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THE OPIOID SYSTEM AND TEMPERATURE REGULATION

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INTRODUCTION

A rapid perusal of the literature on the effects of drugs in a whole organism indicates that a wide variety of drugs, from many different classes of pharmacologic agents, can alter body temperature (T_b). Morphine has long been known to produce changes in T_b; the specific effect of this drug is dependent on a variety of factors, such as species and strain of animal, dose and route of administration of the drug, ambient temperature, circadian rhythms, age, and the degree of restraint imposed on the animal. These and other factors have been treated in a number of reviews (e.g. 1, 2), and some are discussed below. Less is known about the actions of other opioids and about the results of the administration of endogenous opioid peptides and their analogues on T_b. In addition to bringing the reader up to date on the effects of opioids and endogenous opioid peptides and their analogues on T_b, we attempt to develop the thesis that the opioid system (ligands and receptors) plays a role in thermoregulation. Since much of the research on the effects of

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opioids on T_b has been carried out in rats and mice, this review focuses on these two species. Other species are discussed in less detail, but it seems likely that principles derived from studies in rodents will be applicable to other mammalian species as well.

THERMOREGULATION

Although an in-depth discussion of thermoregulation is far beyond the scope of this article, some introductory comments are necessary for understanding the effects of opioids as more than a mere change in T_b. A drug-induced change in body temperature, per se, does not mean that the particular drug plays a role in thermoregulation. Rather, it shows only that T_b can be altered by the drug. Maintenance of T_b requires both regulation and control. The regulation of internal temperature involves the activity of a control system that serves to maintain a constant level of T_b in the face of changing thermal loads applied to the body. The control of T_b, on the other hand, involves the activity of one or more effector systems that results in a change in T_b. All regulators are also controllers, but not vice versa. A regulator uses a controller to achieve the desired state of constancy. T_b is regulated in both homeotherms (endotherms) and heterotherms (ectotherms; poikilotherms). It is generally accepted that T_b regulation is achieved by a neural network, situated in the CNS, that exerts command functions over an array of controllers or controlled systems present throughout the body. The integration of central and peripheral thermal information results in the appropriate thermoregulatory responses necessary for the maintenance of normal T_b. While the homeotherm maintains a constant internal temperature by balancing heat production and heat loss through the activation of autonomic nervous system mechanisms as well as by altering behavior, heterotherms do not possess such controlled systems but use only behavioral means to change their environment and thereby regulate their T_b.

There is general agreement that the primary site of thermoregulatory control in mammals is the preoptic anterior hypothalamus (POAH), with its array of thermosensitive neurons that receive afferent neural input from cold and warm sensors in both the periphery and other parts of the central nervous system. However, other sites in the brain, spinal cord, and periphery are also of great importance. For example, thermosensitive and thermoregulatory structures are located in the septum, posterior hypothalamus, midbrain, pons, medulla, and the abdominal wall (3–5). It should be borne in mind that even though a substance exerts a direct action on temperature control in the hypothalamus, it can have an opposite effect on T_b by its actions in the periphery (6). What we see as T_b is the endproduct of heat production, heat loss, and heat storage. At a minimum, an understanding of the mechanisms

involved in the actions of a drug on T_b must include the measurement of metabolic heat production (usually by determining oxygen consumption) and heat loss. The most accurate way of quantitating the latter is by use of a whole-body calorimeter. The concept of set point is crucial. Normally, the body maintains a temperature (thermoregulates) around a given temperature, the *set point*. If a drug acts by changing the set point, the body can still maintain its temperature in a narrow range around that new temperature. On the other hand, if a drug alters thermoregulation, then it prevents or decreases the ability of the body to maintain a given core temperature. At the extreme, the body loses all ability to control its temperature and drifts towards the temperature of the environment *(poikilothermia)*.

One approach that can aid in determining whether a drug affects set point or the ability to thermoregulate is to measure its effect on heat production and heat loss at different ambient temperatures. Coordinated changes in heat gain and heat loss mechanisms indicate a change in set point, whereas the lack of appropriate responses in these systems suggests an alteration in thermoregulatory control. Another method is to determine if the subject will engage in behavioral thermoregulation, i.e. perform some task or move to a temperature that will aid in maintaining a given T_b. Thus, if a drug that decreases T_b causes the animal to move to a warmer environment, then the set point has not been affected. If, on the other hand, the subject seeks a colder ambient in conjunction with a lowered core temperature, then an altered set point is to be inferred. Lack of movement towards either a higher or lower environmental temperature indicates loss of thermoregulatory control (assuming that physical ability to respond remains intact).

Although several neurotransmitters have been implicated in thermoregulation, norepinephrine, acetylcholine, and serotonin have received the most comprehensive attention (4, 7–11). Because the effects that the transmitters exert on T_b vary with species, site of injection, and dose (9), it is not possible to categorize unequivocally the effect of each substance, even in a given species. However, if one approaches the available data with the requirement that the role of a transmitter in a given species be assigned on the basis of experiments that (collectively) (*a*) measure temperature responses continuously following microinjection of low doses directly into the hypothalamus of unrestrained animals, (*b*) include observations of concomitant behavioral thermoregulatory responses, and (*c*) measure the responses of hypothalamic thermosensitive neurons to local application, then consistent patterns appear. In the rat, for example, hypothalamic application of acetylcholine produces a dose-dependent, atropine-blocked fall in T_b, a concomitant increase in cutaneous (tail) temperature, activation of behavioral heat-loss responses, and excitation of temperature-sensitive (i.e. warm-sensitive) neurons (8, 12–14). Collectively, these data suggest that acetylcho-

line acts in the POAH of the rat to lower the temperature set point through action on hypothalamic temperature-sensitive neurons. On the other hand, norepinephrine appears to act in the POAH to raise the set point. That is, several experiments have shown that POAH microinjections of norepinephrine produce an increase in temperature, parallel increases in behavioral heat-gain responses, and inhibition of hypothalamic warm-sensitive cells (7, 12). Intrahypothalamic administration of 5-hydroxytryptamine to rats in low doses produces dose-dependent increases in T_b, inhibition of hypothalamic warm-sensitive cells, and excitation of cold-sensitive cells (12, 15; A. L. Beckman, unpublished observations). The failure to demonstrate clear parallel behavioral thermoregulatory responses (15) suggests that the action of 5-hydroxytryptamine in the hypothalamus, while causing an increase in T_b, does so without increasing the thermoregulatory set point.

EXOGENOUS OPIOIDS

With the above brief discussion in mind, we can proceed to a consideration of the effects of opioids. Most studies have been conducted with morphine, although some have also been carried out with other opioids. Several reviews of this work have appeared, the most comprehensive being those by Clark (2, 16). The effects of morphine are species-specific. Hypothermia is the predominant response in the dog (17, 18), rabbit (19–21), and bird (22). On the other hand, hyperthermia is the predominant response in a number of other species, particularly those that become excited after treatment with morphine, such as cats (23–28), cattle, goats, and horses (29). The species-specific nature of the T_b response to morphine is further demonstrated by the fact that a dose-dependent dual response (low-dose hyperthermia and high-dose hypothermia) occurs in the rat (17, 30–33), the mouse (34–36), and primates (37–39). There is general agreement that naloxone blocks and antagonizes the effects of morphine on T_b.

Isolated reports have appeared that describe the actions of opioids other than morphine on T_b in a variety of species (for review see 2, 16). Only a few laboratories, however, have reported full dose-response studies for a large range of opioids. One series, dealing with the mouse (36), has shown that morphine and 10 other opioids produced complex but qualitatively similar effects on T_b. At 20°C, the dual response was noted. At 25°C the hypothermic responses were diminished, whereas at 30°C, all except meperidine produced dose-related hyperthermia. The same investigators (C. E. Rosow & J. Cochin, unpublished data) found that the *l*-isomers were more effective, but the *d*-enantiomers had some effect. In another study, Rosow et al (40) found that agonist-antagonist opioids could be divided into two groups, according to their effects on T_b.

Another series of reports deals with the rat. In that species, subcutaneously administered opioids can be categorized into five groups, using the criteria of dose-response relationships, naloxone sensitivity, and stereospecificity. These groups are: (*a*) those producing a hyperthermia at low doses and a hypothermia at high doses, with both actions being naloxone-sensitive and with stereospecificity for the *l*-enantiomer (e.g. *l*-methadone); (*b*) those producing only a dose-related hyperthermia but also sensitive to naloxone blockade and stereospecific (e.g. *l*-pentazocine); (*c*) those causing only a hypothermia and only partially blocked by naloxone (e.g. *l*-ethylketazocine); (*d*) those exhibiting little effect on T_b by themselves but producing hypothermia when combined with naloxone (e.g. normorphine); and (*e*) those producing only small, inconsistent changes in T_b (e.g. N-allylnormetazocine). Details may be found in papers by Geller et al (33, 41).

In cats, N-allylnormetazocine (100–500 μg) injected into the third ventricle caused hypothermia at an ambient of 22°C and 0°C, and hyperthermia at 34°C (42). Pentazocine (125–1000 μg) and ethylketazocine (250–1000 μg) caused dose-related biphasic temperature responses that were not blocked by naloxone (43, 44).

The temperature response to morphine is not always exclusively hypo- or hyperthermia. Even in the rat and mouse one may see a biphasic temperature response; that is, hypothermia followed by hyperthermia (36, 45, 46). This sort of response is not unique to opiates and neither is the bimodal dose-response curve. For example, intraventricular injection of norepinephrine in rats (47) or serotonin in dogs (48) produces hyperthermia at low doses and hypothermia as the dose is increased. Intraventricular nicotine causes a biphasic hypothermic-hyperthermic response in the rat (49). Adrenergic, serotonergic, and cholinergic mechanisms have all been implicated in morphine's thermoregulatory effects.

Locomotor activity and other behavioral parameters in mice and rats given morphine show the same pattern of depression followed by excitation (50). It is tempting to ascribe temperature changes to heat generated by muscular activity. However, since morphine-induced hyperthermia frequently accompanies a cataleptic state in rats, and since hypothermia may accompany "running fits" in mice, heat production due to activity seems to be an insufficient explanation for changes in temperature (45, 51, 52).

Ambient Temperature

Any drug exerting its effects on temperature through action on central thermoregulatory pathways can be expected to show some interaction with environmental temperature, and morphine is no exception. Paolino & Bernard (53) investigated the temperature response of rats to morphine in environments at 5°, 24°, and 32°C. These authors reported that intraperitoneal or intracerebral

morphine produced hypothermia at 4°, no change at 24°, and hyperthermia at 32°. At 24°, the response was actually biphasic, although not statistically significant. Rosow et al (36) described precisely the same changes in restrained mice given subcutaneous injections of morphine at 20°, 25°, or 30°C ambient. Nearly all of the opioid agonists produce the same pattern of temperature responses in the mouse: hypothermia occurs at ambient temperatures below thermoneutrality; biphasic responses appear as the ambient temperature increases; and ultimately hyperthermia predominates at the highest ambient temperatures. Lotti et al (46) established that morphine lowers body temperature in the rat by centrally mediated suppression of the thermogenic (i.e. metabolic) response to cold. Hypothermia, therefore, is only demonstrable at the low ambient temperatures necessary to elicit a thermogenic response. Presumably, high environmental temperatures have already maximally activated heat loss pathways and maximally decreased heat production. Most of the studies reviewed here have specified ambient temperature conditions, but the selection of a particular temperature appears to be arbitrary in most cases. The influence of the ambient temperature is such that ambients above 25°C favor hyperthermia and ambients below 20°C favor hypothermia (36). Laboratory temperatures are most often controlled at some point between 20° and 23°---conditions that are well below thermoneutrality for small laboratory animals, and that tend to favor the production of hypothermia. Since opioid-induced hypothermia and hyperthermia may well be dissimilar phenomena (1), the choice of ambient temperature appears to be at least as critical as drug dose in determining experimental results.

Restraint

Nearly all of the older studies on T_b were conducted with animals subjected to some form of body restraint. Such restraint has been shown to be a significant source of variability in these experiments. In general, restraint of the animal diminishes or prevents the low dose hyperthermia and enhances the high dose hypothermia (1), thereby shifting the dose-response curve towards hypothermia. Although hypothermia can be produced in freely moving Sprague-Dawley rats, the morphine dose required is much higher than in restrained animals (54). In fact, Szikszay & Benedek (55) reported that the same dose of morphine that produced hyperthermia in the unrestrained rat, produced hypothermia in the restrained rat. Similarly, Wistar rats enclosed in typical plastic restraint devices became hyperthermic at 22°C ambient after low doses of morphine or heroin, and hypothermic with higher doses. When the same drugs and doses were administered to freely moving rats (56, 57), only hyperthermia was produced.

Restraint can alter the response to systemically, intracerebroventricularly, and intracerebrally administered morphine (39, 54, 58, 59) and may actually

mask the development of tolerance (56). Various explanations have been offered for the effects of restraint on T_b; these include interference with postural or behavioral thermoregulation, decreased locomotion (50), insulation by the device, and stress responses. The type of restraint may also influence the response (60). Mice restrained only by adhesive tape on the tail may still have dual responses to morphine (36). Depending on the question being asked, experiments using telemetry or freely moving animals are not necessarily more "valid" than those in which restraint is employed. The aim in choosing a particular method should be to mimic as closely as possible the natural condition of the animal. If one wants to study the interaction of stress with a drug affecting T_b, then restraining the animal may very well be appropriate. However, if the study is intended to determine thermoregulatory mechanisms or physiological function, then restraint may be a confounding factor. Restraint is an important consideration when comparing data from different studies, and the presence and type of restraint should be clearly indicated and taken into account when drawing conclusions.

Route of Administration

Recent studies have demonstrated that, at least in the rat, the response to morphine is dependent on the route of administration (61, 62) (See Table 1). Thus, the dual response of T_b to morphine after parenteral administration at an ambient of 20°C is no longer seen if morphine is administered into the cerebral ventricles; only a dose-related hyperthermia occurs, even with doses as high as 150 μg (63). Morphine (4 μg) directly injected into the POAH of rats at 21°C caused hyperthermia (64), as did 1–8 μg, regardless of ambient temperature (8°, 22°, 30°C) (65). Injections of 25 and 50 μg of morphine into the POAH of Holtzman rats caused hyperthermia but had no consistent effect when injected into the medulla (59). Administering a large dose of morphine (50 μg) into the POAH of restrained rats, however, resulted in hypothermia (51). Route is a critical determinant of not only quantitative effects, but qualitative ones as well.

Tolerance

For many years, it was a dictum in pharmacology that tolerance develops to the depressant effects of opioids, but not to the excitatory ones, such as those on the gastrointestinal tract or the pupil. We now know that tolerance develops to all of the actions, including excitatory ones (66–68), although the rate and extent of tolerance development varies. With regard to the actions of opioids on T_b, it has long been known that tolerance develops rapidly to the hypothermic effects of morphine in rats (45, 69, 70). A good discussion of tolerance to hypothermia may be found in a review by Burks & Rosenfeld (71).

Table 1 Opioid administration to rats: subcutaneous vs intracerebroventricular route

		Body temperature change			
		Opioid alone		Opioid + naloxone	
Drug	Dose	SC	ICV	SC	ICV
Morphine	low	+	+	0	0
	high	−	+	0	0
Heroin	low	+	+	0	0
	high	−	+	0	0
U50,488H	low	−	0	0	0
	high	−	0	0	0
I-Ethylketazocine	low	−	0	0 or −	0
	high	−	+	0 or −	−
I-Pentazocine	low	+	+	0	0
	high	+	+	0	+

+, increase; −, decrease

Since repeated injections of doses that produce hypothermia in rats result in a change from hypothermia to a total lack of effect, or even to hyperthermia (45, 72), it was thought that tolerance did not develop to the hyperthermia induced in rats and mice by low doses of morphine. Cox et al (64) reported that tolerance did not develop, but their study examined only the effect of a hypothermic dose of morphine 24 hr after a single administration of that dose. Thus, tolerance to a hyperthermic dose of morphine was not tested. Similar conclusions were reported by McDougal et al (73), who again used only a single prior administration of morphine. Like the earlier experiments of Gunne (45), these studies were not designed to allow an unequivocal answer to the question of whether or not tolerance develops to hyperthermic doses of morphine. Holtzman & Villarreal (39) reported that little or no tolerance develops to low dose morphine hyperthermia in monkeys. However, no detailed data were presented to support such a conclusion. Clark & Bernardini (74) found that in the cat tolerance to the increase in T_b produced by the icv administration of morphine developed after repeated icv administration. Rosow et al (75) investigated the effects of a range of doses of morphine given twice daily to mice for nine weeks. Although tolerance to the hypothermia was produced, no tolerance to morphine-induced hyperthermia was seen. However, subcutaneous implantation of morphine pellets did result in tolerance to morphine-induced hyperthermia. The authors reasoned that twice-daily injections, unlike the pellets, were not able to maintain high levels of

drug over sustained periods. Results in rats obtained from use of implanted morphine pellets (M. W. Adler & E. B. Geller, unpublished results), also indicate that tolerance develops to low dose morphine-induced hyperthermia. A recent study of rats chronically injected with morphine confirms the finding of tolerance to hyperthermia (132).

Mechanism of Action

The exact mechanisms involved in the body temperature changes induced by morphine are still not known with certainty. However, the effects may result primarily from actions on oxygen consumption. A number of studies have demonstrated that morphine-induced hypothermia is associated with decreased oxygen consumption and metabolic heat production in a variety of animal species (34, 46, 76, 77). Lotti et al (46, 69), Lin et al (78), and Thornhill & Desautels (57) have concluded that the decrease in T_b in the rat resulting from high doses of morphine is due to a fall in oxygen consumption rather than to an increase in heat loss, as measured by cutaneous blood flow and skin temperature. On the other hand, a study by Cox et al (64), of the hyperthermic action of small doses of morphine in the rat in which tail temperature was measured, indicates that this response is due to peripheral vasoconstriction that decreases heat loss. However, O_2 consumption was not determined. External heating of morphine-treated rats caused an increase in core temperature and a small increase ($<2°C$) in tail skin temperature. In contrast, heating of untreated rats produced no change in core temperature and a marked increase ($>6°C$) in tail skin temperature. Morphine-treated rats also displayed a delayed escape time from a heat lamp. These findings suggest that the hyperthermic response to low doses of morphine is due to an upward setting of the hypothalamic set point and a consequent vasoconstriction that decreases heat loss. Thornhill & Desautels (57) found that increased thermogenesis by activation of brown fat was not involved in the hyperthermia induced by low doses of morphine given either peripherally or into the ventricles. Their results also indicated that morphine (10 mg/kg, i.p.) did not minimize heat loss via vasoconstriction of the peripheral vasculature. Lin (65), however, attributed the hyperthermia of intrahypothalamic morphine and β-endorphin to both increased metabolism and cutaneous vasoconstriction. The temporal sequence was not determined. The hyperthermia observed in morphine- or β-endorphin-tolerant rats at 22°C was caused only by an increase in heat production (78).

Rudy & Yaksh (79) demonstrated that morphine may also induce hyperthermia by a direct spinal action. In rats with chronically implanted subarachnoid catheters, lumbar cisternal injection of morphine produces dose-dependent increases in rectal temperature. The small volumes of opiate

solution injected and the rapid onset of the response make it unlikely that these effects are due to rostrad diffusion of morphine. The hyperthermic response was blocked by systemically administered naloxone or attenuated by chronic treatment with morphine. The response to intrathecal morphine was accompanied by shivering and cutaneous vasoconstriction. When the animals were warmed, an immediate increase in tail skin temperature occurred, indicating that thermoregulatory vasomotor function was still intact. This suggests, once again, that morphine may produce an upward shift in temperature set point, but this time it may be due to a direct effect at the level of the spinal cord.

Recent studies by Adler and his colleagues (80, 81) further explore the relationships among T_b, oxygen consumption (VO_2), and heat flux (loss, Q) in terms of the actions of morphine in rats. Using gradient-layer calorimeters, preliminary findings indicate that, although changes in VO_2 are the dominant influence in the onset of both morphine-induced hyper- and hypothermia, significant changes in Q also occur. Change in the Q/VO_2 ratio determines the direction of temperature change. Thus, in low dose morphine-induced hyperthermia, both VO_2 and Q increase, but Q/VO_2 decreases. In high dose hypothermia, both VO_2 and Q decrease, but the initial temperature decrease is associated with increased Q/VO_2. The changes seen are consistent with the view that morphine's effects on T_b are due to a change in thermal set point.

In the dog, increased heat loss after morphine administration may be important. Martin (18) noted that a dog, acclimated to a 35°C ambient temperature and given intravenous morphine, became tachypneic for 30–40 min, and that its rectal temperature dropped from 38°C to 36°C. When the dog was warmed externally with heat lamps, that temperature rose, and panting recurred until its body temperature fell once again to 36°C. The panting continued until external heating was stopped. Martin concluded that thermoregulatory capability was unimpaired, but that morphine had acted to lower the set point.

In adult ducks, hyperthermia induced by morphine was the result of increased heat production, as measured by oxygen consumption, in combination with vasoconstriction of the peripheral vasculature and inhibition of respiration (82).

As indicated in the first section of this paper, the POAH contains thermosensitive neurons. Baldino and his colleagues (83, 84) identified warm-sensitive and cold-sensitive cells in the POAH by means of direct heating and cooling of the area with thermodes. They demonstrated that iontophoretic administration of morphine to those neurons in the rat increased the firing rate in the majority of warm-sensitive cells (mediating heat dissipation) and inhibited the rate in cold-sensitive cells (mediating heat gain responses). Naloxone, also given iontophoretically, antagonized both effects. These stud-

ies suggest that the hypothermia induced by morphine occurs through a coherent action on thermosensitive neurons that contain opioid receptors. The findings with respect to single neurons support the conclusions of Lotti et al (46) regarding whole animals, discussed above in terms of morphine's suppression of heat-gain responses. As stated earlier, morphine's actions in the rat are characterized by a dual response: a low dose hyperthermia and a high dose hypothermia. Baldino's studies (83, 84) account only for the hypothermia. Of particular interest, then, is the report by Lin et al (85). These investigators identified the cells in the POAH that responded to thermal stimulation of the scrotum, rather than using direct heating of neurons in the POAH (as done by Baldino). Iontophoretic application of morphine to those cells showed that cold-responsive cells were excited and heat-responsive cells were inhibited—exactly the opposite of the results reported by Baldino. Lin's findings account for the hyperthermic actions of morphine that result from low doses parenterally and from direct injection into the hypothalamus. It seems plausible to hypothesize that two populations of temperature-sensitive neurons exist in the POAH; one would account for opioid-induced hyperthermia, and the other for the hypothermia. Whether the same type of opioid receptor is involved in the two populations remains to be determined.

An elevation of sodium ions in the cerebral ventricles of the rat may produce hyperthermia, while an excess of calcium ions may result in hypothermia (86). This ionic theory of set point control gains support from recent studies that demonstrated opposite effects on hypothalamic Ca^{++}/Mg^{++} ATPase activity with hyperthermic μ (i.e. morphine) and hypothermic K (i.e. U-50,488H) agonists, as well as potentiation of hypothermia with calcium channel blockers (87–89). It is not yet known whether these are primary or secondary actions of the opioids.

Since several neurotransmitters have been implicated in thermoregulation (see above), it is not surprising that investigators have tried to relate the effects of opioids on T_b to these other transmitters. It is beyond the scope of this review to deal with this topic in any detail, but studies such as those by Cox et al (90, 91), Way et al (92), and Adler et al (93), involving the dopaminergic and cholinergic systems, are indicative of the types of experiments that have been carried out. It should be apparent, however, that if the opioid system plays a role in thermoregulation, there must be interactions with other neurotransmitter systems.

ENDOGENOUS OPIOID PEPTIDES

Since identification of the precursor molecules for the three families of endogenous opioid peptides (proopiomelanocortin, proenkephalin, and prodynorphin), intense efforts have been under way to determine both the in vivo

and the in vitro effects of these substances and the possible functional roles played by the opioid receptor types with which they interact. In this section, we deal not only with the effects of the endogenous substances themselves, but with the actions of a number of related peptides that have affinity for the μ, K, and δ opioid receptors.

A number of studies have shown that injection of β-endorphin into rodents produces hyperthermia with lower doses (94–96) and hypothermia with higher doses (97, 98). A dose-dependent dual effect on body temperature has been demonstrated with full icv dose-response data in rats (63, 99), similar to the effect of morphine given by a parenteral route. Restraint stress can alter the effect of icv β-endorphin (58), as can ambient temperature (98). Similarly, the icv administration of the met-enkephalin analogues D-ala^2-met-enkephalinamide (DAME) and D-ala^2-mePhe^4-met(o)^5-ol (FK33-824) produces a dual response, while D-ala^2-D-leu^5-enkephalin (DADLE), a stable analogue of leu-enkephalin, produces only a dose-related hyperthermia in rats (63, 100). D-ala^2-N-MePhe^4-Gly^5(ol)-enkephalin (DAGO), a selective μ agonist, and DADLE, which has both μ and δ activity, cause hyperthermia in unrestrained rats and decrease core temperature in restrained animals (101, 102). Preliminary studies with the delta-selective peptide DPDPE (D-Pen^{2,5}-enkephalin) reveal no significant temperature effects in rats with doses of 12.5–100 μg icv (M. W. Adler, E. B. Geller, unpublished results). The endogenous opioid peptide dynorphin A_{1-17}, postulated to be a ligand at the K receptor, produces a dose-related hypothermia (63). In the rat, the ability of naloxone to block body temperature responses to the opioid peptides is complex. A dose of 1 mg/kg sc was able to completely block the actions of DAME, but the effects of high doses of DADLE and dynorphin were more resistant to blockade (63). This resistance may be only an indication that higher doses of naloxone are necessary to achieve blockade. In the case of β-endorphin, low dose hyperthermia was not modified by naloxone. In rabbits, the icv administration of morphine, SKF10047, ketazocine, β-endorphin, met-enkephalin, and DAME over a broad dose range resulted in hyperthermia (103). In cats, β-endorphin (5–50 μg), met-enkephalin (1000–2000 μg), and DAME (<200 μg) induced hyperthermia at 4°, 22°, and 34°C (104–106).

Several studies have examined the thermal effects of opioids administered directly into the POAH. Met-enkephalinamide (1–100 μg) produced dose-dependent increases in T_b preceded by dose-dependent increases in metabolic rate, both of which could be antagonized by naloxone (107). The same investigators found that the enkephalinase inhibitor thiorphan drove the temperature in the same direction as the exogenously injected enkephalin. β-endorphin (1.1–8.5 μg) injected into the preoptic area or nucleus accumbens of rats was reported to produce a dual response (108). At an ambient of

20°–22°C, other investigators have found only hyperthermia with this peptide (2.5–25 μg) (109, 110). Similarly, lower doses (1–3 μg) caused hyperthermia at 8°, 22°, and 30°C (65). The difference in the findings of Tseng et al may be the result of the aftereffects of anesthesia or of the stress of multiple testing procedures. Microinjected into the periaqueductal gray (PAG) of Sprague-Dawley rats at 21°C ambient, β-endorphin (1–5 μg) caused a dose-dependent increase of up to 2°C (111). Hyperthermia was also found in Wistar rats at 26°C (112). DADLE (2 μg), dynorphin A_{1-17} and $_{1-8}$ (5 μg), and ethylketazocine (2 μg) had no significant effect, but DAGO (0.5–2 μg) induced a dose-dependent rise in temperature (111). Naltrexone injected into the PAG reversed the effects of β-endorphin and DAGO. Infused intrathecally, β-endorphin elicited a naloxone-reversible hyperthermia (109). In rabbits, direct injection of 2.5–5 μg β-endorphin into the POAH enhanced peripheral vasoconstriction and lowered skin temperature, evaporative heat loss, and peripheral thermosensitivity, resulting in a rise in body temperature (113, 114). These findings stand in contrast to the dose-dependent hypothermia found after icv injection of 20 μg β-endorphin into rabbits at 2° and 20°C (115).

Few studies have dealt with tolerance to the effects on T_b of the opioid peptides. When a hyperthermic dose of β-endorphin was administered icv to mice, tolerance developed, but it lasted for only a few hours (94). If the β-endorphin was preceded by leucine or methionine enkephalin administered 24 hr earlier, increase in T_b produced by β-endorphin was reduced; this effect suggests that the same pharmacological receptor might be involved in both cases. Clark & Bernardini (74) reported that when tolerance to the hyperthermic actions of morphine was produced in the cat, no cross-tolerance occurred to the hyperthermia induced by two enkephalin analogues, which indicates that the same receptors were not involved.

ROLE OF THE OPIOID SYSTEM IN THERMOREGULATION

The final section of this paper deals with the question of whether or not the opioid system (ligands and receptors) plays a functional role in thermoregulation. The fact that the narcotic antagonist naloxone will both block and antagonize the effects of morphine on T_b indicates that all of its effects on T_b are probably the result of actions mediated through opioid receptors (28, 33, 116). As stated above, the ability of a drug to alter body temperature is not necessarily indicative of a role in thermoregulation. Does the fact that opioids profoundly modify T_b mean that opioid receptors have a thermoregulatory function? It appears that they do. Furthermore, the data that has recently been

obtained using more selective ligands favors the thesis that, at least in the rat, μ opioid receptors play a role in hyperthermic responses, and that K opioid receptors participate in hypothermic responses. Morphine, the prototypic μ ligand (117), produces hyperthermia in many species when administered parenterally, a dual effect in other species, and only a hyperthermia when injected icv into the rat. Evidence for each of these findings is cited in previous sections of this paper. Other μ- selective receptor agonists, such as DAGO, which was mentioned above, also produce hyperthermia. On the other hand, K agonists seem to produce only hypothermia; the magnitude of effect is related to the degree of selectivity for the K receptor. The exogenous agonist with the greatest affinity for the K receptor, U-50,488H, produces dose-related hypothermia (88, 93, 118), as does dynorphin A_{1-17}, the most selective endogenous K ligand (63). Agonists like ethylketazocine having both μ and K activity produce less of a drop in temperature. In addition, the combination of a K receptor agonist and a neuroleptic that blocks postsynaptic dopamine receptors results in an apparent poikilothermia with a sharp drop in T_b at normal ambients (93). Of particular interest is the fact that the drop in T_b in the rat can amount to as much as 12°C, but all subjects recover spontaneously after several hours. Because of the paucity of data relative to the effects of selective δ agonists on T_b, and because of the close relationships that appear to exist between the μ and δ receptors, a role for the δ receptor in terms of thermoregulation cannot be ruled out completely.

Now, what about the sites at which the thermoregulatory function of the opioids may take place? Although far from certain, it appears likely that the μ site is in the brain, while the K sites lie primarily outside the brain, perhaps even outside the central nervous system. Agonists active at μ sites produce hyperthermia whether injected sc, icv, or directly into the POAH (33, 41, 62, 63). U50,488H, the K-selective ligand, produces dose-related hypothermia when given sc, but not when given icv, even in doses as high as 500 μg (93). It is interesting that ethylketazocine, a compound having agonist activity at both K and μ sites, produces hypothermia sc and dose-related hyperthermia when administered icv (62). The hypothermic response following icv administration of dynorphin might be due to the entrance of the peptide into the general circulation and to stimulation of K receptors outside the brain. In any case, dynorphin is the only opioid-related substance thus far studied that produces just hypothermia after icv administration in rats. With substances showing dual effects, hypothermia occurs only with high doses, which would favor wider distribution. The lack of correspondence between sites containing opioid peptide ligands and opioid receptors (119) and the limited supply of antagonists that are highly selective for the different types of opioid receptors increase the difficulty in obtaining definitive proof for the thesis. Nevertheless, the evidence available thus far substantiates the hypothesis, and the hypothesis can serve as a take-off point for further experiments. Since sub-

types of receptors occur in other neurotransmitter systems (e.g. adrenergic, serotonergic, and dopaminergic), it is quite possible that subtypes also occur in the opioid system. For example, Pasternak has offered evidence for the existence of μ_1 and μ_2 sites (120). Such subtypes of the different receptors may well mediate different actions and may, for example, explain the different effects of morphine on temperature-sensitive cells in the POAH (83–85). Whether one or more subtypes of the various opioid receptors do exist, transductional processes and neuroanatomical connections play a vital role in determining the exact response that results from a particular drug-receptor complex. Differences among species, therefore, are dependent not only on the receptor but on post-receptor processes as well.

If the opioid system plays a role in thermoregulation, this could occur in either or both of two ways. The system may be tonically activated; that is, it may be operating under normal conditions. If so, then the administration of an opioid antagonist should perturb the system and produce an effect. Goldstein & Lowery (121) reported a small but significant hypothermia at 20 and 23°C in male Wistar rats given 10 mg/kg naloxone sc. These changes were dismissed by the authors as too small to lend support to the theory of opioid regulation of body temperature. A recent paper by Eikelboom (122) reported that both naloxone and naltrexone produced a dose-dependent hypothermia in male Wistar rats, followed by hyperthermia several hours later. Although the changes in T_b were small and amounted to less than 1°C, these results suggest that the opioid system may be tonically active. Similar results for naloxone have also been seen in male Sprague-Dawley rats, but these slight decreases were not considered meaningful (M. W. Adler, E. B. Geller, unpublished results). In the cat, however, naloxone was found to have no appreciable effect on T_b regardless of ambient temperature, restraint, or stress (123). The other possibility is that the opiod system does not operate under normal circumstances, but only when homeostasis is perturbed, as in pathological conditions.

Finally, the relationship between the opioid system and other neurotransmitters remains to be explored. Anatomical, histochemical, and pharmacological evidence already obtained suggests that the opioid system probably interacts with the dopaminergic, adrenergic, serotonergic, cholinergic, and other transmitter systems (91, 93, 94, 124–127). Studies carried out thus far, however, do not present a clear picture of the interrelationships among these systems in terms of thermoregulation. As stated above, it is logical to assume that the opioid system interacts with other neurotransmitter systems known to be involved in thermoregulation. In view of the recent findings that several neuropeptides have marked effects on T_b (see above and reviews 128–131), exploration of opioid interactions with these systems should prove to be a fruitful approach to deepening understanding of the opioid system and its function in the regulation of T_b.

SUMMARY

Opioid drugs and endogenous opioid peptides exert profound effects on body temperature. The particular effect seen is dependent on species, ambient temperature, degree of restraint imposed on the subject, route of drug administration, and a number of other factors. A major determinant is the opioid receptor type with which the agonist forms a complex.

Evidence is accumulating that opioid ligands and opioid receptors play a functional role in thermoregulation, even though the opioid system may not be tonically active. Although further studies are needed to fully define the role and the mechanisms involved, as well as the generality of the role in a variety of species, a reasonable working hypothesis is that μ receptors in the rat and the mouse are involved in responses that result in heat gain, while K receptor activation results in opposite responses. To a large extent, the μ receptors in the rat appear to be located primarily in the brain, while the K receptors are outside the brain and perhaps even outside of the central nervous system. At present there is no evidence of involvement of delta receptors in thermoregulation. A fuller understanding of the opioid system and its role in thermoregulation will have broad clinical implications, as well as provide insights into interactions among the several neurotransmitter systems involved in thermoregulatory control of body temperature.

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