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Guest Editorial

Fifty Years of the "Feeding Center": Not yet Satiated

Food intake involves a complex behavioural process. Many factors interact in determining the type of food, the amount and the frequency of food intake. The regulation of food intake is fundamental to all homeostatic mechanisms. It has been a topic of intense scientific investigation for over a century now, of which half a century has passed since the discovery of feeding center by Anand and Brobeck in 1951 (1).

The story of discovery of feeding center is indeed very interesting. Until 1910, there were three major theories regarding the regulation of food intake. According to the peripheral origin theory, physiological changes in the peripheral tissue like stomach were thought to be responsible for hunger and food intake. On the contrary, the central origin theory held that 'hunger centers' in the brain were sensitive to starvation state of blood. According to the general sensation theory, it was believed that both central and peripheral components together sense the starvation state of blood and initiate food intake. But there was still no clue as to what is 'sensed', what is the nature and location of 'sensors' and how food intake is regulated.

Cannon and Washburn in 1912 showed that hunger pangs resulted from contractions of empty stomach and this generally led to food intake (2). It was also shown that distension of stomach, even with a balloon, brought down stomach contractions and gave a sense of satiety. This supported the peripheral origin of hunger sensations and led to the belief that the general body status did not play any role in feeding behaviour. In 1916, Carlson showed that insulin-induced hypoglycemia was associated with gastric contractions and proposed that hypoglycemia stimulated food intake by generating gastric contractions (3). But later investigations documented that total denervation of the gastro-intestinal tract did not affect food intake, while hypoglycemia induced by insulin did trigger food intake in such animals. This shifted the focus to 'sensors' of general body status or starvation status of blood and to the possible location of the 'sensors'.

In early 20th century, Frohlich had noted that pituitary tumours were often associated with poor development of secondary sexual characters

and obesity. Camus and Roussy in 1913, noted that hypothalamic lesions also had similar features, which was later confirmed by Bailey and Bremer in 1921 by artificially producing hypothalamic lesions (4). This indicated that 'central components' do play a role in feeding behaviour but it was not clear which those areas were. Hetherington and Ranson in 1940 produced discrete lesions in the ventromedial hypothalamic nuclei stereotaxically, and demonstrated for the first time the presence of 'satiety center', the loss of which made the animal to eat excessively and gain weight, thus confirming the role of hypothalamus in the regulation of feeding behaviour (5).

Most of the experimental work and evidence during that time mainly dealt with the regulation of size of each meal. But Adolph in 1947 showed that animals intrinsically regulated their body weights and total energy intake depending on long-term needs even though meal size varied with each meal, and thus proposed the concept of long term regulation of food intake (6). At this time, how this energy level is sensed and regulated was not clear. In 1948, Brobeck proposed the "thermostatic theory" (7). According to this theory, an individual senses the 'blood temperature' and regulates its food intake depending on the environmental temperature and specific dynamic action of food.

Under these circumstances, when Brobeck was working on 'satiety center', Bal Krishan Anand reached Yale University School of Medicine in November 1950 as a Rockefeller Foundation Fellow to study under John Fulton. Here, Brobeck taught him the technique of stereotaxy and asked him to produce lesions in the 'satiety center'. Anand carried out the experiment with meticulous precision. However, to his dismay, all the rats in which he had produced lesions, instead of becoming voracious eaters and putting on weight, stopped eating altogether and as a result, lost weight and died. Even placing food in their mouth could not persuade those rats to eat. Anand cross checked all the steps and made sure that he had followed all the steps properly. Anand and Brobeck did the histology of the brains of those rats and found that Anand had produced giant lesions instead of the small lesions that Brobeck was producing. On investigation, the culprit was found to be the instrument used to produce electrolytic lesions which, instead of delivering 2 mA at the set point, had suddenly started giving 20 mA, leading to giant lesions. Anand proposed that there are two centers in the hypothalamus, very near to each other: one for satiety and another for feeding; and he had destroyed the latter. To test Anand's hypothesis, they repeated the experiments with small lesions in the neighbouring areas and ultimately 'discovered' the "feeding center".

It is quite characteristic of scientific research that a piece of work raises more questions than it answers. True to this, instead of solving the question regarding the regulation of feeding behaviour, this discovery generated many more questions and a lot of research in this field in the next fifty years. Further studies by Anand himself and others confirmed the existence of 'feeding center'. Stimulation of feeding center by chronically implanted electrodes was found to increase the amount of food eaten leading to weight gain, which

persisted as long as the stimulation continued. Although the opposite occurred with stimulation of satiety center, it was neither so dramatic nor long lasting. Furthermore, an increase in the activity and oxygen consumption in the feeding center during fasting and in satiety center after feeding was observed. So, it appeared that satiety center has a constant inhibitory influence on feeding center and during fasting, when the activity of satiety center decreases, the inhibition is removed and feeding center initiates food intake. Other studies also demonstrated effects similar to those of hypothalamic lesions with lesions in the lower brain areas and a few studies showed slightly different effects of lesions in higher brain areas. A neural model was proposed based on these findings wherein the hypothalamic centers provided 'drive', acting on the lower brain areas to carry out a 'reflex', with higher centers like limbic system and cortical areas acting as modulators, mainly concerned with discriminative aspects of food such as appetite.

Despite the availability of a neural model for the regulation of feeding behaviour, the basic questions mentioned above still remained unanswered. Many theories were proposed, including the already mentioned "thermostatic theory". In 1950s, Mayer proposed the "glucostatic theory" which attempted to explain the regulation of food intake depending on the glucose utilization (arterio-venous glucose difference) of the neural structures (8). Studies using gold thioglucose showed that there is increased uptake of glucose by satiety center, and established that glucose sensitive neurons are present in the hypothalamus. While this theory explained short-term regulation, the long-term regulation, as proposed by Kennedy in 1953, could be explained by "lipostatic theory" (9). In this, the body fat stores somehow generate an unknown signal, which is sensed by the central nervous system, and thus a lipostatic point maintains a reasonably constant body weight. But, here also, the 'signal' and the 'sensors' remained to be identified.

During 1950s and 1960s, the importance of peripheral tissues was re-established by many findings. The role of oropharynx, stomach and intestine in the short-term regulation were emphasized. In 1970s, the compelling evidence for many of the gastro-intestinal hormones as 'satiety factors' was brought into light. It was shown that cholecystokinin, bombesin and glucagon play important role in the genesis of satiety, both by stimulating peripheral nerve endings and by their direct actions on central nervous system. In the 1980s, their role was further confirmed by identification of receptors and also synthesis of specific receptor blockers. In the 1990s, in addition to the already existing hormones, the newer molecular biology techniques identified "leptin", a hormone from adipose tissue, and "leptin receptors", which seemingly are involved in the long term regulation of feeding. Later on, the role of insulin in feeding behaviour, the interaction of insulin and leptin, the involvement of neurotransmitters like neuropeptide Y and melanocortin systems in the control of food intake at the neural level were identified. Recently, elucidation of the role of "orexins" in the feeding

behaviour has not only generated newer insights, but also has generated many more new questions regarding the regulation of food intake.

Our progress regarding the understanding of feeding behaviour over the period of last hundred years has been quite eventful, especially so in the last 50 years. With this new knowledge, we have a much better picture as to how we regulate our own food intake. At the same time, it is true that we do not have, as yet, the complete picture of it. Even after 50 years of the discovery of 'feeding center' and over a century of intense research in the related areas, there remains ample scope and need for further research to solve the mystery of mechanisms involved in one of the 'basic needs' of our existence and this is the most heartening and stimulating thing for a scientist.

MANJUNATHA S.
Department of Physiology,
All India Institute of Medical Sciences,
New Delhi – 110 029

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