Regulating food intake

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EVERY ORGANISM INGESTS FOOD (energy). If it takes in too little, it will starve; if it takes in too much, it will become obese. Too little is readily defined as caloric intake less than expenditure, and too much is simply the opposite. Multiple regulatory pathways are known that promote and inhibit feeding and thus regulate energy balance. However, these pathways and their interactions remain incompletely understood. As we are in the midst of an epidemic of obesity, there is considerable urgency to understand how food intake is regulated. Recent publications in the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology have addressed a number of important questions in this field.

Monogenic obesity, such as the various loss of function mutants of leptin and its receptors, is rare outside the laboratory. Much of human obesity is instead multifactorial and usually involves relative overconsumption. Both internal and external factors contribute to this overconsumption. As with humans (17), so with rats (16), palatability of a meal affects the amount consumed, the rate of consumption, and subsequent metabolic processing. Rats given a diet with high-energy density (typically a high-fat diet) can be separated a posteriori into individuals that are susceptible or resistant to diet-induced obesity (18), and selective breeding indicates that this is a polygenic trait. Commerford et al. (7) could show no difference in lipogenic capacity or dietary fat retention between obesity-prone and obesity-resistant rats. Accordingly, they concluded that increased energy intake was necessary for the accelerated weight gain. Both energy density and palatability of the diet appear to contribute independently to weight gain (19). Recent work also addresses the question of why some individuals are more responsive than others to changes in caloric intake. Leptin is secreted by white adipocytes in proportion to fat mass and thus may induce leptin resistance. A study by Lin et al. (21) demonstrated rapid induction of leptin resistance when rats were switched from a low- to a high-fat diet and vice versa. These results were interpreted to indicate that dietary fat per se may induce leptin resistance. In another study, leptin sensitivity was assessed before exposure to high-energy diet. Those rats with the lowest leptin sensitivity (i.e., leptin resistance) had the largest subsequent weight gain, indicating that leptin resistance predicts diet-induced obesity (20).

Despite the emphasis on diet-induced obesity, these and other studies also highlight the extent to which body weight is regulated and some of the variables that are monitored to do so. Sequential dietary manipulation showed that both obesity-prone and obesity-resistant rats defend their body weights (19). Female musk shrews, which have little stored energy, must monitor multiple variables related to energy availability to ensure that mating occurs when available energy is adequate (31). Many species increase and decrease their body weights and adiposity on a photoperiodic, circannual basis (9, 22, 23). The king penguin fasts for extended periods while incubating its egg. A switch from fatty acid to protein catabolism appears to be perceived as a “refeeding signal” (5). Feeding the fructose analog 2,3-anhydro-D-mannitol stimulates food intake in rats fed a low-fat, but not a high-fat, diet (13). Magnetic resonance spectroscopy, both in vivo (13) and in vitro (14), indicates that the analog depresses hepatocyte ATP content to a lesser extent on the high-fat diet, thus minimizing the putative feeding signal.

Orexin-A and orexin-B (also known as hypocretins-1 and -2) were so named because they are synthesized only in a small group of neurons in the lateral hypothalamus, a region of the brain long known to be an important contributor to feeding behavior. Although they are indeed orexigenic, they have multiple actions, as illustrated by several reports in the journal. Orexin-B depolarizes postsynaptically both parvocellular and magnocellular neurons on the hypothalamic

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paraventricular nucleus (30). This action is consistent both with an orexigenic action (15) and with autonomic activation. Certainly intrathecal application of orexins activates sympathetic preganglionic neurons (4). Orexins also inhibit the secretion of ACTH mediated by CRH (29). Interestingly, Wu et al. (35) showed in dogs that orexin levels in cerebrospinal fluid vary substantially with sleep deprivation or with physical activity, but not with food deprivation or refeeding. Wang and Kotz (32) showed in rats that injection of urocortin into the lateral septum inhibits feeding induced both by food deprivation and by injection of orexin A into the lateral hypothalamus. This inhibition is blocked by a CRH type 2 receptor antagonist in the lateral septum and the effect of urocortin is not due to production of a conditioned taste aversion.

Given the ballooning incidence of obesity, it is perhaps not surprising that a large number of recent studies have addressed anorexigenic pathways and signals. One of the best characterized of these signals is CCK, which signals via the vagus the presence of nutrients, particularly fats and proteins (8), and gastric distension. Its importance is shown by the Otsuka Long Evans Tokushima Fatty rat, which lacks the CCK-A receptor (6). This rat has a satiety defect resulting in increased meal size, hyperphagia, and obesity. Both preobese and pair-fed (nonobese) individuals show prominent staining for neuropeptide Y in the dorsomedial hypothalamus that is not evident in obese rats or in lean control rats (6). Presumably, the lack of CCK signal results in overexpression of neuropeptide Y. Certainly CCK interacts with other signals. Matson et al. (25) report an interaction whereby CCK enhances the weight loss response, but not the anorexic response, to leptin. In ovariectomized rats estradiol increased the number of feeding-induced c-Fos-positive cells in regions of the nucleus of the solitary tract that process satiety signals, but not regions that process gustatory signals (10). The same group subsequently showed that estradiol enhanced CCK-induced c-Fos labeling in the same region as well as in the paraventricular nucleus and the central nucleus of the amygdala, other regions involved in regulation of food intake (11). Interestingly, estradiol also augmented glucagon-mediated satiety signaling in ovariectomized rats (12).

Another peripherally generated peptide that has attracted attention as a satiety signal is amylin, which is cosecreted with insulin. Amylin crosses the blood-brain barrier and has receptors in multiple brain nuclei. It is a potent inhibitor of both gastric emptying and food intake (27), whereas the related peptides, rat calcitonin, calcitonin gene-related peptide, and adrenomedullin, are relatively inactive (28). The anorexic response to amylin involves D₂, but not D₁, dopamine receptors (24). Among other brain sites, nucleus accumbens possesses high levels of amylin binding sites and contributes to regulation of food intake. Injection of amylin into the nucleus accumbens indeed reduces deprivation-stimulated ingestion of food and water, but more potently inhibits motor activity (3). This result was suggested to be due to diminution of exploratory drive. This pattern of combined motor plus ingestive responses to effector peptides is seen not only with orexin-A (32) and amylin (3), but also with peptides from cocaine- and amphetamine-related transcript (1, 2).

Urocortin, a member of the CRH family, is found both centrally and peripherally and inhibits food intake when administered in either location (31, 33, 34). There is evidence that urocortin acts in the paraventricular nucleus (15, 33), although the lateral septum would appear to be a more important locus of urocortin action (32). Injection of urocortin into the lateral septum reduced deprivation-induced feeding as well as feeding induced by injection of orexin-A into the lateral hypothalamus (32). CRH injected into the lateral ventricle, where it could be expected to activate CRH type 2 receptors in the lateral septum (32), caused dose-dependent reductions of food intake (26) that were augmented by a central infusion of insulin, which, alone, had no effect on intake or body weight.

REFERENCES


