Peptides that regulate food intake

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In this issue of the Journal are published the first group of papers submitted to the Special Call for Papers on the subject "Peptides that Regulate Food Intake." These nine papers (7a, 32a, 37a, 37b, 41a, 42a, 43a, 46a, 49a) illustrate both the breadth and depth of the subject. They continue the contribution made by papers published in the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology toward understanding of the regulation of food intake and body weight. What are these peptides? How do they act? How do they interact among themselves and with other control systems? These are all important questions addressed by recent publications in this journal and highlighted below.

Leptin is secreted by adipocytes and signals fat content to neurons in the arcuate nucleus of the hypothalamus. Leptin inhibits release of the potent orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP), which are coexpressed in neurons of the arcuate nucleus of the hypothalamus. Leptin also increases release, from adjacent neurons, of anorexigenic α-melanocyte stimulating hormone (α-MSH) and cocaine-and amphetamine-regulated transcript (CART), which are also coexpressed (38). Food deprivation increases NPY and AgRP mRNA and decreases that of proopiomelanocortin (POMC) in the arcuate nucleus. These changes are largely reversed 6 h after refeeding (43), but not by leptin infusion or a palatable, noncaloric mash, indicating the importance of other postabsorptive factors (43). Zhang et al. (49) showed in several different fat depots of mice that leptin mRNA content varied directly with adipocyte volume, whereas messages for tumor necrosis factor-α, insulin receptor, and glucocorticoid receptor were all independent of cell volume. Obesity induced by feeding rodents a high-fat or high-energy diet is associated with leptin resistance; leptin becomes less effective at reducing food intake. The leptin resistance caused by changing from chow to a high-fat diet occurred rapidly and was apparent before any change of body composition could take place (26), suggesting that dietary fat, per se, can induce leptin resistance. Importantly, in rats maintained on chow, leptin sensitivity predicts the development of diet-induced obesity when the animals are subsequently placed on a high-energy diet (24). Rats with the lowest leptin sensitivity become most obese. Changes in circulating leptin can be of varying importance in different models of weight loss. For example, lactating sheep are in negative energy balance despite hyperphagia. Here the reduction of plasma leptin appears to be a primary signal for the hyperphagia (42). In contrast, the weight loss induced by acute stress, although associated with reduced circulating leptin, is unchanged when plasma leptin is clamped high (17). In addition to its effects on food intake, leptin also has significant metabolic actions. With the use of different strains of db/db mice having profound leptin resistance due to absence of the long form of the leptin receptor, it was possible to show some degree of metabolic signaling through short forms of the receptor (18). The same group showed with partial lipectomy experiments that leptin is not required for regulation of total body fat (16). A number of studies have explored other aspects of leptin’s function. Transduction of leptin signals in the arcuate nucleus proceeds through the JAK-STAT pathway (16). A number of studies have explored other aspects of leptin’s function. Transduction of leptin signals in the arcuate nucleus proceeds through the JAK-STAT pathway (16).
that rats with diet-induced obesity showed delayed and disordered changes in arcuate NPY mRNA when diet, body weight, and leptin were altered (24). In rats undergoing senescent weight loss, the ingestive response to intracerebroventricular NPY was markedly reduced (7). Another potentially related action of NPY is to delay gastric emptying, an action mediated by Y2 receptors (20). In female Syrian hamsters, NPY effects on eating (stimulation) and estrous behavior (inhibition) involve similar pathways but different NPY receptors (8).

AgRP acts as an antagonist at melanocortin-4 receptors and causes profound and prolonged hyperphagia; under some conditions the hyperphagia may be apparent for as long as 7 days after intracerebroventricular administration (15, 38, 50). Pharmacological characterization of the human agouti signaling peptide showed that, as expected, it behaves as a competitive antagonist of a-MSH and melanocortin receptors (48). As noted above, food deprivation in mice results in increased arcuate NPY and AgRP mRNA. The former was partially corrected 6 h after refeeding, whereas the latter was unaffected (43). The prolonged response clearly employs multiple signaling pathways. Thus simultaneous administration of the opioid antagonist naloxone blocks AgRP-induced hyperphagia, whereas naloxone given 24 h after AgRP does not block the established hyperphagia (15). Zheng et al. (50) used double labeling to map neurons that were activated 1 day after intracerebroventricular AgRP. In the lateral hypothalamus, orexin neurons, but not those expressing CART or melanin-concentrating hormone, showed increased c-Fos labeling. In the arcuate nucleus, CART, but not NPY, neurons showed increased c-Fos labeling.

One concern that arises repeatedly in the study of ingestive behavior is whether an experimentally induced anorectic response is related to regulation of energy input or whether it is due to development of a conditioned taste aversion. Olszewski et al. (32) showed that α-MSH neurons were activated (increased c-Fos immunoreactivity) during meal termination, but not by aversive agents. Nor did α-MSH activate oxytocin and vasopressin neurons in the paraventricular nucleus, as would be expected of an aversive agent. The melanocortin pathway plays a substantial role in several models of obesity in humans and other animals. Thus, in the obese Zucker rat, unlike its lean littermate, intracerebroventricular infusion of a melanocortin antagonist did not increase food intake (19). Conversely, a melanocortin agonist reduced food intake more potently in the obese rats. Expression of CART in arcuate neurons is reduced during negative energy balance (42) and increased, perhaps in counterregulatory fashion, during long-term hyperphagia due to AgRP injection (50). Injection of CART into the lateral ventricle resulted in reduced food intake in association with altered meal microstructure. These changes were interpreted in terms of altered oral motor function and, perhaps, of palatability perception (2). A subsequent study compared CART injections into third and fourth ventricles, without and with blockade of the aqueduct. The major anorectic effect occurred at a hindbrain site and again was associated with altered motor behavior (1).

Although the peptides discussed above can be considered to have control of food intake as their major or primary functions, such is not the case for orexins A and B (also known as hypocretins 1 and 2). These peptides are made by a small group of neurons in the perifornical region of the lateral hypothalamus that project widely throughout the brain. As exemplified by recent publications in this journal, they are involved in many physiological control systems. Patch-clamp studies revealed that orexins depolarized a high proportion of neurons in the paraventricular nucleus (41). Similarly in vitro data showed that orexin A, acting via the type 1 receptor on pituitary corticotrophs, altered CRH-stimulated secretion of ACTH (37). Intrathecal orexins increased blood pressure and heart rate, effects that were blocked by adrenergic α- and β-antagonists, respectively. The stimulation of sympathetic preganglionic neurons was shown to be postsynaptic (3). In dogs, sleep deprivation, but not food deprivation, increased orexin levels in cerebrospinal fluid. Interestingly, the strongest correlation was between orexin and activity during the awake period (47). Certainly the orexins are involved in integrative aspects of the regulation of food intake. Injection of urocortin into the lateral septum reduced feeding in food-deprived rats, an effect that was mediated partly by an orexin pathway (44). Similarly, activation of perifornical orexin neurons is a late response to intracerebroventricular injection of AgRP (50). Injection of orexin A into the shell region of nucleus accumbens failed to affect motor activity and ingestive behaviors, although injection of amylin, a satiety signal, into the same sites reduced motor activity, feeding, and drinking (4).

Both CRH and the closely related urocortin reduce food intake, and recent studies of their actions have illuminated the integrating nature of their actions. In baboons, as in rodents, intracerebroventricular CRH or urocortin reduced food intake, but did not affect water intake (39). Injection of urocortin into the paraventricular nucleus reduced feeding at doses that did not cause conditioned taste aversion (45). These injections also had peripheral metabolic consequences at 1 day after injection that were consistent with a role in regulation of energy balance (22). Subsequently, the lateral septum was shown to be an important site for urocortin’s anorectic action (44). Urocortin also acts peripherally to reduce food intake and part of the action involves delayed gastric emptying (46). Acute stress in rats was shown to result in a short-term hypophagia and a long-term reduction in the rate of weight gain (17). Undernutrition causes inhibition of estrous behavior in female Syrian hamsters, and this was shown to involve activation of CRH receptors as a final step (21). Similar to leptin, insulin conveys adi-
pository-related signals to the brain (11, 35, 38). Richardson et al. (35) demonstrated that intracerebroventricular insulin, in a dose that did not affect food intake, augmented the ability of CRH to reduce food intake. This result was interpreted to suggest a link between stress-related signals and adiposity-related signals.

Motivational, or reward, circuitry in the brain also plays a significant, although complex role in the regulation of food intake (11). Thus the anorectic response to the opioid antagonist naloxone was mediated in part by sensory properties of food (reward) and by the energy status of the organism (13). This group also provided evidence for an opioid feeding pathway from the nucleus of the solitary tract to the amygdala (12). Chronic interruption of this pathway by naltrexone did not alter NPY mRNA in the arcuate nucleus, but did increase circulating leptin compared with pair-fed controls. This illustrates the complex nature of opioid regulation of food intake because naloxone blocked the hyperphagia induced by intracerebroventricular AgRP, although only when given simultaneously (15). Also, naloxone inhibited redevelopement, after a period of abstinence, of preference for a high-sucrose diet, but did not affect that preference if the high-sucrose diet were present throughout the protocol (25).

All the peptides discussed above are central; they are made and act primarily within the central nervous system. Other relevant peptides are primarily peripheral; examples include amylin, CCK, and ghrelin. Amylin and CCK function as satiety signals to terminate meals, whereas ghrelin has among its actions the stimulation of food intake. The satiety signaling effect of CCK was confirmed in humans; treatment with a CCK type A receptor antagonist increased caloric intake and sensation of hunger (5). This response displays plasticity as chronic CCK infusion, as would be seen with a high-fat or high-protein diet, results in reduced sensitivity of the response (9). Antagonist studies in rats provided evidence that CCK is important to postprandial sleeping (40). Signaling by CCK involves vagal pathways that activate neurons in several brain areas (10, 14). Neuron activation (c-Fos immunoreactivity) was greater in estradiol-treated ovariectomized rats, suggesting that estradiol increased processing of the vagal CCK signal (10). CCK signaling does not involve histamine H1 receptors (30). Amylin is a pancreatic peptide, secreted with insulin, that has actions similar to those of CCK. Both reduce gastric emptying and food intake with ED₅₀ values consistent with postprandial values (33). Dose-response curves for related peptides (calcitonin, calcitonin gene-related peptide, adrenomedullin) show them to be much less effective (34). Several central sites of amylin signaling were reported including the amygdala (4) and area postrema (36). Both dopaminergic (27) and histaminergic (30) receptors have been implicated in processing of amylin signals. Nagaya et al. (31) demonstrated that ghrelin effectively stimulates growth hormone release in humans as in other mammals. They also showed a substantial vasodepressor response to ghrelin that was associated with elevated cardiac output. On the basis of RT-PCR examination of rat tissues they proposed cardiovascular actions of ghrelin that are independent of growth hormone.

REFERENCES


