Nervous Regulation of Food Intake

B. K. ANAND, M.D.*

CALORIC BALANCE depends upon the regulation of biologic energy exchange. Four important variables are concerned in energy balance: (1) food intake, (2) energy storage, (3) energy utilization through activity or work and (4) loss of energy in the production of heat. The caloric balance would thus be regulated by the various mechanisms which regulate the caloric intake in the form of food intake on the one hand and caloric loss on the other. In this communication the nervous mechanisms regulating food intake are discussed.

Cannon[1] in 1915 demonstrated rhythmic contractions of the stomach accompanying feelings of hunger, and on the basis of this, Carlson[2] built an entire theory of the regulation of appetite. Subsequent studies demonstrated, however, that this "peripheral" gastric mechanism was overemphasized as experimental observations showed that elimination of gastric contractions due to hunger or their central projection in a variety of ways did not alter the sensations of hunger.[3,4]

Meanwhile attention was focused on the central nervous system as a regulating mechanism for food intake. Hetherington and Ranson[5] demonstrated that obesity could be produced by lesions confined to medial hypothalamic regions, and Brobeck, Tepperman and Long[6] observed that such obesity was a result of hyperphagia. Hypothalamic hyperphagia was produced in several species of animals such as the rat, cat, dog and monkey.

From the All India Institute of Medical Sciences, New Delhi, India.

* Professor and Head of the Department of Physiology.

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ROLE OF HYPOTHALAMUS

Anand and Brobeck[7] observed that hypothalamic injuries in rats could produce not only hyperphagia but also aphagia. Bilateral lesions in a restricted area of the lateral hypothalamus in the same rostrocaudal plane as the ventromedial nucleus, led to complete aphagia, and to death of the animal from starvation. On the other hand, lesions restricted to the medial hypothalamic regions of the ventromedial nuclei, and the regions in between these and the lateral hypothalamic areas, led to hyperphagia and obesity, provided that lateral hypothalamic centers were undamaged. It was suggested that the lateral hypothalamic area be designated the "feeding center" and the medial one the "satiety center."

Anand and his co-workers[8] extended these studies to include cats and monkeys and confirmed that the dual hypothalamic mechanisms regulated food intake. It was also demonstrated by Delgado and Anand,[9] and by Anand and Dua,[10] that electrical stimulation for one hour of the lateral hypothalamic areas in cats markedly increased their daily food intake on the days of stimulation, while stimulation of the medial hypothalamic areas for one hour produced only a slight decrease in their daily food intake on the days of stimulation. Complete aphagia never occurred. This finding was confirmed by Larsson[11] in goats.

These observations provided an anatomic basis for a possible central mechanism in the hypothalamus regulating food intake. It seemed that the lateral feeding mechanism was the basic urge, while the medial satiety mechanism acted by inhibiting the lateral mechanism for the following reasons: (1) Injury to the lateral regions invariably produces complete aphagia whether or not the medial regions are intact. (2) Injury to the medial regions produces hyperphagia only when the lateral region

is intact. (3) Stimulation of the lateral region markedly increases food intake, while stimulation of the medial region only slightly decreases it.

The nature of the nervous mechanism regulating feeding behavior would be expected to follow the same pattern as those serving other functions of the brain and spinal cord. These functions have been shown to have an important substructure of reflex actions with the brain stem, the diencephalon and the telencephalon leading either to their facilitation or inhibition. It may, therefore, be suggested that the regulation of feeding also is reflex in nature, with superimposed facilitation and inhibition from higher centers including the hypothalamus. It would appear that the lateral hypothalamic mechanism facilitates and the medial one inhibits the feeding reflexes.

The brain stem containing the nuclei of the cranial nerves is probably the level of the neuroaxis most directly concerned with the feeding reflexes, the motor and sensory components of which take part in normal feeding reflexes which aid in chewing, salivating, swallowing and in rejecting unacceptable objects. This was indicated as early as 1916 by Miller and Sherrington.[12]

Brobeck[13] has proposed two different tentative classifications of feeding reflexes. One is based on the nature of the stimulus inducing the reflex which may be tactile, gustatory; auditory, or visual, by making the animal aware of food, or enteroceptive from the gastrointestinal tract. The second is based on the sequence of behavior in normal feeding, including reflexes of attention, approach, examination, incorporation and rejection.

CEREBRAL INFLUENCES

Experimental work has also suggested cerebral influence over normal feeding responses. Pribram and Bagshaw[14] reported increased food intake after surgical lesions involving temporal polar-amygdaloid formations in dogs. Anand et al.[8] had observed that bilateral destruction of hypothalamic feeding centers in some monkeys produced a response somewhat different from that seen in cats and rats with similar lesions. Such monkeys would not eat the food available in the cage although they would swallow it when it was put directly into their mouths. Aphagic cats and rats with similar lesions would always reject the food even when it was put into their mouths. It was presumed that this difference in the monkeys' behavior was due to higher encephalization, suggesting that, at least in primates, control over food intake was also mediated through higher cerebral centers.

Anand, Dua and Chhina[15] further demonstrated that bilateral lesions in certain portions of the cerebral cortex or of the limbic system altered the intake of food in monkeys and cats. For example, lesions of the frontal lobe, including or restricted to the posterior orbital cortex, led to a decrease in food intake, but those involving only the frontal tips and sparing the posterior orbital cortex led to an increase. Extensive lesions of temporal lobe also led to an increase in the intake of food; lesions in the amygdaloid and periamygdaloid regions of the temporal lobe produced temporary aphagia; but lesions restricted to anterior cingulate gyri had no effect. Those changes observed in intake of food were more noticeable in monkeys than in cats, were never so pronounced as those associated with lesions of the hypothalamus, and also tended to disappear after some weeks. Therefore, it was concluded that the limbic structures in the frontal and temporal lobes modified the intake of food through a discriminating mechanism (appetite), while the primitive urge (hunger) originated at the hypothalamic levels. From experiments with rats, Bruce and Kennedy[16] had also postulated a similar hypothesis. The cerebral influences are possibly mediated through the hypothalamus modifying the effects of hypothalamic centers.

Stimulation of the various limbic structures did not produce any change in the daily intake of food. However, such stimulation produced responses of chewing, licking, sniffing, salivation and repetitive opening and closing of the mouth with protrusion of the tongue; these have been grouped under the heading of "eating" automatisms.[17] Eating responses were also produced during stimulation of the lateral hypothalamic feeding centers,[9,10] but these

were accompanied by an increase in the intake of food.

We[18] have also produced bilateral lesions in some neocortical regions. We observed that there was a slight change in food intake for a short time only after lateral frontal lesions had been produced; while lesions in the parietal, occipital and temporal neocortical regions did not produce any change in food intake.

Enough evidence is thus available to classify the central nervous mechanisms regulating food intake in a manner similar to that employed in the classification of regulatory mechanisms for other autonomic and visceral activities, such as the regulation of blood pressure, pulmonary ventilation and body temperature. Feeding behavior is probably regulated by certain reflex mechanisms mediated from the spinal cord and brain stem levels, which are definitely facilitated and inhibited from the hypothalamic regions and further regulated from the higher cerebral limbic and possibly neocortical regions. In common with the other visceral reflexes, the regulation from the limbic levels is more pronounced than from the neocortical levels.

MECHANISM OF NERVOUS REGULATION

Since adult men and animals can maintain their body weights, and since growing organisms continue to grow at well defined rates, food intake must be adapted to caloric needs. Gasnier and André Mayer[19] demonstrated that animals varied their food intake in a way which indicated that two regulations were at work. One, which is more important than the other, adjusts the calories eaten to the calories spent from day to day; and the other, working more slowly, corrects over a period of time whatever error the rapid mechanism could have made.

A simplified explanation for these adjustments would be that when food is eaten by a normal animal, certain changes occur within the body which either directly or indirectly affected the hypothalamic centers and possibly also the higher cerebral centers, thereby changing the feeding reflexes. These changes stimulate the activity of the medial or inhibiting hypothalamic mechanisms and suppress the lateral facilitating mechanisms, thus producing satiety. On the other hand, when the food eaten is disposed of through conversion to heat, work or some form of stored energy, the changes produced by the feeding tend to disappear; consequently, activation of the satiety mechanism is removed and the lateral facilitating mechanism becomes more active leading to a state of hunger.

Various suggestions have been made regarding the nature of the change or changes, produced as a result of feeding, which influence the regulating system. The factors suggested by various workers are the following: (1) the specific dynamic action of food, increasing the heat stress of the body as a whole (the thermostatic hypothesis of Strominger and Brobeck[20]); (2) the availability and utilization of glucose from body fluids (the glucostatic hypothesis of Mayer[21]); (3) the concentration of certain metabolites, as yet unspecified (the lipostatic hypothesis of Kennedy[22]); (4) concentration of serum amino acids[23] and (5) sensations from the digestive tract associated with eating, swallowing and the presence of food in the stomach and in the intestine.[24,25] The ingestion of a single meal is accompanied by a number of changes in the animal body and more than one such change could act as a signal to the regulatory mechanism. On the basis of existing evidence, it would seem unwise to incriminate a single specific factor. A multiple factor theory of regulation appears to be most reasonable.

The two hypotheses of regulation of food intake, which today compete for emphasis, are the "thermostatic" and the "chemostatic" (especially the glucostatic) regulation hypotheses.

THERMOSTATIC REGULATION OF FOOD INTAKE

Brobeck wrote, "animals eat to keep warm, and stop eating to prevent hyperthermia."[20a] He and his colleagues[20,26] concluded that the day-to-day regulation of food intake is not in terms of a definite quantity of energy (a quantity equal to the total expenditure of energy); instead it is the specific dynamic action of the ration which determines the amount of food eaten. Rats placed on a high fat diet often ingested three times their normal caloric

intake on the first day following the change in diet. Another point in favor of the thermostatic regulation is that there is no direct evidence for a specific sensitivity of the hypothalamic neurons, except to temperature change.[13]

CHEMOSTATIC REGULATION OF FOOD INTAKE

For short-term regulation of energy intake, Mayer[21,27,28] proposed the glucostatic theory, which postulates that somewhere, possibly in the hypothalamus, there are glucoreceptors sensitive to blood glucose in the measure that they can utilize it. He reasoned that during the interval between meals the content of fats and proteins within the body, which are proportionately enormous, would decrease insignificantly; while the stores of carbohydrates, which are limited, would decrease proportionately more. Glucose is the essential fuel of the central nervous system.

It seemed reasonable to postulate, therefore, that hypothalamic centers may be glucoreceptors. Mayer and Bates[29] showed that in normal and diabetic animals and in animals subjected to various hormonal treatments, decreased availability or utilization of glucose correlated well with increased food intake. A generally reliable representation of the utilization of glucose can be obtained from the arteriovenous differences of glucose (Δ-glucose) rather than from absolute levels of blood glucose.[30] It was demonstrated that hunger is a state in which the Δ-glucose tends toward zero while in the state of satiety there is an appreciable Δ-glucose. Stunkard and Wolff[31] found that small Δ-glucose coincided generally with gastric contractions due to hunger and subjective feelings of hunger in human beings, while large Δ-glucose accompanied satiety and disappearance of contractions of the stomach.

Mayer and Marshall[32] also demonstrated that injection of gold thioglucose in mice produced overeating and obesity by causing selective destruction in the medial satiety centers of the hypothalamus, while other gold thio-compounds did not produce any hypothalamic lesions or obesity. It was suggested that the affinity of the glucoreceptors in the ventromedial nuclei of the hypothalamus for the glucose moiety of the compound causes the glucoreceptors to accumulate proportionately more gold than other regions, sufficient to damage these particular neurons. Perry and Liebelt[33] have demonstrated that gold thioglucose, in addition to producing lesions in the ventromedial nuclei and obesity, also produces extrahypothalamic lesions. All the loci where these lesions are produced have in common a proximity to areas with increased permeability of the blood-brain barrier.

Anand, Dua and Singh have also studied this problem using a different method. Depth electrodes were implanted in the lateral feeding and the medial satiety hypothalamic centers of monkeys and cats and the activity of these regions were recorded electroencephalographically. After taking the normal recordings, blood glucose levels were changed either by intravenous infusion of glucose saline or by intravenous injection of insulin. Control electrodes were also implanted in the other hypothalamic and cortical regions. It was observed that with the production of hyperglycemia the activity of the satiety center was increased while that of the feeding center was slightly decreased. With hypoglycemia, the activity of the satiety center was slowed down while that of the feeding center was increased. These changes were observed both in monkeys and cats. Changes in blood glucose levels did not alter the recorded activity from the other hypothalamic and cortical regions. Intravenous transfusion of protein hydrolysate did not alter the activity of either the feeding or the satiety centers. Larger doses produced a generalized inhibition of activity as a result of protein shock. Intravenous infusion of fat emulsion (Lipomul®) also did not change the activity of hypothalamic centers. Therefore, our studies support the hypothesis that the hypothalamic centers are sensitive to changes in blood glucose, rather than changes in blood protein or fat.

Forssberg and Larsson[34] demonstrated that in hungry rats the uptake of P^{32} was greater in the regions of the hypothalamus, which have the feeding mechanisms, than in other regions. Their studies of the uptake of glucose containing C^{14} were inconclusive. Studies of the uptake of glucose by the feeding and satiety

regions of the hypothalamus in fed and starving monkeys have been made by Anand, Talwar, Dua and Mhatre. In the first series of experiments, glucose containing C^{14} was injected into the carotid arteries of both fed and starving monkeys. The monkeys were beheaded immediately after the injection was given and the brains were frozen in liquid air. Pieces from the satiety and the feeding regions and from two other adjacent hypothalamic regions were studied then for radioactivity. No significant activity was detected in any region.

In other experiments, uptake of glucose and oxygen by various hypothalamic regions in fed and starving monkeys has been investigated with the Warburg technic. Preliminary observations suggest that in the fed animals there is a relative increase in the uptake of oxygen and glucose per unit of nucleic acid activity by the satiety region, as compared with that of the feeding center. In the starved animal, the uptake of oxygen and glucose by the satiety region is less than that of the feeding region. The arteriovenous glucose difference was low in starved animals and high in the ones which had been fed. These results indicate an increase in activity of the satiety centers during fed states, which is accompanied by an increase in the uptake of glucose. They also suggest that the satiety region of the hypothalamus contains the glucoreceptor mechanism. They also support the original hypothesis of Anand and Brobeck,[7] that the basic urge to eat is located in the lateral hypothalamic regions; while the medial regions are activated as a result of changes in the levels of the blood sugar produced by food intake, which subsequently produces satiety and abolition of further eating by inhibiting the lateral mechanisms. The electroencephalographic recordings from feeding and satiety centers under conditions of hyperglycemia and hypoglycemia (mentioned previously) lend further support to this hypothesis, as the changes in the activity of satiety centers are more pronounced than changes in the activity of feeding centers.

AFFERENTS FROM THE STOMACH

Experiments using the evoked potential technic are being conducted to determine whether or not the gastric afferent impulses, traveling centrally through the vagus, project to the hypothalamic centers. Preliminary studies have shown a projection into the medial hypothalamus just anterior to the satiety center. Ballooning of the stomach, *in situ*, also evokes potentials in the medial hypothalamic regions, which correlate well with increasing intragastric pressures.

CORRELATION OF WATER INTAKE WITH FOOD INTAKE

Strominger[35] had noted that, within limits, the higher the water concentration of the diet, the greater the food intake; animals given no water ate little or no dry food and those given no dry food drank little or no water. The regulation of food intake appears to be correlated with the regulation of water exchange. It has been suggested by various authors that, if these two are so intimately correlated, after hypothalamic lesions have been produced the changes in food intake may be the indirect result of the changes in water intake which may be the primary function regulated from the hypothalamic levels. Anderson and McCann described a hypothalamic "drinking area" which produces polydipsia when electrically stimulated.[36] Similar results were obtained by microinjection of hypertonic saline into the same regions. Montemurro and Stevenson[37] demonstrated that the hypothalamic area regulating water intake was situated in the same region as the feeding center. Studies of Anand and Dua[38] have demonstrated that, after hypothalamic lesions have been produced, rats fail to show the correlation of water with food intake observed in normal animals. Lesions in the lateral hypothalamic feeding center resulted in complete adipsia in addition to complete aphagia. Lesions near this region (1 mm. medial or anterior) produced hypodipsia, irrespective of increase in food intake. Lesions farther away from this region did not significantly change the water intake despite changes in food intake. It can be concluded, therefore, that the hypothalamic regions controlling water and food intake, although present in adjacent regions, act separately and independently. Morrison and Mayer[39] have made similar observations. It may be noted here

that lesions in the limbic structures of rats do not change their water intake.

SUMMARY

On the basis of studies presented herein, it is possible to say that the mechanisms of the nervous regulation of food intake can be categorized with those governing the nervous regulation of other visceral activities. Experimental evidence has been furnished suggesting certain modes of activation of the higher nervous mechanisms. More knowledge is required before a complete picture of the nervous regulation of food intake is finally revealed.

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DISCUSSION

Dr. C. N. H. Long (*New Haven, Connecticut*): Dr. Anand, why is the diabetic animal hungry?

Dr. Anand: I do not think I can give a straight answer to this. If one were to hypothesize why a diabetic animal is hungry, an explanation might be that although the blood sugar is high, there is less sugar available within the cells of the satiety center.

Dr. Rachmiel Levine (*Chicago, Illinois*): There is no evidence that neurons need insulin for consumption of glucose. Perhaps these neurons are different, but it would first have to be demonstrated.

Dr. Jean Mayer (*Boston, Massachusetts*): I do not want to anticipate on my paper, however, there is considerable and cumulating evidence that those neurons are different.

Dr. Henry D. Janowitz (*New York, New York*): I would like to ask Dr. Anand, who has shown us that the satiety center is activated by distention of the stomach, whether he has picked up any spontaneous activity of the feeding center during spontaneous or hunger contractions.

Dr. Anand: Ordinarily we have not seen any marked changes in the activity, either from the satiety or the feeding areas, but when we inflate the stomach with a balloon, we find that there is increased firing from the satiety area only and not from the feeding area.