Pharmacology Biochemistry & Behavior, Vol 10, pp 609–613 Printed in the U S A

THEORETICAL REVIEW

Influence of Opioids on Central Thermoregulatory Mechanisms

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(Received 13 February 1979)

CLARK, W G *Influence of opioids on central thermoregulatory mechanisms* PHARMAC BIOCHEM BEHAV **10**(4) 609–613, 1979 —Of the effects of morphine and endogenous opioid peptides on thermoregulation, the one which is most likely to be of physiologic significance is hyperthermia This increase in body temperature is the result of coordinated changes in both physiological and behavioral thermoregulatory activities and, like fever, reflects an increase in the level about which body temperature is regulated Morphine, endogenous opioid peptides and other opioids such as pentazocine all cause hyperthermia, but the considerable variation in the dose of naloxone required to antagonize the different agonists indicates that more than one type of opiate receptor is involved in these pharmacologic responses The minimal effect of naloxone and naltrexone on normal body temperature and on pyrogen-induced fever indicates that endogenous opioid peptides are unlikely to act physiologically via stimulation of receptors specifically sensitive to morphine However, methionine-enkephalin is less readily antagonized by naloxone and could have a physiologic role in thermoregulation through stimulation of another type of opiate receptor

Endogenous opioid peptides Thermoregulatory mechanisms Opiate receptors Restraint Narcotics Morphine Pentazocine Narcotic antagonists

AMONG the most rapidly developing areas in pharmacology during the past five years have been the study of opiate receptors and the chemical and pharmacological characterization of endogenous opioid peptides [29, 55, 60] Narcotics have long been known to alter body temperature [30], but only since the discovery of endogenous opioid peptides has a physiologic role of morphine-like substances in thermoregulation been considered This article summarizes recent advances in the understanding of the central effect on thermoregulation of low doses of morphine and evidence that central administration of endogenous opioid peptides can also alter body temperature. The possibility that these peptides mediate thermoregulatory processes by stimulation of naloxone-resistant opiate receptors is also considered

EFFECT OF RESTRAINT ON THERMOREGULATORY RESPONSES OF RATS TO MORPHINE

Differences in methodology have contributed to confusion about the primary effect of morphine on body temperature This confusion has originated mainly from studies of the effects of morphine on thermoregulation in the rat This species has often been reported to develop biphasic responses in which hyperthermia is preceded by hypothermia [5, 22, 47] or to respond to lower doses with hyperthermia and to higher doses with hypothermia [15, 17, 22, 25, 35, 47, 53, 56] Recent evidence indicates that restraint can greatly affect the thermoregulatory response of rats to morphine and favors development of hypothermia In one study [63], unrestrained rats given injections of morphine into the preoptic/anterior hypothalamic region of the brain or IP responded with hyperthermia while rats restrained in plastic holders and given the same doses developed hypothermia. In this study and in another in which hyperthermia was evoked by SC injections of doses of morphine sulfate as high as 80 mg/kg [62], body temperature was measured by insertion of a thermistor probe into the rectum at 15–30 min intervals, and it might be argued that these periodic disturbances of the otherwise unrestrained rats evoked struggling or in some other way increased heat production, thereby favoring development of hyperthermia. However, these animals were generally quiet, immobile or catatonic and did not struggle when their temperatures were measured Furthermore, in two other studies [36,37], when body temperature was monitored in free-moving rats with a thermistor implanted into the peritoneal cavity, morphine still elicited hyperthermia Hypothermia or less hyperthermia was evoked by the same doses after peripheral and central administration, respectively, when the rats were enclosed in a plastic restraining device Therefore, in the rat hypothermia in response to morphine occurs primarily after acute administration of higher doses and/or in association with restraint Although

the hypothermic effect of morphine in rats is also of considerable interest [34,45], it is more likely that hyperthermia, which is elicited by lower opiate doses whether or not restraint is used, reflects a possible physiologic action of related endogenous peptides Studies of thermoregulatory effects of drugs in restrained animals should be evaluated with caution and, if restraint is used, additional experiments should be done in unrestrained animals to assess potential qualitative and quantitative variations attributable to the restraint

EFFECTS OF MORPHINE ON CENTRAL THERMOREGULATORY MECHANISMS

Two approaches have been used to assess drug actions on different components of the thermoregulatory system One approach utilizes changes in body temperature evoked by drugs in animals exposed to a series of different ambient temperatures [2] An agent which alters the thermoregulatory set-point or afferent feedback from thermoreceptors should cause coordinated changes in behavioral and other effector activities all of which favor a shift in temperature in the same direction Within a range of environmental temperatures from above to below the thermoneutral range of the species, the change in body temperature is essentially independent of environmental temperature This type of result has been reported for pyrogens [48], prostaglandins [23,58], tetrodotoxin [8] and histamine [9]

Drugs which act on specific effectors or neuroeffector pathways can alter body temperature but, since the other components of the thermoregulatory system still function normally, opposing effectors are activated to counteract or buffer the primary drug effect For example, 2,4-dinitrophenol-induced hyperthermia in the dog evoked panting and salivation [59]. The magnitude of the drug-induced change in body temperature will vary somewhat with ambient temperature since the effectiveness of both the direct drug-induced alteration and of the compensatory mechanisms will be influenced by the initial levels of activity of the various effector systems. Other drugs which act on effector systems include N-methyldiphenhydramine and triiodothyronine [16]

Drugs that depress thermoregulatory control mechanisms impair ability to correct for changes in body temperature caused by environmental thermal stress whether or not the change in body temperature is detected by the thermoreceptors Therefore body temperature tends to passively drift, upward in a warm and downward in a cold environment; i e. the subject becomes poikilothermic Anesthesia and chlorpromazine are examples

Several reports indicate that morphine, given peripherally [10, 18, 41, 42, 57, 65] or centrally [3, 4, 10], consistently causes hyperthermia in the cat. When morphine was injected into the third ventricle of this species, very similar changes in body temperature developed regardless of whether ambient temperature was cold (4–6°C), hot (33–36°C) or usual room temperature (21–23°C) [10] The increase in body temperature was associated with shivering at the lower ambient temperatures At the highest ambient temperature shivering was not evoked, but respiratory rate decreased after morphine if it was already elevated These results indicate that morphine increased the level at which body temperature is regulated, much as does pyrogen Injections of morphine into the lumbar spinal subarachnoid space also evoked hyperthermia in restrained rats [52], and comparable responses were elicited at ambient temperatures of 4, 22 and 32°C, again indicating an increase in the level of regulation Since the drug did not reach the thermoregulatory control centers in the hypothalamus, it is likely that morphine altered feedback from peripheral thermosensors

A behavioral approach has also been useful in evaluating thermoregulatory effects of drugs In these tests an animal is given the opportunity to alter the temperature of its environment by changing its position within a chamber in which there is a thermal gradient or by pressing a lever to heat or cool its environment A change in the animal's behavior which facilitates a drug-induced change in body temperature indicates that the drug altered the level about which body temperature is regulated whereas a behavioral change that opposes the drug-induced effect indicates some other drug effect on thermoregulation such as a change in effector activity [12, 16, 50, 54] In a study of the hyperthermic action of morphine given IP to unrestrained rats [15], when the animals were placed into an enclosure in which they were free to move away from a heat lamp, they waited longer before escaping from the heat after administration of morphine, thereby facilitating the morphine-induced rise in body temperature Thus the use of both types of approach in the rat indicate that, as in the cat, the hyperthermic effect of morphine was due to an increase in the level of thermoregulation On the other hand, the magnitude of the hypothermic response of rats to morphine is dependent on ambient temperature, being enhanced at lower ambient temperatures and lessened or reversed to hyperthermia at hot ambient temperatures [13, 24, 31, 44, 49] The hypothermia, therefore, is not the result of a decrease in the level about which body temperature is regulated but is more likely due to depression of thermoregulatory control

EFFECTS OF CENTRAL ADMINISTRATION OF ENDOGENOUS OPIOID PEPTIDES ON BODY TEMPERATURE

Injections of methionine-enkephalin into lateral cerebral ventricles of cats caused small hyperthermic responses which were not diminished by naloxone [14] Leucine-enkephalin caused hypothermia which, likewise, was not antagonized by naloxone Rapidly developing, brief hyperthermias were also produced in cats with third cerebral ventricular administration of methionine-enkephalin [6] Unlike emetic responses to methionine-enkephalin which were prevented by naloxone, these hyperthermic responses were only partially attenuated by giving naloxone intraventricularly prior to challenge with the enkephalin Lateral ventricular injection of low doses of methionine-enkephalin also caused hyperthermia in the unrestrained rat [17], but larger doses initially caused hypothermia which was succeeded by small hyperthermic responses These responses to methionine-enkephalin were less readily antagonized by naloxone than were comparable responses to morphine

Central administration of low doses of β-endorphin to rats caused hyperthermia [26] while larger doses lowered body temperature [1, 26, 27, 64] unless ambient temperature was relatively high [27] The hypothermic effect of β-endorphin was antagonized by naloxone [1,28] Hyperthermia also occurred in response to γ-endorphin in rats [1]

This current evidence indicates that endogenous opioid peptides produce changes in body temperature qualitatively similar to those after morphine although the hyperthermic responses to methionine-enkephalin were resistant to antagonism by naloxone

OPIOIDS MAY ALTER BODY TEMPERATURE BY STIMULATION OF MORE THAN ONE TYPE OF RECEPTOR

The existence of more than one type of opiate receptor has been postualted [38,51], and studies in chronic spinal dogs [19,40] have led to the proposal of three distinct receptors [39] According to this proposal, morphine stimulates μ (for morphine) receptors to produce analgesia and euphoria Agonist-antagonists, such as nalorphine and pentazocine are competitive antagonists at the μ receptor and are agonists at a κ (for ketocyclazocine) receptor. Relatively pure κ agonists, such as ketocyclazocine, do not exhibit cross-tolerance with morphine and neither precipitate nor totally suppress the morphine withdrawal abstinence syndrome Thus they interact weakly, if at all, with μ receptors The dysphoric effects of the agonist-antagonists are attributed to stimulation of σ (for SKF-10,047) receptors Finally, higher doses of antagonists, such as naloxone and naltrexone, are required to antagonize at κ and σ receptors than at μ receptors There is also evidence for an additional opiate receptor [33] which has been designated δ [32] Third ventricular administration of pentazocine to unrestrained cats caused a dose-related hyperthermia which began 2–4 hr after injection [7] With higher doses, hyperthermia was preceded by a dose-related hypothermia Neither of these temperature changes was reduced by administration of up to 1 mg or 5 mg/kg naloxone given intraventricularly or IV, respectively This lack of antagonism by naloxone is in marked contrast to the hyperthermic response to morphine which was antagonized by doses of naloxone as low as 5μg and 25 μg/kg by the same routes Although the hyperthermogenic action of morphine in the rat has been reported to be resistant to antagonism by naloxone [15], most investigators have also demonstrated antagonism of morphine in this species [37, 43, 46, 52, 62] The resistance of pentazocine to antagonism by naloxone supports its classification as an agonist at κ and σ receptors [19], rather than at μ receptors Since agonists at κ receptors evoke some effects similar to those of μ-receptor agonists, it is likely that the hyperthermogenic action of pentazocine results from κ receptor stimulation and that perhaps the initial hypothermic response resulted from σ receptor stimulation This conclusion is supported by a study with ketocyclazocine, an agonist more specific for κ receptors [40], which caused hyperthermia but not hypothermia in the cat [14] Naloxone did not reduce the hyperthermic response to ketocyclazocine.

ARE ENDOGENOUS OPIOID PEPTIDES OF PHYSIOLOGICAL SIGNIFICANCE IN MAINTANENCE OF NORMAL BODY TEMPERATURE OR IN FEVER?

It has been concluded [20] that a role of endogenous opioid peptides in normal thermoregulation is unlikely, in line with the frequent observation that the antagonists naloxone and naltrexone alter normal body temperature little, if at all, in several species [11, 15, 17, 18, 20, 21, 40, 46, 52, 62] Furthermore, pretreatment with central administration of a large dose of naloxone did not alter febrile responses to leukocytic pyrogen [11] The lack of effect of these antagonists on normal body temperature or on fever indicates that activation of μ receptors by an endogenous peptide is of little or no importance in thermoregulation. However, transmission of information from sites of noxious and thermal stimulation follows similar neuronal pathways. Endogenous opioid peptides may be intimately involved in altering transmission in pathways and nuclei involved in perception of pain [60, 61, 66], and it would not be surprising if such peptides were also involved in transmission of thermal information Methionine-enkephalin is dissimilar to morphine and more closely resembles pentazocine in the resistance of its thermoregulatory action to blockade by naloxone. If such a peptide were required to maintain body temperature or for production of fever by stimulation of a naloxone-insensitive κ receptor, then naloxone would be a poor antagonist for assessing the physiologic role of this peptide Studies with more effective antagonists of endogenous opioid peptide-induced temperature changes are now needed to evaluate possible thermoregulatory functions of these peptides

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ACKNOWLEDGEMENT

Supported by USPHS Research Grant DA 02188