



Metabolic actions of morphine in conscious chronically instrumented pigs

DTIC
ELECTE

SEP 03 1991

D

91-09341

CAROL A. BOSSONE AND JOHN P. HANNON

Division of Military Trauma Research, Letterman Army Institute of Research,
Presidio of San Francisco, California 94129

BOSSONE, CAROL A., AND JOHN P. HANNON. *Metabolic actions of morphine in conscious chronically instrumented pigs*. Am. J. Physiol. 260 (Regulatory Integrative Comp. Physiol. 29): R1051-R1057, 1991.—Effects of a modest dose of morphine sulfate (1 mg/kg) on total body energy metabolism, body thermal status, and the plasma concentrations of certain electrolytes and metabolites were investigated in conscious chronically instrumented pigs ($n = 8$). Control pigs ($n = 8$) received an equivalent volume of normal saline. Intravenous morphine injection led to an excitatory state associated with significant ($P \leq 0.05$) immediate increases in O_2 consumption, CO_2 production, respiratory exchange ratio, and plasma concentrations of lactate, glucose, potassium, phosphate, epinephrine, and norepinephrine. Significant more gradual increases were observed in rectal and skin temperatures, body heat content, and the plasma concentrations of adrenocorticotrophic hormone, cortisol, and phosphate. The hypermetabolic state persisted for ~ 1 h. Thereafter, most functional variables regressed toward, but did not reach, control levels. Increased muscle activity appeared to be the major factor underlying the rise in energy metabolism. Body heat storage after morphine injection appeared to be attributable to increased heat production coupled with an inadequate rise in heat loss.

morphine hyperthermia; conscious swine; metabolic rate; body heat content; heat balance; pituitary-adrenal axis

ALTHOUGH THE NARCOTIC and analgesic actions of morphine in humans and dogs were clearly recognized during the first half of the nineteenth century, some early investigators were reporting divergent actions in other species. In 1824, for instance, Dupuy et al. (11) showed that a large dose of morphine produced deep sleep and bradycardia in the dog but that, in the cat, a similar or even larger dose produced agitation and tachycardia. There was no general agreement, however, concerning the type of response to be expected in each species. Bernard (2) claimed that morphine had only soporific effects in a wide variety of the species, including cats, dogs, rabbits, guinea pigs, rats, pigeons, sparrows, and frogs. In the horse, some workers reported sedative and analgesic effects (27); others reported excitatory effects (13, 17). By the turn of the century, most such inconsistencies were resolved, largely because of an extensive series of studies conducted in the 1890s by Guinard (15-18). In a 1898 monograph summarizing his observations and measurements, Guinard (18) clearly distinguished between those species that were sedated or narcotized and those that were excited by morphine. He even ranked

species in terms of their sensitivity; sensitivity to sedative action was greatest in the dog, followed by the rabbit, guinea pig, rat, and mouse, whereas sensitivity to excitatory action was greatest in the horse, followed by the donkey, ox, cat, sheep, pig, and goat (18). (2)

In addition to these subjective observations, early investigators also reported a variety of functional changes, including alterations in metabolic rate and body thermal status. Indeed, Dupuy et al. (11) noted an increase in the body temperature of one of their excited cats but did not indicate the magnitude of change. Subsequent reports were often contradictory; increases, decreases, or no changes in body temperature were recorded after morphine administration. Sometimes, opposite results were obtained within the same species. It would appear that most, if not all, of these inconsistencies were attributable to differences in dosage or experimental conditions, particularly environmental temperature. As might be anticipated, most recent reports show that core temperature decreases during morphine narcosis but increases during morphine excitation (8, 23).

Functional changes responsible for the hypo- or hyperthermic effects of morphine have yet to be fully resolved but clearly involve an imbalance between heat production and heat loss. In the experimental work reported here, we investigated functional changes associated with morphine-induced hyperthermia in swine, a species that shows a distinct excitatory or manic response. In the past, this species has received little attention as an animal model for studies of morphine action, but it offers certain distinct advantages. Because of their size, multiple functions can be investigated simultaneously in pigs, a sometimes difficult task in smaller species. In conducting this study, we were particularly concerned with the following questions. Does morphine-induced excitation lead to an increase in energy metabolism? If so, what factor(s) are responsible for the increase? Does morphine-induced excitation lead to hyperthermia and a rise in body heat content? Do changes in body heat loss contribute to alterations in body thermal status? Finally, does morphine-induced excitation lead to hormonal changes that could contribute to alterations in body energy metabolism?

METHODS

Sixteen immature (26.1 ± 2.34 kg) duroc-cross pigs were obtained from a commercial breeder (Boswell, Cor-

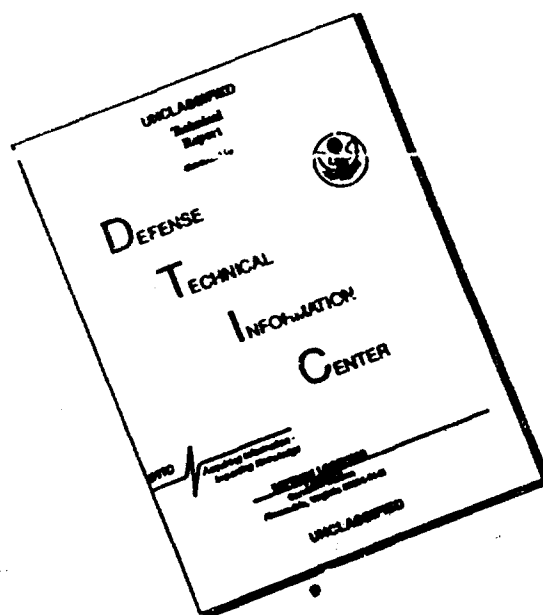
91 8 30 015

DISTRIBUTION STATEMENT A

Approved for public release;
Distribution Unlimited

R1051

DISCLAIMER NOTICE



THIS DOCUMENT IS BEST
QUALITY AVAILABLE. THE COPY
FURNISHED TO DTIC CONTAINED
A SIGNIFICANT NUMBER OF
PAGES WHICH DO NOT
REPRODUCE LEGIBLY.

coran, CA) and were maintained in a common indoor holding pen until studied 2–4 wk after arrival. They were fed a commercial ration (Purina Pig Chow; Ralston Purina, St. Louis, MO) and received water ad libitum. Seven to ten days before study, after an overnight fast, each pig received a preanesthetic injection of 0.8 mg/kg atropine sulfate, 2.2 mg/kg ketamine HCl, and 2.2 g/kg xylazine. Halothane anesthesia was induced by face mask and was maintained with an endotracheal catheter. The left carotid artery and jugular vein were exposed, and polyvinylidene catheters were inserted into the aortic arch and pulmonary artery; positioning was verified by recording desired pressure characteristics. The free ends of these catheters were tunneled beneath the skin and were exited on the dorsal surface of the neck, where they were fitted with Intramedic Luer stub adapters (Clay-Adams, Parsippany, NJ) and Argyle intermittent infusion plugs (Brunswick, St. Louis, MO). After wound closure, the catheters were filled through the infusion plugs with heparin (1,000 U/ml).

Commencing 3 to 5 days before surgical preparation, the pigs were trained for 30 min daily to accept a respiratory mask (Central City Medical, San Carlos, CA) and physical restraint in a Pavlov sling. This training schedule was interrupted on the day of surgery but was reinstated 2 days thereafter. In addition, the catheters were flushed daily with fresh heparinized saline (100 U/ml).

On the day of study, each pig was brought into the laboratory after an overnight fast, placed in the sling, and the respiratory mask was secured over the snout. The respiratory mask was fitted with a Rudolph valve and was connected by plastic tubing (25 mm inner diameter) to a metabolic apparatus (Horizons Systems, Anaheim, CA) for measurements of energy metabolism. This apparatus was calibrated daily before use and periodically over the course of each experimental period as specified by the manufacturer. The infusion plugs were removed from the stub adapters, and the catheters were connected to 30-cm pressure-monitoring injection lines with 3-way stopcocks. Stagnant blood and heparinized saline contained within the catheters were removed, and the catheters were refilled with heparinized saline (100 U/ml). Finally, internal and skin temperatures were measured with appropriate thermistor probes (Yellow Springs Instrument, Yellow Springs, OH); one was inserted 15 cm into the rectum, and the other was attached to the dorsal surface of the neck midway between the scapulae and the ears. The pig was then allowed to lie quietly in the sling until O_2 consumption achieved stable values for at least 10 min. Control values were then obtained in triplicate at 10-min intervals after which the pigs were assigned alternately to either an experimental group ($n = 8$) or a control group ($n = 8$). The former received 1.0 mg/kg morphine sulfate injected as a bolus into the pulmonary artery, the latter an equivalent volume (<2 ml) of normal saline. The dose of morphine sulfate was based on preliminary studies that showed a threshold response at 0.2–0.4 mg/kg and a consistent response to doses >1.0 mg/kg. Experimental measurements were recorded at 5, 10, 30, 60, 120, 180, and 240 min after injection.

During the control period and at each of the aforemen-

tioned time points, O_2 consumption and CO_2 production ($ml \cdot min^{-1} \cdot kg^{-1}$, standard temperature and pressure, dry) were measured, and blood samples were withdrawn from the aorta. These samples were immediately partitioned to chilled test tubes containing heparin, EDTA, or EDTA and sodium metabisulfite and were then placed in ice-cold water. Plasma was subsequently removed, distributed to individual tubes, and frozen ($-70^\circ C$) for later analyses.

Glucose and lactate concentrations were determined enzymatically with a Cobas Fera centrifugal analyzer (Roche Analytical Instruments, Belleville, NJ) using Beckman (Brea, CA) and Sigma (St. Louis, MO) reagents, respectively. The same analyzer was used to measure plasma sodium and potassium concentrations with ion-selective electrodes, and phosphate was measured by the procedure of Crouch and Malmstadt (9). For each hormone, all of the samples from a given pig were measured within the same assay. Plasma epinephrine and norepinephrine levels were determined by electrochemical detection (Bioanalytical Systems, West Lafayette, IN) after separation by high-performance liquid chromatography (HP 1050; Hewlett-Packard, Palo Alto, CA). The within-assay coefficient of variability for both catecholamines was 10%, and sensitivity was 20 pg/ml. Plasma adrenocorticotrophic hormone (ACTH) and cortisol concentrations were measured by radioimmunoassay with kits from Nichols Laboratories (San Juan Capistrano, CA) and Diagnostic Products (Los Angeles, CA), respectively. The ACTH procedure had a 10% within-assay coefficient of variability and a sensitivity of 11 pg/ml. The cortisol procedure had within-assay coefficients of variability and sensitivity of 3% and 0.2 $\mu g/ml$, respectively.

Alterations in body heat content during the course of the experimental period were estimated by the following equation

$$\Delta h = 0.78[(0.8)(\Delta T_r) + (0.2)(\Delta T_s)]$$

where Δh is the change in body heat content in calories per kilogram of body weight, ΔT_r and ΔT_s are the changes in rectal and skin temperatures, respectively, and 0.78 is the specific heat per kilogram of body weight for young pigs. The latter value was calculated from data on the body composition of young pigs (5) and from the fractional specific heat contributions of body water, body fat, and fat-free dry mass (10). The partition coefficients, 0.8 and 0.2, were chosen arbitrarily to represent the relative core and shell contributions to total body heat, respectively. The rate of body heat storage, or loss ($\Delta h/min$), was calculated for successive time increments of the experimental period, and changes in this rate were used to estimate alterations in heat loss. Thus, since heat production and heat loss were equal during the control period (rectal and skin temperature remained constant), heat production, or loss, could be calculated by the following equation

$$\text{heat production (cal/min)} = K (O_2 \text{ consumption})$$

where K is the thermal equivalent of O_2 (29) at the respiratory exchange ratio measured during the control period. During the experimental period after morphine

injection, the respiratory exchange ratio increased largely, if not entirely, because of hyperventilation. Arbitrarily, therefore, it was assumed that the nutrients supporting energy metabolism remained unchanged during this period, and the control value for K (4.825 on the average) was used to calculate heat production. Heat loss during the experimental period was then estimated as the algebraic sum of heat production and heat loss.

All data were evaluated by the two-factor analysis of variance model, with treatment (morphine, control) taken as a fixed effect and time as a repeated measure. In addition, a single-factor analysis of variance model was used to examine time effects within each of the two groups, particularly in an effort to detect subtle changes that may have occurred in the control animals. Differences were considered significant when $P \leq 0.05$.

RESULTS

Shortly after intravenous injection, morphine produced an excitatory state, characterized by vigorous bouts of struggling and vocalization. These symptoms persisted 30–60 min and gradually abated thereafter. Individual animals exhibited periods of elevated muscle activity that coincided with periods of elevated metabolic activity, and morphine-injected animals, as a group, exhibited significant increases in both O_2 consumption and CO_2 production. At 10 min into the experimental period, for example, O_2 consumption had risen from 8.1 ± 0.92 to 15.0 ± 1.30 ml·min⁻¹·kg⁻¹, and CO_2 production had risen from 6.7 ± 0.89 to 15.6 ± 0.91 ml·min⁻¹·kg⁻¹ (Fig. 1). Because CO_2 production increased to a slightly greater extent than O_2 consumption, the respiratory exchange ratio rose significantly during the experimental period,

from 0.83 ± 0.018 to a peak value of 0.97 ± 0.025 ml·min⁻¹·kg⁻¹. Hypermetabolism was sustained for 30–60 min after morphine injection but, subsequently, both O_2 consumption and CO_2 production reverted gradually toward control levels. At 3–4 h after injection, however, slightly elevated values for both variables were still being recorded. The excitatory state also produced a significant rise in plasma lactate concentration, from 1.2 ± 0.28 to a peak value of 6.6 ± 0.99 meq/l at 10 min into the experimental period. Thereafter, lactate concentration decreased and approached control levels 2–3 h after morphine injection. Only one significant metabolic change was seen in control pigs injected with normal saline, a decrease in the respiratory exchange ratio (from 0.79 ± 0.022 to 0.73 ± 0.014) over the course of the experimental period.

Increases in both skin and rectal temperature were observed after morphine administration (Fig. 2). The rise in skin temperature was greater and occurred over a shorter period of time (from 34.0 ± 0.63 to $38.0 \pm 0.53^\circ\text{C}$ over 1 h) than the rise in rectal temperature (from 38.7 ± 0.18 to $40.9 \pm 0.30^\circ\text{C}$ over 2 h). Subsequent to these maxima, decreasing values were recorded at both sites. Nevertheless, hyperthermia was clearly evident 4 h after morphine injection. As would be expected, calculations based on these changes in temperature revealed significant increases in body heat content. A total of 2.06 ± 0.230 kcal/kg were thus stored in body tissues over a 2-h period after morphine injection. This heat load was only partially dissipated over the remainder of the experimental period. Heat balance calculations, based on the caloric equivalent of O_2 consumption and changes in body heat content as a function of time, showed that morphine-induced heat storage was caused by an ine-

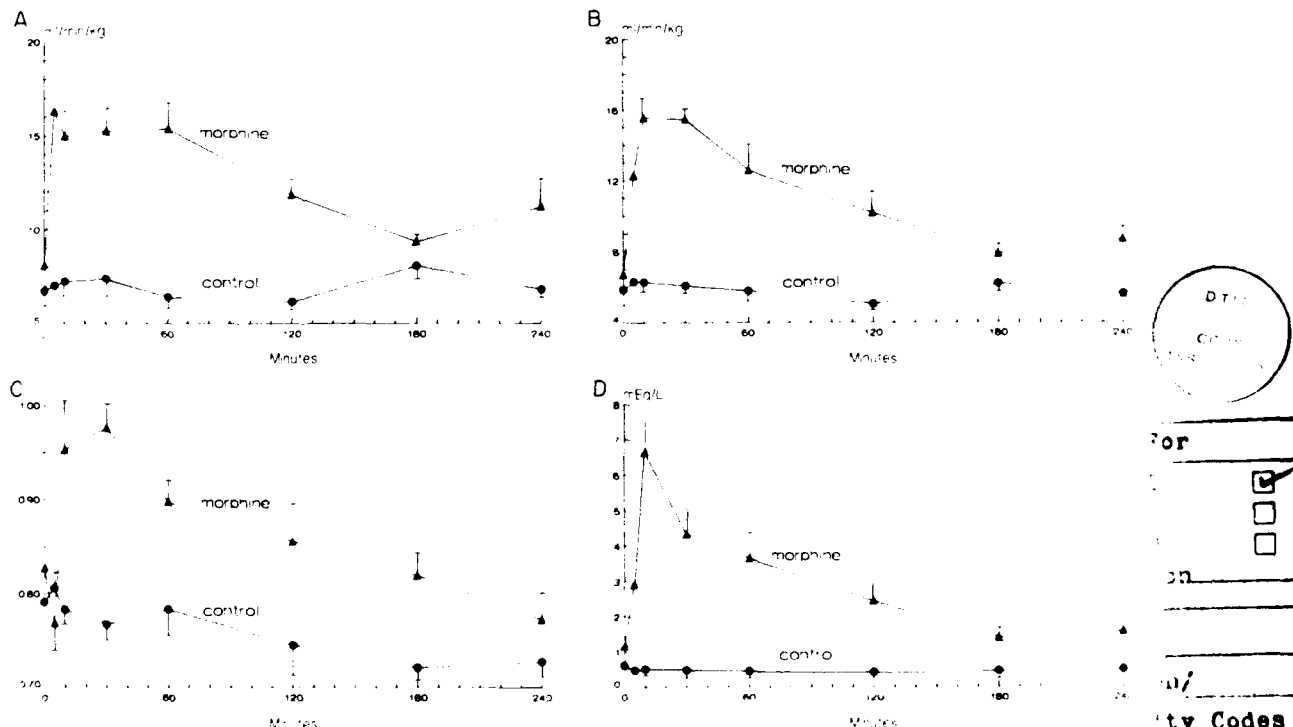


FIG. 1. Effects of morphine sulfate (1 mg/kg) on energy metabolism of conscious pigs ($n = 8$). A: oxygen consumption. B: CO_2 production. C: respiratory exchange ratio. D: plasma lactate.

Dist	Special
A-1	20

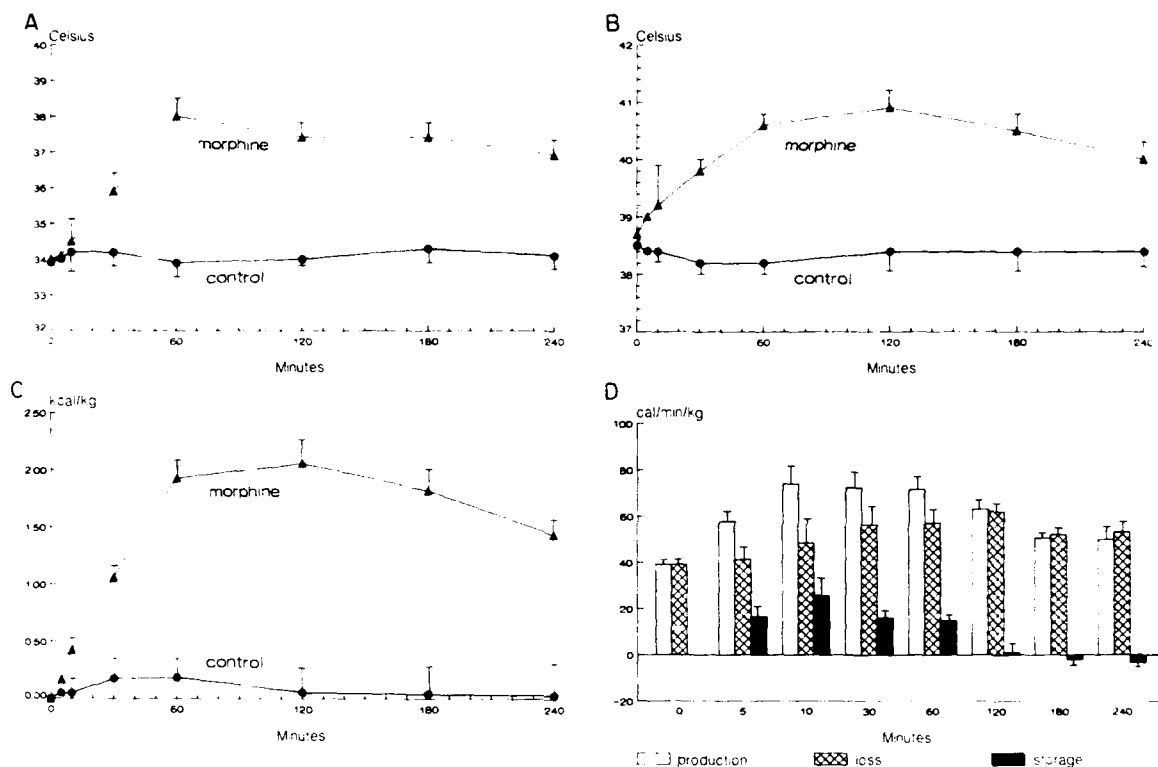


FIG. 2. Effects of morphine sulfate (1 mg/kg) on body thermal status of conscious pigs ($n = 8$). A: skin temperature B: rectal temperature. C: body heat storage. D: heat balance.

quality of body heat production relative to body heat loss. Thus, as heat was being stored, the rate of heat production exceeded the rate of heat loss and subsequently, as stored heat was being dissipated, the rate of loss exceeded the rate of production. Control pigs showed no significant changes in the body temperature or thermal status over a 4-h period after normal saline injection.

The hypermetabolic response to morphine was accompanied by hyperglycemia and alterations in certain plasma electrolyte concentrations (Fig. 3). Blood glucose concentration thus rose from a control level of 93 ± 3.0 mg/dl to a maximum value of 159 ± 24.9 mg/dl over the first 10 min of the experimental period. Thereafter, glucose concentration decreased progressively and reached control levels 2–3 h after morphine injection. A rapid rise in plasma potassium concentration (from 4.3 ± 0.13 to 5.4 ± 0.36 meq/l) was also observed after morphine injection, but, in this instance, the effect was sustained for about 2 h before the values regressed toward control levels. Plasma phosphate showed a more gradually evolving increase in concentration, from a control level of 6.7 ± 0.15 mg/dl to a peak level of 8.2 ± 0.29 mg/dl at 30 min after morphine injection. Other plasma electrolytes, such as bicarbonate and sodium (data not shown), were not significantly affected by morphine. Plasma glucose and electrolyte levels of control animals showed no significant changes as a function of time after normal saline injection.

Hormonal responses to morphine injection fell into two categories, those that occurred rapidly and those that evolved slowly (Fig. 4). In the former category, a highly significant rise in plasma norepinephrine concentration (from 203 ± 20.3 to $2,289 \pm 490.3$ pg/ml) was

observed over the first 10 min of the experimental period, and a highly significant rise in plasma epinephrine concentration (from 94 ± 24.2 to 633 ± 106.8 pg/ml) was observed over the first 30 min of the experimental period. Plasma ACTH concentration, in contrast, increased gradually from a control level of 51 ± 10.8 to a maximum of 307 ± 76.7 pg/ml at 120 min after injection. This increase, as would be anticipated, led to a delayed rise in plasma cortisol concentration, from a control level of 5.6 ± 1.35 μ g/dl to a peak level of 18.8 ± 1.31 μ g/dl at 180 min into the experimental period. No significant changes in plasma hormone concentrations were observed in control animals.

DISCUSSION

The present study shows that a relatively small dose of morphine (1 mg/kg) produces an excitatory state in immature pigs, a response accompanied by a near doubling of total body energy metabolism and a rise in both core and shell temperatures. The excitatory response is consistent with the early reports of Guinard (15, 18) and Medjakow (24). Guinard (15), furthermore, reports a body temperature rise to 41.3°C in one pig after a 2,600-mg/kg injection of morphine chlorhydrate. The hyperthermic response is also seen in other species that become excited or manic after morphine administration, including horses (14, 17), donkeys (17), cattle (12, 14, 16), goats (14), sheep (12), cats (6, 8, 11, 20, 28), and, under certain experimental circumstances, guinea pigs, rats, and mice (6, 7, 23). Rodents, it should be noted, may exhibit either hyper- or hypothermia, depending on the dose of morphine administered (6, 23).

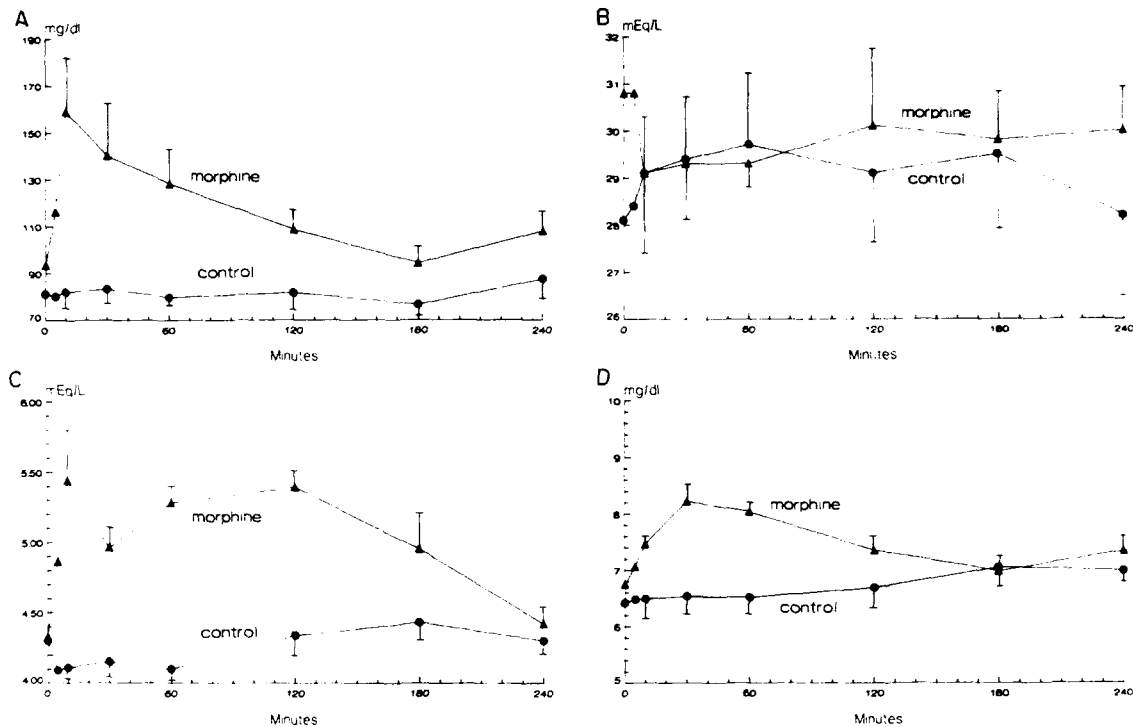


FIG. 3. Effects of morphine sulfate (1 mg/kg) on plasma glucose and electrolyte levels of conscious pigs ($n = 8$). A: plasma glucose. B: plasma bicarbonate. C: plasma potassium. D: plasma phosphate.

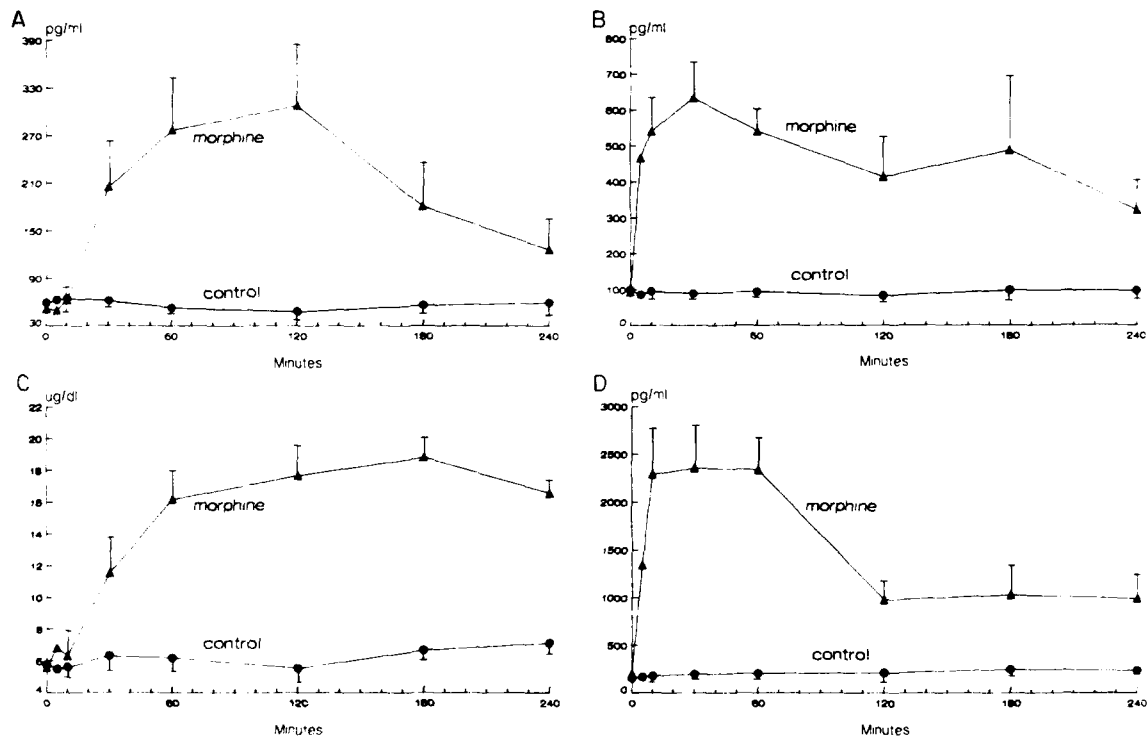


FIG. 4. Effects of morphine sulfate (1 mg/kg) on plasma hormone levels of conscious pigs ($n = 8$). A: plasma ACTH. B: plasma epinephrine. C: plasma cortisol. D: plasma norepinephrine.

The effects of morphine on the total body energy metabolism are rarely investigated in animals that are excited by morphine. In fact, we are aware of only two reports. In one, Boeck and Bauer (4) report an average 13% increase in O_2 consumption and a 42% increase in CO_2 production of one cat, measured over a 6-h period

after injection of a relatively high dose of morphine (~50 mg/kg). Their results are at least qualitatively consistent with data recorded here, including our observation of a rise in the respiratory exchange ratio. The second report, by Thornhill and Saunders (30), is a bit perplexing. In a study of morphine-induced hyperthermia in conscious

rats, they report a decrease in O_2 consumption concomitant with increases in both rectal and skin (tail) temperatures, a seemingly incompatible set of results. Thornhill and Saunders (30) do not explain how both core and shell temperature can rise while heat production, as reflected by O_2 consumption, is decreasing.

Results of the present study seem to indicate that an imbalance between the rate of heat production and the rate of heat loss is largely responsible for the morphine-induced hyperthermia observed in pigs. Thus, during the first hour after morphine injection, heat production, as calculated from O_2 consumption, exceeded heat loss, as calculated from differences between heat production and heat storage. It should be emphasized that these calculated values for body thermal status are only estimates and are based on assumptions that may or may not be totally valid. The caloric equivalent of O_2 consumption, for example, is assumed to remain constant after morphine injection. The selected value, 4.825 kcal/l of O_2 consumed (12), is based on a steady-state respiratory exchange ratio measured before morphine injection. After morphine injection, our data show a rise in this ratio from 0.83 to 0.97, suggesting a shift toward carbohydrate metabolism. If this does indeed occur, the caloric equivalent would increase by 4% to 5.022 kcal/l O_2 consumed. However, after morphine injection the pigs were no longer in a steady state, hence the altered respiratory exchange ratio could reflect changes in acid-base status or ventilatory function. In any event, a 4% increase in the caloric equivalent or a 3% decrease if only fat were being oxidized (29) would have little effect on our calculated values for heat production.

The calculated changes in body heat content presented here are also based on assumptions that may not be totally valid. In calculating these changes, we used conventional partitioning coefficients to reflect the contributions of core (0.8) and shell (0.2) temperatures to body heat content. These coefficients are arbitrary estimates that are assumed to be applicable to humans under steady-state conditions (10); they may or may not be applicable to pigs. Calculated changes in body heat content could be altered if the relative magnitude of these coefficients were to change significantly during the course of an experiment. Unfortunately, no methods are presently available for measuring their true values, at least insofar as we can determine. Skin temperatures used in this study are taken from one site, the back of the neck, and are assumed to reflect the average skin temperature of the entire body. Actual measurement of average skin temperature is technically difficult in conscious pigs, particularly when they are agitated. In separate experiments with quietly resting pigs (unpublished observations), we find that most body sites have values that are within $1^\circ C$ of the value measured on the dorsal surface of the neck; the feet are a major exception and may have temperatures several degrees below neck values. Minor variations in the absolute values for average skin temperature have little effect on calculated increases or decreases in body heat content, provided the changes in skin temperature were of similar magnitude over the body surface as a whole. Dissimilar changes could introduce significant errors in the calculations. Despite these

potential sources of error, alterations in the calculated variables contributing to body thermal status would seem to be reasonably consistent with alterations in the variables that are actually measured. Accordingly, as core and skin temperatures rise after morphine injection, heat production increases at a faster rate than heat loss, a disparity that leads to a rise in body heat content. Similarly, as core temperature falls during the later stages of the experimental period, heat loss exceeds heat production, and body heat content decreases.

Some investigators have suggested that hyperthermic responses to morphine are attributable to a rise in the thermoregulatory set point (7), and our data do not unequivocally rule out this possibility. Morphine may have had a dual effect; it could raise the set point and elicit sufficient excitation and motor activity to produce the added heat needed to attain the newly regulated temperature. Under non-steady-state conditions, as in this study, true changes in set point are difficult, if not impossible, to verify. The near equality of heat production and heat loss at 2-3 h after morphine injection would be consistent with such a change. However, the imbalance between heat production and loss during the first hour after injection would seem to favor a simpler explanation, namely that the hypermetabolic effect of morphine, at least in pigs, is analogous to that seen during exercise. It is now well established that swine do not sweat, have a limited capacity to increase heat loss by panting, and readily become hyperthermic when exercised or exposed to hot environments (21, 26). During exercise, therefore, hyperthermia is not attributable to a change in thermoregulatory set point but rather to an inability to raise heat loss to a level commensurate with heat production. It seems likely, at least to us, that a similar imbalance is largely responsible for the morphine-induced hyperthermia observed in the present study.

Other data recorded here seem to support our opinion that muscle activity is the primary mechanism underlying the morphine-induced hyperthermia observed in swine. Plasma lactic acid levels, for example, rise in parallel with the rise in O_2 consumption as they commonly do during heavy exercise (1). The hyperkalemia observed here after morphine injection is comparable to that seen during exercise in humans; loss of muscle potassium is the responsible mechanism (22). Finally, the rise in plasma phosphate concentrations after morphine administration suggests a breakdown of high-energy phosphates, presumably phosphocreatine, a breakdown that is also seen during muscle activity (1).

Studies in other species, principally in rats and cats, have produced conflicting opinions regarding the cause of morphine-induced hyperthermia. Some workers attribute the response to muscle activity (4, 23, 28), whereas others (31) state that morphine-induced hyperthermia can occur in the absence of muscle activity. Indeed, other factors could have contributed to the increases in O_2 consumption, core and shell temperatures, and body heat content recorded here. As indicated above, a relative attenuation of heat loss would be expected to lead to a rise in core temperature, a rise that could contribute to the increase in O_2 consumption by means

of the van't Hoff-Arrhenius effect; however, calculation of temperature coefficient values over the course of the entire experimental period (data not shown) indicate that van't Hoff-Arrhenius effects could only have a major impact on body energy metabolism during the later stages of recovery. In addition, the increased circulating catecholamine levels could produce a hypermetabolic state either directly by their actions of cellular energy metabolism (19) or indirectly by inducing excitation and muscle activity. Furthermore, a morphine-induced increase in circulating catecholamine levels, particularly epinephrine, is probably responsible for the hyperglycemia recorded here as well as elsewhere (3, 28). Such hyperglycemia would support an elevated energy turnover in active skeletal muscles (1). Activation of the pituitary-adrenal axis, seen here and in some other studies (25), could provide additional support by enhancing gluconeogenesis.

In summary, our data suggest that the hypermetabolic effect of morphine in pigs is largely due to increases in muscle activity and that the hyperthermic effect is attributable to an inability to increase heat loss to levels commensurate with the increase in heat production.

We acknowledge the superb assistance of Dr. Charles E. Wade, Marjorie M. Hunt, Janice A. Loveday, and Robert I. Coppes in conducting the hormonal, metabolite, and electrolyte assays reported here, Dr. Virginia L. Gildengorin for statistical evaluation of data, and Susan E. Siefert for editorial review of the manuscript.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official nor do they reflect the views of the Department of Army or the Department of Defense.

The studies described in this report were reviewed and approved by the Institutional Review Committee/Animal Care and Use Committee at Letterman Army Institute of Research. The manuscript was peer reviewed for compliance before submission for publication. In conducting the research described here the investigators adhered to the Guide for the Care and Use of Laboratory Animals, DHEW Publication No. (NIH) 85-23, Revised 1985, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20205.

Address reprint requests to J. P. Hannon.

Received 27 August 1990; accepted in final form 8 January 1991.

REFERENCES

- ÅSTRAND, P.-O., AND K. RODAHL. *Textbook of Work Physiology*. New York: McGraw-Hill, 1970.
- BERNARD, C. Recherches expérimentales sur l'opium et ses alcaloïdes. *Comp. Rend. Acad. Sci.* 59: 406-415, 1864.
- BODO, R. C., F. C. COTUI, AND A. E. BENAGLIA. Studies of hyperglycemia. The role of the sympathetic nervous system with special reference to the sympathetic supply to the liver. *J. Pharmacol. Exp. Ther.* 62: 88-105, 1938.
- BOECK, H. V., AND J. BAUER. Ueber den Einfluss einiger Arzneimittel auf den Gasaustausch bei Thieren. *Z. Biol.* 10: 336-372, 1874.
- BOSSONE, C. A., AND J. P. HANNON. A multi-isotope procedure for simultaneously estimating the volume of body fluid compartments of swine. In: *Swine in Biomedical Research*, edited by M. E. Tumbleson. New York: Plenum, 1986, p. 49-59.
- CLARK, W. G., AND Y. L. CLARK. Changes in body temperature after administration of acetylcholine, histamine, morphine, prostaglandins and related agents. *Neurosci. Biobehav. Rev.* 4: 175-240, 1980.
- CLARK, W. G., AND H. R. CUMBY. Hyperthermic responses to central and peripheral injections of morphine sulphate in the cat. *Br. J. Pharmacol.* 63: 65-71, 1978.
- CLARK, W. G., AND J. M. LIPTON. Changes in body temperature after administration of acetylcholine, histamine, morphine, prostaglandins and related agents. II. *Neurosci. Behav. Rev.* 9: 479-552, 1985.
- CROUCH, S. R., AND H. V. MALMSTADT. An automatic reaction rate method for determination of phosphate. *Anal. Chem.* 39: 1090-1093, 1967.
- DUBOIS, E. F. *Basal Metabolism in Health and Disease*. Philadelphia, PA: Lea & Febiger, 1936.
- DUPUY, DEGUISE, AND LEURET. Expériences sur l'action de l'acétate de morphine dans les animaux, et sur les moyens de reconnaître l'empoisonnement par cette substance. *J. Gén. Méd. Chir. Pharm.* 86: 13-30, 1824.
- FESER. Die in neuester Zeit in Anwendung gekommenen Arzneimittel. *Z. Prakt. Vet.-Wissensch. Thierarzt.* 14: 212-217, 1875.
- FRIEDBERGER. Unangenehme Folgen einer Morphinum-injection bei einem Pferde. *Wochenschr. Thierheilk. Viehzucht.* 21: 121-124, 129-136, 1877.
- FRÖHNER. Untersuchungen über das Codein und Apocodein als Ersatzmittel des Morphiums und Apomorphins nebst einigen Beiträgen zur Toxikologie des Morphiums. *Monatsschr. Prakt. Thierheilk.* 4: 249-272, 1893.
- GUINARD, M. L. Étude de physiologie comparée sur le morphinisme. La morphine chez le porc. *J. Méd.-Vét. Zootech.* 18: 199-207, 1893.
- GUINARD, M. L. A morphine chez les bovins. *J. Méd.-Vét. Zootech.* 18: 262-277, 1893.
- GUINARD, M. L. La morphine chez les solipèdes. Citation de quelques travaux relatifs à l'action de ce médicament chez le boeuf et le cheval. I. La morphine chez le cheval et l'âne. *J. Méd.-Vét. Zootech.* 18: 385-397, 1893.
- GUINARD, L. *La Morphine et L'Apomorphine*. Paris: Asselin et Houzeau, 1898.
- HAGEN, J. H., AND P. B. HAGEN. Actions of adrenalin and noradrenalin on metabolic systems. In: *Actions of Hormones on Metabolic Processes*, edited by G. Litwack and D. K. Kritchewsky. New York: Wiley, 1964, p. 268-319.
- HELFRICH, L. S. The effect of morphine sulfate on temperature of various animals. *Arch. Int. Pharmacodyn. Ther.* 49: 259-261, 1935.
- INGRAM, D. L., AND K. F. LEGGE. The effect of environmental temperature on respiratory ventilation in the pig. *Respir. Physiol.* 70: 1-12, 1969.
- KILBURN, K. H. Muscular origin of elevated plasma potassium during exercise. *J. Appl. Physiol.* 21: 675-678, 1966.
- LOTTI, V. J. Body temperature responses to morphine. In: *The Pharmacology of Thermoregulation*, edited by E. Schönbaum and P. Lomax. Basel: Karger, 1973, p. 382-394.
- MEDJAKOW, F. S. Über die Wirkung von Adrenalin und Morphin auf die Magensaftsekretion beim Schwein. *Bull. Biol. Med. Exp. URSS* 8: 170-171, 1939.
- MEITES, J., J. F. BRUNI, D. A. VAN VUGT, AND A. F. SMITH. Relation of endogenous opioid peptides and morphine to neuroendocrine functions. *Life Sci.* 24: 1325-1336, 1979.
- PARSONS, A. H., S. C. SMITH, R. KERTZER, AND I. A. SALKOVITZ. Endurance exercising in pigs—a review of methodology. In: *Swine in Biomedical Research*, edited by M. E. Tumbleson. New York: Plenum, 1986, vol. 1, p. 143-151.
- ROSSIGNOL. Emploi des injections hypodermiques d'une solution de chlorhydrate de morphine pour ferrer et tondre les chevaux difficiles. *Bull. Soc. Méd. Vét.* 9: 82-88, 1889.
- STEWART, G. N., AND J. M. ROGOFF. The influence of morphine on normal cats and on cats deprived of the greater part of the adrenals, with special reference to body temperature, pulse and respiratory frequency and blood sugar content. *J. Pharmacol. Exp. Ther.* 19: 97-130, 1922.
- SUNDERMAN, F. W., AND F. BOERNER. *Normal Values in Clinical Medicine*. Philadelphia, PA: Saunders, 1950.
- THORNHILL, J. A., AND W. S. SAUNDERS. The role of the pituitary-adrenal axis in the hyperthermia induced by acute peripheral or central (preoptic anterior hypothalamus) administration of morphine to unrestrained rats. *Can. J. Physiol. Pharmacol.* 63: 1590-1598, 1985.
- WALLENSTEIN, M. C. Temperature responses to morphine in paralyzed cats. *Eur. J. Pharmacol.* 49: 331-333, 1978.