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THE BEHAVIORAL NEUROSCIENCE OF EATING

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Clinical syndromes stimulate basic science by providing unexpected combinations or dissociations of phenomena that basic science did not predict or cannot explain. That clinical eating disorders in which abnormally large meals can occur in patients with low, normal, or high body weight contradicts the assumption that the only function of eating is to provide energy intake for nutritional homeostasis. In the past decade the basic science of eating has responded to this problem in such a fundamental way that it has undergone a paradigm shift. Instead of seeking the neurobiological mechanisms of eating solely in the molecular transformations of energy homeostasis, eating is now seen as a problem in behavioral neuroscience. This shift promises for the first time an adequate basic science of eating because the new view includes genetic and sexual vulnerabilities, learning, and a coherent neural system composed of peripheral feedbacks and central integrations that use amines, peptides, and steroids. The shift has been driven by the recent progress in a "top-down" analysis of meals, the functional unit of eating (1). This analysis has included the application of molecular genetics that revealed a central cascade of neuropeptides, the recognition that the neurology of eating was a system that integrated peripheral feedback and central information to turn a central pattern generator for oromotor movements on and off, the realization that learned controls of eating developed rapidly and acted frequently, and a renewed attack on the mechanisms by which estrogen inhibits eating. We review these areas in this chapter.

MOLECULAR GENETICS AND CENTRAL NEUROPEPTIDE CASCADE

Although peptides have been implicated in the control of eating since 1957 (2) and more than 20 peptides had been

shown to have effects before 1990, the use of molecular genetic techniques to discover agouti protein in 1993 and leptin in 1994 galvanized an intensive search for new brain peptides relevant to the control of food intake and metabolism. The search succeeded (Table 115.1).

Of the new peptides, leptin was the most intensively investigated because it was hoped that it was the long sought negative-feedback signal synthesized from and released by adipose tissue that was hypothesized by Kennedy in 1953 to be the crucial link between food intake and energy storage (3). The hyperphagia and obesity that occurred in mice that had a genetic deficit in leptin production (*ob/ob*) or in leptin receptors (*db/db*) apparently substantiated the importance of leptin as a negative-feedback signal. However, the euphoria evaporated when it was discovered that circulating leptin was abnormally high, rather than low, in almost all obese humans as well as in mice and rats that became obese on a high-fat diet.

The nature of this leptin "resistance" is under intensive investigation. It appears to involve decreased transport into the brain and decreased intracellular signal transduction after leptin binds to its receptor (4). Its common occurrence shows that the negative-feedback effect of leptin is easily overcome by diets that increase eating. This is a compelling demonstration of a central theme in behavioral neuroscience: Reinforcement frequently overcomes regulation.

Although leptin was not a "magic bullet" for the treatment of obesity, a crude idea driven by commercial hopes rather than scientific knowledge, the analysis of its inhibition of food intake and increased metabolism has stimulated an enormous amount of work that can be summarized briefly. (See refs. 4 and 5 for extensive reviews.) The arcuate nucleus in the ventromedial hypothalamus is a nodal point for leptin's action. Leptin stimulates a lateral population of proopiomelanocortin (POMC) neurons and inhibits a medial population of neurons that express neuropeptide Y (NPY), a potent stimulant of eating, and agouti-related peptide (AGRP), an antagonist of melacortin (MC) receptors, especially MC₄, that also stimulates eating. The MC₄ recep-

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TABLE 115.1. CHRONOLOGY OF PEPTIDE EFFECTS ON FOOD INTAKE AFTER CENTRAL OR PERIPHERAL ADMINSTRATION

Peripheral	Central
1957 Glucagon	1974 Opioids
1973 Cholecystokinin	1977 Thyrotropin-releasing hormone
1979 Bombesin	1979 Cholecystokinin, insulin
1980 Insulin	1981 Bombesin
1981 Somatostatin	1982 Neurotensin
1983 Neurotensin	1983 Corticotropin-releasing factor
1984 Calcitonin	1984 Calcitonin gene-related
gene-related	peptide, somatostatin
peptide	1985 Neuropeptide Y
1987 Tumor necrosis	1986 Galanin, alpha melanocyte-
factor	stimulating hormone
1988 Enterostatin	1988 Interleukin-1 beta, tumor
1989 Interleukin 1-beta	necrosis factor alpha
1991 Amylin	1991 Amylin, enterostatin
1992 Apolipoprotein AlV	1992 Tumor necrosis factor beta
1998 Glucagon-like	1993 Apolipoprotein AIV
peptide -1	1994 Agouti protein
	1995 Leptin
	1996 Urocortin, Glucagon-like
	peptide 1, melanin
	concentrating hormone
	1997 Agouti related protein
	1998 Orexins, cocaine and
	amphetamine regulated
	transcript

The year listed is the first report of the effect according to a search of the literature using Pub Med in 1999 and references in the reviews that accompanied this article. Smith GP. Introduction to the reviews on peptides and the control of food intake and body weight. *Neuropeptides* 1999;33:323–328.

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tor is necessary for leptin's inhibition of food intake because the effect of leptin is abolished when an antagonist blocks MC_4 . Furthermore, MC_4 knockout mice are hyperphagic and obese despite high circulating leptin. The endogenous agonist for the MC_4 receptor is α -melanocyte-stimulating hormone (MSH), a translational product of the POMC neurons. The roles of other peptides, such as orexin A, cocaine and amphetamine-regulated transcript (CART), glucagon-like peptide-1 (GLP-1), apolipoprotein-IV, melanin concentrating hormone (MCH), and mahogany protein in the physiologic control of eating, and their relationship (if any) to leptin's action remain to be determined.

Identification of these peptides sparked anatomic investigations that used immunocytochemical techniques to trace connections from NPY-AGRP neurons to orexin neurons in the lateral hypothalamus, and projections of NYP-AGRP neurons and POMC neurons to the paraventricular nucleus in the anteromedial hypothalamus and to the hindbrain, especially to the region of the nucleus tractus solitarius (NTS). Discussion of these results has attempted to extract their meaning from the medial and lateral hypothalamic syndromes. This is not illuminating because those syndromes never clarified the normal control of eating and the extent of the anatomic damage was not determined; they were problems, not explanations.

The current status of this work on central neuropeptides can be described as "a few small islands of scientific understanding surrounded by a vast area of uncertain phenomena" (2). The progress represented by the work with these peptides has been real and has been trumpeted loudly in the scientific literature and lay press. Its limitations have been less emphasized. They include the facts that leptin resistance is a significant problem in dietary-induced obesity and that high-fat diets decrease the potency of a variety of peptides. Furthermore, the central neuropeptide cascade defined by leptin action has been described in the unusual situation of 24 or 48 hours of food deprivation. This makes the relevance of this cascade to the controls of food intake and body weight under more normal conditions problematic. It is particularly important to understand that most of the progress in the field has been horizontal, that is, it has added new peptides to the list that affect energy intake, storage, and expenditure. Relatively little progress has been made in the vertical problems of physiologic function, interactions, and generalizations. Despite their difficulty, the vertical problems must be pursued in order to decipher the meaning of these molecules. To say that a peptide increases or decreases food intake is to pose a problem for scientific investigation rather than to state a conclusion about physiologic function. The physiologic function of a peptide is learned only when we can specify the function of that peptide in the central neural networks that control food intake and body weight.

The example of cholecystokinin makes this point. Cholecystokinin (CCK) released from the small intestine during a meal provides a negative-feedback signal for the control of the size of that meal in animals (6) and humans (7). An important part of the evidence for this was that administration of a specific antagonist of CCK_A receptors produced a significant increase in meal size in rodents, pigs, monkeys, and humans under a variety of conditions. This satiating action of CCK is mediated by CCK_A receptors on vagal afferent fibers that project to the medial and caudal NTS. The disconnected caudal brainstem of the chronic decerebrate rat has sufficient neural complexity to process this visceral information into a stop signal to the central pattern generator (cpg) that controls oromotor movements (8), but in the intact brain, forebrain structures, such as the paraventricular nucleus, are also involved (6). Thus in this case, we know the biological meaning of CCK in the control of food intake because we can define it as one of the stimuli of the peripheral negative feedbacks that control meal size.

The experimental history of the extensive and convergent results required to prove that the satiating effect of CCK was a physiologic function of the peptide is a case study for those pursuing the meaning of other peptides (9). Behavioral specificity, receptor mechanism, predictable results with reversible antagonists, afferent neural mediation, and the effect of experimental context (genetic, dietary, metabolic, and prior experience) had to be assessed and interpreted. The experience teaches that physiologic meaning is not read out directly from molecular structure or from an increase or decrease of food intake.

NEURAL CONTROL OF EATING

Because the biological meaning of a peptide for the control of eating is defined by its role in the neural network that integrates peripheral and central stimuli into oromotor output, we now review the important progress that has been made in that area in the past decade.

Although it is common to refer to this area of research as the Neural Control of Food Intake, this is imprecise and misleading because food intake denotes a measurement made by investigators, not a movement made by animals or people. The somatic nervous system controls the oromotor movements of eating; the autonomic nervous system controls movements of the digestive tract through its effects on the enteric nervous system, intraluminal digestion, neuroendocrine release, and metabolic transformations. The sensory stimuli from these efferent effects are integrated in the central nervous system to affect somatic and visceral efferent output. The major advance in the understanding of this vast, complicated neural system has been in the somatic nervous system's control of eating.

Eating consists of rhythmic oromotor movements, such as licking, lapping, and mastication. These movements have a relatively fixed rate. For example, rats make five to eight licks per second (the range in individual rats is less). This is the motor signature of a group of neurons acting as a cpg. The cpg for licking in the rat is in the medial, intermediate, and lateral reticular formation of the medulla (10). A network of premotor neurons extends forward from the caudal brainstem to the region of the substantia nigra (11). Thus, the neural control of eating can be reduced to what turns the cpg on and off (12).

Eating can be initiated by a variety of external stimuli, such as visual, social, olfactory, and auditory. Internal stimuli, such as a slight decrease in plasma glucose (13), a rise in liver temperature (14), and a decrease in basal metabolism (15) are also effective. The efficacy of most, if not all, of these stimuli can be modified by experience. It is important to note that the adequate stimuli for the initiation of eating do not determine the duration or size of the subsequent meal. These aspects of a meal are determined by the mechanisms that maintain eating.

The fact that the initiation of eating does not determine how long eating will continue or how much will be ingested means that eating a meal is not produced by a ballistic control system. Eating, once initiated, is under feedback control. Positive feedback is stimulated by orosensory stimuli and negative feedback is stimulated by gastric and small intestinal stimuli. The positive feedback turns the cpg on and the negative feedback turns it off.

The brain processes these feedbacks within the neural context of other stimuli that are relevant to the control of eating, but are not produced by ingested food stimuli acting on the mucosa of the gastrointestinal tract. A network that compares the relative potency of positive and negative feedbacks analyzes the result of this distributed processing of the peripheral feedback information. Eating is maintained as long as positive feedback exceeds negative feedback; eating stops and the meal ends when negative feedback exceeds positive feedback for a considerable time (Fig. 115.1).

The oromotor output of this continuous integration of positive and negative feedbacks is a sequence of clusters of licks separated by short intervals of nonlicking (16). The number of licks in a cluster is a measure of orosensory positive feedback (palatability). The number of clusters is a measure of the relative potency of the positive and negative feedbacks (1,17). The meal ends when the animal no longer reinitiates licking for a relatively long time (15 to 120 minutes in the rat).

There are two important points about these feedback effects: First, the site of action of the adequate stimuli is preabsorptive. In addition to its classic motor and secretory functions, the gastrointestinal tract is a sensory sheet from the tip of the tongue to the end of small intestine. It is peppered with mechanical and chemical receptors; their dis-



FIGURE 115.1. This depicts the temporal interaction of positive and negative afferent feedbacks produced by ingested carbohydrate solutions during a representative meal. Note that the meal ends when the potencies of the positive and negative feedbacks are judged to be equal by a comparator function(s) of the central networks for the control of ingestion. ●, positive feedback; ○, negative feedback. Reproduced from Smith GP. Feeding: control of eating. In: Adelman G, Smith BH, eds. *Elsevier's encyclopedia of neuroscience*. New York: Elsevier, 1999:711–714, with permission of the publisher.



FIGURE 115.2. Flow diagram of the direct controls of meal size stimulated by ingested food acting on preabsorptive receptors of the gastrointestinal tract. Note that food stimuli activate afferent neurons providing positive and negative feedbacks directly and indirectly through effects on paracrine, endocrine, and metabolic signals. The efferent output of the central networks for the control of eating is carried over somatic efferent fibers. Because some of the direct controls of meal size exert their effects by modulating direct controls. (See the unidirectional arrow between indirect and direct controls.) Reproduced from Smith GP. Feeding: control of eating. In: Adelman G, Smith BH, eds. *Elsevier's encyclopedia of neuroscience*. New York: Elsevier, 1999:711–714, with permission of the publisher.

persion over large areas provides for the effect of stimulus load (i.e., concentration and volume of stimuli).

The second point is that all of the afferent fibers from the mouth, stomach, and small intestine project to the caudal brainstem.

The direct preabsorptive stimulation by the stimuli of ingested food and its digestive products that provide feedback control during a meal is a criterion for distinguishing these feedback controls from all other controls. These feedback controls are direct controls of meal size (Fig. 115.2) and all other controls are indirect controls (Table 115.2).

This is not an arbitrary classification because it is based on a biological criterion of site of action. The classification

TABLE 115.2. INDIRECT CONTRO	LS U	F MEAL	SIZE
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Categories	Examples
Rhythmic	Diurnal, estrogen
Metabolic	Changes in leptin, insulin, and fatty acids
Thermal	Environmental and fever
Conditioned	Preferences, aversions, and satiations
Cognitive	Social and, in humans, cultural and esthetic
Ecological	Relative densities of predators and foods

^aThe list of categories is neither mutually exclusive nor exhaustive; this is particularly true for conditioned, cognitive, and ecological.

also carries neurologic meaning. That meaning comes from experiments in the chronic decerebrate rat. Because the caudal brainstem contains the cpg and all of the projections of the afferent nerves mediating peripheral feedback effects, the decerebrate rat responds to direct controls (18,19). In contrast, none of the indirect controls that have been tested affect eating in the chronic decerebrate rat. Because indirect controls require the forebrain to be connected to the caudal brainstem in order to control eating, the reciprocal connections between forebrain and hindbrain are necessary for the modulation of the direct controls by the indirect controls. This theory asserts that indirect controls have no direct action on the cpg during a meal in the absence of direct controls activated by ingested food. Specifying the peptidergic and aminergic connections that mediate an indirect control's effect on the direct controls is the next step and it is the place where the recent advances in central peptides and the neural control of eating converge.

The identification of the importance of the positive and negative feedbacks from the periphery in the direct controls of eating that are modulated by the indirect controls facilitates the investigation of human eating disorders in three ways.

- 1. The peripheral, preabsorptive sites of action are accessible to controlled stimulation in the conscious human before, during, and after test meals.
- 2. An increase or a decrease in meal size can be explained by changes in feedback potency (Table 115.3).
- Identifying which combination of changes in feedback underlies the change in meal size focuses the search for neurobiological mechanism because the feedbacks have

TABLE 115.3. CHANGES IN POTENCY OF AFFERENT FEEDBACKS THAT DETERMINE CHANGES IN MEAL SIZE^a

Change of Meal Size	Afferent Feedback		
	Positive	Negative	
Increase	Increase	Decrease	
Increase	Increase	No change	
Increase	Increase	Smaller increase	
Increase	No change	Decrease	
Decrease	Decrease	Increase	
Decrease	Decrease	No change	
Decrease	Decrease	Smaller decrease	
Decrease	No change	Increase	

^aSome changes of afferent feedbacks responsible for increased or decreased meal size. Identification of the mechanisms of a specific change(s) in potency of feedbacks is an experimental problem. (See Table 115.4 for candidates.)

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Direct controls	Peripheral	Central
Orosensory	Gustatory and olfactory transducers	Dopamine ^a Opioids ^a
Gastric	CCK ^a at CCK _A vagal mechanoreceptors, other mechanoreceptors, and bombesin-like peptides	Amino acids from gastric vagal afferent terminals in NTS Serotonin ^a
Small intestinal	CCK ^a at CCK _A receptors on vagal mechanoreceptors and chemoreceptors; glucagon, ^a amylin, enterostatin, apolipoprotein IV, and insulin released by nutrient or digestive stimuli through contact with mucosal receptors or by the release of incretins	Amino acids from duodenal and hepatic vagal afferent terminals in NTS Serotonin ^a

TABLE 115.4. MOLECULAR MECHANISMS OF DIRECT CONTROLS OF MEAL SIZE

NTS, nucleus tractus solitarius.

^aIndicates that a molecule has been demonstrated to be a physiologic mechanism. The physiologic status of the other molecules is uncertain.

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different mechanisms in the rat and are likely to be similarly differentiated in the human (Table 115.4).

An example of the use of this theory of the control of meal size is the recent work concerning the pathophysiology of the abnormally large meals that characterize patients with bulimia nervosa. Since the 1970s there has been evidence that these patients do not feel as full as normal after the same size meal. This has been confirmed more precisely in recent work that showed that bulimics require more food to report equal fullness (20). This suggests a defect in the satiating process (21), specifically a defect in the potency of negative feedback. This hypothesis was strengthened when orosensory positive feedback measured psychophysically did not reveal large increased responses to carbohydrate or fat stimuli (22). Thus, using Table 115.3, the hypothesized combination was decreased negative feedback and no change in positive feedback. The decreased negative feedback could involve peripheral mechanisms or central modulation. Two peripheral abnormalities have been found: an enlarged stomach capacity (23) and a decreased release of CCK (24). The decreased release of CCK was ameliorated when binge eating stopped in one experiment (25), but further experiments are required to evaluate this phenomenon.

There may also be a defect in the central processing of the decreased peripheral negative feedback information owing to abnormal function of the central serotonin system. If central serotonin function is decreased in bulimia patients, they should be more vulnerable than controls to a further decrease in serotonin function produced by serotonin depletion. This prediction has been confirmed: Acute tryptophan depletion that probably decreased central serotonin activity increased meal size in patients with bulimia (26).

The combination of decreased central serotonergic processing with decreased peripheral negative feedback could be particularly disruptive of satiation because the satiating potency of CCK in rats is synergistic with gastric distension and is reduced by decreased central serotonergic function, particularly at 5-HT_{2C} receptors (6).

In addition to decreased negative feedback, bulimia patients also have an abnormal cognitive indirect control. They eat much larger meals when they are instructed to binge compared to when they are instructed not to binge (27).

LEARNING AND EATING

Numerous regions of the brain can be implicated in eating by a variety of techniques in animals and humans. This reflects the fundamental biological importance of eating to individual life and reproduction, and the functional requirements of a foraging omnivore. From this viewpoint, it is not surprising that learning and memory are important processes in the control of eating. Three important types of learning have been identified using Pavlovian procedures and theory: conditioned preference, conditioned aversion and avoidance, and conditioned satiation.

Conditioned preferences are formed by flavor-flavor associations or flavor-postingestive associations (28). Once formed, the preferences increase the size of meals. When the postingestive unconditioned stimulus is omitted, the conditioned preference persists for months, but its effect on intake extinguishes rapidly. The acquisition of a conditioned flavor-postingestive preference requires dopamine acting at D_1 receptors, perhaps in the nucleus accumbens (29). Opioid mechanisms are apparently not necessary.

Conditioned aversions and avoidance are formed by associations between orosensory stimuli (especially gustatory) and aversive postingestive stimuli. Nausea is commonly reported in humans who have conditioned aversions.

The anorexia that accompanies amino acid imbalance may be an example of a conditioned avoidance. It involves a serotonergic mechanism because a 5-HT₃ antagonist abolishes it (30). The same 5-HT₃ mechanism is observed in the conditioned aversions and avoidances observed in cancer patients undergoing chemotherapy (31). The recent report of successful treatment of binge eating with a 5-HT₃ antagonist suggests that conditioned avoidance may also be involved in that eating disorder (32).

Certainly, conditioned avoidance of food characterizes patients with anorexia nervosa. This aversive stimulus appears to be cognitive and part of the morbid fear of fatness. The strong potency of this psychopathological inhibitory control of eating can be appreciated when it is remembered that the low circulating leptin of the emaciated patient (4) disinhibits the central cascade of peptides so that the neurological drive to eat is intense (see section on molecular genetics and central neuropeptide cascade).

The *c-fos* technique has been used to detect changes in the neural network that underlies the acquisition and expression of a conditioned taste aversion (CTA) (33,34). The most significant changes occur in the NTS in the hindbrain and central nucleus of the amygdala in the forebrain. The increased C-Fos in the NTS correlates with the acquisition, extinction, and forgetting of the CTA (35). The meaning of this correlation is under active investigation.

The changes in the NTS depend on connections with the forebrain because they are abolished ipsilateral to surgical hemidecerebration at the level of the superior colliculus (36). This is a nice example of how an indirect control, learning, requires connections between the forebrain and hindbrain in order to affect eating. (See ref. 37 for other examples.)

There is evidence that D_1 receptor mechanisms are necessary for the acquisition of a CTA as well as a conditioned preference. Injection of a D_1 antagonist into the lateral hypothalamus blocked the acquisition of a CTA (38).

The third type of learning is conditioned satiation. Like conditioned preference of the flavor-postingestive type, it depends on the association between orosensory stimuli and a postingestive stimulus. Unlike conditioned preferences and aversions, conditioned satiation is hedonically neutral. Its function is to decrease the rate of eating concentrated liquids during the early part of a meal (39). It can be acquired or extinguished within one or two meals. The postingestive stimulus acts in the stomach and beyond the pylorus (40). Increases of plasma glucose are not a sufficient UCS to form a conditioned satiation (41). Nothing is known about the mechanisms that mediate this type of learning.

It is interesting that the way to extinguish conditioned satiation in the rat is to prevent the accumulation of ingested food in the stomach and small intestine by draining the gastric contents out through a chronic gastric fistula. This form of sham feeding leads to a significant increase in meal size owing to the removal of unconditioned negative feedback from the stomach and small intestine. After three to five consecutive sham-meals, conditioned satiation is extinguished and meal size is maximal. If real-feeding meals are given between sham-feeding meals, however, the size of a sham-fed meal is larger than normal, but not maximal, because some conditioned satiation is present (42). These phenomena in the sham-feeding rat (Fig. 115.3) may be rele-



FIGURE 115.3. The potency of learned controls of meal size based on postingestive food stimuli is revealed by the progressive increase in test meal size during repeated sham-feeding trials. During sham feeding, liquid food drains from open gastric cannulas without significant accumulation in the stomach or small intestine, so that learned controls based on gastrointestinal food stimuli extinguish. In this experiment 13 rats were offered a sweet liquid diet once daily, after 3 hours of deprivation of their maintenance diet. During week 1, rats fed normally (real feeding, RF); during weeks 2 to 7, sham-feeding (SF) tests alternated with realfeeding tests, and during weeks 8 to 11, rats were only sham fed. The figure shows the average real and sham meal sizes in each week. During the first sham-feeding test, rats still ate well-defined meals terminated by behavioral signs of normal satiety, indicating that after this short period of food deprivation, pregastric food stimuli can elicit satiety. However, meal size nearly doubled during this test, because of the absence of direct, unconditioned gastric and postgastric controls of eating. Sham meal size doubled during weeks 3 to 7, when sham- and real-feeding tests were alternated, whereas real meal size increased only a small amount, and sham meal size almost doubled a third time during weeks 8 to 11, when there were no real feeding tests. These further increases during the last 4 weeks reflect the extinction of conditioned satiety. Reproduced from Geary N, Smith GP. Appetite. In: Sadock BJ, Sadock VA, eds. Kaplan & Sadock's comprehensive textbook of psychiatry. Philadelphia: Lippincott Williams & Wilkins, 2000:209-218, with permission of the publisher.

vant to the abnormally large meals that occur with repetitive bingeing followed by vomiting or purging.

ESTROGEN AND EATING

Given the high incidence of eating disorders in women and the frequent onset of them when the ovarian rhythm begins, the recent renewed interest in the control of eating by estrogen in rats is most welcome.

Estrogen has two inhibitory effects on eating. The first occurs during the periovulatory phase of the estrus cycle in rats. The decrease in food intake is owing to a decrease in meal size (43). The combination of feedback potencies (Table 115.3) that accounts for the decrease in meal size is no change in positive feedback and increased negative feedback (44). The increased negative feedback is the result of estrogen increasing the potency of endogenous CCK released from the small intestine (Fig. 115.4) (45,46). Pre-



FIGURE 115.4. Antagonism of CCK_A receptors with devazepide (Dev) increased rats' spontaneous meal size throughout the nocturnal period of estrus, but not during diestrus. Thus, an increase of endogenous CCK's satiating potency contributes to the cyclic decrease in meal size during estrus that is mediated by estradiol. Furthermore, endogenous CCK does not appear to contribute to the tonic inhibitory effect of estradiol on meal size because devazepide did not increase meal size during diestrus. Data are mean meal sizes per 3-hour quartile of the nocturnal phase. Note that meal size increased across the dark phase in both estrus and diestrus and that meal size after vehicle (Veh) treatment during the fourth quartile of estrus, when devazepide increased meal size, was as large as control meal size during the first two quartiles of diestrus, so that devazepide's selective effect during estrus was not an artifact of the cyclic differences in meal size. *Nocturnal meal size after devazepide larger than after vehicle, P < .05. Reproduced from Eckel LA, Geary N. Endogenous cholecystokinin's satiating action increases during estrus in female Long-Evans rats. Peptides 1999;20(4):451-456, with permission of the publisher.

sumably this synergism is a central action of estrogen changing the processing of the vagal afferent stimulation of the NTS in response to CCK acting on CCK_A receptors of vagal afferent terminals in the upper small intestine, but it is not known where this synergism occurs or where the receptors are that mediate it (47-49).

The inhibitory effect of estrogen on food intake during the periovulatory phase has been reported in women (50, 51). The role of CCK in this effect has not been investigated.

The facts that the ovarian rhythm is disrupted in anorexia nervosa and circulating estrogen is low adds a further disinhibition to the central network that controls eating in these patients.

The second inhibitory effect of estradiol on eating is a tonic inhibition of meal size that acts throughout the ovarian cycle in rats. Release from this inhibition by ovariectomy causes a sustained increase in meal size and obesity. This effect of estrogen, however, does not appear to be mediated by a change in the satiating potency of CCK.

Both effects of estrogen depend on binding to the estrogen receptor α because mice with this receptor knocked out do not show either effect (52).

There are sex differences in the incidence or clinical course of many diseases associated with anorexia as well as in the anorectic response to many immune-system mediators, such as IL-1 and α -TNF. Some of these sex differences appear to be related to estrogenic function. Crohn disease, an inflammatory bowel disease in which anorexia is an early sign (53), is one such. The incidence of Crohn disease is higher in women than men (54) and use of estrogen-containing contraceptives increases women's risk further (55).

Anorexia caused by Gram-negative bacterial infection is also estradiol-sensitive. The effect of estradiol to increase the anorexia produced in rats by intraperitoneal administration of bacterial lipopolysaccharide is expressed by a decrease in meal frequency without a change in meal size (56), indicating that this effect of estrogen is separate from the effects on meal size.

CONCLUSION

Our understanding of the controls of eating in rodents has been transformed in the past 5 years. Although the relationship of eating to nutritional and energetic homeostasis continues to be investigated, particularly in relationship to the new peptides that have been discovered with molecular genetic techniques, the investigation of eating has been broadened in several ways. More attention to behavioral analysis has paid off, especially the microstructure of eating. It has revealed the operation of a cpg as the final common path for the neural control of oromotor movements and provided a continuous measure of the integrated output of the central neural network controlling the cpg during a meal, the functional unit of eating behavior.

The recognition that the size of a meal is under positive and negative feedback controls has been exploited. Specific aminergic and peptidergic mechanisms have been demonstrated to be involved in these feedbacks. The afferent nerves that carry the peripheral information generated along the preabsorptive surface of the gut from the tip of the tongue to the small intestine have been identified. Because some of these peripheral mechanisms are activated in every meal, all controls of eating not related to the food being ingested during a meal act on eating by modulating the central processing of the peripheral feedback stimuli. This has led to a new theory of the controls of eating that is more biological, comprehensive, quantitative, and testable than previous ones (1).

The widely distributed processing of information relevant to the control of eating in the brain reflects the importance and complexity of eating in omnivores such as rodents and humans.

What to eat? Where? When? With whom? These are pressing questions for rodents as well as humans. The ability to answer them with apparent ease requires learning and memory. Recognition of this fact increasingly affects research on eating.

The paradigm shift that the study of eating has undergone, that is, from viewing eating as serving only nutrient and energetic homeostasis to a recognition that the search for the controls of eating is a fundamental problem in behavioral neuroscience (1), makes the basic science more useful for and more relevant to the investigation of clinical eating disorders. Using the similarity in eating behavior, gastrointestinal function, and peripheral visceral afferent neurons as a bridge, the transfer of new information from the laboratory to the clinic should accelerate markedly in the next 5 years.

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