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THE PHARMACOLOGY OF EATING BEHAVIOR[1]

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Fatophobia is rampant throughout America and the Western world. The economic impact of this ubiquitous desire for a lean body image is reflected in the rapid and continued success of diet books. Despite various claims, however, few efficacious pharmacological agents cure obesity. In 1972, the FDA assessed the results of the effects of eleven anorexic agents in over 10,000 patients and found that drugs produced an advantage over placebo of 0.56 pounds of weight loss per week (1). Although such an advantage maintained over months or years would clearly represent a major effect, it has in general failed to satisfy the appetites of those hungry for miracle cures. As a result, over the last decade the pharmaceutical industry has expended a tremendous effort to find the Holy Grail of Satiety.

We will review here much of the recent research on the pharmacology of eating behavior and develop the thesis that the complexities of the regulation of appetite are so great that it is highly unlikely that any single pharmacological agent will produce and maintain the degree of weight loss demanded by worshipers of the body skinny. The closely interwoven nature of the regulatory systems of feeding and other life preserving systems, e.g. temperature and glucoregulation, further suggests that any agent that could truly produce the dramatic alterations in eating behavior demanded of an ideal satiety agent would result in far too many serious side effects to allow it to be marketed.

As already stated, the regulation of food intake is an extremely complex process. It involves the hedonic qualities of food conveyed by olfactory, visual, and gustatory signals, neural and hormonal signals from the gastrointestinal tract, and the physicochemical qualities of the ingested food. In addition, a number of signals relay the overall state of nutrient homeostasis of the organ-

ism, including messages about the status of energy stores and essential nutrients (specific hungers). Superimposed on these biological substrates are psychological factors, such as learned aversions to substances that induce illness and a variety of ecological and sociological factors responsible for determining the availability of food and what is fit (or appropriate) to eat. These multiple inputs eventually must be integrated to determine the timing and quantity of food to be eaten. Much of this integration takes place in the central nervous system, making the brain the most important regulator of digestive processes in the body.

This review focuses mainly on the advances made in our understanding of the pharmacologic control of feeding in the eight years since the publication of Hoebel's article in this series (2). This means a concentration predominantly on the findings concerning the effects of peptides on feeding at the expense of the better established knowledge on the role of monoamines. Those wishing more detail on the monoaminergic regulation of feeding are referred to Hoebel's article (2) or the more recent review by Leibowitz (3).

In view of the complexities of the regulatory systems involved in feeding, it has become convenient to divide the control of feeding into a peripheral satiety system and a central feeding system. The peripheral satiety system appears to send its signals to the brain through both neuronal and hormonal messenger systems. In addition, the processing of foods gives rise to a number of simple nutrients that in turn can themselves act as neuromodulators, the so-called appetostats. The central feeding system(s) responsible for integrating these inputs involves a variety of neurotransmitters. We have suggested that within the central nervous system these interacting neurotransmitters are arranged in a cascade system similar to the classical cascade system regulating clotting and complement fixation (4). Figure 1 illustrates this appetite cascade system. Although the model is grossly oversimplified, it represents a useful malleable matchstick model to aid in understanding the complexities of the system. It also has helped in the design of pharmacological experiments on the nature of appetite control.

Before describing the pharmacological regulation of the peripheral and central feeding systems, we want to briefly discuss an apparent paradox. It is clear that, whereas many agents appear to inhibit feeding in animals, few have proved to be successful longterm modulators of human feeding. There are two major reasons for this discrepancy: first, most of the experiments in animals are carried out over a single meal whereas most human studies are carried out over weeks. In most cases, animals subjected to chronic administration of even the most potent inhibitors of feeding rapidly develop some degree of tolerance. Second, when calculated on a per-kilogram basis, the doses administered to animals are usually much higher and more toxic than those administered to humans. Based on these observations, it appears that the most successful

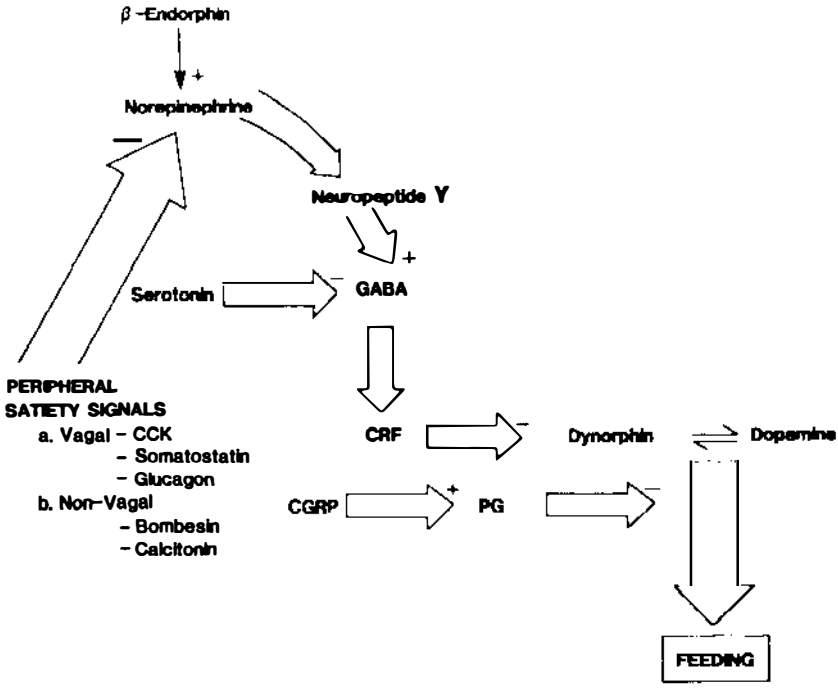

Figure 1 Simplified version of the satiety cascade in the rat. This represents the putative interconnections of the opioid feeding system. Other feeding systems clearly also exist. CCK = cholecystokinin; GABA = gamma amino butyric acid; CRF = corticotropin-releasing factor; CGRP = calcitonin gene-related peptide; PG = prostaglandin.

pharmacological approach for the treatment of obesity may be a sequentially administered, multi-drug approach.

THE PERIPHERAL SATIETY SYSTEM

The Pharmacological Modulation of Taste

Palatability has been suggested to play a role in the pathogenesis of obesity (5). Not surprisingly, all studies have shown that, when the foods are highly palatable, more calories are consumed. In addition, overweight subjects ingest more in response to highly palatable stimuli than do normal-weight people. Cabanac & Duclaux (6) found that in normal-weight people, the ingestion of glucose transforms the normally pleasant sensation of sucrose to an unpleasant sensation, whereas obese subjects continue to perceive the sucrose as pleasant. Occurrence of this alliesthesia has been shown to occur outside the laboratory in Jerba, North Africa, where the premarriage custom of overfeeding young

females decreases the rate of pleasantness of sucrose solutions (and presumably increases the appetite for other pleasures!) (7).

Recently a number of studies have explored the possibility of developing pharmacological agents that either substitute for preferred tastes without containing as many calories or that alter the perception of the taste, thus leading to an altered intake.

Studies with the dipeptide aspartame (NutraSweet®; L-aspartyl-L-phenylalanyl-methyl-ester) have suggested that it can satisfactorily mimic sucrose. Brala & Hager (8) found that there was no significant difference in calories ingested after a preload of aspartame compared to sucrose, despite the tremendous difference in the caloric content of the two treatments. In a chronic study, Porikos (9) found that surrepitiously substituting aspartame for sucrose resulted in a decreased caloric intake during the aspartame period compared to when the subjects were ingesting sucrose.

Recently a number of neuropeptides have been demonstrated to modulate taste. The antidipsogenic effect of the opioid antagonist naloxone is enhanced by sweet and salty flavors (10, 11), and naltrexone, a long-acting opioid antagonist, more efficiently reduces the intake of a palatable diet compared to the intake of normal chow (12). In contrast, morphine increases the intake of a relatively preferred saccharin solution (10%) while not affecting lower concentrations (13), and repeated pairings of morphine injections with sucrose or quinine solutions increase both the sucrose preference and the quinine aversion (14). These results suggest that the endogenous opioids may play a role in mediating or producing changes in the incentive values of certain tastes.

Substance P is an undecapeptide present in fibers innervating the circumvallate and fungiform papillae of the rat tongue (15) as well as in the nucleus of the solitary tract (16). Substance P has been shown to have a selective antidipsogenic effect. This effect is markedly attenuated when sucrose or saccharin is added to the drinking water (17). Thus, as is the case for endogenous opioids, flavor can modulate the antidipsogenic effect of substance P.

An established role for substance P in taste is as a mediator of the burning taste of chili pepper. Chili contains capsaicin, a chemical that blocks the re-uptake and promotes the release of substance P at nerve terminals. This produces increased concentrations of substance P in the tongue, leading to the burning sensation associated with chili. Why some acquire a liking for the oral pain sensations produced by chili pepper, why some like it hot, is unclear (18). One psychological theory suggests that the initially negative effect gives rise to an internally generated compensatory positive effect (19). Given our knowledge that the release of substance P results in a compensatory increase in endogenous opioids (20), it may not be unreasonable to speculate that the neurochemical substrate of a liking for chili may be secondary to the reward produced by an increased release of endogenous opioids in the brain.

Cholecystokinin (CCK) is another peptide that has been shown to produce effects on taste perception in addition to its better documented effects on satiety (vide infra). CCK reduces the short-term (three-minute) intake of sucrose solutions (21, 22) and inhibits sham feeding (23), suggesting a pregastric component to its satiety effect. Compatible with this concept, CCK has been shown to inhibit the activity of neurons in the nucleus of the solitary tract (24), and intravenous infusion of CCK-8 increases integrated responses to sucrose from the uncut chorda tympani of the rat (25). Thus, the orosensory qualities of the food appear to play a role in producing the full CCK effect on ingestive behavior.

Gut Hormones as Modulators of Satiety

Studies by Davis et al (26) using cross-perfused rats showed that an unfed rat ate considerably less after being cross-perfused with the blood of a fed rat. This suggests that circulating hormonal factors released during a meal played a role in the satiety syndrome. Cross-perfusion studies with the obese (ob/ob) mouse and with destructive lesions of the ventromedial hypothalamus (VMH) provided further evidence for a circulating satiety factor. When the ob/ob mouse is parabiosed to its lean littermate, it decreases the amount it eats, suggesting that ob/ob mice become obese because of failure to produce a circulating satiety factor (27). On the other hand, when normal rats are parabiosed to rats with VMH lesions, the normal rats decrease their food intake, suggesting overproduction of circulating satiety factors in the rats with VMH lesions (28). These parabiosis experiments have led to an intensive search for these circulating satiety factors. At present the best studied candidate for a circulating satiety factor is cholecystokinin.

Cholecystokinin

Cholecystokinin (CCK) is a polypeptide hormone that was first isolated as a 33-amino acid hormone from the porcine gastrointestinal tract. Subsequently, it has been shown that the active portion of the molecule consists of the eight carboxy terminal amino acids (CCK-8). CCK has subsequently been demonstrated to have a variety of actions both on the gastrointestinal tract and on the central nervous system (29).

In 1973, Gibbs et al (30) proposed that CCK may be a peripheral satiety signal when they found that both a partially purified preparation of CCK and synthetic CCK-8 suppressed solid and liquid food intake in rats. Subsequently, Smith & Gibbs (31) found that L-phenylalanine, a potent releaser of CCK, suppressed food intake in monkeys, whereas its inactive isomer did not. Studies by McLaughlin et al (32) found that the administration of the trypsin inhibitor trasylol decreases food intake in lean and obese rats. Since trypsin

inhibitors increase CCK by inhibiting the negative feedback signal for its release, this provides further evidence for a physiological role for CCK in appetite regulation.

Much controversy exists over whether the CCK effect on decreasing food intake represents a true satiety effect or whether its effects are secondary to toxicity or aversion. Studies using classical tests for conditioned taste aversion have given both positive and negative results (33). Recently, we developed the paradigm of different degrees of starvation to measure the satiating effect of peptides (34). Reasoning that a satiety factor should inhibit food intake to a lesser degree as the period of food deprivation is increased, whereas an aversive agent should uniformly inhibit food intake independent of length of deprivation, we studied the effects of CCK at two different degrees of starvation. In this study, CCK reduced intake in the manner we predicted a satiety factor would, whereas lithium chloride effects were those predicted for an aversive agent. Thus, based on the available evidence, it seems that CCK may be a true satiety factor.

Besides decreasing feeding in rats, CCK has been shown to decrease food intake in a variety of species, including humans. Kissileff et al (35) and Pi-Sunyer et al (36) have shown that CCK-8 infusions decreased food intake in lean and obese humans, although previous studies had produced conflicting results (37, 38). Stacher et al (39) confirmed these findings, showing that CCK-8 decreased feeding in humans by about 17%. Our studies in humans have also found that CCK-8 decreases food intake; the data suggest that this effect on food intake may be linked to the ability of CCK to decrease gastric emptying (unpublished observations).

The mechanism by which CCK signals its satiety effect is uncertain and appears to differ in different species. Studies in the rat have shown that peripherally administered CCK-8 acts in the abdomen through vagal fibers and not directly in the brain to produce satiety (40, 41). Both total abdominal vagotomy and selective gastric (but not celiac or hepatic) vagotomy reduce the satiety effect of CCK. Further, Smith et al (40) found no effect of atropine on CCK-induced satiety, suggesting that the effect is mediated by afferent rather than efferent vagal fibers. However, in the dog, vagotomy produces minimal attenuation of the satiety effect of CCK (42).

Although in the rat the major effect of CCK on satiety appears to be through activation of peripheral satiety signals, in the sheep the effect of CCK on feeding seems to involve central mechanisms. Continuous injections of picomole quantities of CCK-8 into the cerebral ventricles of sheep decreases feeding (43), and antibody to cholecystokinin injected into the cerebral ventricles stimulates feeding in sheep but not in rats (44). Recently, studies by Denbow & Myers (45) have suggested that in the chicken, like the sheep, the major site of action of CCK in suppressing feeding is within the central nervous system.

Other Gut Hormones That Modulate Feeding

Bombesin is a tetradecapeptide originally isolated from the skin of the frog *Bombina bombina* and subsequently shown to be widely distributed in mammalian systems. In 1979, Gibbs et al (46) reported that peripheral injections of bombesin suppresses food intake in rats. Bombesin was five times less potent at suppressing feeding than cholecystokinin-octapeptide on a molar basis. Bombesin had no effect on water intake and no major effects on locomotor activity, which suggests a fairly specific effect on feeding behavior when administered peripherally. Unlike CCK, peripherally administered bombesin still decreases feeding in the rat following vagotomy (41). Also, bombesin potently decreases feeding after central administration in the rat, suggesting that at least some of its effects may be mediated within the central nervous system (47, 48). Recently, bombesin when infused intravenously has been shown to decrease food intake in humans at doses below those that produce nausea (49). Gastrin-releasing peptide is a 27–amino acid peptide that shares marked structural similarity with bombesin. It too has been shown to decrease feeding in the rat (50, 51).

Somatostatin is another gut hormone that has been shown to decrease feeding after peripheral administration in the rat and the baboon (52, 53). Like CCK, somatostatin appears to produce its effect through a vagal mechanism (53).

Two pancreatic hormones, glucagon and pancreatic peptide, have been suggested to play a role in satiety, at least in some species. In 1957, Schulman et al (54) reported that glucagon decreased caloric intake in humans. It was felt that glucagon's effect was secondary to its effects on glycogenolysis with mobilization of glucose stores from the liver. Subsequently, glucagon was shown to decrease feeding in rats and rabbits; this effect was dependent on an intact vagus (55, 56). Geary & Smith (57) have shown that the glucagon effect on satiety can be blocked by a selective hepatic vagotomy. The most convincing evidence in support of glucagon as a satiety agent is the finding by Langhans et al (58) that intraperitoneal injections of glucagon antibodies increase food intake by increasing both the duration and the length of the meal while at the same time reducing the increases in hepatic portal glucose concentrations normally associated with a meal.

Pancreatic polypeptide is a 36–amino acid peptide secreted predominately from the cephalic part of the pancreas. As its circulating levels rise following a meal, its effects on food intake were tested. Malaisse-Lagae et al (59) reported that peripherally administered pancreatic polypeptide decreases food intake and body weight in the genetically obese (ob/ob) mouse. However, pancreatic polypeptide could not be shown to decrease feeding in the rat (34).

The role of the various peripheral satiety agents is summarized in Figure 2.

Appetostats

The concept that nutrients themselves are directly responsible for producing satiety represents one of the earliest hypotheses concerning weight regulation.

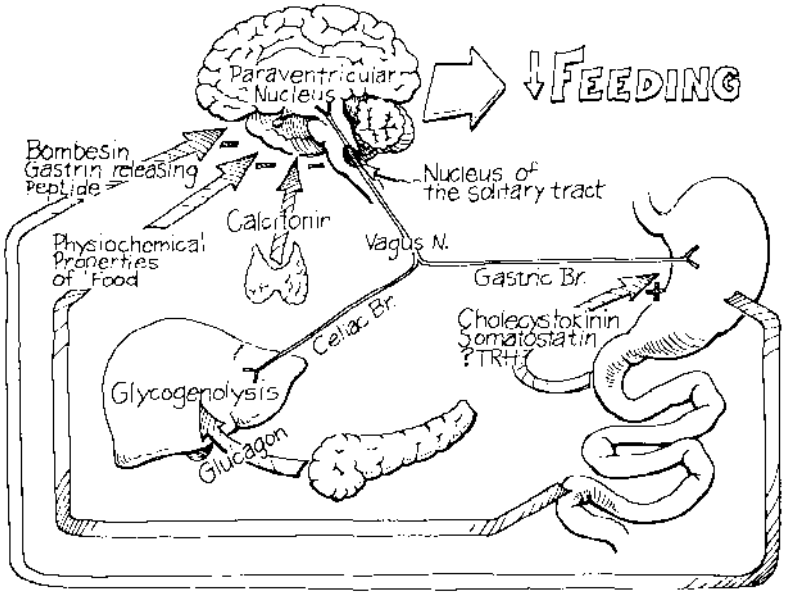

Figure 2 The peripheral satiety system. TRH = thyrotropin-releasing hormone.

As early as 1916, Carlson (60) suggested that falls in circulating glucose levels served as the hunger signal and that eating ceased when glucose levels returned to normal. In 1952, Jean Mayer (61) modified this theory in an attempt to explain why the hyperglycemia of diabetes mellitus was associated with hyperphagia. He suggested that the rate of glucose utilization rather than the absolute glucose concentration was the crucial regulatory mechanism. Further support for glucose as a modulator of neuronal hunger comes from the studies of Oomura (62) showing that iontophoretic application of glucose increases firing of neurons in the medial hypothalamus and lowers the frequency of discharge in the lateral hypothalamus.

There is an inverse relationship between plasma levels of amino acids and food intake. This led Mellinkoff (63) to propose the amino-static hypothesis of feeding. He suggested that excesses and deficiencies of amino acids play a role in the initiation and inhibition of food intake. In view of the fact that certain amino acids, e.g. γ-amino butyric acid (GABA), both act as neurotransmitters and inhibit food intake, this represents an attractive scientific theory of appetite regulation. Wurtman (64) has attempted to link the glucostatic and aminostatic hypotheses by showing that glucose faciliates the transport of tryptophan, the serotonin precursor, across the blood-brain barrier.

Others have suggested that free fatty acids released during lipolysis may signal feeding behavior (65), or that glycerol, which is released into the circulation proportionally to the rate of triglyceride hydrolysis, acts as a signal

of the status of body fat stores (66). In 1958, Brobeck (67) proposed that the heat generated by metabolic fuels, i.e. the specific dynamic action of food, was responsible for the regulation of feeding. This concept was supported by studies in goats showing that local cooling or warming of the anterior hypothalamus induced and decreased feeding respectively (68). Recent studies have shown a role for multiple peptides and neurotransmitters in thermoregulation, suggesting that some of the effects of peptides on food intake may be secondary to their effects on central thermoregulatory mechanisms (69).

Both peripheral and central administration of purines decreases feeding (70–72). As there is extensive evidence for a purinergic nervous system, we proposed, somewhat tongue-in-cheek, a purinostatic model of feeding (73). Some of our studies have supported the concept that purinergic modulation of feeding may involve an interaction with the diazepam receptor, and recently we have reported evidence of a close interrelationship between the purinergic feeding system and the opioid feeding system (74). Finally, levels of xanthine in the cerebrospinal fluid are associated with poor appetite in depressed patients, suggesting a possible role for purines in the appetite regulation of humans (75).

Another nutrient-linked theory of longterm appetite regulation suggests that insulin plays a key role as a body-adiposity signal. This hypothesis is based on the impressive correlation between the degree of adiposity and plasma insulin levels (76), and the finding that plasma insulin levels increase proportionately when insulin is infused intravenously (77). Woods et al (77–79) have reported that, in contrast to the effects of peripherally administered insulin, when insulin is administered centrally it markedly decreases feeding in baboons and in lean but not obese (fa/fa) Zucker rats. Instillation of insulin antibodies into the ventromedial hypothalamus of rats results in an increased food intake (80). Tannenbaum et al (81) have found that central administration of a partially purified insulin growth factor is an extremely potent inhibitor of feeding in rats.

The proliferating theories of nutrient control of food intake suggest that the brain possesses multiple mechanisms for modulating the levels of essential nutrients. Such mechanisms are in keeping with the known ability of animals to select a proper balance of macronutrients and micronutrients when feeding freely. Modern knowledge suggests that there are numerous windows on the brain that act as monitors of the milieu interieur. Information from these sensors is then processed within the central nervous system through a cascade system involving multiple neurotransmitters.

THE NEUROPHARMACOLOGY OF THE CENTRAL REGULATION OF APPETITE

A variety of substances have been demonstrated to increase or decrease feeding after central administration (Table 1).

Table 1 Centrally acting neuropharmacological modulators of feeding behavior

	Feeding enhancers	Feeding inhibitors
Monoamines	Norepinephrine (α-agonist)	Epinephrine
		β-agonists
	Dopamine	Dopamine
		Serotonin
		Phenylethylamine
Peptides	Opioid peptides—dynorphin	Corticotropin-releasing factor
	α-neo-endorphin	Thyrotropin-releasing hormone
	β-endorphin	Cyclo-histidyl proline diketopiperazine
	D-Ala^5-d-leu-enkephalin	Neurotensin
	Neuropeptide Y	Bombesin
		Calcitonin
		Calitonin gene-related peptide
		Cholecystokinin (species variability)
		Insulin
		Insulin growth factor
Amino acids	GABA (muscimol)	GABA
		Adenosine
Miscellaneous	Acetylcholine	Acetylcholine
	Benzodiazepines	Adenosine
	Calcium	Prostaglandins

Opioid Feeding Systems

Since the pioneering study by Holtzman (82) demonstrating that the opioid antagonist naloxone decreases feeding in rats, many studies have suggested a role for endogenous opioid peptides in feeding modulation (83). Naloxone decreases feeding in rats under a variety of conditions, including spontaneous (84), starvation-induced (85), norepinephrine-induced (86), muscimol-induced (87), 2-deoxyglucose-induced (88), and stress-induced (88, 89) feeding. However, naloxone poorly antagonizes feeding induced by chronic starvation for three weeks (90), schedule feeding (91) and insulin hypoglycemia (88) suggesting that the opioid feeding system is not the only feeding system. In fact, it has been suggested that the opioid system may play a more important role in macronutrient selection than in the feeding drive per se (92). Also, chronic administration of naloxone, or of the long-acting opioid antagonist naltrexone, produces only small decreases in food intake and body weight in non-obese rats and mice (93, 94). Further, it is clear that the effect of opioid antagonism on feeding is modulated by a variety of hormones (Table 2).

Besides its effects in rodents, naloxone decreases feeding in a variety of other species ranging from wolves (99) to humans (100). Although naloxone clearly decreases feeding over a single meal in humans, chronic naltrexone

Table 2 Effect of hormonal manipulations on opioid antagonism of feeding

Increase effect of naloxone on feeding	Decrease effect of naloxone on feeding	References
Hyperglycemia	Hypoglycemia	88, 95, 96
Ovariectomy	Estradiol	97
Progesterone antagonizes estradiol effect	Adrenalectomy	97, 98

administration to humans has so far yielded equivocal results, with only mild decreases in weight gain in obese females being demonstrated (101). Further, in some species opioid antagonism fails to alter feeding. These species include the golden hamster (102), the Chinese hamster (103), and the racoon (104).

Just as opioid antagonism decreases feeding in rats, a variety of opiate agonists have been shown to increase feeding. The mixed kappa opiate agonists/antagonists, such as ketocyclazocine (105) and butorphanol tartrate (106), appear to be more potent than mu agonists at stimulating feeding. This has led to the suggestion that the kappa opioid receptor plays an integral role in the initiation of feeding. Support for this comes from the finding that the kappa opioid peptide dynorphin is a potent enhancer of feeding after central administration (107). Recent evidence has suggested that the effect of this peptide on feeding involves both the opioid and the non-opioid portion of the molecule (108) (Figure 3). This concept of a double-lock receptor suggests that the non-opioid portion of the dynorphin molecule (5–13) targets the molecule to the receptor and unlocks access to the opioid portion of the receptor. In vitro studies by Chavkin & Goldstein (109) have resulted in a similar concept for the mode of action for dynorphin. Further evidence for a role for dynorphin in feeding comes from studies showing that its levels alter in the central nervous system under conditions that modulate the feeding drive (110, 111).

Although much evidence has accumulated on a primary role for dynorphin and the kappa opioid receptor as the major mediators of the opioid feeding drive, we must point out that other opioid peptides, such as β-endorphin (112) and the delta receptor analog D-ala^{2}D-leu^5-enkephalin (113), also stimulate feeding after central administration. Recently, we obtained preliminary evidence suggesting that more than one opioid receptor and more than one brain site may be involved in the opioid modulation of feeding.

To conclude this section on opioid modulation of feeding, we want to speculate that, from a teleological point of view, the original function of opioids was to stimulate the feeding drive. This forced the animal to go out and forage for food, at times inflicting pain on the animal species; thus, survival would be enhanced by a gene mutation that resulted in a similar peptide subserving the function of analgesia. The fact that opioids also decrease sexual activity (114) makes further teleological sense, as starving animals (increased

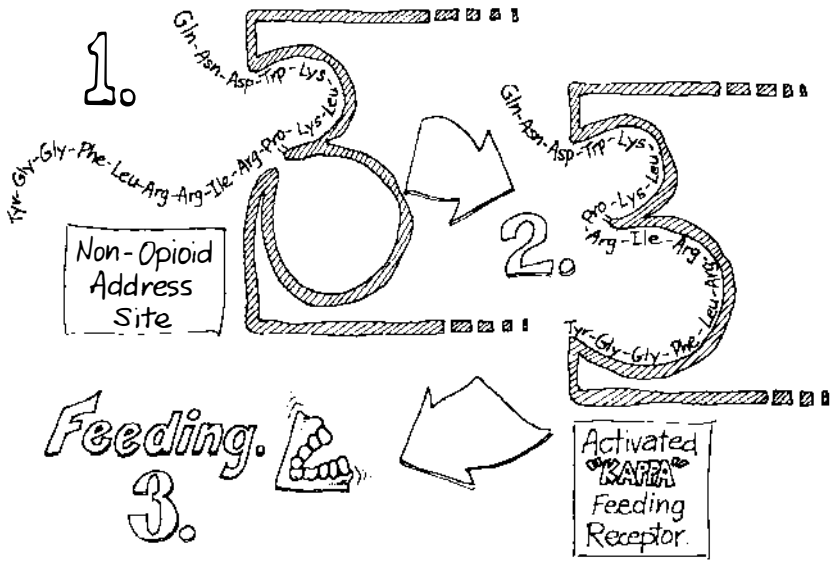

Figure 3 Illustration of the dual nature of the dynorphin-kappa opioid feeding receptor.

opioid activity) are at a disadvantage for procreation and it would be better to procreate at a time when food was readily available.

Monoamines as Feeding Modulators

In 1962, Sebastian Grossman showed that intrahypothalamic injection of norepinephrine induces vigorous feeding and that acetylcholine inhibits feeding (115). Subsequently, Sarah Leibowitz has established that α-adrenergic stimulation in the area of the paraventricular nucleus stimulates feeding and β-adrenergic stimulation in the lateral hypothalamus is inhibitory to feeding (116). The norepinephrine increases in feeding are due to an increase in meal size rather than meal frequency and create a preference for carbohydrate-rich foodstuffs (3). The facilitatory effects of centrally administered norepinephrine on feeding requires an intact vagus (117) and adrenalectomy abolishes the effect, which can be restored by administration of corticosterone (118). As lesions of the paraventricular nucleus result in hyperphagia rather than in decreased eating, while attenuating norepinephrine induces eating (119), it appears that norepinephrine-induced feeding is secondary to inhibition of the release of a satiety factor in this nucleus.

A variety of studies have suggested, but not proven, that serotonin functions as a satiety agent (120). Serotonin agonists and drugs that potentiate serotonin actions, e.g. fenfluramine, decrease feeding, whereas serotonergic antagonists and the serotonergic neurotoxins 5,6- and 5,7-dihydroxytryptamine enhance feeding. Serotonergic stimulants decrease meal size without affecting the

initiation of feeding or meal frequency (3). In addition, serotonin results in a decrease in carbohydrate intake while preserving or even potentiating protein intake (3). Serotonin exerts its major site of action in either the paraventricular or ventromedial hypothalamus and inhibits norepinephrine-induced eating (3). Recently, it has been suggested that some of the effects of serotonin stimulators may be mediated through peripheral effects, resulting in a slowing of gastric emptying (121).

Destruction of dopaminergic and other catecholaminergic fibers with the neurotoxin 6-hydroxydopamine can lead to hypophagia and weight loss (122). Dopamine infusion into the hypothalamus can increase or decrease feeding (3). The dopamine agonist bromergocryptine stimulates feeding at low doses after central administration and inhibits it at higher doses, a result associated with stereotypic behaviors (123).

The structures of many of the more widely used anorectic drugs in humans are closely related to the β-phenylethylamine nucleus, e.g. amphetamines, diethylpropion. Multiple studies have demonstrated that amphetamine inhibits eating while leading to hyperactivity and stereotypy (124). The amphetamines' anorectic effect appears to be mediated predominantly in the area of the lateral hypothalamus (116). At present the general consensus is that amphetamine produces its effect by release of catecholamines in the perifornical area, resulting in stimulation of the β-adrenergic satiety system (2).

Peripheral administration of high doses of phenylethylamine inhibits feeding, although the specificity of this effect is unclear (125). Interest in the possibility of a phenylethylamine satiety system was recently stimulated by the study of Paul et al (126), who found highly specific amphetamine receptors in the central nervous system. Phenylethylamine appears to be the endogenous ligand for the amphetamine receptor. In their studies, they found that the anorectic potency of a variety of phenylethylamine derivatives was related to their ability to bind the phenylethylamine receptor.

Neuropeptide Y: A Potent Stimulator of Feeding

Neuropeptide Y is a 36–amino acid peptide isolated by Tatemoto (127) from the porcine hypothalamus. It belongs to the pancreatic polypeptide family and has been shown to co-exist in norepinephrine-containing neurons (128). Neuropeptide Y is the most potent known stimulator of feeding (129; J. Morley, A. Levine, unpublished observations) (Figure 4). Neuropeptide Y also increases water intake. The effect of neuropeptide Y on feeding is not blocked by the α-antagonist phentolamine, but is decreased by naloxone and the dopamine antagonist haloperidol. The discovery of the potent stimulatory effect of neuropeptide Y on feeding may represent one of the more exciting discoveries of the last decade in the study of appetite regulation. Development

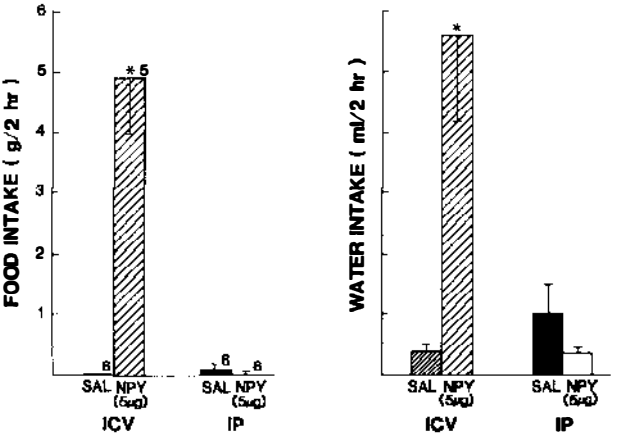

Figure 4 Effect of neuropeptide Y (NPY) on feeding and water intake after central (ICV) administration. Note the lack of effect after the same dose of NPY given peripherally (IP). *$p < 0.01$ by two-tailed student t-test.

of specific antagonists to neuropeptide Y may represent a potential treatment for the regulation of feeding in obese patients.

Neuropeptides as Satiety Agents

In contrast to neuropeptide Y and the opioid peptides, most other neuropeptides appear to inhibit rather than stimulate feeding. Whether or not this ability of neuropeptides to suppress feeding after central administration represents a true satiety effect or a non-specific disruption of behavior is a subject of intensive debate at the present time.

Calcitonin is a potent inhibitor of feeding after central administration (130). It appears to produce its satiating effects by inhibiting calcium uptake at the hypothalamic level (131). Recently, Rosenfeld et al (132) showed that the calcitonin gene is processed differently in the central nervous system, giving rise to calcitonin gene–related peptide (CGRP). CGRP is distributed in the brain into many anatomical areas connected with the regulation of taste. CGRP suppresses feeding after central administration in rats (133). This effect is less potent than calcitonin on a molar basis. Although CGRP shows some degree of behavioral specificity, it has also been shown to produce a conditioned taste aversion.

Bombesin, a tetradecapeptide originally isolated from the skin of frogs, besides inhibiting feeding after peripheral administration, also decreases feeding when centrally administered (134, 135). It also slows gastric emptying (136) and decreases gastric acid secretion (137). The site of action of bombesin on feeding appears to be in the lateral hypothalamus (138).

Corticotropin-releasing factor (CRF) is a 41–amino acid peptide that releases

ACTH and β-endorphin from the anterior pituitary (139). CRF is a potent inhibitor of feeding after central administration in the rat (140, 141). Animals administered CRF display a marked increase in grooming (140). The effects of CRF on food intake are partially dependent on the presence of an intact adrenal gland (141). We have previously suggested that CRF may play a role in the pathogenesis of anorexia nervosa (142).

Neurotensin is an undecapeptide that has been shown to decrease feeding under a variety of circumstances (143–145). It appears to exert its major action in the region of the paraventricular nucleus (143). Thyrotropin-releasing hormone and its metabolite, cyclohistidyl proline diketopiperazine, have also been demonstrated to decrease feeding under certain circumstances (146–148).

CONCLUSION

The last decade has led to the discovery that a variety of chemical messengers can modulate feeding. Although the physiological significance of these substances remains uncertain, it is clear that the development of pharmacological agonists and antagonists of these substances offers the hope of powerful tools to help modulate appetite control. In view of the multiplicity of factors involved in appetite regulation, it seems clear that no single factor is likely to emerge as the one single regulator of satiety. The etiology of appetite disorders is likely to prove to be multifactorial, with a resulting need to tailor the pharmacotherapy to the individual.

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