Chapter 2

Neurotransmitter Regulation of Appetite and Eating

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The regulation of feeding is an extremely complex process involving a variety of peripheral inputs including the hedonic qualities of food, neuronal and hormonal signals from the gastrointestinal tract, the physicochemical qualities of absorbed food, the state of glycogen stores in the liver, the status of the organism's fat stores, and possibly the activity of brown adipose tissue. In addition to these internal cues, external cues such as the availability and types of food, and psychological factors in higher animals and cultural factors (eg, the need to eat only kosher foods), in humans also play a role. In the feeding literature, the classical approach to handling this excess of regulatory factors has been to stress the importance of one or another factor while ignoring the potential interplay of multiple factors. Further, there has been a marked tendency to underemphasize the mechanism(s) by which these factors are integrated within the central nervous system. While this underemphasis of central factors was perhaps a natural response to the practical difficulties involved in studying central mechanisms of appetite control, these central factors have contined to be slighted despite the emergence of technologies that make central studies feasible.

With the recent discovery of the existence of multiple neurotransmitters (more than 55 have now been identified), it is becoming possible to dissect the neurochemical messengers responsible for integrating the multiple peripheral signals concerning the status of the energy stores of the organism. It has become convenient to artificially divide the control of feeding into a *peripheral satiety system* and a *central feeding system.* In this chapter we will concentrate on the role of neurotransmitters as integrators of the central feeding system.

There are three major families of neurotransmitters: amino acids, eg, gamma-aminobutyric acid (GABA); amines, eg, catecholamines and serotonin; and neuropeptides. The concentrations of neurotransmitters in the brain range from micromolar (μM) to fentomolar (fM). The critical functional concentration of a neurotransmitter, however, is that existing in the synapse. Because synaptic neurotransmitter levels are not measureable, it is not possible to clearly establish which concentration of any neurotransmitter is physiological as opposed to pharmacological. The behavioral effect of any specific neurotransmitter is highly dependent on the anatomical site at which it is released (eg, norepinephrine increases feeding when infused into the paraventricular nucleus but decreases feeding when injected into the lateral hypothalamus).

Studies using lesioning and stimulation of various areas of the central nervous system have placed the soul of appetite regulation in the hypothalamus. Simplistically, the hypothalamus can be perceived as a powerful computer responsible for integrating all of the inputs concerning the nutrient status of the organism and making the output decision of whether or not the organism should feed. From a teleological point of view, one might postulate that an older system (developed

when food was scarce) would be the feeding drive system(s) ordering the organism to eat whenever food was available. In transition from times of famine to feast, organisms developed a secondary satiety system responsible for attempting to restrain the unbridled feeding system. Thus, feeding is thought to be dependent on the balance between a feeding initiation system and a feeding cessation (or satiety) system. A large number of neurotransmitters have been identified as being capable of initiating or inhibiting feeding. At the outset it should be stressed that it is not well delineated at this time whether these represent true satiety factors or nonspecific disruptors of behavior (including food intake).

If the hypothalamus is likened to a computer, the neurotransmitters can be thought of as computer chips. The release of a neurotransmitter into a specific area represents the release of a prepackaged set of information, which sets in motion a variety of neuronal impulses leading to the switching on of a number of closely related behaviors. The most simple example of a peptide regulating two closely related species-preserving functions is seen in a shellfish, the *Pleurobranchea*. This mollusk has a voracious appetite and devours anything up to one-third its size that comes in its vicinity. This habit of eating everything would have resulted in extinction of this species, because everytime it laid eggs, it would have eaten them. Nature, therefore, endowed this shellfish with an interesting peptide hormone called the egg-laying hormone [1]. About 15 minutes after injecting this mollusk 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 demonstrates the potential advantages of a single substance regulating two closely related functions.

HISTORICAL BACKGROUND

Historically, the understanding of a central feeding system began with the studies of Heatherington and Ranson [2], who in 1940 demonstrated that lesions of the ventromedial hypothalamus (VMH) resulted in obesity. Later, electrical stimulation of this area was shown to inhibit feeding and a variety of catabolic responses, leading to the designation of the VMH as the satiety center. In 1951, Anand and Brobeck [3] showed that destruction of the lateral hypothalamus (LH) produced aphagia and weight loss. Electrical stimulation of the lateral hypothalamus was then shown to increase feeding and to initiate a variety of anabolic responses. It was then suggested that the LH was the feeding center.

It has subsequently been realized that these original anatomical studies represented a great oversimplification of the true situation [4]. Ablation and electrical stimulation studies have shown that a variety of central nervous system areas are involved in feeding regulation (Table 1). In addition, it appears that in many instances, the fibers coursing through the area are mainly responsible for appetite regulation. The satiety center is associated with two major pathways—a serotonergic pathway originating in the raphe nuclei of the pontine-midbrain area and then coursing through the VMH (the median raphe nuclei tracts) and the ventral adrenergic bundle, which passes through the perifornical area in the vicinity of the ventral hypothalamus. The LH is associated with the dopaminergic nigrostriatal tract. Apart from feeding, these tracts also appear to be associated with the reward or pleasure centers of the brain.

Table 2.1 Anatomical site involved in feeding

Site	Lesion	Electrical Stimulation
Ventromedial Hypothalamus	Increases feeding	Decreases feeding
Paraventricular Nucleus	Increases feeding	?
Dorsomedial Nucleus	Increases feeding	?
Lateral Hypothalamus	Decreases feeding	Increases feeding
Striatum	Decreases feeding	?
Globus Pallidus	Decreases feeding	?
Midbrain Tegmentum	Decreases feeding	Facilitates feeding

The association of tracts of neurochemical specificity with lesions having specific effects on feeding suggested a new route for investigating feeding control. In 1962, in a pioneering article in the American Journal of Physiology, Grossman showed that intrahypothalamic injection of norepinephrine (NE) induced vigorous feeding and that acetylcholine inhibited feeding [5]. Subsequently elegant studies by Leibowitz at the Rockefeller University in New York have clearly established that alpha-adrenergic stimulation in the area of the paraventricular nucleus (PVN) and VMH stimulated feeding, and ß-adrenergic stimulation in the LH inhibits feeding [6].

In 1976 and 1977 a series of studies by Blundell, Coscina and Hoebel and their colleagues were published demonstrating that depletion of brain serotonin by either neurotoxins (eg, 5,6 hydroxytryptamine) or serotonin synthesis depletors resulted in hyperphagia and obesity [7]. Earlier studies in 1971 had demonstrated that local injections of serotonin into the brain decreased feeding [8]. However, it is now recognized

Table 2.2 Neurotransmitters that play a putative role in feeding regulation

	Increase Feeding	Decrease Feeding
Monoamines	Norepinephrine (α- agonists)	Norepinephrine (ß) Serotonin
Amino Acids	GABA (muscimol)	GABA
Peptides	Opioid peptides Neuropeptide Y Galanin	Corticotropin Releasing Factor Neurotensin Bombesin Calcitonin Calcitonin Gene-Related Peptide Somatostatin Thyrotropin Releasing Hormone Cyclo-histidyl Proline Diketopiperazine Cholecystokinin
Miscellaneous	Endogenous benzodiazepines Acetylcholine	Adenosine Acetylcholine Prostaglandins

that while serotonin 5-HT_{1A} inhibits food intake, the 5-HT_{1B} serotonin receptor enhances feeding [51].

A number of studies have shown that destruction of dopaminergic and other catecholaminergic fibers with the neurotoxin 6-hydroxydopamine can lead to hypophagia and weight loss. Morley et al [9] found that the dopamine agonist, bromergocriptine, stimulated feeding at low doses after central administration and inhibited it at higher doses, which are associated with stereotypic behaviors.

In a classical study in 1976, Grandison and Guidotti showed that direct injection of ß-endorphin into the VMH initiated feeding [10]. This study, coupled with the studies by Holtzman at Emory University showing that the opioid antagonist, naloxone, decreased feeding [11], led to the concept that endogenous opioid peptides were involved in initiating feeding. In 1977, Vijayan and McCann found that centrally administered thyrotropin-releasing hormone and somatostatin inhibited feeding after central injection [12]. Subsequently, a large number of neuropeptides have been shown to inhibit feeding after central administration [13]. Table 2 lists the neurotransmitters that appear to be involved in the central regulation of appetite.

In 1980, in an attempt to bring some order to the rapidly proliferating field of feeding inhibiting and initiating neurotransmitters, Morley [4] postulated the concept of a central satiety cascade in which a dopamine-opioid interaction was responsible for the initiation of feeding and that this interaction was held in check by a variety of inhibitory and disinhibitory neurotransmitters. This cascade system would be similar to the well-recognized biological cascades for clotting and complement fixation. Despite the fact that the original model was an oversimplification, this model has aided us and others in the design of further experiments that attempt to unravel the complexities of central regulation of appetite.

CURRENT STUDIES

Norepinephrine

A variety of studies have shown that norepinephrine has a facilitatory effect on enhancing food intake when injected into the central nervous system [6]. The primary site for norepinephrine-induced eating appears to be the paraventricular nucleus [6]. This norepinephrine-induced feeding is mediated through alpha-adrenergic receptors [6]. Norepinephrine increases in feeding are due to an increase in meal size rather than in meal frequency and to create a preference for carbohydrate-rich foodstuffs [6]. The facilitatory effects of centrally administered norepinephrine on feeding requires an intact vagus [14], and corticosterone has been shown to be an essential humoral factor for norepinephrine-induced feeding to occur [15].

The potential physiological role of norepinephrine in feeding has been suggested by studies showing that spontaneous and deprivation-induced feeding are associated with increased turnover of endogenous norepinephrine and down-regulation of alpha-adrenoreceptors in the paraventricular nucleus [16]. Further, Myers and McCaleb [17] have shown that infusion of nutrients into the duodenum inhibits synaptic release of norepinephrine from medial hypothalamic sites.

Lesions of the paraventricular nucleus result in hyperphagia rather than decreased eating while attenuating norepinephrine-induced eating [18]. This suggests that the norepinephrine-induced feeding is secondary to inhibition of the release of a satiety factor in this nucleus.

Besides the evidence for an alpha-adrenergic feeding system in the paraventricular nucleus, it has been shown that norepinephrine injected into the lateral hypothalamus decreases feeding, and lesions of the ventral norepinephrinergic bundle cause mild hyperphagia [6]. Myers and McCaleb [17] found that duodenal nutrient infusion enhanced synaptic norepinephrine release from lateral hypothalamic sites. These and other studies have led Leibowitz [6] to suggest there may be a ß-adrenergic satiety system in the region of the perifornical bundle.

Serotonin

A variety of studies have suggested, but not proved, that serotonin functions as a satiety agent [7]. Serotonin agonists and drugs that potentiate serotonin actions (eg,

fenfluramine), decrease feeding, whereas serotonergic antagonists and the serotonergic neurotoxins (5,6 and 5,7 dihydroxytryptamine) enhance feeding.

Studies by Blundell and Latham [19] have shown that drugs which enhance serotonin release or block serotonin uptake have specific effects on the meal pattern. These serotonergic stimulants decrease meal size without affecting the initiation of feeding or the meal frequency. Serotonin results in a decrease in carbohydrate and/or caloric intake while preserving or even potentiating protein intake [20]. Serotonin inhibits norepinephrine-induced feeding, and like norepinephrine, appears to exert its major action in either the paraventricular nucleus or the VMH. 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 [21].

Phenylethylamine and Amphetamine

The structures of many of the more widely used anorectic drugs in humans are closely related to the ß-phenylethylamine nucleus (eg, amphetamines, diethylpropion). Multiple studies have demonstrated that amphetamine inhibits eating while leading to hyperactivity and stereotypy. Amphetamine's anorectic effect appears to be mediated predominantly in the area of the lateral hypothalamus [6]. At present the general consensus is that amphetamine produces its effect by releasing catecholamines in the perifornical area resulting in stimulation of the ß-adrenergic satiety system [6].

Peripheral administration of high doses of phenylethylamine inhibits feeding, but the specificity of this effect is unclear [22]. Interest in the possibility of a phenylethylamine satiety system was recently stimulated by the study of Paul et al [23] at the National Institute of Mental Health. They demonstrated that there are highly specific amphetamine receptors in the central nervous system. The endogenous ligand for the "amphetamine receptor" appears to be phenylethylamine. In their studies, they found that the anorexic potency of a variety of phenylethylamine derivatives are related to their ability to bind to the phenylethylamine receptor.

Gamma-amino Butyric Acid (GABA), the Benzodiazepine Receptor and Purines

GABA has a dual action on food intake [24,25]. When administered centrally, the GABA analog, muscimol, stimulates food intake. This effect is present after local minor injections of GABA or its analog into the cell bodies of the nucleus dorsalis raphe, the paraventricular nucleus, and the ventromedical nucleus. Norepinephrine-induced feeding is inhibited by GABA antagonists, suggesting that the alpha-adrenergic feeding system may operate through stimulation of GABA releases, which inturn inhibits the release of a major satiety factor. On the other hand, GABA injected into the nigrostriatal tracts inhibits feeding possibly by reducing dopaminergic transmission from the substantia nigra. Thus, it appears that the universal inhibitory neurotransmitter GABA elevates appetite by inhibiting the satiety center and its connections and decreases food intake by inhibiting the lateral hypothalamic dopaminergic system.

A number of studies have shown that benzodiazepines enhance feeding in rats [26]. Benzodiazepine-induced feeding has been shown to involve interactions with serotonergic, opioid, and GABAergic mechanisms.

Levine and Morley [27] have shown that the purine, inosine, suppresses diazepam-induced feeding. 7-methylinosine, which *in vitro* fails to bind to the benzodiazepine-binding site, had no effect on starvation-induced eating, whereas other purines that bind to the diazepam receptor decreased feeding in this paradigm. This led to the suggestion that purines may represent endogenous substances that regulate food intake through interactions with the benzodiazepine receptor. However, the finding that centrally administered adenosine (which doesn't interact with benzodiazepine receptor) is a more potent inhibitor of feeding than inosine suggests that the central purinergic regulation of feeding may be independent of an interaction with the diazepam receptor. Recently, Agren et al [28] found elevated xanthine levels in the CSF are associated with poor appetite in depressed patients, suggesting a link between purines and appetite in humans.

Opioid Feeding Systems

Opioid antagonists have been shown to decrease feeding under a variety of conditions in a large number of species, including humans [29]. There is some evidence to suggest that opioid antagonists preferentially decrease fat intake [30]. A variety of studies have shown that exogenous opiates are capable of increasing food intake in rats and mice, and recently we have found that butorphanol tartrate increases feeding in humans [29 and unpublished observation].

Evidence exists that a variety of endogenous opioids including ß-endorphin, D-ala-leu-enkephalin and dynorphin increase feeding in rats after central administration [31,32,33]. Studies in our laboratory with the endogenous kappa opioid receptor ligand, dynorphin-(1-17) and a variety of exogenous kappa opiates has suggested that the dynorphin-kappa opioid receptor plays a major role in modulation of feeding [33]. In addition, measurements of ir-dynorphin levels in the central nervous system have demonstrated that they are altered in

a variety of situations in which feeding is initiated.

Other studies have, however, suggested a role for other opioid receptors in appetite regulation. Thus, analogous to the findings for the role of opioid receptors in analgesia, it appears that multiple opioid receptors may be involved in appetite regulation, each producing an effect on different aspects of feeding and acting at different anatomical sites. Finally, it should be pointed out that the effect of opioids on feeding appears to be modulated by the prevailing glucose levels, adrenal secretions, the time of the day, and whether the animal is tested in a home or in a foreign cage.

Neuropeptide Y

Neuropeptide Y (NPY) is the most potent orexigenic agent yet identified [52]. It produces a highly specific increase in carbohydrate ingestion. Chronic administration leads to weight gain. It has been suggested that it may play a roll in the pathogenesis of bulimia.

Other Neuropeptides

In contrast to the opioid peptides and NPY, 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 nonspecific disruption of behavior is a subject of intense debate at the present time (*vide infra*).

Calcitonin is a potent inhibitor of feeding after central administration [34]. It appears to produce its satiating effects by inhibiting calcium uptake at the hypothalamic level [35]. Recently, Rosenfeld et al [36] showed that the calcitonin gene is processed differently in the central nervous sytem, giving rise to calcitonin gene-related peptide (CGRP). Studies in our laboratory have shown that CGRP suppresses feeding after central administation in rats; that this effect is less potent than CGRP on a molar basis, and that CGRP produces a conditioned taste aversion.

Besides inhibiting feeding after peripheral administration, bombesin, a tetradecapeptide originally isolated from the skin of frogs, also decreases feeding when centrally administered [37,38]. It also induces marked grooming, slows gastric emptying, and decreases gastric acid secretion. The site of action of bombesin on feeding appears to be in the lateral hypothalamus.

The role of cholecystokinin (CCK) in feeding after central administration in the rat is somewhat unclear, but the effect appears to be minor. However, infusion of CCK into the ventricles of sheep decreases feeding, and infusion of antisera to CCK-8 into the left ventricle of sheep resulted in a significant increase in feeding [39]. These data suggest that there may be marked species differences in the site of action of CCK on feeding.

Porte and Woods [40] have found that centrally infused insulin decreases feeding in baboons in contrast to its peripheral effect of increasing feeding, probably secondary to the hypoglycemia that insulin produces peripherally. They have suggested that insulin serves as the key body adiposity signal to the central nervous system. Their feeling is based, in part, on the impressive correlation between the degree of adiposity and plasma insulin levels and the presence of immunoreactive insulin in the CSF. Recently, an insulin-like peptide, Insulin Growth Factor, has also been shown to decrease food intake after central administration [41].

Among the other peptides postulated to decrease feeding by a central mechanism are thyrotropin-releasing hormone and its metabolite, cyclohistidyl proline diketropiperazine; corticotropin-releasing factor and its homologue, sauvagine; and neurotensin.

CONTROVERSIES AND FUTURE DIRECTIONS

Two major controversies in the role of central neurotransmitters in feeding have already been alluded to, namely, the specificity of the effect and the problem of species diversity.

Specificity of Effect

It has been suggested that almost anything found in the vicinity of the kitchen sink will decrease feeding in the rat, presumably by inducing sickness rather than physiological satiety. Most of the studies conducted on the effects of neurotransmitters on feeding have been pharmacological in nature, and there is little data concerning the specificity of these effects. Thus, at present, the conclusion that these agents represent physiological satiety substances is tenuous. However, their distribution in sites within the central nervous system known to be involved in feeding regulation and the obvious requirements for multiple neurotransmitters to regulate the complexities of feeding suggests that some of these agents will eventually turn out to be satiety coordinators.

Because much controversy revolves around whether or not these agents cause "sickness," it needs to be pointed out that, unlike the human, the rat cannot be asked whether or not it is sick. Also, the rat does not display emesis. The available paradigms for discerning "sickness" in the rat all have many problems [42]. Further, any of us who have gorged ourselves, as was the custom of the ancient Romans, clearly realize that there is a continuum between the sensations of satiety, abdominal discomfort, nausea, and eventually vomiting. Thus, although we need to avoid exaggerating the role of the neurotransmitters in feeding regulation until it is better defined, we need to realize that many of these will turn out to be involved in feeding regulation and that

the present neuropharmacological studies represent important first steps in the ultimate teasing out of the complexities of feeding regulation within the central nervous system.

We would like to suggest that the following criteria represent the ultimate proof of the role for a neurotransmitter in feeding: (1) The neurotransmitter produces its effect in one or more localized sites, and the concentration required to produce the effect at that site is less than that necessary to produce the effect after intraventricular administration. (2) Discrete lesions of the same site result in the obliteration of the feeding effect. (3) There is some degree of behavioral specificity after injection into a localized site of action. (4) Concentrations or turnover of the neurotransmitter or its receptors alter in the specific site of action during states of altered satiety. At present, only norepinephrine (alpha-agonist properties) and possibly serotonin come close to meeting these criteria.

Species Diversity

It is becoming abundantly clear that the rat is not necessarily a universal model for the understanding of feeding behavior. Thus, although the opiate antagonist, naloxone, deceases feeding in many species from wolves and humans to mice, it is ineffective at doing so in the racoon and the Chinese hamster. To further illustrate the complexities of the situation, naloxone's effects are severely attenuated in neonatal and very old rats. Similarly, the opiate agonist, butorphanol tartrate, while increasing feeding in the rat, decreases feeding in the guinea pig. We have already alluded to similar species diversity of responsiveness to CCK. Further, the effects of opiate agonists on feeding display a marked circadian rhythm, producing an increase in feeding during the daytime but often decreasing feeding at night. Thus, for full understanding of the effects of a neurotransmitter, the test conditions and the species used in testing a neurotransmitter are of paramount importance.

CURRENT HYPOTHESES AND POSSIBLE CLINICAL APPLICATIONS

The Central Satiety Cascade

Bearing in mind the caveats presented in the previous section, we have found it useful to develop a malleable matchstick diagram of neurotransmitter interactions in feeding as an aid to remembering the putative interactions occuring in the hypothalamus and to help in the design of future pharmacological experiments [4]. Neurotransmitter interactions can somewhat artificially be divided into those that occur in the paraventricular nucleus (and/or VMH) and those that occur in the region

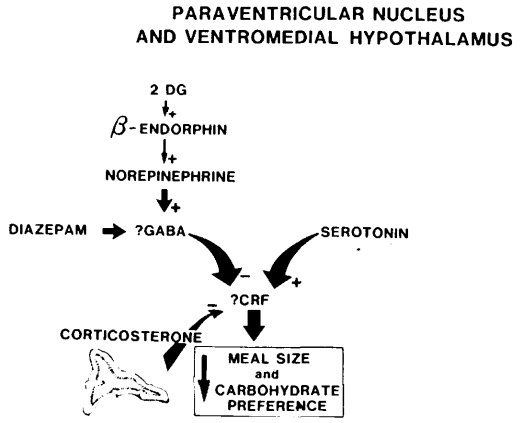

Figure 2.1 Interactions of neurotransmitters modulating feeding in the paraventricular and ventromedial hypothalamus. 2-DG = 2-deoxyglucose; GABA = gamma-amino butyric acid; CRF = corticotropin releasing factor.

of the lateral hypothalamus.

The major defined system in the paraventricular nucleus is that involved with the norepinephrine (alpha-agonist) increase in meal size (figure 1). Norepinephrine release is stimulated by ß-endorphin from the arcuate nucleus [31], which in turn may be released by 2-deoxyglucose [43]. Vagal inputs (not shown) from the periphery would modulate norepinephrine release to integrate central and peripheral mechanisms. Norepinephrine itself stimulates GABA release, which in turn inhibits the release of a satiety factor responsible for the inhibitory effect of the PVN-VMH. Release of this satiety factor would be stimulated by serotonin. One possible candidate for this satiety factor is corticotropin-releasing factor (CRF), which besides inhibiting feeding, is inhibited by norepinephrine and stimulated by serotonin [44].

In the lateral hypothalamus the major interaction appears to be the close relationship between dynorphin

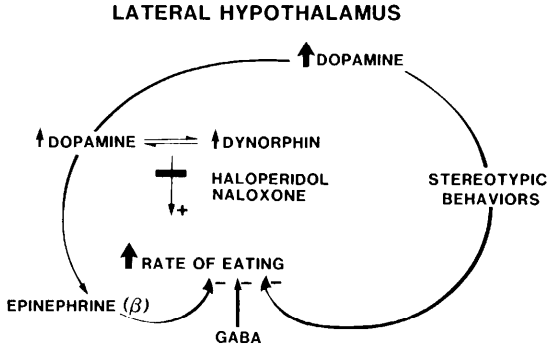

Figure 2.2 Interactions of nurotransmitters modulating feeding in the lateral hypothalamus.

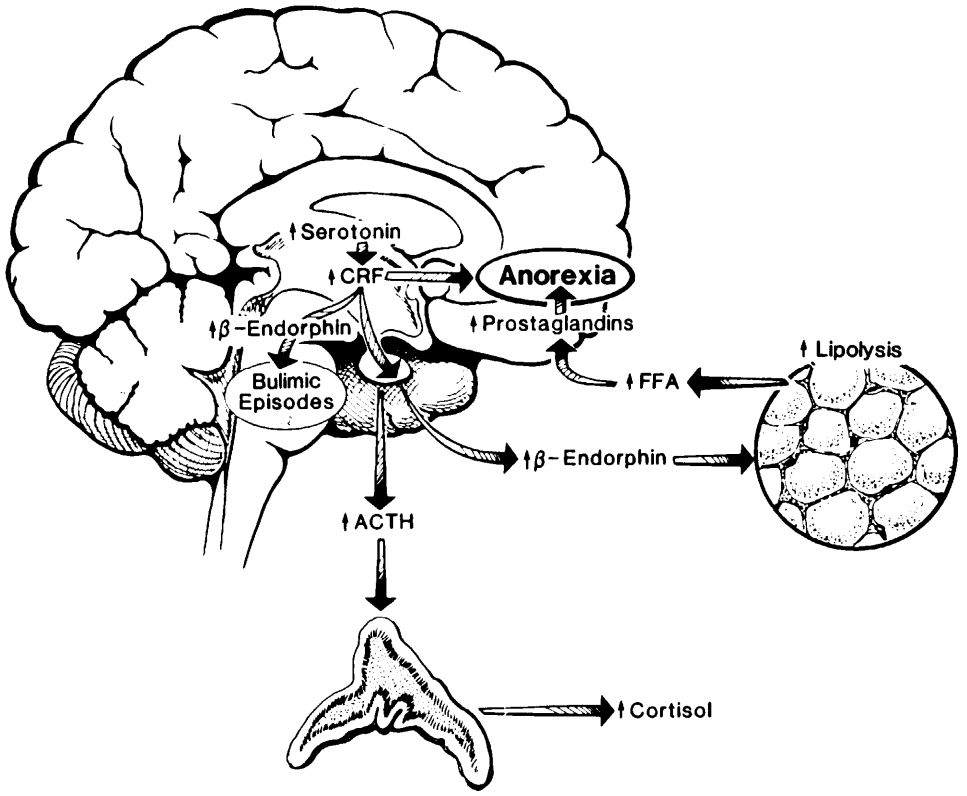

Figure 2.3 Hypothesized model for neurotransmitter abnormalities in anorexia nervosa. FFA = free fatty acids.

and dopamine, which is responsible for stimulating feeding (figure 2). This system is held in check by satiety inputs from the PVN/VMH. These may include CRF, ß-agonist, CGRP, and bombesin. The understanding and localization of this system is far less well established than the PVN/VMH interrelationships.

Stress and Feeding

Numerous studies in the wild have shown that when animals are under stress (eg, birds during boundary disputes), they indulge in displacement eating. Using the mild tail pinch model of stress-inducing eating in the rat, a number of groups have provided evidence that this behavior is dependent on the activation of endogenous opioids and the dopaminergic system [45]. Overall the primary behavior appears to be stereotypic chewing with eating being an epiphenomenon. Recently it has been shown that when a small mouse is defeated by a larger mouse, the smaller mouse displays stress-induced eating which is naloxone reversible [46].

CRF is a 41 amino acide peptide, which appears to fulfill Hans Selye's criteria for the central mediator of the "general adaptation to stress" syndrome. Centrally administered CRF causes decreased feeding and increased grooming activity [47]. Because patients with anorexia nervosa have an overactive hypothalamic-pituitary adrenal axis, the possibility that CRF represents a biological substrate for some of the manifestations of anorexia nervosa needs to be considered (figure 3). If CRF levels are elevated in patients with anorexia nervosa, then the bouts of binge eating in some of these patients could be explained by excessive CRF production releasing ß-endorphin from the arcuate nucleus. Further, it has been reported that administration of naloxone to patients with anorexia nervosa results in a paradoxical weight gain without increase in appetite [48]. This could be secondary to inhibition of the effects of circumlating ß-endorphin producing lipolysis.

Development of New Pharmacological Agents

As we obtain more exciting information concerning the neurotransmitters involved in appetite regulation, this should lead to an increasingly sophisticated ability to create agonists and antagonists that will turn out to be useful in the treatment of obesity or anorectic states. Preliminary observations showing this have been re-

ported in the studies of Atkinson [49] who has shown that a long-acting opioid antagonist, naltrexone, produces a mild decrease in weight in obese females. However, subsequent studies have produced disappointing results as far as the use of opiate antagonists in obesity are concerned [53]. In view of the potent nature of kappa agonists in increasing feeding it is possible that the development of a selective kappa opioid antagonist may lead to an even more potent anorectic agent. In addition, these basic studies have clearly shown that appetite regulation is multifactorial, and therefore, multiple clinical approaches need to be developed rather than expecting one agent to turn out to be the universal panacea. Finally, with our increasingly sophisticated knowledge of neurotransmitters, we will begin to recognize specific syndromes of obesity and anorexia for which we can tailor specific treatments. An early example of this was the young boy reported by Dunger et al [50] who had a syndrome characterized by increased endogenous opioid activity and was obese.

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