0.3

*$p<0.05$ vs. controls, two-tailed t-test. Each mean value (±SEM) represents 8 mice from Experiment 1. All body temperatures were determined by radio telemetry.

TABLE 2

PERCENT PREFERRING 35°C VS. 23°C IN A TWO-CAGE CHOICE APPARATUS

	35°C	23°C	p	N obs.
Controls (no morphine)	43%	57%		86
Morphine Intoxication, Days 3, 8, 11 and 13	82%	18%	$p<0.005$	88
Morphine Withdrawal, Hours 7 to 10	27%	73%	$p=0.12$	30

N obs. is the number of independent observations per preference condition in Experiment 2. There were a total of 8 morphine-treated mice and 8 control (vehicle) mice. Chi-Square tests were used to determine statistical significance vs. controls. Occasionally, a mouse was found in the interconnecting tube rather than in either cage; these data were omitted from analysis.

In Experiment 2, the control (no morphine) group showed no statistically significant preference for one ambient temperature over the other in this two-cage choice situation (Chi-Square). In fact, these two temperatures (22 vs. 35°C) were chosen because untreated mice appear to be indifferent when given this choice of ambient temperatures (3). In contrast, the morphine-treated mice during the chronic intoxication phase showed a strong and consistent preference for the warmer of the two home cages ($p<0.005$, Chi-Square), even though their body temperatures are typically above normal (hyperthermic) at these times. However, at 7–10 hours after withdrawal, when hypothermia predominates, the mice showed no significant preference, although a trend in favor of the 23°C cage was observed ($p=0.12$, Chi-Square). These results are shown in Table 2. Body temperatures via rectal probe showed significant hyperthermia (two-tailed t-tests) on the last day of morphine treatment compared to the controls (38.4 ± 0.5 vs. 37.0 ± 0.3°C, means $\pm$ SEM), while 10 hr after withdrawal, significant hypothermia was evident (34.5 ± 0.4 vs. 36.4 ± 0.2°C).

DISCUSSION

The morphine-saccharin method of inducing physical dependence on morphine was remarkably effective and convenient in C57BL/6J inbred mice. The use of gradually increasing concentrations of morphine in the drinking fluid in the present studies produced much higher (2-fold) levels of morphine consumption, and a much higher degree of physical dependence induction, than that noted by Horowitz (9), who used a fixed (0.375 mg/ml) concentration. The degree of physical dependence produced was correspondingly much greater than that noted by Horowitz (9). The saccharin is necessary to induce the consumption of large doses of morphine, presumably because it helps to mask the bitter taste of the alkaloid (9). This approach is probably not suited to most other inbred strains, however, since a number of strains have been shown to reject the morphine-saccharin drinking fluid, although the saccharin alone is highly preferred (9). The DBA/2J strain, in particular, will undergo severe dehydration rather than consume the morphine-saccharin fluid (unpublished observations). Throughout the present work, mean daily fluid consumption in the morphine group more than doubled what is usually seen when tap water alone is the fluid source (11.2 vs. 5.4 ml, unpublished observations), indicating that the morphine-saccharin fluid was well-accepted, and consumption was much above that required to meet the needs of thirst. When mice of this strain are given a second bottle containing tap water, they will continue to consume about 90% of their daily fluid intake from the morphine-saccharin bottle (unpublished observations).

In Experiment 1, body temperatures were monitored by radio telemetry without the use of restraint, handling or otherwise disturbing the animals. This is an important consideration, since the effects of morphine and similar opioids on body temperature can interact strongly with the degree of restraint, handling or stress associated with rectal probe mesurements in rats (4, 5, 12–14, 19, 20), and presumably in mice also, although data are scant. The reasons for this interaction are not clear, but likely possibilities include stress, postural interference, impaired behavioral thermoregulation, and discomfort due to insertion into the rectum (1, 4, 12–14, 19, 20). In our chronic morphine study (Experiment 1), without restraint, hyperthermia was the consistent finding during chronic morphine intake, to which tolerance gradually developed over the 14-day period. Straub tail was commonly seen at this time, indicative of hypertonia. Since this is presumably a heat-generating (thermogenic) response, it would be expected to contribute to the hyperthermia seen at this time, as has been shown to occur in rats (15). The morphine-exposed mice appeared to be more active than the controls, although we did not attempt to quantify this difference.

When withdrawal was precipitated by naloxone challenge after 12–14 days of chronic morphine consumption, hypothermia rapidly developed at room temperature as part of the morphine withdrawal syndrome (Table 1). However, when withdrawal hypothermia was prevented by the use of a warm ambient temperature (34.5°C), the withdrawal signs of tremor and wet dog shakes did not occur (Fig. 2). Therefore, these two withdrawal signs, which are presumably heat-generating responses, only came into play when body temperatures were abnormally low. The other withdrawal signs monitored were not significantly affected by ambient temperature (22.5 vs. 34.5°C), although the increased incidence of jumping and lacrimation seen at 34.5°C approached statistical significance ($p=0.07$). In rats, naloxone-precipitated jumping has been reported to increase at high ambient temperatures (22).

In Experiment 2, temperature preference was determined by the relative frequency of finding the mice in one home cage (23°C) compared to another (35°C) over a 14-day morphine consumption period and subsequent withdrawal. Since the ambient temperature preference apparatus was also the animal's living quarters, no handling or other disturbances were required, and a thorough familiarity with the apparatus was assured. This was judged to be important, since the behavior of mice can be strongly affected by novel environments or by handling. When C57BL/6J mice were given a choice between home cages at either 23°C or 35°C ambient, they showed roughly equal preference in the absence of any drug exposure (controls). With chronic morphine exposure, a strong preference (82%) for the warmer ambient temperature was consistently evident despite the hyperthermia occurring at this time. This behavior would serve to facilitate drug-induced hyperthermia, and thus is indicative of a drug-induced elevation in set point as the primary mechanism (4,8). Following withdrawal, when hypothermia is evident, the animals showed no significant preference for either ambient temperature, although most (73%) preferred the cooler ambient temperature ($p=0.12$, n.s. vs. controls). This behavior allows the hypothermic state to remain, since the choice of the warm temperature would have eliminated the hypothermia associated with drug withdrawal. This indicates that a downward change in set point is a likely mechanism for the hypothermic state following the withdrawal of morphine in C57BL/6J mice. These results are broadly similar to those reported by others in rats (2, 4, 5, 7, 22).

In summary, hyperthermia was consistently evident in mice consuming very large doses of morphine sulfate in the drinking fluid. Following precipitated withdrawal with naloxone (Experi-

ment 1) or natural withdrawal (Experiment 2), hypothermia develops at room temperature, which is a necessary condition for tremor and wet dog shakes to occur as part of the withdrawal syndrome. Temperature choice behavior either served to facilitate or did not oppose drug-induced changes in body temperature during chronic intoxication, and also subsequent to withdrawal, indicating that a change in set point is likely to be the primary morphine-induced mechanism rather than activation of strong heat gain (hyperthermia) or heat loss (hypothermia) mechanisms.

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