COMMENTARY ON CLASSICS IN OBESITY

Static Theories in a Dynamic World: A Glucodynamic Theory of Food Intake

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"Knowledge comes, but wisdom linger"

Locksley Hall, Tennyson

"The central method of science is the experimental method, but it has taken thousands of years to discover it. That method consists essentially in arranging things in such a way that the answers to our questions are given by nature itself, thus apparently eliminating ourselves"

Sarton

The papers that I have selected for this issue of Classics in Obesity relate to glucose as a peripheral signal in the control of food intake. The first is the paper entitled *Glucostatic Mechanism of Regulation of Food Intake* by Jean Mayer, which was published in 1953 (23). The second paper by Louis-Sylvestre and Le Magnen (21) recast the glucostatic theory as a glucodynamic theory and opened the way to rethink other "static" theories in dynamic terms.

From the early 20th century until World War II, the theories about control of food intake were dominated by the work of Cannon and Washburn (8) and Carlson (9) who argued that contractions in the stomach were the keys to stimulating hunger. These "peripheral" theories were only gradually replaced by theories of central integration (2). It was the technical ability of Hetherington and Ranson to place discrete anatomic lesions in the hypothalamus that provided the definitive experiment to show that it was the hypothalamus not the pituitary that was central. From their work a key role for the brain could no longer be denied. Brobeck and Anand using similar precise techniques showed that lesions in lateral hypothalamus would produce hypophagia (1). The pendulum was now swinging toward central theories of food intake regulation. Using the experimental work of Hetherington and Ranson (18) and of Brobeck and his colleagues (5) Stellar formulated the Dual Center hypothesis for regulation of food intake (26). This theory postulated that the ventromedial hypothalamus functioned as a "satiety" center and the lateral hypothalamus as a "hunger" center.

Close on the heels of the dual center hypothesis came several ideas about the nature of the signals from the periphery to the brain, which were called for by this theory (22). Under the name of "static," glucostatic, lipostatic, aminostatic theories (19) and thermostatic concepts (6) were proposed as a way of modulating food intake. An underlying assumption for all of these "static" proposals is that body weight and fat stores are stable. This apparent stability in the short term is associated with variations of intake above and below the "stable" or preferred weight. Studies in both humans (11) and monkeys (Kemnitz, unpublished data) have shown that day-to-day food intake is a weak predictor of energy expenditure and body weight in the short term suggesting that these oscillations in intake provide error signals on which compensatory systems make corrections.

In a very readable paper in the Annals of the New York Academy of Sciences, Mayer argued that body weight and fat stores are regulated, and he suggested that glucose was the primary, if not the only, signal that can provide this regulation (24). To support the concept that there is regulation of food intake, Mayer used the


From the Department of Medicine, Louisiana State University School of Medicine, and the Pennington Biomedical Research Center, Baton Rouge, LA. Reprint requests to Dr. Bray, 6400 Perkins Rd., Baton Rouge, LA 70808. Copyright ©1996 NAASO.
work of Gasnier and Adolph Mayer, his father (13-17). With rabbits as their subjects, these workers showed that there was only a very small short-term variation in the body reserves about the “preferred weight.” There was also only a small variation in the day-to-day intake of food in rabbits which had access to food under uniform conditions. To show that the animals would adjust their food intake to changing conditions, these scientists measured food intake at several different ambient temperatures. Over the 80 days of this study there was a spread of intake and expenditure indicating the presence of day-to-day errors which were compensated for. Based on these studies, Gasnier and A. Mayer defined four parameters which described the day-to-day adjustments of energy intake to energy expenditure. These parameters were the precision, reliability, sensitivity and rapidity of response of the system.

Precision is inversely proportional to the short-term difference between energy intake and expenditure and in the long term to the amplitude in body fat reserves for any given value of fat. Reliability refers to the temporal periodicity. Sensitivity, according to Mayer, is the distribution of values around the zero or privileged value of composition of fat or carbohydrate stores. Rapidity refers to the time constant or rate of oscillations.

From this analysis of the work by Gasnier and Mayer on rabbits, Jean Mayer concluded several things (24). First, that there are biometric upper and lower limits to food intake and energy expenditure, which are related to the biology of the stomach and other digestive organs and the ability to use or conserve energy. Second there are day-to-day adjustments of energy intake to energy output. Third, there is regulation of body fat reserves. Fourth the precision, reliability, sensitivity, and rapidity of response of the regulated system can be specified. Fifth, a number of factors including cold and exercise can influence the regulation of this system. Sixth, that obese animals regulate intake albeit with greater oscillations.

In looking for a short term mechanism to explain the control of feeding, Mayer set out several criteria (24). First, the signal he was looking for must be integrated into the metabolic processes. Second, it must have both an anatomic and physiologic basis. Third, it must account for the effects of variations in environmental conditions. Fourth, hormones such as insulin, growth hormone and thyroxine must be integrated into the system. Finally it must account for the state of hunger and satiety. Mayer believed that the only mechanism which fulfilled all of these criteria was the availability of carbohydrates, primarily glucose.

As Mayer points out, glucose metabolism is pivotal for overall metabolic processes, and is an essential fuel for the brain. In addition, there is anatomic evidence for glucose responsive elements in the brain. When goldthioglucose is administered to animals it is taken up into the brain and destroys areas of the ventromedial hypothalamus with subsequent development of obesity (10). Other data which are consistent with the idea of Mayer include the following: 1) that injections of insulin which lower glucose can stimulate feeding; 2) that 2-deoxy-D-glucose an analogue of glucose which blocks glucose metabolism will stimulate feeding; 3) that glucose injection (29) or mobilization of glycogen by glucagon (28) which will reduce arterio-venous differences for glucose and also reduce gastric contractions and abolish hunger.

Following the publication of Mayer’s hypothesis, Oomura and his colleagues in Japan demonstrated the presence of glucosensitive and glucoseresponsive elements in the ventromedial and lateral hypothalamus respectively (25). Moreover, metabolic hormones such as insulin and growth hormone have important effects in the metabolism of glucose and on food intake. Finally, in the study of diabetics and normal subjects given glucagon, which enhances glucose release, Mayer and his colleagues were able to show that it was the change in glucose utilization measured as the arterio-venous difference which was the critical variable.

Stunkard, who was a contributor to work on the “glucostatic theory” for satiety, has given us a glimpse into the excitement that this theory brought to his early research career and to his eventual disillusion with it. In his very readable autobiographical work, “The Pain of Obesity,” he summarizes the status of the Glucostatic Theory in 1972 as follows:

“The more I thought about (the glucostatic) theory, the better it sounded. And it led directly into the next question. What went wrong in obesity... Two distinct possibilities suggested themselves. First, the glucostatic mechanism itself might break down. The second possibility was that the glucostatic mechanism itself might be intact, but for some reason the obese person might not have enough blood sugar available.... There is a certain drama in any research, a drama that may hang on the simple behavior of a recording pen.... After all the time spent in preparations, the actual experiments took only a few days.... The experiments showed that the glucostatic mechanism seemed to work for both obese and non-obese people.... In short, the results of all those years of work on sugar tolerance were negative. This long digression taught me a bitter lesson. Dogged persistence does not of itself bring rewards in the scientific enterprise... there is a law of diminishing returns in the pursuit of technical improvements.... Where has all of this research brought the glucostatic theory, in the years since I left it?... Glucostatic mech-
organisms play a part in [the regulation of food intake]; but they cannot account fully for either short-term control, such as the ending of a meal, or for long-term control, such as the stability of body weight over months and years" (28).

The role of glucose in the modulation of feeding has not disappeared but the focus has changed. The change was brought about by improved methodology which often leads to improved theory (3,12). Le Magnen viewed the periodicities of feeding as a measure of circulating metabolites, With an moreover, its role in glucose and free fatty acids which often leads to improved theory (3,12). Le Magnen viewed the periodicities of feeding as a measure of circulating metabolites. Earlier studies with measurements of glucose made at intervals of 10 to 30 minutes had failed to find regular patterns of glucose change (27). To test this hypothesis required him to make more frequent measurements of circulating metabolites. With an improved method for continuous measurement of blood glucose concentration Louis-Sylvestre and Le Magnen (21) in our second classic observed a 6% to 8% decline in glucose concentration that occurred 5 ± 0.3 minutes before the onset of most meals in both the light and dark phases. Campfield et al. showed that blocking this decrease in glucose would delay or prevent initiation of a meal and has recently extended these findings to human beings (7).

The role of glucose in regulation of food intake has shifted from a satiety signal to an initiation signal. Moreover, its role has shifted from a static one aimed at maintaining constant levels to a dynamic one in which the brain or liver are responding to dynamic changes in glucose concentration to initiate food seeking. Thus along with contractions of the stomach a dip in glucose may be signals which periodically initiate the search for food. Figure 1 shows schematically how these two signals may be put into a simple model for initiating the onset of food intake.

The use of the word static for the "glucostatic" theory is unfortunate, since it implies a static or unchanging system. Glucose oscillates in the plasma under normal circumstances and responds to a variety of external circumstances. The word "dynamic" would be more appropriate in light of the way in which food intake begins after the nadir in glucose suggesting that it is the pattern of dynamic change in glucose which is sensed rather than its level. It would thus be preferable to refer to this as the glucodynamic theory of food intake rather than the glucostatic theory.

Jean Mayer was born in Paris on February 19, 1920. He received his undergraduate education in Paris before World War II and he was active in the resistance movement during the war. When peace arrived in 1945, Mayer began his work for the Ph.D. which was awarded in 1948 by Yale University, followed by a Sc.D. from the Sorbonne in 1950. During the 1950's Mayer was an active scholar in obesity and nutrition. He was chairman of the White House Conference on Food and Nutrition in 1970, which developed many of the models for nutrition policy for the next 25 years. He became President of Tufts university in 1976.

References


Figure 1: Two dynamic factors which enhance the likelihood of food seeking.