What do “eating peptides” really control? Potent stimulation of food acquisition by AgRP

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MOTIVATED OR GOAL-DIRECTED behaviors are characterized by two principal phases. In the appetitive phase, organisms show increased activity, including the execution of learned behavior sequences that will bring them in contact with an appropriate goal object. This phase is often, but not always, driven by a physiological need state. In the consummatory phase, organisms interact with that goal object in an appropriate amount or manner, often in a more or less reflexive or stereotyped manner. Both classes of behavior, and the underlying genes, are likely to have been highly selected to enhance inclusive fitness.

In the case of feeding, animals often have to endure natural cycles of feast and famine, and higher vertebrates in particular may engage in elaborate food procurement strategies. For example, avian species are known to engage in elaborate spatial searches and food caching, behaviors that are critically dependent on the hippocampus (15). Likewise, omnivorous and granivorous mammals often hoard large amounts of food when it is available (1); analogous behaviors have been reported in humans (8). Hoarding is a purely appetitive behavior that, like some feeding episodes, may be considered “opportunistic” rather than “regulatory.”

Despite this rich diversity of natural behaviors, our understanding of the neurobiology or physiology of feeding behavior is predicated almost exclusively on regulatory models, and in particular models that focus on body weight or mass regulation. These ideas can be traced to Canon’s (3) formulations of homeostasis and Stellar’s (17) dual-center model of motivated behavior. Some years ago Mrosovsky (13) reminded us that, for Canon, freedom from the internal environment (through homeostatic mechanisms) meant freedom for something else: “Homeostasis was for poetry rather than for producing grand-children” (p. 12).

Yet, as far as I can tell, all of the current neurobiological models of feeding behavior are either implicitly or explicitly founded in a homeostatic/negative feedback philosophy. Over the years, many writers have argued for the inadequacy of such an approach. For example, Moore-Ede (12) called for a distinction between predictive and reactive homeostasis, Blundell et al. (2) included a variety of cognitive factors in modeling food intake, and DeCastro and Plunkett (7) used both “compensated” and “noncompensated” factors in a computer simulation of body weight control. These two categories correspond to the above regulatory/reactive/homeostatic and nonhomeostatic constructs. Regulatory or reactive behaviors are convenient to study in the laboratory: they usually involve little or no training of subjects and are associated with a high degree of experimental control, such as hours of food deprivation and a defined diet. “Nonregulatory” behaviors are difficult to study in the laboratory: they usually involve some training of subjects, repeated measurements, and allow the subjects some degree of control over when and where the behaviors are performed. Perhaps justifiably, most investigators have chosen the former road and studied a “neurobiology of convenience.”

In this issue of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology, Day and Bartness (6) have taken a major step toward breaking out of this conceptual confinement by examining the effect of central administration of agouti-related protein (AgRP) on both food hoarding and intake in a seminatural setting. AgRP is the endogenous antagonist for central melanocortin type 3 and 4 receptors (MC3-R, MC4-R), previously implicated in feeding from purely consummatory/regulated perspectives (5). Their experimental subjects are Siberian hamsters (Phodopus sungorus), small rodents that exhibit seasonal changes in food intake and body weight that are driven entirely by the photo-period (11). Their study was performed in long days, simulating a time of year when food is available in the environment and would be associated with a high level of appetitive and consummatory food-directed behaviors, high intake and body weight, and reproductive activity. They have developed a two-compartment living environment, in which a lower and shaded “burrow” is connected to an upper cage in which food is available from a dispenser by running a fixed number of revolutions in an attached wheel.

Four doses of AgRP were injected into the third cerebral ventricle at the beginning of the nocturnal cycle, and food procurement, hoarding, and intake were measured at intervals thereafter (6). AgRP produced increases in both food intake and hoarding, but hoarding occurred at lower doses and in some cases sooner than stimulation of intake. This is consistent with previous work in several species of hamster showing that food deprivation does not increase intake but does promote either hoarding or pouching of food in many situations (e.g., Refs. 1, 13, 16). Thus studies in which animals are allowed only reflexive eating have failed to account for the broader organization of the food-directed behavior. Along these lines, recent work in our laboratory has extended Collier and Johnson’s (4) operant foraging protocol to mice, showing that meal size and frequency are reciprocally related. The fundamental nature of this relationship is not altered in leptin-deficient mice (ob/ob) (18).

Meal size is one of the most studied factors in the control of food intake. However, Day and Bartness’ work, as well as those studies cited above, serves to deemphasize “the meal” as the fundamental unit of interest in the analysis of eating, but instead examines food procurement in terms of the overall environmental context in which it occurs. Finally, for those of us who are finding that mice are not just small rats with regard to ingestive behavior, it is appropriate to emphasize that comparative study is needed to assess the generality of con-
conclusions and eventually their extrapolation to advance human health. The epidemic of human obesity has often been attributed to an “obesifying” environment, but that analysis embraces the important observation that we as a species behave like opportunistic rather than regulatory feeders (9, 10). Thus, until we understand how the chemical signals/genes that modulate reflexive feeding actually control behavior in a range of real environments, we have no useful empirical grounds on which to predict the success of potential biologically based interventions.

REFERENCES