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Hormonal Regulation of Food Intake

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I. Introduction	1131
II. Peripheral Regulators of Appetite	1131
A. Adipose tissue hormones	1131
B. Pancreatic hormones	1134
C. Gut hormones	1135
III. Central Regulators of Appetite	1139
A. Hypothalamic structure and neuronal pathways regulating appetite	1139
B. Hypothalamic regulators of appetite	1141
C. Reward and regulation of appetite	1143
D. Brain stem regulators of appetite	1144
IV. Future Directions	1145

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 hyperphagia.

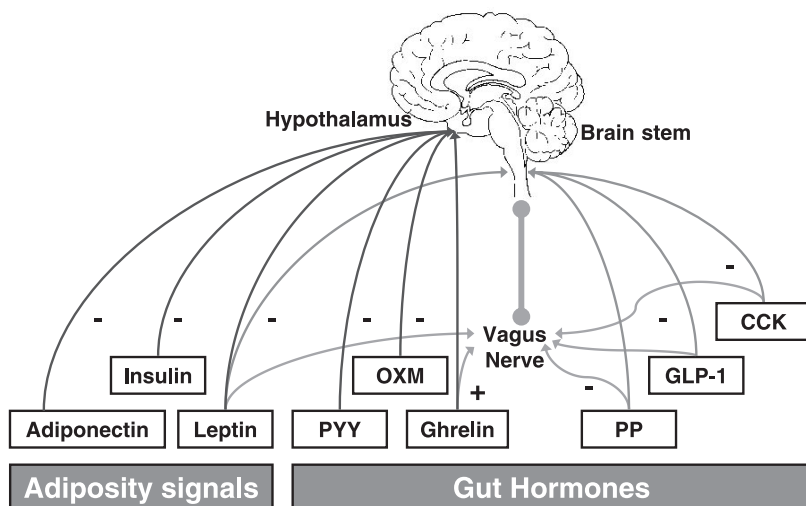


FIG. 1. Energy homeostasis is controlled by peripheral signals from adipose tissue, pancreas, and the gastrointestinal tract. Peripheral signals from the gut include peptide YY (PYY), oxyntomodulin (OXM), ghrelin, pancreatic polypeptide (PP), glucagon-like peptide 1 (GLP-1), and cholecystikinin (CCK). 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 has a 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 effec-

tive 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: PYY₁₋₃₆ and PYY₃₋₃₆ (158). PYY₃₋₃₆ binds with greatest affinity at the presynaptic autoinhibitory Y₂ 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 PYY₁₋₃₆ (116). DPP-IV is involved in the cleavage of multiple hormones including products of the proglucagon gene (48). However, the accurate proportions of PYY₁₋₃₆ and PYY₃₋₃₆ 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 PYY₃₋₃₆ 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). PYY₃₋₃₆ is also effective in reducing food intake in humans. Intravenous administration of PYY₃₋₃₆ 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 PYY₃₋₃₆ infusion has finished and long after circulating PYY₃₋₃₆ has returned to basal levels (32). These data suggest PYY₃₋₃₆ 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 PYY₃₋₃₆ may be mediated via the presynaptic inhibitory Y₂ receptor present on arcuate NPY neurons (54). PYY₃₋₃₆ 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 PYY₃₋₃₆ is absent in Y₂ receptor knockout mice and diminished by a selective Y₂ antagonist (32). Reduction in NPY neuronal activity also increases activation of arcuate neurons expressing POMC, which may contribute to reduced food intake.

Although peripheral PYY₃₋₃₆ 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. PYY₃₋₃₆ 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 PYY₃₋₃₆ on appetite (80). However, peripheral administration of PYY₃₋₃₆ also reduces plasma ghrelin levels (31), which may contribute to its anorectic effect. However, the ano-

rectic effect of PYY₃₋₃₆ does appear to depend on minimization of environmental stress (169) and therefore some have found its actions difficult to reproduce (402). Both stress and PYY₃₋₃₆ act via the arcuate nucleus to alter food intake (86, 260). When appetite is inhibited by stress, no further inhibition can occur with PYY₃₋₃₆ administration. Because rodents are easily stressed, inappropriate experimental conditions would mask the anorectic effect of PYY₃₋₃₆ leading to the variability reported.

The role of PYY in regulation of body weight is less clear. In rodents, chronic peripheral administration of PYY₃₋₃₆ 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 PYY₃₋₃₆ 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 PYY₃₋₃₆ has the potential to be an effective obesity therapy.

In contrast to peripheral PYY₃₋₃₆, centrally administered PYY₁₋₃₆ and PYY₃₋₃₆ increase food intake. PYY injection into the third, lateral or fourth cerebral ventricles (77, 89), the PVN (376), or the hippocampus (163) potentially stimulates food intake in rodents. However, this effect is reduced in both Y₁ and Y₅ receptor knockout mice (205). Therefore, while circulating PYY₃₋₃₆ may access the higher affinity ARC Y₂ receptors (32), the central feeding effects of PYY₁₋₃₆ and PYY₃₋₃₆ may be mediated by the lower affinity Y₁ and Y₅ 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 proglucagon 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 *Heterodermis*), 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

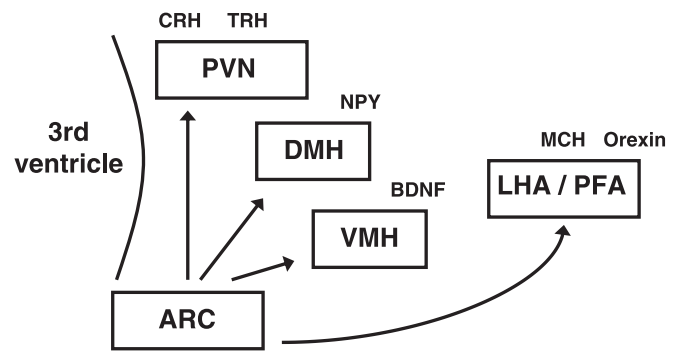


FIG. 2. Morphologically defined regions of the hypothalamus such as the arcuate nucleus (ARC), paraventricular nucleus (PVN), dorsomedial nucleus (DMH), ventromedial nucleus (VMH), lateral hypothalamic area (LHA), and perifornical area (PFA) appear to play a major role in the regulation of body weight. 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.

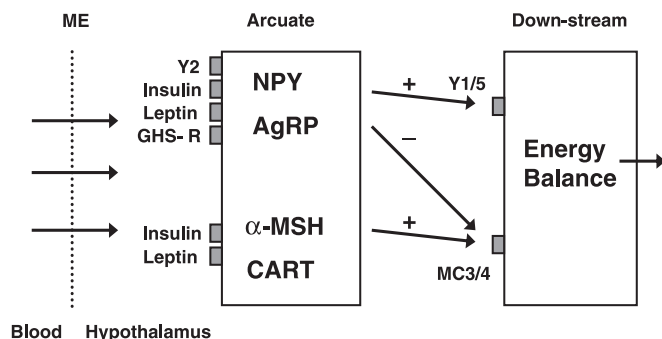


FIG. 3. A schematic representation of arcuate nucleus of the hypothalamus. The arcuate nucleus (ARC) is thought to play a pivotal role in the integration of signals regulating appetite. The ARC neurons express many receptors including those for insulin and leptin, Y2 receptors, and growth hormone secretagogue 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 up-regulated 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 D₁ and D₂ 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

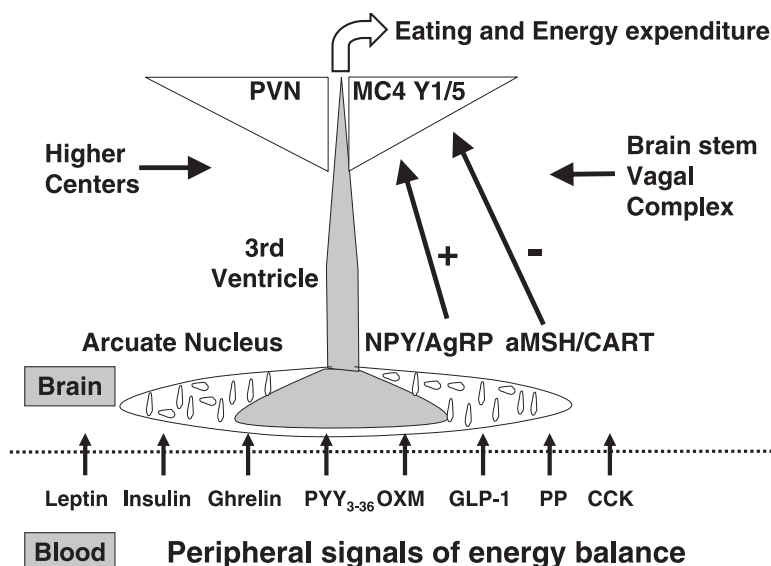


FIG. 4. Working model for energy homeostasis. Peripheral signals of energy balance including leptin, ghrelin, peptide YY₃₋₃₆ (PYY₃₋₃₆), oxyntomodulin (OXM), glucagon-like peptide-1 (GLP-1), pancreatic polypeptide (PP), and cholecystokinin (CCK) cross the blood-brain barrier and act on brain regions such 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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REFERENCES

1. **Abbott CR, Rossi M, Kim M, AlAhmed SH, Taylor GM, Ghatei MA, Smith DM, and Bloom SR.** Investigation of the melanocyte

stimulating hormones on food intake. Lack of evidence to support a role for the melanocortin-3-receptor. *Brain Res* 869: 203–210, 2000.

2. **Abbott CR, Rossi M, Wren AM, Murphy KG, Kennedy AR, Stanley SA, Zollner AN, Morgan DG, Morgan I, Ghatei MA, Small CJ, and Bloom SR.** Evidence of an orexigenic role for cocaine- and amphetamine-regulated transcript after administration into discrete hypothalamic nuclei. *Endocrinology* 142: 3457–3463, 2001.
3. **Abel EL.** Cannabis: effects on hunger and thirst. *Behav Biol* 15: 255–281, 1975.
4. **Adrian TE, Bloom SR, Bryant MG, Polak JM, Heitz PH, and Barnes AJ.** Distribution and release of human pancreatic polypeptide. *Gut* 17: 940–944, 1976.
5. **Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, and Bloom SR.** Human distribution and release of a putative new gut hormone, peptide YY. *Gastroenterology* 89: 1070–1077, 1985.
6. **Adrian TE, Savage AP, Sagor GR, Allen JM, Bacarese-Hamilton AJ, Tatemoto K, Polak JM, and Bloom SR.** Effect of peptide YY on gastric, pancreatic, and biliary function in humans. *Gastroenterology* 89: 494–499, 1985.
7. **Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, and Flier JS.** Role of leptin in the neuroendocrine response to fasting. *Nature* 382: 250–252, 1996.
8. **Air EL, Strowski MZ, Benoit SC, Conarello SL, Salituro GM, Guan XM, Liu K, Woods SC, and Zhang BB.** Small molecule insulin mimetics reduce food intake and body weight and prevent development of obesity. *Nat Med* 8: 179–183, 2002.
9. **Allen JM, Fitzpatrick ML, Yeats JC, Darcy K, Adrian TE, and Bloom SR.** Effects of peptide YY and neuropeptide Y on gastric emptying in man. *Digestion* 30: 255–262, 1984.
10. **Allen YS, Adrian TE, Allen JM, Tatemoto K, Crow TJ, Bloom SR, and Polak JM.** Neuropeptide Y distribution in the rat brain. *Science* 221: 877–879, 1983.
11. **Alvarez BM, Borque M, Martinez-Sarmiento J, Aparicio E, Hernandez C, Cabrerizo L, and Fernandez-Represa J.** A peptide YY secretion in morbidly obese patients before and after vertical banded gastroplasty. *Obesity Surg* 12: 324–327, 2002.
12. **Anand BK and Brobeck JR.** Localization of a “feeding center” in the hypothalamus of the rat. *Proc Soc Exp Biol Med* 77: 323–324, 1951.
13. **Andersson U, Filipsson K, Abbott CR, Woods A, Smith K, Bloom SR, Carling D, and Small CJ.** AMP-activated protein kinase plays a role in the control of food intake. *J Biol Chem* 279: 12005–12008, 2004.
14. **Araki E, Lipes MA, Patti ME, Bruning JC, Haag B III, Johnson RS, and Kahn CR.** Alternative pathway of insulin signalling in mice with targeted disruption of the IRS-1 gene. *Nature* 372: 186–190, 1994.
15. **Argyropoulos G, Rankinen T, Neufeld DR, Rice T, Province MA, Leon AS, Skinner JS, Wilmore JH, Rao DC, and Bouchard C.** A polymorphism in the human agouti-related protein is associated with late-onset obesity. *J Clin Endocrinol Metab* 87: 4198–4202, 2002.
16. **Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoaka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, and Matsuzawa Y.** Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 257: 79–83, 1999.
17. **Ariyasu H, Takaya K, Tagami T, Ogawa Y, Hosoda K, Akamizu T, Suda M, Koh T, Natsui K, Toyooka S, Shirakami G, Usui T, Shimatsu A, Doi K, Hosoda H, Kojima M, Kangawa K, and Nakao K.** Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. *J Clin Endocrinol Metab* 86: 4753–4758, 2001.
18. **Arosio M, Ronchi CL, Gebbia C, Cappiello V, Beck-Peccoz P, and Peracchi M.** Stimulatory effects of ghrelin on circulating somatostatin and pancreatic polypeptide levels. *J Clin Endocrinol Metab* 88: 701–704, 2003.

19. **Asakawa A, Inui A, Ueno N, Fujimiya M, Fujino MA, and Kasuga M.** Mouse pancreatic polypeptide modulates food intake, while not influencing anxiety in mice. *Peptides* 20: 1445–1448, 1999.
20. **Asakawa A, Inui A, Yuzuriha H, Ueno N, Katsuura G, Fujimiya M, Fujino MA, Nijima A, Meguid MM, and Kasuga M.** Characterization of the effects of pancreatic polypeptide in the regulation of energy balance. *Gastroenterology* 124: 1325–1336, 2003.
21. **Asin KE, Gore PA Jr, Bednarz L, Holladay M, and Nadzan AM.** Effects of selective CCK receptor agonists on food intake after central or peripheral administration in rats. *Brain Res* 571: 169–174, 1992.
22. **Atkinson RL and Brent EL.** Appetite suppressant activity in plasma of rats after intestinal bypass surgery. *Am J Physiol Regul Integr Comp Physiol* 243: R60–R64, 1982.
23. **Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Marchand-Brustel Y, and Lewin MJ.** The stomach is a source of leptin. *Nature* 394: 790–793, 1998.
24. **Bagdade JD, Bierman EL, and Porte D Jr.** The significance of basal insulin levels in the evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. *J Clin Invest* 46: 1549–1557, 1967.
25. **Bagnasco M, Dube MG, Kalra PS, and Kalra SP.** Evidence for the existence of distinct central appetite, energy expenditure, and ghrelin stimulation pathways as revealed by hypothalamic site-specific leptin gene therapy. *Endocrinology* 143: 4409–4421, 2002.
26. **Bai FL, Yamano M, Shiotani Y, Emson PC, Smith AD, Powell JF, and Tohyama M.** An arcuato-paraventricular and -dorsomedial hypothalamic neuropeptide Y-containing system which lacks noradrenaline in the rat. *Brain Res* 331: 172–175, 1985.
27. **Banks WA.** The source of cerebral insulin. *Eur J Pharmacol* 490: 5–12, 2004.
28. **Banks WA, Kastin AJ, Huang W, Jaspan JB, and Maness LM.** Leptin enters the brain by a saturable system independent of insulin. *Peptides* 17: 305–311, 1996.
29. **Bannon AW, Seda J, Carmouche M, Francis JM, Norman MH, Karbon B, and McCaleb ML.** Behavioral characterization of neuropeptide Y knockout mice. *Brain Res* 868: 79–87, 2000.
30. **Baskin DG, Schwartz MW, Sipols AJ, D'Alessio DA, Goldstein BJ, and White MF.** Insulin receptor substrate-1 (IRS-1) expression in rat brain. *Endocrinology* 134: 1952–1955, 1994.
31. **Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, and Bloom SR.** Inhibition of food intake in obese subjects by peptide YY3–36. *N Engl J Med* 349: 941–948, 2003.
32. **Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, and Bloom SR.** Gut hormone PYY(3–36) physiologically inhibits food intake. *Nature* 418: 650–654, 2002.
33. **Batterham RL, Le Roux CW, Cohen MA, Park A, Ellis SM, Patterson M, Frost GS, Ghatei MA, and Bloom SR.** Pancreatic polypeptide reduces appetite and food intake in humans. *J Clin Endocrinol Metab* 88: 3989–3992, 2003.
34. **Baura GD, Foster DM, Porte D Jr, Kahn SE, Bergman RN, Cobelli C, and Schwartz MW.** Saturable transport of insulin from plasma into the central nervous system of dogs in vivo: A mechanism for regulated insulin delivery to the brain. *J Clin Invest* 92: 1824–1830, 1993.
35. **Bays H and Dujovne C.** Pharmacotherapy of obesity: currently marketed and upcoming agents. *Am J Cardiovasc Drugs* 2: 245–253, 2002.
36. **Beglinger C, Degen L, Matzinger D, D'Amato M, and Drewe J.** Loxiglumide, a CCK-A receptor antagonist, stimulates calorie intake and hunger feelings in humans. *Am J Physiol Regul Integr Comp Physiol* 280: R1149–R1154, 2001.
37. **Benoit SC, Air EL, Coolen LM, Strauss R, Jackman A, Clegg DJ, Seeley RJ, and Woods SC.** The catabolic action of insulin in the brain is mediated by melanocortins. *J Neurosci* 22: 9048–9052, 2002.
38. **Benoit SC, Schwartz MW, Lachey JL, Hagan MM, Rushing PA, Blake KA, Yagaloff KA, Kurylko G, Franco L, Danhoo W, and Seeley RJ.** A novel selective melanocortin-4 receptor agonist reduces food intake in rats and mice without producing aversive consequences. *J Neurosci* 20: 3442–3448, 2000.
39. **Berg AH, Combs TP, Du X, Brownlee M, and Scherer PE.** The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 7: 947–953, 2001.
40. **Bernardis LL and Bellinger LL.** The lateral hypothalamic area revisited: ingestive behavior. *Neurosci Biobehav Rev* 20: 189–287, 1996.
41. **Bernardis LL and Bellinger LL.** The dorsomedial hypothalamic nucleus revisited: 1986 update. *Brain Res* 434: 321–381, 1987.
42. **Berntson GG, Zipf WB, O'Dorisio TM, Hoffman JA, and Chance RE.** Pancreatic polypeptide infusions reduce food intake in Prader-Willi syndrome. *Peptides* 14: 497–503, 1993.
43. **Berridge KC.** Modulation of taste affect by hunger, caloric satiety, and sensory-specific satiety in the rat. *Appetite* 16: 103–120, 1991.
44. **Besterman HS, Cook GC, Sarson DL, Christofides ND, Bryant MG, Gregor M, and Bloom SR.** Gut hormones in tropical malabsorption. *Br Med J* 2: 1252–1255, 1979.
45. **Bi S, Ladenheim EE, Schwartz GJ, and Moran TH.** A role for NPY overexpression in the dorsomedial hypothalamus in hyperphagia and obesity of OLETF rats. *Am J Physiol Regul Integr Comp Physiol* 281: R254–R260, 2001.
46. **Billington CJ, Briggs JE, Grace M, and Levine AS.** Effects of intracerebroventricular injection of neuropeptide Y on energy metabolism. *Am J Physiol Regul Integr Comp Physiol* 260: R321–R327, 1991.
47. **Blevins JE, Stanley BG, and Reidelberger RD.** Brain regions where cholecystokinin suppresses feeding in rats. *Brain Res* 860: 1–10, 2000.
48. **Boonacker E and Van Noorden CJ.** The multifunctional or moonlighting protein CD26/DPPIV. *Eur J Cell Biol* 82: 53–73, 2003.
49. **Borowsky B, Durkin MM, Ogozalek K, Marzabadi MR, DeLeon J, Lagu B, Heurich R, Lichtblau H, Shaposhnik Z, Daniewska I, Blackburn TP, Brancheck TA, Gerald C, Vaysse PJ, and Forray C.** Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist. *Nat Med* 8: 825–830, 2002.
50. **Bray GA.** Afferent signals regulating food intake. *Proc Nutr Soc* 59: 373–384, 2000.
51. **Broadwell RD and Brightman MW.** Entry of peroxidase into neurons of the central and peripheral nervous systems from extracerebral and cerebral blood. *J Comp Neurol* 166: 257–283, 1976.
52. **Broberger C, De Lecea L, Sutcliffe JG, and Hokfelt T.** Hypocretin/orexin- and melanin-concentrating hormone-expressing cells form distinct populations in the rodent lateral hypothalamus: relationship to the neuropeptide Y and agouti gene-related protein systems. *J Comp Neurol* 402: 460–474, 1998.
53. **Broberger C, Johansen J, Johansson C, Schalling M, and Hokfelt T.** The neuropeptide Y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. *Proc Natl Acad Sci USA* 95: 15043–15048, 1998.
54. **Broberger C, Landry M, Wong H, Walsh JN, and Hokfelt T.** Subtypes Y1 and Y2 of the neuropeptide Y receptor are respectively expressed in pro-opiomelanocortin- and neuropeptide-Y-containing neurons of the rat hypothalamic arcuate nucleus. *Neuroendocrinology* 66: 393–408, 1997.
55. **Bronstein DM, Schafer MK, Watson SJ, and Akil H.** Evidence that beta-endorphin is synthesized in cells in the nucleus tractus solitarius: detection of POMC mRNA. *Brain Res* 587: 269–275, 1992.
56. **Bruning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W, Muller-Wieland D, and Kahn CR.** Role of brain insulin receptor in control of body weight and reproduction. *Science* 289: 2122–2125, 2000.
57. **Bullock BP, Heller RS, and Habener JF.** Tissue distribution of messenger ribonucleic acid encoding the rat glucagon-like peptide-1 receptor. *Endocrinology* 137: 2968–2978, 1996.
58. **Burks DJ, de Mora JF, Schubert M, Withers DJ, Myers MG, Towery HH, Altamuro SL, Flint CL, and White MF.** IRS-2 pathways integrate female reproduction and energy homeostasis. *Nature* 407: 377–382, 2000.
59. **Butler AA.** Studies defining the role of the melanocortin-3 receptor in the development of obesity and insulin resistance (Abstract). *Proc Annu Meet Am Endocr Soc* 2004.

60. Butler AA, Kesterson RA, Khong K, Cullen MJ, Pelley-mounter MA, Dekoning J, Baetscher M, and Cone RD. A unique metabolic syndrome causes obesity in the melanocortin-3 receptor-deficient mouse. *Endocrinology* 141: 3518–3521, 2000.
61. Cai XJ, Widdowson PS, Harrold J, Wilson S, Buckingham RE, Arch JR, Tadayyon M, Clapham JC, Wilding J, and Williams G. Hypothalamic orexin expression: modulation by blood glucose and feeding. *Diabetes* 48: 2132–2137, 1999.
62. Callahan HS, Cummings DE, Pepe MS, Breen PA, Matthys CC, and Weigle DS. Postprandial suppression of plasma ghrelin level is proportional to ingested caloric load but does not predict inter-meal interval in humans. *J Clin Endocrinol Metab* 89: 1319–1324, 2004.
63. Campbell RE, Smith MS, Allen SE, Grayson BE, French-Mullen JM, and Grove KL. Orexin neurons express a functional pancreatic polypeptide Y4 receptor. *J Neurosci* 23: 1487–1497, 2003.
64. Campfield LA, Smith FJ, Guisez Y, Devos R, and Burn P. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science* 269: 546–549, 1995.
65. Challis BG, Coll AP, Yeo GS, Pinnock SB, Dickson SL, Thresher RR, Dixon J, Zahn D, Rochford JJ, White A, Oliver RL, Millington G, Aparicio SA, Colledge WH, Russ AP, Carlton MB, and O'Rahilly S. Mice lacking pro-opiomelanocortin are sensitive to high-fat feeding but respond normally to the acute anorectic effects of peptide-YY(3–36). *Proc Natl Acad Sci USA* 101: 4695–4700, 2004.
66. Challis BG, Pinnock SB, Coll AP, Carter RN, Dickson SL, and O'Rahilly S. Acute effects of PYY3–36 on food intake and hypothalamic neuropeptide expression in the mouse. *Biochem Biophys Res Commun* 311: 915–919, 2003.
67. Chehab FF, Lim ME, and Lu R. Correction of the sterility defect in homozygous obese female mice by treatment with the human recombinant leptin. *Nat Genet* 12: 318–320, 1996.
68. Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato M, Hammer RE, Saper CB, and Yanagisawa M. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell* 98: 437–451, 1999.
69. Chen H, Charlat O, Tartaglia LA, Woolf EA, Weng X, Ellis SJ, Lakey ND, Culpepper J, Moore KJ, Breitbart RE, Duyk GM, Tepper RI, and Morgenstern JP. Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in *db/db* mice. *Cell* 84: 491–495, 1996.
70. Chen HY, Trumbauer ME, Chen AS, Weingarth DT, Adams JR, Frazier EG, Shen Z, Marsh DJ, Feighner SD, Guan XM, Ye Z, Nargund RP, Smith RG, Van der Ploeg LH, Howard AD, MacNeil DJ, and Qian S. Orexigenic action of peripheral ghrelin is mediated by neuropeptide Y (NPY) and agouti-related protein (AgRP). *Endocrinology* 145: 2607–2612, 2004.
71. Chen P, Williams SM, Grove KL, and Smith MS. Melanocortin 4 receptor-mediated hyperphagia and activation of neuropeptide Y expression in the dorsomedial hypothalamus during lactation. *J Neurosci* 24: 5091–5100, 2004.
72. Cheng X, Broberger C, Tong Y, Yongtao X, Ju G, Zhang X, and Hokfelt T. Regulation of expression of neuropeptide Y Y1 and Y2 receptors in the arcuate nucleus of fasted rats. *Brain Res* 792: 89–96, 1998.
73. Cheung CC, Clifton DK, and Steiner RA. Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. *Endocrinology* 138: 4489–4492, 1997.
74. Christofides ND, Sarson DL, Albuquerque RH, Adrian TE, Ghatei MA, Modlin IM, and Bloom SR. Release of gastrointestinal hormones following an oral water load. *Experientia* 35: 1521–1523, 1979.
75. Chua SC Jr, Koutras IK, Han L, Liu SM, Kay J, Young SJ, Chung WK, and Leibel RL. Fine structure of the murine leptin receptor gene: splice site suppression is required to form two alternatively spliced transcripts. *Genomics* 45: 264–270, 1997.
76. Clark JT, Kalra PS, Crowley WR, and Kalra SP. Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. *Endocrinology* 115: 427–429, 1984.
77. Clark JT, Sahu A, Kalra PS, Balasubramanian A, and Kalra SP. Neuropeptide Y (NPY)-induced feeding behavior in female rats: comparison with human NPY ([Met17]NPY), NPY analog ([norLeu4]NPY) and peptide YY. *Regul Pept* 17: 31–39, 1987.
78. Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelin M, Dina C, Chambaz J, Lacorte JM, Basdevant A, Bougneres P, Lebouc Y, Froguel P, and Guy-Grand B. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 392: 398–401, 1998.
79. Cohen MA, Ellis SM, Le Roux CW, Batterham RL, Park A, Patterson M, Frost GS, Ghatei MA, and Bloom SR. Oxyntomodulin suppresses appetite and reduces food intake in humans. *J Clin Endocrinol Metab* 88: 4696–4701, 2003.
80. Coll AP, Challis BG, and O'Rahilly S. Peptide YY3–36 and satiety: clarity or confusion? *Endocrinology* 145: 2582–2584, 2004.
81. Colombo G, Agabio R, Diaz G, Lobina C, Reali R, and Gessa GL. Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. *Life Sci* 63: L113–L117, 1998.
82. Combs TP, Pajvani UB, Berg AH, Lin Y, Jelicks LA, Laplante M, Nawrocki AR, Rajala MW, Parlow AF, Cheesebore L, Ding YY, Russell RG, Lindemann D, Hartley A, Baker GR, Obici S, Deshaies Y, Ludgate M, Rossetti L, and Scherer PE. A transgenic mouse with a deletion in the collagenous domain of adiponectin displays elevated circulating adiponectin and improved insulin sensitivity. *Endocrinology* 145: 367–383, 2004.
83. Combs TP, Wagner JA, Berger J, Doebber T, Wang WJ, Zhang BB, Tanen M, Berg AH, O'Rahilly S, Savage DB, Chatterjee K, Weiss S, Larson PJ, Gottesdiener KM, Gertz BJ, Charron MJ, Scherer PE, and Moller DE. Induction of adipocyte complement-related protein of 30 kilodaltons by PPARgamma agonists: a potential mechanism of insulin sensitization. *Endocrinology* 143: 998–1007, 2002.
84. Cone RD, Cowley MA, Butler AA, Fan W, Marks DL, and Low MJ. The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. *Int J Obesity Related Metab Disorders* 25 Suppl 5: S63–S67, 2001.
85. Conlon JM. The origin and evolution of peptide YY (PYY) and pancreatic polypeptide (PP). *Peptides* 23: 269–278, 2002.
86. Conrad CD and McEwen BS. Acute stress increases neuropeptide Y mRNA within the arcuate nucleus and hilus of the dentate gyrus. *Brain Res* 79: 102–109, 2000.
87. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, and Bauer TL. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 334: 292–295, 1996.
88. Corp ES, Woods SC, Porte D Jr, Dorsa DM, Figlewicz DP, and Baskin DG. Localization of ¹²⁵I-insulin binding sites in the rat hypothalamus by quantitative autoradiography. *Neurosci Lett* 70: 17–22, 1986.
89. Corpa ES, McQuade J, Krasnicki S, and Conze DB. Feeding after fourth ventricular administration of neuropeptide Y receptor agonists in rats. *Peptides* 22: 493–499, 2001.
90. Cota D, Marsicano G, Tschop M, Grubler Y, Flachskamm C, Schubert M, Auer D, Yassouridis A, Thone-Reineke C, Ortman S, Tomassoni F, Cervino C, Nisoli E, Linthorst AC, Pasquali R, Lutz B, Stalla GK, and Pagotto U. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest* 112: 423–431, 2003.
91. Couceyro PR, Koylu EO, and Kuhar MJ. Further studies on the anatomical distribution of CART by in situ hybridization. *J Chem Neuroanat* 12: 229–241, 1997.
92. Cowley MA, Pronchuk N, Fan W, Dinulescu DM, Colmers WF, and Cone RD. Integration of NPY, AGRP, and melanocortin signals in the hypothalamic paraventricular nucleus: evidence of a cellular basis for the adipostat. *Neuron* 24: 155–163, 1999.
93. Cowley MA, Smith RG, Diano S, Tschop M, Pronchuk N, Grove KL, Strasburger CJ, Bidlingmaier M, Esterman G, Heiman ML, Garcia-Segura LM, Nillni EA, Mendez P, Low MJ, Sotonyi P, Friedman JM, Liu H, Pinto S, Colmers WF, Cone RD, and Horvath TL. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. *Neuron* 37: 649–661, 2003.

94. **Crawley JN and Beinfeld MC.** Rapid development of tolerance to the behavioural actions of cholecystokinin. *Nature* 302: 703–706, 1983.
95. **Crawley JN and Corwin RL.** Biological actions of cholecystokinin. *Peptides* 15: 731–755, 1994.
96. **Cummings DE, Clement K, Purnell JQ, Vaisse C, Foster KE, Frayo RS, Schwartz MW, Basdevant A, and Weigle DS.** Elevated plasma ghrelin levels in Prader Willi syndrome. *Nat Med* 8: 643–644, 2002.
97. **Cummings DE, Frayo RS, Marmonier C, Aubert R, and Chapelot D.** Plasma ghrelin levels and hunger scores among humans initiating meals voluntarily in the absence of time- and food-related cues. *Am J Physiol Endocrinol Metab* 287: E297–E304, 2004.
98. **Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, and Weigle DS.** A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes* 50: 1714–1719, 2001.
99. **Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, and Purnell JQ.** Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* 346: 1623–1630, 2002.
100. **Dakin CL, Gunn I, Small CJ, Edwards CM, Hay DL, Smith DM, Ghatei MA, and Bloom SR.** Oxyntomodulin inhibits food intake in the rat. *Endocrinology* 142: 4244–4250, 2001.
101. **Dakin CL, Small CJ, Batterham RL, Neary NM, Cohen MA, Patterson M, Ghatei MA, and Bloom SR.** Peripheral oxyntomodulin reduces food intake and body weight gain in rats. *Endocrinology* 145: 2687–2695, 2004.
102. **Dakin CL, Small CJ, Batterham RL, Neary NM, Cohen MA, Patterson M, Ghatei MA, and Bloom SR.** Peripheral oxyntomodulin reduces food intake and body weight gain in rats. *Endocrinology* 145: 2687–2695, 2004.
103. **Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T, Matsukura S, Kangawa K, and Nakazato M.** Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology* 141: 4255–4261, 2000.
104. **Date Y, Murakami N, Kojima M, Kuroiwa T, Matsukura S, Kangawa K, and Nakazato M.** Central effects of a novel acylated peptide, ghrelin, on growth hormone release in rats. *Biochem Biophys Res Commun* 275: 477–480, 2000.
105. **Date Y, Murakami N, Toshinai K, Matsukura S, Nijima A, Matsuo H, Kangawa K, and Nakazato M.** The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats. *Gastroenterology* 123: 1120–1128, 2002.
106. **Date Y, Nakazato M, Hashiguchi S, Dezaki K, Mondal MS, Hosoda H, Kojima M, Kangawa K, Arima T, Matsuo H, Yada T, and Matsukura S.** Ghrelin is present in pancreatic alpha-cells of humans and rats and stimulates insulin secretion. *Diabetes* 51: 124–129, 2002.
107. **Davis HR Jr, Mullins DE, Pines JM, Hoos LM, France CF, Compton DS, Graziano MP, Sybertz EJ, Strader CD and Van Heek M.** Effect of chronic central administration of glucagon-like peptide-1 (7–36) amide on food consumption and body weight in normal and obese rats. *Obesity Res* 6: 147–156, 1998.
108. **Debons AF, Krimsky I, Maayan ML, Fani K, and Jemenez FA.** Gold thioglucose obesity syndrome. *Federation Proc* 36: 143–147, 1977.
109. **De Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett FS, Frankel WN, van den Pol AN, Bloom FE, Gautvik KM, and Sutcliffe JG.** The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci USA* 95: 322–327, 1998.
110. **Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffing G, Gibson D, Mandelbaum A, Etinger A, and Mechoulam R.** Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 258: 1946–1949, 1992.
111. **Dhillo WS, Small CJ, Stanley SA, Jethwa PH, Seal LJ, Murphy KG, Ghatei MA, and Bloom SR.** Hypothalamic interactions between neuropeptide Y, agouti-related protein, cocaine- and amphetamine-regulated transcript and alpha-melanocyte-stimulating hormone in vitro in male rats. *J Neuroendocrinol* 14: 725–730, 2002.
112. **Di M, V, Goparaju SK, Wang L, Liu J, Batkai S, Jarai Z, Fezza F, Miura GI, Palmiter RD, Sugiura T, and Kunos G.** Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature* 410: 822–825, 2001.
113. **Donahay JC, Van Dijk G, Woods SC, and Seeley RJ.** Intraventricular GLP-1 reduces short- but not long-term food intake or body weight in lean and obese rats. *Brain Res* 779: 75–83, 1998.
114. **Drewnowski A, Krahn DD, Demitrack MA, Nairn K, and Gonnell BA.** Taste responses and preferences for sweet high-fat foods: evidence for opioid involvement. *Physiol Behav* 51: 371–379, 1992.
115. **Dumont Y, Fournier A, and Quirion R.** Expression and characterization of the neuropeptide Y Y5 receptor subtype in the rat brain. *J Neurosci* 18: 5565–5574, 1998.
116. **Eberlein GA, Eysselein VE, Schaeffer M, Layer P, Grandt D, Goebell H, Niebel W, Davis M, Lee TD, and Shively JE.** A new molecular form of PYY: structural characterization of human PYY(3–36) and PYY(1–36). *Peptides* 10: 797–803, 1989.
117. **Edwards CM, Abusnana S, Sunter D, Murphy KG, Ghatei MA, and Bloom SR.** The effect of the orexins on food intake: comparison with neuropeptide Y, melanin-concentrating hormone and galanin. *J Endocrinol* 160: R7–R12, 1999.
118. **Egawa M, Yoshimatsu H, and Bray GA.** Neuropeptide Y suppresses sympathetic activity to interscapular brown adipose tissue in rats. *Am J Physiol Regul Integr Comp Physiol* 260: R328–R334, 1991.
119. **Ehrstrom M, Naslund E, Levin F, Kaur R, Kirchgessner AL, Theodorsson E, and Hellstrom PM.** Pharmacokinetic profile of orexin A and effects on plasma insulin and glucagon in the rat. *Regul Pept* 119: 209–212, 2004.
120. **Ekblad E and Sundler F.** Distribution of pancreatic polypeptide and peptide YY. *Peptides* 23: 251–261, 2002.
121. **El Haschimi K, Pierroz DD, Hileman SM, Bjorbaek C, and Flier JS.** Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity. *J Clin Invest* 105: 1827–1832, 2000.
122. **Elias CF, Aschkenasi C, Lee C, Kelly J, Ahima RS, Bjorbaek C, Flier JS, Saper CB, and Elmquist JK.** Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. *Neuron* 23: 775–786, 1999.
123. **Elias CF, Lee C, Kelly J, Aschkenasi C, Ahima RS, Couceyro PR, Kuhar MJ, Saper CB, and Elmquist JK.** Leptin activates hypothalamic CART neurons projecting to the spinal cord. *Neuron* 21: 1375–1385, 1998.
124. **Elias CF, Saper CB, Maratos-Flier E, Tritos NA, Lee C, Kelly J, Tatro JB, Hoffman GE, Ollmann MM, Barsh GS, Sakurai T, Yanagisawa M, and Elmquist JK.** Chemically defined projections linking the mediobasal hypothalamus and the lateral hypothalamic area. *J Comp Neurol* 402: 442–459, 1998.
125. **Ellacott KL and Cone RD.** The central melanocortin system and the integration of short- and long-term regulators of energy homeostasis. *Recent Prog Horm Res* 59: 395–408, 2004.
126. **Ellacott KL, Lawrence CB, Pritchard LE, and Luckman SM.** Repeated administration of the anorectic factor prolactin-releasing peptide leads to tolerance to its effects on energy homeostasis. *Am J Physiol Regul Integr Comp Physiol* 285: R1005–R1010, 2003.
127. **Elmquist JK, Ahima RS, Maratos-Flier E, Flier JS, and Saper CB.** Leptin activates neurons in ventrobasal hypothalamus and brainstem. *Endocrinology* 138: 839–842, 1997.
128. **Elmquist JK, Bjorbaek C, Ahima RS, Flier JS, and Saper CB.** Distributions of leptin receptor mRNA isoforms in the rat brain. *J Comp Neurol* 395: 535–547, 1998.
129. **Elmquist JK, Maratos-Flier E, Saper CB, and Flier JS.** Unraveling the central nervous system pathways underlying responses to leptin. *Nat Neurosci* 1: 445–450, 1998.
130. **English PJ, Ghatei MA, Malik IA, Bloom SR, and Wilding JP.** Food fails to suppress ghrelin levels in obese humans. *J Clin Endocrinol Metab* 87: 2984, 2002.
131. **Fan W, Boston BA, Kesterson RA, Hruby VJ, and Cone RD.** Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. *Nature* 385: 165–168, 1997.
132. **Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA, and O'Rahilly S.**

- Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med* 341: 879–884, 1999.
133. **Farooqi IS, Yeo GS, Keogh JM, Aminian S, Jebb SA, Butler G, Cheetham T, and O'Rahilly S.** Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. *J Clin Invest* 106: 271–279, 2000.
 134. **Fehmann HC, Jiang J, Schweinfurth J, Wheeler MB, Boyd AE III, and Goke B.** Stable expression of the rat GLP-I receptor in CHO cells: activation and binding characteristics utilizing GLP-I(7–36)-amide, oxyntomodulin, exendin-4, and exendin(9–39). *Peptides* 15: 453–456, 1994.
 135. **Fei H, Okano HJ, Li C, Lee GH, Zhao C, Darnell R, and Friedman JM.** Anatomic localization of alternatively spliced leptin receptors (Ob-R) in mouse brain and other tissues. *Proc Natl Acad Sci USA* 94: 7001–7005, 1997.
 136. **Fekete C, Legradi G, Mihaly E, Huang QH, Tatro JB, Rand WM, Emerson CH, and Lechan RM.** alpha-Melanocyte-stimulating hormone is contained in nerve terminals innervating thyrotropin-releasing hormone-synthesizing neurons in the hypothalamic paraventricular nucleus and prevents fasting-induced suppression of prothyrotropin-releasing hormone gene expression. *J Neurosci* 20: 1550–1558, 2000.
 137. **Fekete C, Sarkar S, Rand WM, Harney JW, Emerson CH, Bianco AC, and Lechan RM.** Agouti-related protein (AGRP) has a central inhibitory action on the hypothalamic-pituitary-thyroid (HPT) axis: comparisons between the effect of AGRP and neuropeptide Y on energy homeostasis and the HPT axis. *Endocrinology* 143: 3846–3853, 2002.
 138. **Finer N.** Pharmacotherapy of obesity. *Best Pract Res Clin Endocrinol Metab* 16: 717–742, 2002.
 139. **Flint A, Raben A, Ersboll AK, Holst JJ, and Astrup A.** The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. *Int J Obesity Related Metab Disorders* 25: 781–792, 2001.
 140. **Flynn MC, Turrin NP, Plata-Salaman CR, and French-Mullen JM.** Feeding response to neuropeptide Y-related compounds in rats treated with Y5 receptor antisense or sense phosphothio-oligonucleotide. *Physiol Behav* 66: 881–884, 1999.
 141. **Fodor M, Sluiter A, Frankhuijzen-Sierevogel A, Wiegant VM, Hoogerhout P, De Wildt DJ, and Versteeg DH.** Distribution of Lys-gamma 2-melanocyte-stimulating hormone- (Lys-gamma 2-MSH)-like immunoreactivity in neuronal elements in the brain and peripheral tissues of the rat. *Brain Res* 731: 182–189, 1996.
 142. **Fogtelloo AJ, Pijl H, Frolich M, McCamish M, and Meinders AE.** Effects of recombinant human leptin treatment as an adjunct of moderate energy restriction on body weight, resting energy expenditure and energy intake in obese humans. *Diabetes Nutr Metab* 16: 109–114, 2003.
 143. **Frederich RC, Lollmann B, Hamann A, Napolitano-Rosen A, Kahn BB, Lowell BB, and Flier JS.** Expression of ob mRNA and its encoded protein in rodents. Impact of nutrition and obesity. *J Clin Invest* 96: 1658–1663, 1995.
 144. **Fride E, Foox A, Rosenberg E, Faigenboim M, Cohen V, Barda L, Blau H, and Mechoulam R.** Milk intake and survival in newborn cannabinoid CB1 receptor knockout mice: evidence for a “CB3” receptor. *Eur J Pharmacol* 7: 27–34, 2003.
 145. **Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, and Lodish HF.** Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci USA* 98: 2005–2010, 2001.
 146. **Fu-Cheng X, Anini Y, Chariot J, Castex N, Galmiche JP, and Roze C.** Mechanisms of peptide YY release induced by an intraduodenal meal in rats: neural regulation by proximal gut. *Pflügers Arch* 433: 571–579, 1997.
 147. **Fujimoto S, Inui A, Kiyota N, Seki W, Koide K, Takamiya S, Uemoto M, Nakajima Y, Baba S, and Kasuga M.** Increased cholecystokinin and pancreatic polypeptide responses to a fat-rich meal in patients with restrictive but not bulimic anorexia nervosa. *Biol Psychiatry* 41: 1068–1070, 1997.
 148. **Fulton S, Woodside B, and Shizgal P.** Modulation of brain reward circuitry by leptin. *Science* 287: 125–128, 2000.
 149. **Fuxe K, Tinner B, Caberlotto L, Bunnemann B, and Agnati LF.** NPY Y1 receptor like immunoreactivity exists in a subpopulation of beta-endorphin immunoreactive nerve cells in the arcuate nucleus: a double immunolabelling analysis in the rat. *Neurosci Lett* 225: 49–52, 1997.
 150. **Ge H, Huang L, Pourbahrami T, and Li C.** Generation of soluble leptin receptor by ectodomain shedding of membrane-spanning receptors in vitro and in vivo. *J Biol Chem* 277: 45898–45903, 2002.
 151. **Ghatei MA, Uttenthal LO, Christofides ND, Bryant MG, and Bloom SR.** Molecular forms of human enteroglucagon in tissue and plasma: plasma responses to nutrient stimuli in health and in disorders of the upper gastrointestinal tract. *J Clin Endocrinol Metab* 57: 488–495, 1983.
 152. **Gibbs J, Fauser DJ, Rowe EA, Rolls BJ, Rolls ET, and Madison SP.** Bombesin suppresses feeding in rats. *Nature* 282: 208–210, 1979.
 153. **Gibbs J, Young RC, and Smith GP.** Cholecystokinin decreases food intake in rats. *J Comp Physiol Psychol* 84: 488–495, 1973.
 154. **Giraud SQ, Billington CJ, and Levine AS.** Feeding effects of hypothalamic injection of melanocortin 4 receptor ligands. *Brain Res* 809: 302–306, 1998.
 155. **Glaser B, Zoghlin G, Pienta K, and Vinik AI.** Pancreatic polypeptide response to secretin in obesity: effects of glucose intolerance. *Horm Metab Res* 20: 288–292, 1988.
 156. **Glass MJ, Chan J, and Pickel VM.** Ultrastructural localization of neuropeptide Y Y1 receptors in the rat medial nucleus tractus solitarius: relationships with neuropeptide Y or catecholamine neurons. *J Neurosci Res* 67: 753–765, 2002.
 157. **Glover I, Haneef I, Pitts J, Wood S, Moss D, Tickle I, and Blundell T.** Conformational flexibility in a small globular hormone: x-ray analysis of avian pancreatic polypeptide at 0.98-Å resolution. *Biopolymers* 22: 293–304, 1983.
 158. **Grandt D, Schimiczek M, Beglinger C, Layer P, Goebell H, Eysselein VE, and Reeve JR Jr.** Two molecular forms of peptide YY (PYY) are abundant in human blood: characterization of a radioimmunoassay recognizing PYY 1–36 and PYY 3–36. *Regul Pept* 51: 151–159, 1994.
 159. **Grauerholz BL, Jacobson JD, Handler MS, and Millington WR.** Detection of pro-opiomelanocortin mRNA in human and rat caudal medulla by RT-PCR. *Peptides* 19: 939–948, 1998.
 160. **Gualillo O, Caminos J, Blanco M, Garcia-Caballero T, Kojima M, Kangawa K, Dieguez C, and Casanueva F.** Ghrelin, a novel placental-derived hormone. *Endocrinology* 142: 788–794, 2001.
 161. **Guan XM, Yu H, and Van der Ploeg LH.** Evidence of altered hypothalamic pro-opiomelanocortin/neuropeptide Y mRNA expression in tubby mice. *Brain Res* 59: 273–279, 1998.
 162. **Hagan JJ, Leslie RA, Patel S, Evans ML, Wattam TA, Holmes S, Benham CD, Taylor SG, Routledge C, Hemmati P, Munton RP, Ashmeade TE, Shah AS, Hatcher JP, Hatcher PD, Jones DN, Smith MI, Piper DC, Hunter AJ, Porter RA, and Upton N.** Orexin A activates locus coeruleus cell firing and increases arousal in the rat. *Proc Natl Acad Sci USA* 96: 10911–10916, 1999.
 163. **Hagan MM, Castaneda E, Sumaya IC, Fleming SM, Galloway J, and Moss DE.** The effect of hypothalamic peptide YY on hippocampal acetylcholine release in vivo: implications for limbic function in binge-eating behavior. *Brain Res* 805: 20–28, 1998.
 164. **Hagan MM, Rushing PA, Benoit SC, Woods SC, and Seeley RJ.** Opioid receptor involvement in the effect of AgRP-(83–132) on food intake and food selection. *Am J Physiol Regul Integr Comp Physiol* 280: R814–R821, 2001.
 165. **Hagan MM, Rushing PA, Pritchard LM, Schwartz MW, Strack AM, Van der Ploeg LH, Woods SC, and Seeley RJ.** Long-term orexigenic effects of AgRP-(83–132) involve mechanisms other than melanocortin receptor blockade. *Am J Physiol Regul Integr Comp Physiol* 279: R47–R52, 2000.
 166. **Hahn TM, Breininger JF, Baskin DG, and Schwartz MW.** Co-expression of Agrp and NPY in fasting-activated hypothalamic neurons. *Nat Neurosci* 1: 271–272, 1998.
 167. **Hakansson ML, Brown H, Ghilardi N, Skoda RC, and Meister B.** Leptin receptor immunoreactivity in chemically defined target neurons of the hypothalamus. *J Neurosci* 18: 559–572, 1998.
 168. **Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, and Friedman JM.** Weight-

- reducing effects of the plasma protein encoded by the obese gene. *Science* 269: 543–546, 1995.
169. Halatchev IG, Ellacott KL, Fan W, and Cone RD. Peptide YY3–36 inhibits food intake in mice through a melanocortin-4 receptor-independent mechanism. *Endocrinology* 145: 2585–2590, 2004.
 170. Halford JC, Harrold JA, Lawton CL, and Blundell JE. Serotonin (5-HT) drugs: effects on appetite expression and use for the treatment of obesity. *Curr Drug Targets* 6: 201–213, 2005.
 171. Hamamura M, Leng G, Emson PC, and Kiyama H. Electrical activation and *c-fos* mRNA expression in rat neurosecretory neurones after systemic administration of cholecystokinin. *J Physiol* 444: 51–63, 1991.
 172. Hansen TK, Dall R, Hosoda H, Kojima M, Kangawa K, Christiansen JS, and Jorgensen JO. Weight loss increases circulating levels of ghrelin in human obesity. *Clin Endocrinol* 56: 203–206, 2002.
 173. Hao S, Avraham Y, Mechoulam R, and Berry EM. Low dose anandamide affects food intake, cognitive function, neurotransmitter and corticosterone levels in diet-restricted mice. *Eur J Pharmacol* 392: 147–156, 2000.
 174. Harfstrand A, Fuxe K, Agnati LF, Benfenati F, and Goldstein M. Receptor autoradiographical evidence for high densities of ¹²⁵I-neuropeptide Y binding sites in the nucleus tractus solitarius of the normal male rat. *Acta Physiol Scand* 128: 195–200, 1986.
 175. Harrold JA, Widdowson PS, and Williams G. Altered energy balance causes selective changes in melanocortin-4(MC4-R), but not melanocortin-3 (MC3-R), receptors in specific hypothalamic regions: further evidence that activation of MC4-R is a physiological inhibitor of feeding. *Diabetes* 48: 267–271, 1999.
 176. Hattori N, Saito T, Yagyu T, Jiang BH, Kitagawa K, and Inagaki C. GH, GH receptor, GH secretagogue receptor, and ghrelin expression in human T cells, B cells, and neutrophils. *J Clin Endocrinol Metab* 86: 4284–4291, 2001.
 177. Haynes AC, Jackson B, Overend P, Buckingham RE, Wilson S, Tadayyon M, and Arch JR. Effects of single and chronic intracerebroventricular administration of the orexins on feeding in the rat. *Peptides* 20: 1099–1105, 1999.
 178. Hayward MD, Pintar JE, and Low MJ. Selective reward deficit in mice lacking beta-endorphin and enkephalin. *J Neurosci* 22: 8251–8258, 2002.
 179. Heisler LK, Cowley MA, Tecott LH, Fan W, Low MJ, Smart JL, Rubinstein M, Tatsoi JB, Marcus JN, Holstege H, Lee CE, Cone RD, and Elmquist JK. Activation of central melanocortin pathways by fenfluramine. *Science* 297: 609–611, 2002.
 180. Herrmann C, Goke R, Richter G, Fehmann HC, Arnold R, and Goke B. Glucagon-like peptide-1 and glucose-dependent insulin-releasing polypeptide plasma levels in response to nutrients. *Digestion* 56: 117–126, 1995.
 181. Hetherington AW and Ranson SW. Hypothalamic lesions and adiposity in the rat. *Anat Rec* 78: 149–172, 1940.
 182. Hewson G, Leighton GE, Hill RG, and Hughes J. The cholecystokinin receptor antagonist L364,718 increases food intake in the rat by attenuation of the action of endogenous cholecystokinin. *Br J Pharmacol* 93: 79–84, 1988.
 183. Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, Lubina JA, Patane J, Self B, Hunt P, and McCamish M. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA* 282: 1568–1575, 1999.
 184. Hinney A, Hoch A, Geller F, Schafer H, Siegfried W, Goldschmidt H, Remschmidt H, and Hebebrand J. Ghrelin gene: identification of missense variants and a frameshift mutation in extremely obese children and adolescents and healthy normal weight students. *J Clin Endocrinol Metab* 87: 2716, 2002.
 185. Hoentjen F, Hopman WP, and Jansen JB. Effect of circulating peptide YY on gallbladder emptying in humans. *Scand J Gastroenterol* 36: 1086–1091, 2001.
 186. Holst JJ. Treatment of Type 2 diabetes mellitus with agonists of the GLP-1 receptor or DPP-IV inhibitors. *Expert Opin Emerg Drugs* 9: 155–166, 2004.
 187. Holst JJ. Glucagon-like peptide 1 (GLP-1): an intestinal hormone, signalling nutritional abundance, with an unusual therapeutic potential. *Trends Endocrinol Metab* 10: 229–235, 1999.
 188. Holst JJ, Schwartz TW, Lovgreen NA, Pedersen O, and Beck-Nielsen H. Diurnal profile of pancreatic polypeptide, pancreatic glucagon, gut glucagon and insulin in human morbid obesity. *Int J Obes* 7: 529–538, 1983.
 189. Holst JJ, Sorensen TI, Andersen AN, Stadil F, Andersen B, Lauritsen KB, and Klein HC. Plasma enteroglucagon after jejunoileal bypass with 3:1 or 1:3 jejunoileal ratio. *Scand J Gastroenterol* 14: 205–207, 1979.
 190. Horvath TL, Diano S, and van den Pol AN. Synaptic interaction between hypocretin (orexin) and neuropeptide Y cells in the rodent and primate hypothalamus: a novel circuit implicated in metabolic and endocrine regulations. *J Neurosci* 19: 1072–1087, 1999.
 191. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, and Matsuzawa Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 20: 1595–1599, 2000.
 192. Hotta K, Funahashi T, Bodkin NL, Ortmeier HK, Arita Y, Hansen BC, and Matsuzawa Y. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. *Diabetes* 50: 1126–1133, 2001.
 193. Howard JK, Cave BJ, Oksanen LJ, Tzamelis I, Bjorbaek C, and Flier JS. Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of *Socs3*. *Nat Med* 10: 734–738, 2004.
 194. Hu E, Liang P, and Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. *J Biol Chem* 271: 10697–10703, 1996.
 195. Huang XF, Han M, South T, and Storlien L. Altered levels of POMC, AgRP and MC4-R mRNA expression in the hypothalamus and other parts of the limbic system of mice prone or resistant to chronic high-energy diet-induced obesity. *Brain Res* 992: 9–19, 2003.
 196. Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JH, Fang Q, Berkemeier LR, Gu W, Kesterson RA, Boston BA, Cone RD, Smith FJ, Campfield LA, Burn P, and Lee F. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* 88: 131–141, 1997.
 197. Iyata Y, Kawakami F, Fukui K, Obata-Tsuto HL, Tanaka M, Kubo T, Okamura H, Morimoto N, Yanaihara C, and Yanaihara N. Light and electron microscopic immunocytochemistry of neurotensin-like immunoreactive neurons in the rat hypothalamus. *Brain Res* 302: 221–230, 1984.
 198. Ikeda H, West DB, Pustek JJ, Figlewicz DP, Greenwood MR, Porte D Jr, and Woods SC. Intraventricular insulin reduces food intake and body weight of lean but not obese Zucker rats. *Appetite* 7: 381–386, 1986.
 199. Inui A. Neuropeptide Y feeding receptors: are multiple subtypes involved? *Trends Pharmacol Sci* 20: 43–46, 1999.
 200. Jamshidi N and Taylor DA. Anandamide administration into the ventromedial hypothalamus stimulates appetite in rats. *Br J Pharmacol* 134: 1151–1154, 2001.
 201. Kalia M and Sullivan JM. Brainstem projections of sensory and motor components of the vagus nerve in the rat. *J Comp Neurol* 211: 248–265, 1982.
 202. Kalra SP, Dube MG, Pu S, Xu B, Horvath TL, and Kalra PS. Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. *Endocr Rev* 20: 68–100, 1999.
 203. Kalra SP, Dube MG, Sahu A, Phelps CP, and Kalra PS. Neuropeptide Y secretion increases in the paraventricular nucleus in association with increased appetite for food. *Proc Natl Acad Sci USA* 88: 10931–10935, 1991.
 204. Kanatani A, Ishihara A, Asahi S, Tanaka T, Ozaki S, and Ihara M. Potent neuropeptide Y Y1 receptor antagonist, 1229U91: blockade of neuropeptide Y-induced and physiological food intake. *Endocrinology* 137: 3177–3182, 1996.

205. **Kanani A, Mashiko S, Murai N, Sugimoto N, Ito J, Fukuroda T, Fukami T, Morin N, MacNeil DJ, Van der Ploeg LH, Saga Y, Nishimura S, and Ihara M.** Role of the Y1 receptor in the regulation of neuropeptide Y-mediated feeding: comparison of wild-type, Y1 receptor-deficient, and Y5 receptor-deficient mice. *Endocrinology* 141: 1011–1016, 2000.
206. **Kastin AJ, Akerstrom V, and Pan W.** Interactions of glucagon-like peptide-1 (GLP-1) with the blood-brain barrier. *J Mol Neurosci* 18: 7–14, 2002.
207. **Katsuura G, Asakawa A, and Inui A.** Roles of pancreatic polypeptide in regulation of food intake. *Peptides* 23: 323–329, 2002.
208. **Kawai Y, Inagaki S, Shiosaka S, Shibasaki T, Ling N, Tohyama M, and Shiotani Y.** The distribution and projection of gamma-melanocyte stimulating hormone in the rat brain: an immunohistochemical analysis. *Brain Res* 297: 21–32, 1984.
209. **Kelly J, Rothstein J, and Grossman SP.** GABA and hypothalamic feeding systems. I. Topographic analysis of the effects of microinjections of muscimol. *Physiol Behav* 23: 1123–1134, 1979.
210. **Kim MS, Rossi M, Abusnana S, Sunter D, Morgan DG, Small CJ, Edwards CM, Heath MM, Stanley SA, Seal LJ, Bhatti JR, Smith DM, Ghatei MA, and Bloom SR.** Hypothalamic localization of the feeding effect of agouti-related peptide and alpha-melanocyte-stimulating hormone. *Diabetes* 49: 177–182, 2000.
211. **Kim MS, Small CJ, Stanley SA, Morgan DG, Seal LJ, Kong WM, Edwards CM, Abusnana S, Sunter D, Ghatei MA, and Bloom SR.** The central melanocortin system affects the hypothalamo-pituitary thyroid axis and may mediate the effect of leptin. *J Clin Invest* 105: 1005–1011, 2000.
212. **King PJ, Widdowson PS, Doods HN, and Williams G.** Regulation of neuropeptide Y release by neuropeptide Y receptor ligands and calcium channel antagonists in hypothalamic slices. *J Neurochem* 73: 641–646, 1999.
213. **King PJ, Williams G, Doods H, and Widdowson PS.** Effect of a selective neuropeptide Y Y(2) receptor antagonist, BIIE0246 on neuropeptide Y release. *Eur J Pharmacol* 396: R1–R3, 2000.
214. **Kinzig KP, D'Alessio DA, and Seeley RJ.** The diverse roles of specific GLP-1 receptors in the control of food intake and the response to visceral illness. *J Neurosci* 22: 10470–10476, 2002.
215. **Kirchgessner AL and Liu M.** Orexin synthesis and response in the gut. *Neuron* 24: 941–951, 1999.
216. **Kissileff HR, Carretta JC, Geliebter A, and Pi-Sunyer FX.** Cholecystokinin and stomach distension combine to reduce food intake in humans. *Am J Physiol Regul Integr Comp Physiol* 285: R992–R998, 2003.
217. **Kissileff HR, Pi-Sunyer FX, Thornton J, and Smith GP.** C-terminal octapeptide of cholecystokinin decreases food intake in man. *Am J Clin Nutr* 34: 154–160, 1981.
218. **Koch JE.** Delta(9)-THC stimulates food intake in Lewis rats: effects on chow, high-fat and sweet high-fat diets. *Pharmacol Biochem Behav* 68: 539–543, 2001.
219. **Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, and Kangawa K.** Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 402: 656–660, 1999.
220. **Korbonits M, Gueorguiev M, O'Grady E, Lecoer C, Swan DC, Mein CA, Weill J, Grossman AB, and Froguel P.** A variation in the ghrelin gene increases weight and decreases insulin secretion in tall, obese children. *J Clin Endocrinol Metab* 87: 4005–4008, 2002.
221. **Kreymann B, Williams G, Ghatei MA, and Bloom SR.** Glucagon-like peptide-1 7–36: a physiological incretin in man. *Lancet* 2: 1300–1304, 1987.
222. **Kristensen P, Judge ME, Thim L, Ribel U, Christjansen KN, Wulff BS, Clausen JT, Jensen PB, Madsen OD, Vrang N, Larsen PJ, and Hastrup S.** Hypothalamic CART is a new anorectic peptide regulated by leptin. *Nature* 393: 72–76, 1998.
223. **Krude H, Biebermann H, Luck W, Horn R, Brabant G, and Gruters A.** Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet* 19: 155–157, 1998.
224. **Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, Eto K, Yamashita T, Kamon J, Satoh H, Yano W, Froguel P, Nagai R, Kimura S, Kadowaki T, and Noda T.** Disruption of adiponectin causes insulin resistance and neointimal formation. *J Biol Chem* 277: 25863–25866, 2002.
225. **Kuo DY.** Co-administration of dopamine D1 and D2 agonists additively decreases daily food intake, body weight and hypothalamic neuropeptide Y level in rats. *J Biomed Sci* 9: 126–132, 2002.
226. **Kushi A, Sasai H, Koizumi H, Takeda N, Yokoyama M, and Nakamura M.** Obesity and mild hyperinsulinemia found in neuropeptide Y-Y1 receptor-deficient mice. *Proc Natl Acad Sci USA* 95: 15659–15664, 1998.
227. **Kyrkouli SE, Stanley BG, Seirafi RD, and Leibowitz SF.** Stimulation of feeding by galanin: anatomical localization and behavioral specificity of this peptide's effects in the brain. *Peptides* 11: 995–1001, 1990.
228. **Ladenheim EE, Moore KA, Salorio CF, Mantey SA, Taylor JE, Coy DH, Jensen RT, and Moran TH.** Characterization of bombesin binding sites in the rat stomach. *Eur J Pharmacol* 319: 245–251, 1997.
229. **Lambert PD, Couceyro PR, McGirr KM, Dall Vechia SE, Smith Y, and Kuhar MJ.** CART peptides in the central control of feeding and interactions with neuropeptide Y. *Synapse* 29: 293–298, 1998.
230. **Lambert PD, Phillips PJ, Wilding JP, Bloom SR, and Herbert J.** *c-fos* expression in the paraventricular nucleus of the hypothalamus following intracerebroventricular infusions of neuropeptide Y. *Brain Res* 670: 59–65, 1995.
231. **Larhammar D.** Structural diversity of receptors for neuropeptide Y, peptide YY and pancreatic polypeptide. *Regul Pept* 65: 165–174, 1996.
232. **Larsson LI and Rehfeld JF.** Distribution of gastrin and CCK cells in the rat gastrointestinal tract. Evidence for the occurrence of three distinct cell types storing COOH-terminal gastrin immunoreactivity. *Histochemistry* 58: 23–31, 1978.
233. **Larsson LI, Sundler F, and Hakanson R.** Immunohistochemical localization of human pancreatic polypeptide (HPP) to a population of islet cells. *Cell Tissue Res* 156: 167–171, 1975.
234. **Lassmann V, Vague P, Vialettes B, and Simon MC.** Low plasma levels of pancreatic polypeptide in obesity. *Diabetes* 29: 428–430, 1980.
235. **Lawrence CB, Ellacott KL, and Luckman SM.** PRL-releasing peptide reduces food intake and may mediate satiety signaling. *Endocrinology* 143: 360–367, 2002.
236. **Lawrence CB, Liu YL, Stock MJ, and Luckman SM.** Anorectic actions of prolactin-releasing peptide are mediated by corticotropin-releasing hormone receptors. *Am J Physiol Regul Integr Comp Physiol* 286: R101–R107, 2004.
237. **Lawrence CB, Snape AC, Baudoin FM, and Luckman SM.** Acute central ghrelin and GH secretagogues induce feeding and activate brain appetite centers. *Endocrinology* 143: 155–162, 2002.
238. **Lee GH, Proenca R, Montez JM, Carroll KM, Darvishzadeh JG, Lee JI, and Friedman JM.** Abnormal splicing of the leptin receptor in diabetic mice. *Nature* 379: 632–635, 1996.
239. **Lee HM, Udipi V, Eglander EW, Rajaraman S, Coffey RJ Jr., and Greeley GH Jr.** Stimulatory actions of insulin-like growth factor-I and transforming growth factor-alpha on intestinal neurotensin and peptide YY. *Endocrinology* 140: 4065–4069, 1999.
240. **Lee Y, Yang SP, Soares MJ, and Voogt JL.** Distribution of prolactin-releasing peptide mRNA in the rat brain. *Brain Res Bull* 51: 171–176, 2000.
241. **Legradi G and Lechan RM.** Agouti-related protein containing nerve terminals innervate thyrotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus. *Endocrinology* 140: 3643–3652, 1999.
242. **Le Quellec A, Kervran A, Blache P, Ciurana AJ, and Bataille D.** Oxyntomodulin-like immunoreactivity: diurnal profile of a new potential enterogastrone. *J Clin Endocrinol Metab* 74: 1405–1409, 1992.
243. **Le Roux CW, Aylwyn SJB, Batterham RL, Wynne K, Borg CM, Hunt C, Wedlake L, Monteiro M, Frost GS, Ghatei M, and Bloom S.** PYY deficiency may reinforce obesity (Abstract). *Br Endocr Soc T* 42, 2004.
244. **Levin BE and Dunn-Meynell AA.** Reduced central leptin sensitivity in rats with diet-induced obesity. *Am J Physiol Regul Integr Comp Physiol* 283: R941–R948, 2002.

245. Levine AS, Kneip J, Grace M, and Morley JE. Effect of centrally administered neurotensin on multiple feeding paradigms. *Pharmacol Biochem Behav* 18: 19–23, 1983.
246. Licinio J, Caglayan S, Ozata M, Yildiz BO, de Miranda PB, O’Kirwan F, Whitby R, Liang L, Cohen P, Bhasin S, Krauss RM, Veldhuis JD, Wagner AJ, DePaoli AM, McCann SM, and Wong ML. Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. *Proc Natl Acad Sci USA* 101: 4531–4536, 2004.
247. Liddle RA, Goldfine ID, Rosen MS, Taplitz RA, and Williams JA. Cholecystokinin bioactivity in human plasma. Molecular forms, responses to feeding, and relationship to gallbladder contraction. *J Clin Invest* 75: 1144–1152, 1985.
248. Lieverse RJ, Jansen JB, van de ZA, Samson L, Masclee AA, Rovati LC, and Lamers CB. Bombesin reduces food intake in lean man by a cholecystokinin-independent mechanism. *J Clin Endocrinol Metab* 76: 1495–1498, 1993.
249. Lin HC and Chey WY. Cholecystokinin and peptide YY are released by fat in either proximal or distal small intestine in dogs. *Regul Pept* 114: 131–135, 2003.
250. Lin L, Martin R, Schaffhauser AO, and York DA. Acute changes in the response to peripheral leptin with alteration in the diet composition. *Am J Physiol Regul Integr Comp Physiol* 280: R504–R509, 2001.
251. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, and Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* 394: 897–901, 1998.
252. Lu D, Willard D, Patel IR, Kadwell S, Overton L, Kost T, Luther M, Chen W, Woychik RP, and Wilkison WO. Agouti protein is an antagonist of the melanocyte-stimulating-hormone receptor. *Nature* 371: 799–802, 1994.
253. Lubrano-Berthelier C, Cavazos M, Dubern B, Shapiro A, Stunff CL, Zhang S, Picart F, Govaerts C, Froguel P, Bougneres P, Clement K, and Vaisse C. Molecular genetics of human obesity-associated MC4R mutations. *Ann NY Acad Sci* 994: 49–57, 2003.
254. Lubrano-Berthelier C, Durand E, Dubern B, Shapiro A, Dazin P, Weill J, Ferron C, Froguel P, and Vaisse C. Intracellular retention is a common characteristic of childhood obesity-associated MC4R mutations. *Hum Mol Genet* 12: 145–153, 2003.
255. MacDonald PE, El Kholly W, Riedel MJ, Salapatek AM, Light PE, and Wheeler MB. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. *Diabetes* 51 Suppl 3: S434–S442, 2002.
256. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, and Matsuzawa Y. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 8: 731–737, 2002.
257. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, Kuriyama H, Hotta K, Nakamura T, Shimomura I, and Matsuzawa Y. PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 50: 2094–2099, 2001.
258. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R, and Ranganathan S. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med* 1: 1155–1161, 1995.
259. Makimura H, Mizuno TM, Mastaitis JW, Agami R, and Mobbs CV. Reducing hypothalamic AGRP by RNA interference increases metabolic rate and decreases body weight without influencing food intake. *BMC Neurosci* 3: 18, 2002.
260. Makino S, Baker RA, Smith MA, and Gold PW. Differential regulation of neuropeptide Y mRNA expression in the arcuate nucleus and locus coeruleus by stress and antidepressants. *J Neuroendocrinol* 12: 387–395, 2000.
261. Malaisse-Lagae F, Carpentier JL, Patel YC, Malaisse WJ, and Orci L. Pancreatic polypeptide: a possible role in the regulation of food intake in the mouse. *Hypothesis Experientia* 33: 915–917, 1977.
262. Marks DL, Boucher N, Lanouette CM, Perusse L, Brookhart G, Comuzzie AG, Chagnon YC, and Cone RD. Ala67Thr polymorphism in the Agouti-related peptide gene is associated with inherited leanness in humans. *Am J Med Genet* 126: 267–271, 2004.
263. Marks JL, Porte D Jr, Stahl WL, and Baskin DG. Localization of insulin receptor mRNA in rat brain by in situ hybridization. *Endocrinology* 127: 3234–3236, 1990.
264. Marsh DJ, Hollopeter G, Kafer KE, and Palmiter RD. Role of the Y5 neuropeptide Y receptor in feeding and obesity. *Nat Med* 4: 718–721, 1998.
265. Marsh DJ, Miura GI, Yagaloff KA, Schwartz MW, Barsh GS, and Palmiter RD. Effects of neuropeptide Y deficiency on hypothalamic agouti-related protein expression and responsiveness to melanocortin analogues. *Brain Res* 848: 66–77, 1999.
266. Marsh DJ, Weingarth DT, Novi DE, Chen HY, Trumbauer ME, Chen AS, Guan XM, Jiang MM, Feng Y, Camacho RE, Shen Z, Frazier EG, Yu H, Metzger JM, Kuca SJ, Shearman LP, Gopal-Truter S, MacNeil DJ, Strack AM, MacIntyre DE, Van der Ploeg LH, and Qian S. Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism. *Proc Natl Acad Sci USA* 99: 3240–3245, 2002.
267. Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, Nishimura H, Yoshimasa Y, Tanaka I, Mori T, and Nakao K. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. *Nat Med* 3: 1029–1033, 1997.
268. Matson CA, Reid DF, Cannon TA, and Ritter RC. Cholecystokinin and leptin act synergistically to reduce body weight. *Am J Physiol Regul Integr Comp Physiol* 278: R882–R890, 2000.
269. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, and Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 346: 561–564, 1990.
270. McGowan MK, Andrews KM, and Grossman SP. Chronic intrahypothalamic infusions of insulin or insulin antibodies alter body weight and food intake in the rat. *Physiol Behav* 51: 753–766, 1992.
271. McLaughlin CL and Baile CA. Obese mice and the satiety effects of cholecystokinin, bombesin and pancreatic polypeptide. *Physiol Behav* 26: 433–437, 1981.
272. McLaughlin CL, Baile CA, and Buonomo FC. Effect of CCK antibodies on food intake and weight gain in Zucker rats. *Physiol Behav* 34: 277–282, 1985.
273. Meeran K, O’Shea D, Edwards CM, Turton MD, Heath MM, Gunn I, Abusnana S, Rossi M, Small CJ, Goldstone AP, Taylor GM, Sunter D, Steere J, Choi SJ, Ghatgei MA, and Bloom SR. Repeated intracerebroventricular administration of glucagon-like peptide-1-(7–36) amide or exendin-(9–39) alters body weight in the rat. *Endocrinology* 140: 244–250, 1999.
274. Meereis-Schwanke K, Klonowski-Stumpe H, Herberg L, and Niederau C. Long-term effects of CCK-agonist and -antagonist on food intake and body weight in Zucker lean and obese rats. *Pepptides* 19: 291–299, 1998.
275. Menendez JA and Atrens DM. Insulin and the paraventricular hypothalamus: modulation of energy balance. *Brain Res* 555: 193–201, 1991.
276. Mercer JG, Hoggard N, Williams LM, Lawrence CB, Hannah LT, Morgan PJ, and Trayhurn P. Coexpression of leptin receptor and preproneuropeptide Y mRNA in arcuate nucleus of mouse hypothalamus. *J Neuroendocrinol* 8: 733–735, 1996.
277. Mercer JG, Moar KM, and Hoggard N. Localization of leptin receptor (Ob-R) messenger ribonucleic acid in the rodent hindbrain. *Endocrinology* 139: 29–34, 1998.
278. Meryn S, Stein D, and Straus EW. Fasting- and meal-stimulated peptide hormone concentrations before and after gastric surgery for morbid obesity. *Metabolism* 35: 798–802, 1986.
279. Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, Xue B, Mu J, Foulfelle F, Ferre P, Birnbaum MJ, Stuck BJ, and Kahn BB. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature* 428: 569–574, 2004.
280. Miraglia dG, Santoro N, Cirillo G, Raimondo P, Grandone A, D’Aniello A, Di Nardo M, and Perrone L. Molecular screening of the ghrelin gene in Italian obese children: the Leu72Met variant is associated with an earlier onset of obesity. *Int J Obes Relat Metab Disord* 28: 447–450, 2004.

281. Mochiki E, Inui A, Satoh M, Mizumoto A, and Itoh Z. Motilin is a biosignal controlling cyclic release of pancreatic polypeptide via the vagus in fasted dogs. *Am J Physiol Gastrointest Liver Physiol* 272: G224–G232, 1997.
282. Moltz JH and McDonald JK. Neuropeptide Y: direct and indirect action on insulin secretion in the rat. *Peptides* 6: 1155–1159, 1985.
283. Mencarelli M, Maestrini S, Tagliaferri M, Brunani A, Letizia Petroni M, Liuzzi A, and DiBlasio AM. Identification of three novel melanocortin 3 receptor (MC3R) gene mutations in patients with morbid obesity. *Am Endocr Soc OR45–1*, 2004.
284. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, and O'Rahilly S. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 387: 903–908, 1997.
285. Moran TH, Baldessarini AR, Salorio CF, Lowery T, and Schwartz GJ. Vagal afferent and efferent contributions to the inhibition of food intake by cholecystokinin. *Am J Physiol Regul Integr Comp Physiol* 272: R1245–R1251, 1997.
286. Moran TH, Katz LF, Plata-Salaman CR, and Schwartz GJ. Disordered food intake and obesity in rats lacking cholecystokinin A receptors. *Am J Physiol Regul Integr Comp Physiol* 274: R618–R625, 1998.
287. Moran TH, Norgren R, Crosby RJ, and McHugh PR. Central and peripheral vagal transport of cholecystokinin binding sites occurs in afferent fibers. *Brain Res* 526: 95–102, 1990.
288. Moran TH, Robinson PH, Goldrich MS, and McHugh PR. Two brain cholecystokinin receptors: implications for behavioral actions. *Brain Res* 362: 175–179, 1986.
289. Moran TH and Schwartz GJ. Neurobiology of cholecystokinin. *Crit Rev Neurobiol* 9: 1–28, 1994.
290. Moran TH, Smedh U, Kinzig KP, Scott KA, Knipp S, and Ladenheim EE. Peptide YY (3–36) inhibits gastric emptying and produces acute reductions in food intake in rhesus monkeys. *Am J Physiol Regul Integr Comp Physiol* 288: R384–R388, 2005.
291. Mori H, Hanada R, Hanada T, Aki D, Mashima R, Nishinakamura H, Torisu T, Chien KR, Yasukawa H, and Yoshimura A. Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. *Nat Med* 10: 739–743, 2004.
292. Moriguchi T, Sakurai T, Nambu T, Yanagisawa M, and Goto K. Neurons containing orexin in the lateral hypothalamic area of the adult rat brain are activated by insulin-induced acute hypoglycemia. *Neurosci Lett* 264: 101–104, 1999.
293. Morris BJ. Neuronal localisation of neuropeptide Y gene expression in rat brain. *J Comp Neurol* 290: 358–368, 1989.
294. Mountjoy KG, Mortrud MT, Low MJ, Simerly RB, and Cone RD. Localization of the melanocortin-4 receptor (MC4R) in neuroendocrine and autonomic control circuits in the brain. *Mol Endocrinol* 8: 1298–1308, 1994.
295. Munro S, Thomas KL, and Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 365: 61–65, 1993.
296. Murakami N, Hayashida T, Kuroiwa T, Nakahara K, Ida T, Mondal MS, Nakazato M, Kojima M, and Kangawa K. Role for central ghrelin in food intake and secretion profile of stomach ghrelin in rats. *J Endocrinol* 174: 283–288, 2002.
297. Murata M, Okimura Y, Iida K, Matsumoto M, Sowa H, Kaji H, Kojima M, Kangawa K, and Chihara K. Ghrelin modulates the downstream molecules of insulin signaling in hepatoma cells. *J Biol Chem* 277: 5667–5674, 2002.
298. Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, and Matsukura S. A role for ghrelin in the central regulation of feeding. *Nature* 409: 194–198, 2001.
299. Naslund E, King N, Mansten S, Adner N, Holst JJ, Gutniak M, and Hellstrom PM. Prandial subcutaneous injections of GLP-1 cause weight loss in obese human subjects. *Br J Nutr* 91: 439–446, 2003.
300. Naslund E, Barkeling B, King N, Gutniak M, Blundell JE, Holst JJ, Rossner S, and Hellstrom PM. Energy intake and appetite are suppressed by glucagon-like peptide-1 (GLP-1) in obese men. *Int J Obes Relat Metab Disord* 23: 304–311, 1999.
301. Naslund E, Bogefors J, Skogar S, Gryback P, Jacobsson H, Holst JJ, and Hellstrom PM. GLP-1 slows solid gastric emptying and inhibits insulin, glucagon, and PYY release in humans. *Am J Physiol Regul Integr Comp Physiol* 277: R910–R916, 1999.
302. Naslund E, Gryback P, Hellstrom PM, Jacobsson H, Holst JJ, Theodorsson E, and Backman L. Gastrointestinal hormones and gastric emptying 20 years after jejunoileal bypass for massive obesity. *Int J Obes Relat Metab Disord* 21: 387–392, 1997.
303. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, and Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7–36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 36: 741–744, 1993.
304. Naveilhan P, Hassani H, Canals JM, Ekstrand AJ, Larefalk A, Chhajlani V, Arenas E, Gedda K, Svensson L, Thoren P, and Ernfors P. Normal feeding behavior, body weight and leptin response require the neuropeptide Y Y2 receptor. *Nat Med* 5: 1188–1193, 1999.
305. Nicolaidis S and Rowland N. Metering of intravenous versus oral nutrients and regulation of energy balance. *Am J Physiol* 231: 661–668, 1976.
306. Niswender KD, Morton GJ, Stearns WH, Rhodes CJ, Myers MG Jr, and Schwartz MW. Intracellular signalling Key enzyme in leptin-induced anorexia. *Nature* 413: 794–795, 2001.
307. Nonaka N, Shioda S, Niehoff ML, and Banks WA. Characterization of blood-brain barrier permeability to PYY3–36 in the mouse. *J Pharmacol Exp Ther* 306: 948–953, 2003.
308. Nowak KW, Mackowiak P, Switonska MM, Fabis M, and Malendowicz LK. Acute orexin effects on insulin secretion in the rat: in vivo and in vitro studies. *Life Sci* 66: 449–454, 2000.
309. Obici S, Feng Z, Karkanias G, Baskin DG, and Rossetti L. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. *Nat Neurosci* 5: 566–572, 2002.
310. Ohki-Hamazaki H, Watase K, Yamamoto K, Ogura H, Yamano M, Yamada K, Maeno H, Imaki J, Kikuyama S, Wada E, and Wada K. Mice lacking bombesin receptor subtype-3 develop metabolic defects and obesity. *Nature* 390: 165–169, 1997.
311. Ollmann MM, Wilson BD, Yang YK, Kerns JA, Chen Y, Gantz I, and Barsh GS. Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein. *Science* 278: 135–138, 1997.
312. Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science* 164: 719–721, 1969.
313. O'Shea D, Morgan DG, Meeran K, Edwards CM, Turton MD, Choi SJ, Heath MM, Gunn I, Taylor GM, Howard JK, Bloom CI, Small CJ, Haddo O, Ma JJ, Callinan W, Smith DM, Ghatge MA, and Bloom SR. Neuropeptide Y induced feeding in the rat is mediated by a novel receptor. *Endocrinology* 138: 196–202, 1997.
314. Otto B, Cuntz U, Fruehauf E, Wawarta R, Folwaczny C, Riepl RL, Heiman ML, Lehnert P, Fichter M, and Tschop M. Weight gain decreases elevated plasma ghrelin concentrations of patients with anorexia nervosa. *Eur J Endocrinol* 145: 669–673, 2001.
315. Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, Engel J, Brownlee M, and Scherer PE. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications for metabolic regulation and bioactivity. *J Biol Chem* 278: 9073–9085, 2003.
316. Parkinson C, Drake WM, Roberts ME, Meeran K, Besser GM, and Trainer PJ. A comparison of the effects of pegvisomant and octreotide on glucose, insulin, gastrin, cholecystokinin, and pancreatic polypeptide responses to oral glucose and a standard mixed meal. *J Clin Endocrinol Metab* 87: 1797–1804, 2002.
317. Pedersen-Bjergaard U, Host U, Kelbaek H, Schifter S, Rehfeld JF, Faber J, and Christensen NJ. Influence of meal composition on postprandial peripheral plasma concentrations of vasoactive peptides in man. *Scand J Clin Lab Invest* 56: 497–503, 1996.
318. Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, and Collins F. Effects of the obese gene product on body weight regulation in *ob/ob* mice. *Science* 269: 540–543, 1995.
319. Peracchi M, Tagliabue R, Quatrini M, and Reschini E. Plasma pancreatic polypeptide response to secretin. *Eur J Endocrinol* 141: 47–49, 1999.
320. Peyron C, Tighe DK, van den Pol AN, De Lecea L, Heller HC, Sutcliffe JG, and Kilduff TS. Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J Neurosci* 18: 9996–10015, 1998.

321. **Pierroz DD, Ziotopoulou M, Ungsuan L, Moschos S, Flier JS, and Mantzoros CS.** Effects of acute and chronic administration of the melanocortin agonist MTII in mice with diet-induced obesity. *Diabetes* 51: 1337–1345, 2002.
322. **Pittner RA, Moore CX, Bhavsar SP, Gedulin BR, Smith PA, Jodka CM, Parkes DG, Paterniti JR, Srivastava VP, and Young AA.** Effects of PYY[3–36] in rodent models of diabetes and obesity. *Int J Obes Relat Metab Disord* 28: 963–971, 2004.
323. **Polonsky KS, Given BD, and Van Cauter E.** Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J Clin Invest* 81: 442–448, 1988.
324. **Porte D Jr, Baskin DG, and Schwartz MW.** Leptin and insulin action in the central nervous system. *Nutr Rev* 60: S20–S29, 2002.
325. **Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, Scherer PE, and Ahima RS.** Adiponectin acts in the brain to decrease body weight. *Nat Med* 10: 524–529, 2004.
326. **Qian S, Chen H, Weingarh D, Trumbauer ME, Novi DE, Guan X, Yu H, Shen Z, Feng Y, Frazier E, Chen A, Camacho RE, Shearman LP, Gopal-Truter S, MacNeil DJ, Van der Ploeg LH, and Marsh DJ.** Neither agouti-related protein nor neuropeptide Y is critically required for the regulation of energy homeostasis in mice. *Mol Cell Biol* 22: 5027–5035, 2002.
327. **Qu D, Ludwig DS, Gammeltoft S, Piper M, Pelleymounter MA, Cullen MJ, Mathes WF, Przyspek R, Kanarek R, and Maratos-Flier E.** A role for melanin-concentrating hormone in the central regulation of feeding behaviour. *Nature* 380: 243–247, 1996.
328. **Ranganath LR, Beety JM, Morgan LM, Wright JW, Howland R, and Marks V.** Attenuated GLP-1 secretion in obesity: cause or consequence? *Gut* 38: 916–919, 1996.
329. **Raposo PD, Pedrazzini T, White RB, Palmiter RD, and Aubert ML.** Chronic neuropeptide Y infusion into the lateral ventricle induces sustained feeding and obesity in mice lacking either Npy1r or Npy5r expression. *Endocrinology* 145: 304–310, 2004.
330. **Reeve JR Jr, Eysselein VE, Ho FJ, Chew P, Vigna SR, Liddle RA, and Evans C.** Natural and synthetic CCK-58. Novel reagents for studying cholecystokinin physiology. *Ann NY Acad Sci* 713: 11–21, 1994.
331. **Reidelberger RD, Hernandez J, Fritzsche B, and Hulce M.** Abdominal vagal mediation of the satiety effects of CCK in rats. *Am J Physiol Regul Integr Comp Physiol* 286: R1005–R1012, 2004.
332. **Reidelberger RD and Solomon TE.** Comparative effects of CCK-8 on feeding, sham feeding, and exocrine pancreatic secretion in rats. *Am J Physiol Regul Integr Comp Physiol* 251: R97–R105, 1986.
333. **Ricardo JA and Koh ET.** Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. *Brain Res* 153: 1–26, 1978.
334. **Riediger T, Bothe C, Becskei C, and Lutz TA.** Peptide YY directly inhibits ghrelin-activated neurons of the arcuate nucleus and reverses fasting-induced c-Fos expression. *Neuroendocrinology* 79: 317–326, 2004.
335. **Rios M, Fan G, Fekete C, Kelly J, Bates B, Kuehn R, Lechan RM, and Jaenisch R.** Conditional deletion of brain-derived neurotrophic factor in the postnatal brain leads to obesity and hyperactivity. *Mol Endocrinol* 15: 1748–1757, 2001.
336. **Roseberry AG, Liu H, Jackson AC, Cai X, and Friedman JM.** Neuropeptide Y-mediated inhibition of proopiomelanocortin neurons in the arcuate nucleus shows enhanced desensitization in *ob/ob* mice. *Neuron* 41: 711–722, 2004.
337. **Rossi M, Kim MS, Morgan DG, Small CJ, Edwards CM, Sunter D, Abusnana S, Goldstone AP, Russell SH, Stanley SA, Smith DM, Yagaloff K, Ghatei MA, and Bloom SR.** A C-terminal fragment of Agouti-related protein increases feeding and antagonizes the effect of alpha-melanocyte stimulating hormone in vivo. *Endocrinology* 139: 4428–4431, 1998.
338. **Sahu A.** Resistance to the satiety action of leptin following chronic central leptin infusion is associated with the development of leptin resistance in neuropeptide Y neurons. *J Neuroendocrinol* 14: 796–804, 2002.
339. **Sahu A, Carraway RE, and Wang YP.** Evidence that neurotensin mediates the central effect of leptin on food intake in rat. *Brain Res* 888: 343–347, 2001.
340. **Sainsbury A, Schwarzer C, Couzens M, Fetisov S, Furtinger S, Jenkins A, Cox HM, Sperk G, Hokfelt T, and Herzog H.** Important role of hypothalamic Y2 receptors in body weight regulation revealed in conditional knockout mice. *Proc Natl Acad Sci USA* 99: 8938–8943, 2002.
341. **Saito Y, Cheng M, Leslie FM, and Civelli O.** Expression of the melanin-concentrating hormone (MCH) receptor mRNA in the rat brain. *J Comp Neurol* 435: 26–40, 2001.
342. **Sakata I, Nakamura K, Yamazaki M, Matsubara M, Hayashi Y, Kangawa K, and Sakai T.** Ghrelin-producing cells exist as two types of cells, closed- and opened-type cells, in the rat gastrointestinal tract. *Peptides* 23: 531–536, 2002.
343. **Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, and Yanagisawa M.** Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 92: 573–585, 1998.
344. **Sanacora G, Kershaw M, Finkelstein JA, and White JD.** Increased hypothalamic content of prepro-neuropeptide Y messenger ribonucleic acid in genetically obese Zucker rats and its regulation by food deprivation. *Endocrinology* 127: 730–737, 1990.
345. **Sanchez J, Oliver P, Palou A, and Pico C.** The inhibition of gastric ghrelin production by food intake in rats is dependent on the type of macronutrient. *Endocrinology* 145: 5049–5055, 2004.
346. **Saper CB, Chou TC, and Elmquist JK.** The need to feed: homeostatic and hedonic control of eating. *Neuron* 36: 199–211, 2002.
347. **Sarkar S and Lechan RM.** Central administration of neuropeptide Y reduces alpha-melanocyte-stimulating hormone-induced cyclic adenosine 5'-monophosphate response element binding protein (CREB) phosphorylation in pro-thyrotropin-releasing hormone neurons and increases CREB phosphorylation in corticotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus. *Endocrinology* 144: 281–291, 2003.
348. **Sarson DL, Scopinaro N, and Bloom SR.** Gut hormone changes after jejunoileal (JIB) or biliopancreatic (BPB) bypass surgery for morbid obesity. *Int J Obes* 5: 471–480, 1981.
349. **Sawchenko PE.** Central connections of the sensory and motor nuclei of the vagus nerve. *J Auton Nerv Syst* 9: 13–26, 1983.
350. **Sawchenko PE and Swanson LW.** The organization and biochemical specificity of afferent projections to the paraventricular and supraoptic nuclei. *Prog Brain Res* 60: 19–29, 1983.
351. **Sawchenko PE, Swanson LW, Grzanna R, Howe PR, Bloom SR, and Polak JM.** Colocalization of neuropeptide Y immunoreactivity in brainstem catecholaminergic neurons that project to the paraventricular nucleus of the hypothalamus. *J Comp Neurol* 241: 138–153, 1985.
352. **Schaffhauser AO, Stricker-Krongrad A, Brunner L, Cumin F, Gerald C, Whitebread S, Criscione L, and Hofbauer KG.** Inhibition of food intake by neuropeptide Y Y5 receptor antisense oligodeoxynucleotides. *Diabetes* 46: 1792–1798, 1997.
353. **Scherer PE, Williams S, Fogliano M, Baldini G, and Lodish HF.** A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 270: 26746–26749, 1995.
354. **Schneider LH.** Orosensory self-stimulation by sucrose involves brain dopaminergic mechanisms. *Ann NY Acad Sci* 575: 307–319, 1989.
355. **Schwartz GJ and Moran TH.** CCK elicits and modulates vagal afferent activity arising from gastric and duodenal sites. *Ann NY Acad Sci* 713: 121–128, 1994.
356. **Schwartz GJ, Whitney A, Skoglund C, Castonguay TW, and Moran TH.** Decreased responsiveness to dietary fat in Otsuka Long-Evans Tokushima fatty rats lacking CCK-A receptors. *Am J Physiol Regul Integr Comp Physiol* 277: R1144–R1151, 1999.
357. **Schwartz MW, Baskin DG, Bukowski TR, Kuijper JL, Foster D, Lasser G, Prunkard DE, Porte D Jr, Woods SC, Seeley RJ, and Weigle DS.** Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in *ob/ob* mice. *Diabetes* 45: 531–535, 1996.
358. **Schwartz MW, Figlewicz DP, Baskin DG, Woods SC, and Porte D Jr.** Insulin in the brain: a hormonal regulator of energy balance. *Endocr Rev* 13: 387–414, 1992.

359. Schwartz MW, Seeley RJ, Woods SC, Weigle DS, Campfield LA, Burn P, and Baskin DG. Leptin increases hypothalamic pro-melanocortin mRNA expression in the rostral arcuate nucleus. *Diabetes* 46: 2119–2123, 1997.
360. Schwartz MW, Sipols AJ, Marks JL, Sanacora G, White JD, Scheurink A, Kahn SE, Baskin DG, Woods SC, and Figlewicz DP. Inhibition of hypothalamic neuropeptide Y gene expression by insulin. *Endocrinology* 130: 3608–3616, 1992.
361. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, and Baskin DG. Central nervous system control of food intake. *Nature* 404: 661–671, 2000.
362. Scrocchi LA, Brown TJ, McClusky N, Brubaker PL, Auerbach AB, Joyner AL, and Drucker DJ. Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide 1 receptor gene. *Nat Med* 2: 1254–1258, 1996.
363. Seal LJ, Small CJ, Dhillo WS, Stanley SA, Abbott CR, Ghatei MA, and Bloom SR. PRL-releasing peptide inhibits food intake in male rats via the dorsomedial hypothalamic nucleus and not the paraventricular hypothalamic nucleus. *Endocrinology* 142: 4236–4243, 2001.
364. Segal-Lieberman G, Bradley RL, Kokkotou E, Carlson M, Trombly DJ, Wang X, Bates S, Myers MG Jr, Flier JS, and Maratos-Flier E. Melanin-concentrating hormone is a critical mediator of the leptin-deficient phenotype. *Proc Natl Acad Sci USA* 100: 10085–10090, 2003.
365. Shimada M, Tritos NA, Lowell BB, Flier JS, and Maratos-Flier E. Mice lacking melanin-concentrating hormone are hypophagic and lean. *Nature* 396: 670–674, 1998.
366. Shintani M, Ogawa Y, Ebihara K, Aizawa-Abe M, Miyanaga F, Takaya K, Hayashi T, Inoue G, Hosoda K, Kojima M, Kangawa K, and Nakao K. Ghrelin, an endogenous growth hormone secretagogue, is a novel orexigenic peptide that antagonizes leptin action through the activation of hypothalamic neuropeptide Y/Y1 receptor pathway. *Diabetes* 50: 227–232, 2001.
367. Shirasaka T, Miyahara S, Kunitake T, Jin QH, Kato K, Takasaki M, and Kannan H. Orexin depolarizes rat hypothalamic paraventricular nucleus neurons. *Am J Physiol Regul Integr Comp Physiol* 281: R1114–R1118, 2001.
368. Shklyaev S, Aslanidi G, Tennant M, Prima V, Kohlbrenner E, Kroutov V, Campbell-Thompson M, Crawford J, Shek EW, Scarpace PJ, and Zolotukhin S. Sustained peripheral expression of transgene adiponectin offsets the development of diet-induced obesity in rats. *Proc Natl Acad Sci USA* 100: 14217–14222, 2003.
369. Shughrue PJ, Lane MV, and Merchenthaler I. Glucagon-like peptide-1 receptor (GLP1-R) mRNA in the rat hypothalamus. *Endocrinology* 137: 5159–5162, 1996.
370. Shutter JR, Graham M, Kinsey AC, Scully S, Luthy R, and Stark KL. Hypothalamic expression of ART, a novel gene related to agouti, is up-regulated in obese and diabetic mutant mice. *Genes Dev* 11: 593–602, 1997.
371. Sipols AJ, Baskin DG, and Schwartz MW. Effect of intracerebroventricular insulin infusion on diabetic hyperphagia and hypothalamic neuropeptide gene expression. *Diabetes* 44: 147–151, 1995.
372. Small CJ, Kim MS, Stanley SA, Mitchell JR, Murphy K, Morgan DG, Ghatei MA, and Bloom SR. Effects of chronic central nervous system administration of agouti-related protein in pair-fed animals. *Diabetes* 50: 248–254, 2001.
373. Small CJ, Liu YL, Stanley SA, Connoley IP, Kennedy A, Stock MJ, and Bloom SR. Chronic CNS administration of Agouti-related protein (Agrp) reduces energy expenditure. *Int J Obes Related Metab Disorders* 27: 530–533, 2003.
374. Smith GP, Jerome C, and Gibbs J. Abdominal vagotomy does not block the satiety effect of bombesin in the rat. *Peptides* 2: 409–411, 1981.
375. Stanley BG, Chin AS, and Leibowitz SF. Feeding and drinking elicited by central injection of neuropeptide Y: evidence for a hypothalamic site(s) of action. *Brain Res Bull* 14: 521–524, 1985.
376. Stanley BG, Daniel DR, Chin AS, and Leibowitz SF. Paraventricular nucleus injections of peptide YY and neuropeptide Y preferentially enhance carbohydrate ingestion. *Peptides* 6: 1205–1211, 1985.
377. Stanley BG, Kyrkouli SE, Lampert S, and Leibowitz SF. Neuropeptide Y chronically injected into the hypothalamus: a powerful neurochemical inducer of hyperphagia and obesity. *Peptides* 7: 1189–1192, 1986.
378. Stanley BG, Magdalin W, Seirafi A, Thomas WJ, and Leibowitz SF. The perifornical area: the major focus of (a) patchily distributed hypothalamic neuropeptide Y-sensitive feeding system(s). *Brain Res* 604: 304–317, 1993.
379. Stephens TW, Basinski M, Bristow PK, Bue-Valleskey JM, Burgett SG, Craft L, Hale J, Hoffmann J, Hsiung HM, and Kriauciunas A. The role of neuropeptide Y in the antiobesity action of the obese gene product. *Nature* 377: 530–532, 1995.
380. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, and Lazar MA. The hormone resistin links obesity to diabetes. *Nature* 409: 307–312, 2001.
381. Stratford TR and Kelley AE. Evidence of a functional relationship between the nucleus accumbens shell and lateral hypothalamus subserving the control of feeding behavior. *J Neurosci* 19: 11040–11048, 1999.
382. Strobel A, Issad T, Camoin L, Ozata M, and Strosberg AD. A leptin missense mutation associated with hypogonadism and morbid obesity. *Nat Genet* 18: 213–215, 1998.
383. Strubbe JH and Mein CG. Increased feeding in response to bilateral injection of insulin antibodies in the VMH. *Physiol Behav* 19: 309–313, 1977.
384. Sugino T, Yamaura J, Yamagishi M, Ogura A, Hayashi R, Kurose Y, Kojima M, Kangawa K, Hasegawa Y, and Terashima Y. A transient surge of ghrelin secretion before feeding is modified by different feeding regimens in sheep. *Biochem Biophys Res Commun* 298: 785–788, 2002.
385. Sul HS. Resistin/ADSF/FIZZ3 in obesity and diabetes. *Trends Endocrinol Metab* 15: 247–249, 2004.
386. Sun Y, Ahmed S, and Smith RG. Deletion of ghrelin impairs neither growth nor appetite. *Mol Cell Biol* 23: 7973–7981, 2003.
387. Sun Y, Wang P, Zheng H, and Smith RG. Ghrelin stimulation of growth hormone release and appetite is mediated through the growth hormone secretagogue receptor. *Proc Natl Acad Sci USA* 101: 4679–4684, 2004.
388. Swart I, Jahng JW, Overton JM, and Houpt TA. Hypothalamic NPY, AGRP, and POMC mRNA responses to leptin and refeeding in mice. *Am J Physiol Regul Integr Comp Physiol* 283: R1020–R1026, 2002.
389. Szczypka MS, Kwok K, Brot MD, Marck BT, Matsumoto AM, Donahue BA, and Palmiter RD. Dopamine production in the caudate putamen restores feeding in dopamine-deficient mice. *Neuron* 30: 819–828, 2001.
390. Tamura H, Kamegai J, Shimizu T, Ishii S, Sugihara H, and Oikawa S. Ghrelin stimulates GH but not food intake in arcuate nucleus ablated rats. *Endocrinology* 143: 3268–3275, 2002.
391. Tang-Christensen M, Vrang N, and Larsen PJ. Glucagon-like peptide 1(7–36) amide's central inhibition of feeding and peripheral inhibition of drinking are abolished by neonatal monosodium glutamate treatment. *Diabetes* 47: 530–537, 1998.
392. Tang-Christensen M, Vrang N, and Larsen PJ. Glucagon-like peptide containing pathways in the regulation of feeding behaviour. *Int J Obes Related Metab Disorders* 25 Suppl 5: S42–S47, 2001.
393. Tartaglia LA. The leptin receptor. *J Biol Chem* 272: 6093–6096, 1997.
394. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richards GJ, Campfield LA, Clark FT, and Deeds J. Identification and expression cloning of a leptin receptor, OB-R. *Cell* 83: 1263–1271, 1995.
395. Ter Horst GJ, de Boer P, Luiten PG, and van Willigen JD. Ascending projections from the solitary tract nucleus to the hypothalamus. A *Phaseolus vulgaris* lectin tracing study in the rat. *Neuroscience* 31: 785–797, 1989.
396. Thorsell A and Heilig M. Diverse functions of neuropeptide Y revealed using genetically modified animals. *Neuropeptides* 36: 182–193, 2002.
397. Todd JF, Stanley SA, Roufosse CA, Bishop AE, Khoo B, Bloom SR, and Meeran K. A tumour that secretes glucagon-like peptide-1 and somatostatin in a patient with reactive hypoglycaemia and diabetes. *Lancet* 361: 228–230, 2003.

398. **Torsello A, Locatelli V, Melis MR, Succu S, Spano MS, Deghenghi R, Muller EE, and Argiolas A.** Differential orexigenic effects of hexarelin and its analogs in the rat hypothalamus: indication for multiple growth hormone secretagogue receptor subtypes. *Neuroendocrinology* 72: 327–332, 2000.
399. **Toshinai K, Date Y, Murakami N, Shimada M, Mondal MS, Shimbara T, Guan JL, Wang QP, Funahashi H, Sakurai T, Shioda S, Matsukura S, Kangawa K, and Nakazato M.** Ghrelin-induced food intake is mediated via the orexin pathway. *Endocrinology* 144: 1506–1512, 2003.
400. **Track NS, McLeod RS, and Mee AV.** Human pancreatic polypeptide: studies of fasting and postprandial plasma concentrations. *Can J Physiol Pharmacol* 58: 1484–1489, 1980.
401. **Tsao TS, Lodish HF, and Fruebis J.** ACRP30, a new hormone controlling fat and glucose metabolism. *Eur J Pharmacol* 440: 213–221, 2002.
402. **Tschop M, Castaneda TR, Joost HG, Thone-Reineke C, Ortman S, Klaus S, Hagan MM, Chandler PC, Oswald KD, Benoit SC, Seeley RJ, Kinzig KP, Moran TH, Beck-sickinger AG, Koglin N, Rodgers RJ, Blundell JE, Ishii Y, Beattie AH, Holch P, Allison DB, Raun K, Madsen K, Wulff BS, Stidsen CE, Birringer M, Kreuzer OJ, Schindler M, Arndt K, Rudolf K, Mark M, Deng XY, Whitcomb DC, Halem H, Taylor J, Dong J, Datta R, Culler M, Craney S, Flora D, Smiley D, Heiman ML, and Withcomb DC.** Physiology: does gut hormone PYY3–36 decrease food intake in rodents? *Nature* 430: 1, 2004.
403. **Tschop M, Smiley DL, and Heiman ML.** Ghrelin induces adiposity in rodents. *Nature* 407: 908–913, 2000.
404. **Tschop M, Wawarta R, Riepl RL, Friedrich S, Bidlingmaier M, Landgraf R, and Folwaczny C.** Post-prandial decrease of circulating human ghrelin levels. *J Endocrinol Invest* 24: RC19–RC21, 2001.
405. **Turnbull AV, Ellershaw L, Masters DJ, Birtles S, Boyer S, Carroll D, Clarkson P, Loxham SJ, McAulay P, Teague JL, Foote KM, Pease JE, and Block MH.** Selective antagonism of the NPY Y5 receptor does not have a major effect on feeding in rats. *Diabetes* 51: 2441–2449, 2002.
406. **Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K, Choi SJ, Taylor GM, Heath MM, Lambert PD, Wilding JP, Smith DM, Ghatei MA, Herbert J, and Bloom SR.** A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* 379: 69–72, 1996.
407. **Ueno N, Inui A, Iwamoto M, Kaga T, Asakawa A, Okita M, Fujimiya M, Nakajima Y, Ohmoto Y, Ohnaka M, Nakaya Y, Miyazaki JI, and Kasuga M.** Decreased food intake and body weight in pancreatic polypeptide-overexpressing mice. *Gastroenterology* 117: 1427–1432, 1999.
408. **Uhe AM, Szmukler GI, Collier GR, Hansky J, O'Dea K, and Young GP.** Potential regulators of feeding behavior in anorexia nervosa. *Am J Clin Nutr* 55: 28–32, 1992.
409. **Ukkola O, Ravussin E, Jacobson P, Perusse L, Rankinen T, Tschop M, Heiman ML, Leon AS, Rao DC, Skinner JS, Wilmore JH, Sjostrom L, and Bouchard C.** Role of ghrelin polymorphisms in obesity based on three different studies. *Obes Res* 10: 782–791, 2002.
410. **Uttenenthal LO, Toledano A, and Blazquez E.** Autoradiographic localization of receptors for glucagon-like peptide-1 (7–36) amide in rat brain. *Neuropeptides* 21: 143–146, 1992.
411. **Vaisse C, Halaas JL, Horvath CM, Darnell JE Jr, Stoffel M, and Friedman JM.** Leptin activation of Stat3 in the hypothalamus of wild-type and *ob/ob* mice but not *db/db* mice. *Nat Genet* 14: 95–97, 1996.
412. **Valsamakis G, McTernan PG, Chetty R, Al Daghri N, Field A, Hanif W, Barnett AH, and Kumar S.** Modest weight loss and reduction in waist circumference after medical treatment are associated with favorable changes in serum adipocytokines. *Metabolism* 53: 430–434, 2004.
413. **Van der Koy D, Koda LY, McGinty JF, Gerfen CR, and Bloom FE.** The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in rat. *J Comp Neurol* 224: 1–24, 1984.
414. **Van Dijk G, Thiele TE, Donahey JC, Campfield LA, Smith FJ, Burn P, Bernstein IL, Woods SC, and Seeley RJ.** Central infusions of leptin and GLP-1-(7–36) amide differentially stimulate c-Fli in the rat brain. *Am J Physiol Regul Integr Comp Physiol* 271: R1096–R1100, 1996.
415. **Van Heek M, Compton DS, France CF, Tedesco RP, Fawzi AB, Graziano MP, Sybertz EJ, Strader CD, and Davis HR Jr.** Diet-induced obese mice develop peripheral, but not central, resistance to leptin. *J Clin Invest* 99: 385–390, 1997.
416. **Verdich C, Flint A, Gutzwiller JP, Naslund E, Beglinger C, Hellstrom PM, Long SJ, Morgan LM, Holst JJ, and Astrup A.** A meta-analysis of the effect of glucagon-like peptide-1 (7–36) amide on ad libitum energy intake in humans. *J Clin Endocrinol Metab* 86: 4382–4389, 2001.
417. **Verdich C, Toubro S, Buemann B, Lysgard MJ, Juul HJ, and Astrup A.** The role of postprandial releases of insulin and incretin hormones in meal-induced satiety—effect of obesity and weight reduction. *Int J Obes Related Metab Disorders* 25: 1206–1214, 2001.
418. **Verty AN, McFarlane JR, McGregor IS, and Mallet PE.** Evidence for an interaction between CB1 cannabinoid and melanocortin MCR-4 receptors in regulating food intake. *Endocrinology* 145: 3224–3231, 2004.
419. **Wang HJ, Geller F, Dempfle A, Schauble N, Friedel S, Lichtner P, Fontenla-Horro F, Wudy S, Hagemann S, Gortner L, Huse K, Remschmidt H, Bettecken T, Meitinger T, Schafer H, Hebebrand J, and Hinney A.** Ghrelin receptor gene: identification of several sequence variants in extremely obese children and adolescents, healthy normal-weight and underweight students, and children with short normal stature. *J Clin Endocrinol Metab* 89: 157–162, 2004.
420. **Wang L, Saint-Pierre DH, and Tache Y.** Peripheral ghrelin selectively increases Fos expression in neuropeptide Y-synthesizing neurons in mouse hypothalamic arcuate nucleus. *Neurosci Lett* 325: 47–51, 2002.
421. **Wank SA, Harkins R, Jensen RT, Shapira H, de Weerth A, and Slattery T.** Purification, molecular cloning, and functional expression of the cholecystokinin receptor from rat pancreas. *Proc Natl Acad Sci USA* 89: 3125–3129, 1992.
422. **Wank SA, Pisegna JR, and de Weerth A.** Brain and gastrointestinal cholecystokinin receptor family: structure and functional expression. *Proc Natl Acad Sci USA* 89: 8691–8695, 1992.
423. **Watson SJ and Akil H.** The presence of two alpha-MSH positive cell groups in rat hypothalamus. *Eur J Pharmacol* 58: 101–103, 1979.
424. **Wei Y and Mojsov S.** Tissue-specific expression of the human receptor for glucagon-like peptide-I: brain, heart and pancreatic forms have the same deduced amino acid sequences. *FEBS Lett* 358: 219–224, 1995.
425. **West DB, Fey D, and Woods SC.** Cholecystokinin persistently suppresses meal size but not food intake in free-feeding rats. *Am J Physiol Regul Integr Comp Physiol* 246: R776–R787, 1984.
426. **West DB, Greenwood MR, Sullivan AC, Prescod L, Marzullo LR, and Triscari J.** Infusion of cholecystokinin between meals into free-feeding rats fails to prolong the intermeal interval. *Physiol Behav* 39: 111–115, 1987.
427. **Whitcomb DC, Taylor IL, and Vigna SR.** Characterization of saturable binding sites for circulating pancreatic polypeptide in rat brain. *Am J Physiol Gastrointest Liver Physiol* 259: G687–G691, 1990.
428. **White JD, Olchovsky D, Kershaw M, and Berelowitz M.** Increased hypothalamic content of prepro-neuropeptide-Y messenger ribonucleic acid in streptozotocin-diabetic rats. *Endocrinology* 126: 765–772, 1990.
429. **Widdowson PS, Upton R, Henderson L, Buckingham R, Wilson S, and Williams G.** Reciprocal regional changes in brain NPY receptor density during dietary restriction and dietary-induced obesity in the rat. *Brain Res* 774: 1–10, 1997.
430. **Wieland HA, Engel W, Eberlein W, Rudolf K, and Doods HN.** Subtype selectivity of the novel nonpeptide neuropeptide Y Y1 receptor antagonist BIBO 3304 and its effect on feeding in rodents. *Br J Pharmacol* 125: 549–555, 1998.
431. **Wilding JP, Gilbey SG, Bailey CJ, Batt RA, Williams G, Ghatei MA, and Bloom SR.** Increased neuropeptide-Y messenger ribonucleic acid (mRNA) and decreased neurotensin mRNA in the hypo-

- thalamus of the obese (*ob/ob*) mouse. *Endocrinology* 132: 1939–1944, 1993.
432. **Williams CM and Kirkham TC.** Anandamide induces overeating: mediation by central cannabinoid (CB1) receptors. *Psychopharmacology* 143: 315–317, 1999.
 433. **Williams CM, Rogers PJ, and Kirkham TC.** Hyperphagia in pre-fed rats following oral delta9-THC. *Physiol Behav* 65: 343–346, 1998.
 434. **Williams DL, Kaplan JM, and Grill HJ.** The role of the dorsal vagal complex and the vagus nerve in feeding effects of melanocortin-3/4 receptor stimulation. *Endocrinology* 141: 1332–1337, 2000.
 435. **Williams G, Gill JS, Lee YC, Cardoso HM, Okpere BE, and Bloom SR.** Increased neuropeptide Y concentrations in specific hypothalamic regions of streptozocin-induced diabetic rats. *Diabetes* 38: 321–327, 1989.
 436. **Wisén O, Bjorvell H, Cantor P, Johansson C, and Theodorsson E.** Plasma concentrations of regulatory peptides in obesity following modified sham feeding (MSF) and a liquid test meal. *Regul Pept* 39: 43–54, 1992.
 437. **Woods SC, Decke E, and Vasselli JR.** Metabolic hormones and regulation of body weight. *Psychol Rev* 81: 26–43, 1974.
 438. **Woods SC, Lotter EC, McKay LD, and Porte D Jr.** Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. *Nature* 282: 503–505, 1979.
 439. **Woods SC, Seeley RJ, Baskin DG, and Schwartz MW.** Insulin and the blood-brain barrier. *Curr Pharm Des* 9: 795–800, 2003.
 440. **Woods SC, Stein LJ, McKay LD, and Porte D Jr.** Suppression of food intake by intravenous nutrients and insulin in the baboon. *Am J Physiol Regul Integr Comp Physiol* 247: R393–R401, 1984.
 441. **Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG, Dhillon WS, Ghatei MA, and Bloom SR.** Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab* 86: 5992, 2001.
 442. **Wren AM, Small CJ, Abbott CR, Dhillon WS, Seal LJ, Cohen MA, Batterham RL, Taheri S, Stanley SA, Ghatei MA, and Bloom SR.** Ghrelin causes hyperphagia and obesity in rats. *Diabetes* 50: 2540–2547, 2001.
 443. **Wren AM, Small CJ, Ward HL, Murphy KG, Dakin CL, Taheri S, Kennedy AR, Roberts GH, Morgan DG, Ghatei MA, and Bloom SR.** The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. *Endocrinology* 141: 4325–4328, 2000.
 444. **Xu B, Goulding EH, Zang K, Cepoi D, Cone RD, Jones KR, Tecott LH, and Reichardt LF.** Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. *Nat Neurosci* 6: 736–742, 2003.
 445. **Yamamoto H, Kishi T, Lee CE, Choi BJ, Fang H, Hollenberg AN, Drucker DJ, and Elmquist JK.** Glucagon-like peptide-1-responsive catecholamine neurons in the area postrema link peripheral glucagon-like peptide-1 with central autonomic control sites. *J Neurosci* 23: 2939–2946, 2003.
 446. **Yamanaka A, Sakurai T, Katsumoto T, Yanagisawa M, and Goto K.** Chronic intracerebroventricular administration of orexin-A to rats increases food intake in daytime, but has no effect on body weight. *Brain Res* 849: 248–252, 1999.
 447. **Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohteki T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kimura T, Shimizu T, Nagai R, and Kadowaki T.** Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature* 423: 762–769, 2003.
 448. **Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, and Kadowaki T.** The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med* 7: 941–946, 2001.
 449. **Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, Chen CL, Tai TY, and Chuang LM.** Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab* 86: 3815–3819, 2001.
 450. **Yasuda T, Masaki T, Kakuma T, and Yoshimatsu H.** Hypothalamic melanocortin system regulates sympathetic nerve activity in brown adipose tissue. *Exp Biol Med* 229: 235–239, 2004.
 451. **Yeomans MR, Wright P, Macleod HA, and Critchley JA.** Effects of nalmefene on feeding in humans. Dissociation of hunger and palatability. *Psychopharmacology* 100: 426–432, 1990.
 452. **Yokosuka M, Xu B, Pu S, Kalra PS, and Kalra SP.** Neural substrates for leptin and neuropeptide Y (NPY) interaction: hypothalamic sites associated with inhibition of NPY-induced food intake. *Physiol Behav* 64: 331–338, 1998.
 453. **Yoshihara T, Honma S, and Honma K.** Effects of restricted daily feeding on neuropeptide Y release in the rat paraventricular nucleus. *Am J Physiol Endocrinol Metab* 270: E589–E595, 1996.
 454. **Zander M, Madsbad S, Madsen JL, and Holst JJ.** Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet* 359: 824–830, 2002.
 455. **Zarjevski N, Cusin I, Vettor R, Rohner-Jeanrenaud F, and Jeanrenaud B.** Chronic intracerebroventricular neuropeptide-Y administration to normal rats mimics hormonal and metabolic changes of obesity. *Endocrinology* 133: 1753–1758, 1993.
 456. **Zhang M, Balmadrid C, and Kelley AE.** Nucleus accumbens opioid, GABAergic, and dopaminergic modulation of palatable food motivation: contrasting effects revealed by a progressive ratio study in the rat. *Behav Neurosci* 117: 202–211, 2003.
 457. **Zhang M and Kelley AE.** Enhanced intake of high-fat food following striatal mu-opioid stimulation: microinjection mapping and fos expression. *Neuroscience* 99: 267–277, 2000.
 458. **Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, and Friedman JM.** Positional cloning of the mouse obese gene and its human homologue. *Nature* 372: 425–432, 1994.
 459. **Zheng H, Corkern MM, Crousillac SM, Patterson LM, Phifer CB, and Berthoud HR.** Neurochemical phenotype of hypothalamic neurons showing Fos expression 23 h after intracranial AgRP. *Am J Physiol Regul Integr Comp Physiol* 282: R1773–R1781, 2002.
 460. **Zipf WB, O'Dorisio TM, Cataland S, and Dixon K.** Pancreatic polypeptide responses to protein meal challenges in obese but otherwise normal children and obese children with Prader-Willi syndrome. *J Clin Endocrinol Metab* 57: 1074–1080, 1983.
 461. **Zipf WB, O'Dorisio TM, Cataland S, and Sotos J.** Blunted pancreatic polypeptide responses in children with obesity of Prader-Willi syndrome. *J Clin Endocrinol Metab* 52: 1264–1266, 1981.