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Hormonal Regulation of Food Intake

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Stanley, Sarah, Katie Wynne, Barbara McGowan, and Stephen Bloom. Hormonal Regulation of Food Intake. *Physiol Rev* 85: 1131–1158, 2005; doi:10.1152/physrev.00015.2004.—Our knowledge of the physiological systems controlling energy homeostasis has increased dramatically over the last decade. The roles of peripheral signals from adipose tissue, pancreas, and the gastrointestinal tract reflecting short- and long-term nutritional status are now being described. Such signals influence central circuits in the hypothalamus, brain stem, and limbic system to modulate neuropeptide release and hence food intake and energy expenditure. This review discusses the peripheral hormones and central neuronal pathways that contribute to control of appetite.

I. INTRODUCTION

The brain regulates energy homeostasis in response to signals from both adipose tissue and the gastrointestinal tract. The drive to eat and energy expenditure are adjusted so that over time, body weight remains stable.

Over the past decade, our knowledge of this homeostatic system has increased dramatically. Important advances have been made in the characterization of hypothalamic neuronal networks and neuropeptide transmitters, along with the discovery of circulating peptides that send signals to the brain regarding the body's nutritional status (see Fig. 1).

Disorders of this essential homeostatic mechanism lead to obesity and its associated complications. Currently, the prevalence of obesity is increasing unabated, bringing with it significant morbidity and mortality. The understanding of the physiological systems regulating food intake and body weight is fundamental to establishing effective therapies for this world-wide epidemic.

II. PERIPHERAL REGULATORS OF APPETITE

A. Adipose Tissue Hormones

1. Leptin

Although originally thought to be inert tissue solely for the storage of energy, it has now become clear that adipose tissue is an active endocrine organ. One of its most important hormones is leptin, a peptide hormone with numerous actions, including influences on energy homeostasis and neuroendocrine and immune function. Leptin is the product of the *ob* gene expressed predominantly in adipocytes (458) but also at lower levels in gastric epithelium (23) and placenta (267). Circulating leptin levels reflect both energy stores and acute energy balance. Plasma leptin levels are highly correlated with adipose tissue mass (258), but food restriction results in suppression of circulating leptin (143, 258), which can be reversed by refeeding or insulin administration. Exogenous leptin administration, both centrally and peripherally, reduces spontaneous and fasting-induced hyperpha-

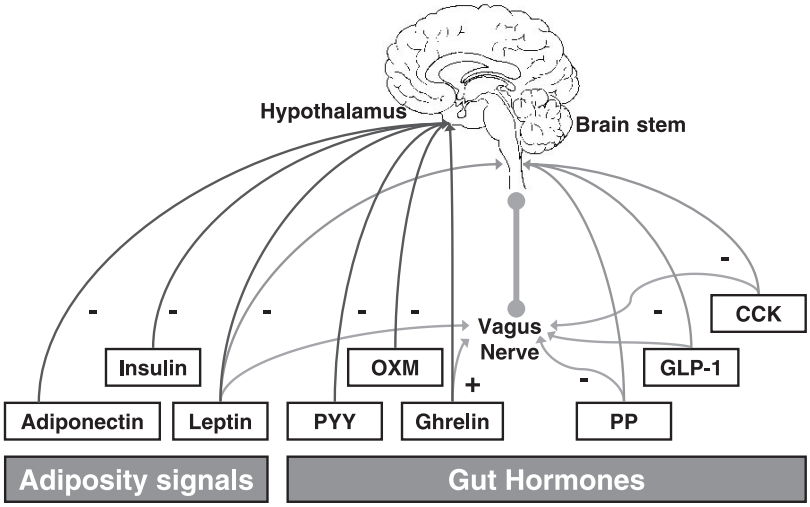

FIG. 1. Energy homoestasis is controlled by peripheral signals from adipose tissue, pancreas, and the gastrointestinal tract. Peripheral signals from the gut include peptide YY (PYY), oxyntomodulin (OXM), ghrelin, pancreatic polypeptide (PP), glucagon-like peptide 1 (GLP-1), and cholecystokinin (CCK). These gut-derived peptides and adiposity signals influence central circuits in the hypothalamus and brain stem to produce a negative (−) or positive (+) effect on energy balance. Thus the drive to eat and energy expenditure are adjusted so that over time, body weight remains stable.

gia (7) whilst chronic peripheral administration reduces food intake resulting in loss of fat mass and body weight (168).

Leptin signals via a single-transmembrane domain receptor of the cytokine receptor family (394). Alternative mRNA splicing and posttranslational processing result in multiple isoforms of the receptor (Ob-R) (75, 393). The alternate splice variants of the receptor may be classified into three forms: long, short, and secreted (150, 393). The long form, Ob-Rb, receptor possesses a long intracellular domain that binds to JAK-kinases (238) and to STAT 3 transcription factors (411) resulting in signal transduction and leptin's effects on food intake (238). Activation of the JAK-STAT pathway induces expression of suppressor of cytokine signaling-3 (SOCS-3), one of a family of cytokine-inducible inhibitors of signaling. SOCS-3 expression is upregulated by leptin in hypothalamic nuclei expressing the Ob-Rb receptor. Overexpression of SOCS-3 blocks leptin's actions on a reporter gene construct in vitro and, therefore, obesity-related leptin resistance has been postulated to be a consequence of increased or excessive SOCS-3 expression. Consistent with this hypothesis, neuron-specific conditional deletion of SOCS-3 in mice results in resistance to diet-induced obesity (291). Similarly, mice heterozygous for global SOCS-3 deficiency are resistant to weight gain and more sensitive to the weight-reducing effect of exogenous leptin administration (193). Thus suppression of SOCS-3 expression may be a potential treatment of leptin-resistant obesity.

Circulating leptin crosses the blood brain barrier (BBB) via a saturable process (28), and it has been proposed the short forms of the receptor play a role in this transport of leptin (121). The secreted (or soluble) form of the leptin receptor is thought to bind circulating leptin, thus modulating its biological availability and hence activity (150).

The long form of the leptin receptor, Ob-Rb, is expressed widely within the hypothalamus but is found particularly in the arcuate nucleus (ARC), ventromedial and dorsomedial hypothalamus (VMH and DMH, respectively), lateral hypothalamic area (LHA) and medial preoptic area (MPOA) (128, 135, 167). Ob-Rb are also expressed in appetite-modulating pathways in the brain stem (277). Peripheral leptin administration alters neuronal activity in these hypothalamic and brain stem regions (127). In the ARC, Ob-Rb mRNA is expressed by the two major neuronal groups: neurons expressing the orexigenic neuropeptides neuropeptide Y (NPY) and agouti related peptide (AgRP) (276) and also by neurons expressing proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) (73). Leptin inhibits the activity of orexigenic NPY/AgRP neurons and reduces expression of NPY and AgRP (122, 166, 357, 379) whilst leptin activates anorectic POMC/CART neurons. Thus, in conditions of low circulating leptin, such as food restriction, NPY and AgRP expression are upregulated and the orexigenic NPY/AgRP neurons are activated, while in times of plenty, with high plasma leptin, the anorectic pathways mediated by POMC and CART are switched on. Although Ob-Rb are expressed in many hypothalamic nuclei, the actions of leptin may differ between these hypothalamic regions. With the use of viral-mediated gene expression, chronic leptin overexpression in the ARC, PVN, and VMH resulted in reduced food intake and energy expenditure. However, leptin overexpression in the MPOA did not alter food intake but did reduce energy expenditure (25).

The absence of leptin has profound effects on body weight. Lack of circulating leptin, due to a mutation in the *ob* gene, leads to hyperphagia, obesity, as well as neuroendocrine and immune disturbance in the *ob*/*ob* mouse, which can be normalized by leptin administration (64,

168, 318). Similarly, human leptin deficiency in both children and adults causes severe obesity and hypogonadism (284, 382), which can be ameliorated by recombinant leptin therapy (132, 246). In addition to its effects on food intake, leptin also modulates energy expenditure in rodents (though not in humans); the hypothalamo-pituitary control of the gonadal, adrenal, and thyroid axes (7, 67); and the immune response (251). Thus the body's response to a decrease in energy stores appears to be integrated by reduced circulating leptin. Similarly, defective leptin receptor signaling also alters body weight and endocrine function. A point mutation in the intracellular domain of the Ob-Rb receptor that prevents signaling results in obesity in *db*/*db* mice (69, 238). Defects in the human leptin receptor have also been described. As with leptin deficiency, these individuals have hypogonadism and early-onset morbid obesity, although, interestingly, the obesity is less severe than that seen in individuals with absent plasma leptin (78).

A small proportion of obese human subjects have an absolute or relative leptin deficiency, but the majority of obese animals and humans have raised plasma leptin (87, 258). This suggests resistance to leptin's actions, and indeed, subcutaneous administration of recombinant leptin to obese humans has only a modest effect on weight (142, 183). Leptin resistance appears to be the combination of several factors, both impaired transport across the BBB and signaling defects in leptin-responsive neurons. Peripheral leptin administration to rodents with diet-induced obesity fails to reduce food intake (415). Although these rodents respond to central leptin administration, hypothalamic STAT3 activation following intracerebroventricular leptin is reduced in animals with diet-induced obesity (121). Continuous central leptin infusion has a biphasic action on hypothalamic NPY expression. As expected, there is an initial suppression of NPY mRNA levels by leptin administration but with continued leptin infusion, NPY expression returns to levels seen in control animals (338). Leptin resistance may be a consequence of obesity, but reduced sensitivity to leptin may contribute to the etiology of obesity. Lack of sensitivity to the anorectic actions of central leptin administration can predict the later development of obesity in rodents on a high-energy diet (244). Furthermore, a high-fat diet itself, before changes in body composition, may induce leptin resistance, since rodents placed on a high-fat diet have an attenuated response to leptin administration even before weight gain (250).

Thus, although leptin deficiency has profound effects on food intake, body weight, and endocrine function, the high leptin levels found in obese individuals are much less effective at reversing weight gain. Thus leptin's primary role may be as a hormone of starvation rather than one of plenty.

2. Adiponectin

Adiponectin, also called adipocyte complement-related protein (Acrp30), apM1 or adipoQ, is a 244-amino acid protein secreted from adipose tissue. Its circulating levels are up to 1,000-fold higher than other circulating hormones such as leptin and insulin (401). Adiponectin has four domains: a cleaved amino-terminal signal sequence, a region with no homology to other known proteins, a collagen-like region, and a carboxy-terminal globular domain. The globular domain forms homotrimers, and additional interactions with collagenous segments cause the formation of higher molecular weight complexes (315). The globular domain shares a sequence homology with several proteins, including the complement factor protein C1q and tumor necrosis factor-α (TNF-α).

The function of adiponectin is largely unknown but is postulated to regulate energy homeostasis (353). The plasma concentration of adiponectin is inversely correlated with adiposity in rodents, primates, and humans (16, 192, 194). Adiponectin is significantly increased after food restriction in rodents (39) and after weight loss induced by a calorie-restricted diet (191) or gastric partition surgery in obese humans (449). Peripheral administration of adiponectin to rodents has been shown to attenuate body weight gain, by increased oxygen consumption, without affecting food intake (39, 145, 448). The effect of peripheral adiponectin on energy expenditure seems to be mediated by the hypothalamus, since adiponectin induces early gene c-*fos* expression in the PVN and may involve the melanocortin system (325). It is perhaps counterintuitive for a factor that increases energy expenditure to increase following weight loss; however, reduced adiponectin could perhaps contribute to the pathogenesis of obesity.

Studies show that plasma adiponectin levels negatively correlate with insulin resistance (192), and treatment with adiponectin can reduce body weight gain, increase insulin sensitivity, and decrease lipid levels in rodents (39, 325, 448). Adiponectin knock-out mice demonstrate severe diet-induced insulin resistance (256) and a propensity toward atherogenesis in response to intimal injury (224). Thus adiponectin, as well as increasing energy expenditure, may also provide protection against insulin resistance and atherogenesis.

The mechanism by which adiponectin improves insulin resistance, glucose metabolism, and attenuation of weight gain is not yet fully understood, although some of these effects may be mediated through metabolic pathways that include regulation of food intake, gluconeogenesis, and lipogenesis (368). Of interest, peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, the thiazolidinediones, can increase circulating adiponectin levels in both rodent models of obesity (83) and in

patients with obesity/type II diabetes mellitus (257). Indeed, chronic transgenic expression of adiponectin causes effects that are similar to those of chronic treatment with thiazolidinediones, suggesting that part of the insulin-sensitizing effects of thiazolidinediones may be mediated by an increase in adiponectin levels (82).

Recently, two distinct adiponectin receptors have been cloned (447). The first, adipoR1, is highly expressed in skeletal muscle, has a high affinity for the globular domain of Acrp30 (gAcrp30), and a has low affinity for the full-length ligand. The second, adipoR2, is highly expressed in the liver and shows preferential binding to the full-length ligand. This is consistent with earlier reports that show a differential effect of gAcrp30 and the full-length ligand in muscle and liver. Adiponectin receptors have also been detected in the brain, and more specifically in the hypothalamus (325).

3. Resistin

Resistin is produced by adipose tissue and appears to increase insulin resistance. Circulating resistin is increased in obese rodents (380) and falls after weight loss in humans (412). Recent studies suggest that resistin knockout mice show increased glucose tolerance with a high-fat diet (385). Transgenic mice overexpressing a dominant negative form of resistin show increased adiposity with elevated leptin and adiponectin levels, as well as enhanced glucose tolerance and insulin sensitivity (385). Although resistin may contribute to the development of insulin resistance and diabetes in obesity (380), its role in the pathogenesis of obesity remains to be defined.

B. Pancreatic Hormones

1. Insulin

The pancreatic hormone insulin was one of the first adiposity signals to be described (358) and, like leptin, is positively correlated with long-term energy balance (24, 437). Plasma insulin concentrations depend on peripheral insulin sensitivity, which is related to both total body fat stores and fat distribution, with visceral fat being a key determinant (324). However, unlike leptin levels, which are relatively insensitive to acute food intake, insulin secretion increases rapidly after a meal (323).

There is considerable evidence that insulin acts as an anorectic signal within the central nervous system (CNS). Centrally administered insulin or an insulin mimetic decreases food intake and body weight (8) and alters expression of hypothalamic genes known to regulate food intake. Insulin infusion into the third cerebral ventricle in rodents (198) or lateral ventricle in primates (438) dose-dependently decreases food intake resulting in weight loss over a period of weeks. Intrahypothalamic (PVN) insulin injection also decreases food intake and weight gain in rats (275). Treatment with novel, orally available insulin mimetics also decreases weight gain, adiposity, and insulin resistance in mice on a high-fat diet (8). Conversely, antibodies to insulin injected into the VMH of rats stimulate food intake (383), and repeated administration of antiserum increases food intake and rate of weight gain (270). Administration of antisense RNA against the insulin receptor precursor protein results in hyperphagia and increased fat mass (309). Similarly, neuron-specific deletion of the insulin receptor results in obesity, hyperinsulinemia, and dyslipidemia in male mice (56).

Insulin enters the CNS via saturable, receptor-mediated uptake across the BBB at levels proportional to circulating insulin concentrations (34). Little or no insulin is synthesized within the brain (27, 439). Therefore, peripheral insulin should have actions similar to central insulin administration. Studies of systemic insulin administration are complicated by hypoglycemia, which in itself potently stimulates food intake, but hyperinsulinemic, euglycemic clamp studies have indeed shown a reduction in food intake in both rodents and baboons (305, 440).

Insulin signals via a cell-surface insulin receptor, which is composed of an extracellular, ligand binding α-subunit and an intracellular β-subunit with intrinsic tyrosine kinase activity. There are two splice variants of the insulin receptor: subtype A with greater affinity for insulin and widespread expression and subtype B with lower affinity and expression in classical insulin-responsive tissues such as fat, muscle, and liver. Insulin receptors are widely distributed in the brain, particularly in hypothalamic nuclei involved in food intake (ARC, DMH, PVN, suprachiasmatic and periventricular regions) (88, 263). Insulin receptor activation is via several insulin receptor substrates (IRSs), which include IRS-1 and IRS-2 (30, 58). Although IRS-1 null mice show no differences in food intake or body weight from their wild-type littermates (14), IRS-2 null mice have increased food intake, increased fat stores and infertility (58). IRS-2 mRNA is highly expressed in the ARC, and therefore, insulin's central actions may be mediated by IRS-2 (58). Insulin and leptin, along with other cytokines, appear to share common intracellular signaling pathways. Both may signal via IRS and the enzyme phosphatidylinositol (PI) 3-kinase (306, 324), allowing intracellular integration of their appetite-regulating actions.

The pathways mediating insulin's effects on food intake remain to be fully elucidated. Hypothalamic NPY may be an effector of insulin's actions. Intracerebroventricular insulin administration prevented the fasting-induced increase in NPY mRNA expression in the PVN and ARC in rats (360). NPY expression is also increased in insulin-deficient, streptozotocin-treated rats but restored by insulin replacement (428, 435). The melanocortin sys-

tem has also been implicated as a mediator of insulin's central actions. Insulin receptors are present on arcuate POMC neurons (37), and third ventricle administration of insulin increases POMC mRNA expression (37). Insulin's anorectic actions are blocked by a melanocortin antagonist (37). Furthermore, POMC expression is greatly reduced in rats with untreated diabetes and partly restored by peripheral insulin treatment (371). Therefore, it is likely that both the NPY and melanocortin systems are important downstream mediators of insulin's actions on food intake and body weight.

2. Pancreatic polypeptide

Pancreatic polypeptide (PP) is a member of the PP-fold family of peptides which also includes peptide YY (PYY) and NPY. They have significant sequence homology including several tyrosine residues (85). They share a common tertiary structure, an α-helix and polyproline helix, connected by a β-turn to produce a characteristic U-shape, the PP-fold (157).

PP is primarily produced by cells at the periphery of the islets of Langerhans but is also secreted by the exocrine pancreas and distal gastrointestinal tract (233). Plasma PP concentrations show diurnal variation, with lowest levels in the early hours of the morning and highest in the evening (400). In addition to this, circulating PP concentrations rise following food intake and remain elevated for ~6 h (4). Postprandial release is biphasic, and although total release is proportional to caloric intake, the contribution of the first phase increases with consecutive meals (400). Circulating PP levels are also elevated by ghrelin, motilin, and secretin and by gastric distension (18, 74, 281, 319) and reduced by somatostatin administration (316). Plasma PP concentrations have been suggested to be inversely proportional to adiposity, with elevated levels in anorexic subjects (147, 408) and both reduced levels (155, 234) and attenuated second phase release in obese subjects (234). Subjects with obesity due to Prader-Willi syndrome have reduced basal and blunted postprandial PP release, which may contribute to their hyperphagia and obesity (460, 461). However, others report no difference in plasma PP concentrations between lean and obese subjects (436) or following weight loss in obese subjects (278).

The actions of PP on food intake depend on the route of administration. Peripheral PP administration decreases food intake, reduces body weight and energy expenditure, and improves insulin resistance and dyslipidemia in obese rodents (20, 261). In keeping with this, mice overexpressing PP have a lean phenotype and reduced food intake compared with wild-type littermates (407). However, the efficacy of PP may be diminished in obesity as obese rodents appear less sensitive to its anorectic actions than normal weight rodents (271). Peripheral PP is also effective in humans. Peripheral PP infusion reduces food intake by 25% over 24 h in normal-weight human volunteers (33) and twice daily PP infusion in Prader-Willi syndrome reduced food intake by 12% (42). However, its efficacy in nonsyndromic obesity remains to be investigated.

The PP-fold peptides bind to a family of seven transmembrane domain, G protein-coupled receptors, Y_1-Y_5 receptors (231). The receptors are classified according to their affinity for PP, NPY, and PYY. PP binds with greatest affinity to Y_4 and Y_5 receptors (231). Circulating PP is unable to cross the BBB but may exert its anorectic effect via the area postrema, which lacks a complete BBB (427). PP may also influence appetite via the vagal pathway to the brain stem, as its anorectic actions are reduced following vagotomy (20). The receptor mediating PP's peripheral effects on appetite are not yet fully elucidated, but there is evidence to suggest they may be mediated by the Y_5 receptor. Y_5 receptor knockout mice do not respond to peripheral PP administration; however, Y_5 receptor antisense oligonucleotides do not inhibit the anorectic effect of PP (207). Peripheral PP administration reduces gastric ghrelin mRNA expression, which may be responsible for the reduction in hyperphagia in Prader-Willi Syndrome (20). In addition, hypothalamic NPY and orexin mRNA expression is significantly reduced by peripheral PP (20). Thus PP sends anorectic signals via brain stem pathways, regulation of hypothalamic neuropeptides, and by modulating expression of other gut hormones.

In contrast to the peripheral actions of PP, PP administered into the third ventricle increases food intake (76). However, the receptors mediating this action and the mechanisms involved are unclear.

C. Gut Hormones

1. PYY

PYY is released from the L cells of the gastrointestinal tract, with increasing tissue concentrations found in the more distal portions, the ileum, colon, and rectum (5, 120). PYY release is correlated with calorie intake, with levels rising to a plateau 1–2 h after a meal and remaining elevated for 6 h (5). Interestingly, the increase in plasma PYY concentrations is seen rapidly after food intake, well before nutrients are in contact with the L cells of the distal intestine. This suggests initial PYY release may be the consequence of a neural reflex though direct contact with nutrients may play a role later (146). Macronutrient composition of food, in addition to total calories, influences circulating PYY concentrations: isocaloric intake of fat elicits a greater rise in plasma PYY than consumption of protein or carbohydrate (249). Circulating PYY levels are also influenced by other signals; gastric acid, cholecystokinin and luminal bile salts, insulin-like growth fac-

tor I, bombesin, and calcitonin-gene related peptide increase PYY levels, whereas levels are reduced by glucagon-like peptide (GLP)-1. Unlike PP, gastric distension has no effect (239, 301, 317).

PYY in the circulation exists in two major forms: $PYY_{1–36}$ and $PYY_{3–36}$ (158). $PYY_{3–36}$ binds with greatest affinity at the presynaptic autoinhibitory Y_2 receptor and is thus a potent, peripherally active anorectic signal. It is the product of cleavage of the amino terminus Tyr-Pro residues by dipeptidyl peptidase IV (DPP-IV) from $PYY_{1–36}$ (116). DPP-IV is involved in the cleavage of multiple hormones including products of the proglucagon gene (48). However, the accurate proportions of $PYY_{1–36}$ and $PYY_{3–36}$ in the circulation in fasting and following food intake remain to be determined.

Peripheral administration of PYY has numerous actions. It delays gastric emptying, delays pancreatic and gastric secretions, and increases ileal absorption of fluids and electrolytes (6, 9, 185). Peripheral $PYY_{3–36}$ administration also inhibits food intake and reduces weight gain in mice, rats, and primates (32, 66, 290) and improves glycemic control in rodent models of diabetes (322). $PYY_{3–36}$ is also effective in reducing food intake in humans. Intravenous administration of $PYY_{3–36}$ reduced food intake by 30% and also reduced subjective hunger in normal-weight human subjects (31, 32). Interestingly, this effect is seen for up to 12 h after the $PYY_{3–36}$ infusion has finished and long after circulating $PYY_{3–36}$ has returned to basal levels (32). These data suggest $PYY_{3–36}$ may be a physiologically important postprandial satiety signal.

Unlike PP, PYY is able to cross the BBB by transmembrane diffusion from the circulation (307). Evidence suggests the anorectic effect of peripheral $PYY_{3–36}$ may be mediated via the presynaptic inhibitory Y_2 receptor present on arcuate NPY neurons (54). $PYY_{3–36}$ inhibits activity of over 90% of all arcuate neurons and reverses fasting-induced c-*fos* expression in the arcuate nucleus (334). In particular, PYY inhibits NPY neurons (32) and reduces hypothalamic NPY mRNA expression (32, 66). Moreover, the anorectic effect of $PYY_{3–36}$ is absent in Y_2 receptor knockout mice and diminished by a selective Y_2 antagonist (32). Reduction in NPY neuronal activity also increases activation of arcuate neurons expressing POMC, which may contribute to reduced food intake.

Although peripheral $PYY_{3–36}$ administration induces expression of the early gene, c-*fos*, in POMC neurons (32, 169) and increases arcuate POMC mRNA expression (66), the melanocortin system does not appear to be vital for PYY's effects on appetite. $PYY_{3–36}$ is equally effective at reducing food intake in MC4R knockout mice (169) and POMC null mice (65). There is some evidence to suggest a role for CART in mediating the effect of $PYY_{3–36}$ on appetite (80). However, peripheral administration of $PYY_{3–36}$ also reduces plasma ghrelin levels (31), which may contribute to its anorectic effect. However, the anorectic effect of $PYY_{3–36}$ does appear to depend on minimization of environmental stress (169) and therefore some have found its actions difficult to reproduce (402). Both stress and $PYY_{3–36}$ act via the arcuate nucleus to alter food intake (86, 260). When appetite is inhibited by stress, no further inhibition can occur with $PYY_{3–36}$ administration. Because rodents are easily stressed, inappropriate experimental conditions would mask the anorectic effect of $PYY_{3–36}$ leading to the variability reported.

The role of PYY in regulation of body weight is less clear. In rodents, chronic peripheral administration of $PYY_{3–36}$ reduced weight gain (32). Obese humans have reduced plasma PYY levels and a relative deficiency of postprandial secretion (243), which might contribute to the maintenance of their obesity. However, obese subjects remain sensitive to the anorectic actions of exogenous $PYY_{3–36}$ administration. In addition, vertical banded gastroplasty (11) or jejunoileal bypass surgery (302) raises plasma PYY levels in obese patients, and this may contribute to their appetite loss. Thus long-term administration of $PYY_{3–36}$ has the potential to be an effective obesity therapy.

In contrast to peripheral $PYY_{3–36}$, centrally administered $PYY_{1–36}$ and $PYY_{3–36}$ increase food intake. PYY injection into the third, lateral or fourth cerebral ventricles (77, 89), the PVN (376), or the hippocampus (163) potently stimulates food intake in rodents. However, this effect is reduced in both Y_1 and Y_5 receptor knockout mice (205). Therefore, while circulating $PYY_{3–36}$ may access the higher affinity ARC Y2 receptors (32), the central feeding effects of $PYY_{1–36}$ and $PYY_{3–36}$ may be mediated by the lower affinity Y_1 and Y_5 receptors.

2. Ghrelin

Ghrelin is the endogenous agonist of the growth hormone secretagogue receptor (GHS-R) and a potent orexigenic factor. It is produced and released primarily by the gastric oxyntic cells; however, total gastrectomy only reduces plasma ghrelin by 50–60%. The remaining circulating ghrelin is released by the duodenum, ileum, cecum, and colon (103, 342). Ghrelin is a 28-amino acid peptide with addition of an acyl side chain, *n*-octanoic acid, to the third serine residue. This octanoylation is essential for binding to the GHS-R type 1a and for ghrelin's effects on food intake (219).

Plasma ghrelin levels are regulated both by an endogenous diurnal rhythm and by food intake. In rats, ghrelin peaks at the end of the light and dark periods (296). In humans, ghrelin levels are in phase with the diurnal variation in leptin, which is high in the morning and low at night (98). In humans with fixed meal times, plasma ghrelin is greatest during fasting and falls after food intake (17, 98, 404). The postprandial reduction in circulating ghrelin is regulated both by calorie intake and circulating

nutritional signals, such as glucose (342, 403). In rodents, plasma ghrelin and gastric ghrelin mRNA fall after ingestion of either fat or carbohydrate. However, the suppression observed after fat intake is transient and has returned to normal after 45 min, unlike the longer lasting fall after carbohydrate consumption (345). Interestingly, plasma ghrelin levels do not fall after ingestion of water, suggesting gastric distension does not inhibit ghrelin release (403). Energy stores also regulate ghrelin. Circulating ghrelin is inversely correlated with adiposity. Thus anorectic subjects have high plasma ghrelin, which normalizes after weight gain (314). Conversely, obese individuals have reduced plasma ghrelin, which rises to normal after diet-induced weight loss (99, 172). Obese subjects appear to have altered postprandial regulation of ghrelin; they do not show the rapid postprandial fall in circulating ghrelin, and this in turn may play a role in continued food intake and obesity (130). The contribution of ghrelin gene polymorphisms to obesity remains controversial (184, 419). Although there are reports of polymorphisms associated with early-onset obesity (220, 280), other polymorphisms have been found to be protective against fat accumulation (409).

An increase in circulating ghrelin levels may occur as a consequence of the anticipation of food, or may have a physiological role to initiate feeding. Peripheral or central ghrelin administration increases food intake and body weight and reduces fat utilization in rodents (403, 442). Furthermore, blockade of ghrelin's actions by central infusion of anti-ghrelin antibodies attenuates fasting-induced refeeding, suggesting ghrelin is an endogenous regulator of food intake (298). Ghrelin also increases food intake in humans. Intravenous ghrelin increased food intake by 28% in healthy subjects (441). In addition, rising preprandial plasma ghrelin levels correlate with hunger scores in humans eating spontaneously (97). The severe hyperphagia in subjects with Prader-Willi syndrome is associated with markedly elevated circulating ghrelin, in contrast to most obese individuals who have suppressed plasma ghrelin (96). Bariatric surgery reduces plasma ghrelin despite weight loss, and this may contribute to the appetite suppression and continued weight loss following this treatment (99). However, Callahan et al. (62) did not demonstrate any correlation between ghrelin levels and spontaneous eating in humans. Similarly, altering the feeding schedule in sheep modulates the timing of ghrelin peaks (384). These data suggest the preprandial rise in ghrelin may be a conditioned response possibly to prepare the metabolism for an influx of calories.

Ghrelin's actions on food intake are thought to be mediated via the growth hormone secretagogue receptor (GHS-R) type 1a. Ghrelin administration does not increase food intake in GHS-R type 1a null mice (70, 387). Ghrelin also increases growth hormone (GH) release via this receptor in the hypothalamus (104, 219, 403, 443). However, the orexigenic action of ghrelin is seen in GH-deficient mice and therefore independent of its GH releasing effects (366, 390, 403). GHS-R type 1a is expressed in numerous tissues: hypothalamus, pituitary, myocardium, stomach, small intestine, pancreas, colon, adipose tissue, liver, kidney, placenta, and peripheral T cells (103, 106, 160, 176, 297). There are studies describing ghrelin analogs that show dissociation between the feeding effects and stimulation of GH, suggesting GHS-R type 1a may not be the only receptor mediating the effects of ghrelin on food intake (398).

Ghrelin's actions on food intake are probably via the ARC nucleus of the hypothalamus. Peripheral ghrelin administration increases c-*fos* in ARC NPY neurons (420), and ghrelin fails to increase food intake following ablation of the ARC (390) or in knock-out mice lacking both NPY and AgRP signaling (70). However, the brain stem may also mediate ghrelin's actions, since GHS-R are expressed on the vagus nerve (105) and ghrelin administration increases c-*fos* in the nucleus of the solitary tract (NTS) and area postrema (237, 298).

Although the majority of ghrelin is synthesized in the periphery, ghrelin is also expressed centrally. Ghrelin immunoreactive neurons are found adjacent to the third ventricle and lie between the DMN, VMH, PVN, and ARC. These ghrelin neurons have terminals on hypothalamic NPY/AgRP, POMC, and corticotrophin-releasing hormone (CRH) neurons and may activate ARC NPY neurons to form a central circuit regulating energy homeostasis (93). In addition, the hypothalamic ghrelin neurons also terminate in the LHA on neurons expressing orexin (399). Central ghrelin administration stimulates orexin-expressing neurons (237, 399), and central ghrelin-stimulated food intake is attenuated after administration of anti-orexin antibody and in orexin null mice (399). However, the physiological roles of peripheral and central ghrelin remain to be fully elucidated.

Although ghrelin has potent actions on food intake in animals and humans, both ghrelin null mice and mice lacking GHS-R type 1a have normal appetite and body composition on a standard diet (70, 386, 387). This absence of phenotype suggests that long-term ghrelin blockade may not alter body weight, and ghrelin receptor antagonists may not be an effective therapy for obesity.

3. GLP-1

The preproglucagon gene product is widely expressed in the L cells of the small intestine, in the pancreas, and in the brain stem NTS (392). Tissue-specific cleavage of proglucagon by the enzymes prohormone convertase 1 and 2 results in different products (186). Glucagon is the major product in the pancreas, whereas in the CNS and intestine, the major products are GLP-1 and GLP-2 and oxyntomodulin (OXM).

GLP-1 is released by the L cells of the small intestine following nutrient ingestion (180), and circulating GLP-1 levels are inversely correlated with body mass (188, 300, 328, 417). GLP-1 acts to inhibit food intake. Acute GLP-1 injection into the third or fourth ventricles or into the PVN reduces calorie intake (406), and chronic central administration decreases weight gain in rodents (273). Peripheral injection also reduces food intake and activates c-*fos* in the brain stem (392, 445). Thus peripheral GLP-1 may influence energy homeostasis via the brain stem. In humans, GLP-1 dose-dependently decreases food intake (416). However, when the infusions mimic postprandial concentrations, the effect is small (139, 417). Despite reported reduced GLP-1 levels in obesity, obese subjects remain sensitive to the anorectic actions of GLP-1 (416). Preprandial subcutaneous GLP-1 injection reduced calorie intake by 15% and resulted in 0.5 kg weight loss over 5 days in obese individuals (299). Therefore, low circulating GLP-1 could contribute to the pathogenesis and maintenance of obesity, and GLP-1 replacement could restore satiety.

GLP-1 is a powerful incretin hormone, potentiating all stages of insulin biosynthesis (221, 255). Both short-term intravenous GLP-1 infusion (303) and 6-wk subcutaneous GLP-1 infusion (454) are effective at normalizing blood glucose in poorly controlled type 2 diabetes. Although not a primary end point, subcutaneous infusion also reduced body weight by 2 kg over the 6-wk period (454). However, GLP-1 has been reported to result in hypoglycemia in nondiabetic subjects (397), which may limit its usefulness as an obesity therapy. In addition, GLP-1's use as an obesity treatment may be hampered by its very short half-life, as it is rapidly broken down by the enzyme DPP-IV. However, albumin-bound GLP-1, which is resistant to DPP-IV, the GLP-1 receptor agonist exendin-4 (a naturally occurring peptide from the lizard *Heloderma*), and DPP-IV inhibitors are currently being developed as therapies for diabetes and may also have useful roles in obesity treatment (see review in Ref. 187).

4. Oxyntomodulin

OXM is released in proportion to calorie intake from the L cells of the small intestine (151, 242). Its release also shows diurnal variation with peak levels in the evening and a nadir in the early morning (242). Both central and peripheral OXM administration acutely reduce food intake in rodents (100, 101), and repeated administration reduces body weight gain and adiposity (101, 102). In addition, OXM-treated animals lose more weight than animals eating the same amount, suggesting increased energy expenditure possibly via an effect on the thyroid axis (102). OXM also reduces hunger and food intake (by 19.3%) in healthy human volunteers, an effect which continues for 12 h postinfusion (79). Conditions such as tropical sprue (44) and jejunoileal bypass surgery (189, 348), which are associated with reduced appetite and intake, also result in elevated circulating OXM. Thus OXM may play a physiological role in regulation of energy balance.

The actions of both GLP-1 and OXM on food intake may be mediated by the GLP-1 receptor. GLP-1 receptors are expressed in the hypothalamus and NTS (369, 410) and are also widespread in the periphery: gastrointestinal tract, pancreas, lung, kidney, and heart (57, 424). Central administration of the GLP-1 receptor antagonist exendin-(9—39) inhibits the anorectic effects of both GLP-1 and OXM (100, 406). However, there is some evidence to suggest the effect of OXM on appetite may be mediated via further receptors. OXM has a lower affinity than GLP-1 for the GLP-1R (by ~2 orders of magnitude), yet they reduce food intake at equimolar doses (134). Peripheral GLP-1 and OXM administration result in different patterns of c-*fos* activation. OXM increases c-*fos* in the ARC but not in the brain stem (101). Furthermore, although exendin-(9—39) blocks the anorectic effects of central OXM and GLP-1, exendin-(9—39) administered into the ARC only inhibits the effect of peripheral GLP-1, not OXM. Thus there appear to be different mechanisms mediating the actions of these gut hormones. Interestingly, OXM may also reduce appetite by inhibition of ghrelin release. Peripheral OXM administration reduces plasma ghrelin by 20 and 44% in rodents and humans, respectively (79, 101).

5. Cholecystokinin

Cholecystokinin (CCK) is expressed widely in the gastrointestinal tract (232) but is found particularly in the duodenum and jejunum. There are multiple bioactive forms derived from the same gene product: CCK-58, CCK-33, and CCK-8 (330). CCK is released locally and into the circulation following nutrient ingestion. Its release is rapid, and plasma levels remain elevated for up to 5 h (247). CCK is also expressed within the CNS, acting as a neurotransmitter regulating reward behavior, anxiety, memory, and satiety (95).

The role of CCK in regulation of digestion and appetite has long been known. It stimulates pancreatic and gall bladder enzyme release, inhibits gastric emptying, and increases intestinal motility (247, 289). CCK acts rapidly to reduce meal size and duration in both humans and animals (153, 217), and this effect is potentiated by gastric distension (216). However, CCK has a half-life of only 1–2 min, and its effects are short-lived. It is ineffective if given more than 15 min before food (153). In animals, repeated CCK administration does not alter body weight for although meal size is reduced, meal frequency increases and there is no overall change in intake (425, 426). Similarly, continuous CCK infusion is not effective after the first 24 h (94). However, the OLETF rat, which lacks CCK_A

receptors (but not the CCK_A receptor knockout mouse), is hyperphagic and obese (286, 356). Similarly, chronic administration of CCK_A antagonists or anti-CCK antibodies increases weight gain in rodents, although without a significant change in food intake (272, 274). The long-term effect of CCK on body weight may be the result of interaction with other signals of adiposity such as leptin, since leptin enhances the satiating effect of CCK (268). The evidence for a role of CCK in long-term body weight regulation, and hence as a potential therapy for obesity, remains contradictory.

CCK acts via seven transmembrane domain G protein-coupled receptors, CCK_A and CCK_B (421). CCK_A receptors are expressed widely in the CNS including the NTS, DMH, and area postrema, while in the periphery they are present in the pancreas and on vagal afferent and enteric neurons. CCK_B receptors are also found on the afferent vagus nerve and within the stomach and are present widely in the CNS (287, 288, 421, 422). The effects of CCK on appetite are thought to be via the CCK_A receptor subtype (21). Only the sulfated form of CCK, which binds with high affinity to CCK_A receptors, inhibits food intake (153). Furthermore, food intake is increased and satiety reduced by administration of a CCK_A receptor antagonist (36, 182). Peripheral CCK may act directly on the CNS by crossing the BBB (331). Evidence from the CCK_A receptor knock-out (OLETF) rat suggests that CCK may act on the DMH to suppress NPY levels (45), and administration of CCK into the DMH reduces food intake (47). Activation of the vagus is also important in mediating the actions of CCK on satiety (285, 355). This action may be in part via a paracrine or neurocrine effect with locally released CCK activating vagal fibers without significant alteration of circulating CCK level (332). Activation of the vagus in turn activates the NTS, which then relays information to the hypothalamus (361).

6. Bombesin

Bombesin is a tetradecapeptide originally isolated from amphibian skin (50). Bombesin-like immunoreactivity is widely distributed in the mammalian gut, and plasma levels have been shown to increase sharply after feeding (152). Bombesin is similar in structure to mammalian gastrin-releasing peptide (GRP) and neuromedin B (50). It binds to three different receptors: a GRP receptor, a neuromedin B receptor, and a bombesin-3 receptor (228). Peripheral or central injections of bombesin reduce food intake that is not blocked by vagotomy (152, 374), and its effect is independent of CCK (248). A bombesin-3 receptor knock-out mouse is moderately obese at 6–8 wk of age, but hyperphagia is only significant 12 wk after obesity has developed (310).

III. CENTRAL REGULATORS OF APPETITE

A. Hypothalamic Structure and Neuronal Pathways Regulating Appetite

Despite wide daily variation in food intake and energy expenditure, for most individuals, body weight remains remarkably stable over long periods of time. For this, food intake and energy expenditure must be constantly modulated and balanced. The hypothalamus is essential for the regulation of appetite and energy balance. Hetherington and Ranson (181) and Anand and Brobeck (12) first proposed a model of lateral hypothalamic feeding centers and ventromedial hypothalamic satiety centers. Lesions of the LHA decrease food intake and eventually lead to starvation and death. In contrast, lesions of several of the mediobasal hypothalamic nuclei result in obesity, decreased activity, and neuroendocrine abnormalities. Destruction of the ARC with systemic monosodium glutamate produces obesity and hyperphagia (312), while lesions of the VMN also result in increased body weight and central hypogonadism (108). Similarly, lesions slightly more dorsally in the PVN also lead to hyperphagia and weight gain. Thus a few morphologically well-defined regions of the hypothalamus appear to play a major role in the regulation of body weight and endocrine function. However, rather than specific hypothalamic nuclei controlling energy homeostasis, it is now thought to be regulated by neuronal circuits, which signal using specific neuropeptides (see Fig. 2).

1. ARC

The ARC is thought to play a pivotal role in the integration of signals regulating appetite. The ARC lies in

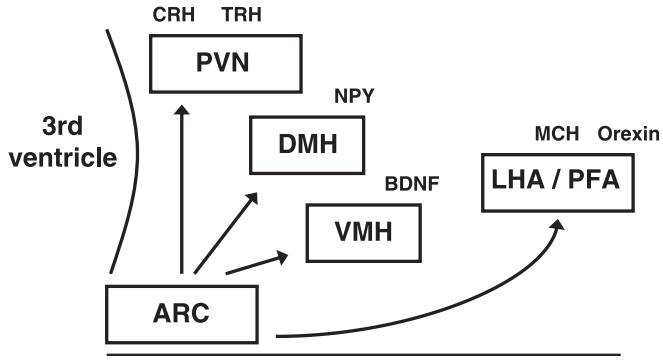

FIG. 2. Morphologically defined regions of the hypothalamus such as the arcuate nucleus (ARC), paraventricular nucleus (PVN), dorsomedial nucleus (DMH), ventromedial nucleus (VMH), lateral hypothalamic area (LHA), and perifornical area (PFA) appear to play a major role in the regulation of body weight. Neuronal circuits within these regions of the hypothalamus signal using specific neuropeptides, for example, corticotrophin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), neuropeptide Y (NPY), brain-derived neurotrophic factor (BDNF), orexin, and melanin-concentrating hormone (MCH).

close proximity to the median eminence, which lacks a complete BBB (51), and thus it is uniquely placed to respond to circulating hormonal signals. Certain plasma hormones, for example, PYY and GLP-1, cross the BBB via nonsaturable mechanisms (206, 307). Other signals, such as leptin, are actively transported from blood to brain via saturable mechanisms (28). Thus the BBB may play a dynamic role in regulating the passage of peripheral signals.

Two primary neuronal populations within the ARC integrate signals of nutritional status and influence energy homeostasis (84) (see Fig. 3). A subpopulation of neurons in the medial ARC express the orexigenic neuropeptides NPY and AgRP (53, 166). These neurons project primarily to the ipsilateral PVN (26) but also locally within the ARC. A subpopulation of ARC NPY neurons release GABA locally to inhibit the adjacent POMC neurons. More laterally lies a second subpopulation that inhibits food intake via the expression of CART and POMC, which is processed to α-melanocyte stimulating hormone (α-MSH) (123, 222). This subpopulation projects much more widely within the CNS, to hypothalamic nuclei such as the DMH, LHA, and perifornical area (PFA) as well as the PVN (124, 129, 202). Schwartz et al. (361) proposed a model of appetite regulation whereby arcuate neurons act as the primary hypothalamic site of action of peripheral hormones, such as insulin and leptin. These modulate activity of arcuate neurons, which in turn project to secondary hypothalamic nuclei, for example, the PVN or LHA. Here, the release of further anorectic or orexigenic peptides is modulated to adjust energy intake and expenditure to maintain a stable body weight.

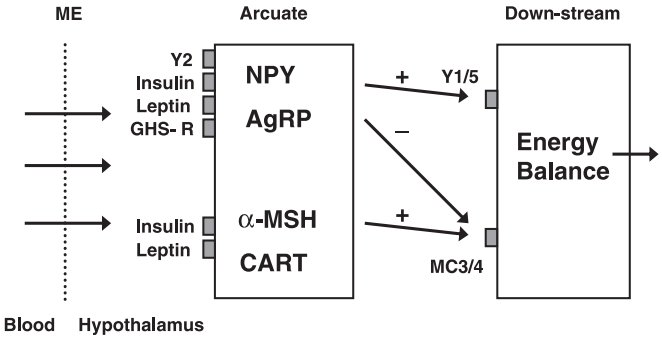

FIG. 3. A schematic representation of arcuate nucleus of the hypothalamus. The arcuate nucleus (ARC) is thought to play a pivotal role in the integration of signals regulating appetite. The ARC neurons express many receptors including those for insulin and leptin, Y2 receptors, and growth hormone secretagogue receptors (GHS-R). The ARC is able to respond to peripheral signals via the median eminence (ME), which lacks a blood-brain barrier. Two subpopulations of neurons within the arcuate nucleus signal energy status. Agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons promote positive energy balance. AgRP is able to signal downstream by antagonizing melanocortin 3/4 receptors (MC3/4) receptors, whereas NPY acts as an agonist at Y1/5 receptors. Cocaine and amphetamine-regulated transcript (CART)/α-melanocyte stimulating hormone (α-MSH) promote negative energy balance, and α-MSH signals downstream by antagonizing MC3/4 receptors.

2. PVN

The PVN acts to integrate neuropeptide signals from numerous CNS regions including the ARC and brain stem (350). Microinjection into the PVN of almost all known orexigenic and anorectic signals alters appetite, for example, NPY (230), ghrelin (237), orexin-A (117, 367), CCK (171), leptin (127, 414), and GLP-1 (414). PVN administration of melanocortin agonists potently inhibits food intake (154, 210). Conversely, PVN injection of a melanocortin antagonist stimulates food intake (154). Electrophysiological recordings from PVN neurons have shown ARC neurons expressing POMC potentiate inhibitory GABAergic signaling within the PVN and thus reduce food intake. In contrast, ARC NPY/AgRP neurons inhibit this GABAergic signaling (92) and stimulate food intake.

Recent work suggests that neuropeptides regulating appetite may signal via a common pathway in the PVN involving AMP-activated protein kinase (AMPK). AMPK is a heterodimer consisting of catalytic α-subunits and regulatory β- and γ-subunits. Multiple anorectic signals such as leptin, insulin, and the melanocortin agonist MT-II reduce α_2-AMPK activity in the ARC and PVN, whilst orexigenic signals such as AgRP and ghrelin increase α_2-AMPK activity (13, 279). Pharmacologically mediated increases in PVN AMPK activity increased food intake (13). Peripheral appetite regulators are unable to modulate α_2-AMPK activity in mice lacking the melanocortin 4 receptor (MC4R), suggesting α_2-AMPK activity may be controlled by MC4R (279).

Many neuropeptides that modulate appetite also influence endocrine function, for example, thyroid function and hence energy expenditure. The PVN plays a major role in integration of these functions. Both NPY/AgRP and melanocortin projections from the ARC terminate on thyrotropin-releasing hormone (TRH) neurons in the PVN (136, 241). NPY/AgRP inhibits pro-TRH gene expression (137), while α-MSH stimulates pro-TRH expression and inhibits the fasting-induced suppression of TRH (136). The PVN also contains CRH-expressing neurons. NPY projections from the ARC influence CRH expression and release, and this in turn may modulate energy homeostasis (347).

3. DMH

There is evidence for a role of the DMN in the modulation of energy intake. Destruction of the DMN results in hyperphagia and obesity, although less dramatically than VMN lesioning (41). Injection of orexigenic peptides, NPY, galanin, and GABA into the DMN increases food intake (209, 227, 375), and central NPY injection induces c-*fos* in the DMN (452). The DMH has extensive connections with other hypothalamic nuclei. It receives AgRP/NPY neurons from the ARC (202) but also contains NPY-expressing cell bodies. α-MSH immunoreactive fibers lie

in close proximity to these NPY-expressing cells, and DMH administration of melanocortin agonists has been demonstrated to reduce both local NPY expression and suckling-induced hyperphagia in rats (71).

4. LHA/PFA

Other hypothalamic areas including the lateral hypothalamic area and perifornical area (LHA/PFA) are involved in downstream signaling. Indeed, the PFA is one of the most sensitive areas for NPY-induced feeding, more so than the PVN (378). The LHA/PFA contains melanin-concentrating hormone (MCH) expressing neurons (266). Here, MCH expression is regulated by nutritional status, since fasting induces MCH mRNA expression. MCH appears to have a powerful role in appetite regulation. Repeated intracerebroventricular injection of MCH increases food intake (327) and adiposity in rats (266). Conversely, MCH-1 receptor antagonists inhibit feeding, and chronic administration leads to a sustained reduction in body weight gain (49). Overexpression of prepro-MCH results in mice that are hyperphagic and centrally obese (266), whereas MCH null mice are lean, hypophagic with increased energy expenditure, despite reduced anorectic signals such as plasma leptin and ARC POMC expression (266, 365). Mice that lack both MCH and leptin have reduced weight gain and adiposity compared with leptin-deficient *ob/ob* mice (364). This suggests MCH may be a downstream mediator of leptin's and POMC's effects on feeding.

The LHA/PFA also contain neurons expressing prepro-orexin and releasing the peptide products orexin A and B (or hypocretin 1 and 2). The orexin-immunoreactive cell population is distinct from that which produces MCH (109, 343). Orexin neurons project widely through the CNS including the PVN, ARC, NTS, and dorsal motor nucleus of the vagus (109, 320) and to areas associated with arousal and attention as well as feeding. Orexin A has high affinity for the orexin-1 receptor, which is highly expressed in the VMH. Orexin A and B have equal affinities for the orexin-2 receptor, and this is expressed primarily within the PVN (343). Prepro-orexin mRNA is upregulated by fasting, and central administration of orexin A results in general arousal and probably a secondary increase in orexigenic behavior (162, 177, 343). However, although central administration of orexin A stimulates daytime feeding, there is no increase in 24-h food intake (177). Furthermore, chronic administration of orexin A does not alter body weight (446). Orexin-knockout mice are thought to be a model of human narcolepsy (68) rather than altered energy balance. However, in circumstances of food deprivation, orexins may mediate both a feeding response and arousal to initiate food-seeking behavior.

It is possible that orexins may also act as peripheral regulators of energy homeostasis. Orexin neurons are found in the gastrointestinal tract. They express both orexin and leptin receptors and appear to be activated by starvation (215). Orexin is also expressed in the gastric, intestinal, and pancreatic endocrine cells (215), and peripheral administration increased plasma insulin levels (308) and decreased circulating glucagon (119).

NPY, AgRP, and α-MSH immunoreactive terminals are extensive in the LHA and are in contact with MCH and orexin-expressing cells (52, 124, 190). Central orexin neurons express both NPY receptors (63) and leptin receptors (190) and hence may be able to integrate their actions. A large number of glucose-sensing neurons are present in the LHA (40), and orexin neurons may play a role in this. Hypoglycemia increases orexin mRNA expression and c-*fos* in the LHA (61, 292). The mechanisms by which the MCH and orexin neurons influence energy homeostasis remain to be fully elucidated. However, major targets are the endocrine and autonomic nervous system, the cranial nerve motor nuclei, and cortical structures (346).

5. VMH

The VMH has been known to play a role in energy homeostasis for many years, since the finding that bilateral VMH lesions induce hyperphagia and obesity. The VMH receives NPY, AgRP, and α-MSH immunoreactive projections from arcuate neurons and, in turn, VMH neurons project onto both hypothalamic nuclei (e.g., DMH) and brain stem regions (e.g., NTS). VMH expression of neuropeptides is modulated by energy status, with altered NPY expression in obese mice (161) and increased MC4R expression in diet-induced obese rats (195). Brain-derived neurotrophic factor (BDNF) is highly expressed in the VMN, and its expression is regulated both by food deprivation and melanocortin agonists (444). Mice with reduced BDNF receptor expression or reduced BDNF signaling have increased food intake and body weight (335, 444). Therefore, BDNF neurons in the VMH may act as an additional downstream pathway through which nutritional status and the melanocortin system modulate energy homeostasis.

B. Hypothalamic Regulators of Appetite

1. NPY

NPY is one of the most abundant neurotransmitters in the CNS (10), but the ARC is the major hypothalamic site of NPY expression (293). Hypothalamic levels of NPY reflect the body's nutritional status with hypothalamic NPY mRNA and NPY release increasing with fasting and decreasing after refeeding (203, 344, 388). NPY is the most potent orexigen known, and repeated third ventricle or

PVN injection of NPY causes marked hyperphagia and obesity (377, 455). Central administration of NPY also inhibits brown fat thermogenesis (46), suppresses sympathetic nerve activity (118), and inhibits the thyroid axis (137) to reduce energy expenditure. In addition, NPY stimulates basal plasma insulin (282, 455) and morning plasma cortisol (455), effects which are independent of increased food intake.

Despite the potency of NPY's actions on food intake, NPY null mice have normal body weight and adiposity (396), with the only demonstrable abnormality of energy homeostasis being a reduction in fasting-induced feeding (29). This normal phenotype may be due to the presence of compensatory mechanisms or redundancy in orexigenic pathways, such as those which signal via AgRP (265) to avert starvation. This redundancy may also contribute to the difficulty elucidating the receptor subtype that mediates NPY-induced feeding (329).

NPY, as part of the PP-fold family of peptides, binds to G protein-coupled receptors designated Y_1-Y_6 (231). Y_1-Y_5 receptors are present in rat brain; however, Y_6 has only been identified as active in mice, being absent in rats and inactive in primates (199). The hypothalamic Y_1, Y_2, Y_4, and Y_5 receptors have all been hypothesized to mediate the orexigenic effects of NPY. Y_5 receptors are thought to play a role in food intake, since antisense oligonucleotides to the Y_5 receptor reduce food intake (352). In addition, Y_5 receptor-deficient mice have an attenuated feeding response to NPY (264). However, contrary to expectation, hypothalamic Y_5 receptor density is reduced by fasting and increased by dietary-induced obesity (429). Furthermore, antagonists to the Y_5 receptor do not significantly alter food intake in rats (405), and Y_5 receptor-deficient mice demonstrate late-onset obesity rather than weight loss (264). It has been suggested that the role of the Y_5 receptor is to maintain rather than initiate the feeding response to NPY. This is supported by the observation that Y_5 receptor antisense decreases food intake only 10 h after the onset of NPY- or PP-induced feeding and has no effect on the initial orexigenic response (140). Similarly, there is evidence for a role of the Y_1 receptor. Y_1 receptor antagonists block both NPY- and fasting-induced feeding (204, 430), and Y_1 receptor null mice have an attenuated feeding response to NPY (205). However, similarly to Y_5 receptors, ARC Y_1 receptor density, distribution, and expression are reduced by fasting, and these changes are moderated by glucose administration (72). NPY fragments with poor Y_1 binding still increase food intake to the same extent as equimolar doses of NPY (313), and Y_1 receptor-deficient mice are obese but not hyperphagic (226). These data suggest the Y_1 receptor is not responsible for the NPY feeding effect but may play a role in energy expenditure (226). There is also some support for a role of Y_4 receptors in the orexigenic NPY response. PP has a relative specificity for the Y_4 receptor, and central administration has been shown to elicit food intake in both mice (19) and rats (63). Y_2 and Y_4 receptors lie presynaptically and have an autoinhibitory effect on NPY neurons (212, 213). As expected, Y_2 receptor null mice are hyperphagic and obese and have increased adiposity (304). However, mice with a conditional knockout of the Y_2 receptor, and thus perhaps with more normal neuronal circuitry, have a temporary reduction in body weight and food intake, which returns to normal after a few weeks (340). Thus it is probable that the effects of NPY on feeding are mediated by a combination of receptors rather than a single subtype.

2. Melanocortin system

The melanocortin system is comprised of the peptide products of POMC cleavage, their receptors, and the endogenous melanocortin antagonists AgRP and agouti. Hypothalamic POMC mRNA expression is regulated by nutritional status with low levels in fasting that are restored by exogenous leptin administration or 6 h after refeeding (359, 388). Human POMC gene mutations or abnormal POMC peptide processing result in early-onset obesity and red hair secondary to lack of α-MSH, along with adrenal insufficiency due to loss of ACTH (223). Haploinsufficiency of the POMC gene is sufficient to render mice susceptible to diet-induced obesity (65).

Five melanocortin receptors have been identified, MC1R-MC5R; however, MC3R and MC4R are likely to play a role in energy homeostasis. They are widely expressed in the hypothalamus and are found in the ARC, VMH, and PVN (175, 294). Absence of MC4R results in hyperphagia and obesity in rodents (131, 196), and abnormalities of this receptor have been implicated in 1–6% of severe early-onset human obesity (133, 253, 254). In addition, polymorphism of this receptor has been implicated in polygenic late-onset obesity in humans (15).

Although MC4R involvement in regulation of feeding is well established, the role of MC3R remains unclear. Relatively selective MC3R agonists do not alter food intake (1), and unlike MC4R expression, which is influenced by energy status, MC3R expression is not (175). However, the MC3R/MC4R antagonist AgRP is reported to increase food intake in MC4R null mice (59). In addition, mice lacking MC3R have increased adiposity, although not body weight, and preferentially metabolize carbohydrate rather than fat (60). On high-fat chow, MC3R null mice develop obesity and have a further increase in adipose tissue compared with wild-type littermates. Furthermore, MC3R mutations have been reported in morbidly obese human subjects (283).

The main endogenous ligand for the MC3R/MC4R is α-MSH, which is expressed by cells in the lateral part of the arcuate nucleus (423) (see above). Central administration of MC4R agonists suppresses food intake, while

administration of antagonists results in hyperphagia (38). In addition to its actions on feeding, α-MSH also increases oxygen consumption (321), suggesting increased energy expenditure. α-MSH activates the thyroid axis (211), sympathetic nervous activity, and brown adipose tissue (450).

Two endogenous antagonists of melanocortin receptors have been described: agouti and AgRP. The agouti protein is a competitive antagonist of α-MSH at MCR1 and MCR4 (252). Agouti expression is normally restricted to the hair follicle where its antagonist effect on the peripheral MC1 receptor results in a yellow pigment. However, the agouti mouse ectopically expresses the agouti protein within the CNS, thereby antagonizing the actions of α-MSH at the hypothalamic MC4R resulting in hyperphagia and obesity (131, 252). Unlike agouti, AgRP is expressed in the CNS, primarily in the medial part of the arcuate nucleus (370). AgRP is partially homologous to agouti peptide and is a potent selective antagonist at MC3R and MC4R (311). AgRP mRNA expression is increased by fasting, and unlike NPY mRNA levels, which are reduced 6 h after refeeding, AgRP levels remain elevated (388). Central administration of AgRP or AgRP-(83—132), the carboxy-terminal fragment, is able to block α-MSH-induced anorexia and increase nocturnal food intake (337). Moreover, this hyperphagia has been reported to persist for up to a week after a single injection (165, 337). This prolonged response results in a greater cumulative effect on food intake than NPY, and probably involves more diverse signaling pathways than the melanocortin pathway alone (164, 165, 459). Independent of its effects on food intake, AgRP may increase body weight via decreased energy expenditure. Repeated central administration of AgRP suppresses TRH, reduces oxygen consumption, and decreases the ability of brown adipose tissue to expend energy (372, 373). Transgenic mice overexpressing AgRP are obese but, as AgRP is inactive at the MC1 receptor, have no alteration in coat color (311). Conversely, reduction of hypothalamic AgRP by RNA interference reduces body weight (259). The role of AgRP in human obesity is less clear cut, although a polymorphism in the AgRP gene in humans has been reported to be associated with reduced body weight and fat mass (262).

AgRP and NPY are colocalized in 90% of ARC neurons (53, 166). Activation of ARC NPY/AgRP neurons potently stimulates feeding via a number of pathways: the orexigenic effect of NPY released in the PVN, AgRP antagonism of MC3R/MC4R in the PVN, and local release of NPY and GABA within the ARC to inhibit the arcuate POMC neurons via Y_1 and GABA receptors, respectively (149, 336). However, NPY/AgRP knock-out mice have no obvious feeding or body weight defects, and AgRP is not present in other hypothalamic nuclei known to be involved in energy homeostasis, such as the VMH (53). Therefore, there must be other signaling pathways regulating energy homeostasis (326).

3. CART

CART is the third most abundant transcript within the hypothalamus and is expressed in the ARC (123, 222) (with POMC), LHA, and PVN (91). Food deprivation reduces ARC expression of CART, whereas peripheral leptin replacement to *ob/ob* mice stimulates CART expression (222). CART-(1—102) and CART-(82—103) injected into the third cerebral ventricle inhibit both normal and NPY-stimulated feeding in rats, but also cause abnormal behavioral responses at high doses (222, 229). Intracerebroventricular injection of antiserum against CART peptide-(1—102) and CART peptide fragment-(82—103) increases nocturnal feeding, suggesting CART is a physiological regulator of energy homeostasis (222, 229). However, injection of CART-(55—102) into discrete hypothalamic nuclei such as the ARC and VMN actually increases food intake (2). Thus there may be several populations of CART-expressing neurons with differing roles in feeding. For example, NPY release could stimulate a population of CART neurons in the ARC that are orexigenic, producing positive orexigenic feedback (111).

C. Reward and Regulation of Appetite

Even in the absence of an energy deficit, the rewarding nature of food may act as a stimulus to feeding. However, there is interaction between nutritional status and the sensation of reward, as the subjective palatability of food differs between the fed and fasting states (43). Signals of energy status, such as leptin, are able to modulate reward pathways (148).

1. Opioids

The reward circuitry is complex, involving interactions between several signaling systems, including opioid, dopaminergic, and cannabinoid systems. Opioids play an important role. Mice lacking either enkephalin or β-endorphin lose the reinforcing property of food, regardless of the palatability of the food tested. However, the reinforcing effect is regained in fasted animals; thus homeostatic mechanisms can override the hedonistic pathways (178). In humans, opiate antagonists reduce food palatability but without altering subjective hunger (114, 451). The nucleus accumbens (NAc) forms an important part of the reward circuit. Microinjection of opioid agonists into the NAc stimulates the preferential consumption of highly palatable sucrose and fat (456, 457). Conversely, opioid antagonists administered into the NAc reduce sucrose ingestion rather than less palatable substances (456).

2. Endocannabinoids

The appetite-stimulating effects of marijuana (*Cannabis sativa*) have been known for a long time (3). The

discovery of cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) (110, 269, 295), as well as the characterization of endogenous ligands for these receptors, the endocannabinoids, have prompted further investigation of this system. Several studies have indicated that administration of cannabinoids stimulates food intake in animal models (218, 433). Appetite is increased by both peripheral and central administration of anandamide, one of the major endocannabinoids, in rodents (173, 200, 432). This orexigenic effect may be mediated via CB1 receptors in the hypothalamus, which colocalize with CART, MCH, and orexin peptides (90). A CB1 receptor antagonist has been shown to reduce food intake (81), and CB1 knock-out ($CB1^{-/-}$) mice show reduced caloric intake and decreased body weight (90). However, $CB1^{-/-}$ mice pups are able to overcome initial absence of milk ingestion, suggesting development of compensatory mechanisms that may involve an additional CB3 receptor (144). Defective leptin signaling is associated with high hypothalamic endocannabinoid levels in animal models (112). A recent study shows a synergistic interaction between the cannabinoid and melanocortin systems in regulating food intake (418). It also suggests that the cannabinoid receptors are located downstream from the melanocortin system and that activation of CB1 receptors is necessary to prevent the melanocortin system from altering food intake (418). Interestingly, CB1 receptors are also present on adipocytes where they appear to act directly to increase lipogenesis (90). There is currently a CB1 selective antagonist, Rimonabant, in phase 3 clinical trials that may be a potentially promising antiobesity drug.

3. Others

The dopaminergic system is also integral to reward-induced feeding behavior. The effects of central dopamine signaling on feeding are thought to be mediated by D_1 and D_2 receptors (225, 354). Mice that lack the tyrosine hydroxylase gene and therefore dopamine have fatal hypophagia. Tyrosine hydroxylase gene replacement, and hence dopamine replacement, into the caudate putamen restores feeding, while gene therapy into either the caudate putamen or NAc restores preference for a palatable diet (389).

Reciprocal GABAergic connections exist between the NAc and LHA, and it is possible that disinhibition of LHA neurons may mediate hedonistic feeding (381). The LHA may also reciprocally influence reward circuits via MCH expressing neuronal projections as MCH receptors are expressed in the NAc (341).

Other systems, including those mediated by serotonin, may also be able to modulate both reward circuitry and homeostatic mechanisms controlling feeding. Serotonin may directly influence the melanocortin pathway in the ARC via 5-hydroxytryptamine (5-HT) receptors (179). The now-discontinued anorectic agent fenfluramine mediates its actions via 5-HT (170). Fenfluramine acts via two mechanisms to increase 5-HT release. First, it binds to 5-HT transporter proteins that move the drug into the nerve terminal in exchange for 5-HT which moves into the synapse, and second, it is a substrate for the vesicular monoamine transporter that disrupts the compartmentalization of 5-HT in vesicles and increases the cytoplasmic pool of 5-HT available for release.

The noradrenergic system also plays a role in appetite regulation, with activation of α_1- and β_2-adrenergic receptors inhibiting food intake. Phentermine acts as a norepinephrine reuptake inhibitor, thereby increasing synaptic norepinephrine to reduce appetite and weight gain (35). In contrast, activation of α_2-adrenergic receptors increases food intake.

Neurotensin, a 13-amino acid peptide with neurons and terminals in hypothalamic areas including the ARC and PVN (197), has also been shown to decrease food intake when administered centrally (245). Expression of neurotensin is downregulated in the *ob/ob* mouse (431). Studies also suggest that neurotensin mediates the central effect of leptin on food intake (339).

D. Brain Stem Regulators of Appetite

Extensive reciprocal connections exist between the hypothalamus and brain stem, particularly the NTS (333, 395, 413). The brain stem plays an important role in the regulation of energy balance. The NTS is in close anatomical proximity to the area postrema, a circumventricular organ with an incomplete BBB (125). Like the ARC, the NTS is therefore in an ideal position to respond to peripheral circulating signals but in addition also receives vagal afferents from the gastrointestinal tract and afferents from the glossopharyngeal nerves (201, 349).

1. GLP-1

The NTS contains NPY, melanocortin, and GLP-1 neuronal circuits. GLP-1 forms the major brain stem circuit regulating energy homeostasis. In the CNS, GLP-1 is synthesized exclusively in the caudal NTS, and these preproglucagon neurons also express leptin receptors. GLP-1 immunoreactive fibers then project widely, but particularly to the PVN and DMN, with fewer projections to the ARC. GLP-1 receptor expression is also widespread, both within the hypothalamus (PVN, DMH, and supraoptic nucleus) and in the brain stem (subfornical organ, organum vasculosum laminae terminalis, and area postrema). Central administration of GLP-1, either into the third or fourth ventricle, potently reduces fasting and NPY-induced food intake (406), and blockade of endogenous GLP-1 with the GLP-1 receptor antagonist exendin-(9—39) increased

food intake (406). This suggested a role of endogenous hypothalamic GLP-1 in energy homeostasis. The anorectic effect of GLP-1 is completely abolished in animals treated with MSG; thus the ARC appears to be vital for GLP-1's anorectic action (391). There is still debate about the role of conditioned taste aversion (CTA) in the reduced food intake seen following central GLP-1 administration. However, Kinzig et al. (214) have dissociated the anorectic actions of GLP-1 from the induction of CTA following fourth ventricle injection (214). Data regarding the long-term effects of central GLP-1 are also conflicting. Continuous infusion of GLP-1 was initially reported not to alter food intake or body weight (113) but later studies with either continuous central administration or repeated intracerebroventricular injection reduced both (107, 273). However, mice lacking the GLP-1 receptor do not show any abnormality of food intake or body weight (362).

2. Others

NPY neurons from the brain stem project forward to the PVN (351), and extracellular NPY levels within the NTS are modulated by feeding (453). A high density of NPY binding sites, including Y_1 receptors and Y_5 receptors, are found in the NTS (115, 156, 174). There is also evidence for a separate melanocortin system in the NTS (208). POMC-derived peptides are synthesized in the NTS of the rat (55, 141, 208) and caudal medulla of humans (159). Brain stem POMC neurons are activated in response to food intake and also by CCK administration (131). MC4R are also expressed in the NTS (294) and act to regulate energy intake. Fourth ventricle injection of a MC3R/MC4R agonist or administration into the dorsal motor nucleus of the vagus nerve reduces food intake. Conversely, MC3/4 receptor antagonist administration to these areas increase intake (434).

Prolactin-releasing peptide (PrRP), the endogenous ligand of the previously orphan G-coupled receptor GPR10, is expressed in the NTS in addition to the hypothalamic DMH (240). PrRP neurons are reduced in fasting rats, and third ventricle administration of PrRP or injection into the DMH decreases nocturnal and fasting-induced food intake (363). These effects may be mediated by CRH (236). In addition, peripheral administration of CCK activates brain stem PrRP neurons, suggesting it mediates CCK's central actions (235). However, repeated administration of PrRP did not alter food intake after the initial 72 h (126) and therefore may play a role in short-term appetite regulation rather than in control of body weight in the longer term.

IV. FUTURE DIRECTIONS

Long-term signals of energy stores and short-term fluctuations in food intake are released from adipose tissue and the gut endocrine system. These signals are integrated in the hypothalamus and brain stem. Important neuropeptide signals such as NPY, AgRP, and the melanocortins are released and influence activity of diverse circuits within other hypothalamic nuclei, which signal using a wide range of transmitter systems (Fig. 4). This homeostatic process results in subsequent changes in appetite, behavior, and energy expenditure.

The recent clarification of the function of gut hormones, adiposity signals, and hypothalamic neurotransmitters has greatly expanded our understanding of the physiology of energy balance. Although this system is designed to maintain body weight, complex interactions between genetic and environmental factors may impinge on both peripheral signals and central pathways to result in obesity. The increasing global prevalence of obesity

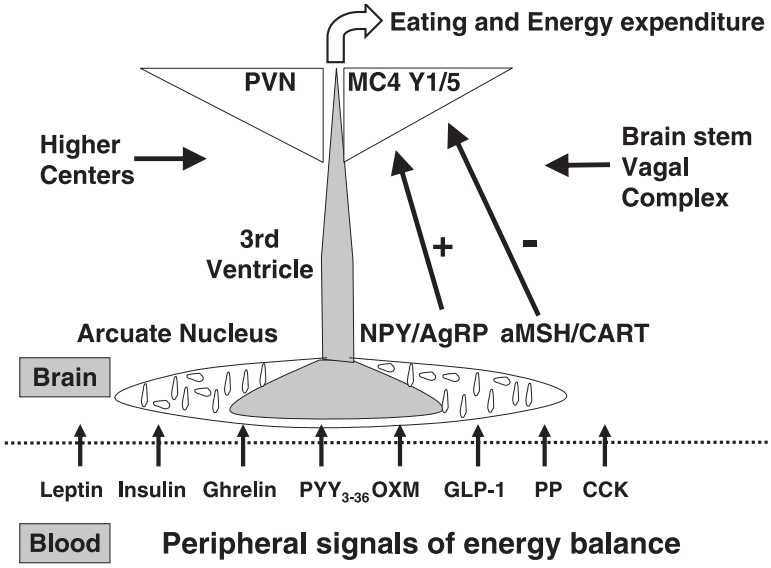

FIG. 4. Working model for energy homeostasis. Peripheral signals of energy balance including leptin, ghrelin, peptide $YY_{3–36}$ ($PYY_{3–36}$), oxyntomodulin (OXM), glucagon-like peptide-1 (GLP-1), pancreatic polypeptide (PP), and cholecystokinin (CCK) cross the blood-brain barrier and act on brain regions such as the hypothalamus and brain stem. The arcuate nucleus of the hypothalamus integrates signals by altering the relative activity of neurons expressing neuropeptide Y (NPY)/agouti-related protein (AgRP) and neurons expressing melanocortin (α-MSH)/cocaine and amphetamine-regulated transcript (CART). These neuropeptide circuits project to downstream nuclei, for example, the PVN, and modulate the release of further anorectic or orexigenic peptides that adjust energy intake and expenditure to maintain a stable body weight.

makes understanding these factors an important priority. A more detailed understanding of the pathogenesis of obesity may make successful treatment possible.

New approaches could be tailored to provide an effective solution for the individual. Leptin replacement has successfully treated the uncommon form of obesity due to leptin deficiency. Similarly, obesity that results, for example, from reduced melanocortin signaling in the brain may respond to a melanocortin receptor agonist. Individually tailored therapy or combination therapy will be more effective than the currently available pharmacological agents that are of limited efficacy and duration (see review in Ref. 138).

Mimicking postprandial satiety by modulation of circulating gastrointestinal hormones may provide a possible means of treating obesity. Interestingly, the reduction in weight and appetite (22) seen in subjects following gastrointestinal bypass surgery may be the result of altered gastrointestinal hormone release, for example, elevated PYY and OXM (302, 348) and/or suppressed ghrelin levels (99). Although surgery is an effective long-term treatment for obesity, it is a major operation with significant associated mortality, and so is rightly restricted to those with severe morbid obesity. The changes in circulating gut hormones secondary to gastrointestinal bypass surgery suggest that modulation of gut hormones, by other means, may be an effective long-term therapy for obese individuals. In addition, in contrast to drugs which affect widely distributed central neurotransmitters or their receptors, modulation of peripheral signals would target regions of the brain controlling appetite more specifically.

Efforts to develop pharmacological treatments for obesity have multiplied over the last decade, and a number of therapies are currently being investigated in phase II and III clinical trials. Attention is turning to the hedonistic aspects of food intake with the development of endocannabinoid antagonists. A fuller understanding of the regulation of food intake will hopefully allow the rational development of drugs that are able to reverse the ongoing acceleration of the current obesity epidemic.

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GRANTS

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