The role of the endogenous opiates as regulators of appetite1,2

John E. Morley, M.B., B.Ch. and Allen S. Levine, Ph.D.

ABSTRACT The popular view of the major function of the opiates is that they produce analgesia. Much evidence has been accumulated that the endogenous opiates play an integral role in the central regulation of appetite. We postulate that the major effect of the endogenous opiates is to induce the feeding drive with their analgesic properties representing an epiphenomenon. Am J Clin Nutr 1982;35:757-761.

KEY WORDS Dynorphin, opiates, enkephalin, appetite, β-endorphin, obesity

"...opium, which the creator himself seems to prescribe, for we often see the scarlet poppy growing in the cornfields, as if it was foreseen that whenever there is hunger to be fed there must also be pain to be soothed..."

Oliver Wendell Holmes
(Address to the Massachusetts Medical Society, May 30, 1860)

Introduction

The initiation and termination of feeding is a complex process involving a variety of factors including the hedonic qualities and physico-chemical properties of food as well as the organism's response to food ingestion. In addition to these short-term regulators of appetite, there exists a second system that monitors body weight attempting to maintain adipose tissue mass at a closely controlled set-point (the set-point theory).

The major region for the integration of all these impulses responsible for the regulation of appetite is in the hypothalamus (1, 2). The hypothalamus acts as a transducer responsible for integrating the multiple sensory inputs describing the milieu interieur and maintaining nutritional homeostasis of the organism by activating or deactivating the food seeking behaviors of the animal. The hypothalamus performs this task through a complex interrelationship of monoamines and neuropeptides on a backdrop of hypothalamic interneurons. The various monoamines and neuropeptides known to alter food ingestion are listed in Table I. The same monoamines and neuropeptides that regulate appetite also play a role in other hypothalamic vegetative functions. This overlap in the regulatory substances allows a close degree of coordination of the hypothalamus over these related life-sustaining processes.

The simplest example of this type of coordination that we are aware of occurs in the shellfish known as the pleurobranchaea (3). This mollusk is a voracious and cannibalistic carnivore that devours anything up to one-third of its size that comes in its vicinity. This habit of eating everything would have rapidly led to extinction of this species, as every time it laid eggs they would have been eaten. Nature, therefore, gave this shellfish an interesting hormone, called the egg laying hor...
TABLE I

Endogenous substances postulated to be involved in appetite regulation

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<tr>
<th>Feeding</th>
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<tbody>
<tr>
<td>Monoamines:</td>
<td>Dopamine α-agonists</td>
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<td>Peptides:</td>
<td>Enkephalins</td>
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<tr>
<td>Miscellaneous:</td>
<td>γ amino butyric acid (Muscimol)</td>
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mone. About 15 min after injecting the pleurobranchea with egg laying hormone it stops eating and shortly after that it lays its eggs. This dual function of the egg laying hormone in producing satiety as well as egg laying nicely demonstrates the advantages of a single substance regulating two closely related functions.

The endogenous opiates and appetite

We have postulated that there is a tonic signal driving the animal to eat and that appetite regulation is predominantly involved with attempting to inhibit this constant food drive (1). Recent evidence has suggested that one of the major groups of substances responsible for producing this food drive are the endogenous opiates.

Naloxone is a highly specific antagonist of the µ and δ opiate receptors. Inasmuch as naloxone has little or no intrinsic activity, it is assumed that the effects observed after naloxone administration reflect the inhibition of endogenous opiate activity. Systemic administration of naloxone decreases feeding in food-deprived animals (4, 5), during stress-induced eating (6, 7), after muscimol-induced (8) or diazepam-induced (9, 10) eating, and in responses on operant schedules for food reinforcement (11). This effect is directed at ingestive behaviors in general as naloxone also inhibits drinking (12, 13). Recently, Jones and Richter (14) have nicely demonstrated that naloxone produces its effects directly on the CNS and not on some peripheral site.

A number of studies have suggested that the classical opiate, morphine, facilitates food intake (15–18). In an elegant study, Grandison and Guidotti (17) showed that intrahypothalamic injection of β-endorphin initiates feeding. The long-acting methionine-enkephalin analogue, D-Alaamide-Met-enkephalin, has also been shown to induce feeding in sated rats (16) and to reverse the satiety effect of a number of putative satiety factors such as cholecystokinin, bombesin, and thyrotropin-releasing hormone (19, 20). Recently, we have found that dynorphin, an endogenous opioid peptide that contains leucine enkephalin as its amino terminal, is a potent and specific inducer of feeding in sated rats (21).

In addition, using a highly specific and sensitive radioimmunoassay for dynorphin we have found that stresses related to food ingestion, i.e., starvation (72 h), mild tail pinch and insulin- (10 U/kg) induced hypoglycemia all produced alterations in cortical dynorphin levels whereas restraint stress and 10-min swim stress produced no changes in dynorphin levels (Morley JE, Levine AS, unpublished observations). Taken together with the pharmacological studies these results suggest a possible physiological role for dynorphin in appetite regulation.

Margules et al. (22) reported that naloxone reduces food intake more effectively in genetically obese mice and rats and that these animals have an increased level of β-endorphin within the pituitary. King et al. (23) demonstrated that the decrease in feeding after naloxone was more pronounced in ani-
showed that food intake was suppressed in diabetic mice (C57BL/Ks-db+/db+) and some detail (24). We used genetically obese, controls.

cells of the islets. These animals had higher streptozotocin, a drug that destroys the fi-
tality to naloxone seen in obese animals in

medial hypothalamus than in their littermate 
mals made obese by knife cuts in the ventro-

mendial hypothalamus than in their littermate controls.

Recently we have studied this supersensi-
tivity to naloxone seen in obese animals in some detail (24). We used genetically obese, diabetic mice (C57BL/Ks-db+/db+) and showed that food intake was suppressed in these animals by a 100-fold lower dose of naloxone than in control animals. We then made mice diabetic by injecting them with streptozotocin, a drug that destroys the β-cells of the islets. These animals had higher blood sugars than the genetically diabetic animals and were even more sensitive to naloxone suggesting that it is the high glucose values rather than the obesity per se which induce the extreme sensitivity to naloxone-induced suppression of food intake. We then studied the effect of naloxone on feeding induced by giving insulin to produce hyperglycemia in rats. Using this model we found that feeding induced in this manner was highly resistant to the suppressive effect of naloxone (no significant effect of 20 mg/kg compared to a significant effect at 1 mg/kg for starvation-induced feeding). These results suggest that glucose is capable of altering the sensitivity of the opiate receptor. Preliminary in vitro studies in our laboratory have confirmed that glucose does indeed alter both the affinity and the number of receptors in the opiate receptor assay when using [3H]-nalox-
one and whole brain membranes (25).

The special relationship of sugar to satiety is well recognized. The effect of glucose on the opiate receptor may provide an explanation as to why it is so easy to eat a sweet dessert when already replete. Along similar lines LeMagnen et al. (26) have shown that naloxone enhances spontaneous aversion to quinine suggesting that like other responses to nociceptive stimuli, this aversion is normally attenuated by the release of endogenous opiates.

Indirect evidence of the physiological role of endogenous opioid peptides in appetite regulation comes from the experiments demonstrating that food deprivation in the rat results in significant analgesia (27, 28). This analgesia was diminished by naloxone. These findings suggest that analgesia induced by food deprivation is mediated in part by opiate receptor systems and that in the hungry ani-

mal there is an increase in endogenous opiate activity. Mild tail pinch-induced eating is also associated with naloxone-reversible analgesia (Morley JE, Levine AS, unpublished observations). Studies on the circadian variation in endogenous opioid levels in rats have shown that the highest levels occur during the nocturnal feeding phase with the lowest levels during the light phase of the cycle (29).

Stress-induced eating is a well recognized syndrome. Besides having been observed in humans (30, 31), it has been best documented in birds where eating occurs during boundary disputes in the prairie horned lark, the great and blue tit, the avocet, the turkey, and the zebra finch (32). Antelman and Caggiula (32) have shown that stress-induced eating can be reliably produced in the laboratory rat by mildly pinching its tail. A variety of other stresses have also been shown to induce sporadic eating in laboratory animals (34). We have postulated and produced experimental evidence to suggest that stress-induced eating in the rat involves activation of peripheral and ascending pain fibers (35, 36) which in turn would presumably lead to activation of the endogenous opioid system. Morley (37) has pointed out that the discovery of the endogenous opiates has proved to be a logical extension of Cannon’s concept of preparation for “Fight or Flight” as enlarged by Hans Selye’s theory of general adaptation to stress and that abundant evidence exists showing that stress activates the endogenous opiate system. Thus it was not surprising to find that stress-induced eating in the rat is blocked by naloxone (6,7) and that induction of stress-induced eating in the rat, multiple times in a day for 10 days, leads to a withdrawal syndrome similar to that seen after opiate addiction (7). McCloy and McCloy (38) have marshalled evidence suggesting that obesity in humans may result from autoaddiction to endogenous opiates.

Of the monoamines involved in the regulation of feeding, the dopaminergic tracts in the nigrostriatal bundle have long been rec-

ognized as playing a major role in the initiation of feeding (1). Opiate binding sites have been demonstrated to be localized on the terminals of dopaminergic neurones of the nigrostriatal pathway (39) and activation of opiate receptors results in an increase in striatal dopamine synthesis and turnover (40).
This close interrelationship of opiates and dopamine in the lateral hypothalamic feeding area provides further circumstantial evidence for the pivotal role that endogenous opiates play in initiating feeding. There are few studies in man implicating the endogenous opiates in appetite regulation. The hyperendorphinemic child reported by Dunger et al. (41) was obese. Recently we had the opportunity to study a patient who developed severe obesity after traumatic damage to the ventromedial hypothalamus. He showed a small but significant decrease in calories ingested (~100 cal) in the amount of breakfast consumed after naloxone (20 mg) administration compared to the days when saline or the putative satiety factor, cholecystokinin, was infused. Kyriakides et al. (42) have reported that naloxone reduces food intake in some obese patients having profound hyperphagia as part of the Prader-Willi syndrome. Finally, Schwartz (43) conducted an anecdotal trial of oral naloxone in himself for 48 days with impressive weight loss over this period.

Conclusion

Mankind is used to thinking of the major function of the opiates as being to decrease pain. We would like to suggest that perhaps the major effect of the endogenous opiates (enkephalins) is to induce the feeding drive. Teleologically it would be of use to an animal when hungry and forced to encounter danger to find food to have some protection against pain. Thus, we postulate that the enkephalins were co-opted by the brain to also play a role in analgesia. The primary role for the enkephalins, therefore, would be the initiation of the food drive and the way we view opiates, namely as an analgesic, would be purely related to an accidental find in the poppy fields. We believe that the evidence presented here provides strong support for this hypothesis although some contrary evidence to the integral role of the endogenous opiates in the regulation of appetite does exist (44–46).

References

23. King BM, Castellanos FX, Kastin AJ, et al. Nalox-