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SIMILARITIES BETWEEN MORPHINE WITHDRAWAL IN THE RAT AND THE MENOPAUSAL HOT FLUSH

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Summary

Skin temperature, cardiovascular and neuroendocrine responses to morphine withdrawal in the rat were evaluated in an effort to develop a potential animal model for the menopausal hot flush in women. Morphine dependency was produced by s.c. implantation of pellets containing morphine alkaloid. In response to precipitous, naloxone-induced withdrawal, rats showed surges in tail skin temperature (TST) which were similar in magnitude (4.8 to 7.2°C) and duration (60 to 90 min.) to peripheral skin temperature increases reported during menopausal hot flushes. Additionally, a brief period of accelerated heart rate (59 %) and a 9-fold hypersecretion of luteinizing hormone (LH) preceded the TST response to morphine withdrawal. These cardiovascular and neuroendocrine responses are observed to precede or coincide with the menopausal hot flush. Additionally, protracted morphine withdrawal subsequent to abstention, resulted in TST instability characterized by spontaneous, high amplitude TST fluctuations. Thus, the alteration in skin temperature, heart rate and LH secretion during precipitated morphine withdrawal in the rat are similar in magnitude, duration and in their temporal relationship to those observed during the hot flush. These data suggest a possible opioid etiology in this vasomotor disturbance. Acute withdrawal in the morphine addicted rats may serve as an animal model by which to study the neural mechanism underlying the menopausal hot flush.

Maintenance of internal body temperature requires heat production and dissipating mechanism which are regulated through temperature sensitive neurons in the central nervous system (1,2). While body core temperature is normally maintained within a narrow range, the central thermoregulatory system can be altered by toxins and drugs, resulting in a hyper- or hypothermic state (3,4). Morphine dependency in rats appears to cause a hyperthermia associated with a decline in heat dissipation in the absence of an appropriate decline in heat production (5-7). In contrast, precipitous morphine withdrawal results in a relative hypothermia (5-12).

Similar alterations in the central thermoregulatory system are thought to precipitate hot flushes following withdrawal from gonadal steroids subsequent to ovariectomy or that which occurs at the menopause (13-18). Each hot flush results in a moderate decline in body core temperature and in some women who

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experience frequent hot flushes, a mild hypothermia results (19,20). In addition to this thermoregulatory alteration, the menopausal hot flush is preceded by an acceleration in heart rate (16-18) and is coincident with a brief period of hypersecretion of luteinizing hormone (LH) (16-18).

These similarities between thermoregulation during morphine withdrawal and hot flushes lead us to speculate that morphine dependent animals might serve as a model with which to study the mechanisms of this vasomotor disturbance in women. In the present report we sought to determine skin temperature, cardiac and LH secretory responses to morphine withdrawal in an effort to evaluate the appropriateness of the addicted rat as an animal model by which to evaluate the neural mechanisms underlying the hot flush.

Materials and Methods

Female Charles Rivers CD rats weighing 200-280g were housed in groups of 2 in hanging, stainless steel cages in a room maintained at 26 ± 1°C and illuminated from 5 AM to 7 PM. Food (Purina Laboratory Rat Chow) and tap water was provided ad libitum.

Morphine (MORP) dependency was produced by subcutaneous (s.c.) implantation of one pellet containing 75 mg morphine (free base, Merck, St. Louis, MO.), 37.5 mg microcrystalline cellulose (avisil, FMC Corporation, Philadelphia, PA.), 0.56 mg Cab-o-sil (Cabot Corp., Boston, MA.) and 1.13 mg Mg Sterate (Fischer Chemical Co., Fair Lawn, N.J.). Two days later, an additional 2 morphine pellets were implanted. The pellets were compounded in our laboratory and this treatment regimen produced morphine dependency as measured by several tests of analgesia and withdrawal (21,22). Control animals were similarly treated, but received placebo pellets formulated with an additional 75 mg of microcrystalline cellulose that replaced the morphine base. All experiments were conducted 2 days after the last morphine pellets were implanted in a room with an ambient temperature of 26 ± 1°C.

In an initial experiment, animals were lightly restrained in wire mesh tunnel cages with a wooden floor. Rectal temperature (Tr) was measured with a YSI thermister probe (#402) inserted 5 cm into the rectum. Tail skin temperature (TST) was measured by means of a YSI surface thermister probe (#427) placed on the tail approximately 2 cm from its base. This thermister probe was bound to the tail with adhesive tape. The temperatures were measured at 5 min. intervals with a Model 46 Tuc Tele-thermometer and a Model 4002 switch box. After being placed in the restraining cages, an acclimation period of 30 min. was allowed before temperatures were monitored at 10 min. intervals for an additional 30 min. At this time animals were administered either naloxone HCl (NAL, 1 mg/kg b.w., s.c.) or saline (SAL) and temperatures were recorded at 5 min. intervals for the next 90 min. This study was repeated in rats which were ovariectomized (OVX) 2 weeks prior to MORP addiction. The response to NAL treatment was nearly identical, therefore all subsequent experiments employed OVX rats.

In a second experiment, OVX rats were either addicted to morphine as described above or received placebo pellets in place of the morphine. On the experimental day, discs for recording electrocardiograms were coated with electrode paste and secured to the chest of each rat with adhesive tape. Heart rates were recorded on a Narco Bio Systems physiograph. Rats were placed in wire mesh cages and TST and Tr were monitored simultaneously with heart rates. After 1 h of acclimation, an initial resting (0 time) heart rate, TST and Tr was measured. Naloxone (1 mg/kg b.w., s.c.) was then administered and heart rate, TST and Tr were recorded every 3 min for the first 30 min and every 5 min for the remaining 50 min of the experiment.

To define the temporal association between TST and LH secretion, OVX rats were addicted to MORP as described above. One day following the last morphine (or placebo) implants, an atrial catheter was inserted through the right jugular vein (23) to allow for repeated blood sampling from unanesthetized animals. One day later animals were lightly restrained and allowed a 1 h acclimation period after which TST's were recorded at 10 min intervals. Prior to the administration of naloxone (1 mg/kg b.w., s.c.), a single 500 µl blood sample was withdrawn (0 time). Additional 500 µl blood samples were obtained at 5, 10, 15, 30 and 60 min after naloxone administration. TST's were recorded at 5 min intervals throughout the 90 min experimental period. Each blood sample was immediately centrifuged, plasma was collected and frozen (-20°C) and red blood cells were resuspended in 500 µl of heparinized saline (5 IU/ml). To maintain a constant hematocrit, cells were returned to the animals after the subsequent blood sample was obtained.

Plasma LH levels were determined by the RIA methods described in the NIAMDD Kits, generously provided by the Hormone Distribution Program. Plasma LH concentrations are expressed in terms of the reference preparation provided (LH-RP-1).

In a final experiment, 6 OVX rats were addicted to MORP while the remaining 6 OVX rats received placebo pellets as described above. Two days following placement of the last implants, the morphine (or placebo) pellets were surgically removed under light ether anesthesia. At 3h, 24h, and 53 hr following removal of the pellets, TST and Tr were monitored for 2 hr periods. Between these observation times animals were returned to their home cages.

Results

In MORP-dependent rats there was no difference in resting TST, however, NAL treatment in these rats resulted in a rapid increase in TST and a subsequent decline in Tr. TST was significantly elevated by 5 min., peaked at 7.2 ± 0.2°C above baseline by 10-15 min. and returned to half of the maximal increase in temperature by 50 min. post-NAL (Fig. 1). In animals treated with placebo pellets, NAL was ineffective in altering TST or Tr (Fig. 1). Further, in MORP-dependent rats, SAL treatment did not significantly effect TST or Tr (Fig. 1). Ovariectomy two weeks prior to morphine treatment, did not alter NAL induced TST or Tr responses. In these OVX rats peak TST was 6.2 ± 0.2°C above baseline and the maximum suppression of Tr was 4.3 ± 0.3°C. Thus, MORP-induced alterations in gonadal steroid secretion may not be a prerequisite for the observed TST or Tr responses to NAL.

Tr in MORP-addicted animals was 0.81°C higher than in placebo treated rats ($p<.05$). A significant decline in Tr was observed by 15 min after NAL treatment and a maximum decline in Tr of 3.4°C was observed by 90 min. In placebo treated rats given NAL and in MORP-dependent rats treated with SAL, Tr did not change significantly over the 90 min period.

Heart rate was 27% lower in MORP-dependent versus placebo implanted rats prior to NAL treatment (Fig 2). While NAL treatment had no significant effect on heart rate in placebo animals, NAL treatment increased heart rate by 59% within 3 min in MORP-dependent rats (Fig 2). Heart rates remained elevated above baseline by 20 to 30% through 40 min after NAL treatment. In these animals TST's were elevated significantly by 6 min, peaked at 4.9 ± 0.3°C above baseline at 18 min and remained elevated through 70 min after NAL treatment. Thus, the positive chronotropic effects of NAL in the MORP-dependent rat precedes the peak TST response by 15 min. Tr showed a significant decline by 12 min, and decreases progressively through 80 min after NAL treatment in MORP-addicted rats, while placebo implanted rats showed no Tr response to NAL (Fig 2).

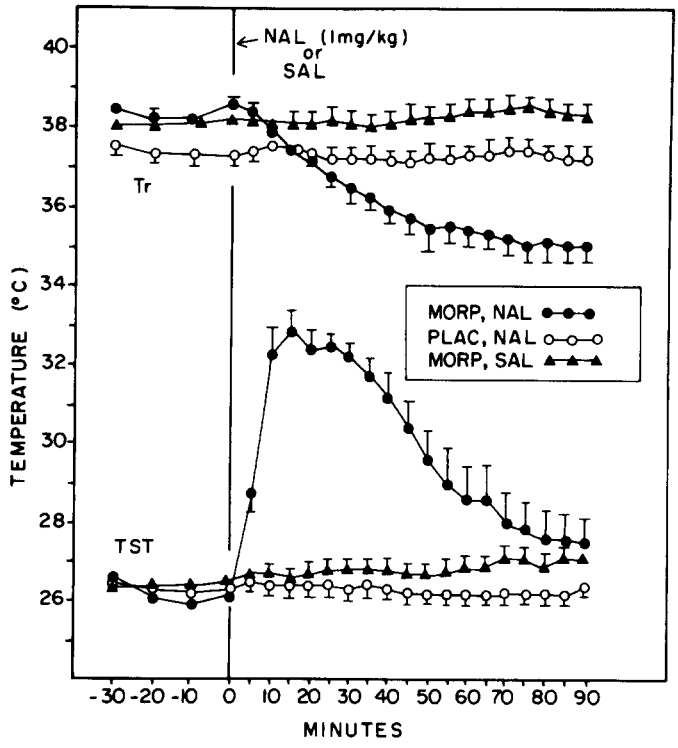

Fig. 1 - Effects of NAL on tail skin temperature (TST) and rectal temperature (Tr) in morphine-dependent rats. Each point represents the mean and the vertical bar represents 1 SEM. The SEM bar is not presented when it is smaller than the symbol used to represent the mean or when it interferes with the expression of the mean value. MORP = morphine-dependent animals, PLAC = placebo implanted animals, NAL = naloxone administration (1 mg/kg body weight, s.c.) and SAL = saline administration in place of naloxone. N = 6 rats per group.

NAL treatment in MORP-addicted rats resulted in a rapid elevation in plasma LH levels (Fig. 3). LH levels increased significantly ($p<0.050$) within 5 min, peaked at 9-times basal levels by 10 min ($p<0.001$) and remained elevated through 30 min after NAL treatment (Fig. 3). This marked hypersecretion of LH was not observed in placebo-implanted rats following NAL treatment or in MORP-dependent rats treated with saline vehicle (Fig. 3). In contrast, both of these control groups showed a 1.5- to 2-fold elevation in plasma LH at the 10 min sampling period. In MORP-dependent animals, TST was moderately elevated by 5 min, peaked at 4.3 ± 0.2°C above baseline at 15 min and remained significantly elevated through 65 min after NAL treatment (Fig. 3). Only moderate response to NAL or vehicle injections were observed in control animals (Fig. 3). In 4 of 6 MORP-dependent rats, the peak LH response preceded by 5 min the peak TST response while in the remaining two animals, LH and TST responses were coincident.

At 3h, 24h and 53h following surgical removal of the MORP (or placebo) pellets, mean TST was not different among treatment group or at any observation time. However, the variation of TST around that mean temperature was increased significantly during MORP withdrawal (Table I). The coefficient of variation (CV) of TST was increased 5-fold, maximum amplitude of TST pulse was increased 7-fold and the number of TST pulses with amplitudes greater than 0.5°C were increased 4-fold at 24 to 26h of morphine withdrawal when compared to placebo controls (Table I). In Fig. 4, 6 individual TST profiles for MORP (upper two panels) and 6 individual placebo (lower two panels) withdrawn animals are shown for the time interval at which maximum TST variability was observed. In the MORP-withdrawal group, one animal showed maximum TST instability at 3 to 5h, 4

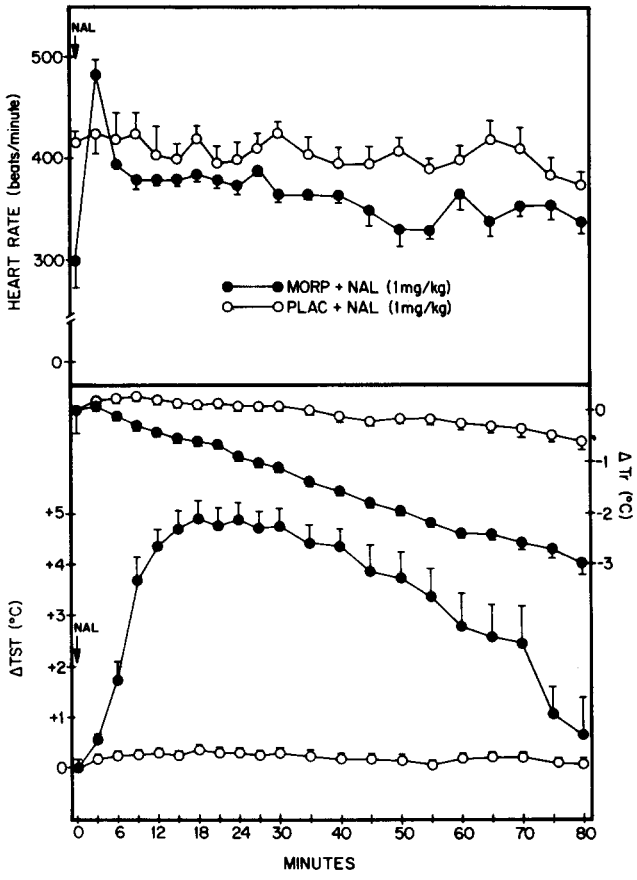

Fig. 2 - Effects of NAL on heart rate, tail skin temperature (TST) and rectal temperature (Tr) in morphine-dependent rats. Each point represents the mean and the vertical bar represents 1 SEM. MORP = morphine dependent animals, PLAC = placebo implanted animals, NAL = naloxone administration (1 mg/kg body weight, s.c.) N = 6 rats per group.

showed maximum TST instability at 24 to 26h and 1 animal failed to exhibit significant TST at any of the observation times.

Discussion

Drugs can alter body temperature by acting at several components of the thermoregulatory system, i.e. heat production or dissipation system, the central thermostat or controllers. The present observation that MORP addiction elevates Tr is consistent with other reports showing a hyperthermic effect of MORP (24). NAL administration to these MORP-dependent, but not control animals, caused a sudden drop in Tr. The components of the thermoregulatory system which are affected by opiate agonists can not be determined by the present study. However, the NAL-induced hypothermia which has been previously reported (25), occurs concurrent with, and perhaps as a result of, peripheral vasodilation and heat loss. Further evidence that this hypothermic effect of NAL is due to antagonism of the MORP receptor is indicated by a significant, albeit mild, hypothermia (37.7 ± 0.2 to 36.6 ± 0.2°C) by 26 h following removal of the MORP pellets. During this protracted withdrawal, spontaneous TST fluctuations result in heat loss which likely contribute to the decrease in core temperature.

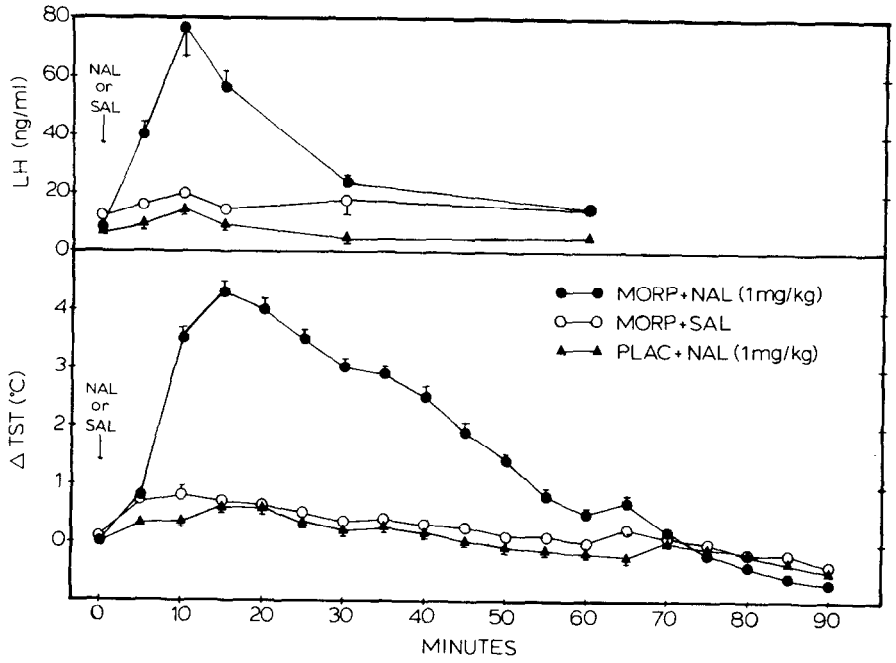

Fig. 3 Effects of NAL on plasma LH concentrations and tail skin temperature (TST) in morphine-dependent rats. Each point represents the mean and the vertical bar represents 1 SEM. MORP = morphine dependent rats, PLAC = placebo implanted animals, NAL = naloxone administration (1 mg/kg body weight, s.c.). N = 6 rats per group.

LH secretion appears to be tonically inhibited by opioid neurons in the rat since acute NAL-treatment enhances LH secretion by 2- to 3-fold in both male and female rats under a variety of experimental conditions (26-28). In the MORP-addicted rat, NAL resulted in a 9-fold increase in LH secretion which preceded or was coincident with the TST surge. This temporal association between LH secretion and the TST surge are of interest since hot flushes in women are consistently associated with an LH surge (16-18). While in women, it has been demonstrated that the LH surge itself is not necessary for generation of the hot flush (29), the involvement of neurons which secrete luteinizing hormone-releasing hormone (LHRH) has been suggested. In the rat, LHRH perikarya has been observed in the preoptic area-anterior hypothalamus (POA-AH) (30). This region is also a site of MORP-responsive, temperature sensitive neurons (2,31,32). Additionally, injection of LHRH into the POA-AH results in a TST surge (33) which is similar in magnitude and duration to the alterations in TST induced by MORP withdrawal. Thus the present observation that in MORP-addicted rats the NAL-induced LH surge precedes or is coincident with the TST surge, is consistent with the involvement of LHRH neurons in the regulation of skin temperature.

While the mechanism by which withdrawal causes an acceleration in heart rate can not be determined from the present study, the rapidity of the response implicates the adrenergic innervation of the heart. In view of our previous observation that NAL-induced LH secretion is mediated by an adrenergic mechanism (28), and several reports of hyperactivity of noradrenergic neurons during withdrawal (34-36), some of the manifestations of withdrawal may be the

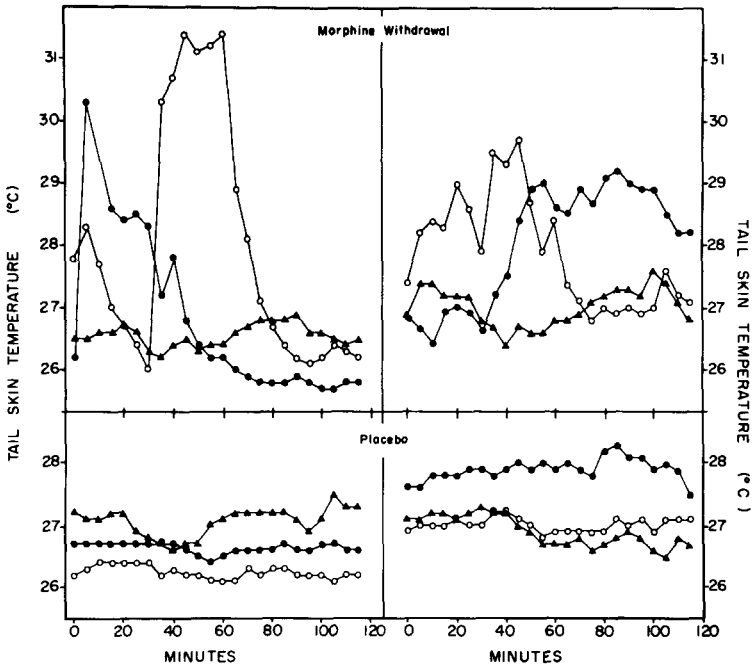

Fig. 4 - Tail skin temperature (TST) profiles of 6 individual morphine-dependent (upper two panels) or 6 individual placebo implanted (lower two panels) rats after removal of morphine containing or placebo pellets. The panels are separated for each treatment for convenience of expression of data. The three sets of symbols employed in each panel represent TST profiles of different animals.

Table I Parameters of Tail Skin Temperature of Rats Surgically Withdrawn from Morphine or Placebo Pellets.

Treatment	Parameter	Time Interval After Withdrawal		
		3-5h	24-26h	53-55h
Placebo	Average TST (°C)	27.0	27.0	27.1
	CV (%)[a]	0.64±0.13	0.56±0.09	0.57±0.18
Morphine	Average TST (°C)	27.0	27.1	26.6
	CV (%)	1.44±0.41	2.97±1.07*	0.98±0.41
Placebo	Maximum Pulse Amplitude (°C)[b]	0.43±0.11	0.33±0.07	0.27±0.06
Morphine	Maximum Pulse Amplitude (°C)	1.08±0.32	2.23±0.84*	0.50±0.06
Placebo	No. of Pulses 0.5°C[c]	5	6	2
Morphine	No. of Pulses 0.5°C	24	24	6

[a]CV = coefficient of variation = mean of all temperatures for 2h ÷ standard deviation about the mean X 100%. [b]The single largest temperature pulse for each animal were grouped and are expressed as mean ± S.E.M. [c]The total number of skin temperature pulse of > 0.5°C for all animals over the two hour interval were grouped. * $P < 0.05$ vs appropriate placebo group. Six morphine and 6 placebo treated animals were employed for the determination of each parameter.

consequence of a generalized sympathetic activation. In this regard, it is of interest that an adrenergic involvement in the hot flush has been suggested (16-18), based upon the synchronized alteration in skin temperature, LH secretion and heart rate, all of which are under adrenergic regulation.

The numerous studies which have implicated opioids in the regulation of body temperature (37), and our present observations raises the intriguing possibility that central opioid neurons may participate in the genesis of the menopausal hot flush. Three consistently observed symptoms of the hot flush, i.e. skin temperature surge, LH surge and accelerated heart rate, are similar in their magnitude and temporal relationship with these alteration induced by morphine withdrawal. Further, in women, hot flushes appear to be a type of withdrawal response. Patients with gonadal dysgenesis, and hence persistently low estrogen levels, do not develop hot flushes, while estrogen treatment and its subsequent withdrawal initiates this vasomotor disturbance (38). It is of interest that ovariectomy in monkeys results in a dramatic decline in hypophyseal portal blood concentrations of β-endorphin (39) suggesting that a decline in activity of hypothalamic β-endorphin neurons follows the loss of ovarian steroids. Further, the symptoms of both MORP withdrawal in addicts (40) and hot flushes in women (41) are each ameliorated by clonidine which has antinociceptic activity (42). Clonidine also increases serum β-endorphin levels and attenuates the hyperactivity of noradrenergic neurons which accompanies MORP withdrawal (43-47). Finally, narcotic addicts frequently report the sensation of hot and cold flushes during withdrawal (40). Thus, the possiblity that opioid neurons participate in the series of neuronal events leading to the hot flush is supported by much indirect evidence.

We have been unable to document spontaneous TST fluctuation within 2 weeks following ovariectomy in the rat. Indeed, in placebo treated animals at 2 weeks following ovariectomy, TST was remarkably stable over the two hour observation period. While these data indicate that acute ovariectomy is not a sufficient stimulus for spontaneous TST fluctuations, temperature regulation in long-term ovariectomized rats remains to be evaluated. The need for such a study is evidence by the observation that in women the delay until the onset of flushing episodes following the loss of ovarian function is considerably variable (48). Thus, the present study does not allow us to ascertain with certainty that in the rat, ovariectomy is without effects on the regulation of TST.

In the present study we observed that at least three manifestations of the menopausal hot flush can be induced in the rat. This suggests that a common neural mechanism may mediate these changes in both the addicted rat and the menopausal woman. Further, the similarities in magnitude and temporal association of the induced TST, LH secretory and heart rate responses with those observed during the hot flush indicates that morphine withdrawal in the rat may serve as a useful model by which to elucidate these neuronal mechanisms underlying this menopausal syndrome.

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