Regulation of body weight

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REGULATION OF BODY WEIGHT is a complex and dynamic process. Many aspects of this regulation have been addressed by recent publications in the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. Among them are delineation of pathways signaling satiation; interactions with other physiological control systems, notably cardiovascular and reproductive systems; exploration of factors that determine susceptibility to diet-induced obesity; and temporal aspects of body weight regulation. The last includes rhythmic events of various cycle lengths, from infradian to circa-annual periods, and also developmental and age-related events.

Today, leptin, neuropeptide Y (NPY), orexins, cocaine- and amphetamine-regulated transcript (CART), amylin, and proopiomelanocortin (POMC) are studied largely in relation to their putative or demonstrated roles in the regulation of food intake and of body weight. Recent studies published in the journal illustrate that most, if not all, of these peptides are also involved in regulation of other behavioral or biochemical processes. Thus orexins A and B given intrathecally are shown to activate sympathetic preganglionic neurons and raise both blood pressure and heart rate (3). Similar effects are seen after central orexin injections that target sites in the medulla known to be involved in cardiovascular control (7). The effect of intracerebroventricular CART to reduce food intake occurs primarily at a hindbrain site and is associated with specific alterations of motor behavior that appear unrelated to ingestion (1). Amylin, infused into the nucleus accumbens, reduces not only feeding and drinking but also ambulation (4). Administration of NPY intracerebroventricularly stimulates feeding and also inhibits sexual behavior in male rats (2) and in female hamsters (10). The latter report shows that the feeding and sexual behavior responses are mediated by different receptor subtypes. Injection of leptin intracerebroventricularly reduces food intake and, as expected, this effect is attenuated by SHU9119, an antagonist of melanocortin receptors. The same leptin injection also elevates circulating gonadotropin levels and increases the weight of seminal vesicle; these effects were not affected by SHU9119, suggesting that leptin affects the two systems via separable circuits (22).

Other interactions between the reproductive system and regulation of body weight are also addressed. In female rats, estradiol reduces meal size, food intake, and body weight largely by increasing the potency of satiation signals such as glucagon (18). In the nucleus of the solitary tract and downstream sites involved in negative feedback control of meal size, estradiol enhances the induction of c-Fos by feeding (16). Typically such studies are performed using ovariectomized animals with or without estradiol replacement. Davidge et al. (14) showed that to assure biological lack of estrogens, it is necessary to either reduce caloric intake to match control body weight or to include an aromatase inhibitor. A similar caution is raised by the report that lack of estrogens induces salt-sensitive hypertension in female spontaneously hypertensive rats and that the phytoestrogens found in regular rat chow are sufficient to prevent the problem (17).

Laboratory rats can be separated either a posteriori (8, 25) or by breeding (27) into groups that differ in their susceptibility to obesity when placed on a high-fat diet. These studies demonstrate the importance of increased caloric intake to gain of body weight and fat content (8). Palatability of the food employed also affects intake over both short and long terms (24, 26), whereas fat content of the diet per se alters responses to satiety signals (11, 12, 28). Different strains of mice show distinct dietary preferences that appear to depend on palatability in some cases and on postigestive signals in others (38, 39). Interestingly, rats that are susceptible to diet-induced obesity show much smaller responses to stressors (plasma corticosterone, norepinephrine excretion, expression of corticotropin-releasing hormone) than do the diet-resistant rats (27).
Given the importance of overeating to weight gain in rodents as in humans, it is not surprising that pathways involved in signaling satiety are under intensive study. CCK is perhaps the archetypal satiety signal, being secreted from the intestine in response to the presence of fatty acids in the lumen. In humans, the satiating effect of CCK is mediated by the CCK-A receptor (5, 20). Under some conditions, responses to CCK can be strong enough to prevent weight gain in rats over extended periods (13). Adaptation to a high-fat diet (12) or chronic CCK infusion (11) blunts the ability of CCK to reduce food intake. There is evidence for a synergistic interaction between CCK and leptin to reduce body weight to a greater extent than can be explained by the reduction of caloric intake (31), although others have failed to detect significant interaction between CCK and leptin (42). Similarly, leptin delivered subcutaneously over 75 days caused substantially more weight loss in ob/ob mice than occurred in pair-fed mice (34). Vagal afferents play an important role in signaling gastric distension (19), and some part of the actions of CCK is mediated by activation of vagal afferents (35). Studies employing destruction of visceral afferents by capsaicin indicate redundant signaling (23, 28). Another satiety signal, amylin, is co-secreted with insulin and acts both peripherally and centrally (4) with similar potency as CCK to inhibit gastric emptying and food intake (36). Lutz and colleagues showed oblate dopaminergic involvement in amylin signaling (30) and also provided evidence for involvement of histamine H1 receptors (33). Dopaminergic signaling in hypothalamic nuclei has also been implicated in the anorexia seen in tumor-bearing rats (37).

Time-dependent events contribute significantly to the regulation of body weight; these include cyclic (e.g., circannual) events as well as developmental or age-related changes. These studies provide insight into the long-term regulation of body weight. Thus short “winterlike” day length induces lipolysis in white adipose tissue that is mediated by direct sympathetic innervation of the fat pads and by epinephrine released from the adrenal medulla (15). Retrograde tracing of sympathetic fibers from these fat pads caused labeling of neurons in the suprachiasmatic nucleus that express melatonin receptors (40). Superimposition of acute food restriction on a long-term short-photoperiod regimen exposed differential regulation of the orexigenic agouti-related protein and NPY mRNA in the arcuate nucleus of the hypothalamus (32). Among other rodents, woodchucks maintained at constant ambient temperature, with variation only of photoperiod, displayed pronounced circannual variation of circulating leptin, body weight, and food intake (9). Body weight and particularly food intake appear to lead leptin levels, although interpretation is perhaps complicated by oblate torpor in this species. Rats also display photoperiod-dependent rates of weight gain and sexual maturation, and differences among strains suggest genetic heterogeneity (21). Lesioning experiments in sheep indicate the arcuate nucleus plays an obligate role in the generation of photoperiod-induced rhythms of food intake and body weight in that species (29).

It is well known that appetite is reduced in the elderly, although the mechanism(s) involved are not clear. A study by Blanton et al. (5) differentiates between aged and senescent rats in their response to intracerebroventricular NPY. In healthy aged rats (i.e., still gaining weight), NPY induced feeding that was not different from that seen in younger animals. In contrast, the senescent rats (i.e., during the terminal weight losing phase of life) had a markedly blunted eating response to NPY. At the other end of life, Truett et al. (41) studied weight gain by baby Zucker rats that were weaned naturally by their mothers. Up to 21 days of age, homozygous fatty rats (fa/fa) had very similar rates of weight gain as their lean (+/+) littermates. Hyperphagia and increased weight gain emerged only at 22–23 days of age, suggesting a developmental switch that enables the program that responds to leptin in older animals.

REFERENCES


