Heat stroke: opioid-mediated mechanisms

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Romanovsky, Andrej A., and Clark M. Blatteis. Heat stroke: opioid-mediated mechanisms. *J. Appl. Physiol.* 81(6): 2565–2570, 1996.—In our previous study in guinea pigs, intensive and prolonged intraperitoneal heating (IPH) caused heat stroke characterized by high mortality and accompanied by two paradoxical phenomena: ear skin vasoconstriction at a high body temperature (T_b) (hyperthermia-induced vasoconstriction) and a post-IPH T_b fall at an ambient temperature (T_a) below thermoneutrality (hyperthermia-induced hypothermia). In this study, we tested the hypothesis that the mechanisms of the two phenomena involve endogenous opioid agonists. Experiments were conducted in 24 unanesthetized, lightly restrained guinea pigs, each chronically implanted with an intraperitoneal thermode and intrahypothalamic thermocouple. The thermoregulatory effects of a wide-spectrum opioid-receptor antagonist, naltrexone (NTX; 50 or 0 µmol/kg sc), were studied in IPH-induced heat stroke and under normal conditions. IPH was accomplished by perfusing (50 ml/min; 80 min) water (45°C) through the thermode. T_a was maintained at ~24°C. Skin vasodilation occurred at the onset of IPH but later changed to vasoconstriction despite high T_b and continuing IPH. IPH-induced hyperthermia (1.8 ± 0.1°C) was followed by a post-IPH T_b fall (-5.1 ± 0.7°C; calculated for the survivors only). The 48-h mortality rate was 50%. NTX prevented the hyperthermia-induced vasoconstriction and attenuated the hyperthermia-induced hypothermia (-1.8 ± 0.4°C). None of the NTX-treated animals died. The effects of NTX on T_b regulation under normal conditions were minor. These results indicate that the phenomena of both hyperthermia-induced vasoconstriction and hyperthermia-induced hypothermia are opioid dependent. The latter is speculated to reflect opioid-mediated inhibition of metabolism; the former is thought to result from opioid-induced hemodynamic alterations. Because both phenomena did not occur in the NTX-treated survivors, the skin vasoconstriction at high T_b and the posthyperthermia T_b fall may be viewed as markers of the severity of heat stroke. It is suggested that opioid antagonists may have therapeutic potential in heat-induced disorders.

hyperthermia; hypothermia; poikilothermia; vasoconstriction; vasodilation

IN OUR PREVIOUS STUDY in guinea pigs (25), intensive and prolonged intraperitoneal heating (IPH) caused a pathological sequela characterized by high mortality (heat stroke). This IPH-induced heat disorder was accompanied by two paradoxical thermoregulatory phenomena. First, although ear skin vasodilation readily occurred at the onset of the IPH-induced hyperthermia, it later changed to vasoconstriction, despite the continuing IPH and high body temperature (T_b); we termed this phenomenon "hyperthermia-induced vasoconstriction." Secondly, when IPH was stopped, the initial hyperthermia was followed by not just a return of T_b to its pre-IPH level but by its fall to below this level; we termed this phenomenon "hyperthermia-induced hypothermia."

The aim of the present study was to test the hypothesis that the mechanisms underlying the two heat stroke-associated paradoxical thermoregulatory phenomena involve endogenous opioid agonists. Opioids possess a variety of thermoregulatory actions (1, 27), participate in fever genesis (6, 27), and are implicated in the mechanisms of heat adaptation (13, 29). They have also been proposed to play a role in the pathogenesis of shock (see Ref. 12 for review). Thus naltrexone (NTX), a wide-spectrum opioid-receptor antagonist with a strong anti-µ-receptor activity, and naloxone, its *N*-allyl congener with a shorter duration of action, have each been demonstrated to lessen the severity of shock of various etiologies, including endotoxin shock (9) and heat stroke (21). A four-fold increase in the plasma level of β-endorphin/β-lipotropin (the most abundant endogenous µ-receptor opioid agonist) has been recorded in patients with heat stroke (4).

To address our aim, we applied IPH to unanesthetized guinea pigs and studied the effect of NTX on the IPH-induced pathological sequela.

METHODS

Animals. Experiments were conducted in 24 male Hartley guinea pigs (Sasco, St. Louis, MO), weighing ~450 g. The animals were housed in individual cages in a temperature-controlled (21–23°C) room with a 12:12-h light-dark cycle. Guinea pig diet (Agway Prolab, New York, NY) and tap water were available ad libitum. Before they were used in an experiment, all the animals were trained (four successive, daily sessions, each 4 h long) to stay in individual, locally fabricated wire-mesh stocks. To obviate possible effects of circadian rhythms, the experiments were started between 9 and 10 A.M. Each animal was used in an experiment only once. At the end of the study, the animals were killed with pentobarbital sodium (200 mg/kg ip). The care and use of animals were in compliance with *The American Physiological Society Guiding Principles for Research Involving Animals and Human Beings*; the protocols were approved by the institutional animal care and use committee.

Surgical preparation. The animals were prepared for the experiments as described in detail previously (25). Briefly, each guinea pig was anesthetized with ketamine-xylazine (65 and 9 mg/kg im, respectively) and implanted with an intraperitoneal thermode and intrahypothalamic thermocouple. The working part of the thermode was a 110-cm segment of silicone tubing (ID 0.062 in.; OD 0.095 in.) rolled into a concentric coil. The inflow and outflow ends of the thermode were tunneled under the skin to the nape, exteriorized, and obturated with plastic plugs. The intrahypothalamic thermocouple was prepared from lengths of copper and constantan wires sealed into polyethylene insulation and connected to copper and constantan sockets (Omega Engineering, Stamford, CT). The sockets were mounted inside a polypropylene

pedestal. The thermocouple was implanted into the preoptic/anterior hypothalamus (1.5 mm rostral to the bregma, 1.0 mm lateral to the sagittal suture, the tip 8.5 mm below the surface of the skull), and the pedestal was fixed to the skull with stainless steel screws and dental acrylic. The animals were allowed at least 1 wk to recover from this surgery.

Instrumentation. For an experiment, each animal was placed in its stock and instrumented as shown in Fig. 1. The sockets of the intrahypothalamic thermocouple were connected to an assembly consisting of a thermocouple amplifier with cold-junction compensation (model AD-595; Analog Devices, Norwood, MA), a multiplexor, and an analog-to-digital converter using a microelectronic data-acquisition system (MDAS-16; Datel, Mansfield, MA). A skin thermocouple probe (attached to the external surface of the right ear pinna with cyanoacrilate adhesive) and an ambient thermocouple were connected to the same measuring system. The system was connected to an Apple IIe microcomputer. The inflow end of the thermode was connected by Tygon tubing to a peristaltic pump (model STA-131900; Desaga, Heidelberg, Germany) and a water reservoir (thermostat). The outflow end was connected to a collection vessel. The inflow and outflow thermocouple probes (mounted inside the connecting tubing at the inflow and outflow ends of the thermode, respectively) were connected to a telethermometer (BAT-8; Bailey Instruments, Saddlebrooke, NJ). All the thermocouples were precalibrated, using a temperature-controlled water bath and a mercury thermometer accurate to 0.1°C.

Experimental protocols. The study was designed to evaluate the effect of NTX on thermoregulatory symptoms of IPH-induced heat stroke. For this, NTX-HCl (Research Biochemicals International, Natick, MA) was injected (0 or 50 μmol/kg sc) in pyrogen-free saline (PFS; 1 ml/kg) immediately before the beginning of IPH. To differentiate the effect observed in heat stroke with the drug's action in normothermia, two other groups of animals were injected with the same doses of NTX (0 or 50 μmol/kg), but no IPH was performed. The 50-μmol/kg dose of NTX was chosen as the dose minimally affecting thermoregulation of guinea pigs under the normal conditions (causing $\sim$ 0.5°C drop in T_b) in a pilot study. In all the experiments, hypothalamic (T_h), ear skin (T_{sk}), and ambient (T_a) temperatures were monitored from 1 h before until at least 9 h after the NTX administration. All three temperatures were used to assess changes in the thermoregulatory vasomotor tone (see *Data processing and analysis* below). T_h was also used as an index of T_b and, for this purpose, was preferred over traditional indexes (such as rectal, colonic, and esophageal temperatures) to insure the minimal possible "contamination" of the measured temperature by the procedure of IPH per se. All thermocouples were

scanned once a minute, and the data were displayed both graphically and digitally and stored on a disk. T_a was maintained at $\sim$24°C. Animals were observed for 48 h after the experiment.

Model of heat stroke. Heat stroke was induced by IPH. The advantage of this method (as compared with the commonly used exposure to a high T_a) is a better standardization of the heat load; this advantage can be developed even further if the technique of feed-forward control (described for the case of intraperitoneal cooling; see Ref. 24) is used. IPH was performed by perfusing water at an inflow temperature (T_{in}) of 45°C through the thermode; the perfusion rate was 50 ml/min, and the perfusion duration was 80 min. T_{in} was checked every 1 min and, if necessary, adjusted. The difference between the outflow temperature and T_{in} was also recorded every 1 min (to verify the efficiency of IPH). The total heat load delivered over the entire 80-min period was $\sim$5 kJ. The maximal temperature to which the internal organs of the animal were actually exposed during IPH was determined in a separate experiment on an anesthetized guinea pig implanted with an intraperitoneal thermode (2 wk before the experiment) and an intraperitoneal thermocouple (inserted immediately before the experiment and attached to the wall of the isolating "bursa" formed by the greater omentum). The abdominal temperature was 2.5–2.8°C lower than T_{in} at the beginning of IPH and 1.2–1.5°C lower than T_{in} at the end of the procedure. The actual temperature to which the internal organs were exposed never exceeded 43.9°C. This is comparable with the solution temperature of 45°C recommended for intraperitoneal dialysis in hypothermic infants (10).

Data processing and analysis. To assess the changes in the peripheral vasomotor tone, the heat loss index (HLI) was calculated according to the formula

$$HLI = (T_{sk} - T_a)/(T_h - T_a) \qquad (1)$$

Originally proposed by Székely (30), formula 1 eliminates direct influences of both T_a and T_b on T_{sk}. The value of HLI varies from 0 (full vasoconstriction) to 1 (full vasodilation). The HLI has been successfully used to evaluate the thermoregulatory vasomotor response of the guinea pig ear (25, 31), rat tail (32), and human finger (5). In the latter, a strong correlation between the HLI and blood flow was found. The statistical analysis was performed by integrating the deviations of T_h and HLI from their preinjection levels (ΔT_h and ΔHLI, respectively) over time and comparing the integrals between the groups with the help of the unpaired Student's *t*-test. The mortality data were evaluated by using Fisher's exact test.

Fig. 1. Schematic representation of experimental setup. In circles: parameters controlled (F, flow rate) or recorded. ΔT, intraperitoneal thermode output-input temperature gradient; T_a, ambient temperature; T_h, hypothalamic temperature; and T_{sk}, ear skin temperature. Open arrows, water flow direction; solid arrows, signal transduction.
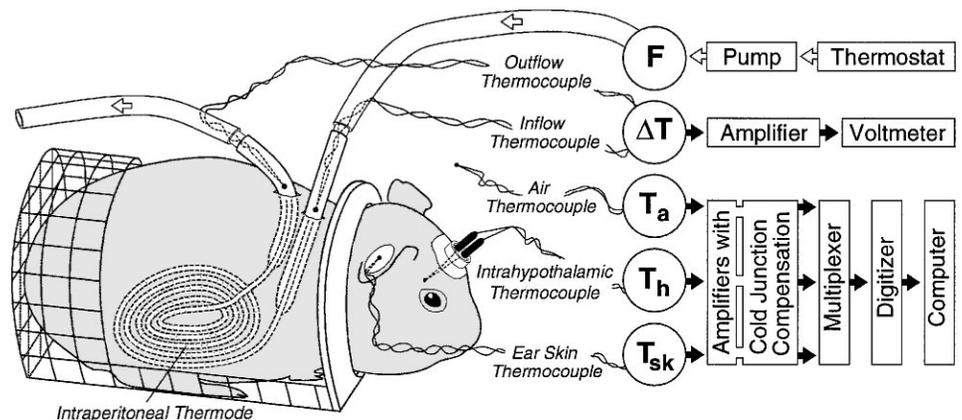
RESULTS

The initial thermal state of the guinea pigs was characterized by normothermia (the mean initial T_h for all experiments was $38.3 \pm 0.2°C$) and moderate skin vasoconstriction (the mean HLI value was 0.49 ± 0.02).

Intensive and prolonged IPH caused heat stroke with a 50% mortality rate (3 of 6 animals died). The thermoregulatory responses to IPH are shown in Fig. 2 (data from a single experiment in a survivor) and Fig. 3 (averaged data from all of the experiments of the series). These responses to IPH included both the hyperthermia-induced hypothermia and hyperthermia-induced vasoconstriction phenomena. IPH-induced hyperthermia (maximal ΔT_h of $1.8 \pm 0.1°C$ at 48 ± 7 min after the beginning of IPH) was later followed by a post-IPH T_h fall (ΔT_h of $-5.1 \pm 0.7°C$ at 302 ± 20 min; calculated for the survivors only). In the survivors, the hypothermia lasted for at least 15 h (the longest recording period) but probably not much longer than this (the duration can be approximated from Fig. 2). Skin vasodilation (maximal HLI of 0.95 ± 0.01) occurred at the onset of IPH (6 ± 1 min) but later changed to vasoconstriction (HLI dropped to 0.44 ± 0.04 at 36 ± 4 min), despite continuing IPH. An important characteristic of the latter phenomenon was its independence of T_h: the whole transition from maximal vasodilation to constriction took place at the same T_h (~40.0°C; Fig. 4).

Fig. 3. Effects of NTX on thermoregulatory signs of pathological sequelae induced by IPH. ΔT_h, changes in hypothalamic temperature; HLI, heat loss index; n = no. of animals. Three of 6 animals in control group (IPH + NTX, 0 μmol/kg sc) died after time-marker (†); all 5 guinea pigs in the experimental group [IPH + NTX (50 μmol/kg sc)] survived for at least 48 h after IPH.
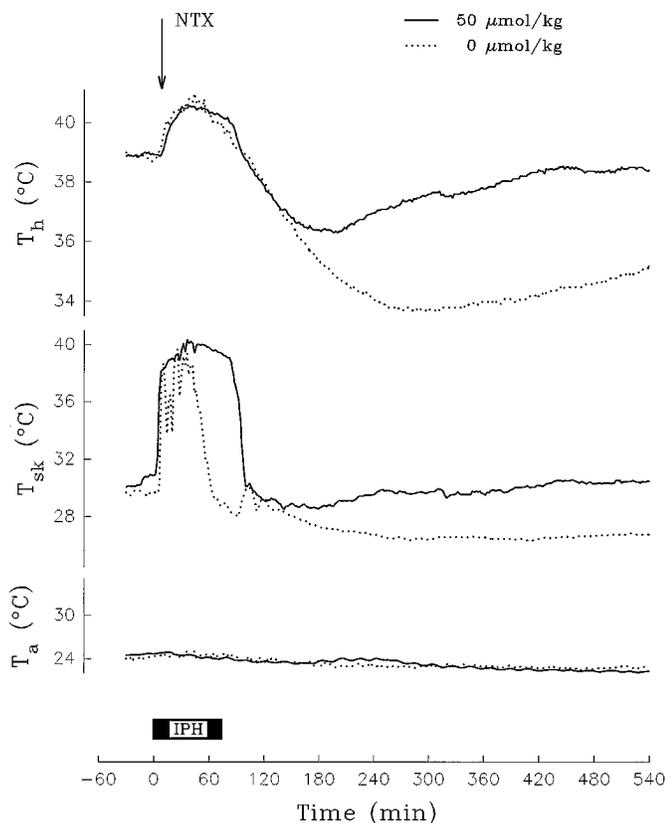

Fig. 2. Effects of subcutaneous injection of naltrexone (NTX; doses indicated) on intraperitoneal heating (IPH)-induced changes in T_h and T_{sk} (plots of 2 typical experiments).
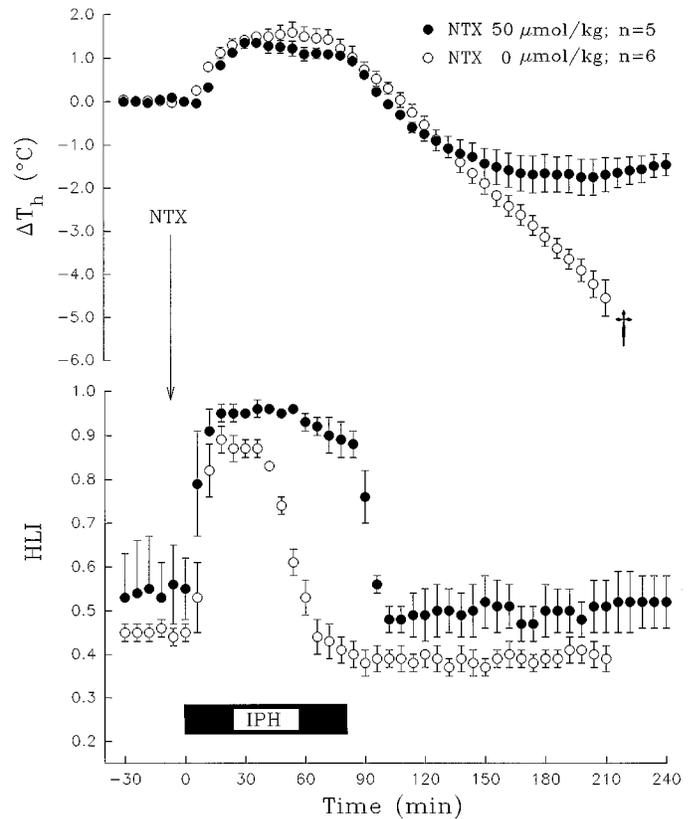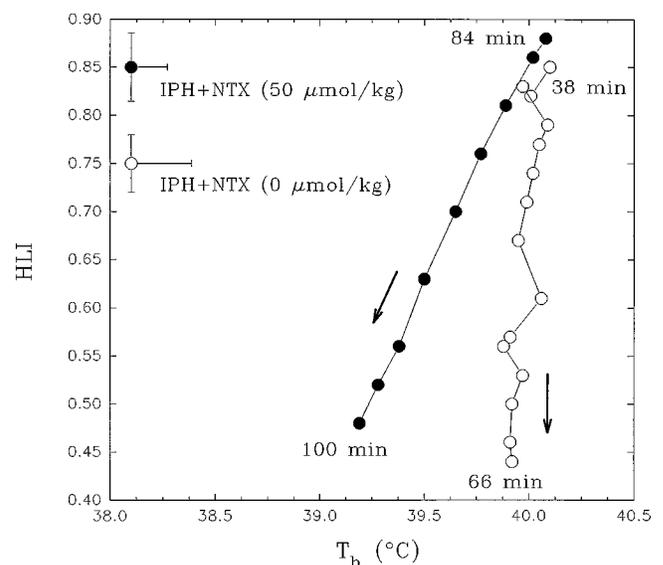

Fig. 4. Dependence of HLI on T_h during transition from vasodilation to constriction in 2 groups (IPH + NTX, 50 μmol/kg sc and IPH + NTX, 0 μmol/kg sc). For each group, times of start and end of transition are indicated; arrows, time direction.

At the dose used, NTX did not affect the development of the IPH-induced hyperthermia but attenuated and shortened the post-IPH hypothermia (the maximal drop of T_h was only $1.8 \pm 0.4°C$, occurring at 199 ± 2 min; the hypothermia lasted for ~ 10 h) and completely prevented the hyperthermia-induced vasoconstriction (Figs. 2 and 3). Comparison between the integrals of ΔT_h over the time period 102–120 min after the injection showed that the effect of NTX on the hyperthermia-induced hypothermia appeared to be statistically significant ($P < 0.03$). To evaluate the effect of NTX on the hyperthermia-induced vasoconstriction, ΔHLI was integrated over the time period 0–102 min after the injection, and the integrals were compared between the two groups; this effect also appeared to be significant ($P < 0.02$). Not only did the transition from vasodilation to constriction occur much later in the NTX-treated animals (Figs. 2 and 3), but the T_h dependence, which is normally characteristic of the skin vasomotor tone, also was restored (Fig. 4). Another important result of this study was that all five animals treated with NTX survived the IPH for the entire observation period (48 h). Although the difference in the mortality between the NTX-treated and nontreated groups did not reach statistical significance, the obtained value of $P (< 0.18)$ could be regarded as suggestive. The experiments with IPH were then terminated for humane reasons.

Despite the high magnitude of the thermoregulatory effects of NTX in the IPH-treated animals, the drug's effect on T_b regulation under normal conditions was minor (Fig. 5). Indeed, in the animals that were not subjected to IPH, NTX caused only a slight decrease of T_h ($-0.5 \pm 0.1°C$ at 40 ± 4 min postinjection), and no change in HLI occurred at the T_a used ($24°C$).

DISCUSSION

Hyperthermia-induced vasoconstriction. Similarly to our previous study (25), IPH caused in guinea pigs both a T_h rise and ear skin vasodilation. However, ~ 40 min after the beginning of IPH, this vasoldilation suddenly changed to vasoconstriction. This paradoxical cancellation of peripheral vasodilation, despite continuing IPH and a high T_h, we have termed hyperthermia-induced vasoconstriction.

The independence of the hyperthermia-induced vasoconstriction of T_h (Fig. 4) indicates that this phenomenon occurs not because of but rather despite thermoregulatory demands. During heat exposure, water-consuming heat-defense responses (in our animals, polypnea) and thermoregulatory redistribution of blood toward the skin eventually lead to dehydration and/or hypovolemia; both have been shown to increase the threshold T_b for cutaneous vasodilation (20, 22). In agreement with this, skin vasoconstriction in humans with heat stroke has been attributed to decreased blood volume and central venous pressure (15). In addition, the hyperthermia-induced vasoconstriction may be related to the selective loss of splanchnic vasculature constrictive ability. Splanchnic vasoconstriction constitutes an adaptive response to hyperthermia and readily occurs in hyperthermic subjects, thus allowing a larger
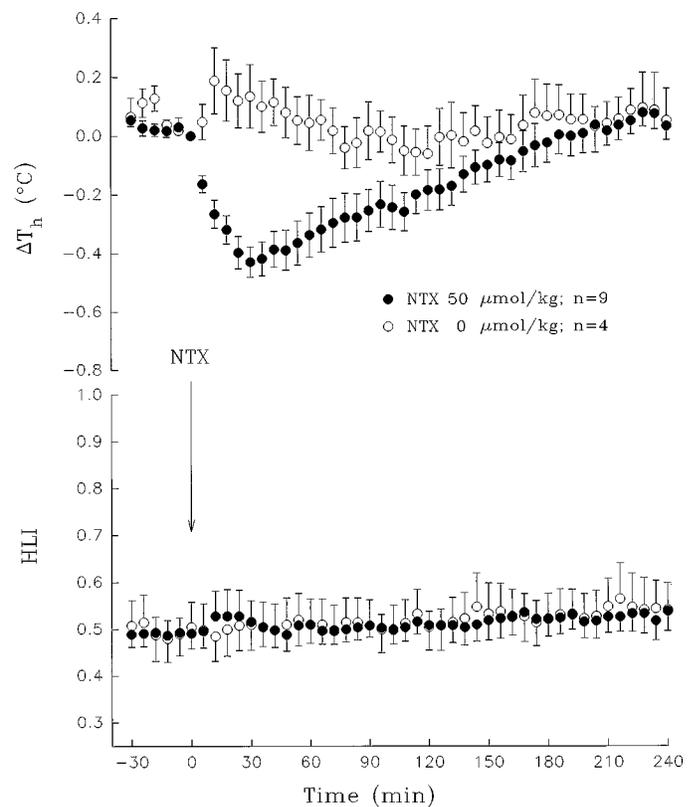

Fig. 5. ΔT_h and HLI of guinea pigs injected subcutaneously with NTX at doses indicated.

portion of the cardiac output to be directed to the skin (see Ref. 14 for review). In severe hyperthermia, however, the splanchnic vasculature becomes unresponsive to constrictor stimuli, presumably due to the release of nitric oxide into the splanchnic circulation (11). This lessens the proportion of the cardiac output available for the skin and precipitates skin vasoconstriction. The idea that circulatory collapse in heat stroke is triggered by splanchnic vasodilation was first proposed by Kielblock and coauthors (16) and further developed in the laboratory of Gisolfi [see Hall et al. (11) and Kregel et al. (17)].

Our results clearly demonstrated that NTX blocked the hyperthermia-induced vasoconstriction. This suggests that the vascular mechanisms activated in heat stroke and resulting in the peripheral vasoconstriction are opioid mediated. An alternative interpretation of the observed effect of NTX as a nonspecific effect (i.e., not mediated via opioid receptors) seems unlikely. Indeed, circulatory collapse, at least that associated with endotoxin shock, was shown to be blocked only by the $(-)$-stereoisomer of naloxone (binds to opioid receptors) but not by the $(+)$-isomer (does not bind to opioid receptors) (9). Our conclusion about the involvement of opioids in the mechanisms of the hyperthermia-induced vasoconstriction is in general agreement with the literature. Thus, endogenous opioid peptides are released into the blood in response to various stressors, including heat; exogenous opioid agonists, even in small doses, induce hypotension; and opioid antago-

nists block hemodynamic alterations in various models of shock (see Ref. 12 for review). Yet the intimate mechanisms of the effect of opioid antagonists on the hyperthermia-induced vasoconstriction, the specific role of endogenous opioids in this phenomenon, and pharmacological characterization of the opioid receptors involved remain to be elucidated.

Hyperthermia-induced hypothermia. Confirming our previous results (25), the cessation of IPH did not result in just a return of T_h to its pre-IPH level but rather was followed by the development of hypothermia. This phenomenon, termed hyperthermia-induced hypothermia, has been demonstrated in various experimental models and in different animal species. Thus not only IPH in guinea pigs (25) but also whole body heat exposure in guinea pigs (2), rats (19), mice (33, 34), and cats (2), as well as IPH in rats (28), all result in a T_b fall occurring after the heating is stopped.

A priori, the thermoregulatory mechanisms of the hyperthermia-induced hypothermia could involve: *1*) inhibition of metabolism; *2*) excessive heat loss (e.g., generalized peripheral vasodilation) that cannot be compensated for by an increase in heat production; *3*) regulation of T_b at a new, decreased level (parallel shifts of thermoeffector thresholds to a lower T_b); *4*) a substantially decreased precision of T_b regulation (development of the wide dead-band, poikilothermic type of control) when T_a is below thermoneutrality; or *5*) partial contributions of several of the mechanisms listed above. It has been demonstrated that hyperthermia-induced hypothermia occurs at low but not high T_a (33). It has also been shown that this phenomenon is associated with the widening of the interthreshold zone (poikilothermia), probably as a result of a decrease of the threshold T_b for cold thermogenesis (unpublished observations; see also Ref. 25). We speculate, therefore, that this metabolic inhibition and the consequent widening of the interthreshold zone constitute the major autonomic mechanisms of hyperthermia-induced hypothermia. It is worth noting that these are exactly the same mechanisms that have been recently found to underlie the hypothermia of endotoxin shock (26).

The present results further demonstrate that hyperthermia-induced hypothermia is opioid dependent because NTX significantly attenuates this phenomenon. If our concept of the thermoregulatory mechanism of post-IPH hypothermia were correct, this would imply that endogenous opioids are involved in the proposed metabolic inhibition. This corollary is in agreement with the existing literature. Indeed, opioids are known to inhibit metabolism and cause hypothermia at T_a below thermoneutral (8, 18). The opioid receptor subtype mediating the metabolic inhibition remains to be determined.

Potential clinical significance. Despite continuing economic development, technical progress, and medical advances, heat stroke remains an important clinical issue. It is pertinent not only to the Makkah Hajj, a famous pilgrimage to Mecca resulting in hundreds of deaths due to heat stroke each year (7, 15), but to our everyday life as well. In the United States, during hot summers, an average of 820 deaths are caused annually by heat injury, with at least 10 times more due to cardiovascular problems exacerbated by heat stress (3). Our present results may have potential clinical applications.

Among the symptoms that have traditionally been used to define heat stroke is high T_b ($>40.6°C$). This criterion should not, however, be considered obligatory because many patients with severe exertional heat stroke have lower T_b, presumably due to the progression of time from the actual heat overload (7). Our present data and several other experimental observations (2, 19, 25, 28, 33, 34) suggest that if the heat exposure is followed by the return of the animal to a near-thermoneutral environment, hypothermia rather than hyperthermia is likely to be recorded. Moreover, the longer and more intensive the initial heat exposure is, the deeper and longer is the consequent hypothermia (25, 33). It is noteworthy that all of the NTX-treated animals in the present study developed only a very mild post-IPH hypothermia and survived heat stroke, whereas deep hypothermia and 50% lethality were observed among the nontreated controls. We propose that when a patient with heat stroke is exposed to an T_a below thermoneutrality, a T_b fall may occur; this fall (hyperthermia-induced hypothermia) can be taken as a marker of the severity of heat stroke.

Another common symptom of heat stroke, a hot and dry skin, indicates the absence of sweating. Although there are several opinions about the mechanisms and significance of the cessation of sweating in heat stroke (see Ref. 7), the consensus is that the disappearance of this heat-loss response worsens the patient's prognosis. Similarly to the cessation of sweating, the reversal of skin vasodilation to vasoconstriction occurring at a high T_b (hyperthermia-induced vasoconstriction) may be taken as an index of the severity of heat stroke. In the present study, survival from heat stroke by NTX-treated animals was accompanied by the blockade of the hyperthermia-induced vasoconstriction.

An important result of this study is that all the guinea pigs treated with NTX survived IPH-induced heat stroke for the whole period of observation (48 h). This agrees with earlier reports that naloxone, an opioid-receptor antagonist with pharmacological properties similar to NTX, substantially increased the survival time in rats exposed to heat (21) and prevented hyperthermia-induced convulsions in rat pups (23). In consideration of the high levels of plasma β-endorphin in Mecca pilgrims with heat stroke (4), the antipyretic properties of naloxone (6, 27), and the beneficial effects of opioid antagonists in shock of various etiologies (12), it may be inferred that the blockade of endogenous opioids in heat stroke has a therapeutic potential.

The majority of studies on the role of the opioid system in the thermoregulatory response to heat, including the present work, were performed with the use of nonselective opioid antagonists such as naloxone and NTX. This design increases the probability of discovering a new effect because of the multiple actions (both

direct and indirect) of opioids on autonomic and behavioral thermoregulation. One of the priorities for future investigations, however, should be the determination of the receptor type(s) mediating beneficial effects of opioids in heat stroke.

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