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Regulation of appetite to treat obesity

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Abstract

Obesity has escalated into a pandemic over the past few decades. In turn, research efforts have sought to elucidate the molecular mechanisms underlying the regulation of energy balance. A host of endogenous mediators regulate appetite and metabolism, and thereby control both short- and long-term energy balance. These mediators, which include gut, pancreatic and adipose neuropeptides, have been targeted in the development of anti-obesity pharmacotherapy, with the goal of amplifying anorexigenic and lipolytic signaling or blocking orexigenic and lipogenic signaling. This article presents the efficacy and safety of these anti-obesity drugs.

Keywords

appetite control; neuropeptides; obesity; pharmacotherapy

The unmet clinical need

Obesity is now a global pandemic [1]. Worldwide, more than 1 billion adults are overweight (BMI >25 kg/m^2), while 300 million adults are obese (BMI >30 kg/m^2) [2]. In the USA, 65% of adults are overweight, and 32.2% are obese [3,4]. This obese population has doubled in only 20 years [5]. Moreover, obesity rates in children have achieved epidemic levels in developed countries and continue to grow worldwide [6,7]. Obesity is associated with striking comorbidities, including cancer, coronary artery disease, hypertension, liver/biliary disease, obstructive sleep apnea, osteoarthritis, stroke and Type 2 diabetes. In that context, life expectancy with chronic obesity is significantly shortened [8]. Notably, chronic obesity is associated with higher rates of health problems and healthcare costs compared with smoking or alcohol abuse [9]. Currently, up to US$100 billion of annual healthcare expenses in the USA can be ascribed to obesity. Within the next 15 years, 20% of US national health-care costs will reflect the care of chronic diseases related to obesity [10].

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Therapeutic approaches to the obese patient

Medical treatment for obese patients has largely focused on complications and comorbidities, such as diabetes, hypertension and hyper-lipidemia. Studies have shown, however, that targeting the underlying disease through weight loss and lifestyle modifications are effective in combating chronic comorbidities, such as cardiovascular disease and diabetes. Lifestyle modification programs and clinical intervention have succeeded in driving approximately a 10% weight reduction within 6 months [11]. In that regard, even a modest loss of weight (<10%) significantly improves blood pressure, cholesterol levels and glycemic control [12,13]. Unfortunately, patients enrolled in lifestyle modification programs typically regain about 35% of their lost weight within 1 year following treatment, while >50% of patients return to their baseline weight in fewer than 5 years [14,15].

Bariatric surgery generates the most rapid and sustained weight loss. Through gastric banding, gastric bypass or sleeve gastrectomy, bariatric surgery achieves long-term weight loss in patients, reduces their risk for obesity-related comorbidities and thereby improves their lifestyle [16,17]. Unfortunately, this treatment is associated with a number of principal adverse effects and, consequently, is recommended only for patients who are morbidly obese (BMI >40 kg/m^2) or suffering serious comorbidities. Therefore, bariatric surgery is an unlikely treatment for the millions of obese patients worldwide [16,18]. However, clinical trials are underway for transoral gastroplasty, in which the stomach is stapled or sutured to reduce its capacity via oral insertion of flexible devices, thereby eliminating surgical incisions [19].

Anti-obesity pharmacotherapy may represent the means by which overweight and obese patients can safely achieve long-term weight reduction. For example, clinical trials have demonstrated that the weight-loss drug orlistat (Alli® [GlaxoSmithKline]; Xenical® [Roche]), which is a lipase inhibitor and prevents some of the fat in food from being absorbed, can produce weight loss that can be sustained for up to 2 years [20–22]. Those observations notwithstanding, the history of anti-obesity pharmacotherapy is characterized by setbacks and dilemmas over safety, efficacy, abuse and adverse effects. For example, the potentially fatal adverse effects of valvular heart disease and pulmonary hypertension of the anti-obesity medication fenfluramine–phentermine (Fen–Phen) led to its withdrawal and legal damages of more than US$13 billion [23]. In fact, with the withdrawal of sibutramine (Meridia®; Abbott) from the market after 13 years owing to cardiovascular risks, orlistat has recently become the only drug that is US FDA approved for long-term use in weight management [24–28].

Anti-obesity drug development research has focused on the regulation of appetite and energy consumption. Endocannabinoid signaling and monoamine neurotransmission are involved in this regulation, but many centrally-acting drugs directed at these pathways induce major cardiovascular and psychological adverse effects. Hormonal regulators, including neuropeptides from gut, pancreatic and adipose tissue, serve as endogenous mediators of energy balance. By targeting these pathways, drug development programs aim to minimize central or peripheral adverse effects, while driving appetite reduction and weight loss. This article discusses the efficacy and safety of these anti-obesity pharmacotherapeutics.

Central appetite regulation

The hypothalamus integrates neurohormonal signaling from gut and adipose tissue. Specific hypothalamic nuclei, including the dorsomedial nucleus (DMN), paraventricular nucleus

(PVN) and ventromedial nucleus (VMN), serve as control centers for appetite. In animals, lateral hypothalamic lesions produce anorexia while VMN lesions produce hyperphagia [29–33]. In that context, more recent studies have demonstrated that appetite reflects the integration of orexigenic and anorexigenic signals from numerous hypothalamic nuclei and tissues outside the CNS (Figure 1).

The arcuate nucleus (ARC) is the major target for peripheral hormones that regulate appetite. The ARC is located at the base of the hypothalamus, outside the blood–brain barrier. As it is surrounded by a permeable barrier, the ARC is accessible to circulating hormones [34]. The ARC contains two distinct neuronal subtypes that are critical for appetite regulation:

- Those expressing the neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART);
- Those expressing neuropeptide Y (NPY) and Agouti-related protein (AgRP).

Pro-opiomelanocortin/CART-expressing neurons suppress appetite, while NPY/AgRP neurons stimulate appetite. It is the balance between these neuronal signals that regulates energy homeostasis [34–36].

Pro-opiomelanocortin is a precursor polypeptide that is cleaved to yield several hormones, including melanocortins such as α-melanocyte stimulating hormone (α-MSH). Melanocortins control appetite by activating the melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors on second-order neurons. Intracerebroventricular (ICV) administration of MC3R and MC4R agonists reduces food intake, while antagonist administration produces hyperphagia [37]. Elimination of MC4R expression in transgenic mouse models produces overeating and obesity [38]. Furthermore, polymorphisms of MC4R are associated with obesity [39].

Cocaine- and amphetamine-regulated transcript is coexpressed with α-MSH and has similar anorexigenic properties. Fasting produces a significant decline in CART expression. ICV administration of CART peptide suppresses feeding, while ICV administration of antiserum to CART stimulates food intake [40]. Some reports, however, have demonstrated that CART injection into specific hypothalamic nuclei produces an orexigenic phenotype [41], indicating that CART's effects depend on signaling location.

Neuropeptide Y belongs to the pancreatic polypeptide family, which activates the seven-transmembrane G protein-coupled receptors (GPCRs) Y1–Y6 [42]. NPY is a potent orexigenic neuro-peptide. Its expression is controlled by nutritional status, and mRNA levels are increased during fasting and reduced following food intake [43,44]. Signaling pathways mediating NPY effects have yet to be definitively characterized. Nevertheless, Y1- and Y5-receptor activation appears to stimulate appetite [45], while Y2- and Y4-receptor activation suppresses food intake via presynaptic inhibition of NPY release [46].

Agouti-related protein (AgRP) expression is localized to the ARC [47]. AgRP is a selective inverse agonist of MC3R and MC4R and a powerful appetite stimulant. AgRP levels rise during fasting and decline following food intake [43]. ICV administration of AgRP stimulates food intake [48,49]. Mice overexpressing AgRP develop hyperphagia and obesity [50].

From the ARC, these first-order POMC/CART and NPY/AgRP neurons project to second-order neurons in several hypothalamic nuclei, including the VMN, DMN, PVN and the lateral hypothalamic area. These second-order neurons subsequently project to such areas as the caudal brainstem, cortex and limbic system, and thereby act to process and integrate

feeding signals. Lesions in these hypothalamic nuclei result in hyperphagia (PVN, DMN and VMN) or hypophagia, and demonstrate the significance of these second-order neurons in generating hunger and satiety responses [29–33].

Second-order neurons in these hypothalamic nuclei are crucial to regulation of feeding, and express potent chemical mediators themselves to serve this function. Corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH) are anorexigenic peptides expressed in the PVN. NPY/AgRP signaling downregulates expression of CRH and TRH, and α-MSH signaling, in turn, upregulates their expression [51–53]. Melanin-concentrating hormone (MCH) is expressed in the lateral and perifornical hypothalamus. As a potent orexigenic neuropeptide, MCH levels rise during fasting and stimulate appetite with ICV administration [54]. Orexin A and B are a pair of neuropeptides that also are expressly found in the lateral hypothalamus and perifornical areas, and function to stimulate appetite [34]. Brain-derived neurotrophic factor (BDNF) has a wide tissue distribution, but has a notably high expression level in the VMN. In rodents, central BDNF administration produces a decline in weight and appetite [55]. In humans, a mutation in *NTRK2*, which encodes TrkB, the BDNF receptor, causes hyperphagia and obesity [56]. Activation of MC4R upregulates BDNF expression and signaling [57], which suggests that central melanocortins may curtail appetite by activating downstream BDNF effectors.

Extensive reciprocal circuits between the hypothalamus and brainstem relay information regarding feeding status. Of note, the dorsal vagal complex (DVC) receives signals from peripheral satiety hormones and vagal afferents from the GI tract [58,59]. In addition, dopamine reward pathways play a role in feeding. Mice deficient in dopamine exhibit hypophagia, and recover with dopamine replacement in the caudate putamen and nucleus accumbens [60]. Furthermore, opioid signaling pathways regulate feeding behavior. In mice, deficiency in the opioid receptor ligands β-endorphin and enkephalin diminish food-seeking behavior [61]. Finally, the endocannabinoid system, notably through central CB_1 receptors, stimulates appetite and promotes lipogenesis in the hypothalamus, mesolimbic system and periphery [62]. In the following section, we will discuss the anti-obesity drugs that the pharmaceutical industry has in various stages of clinical development; Table 1 lists the prominent identifying and distinguishing features of these pharmacotherapeutics.

Antagonists of central neuropeptide signaling

Neuropeptide Y—Neuropeptide Y regulates feeding through Y1- and Y5-receptors. NPY signaling inhibition reduces food intake and bodyweight in mice [63,64]. In patients, the NPY receptor antagonist MK-0557 (Merck; 1 mg/day) induced modest weight loss over the initial 12-week period of administration. Following 52 weeks of therapy, MK-0557 produced a statistically significant, but not clinically meaningful (less than 3 kg), weight loss [65].

Other appetite modulators—The AgRP inhibitor TTP-435 (TransTech Pharma), in Phase II trials, antagonizes the activity of AgRP with no effect on MC4R alone or in the presence of α-MSH [301]. In addition, the MCH-1 receptor antagonist BMS-830216 (Bristol-Myers Squibb) is in Phase I/II clinical testing [302]. The MC4R agonist MK-0493 (Merck) induced a reduction in food intake and minimized weight gain in rodents with diet-induced obesity. However, in Phase II clinical trials, MK-0493 demonstrated only statistically insignificant weight loss relative to placebo in both a 12-week fixed-dose study as well as an 18-week stepped-titration study [66]. As MC4R agonism has been a promising target of anti-obesity pharmacotherapy, drug development studies continue to search for selective small agonists for MC4R. Deficiency of MC4R signaling due to over 150 different mutations is a well-characterized genetic basis of obesity, and potential therapeutics

including exogenous agonists and molecular chaperones continue to be investigated in preclinical studies [67]. However, given the extensive and complex activity of melanocortins in not only energy homeostasis but also cardiovascular and sexual function, significant concerns remain over the potential adverse effects of long-term MC4R agonism, including hypertension and sexual arousal [68]. While neuromedin U (NMU) originally looked promising as an anorexigenic, inducing the release of CRH by neurons of the PVN [69], administration of NMU does not reduce food intake or weight [70], and diet-induced obese rats are relatively insensitive to the effects of NMU [71].

Therapeutic approaches to regulating food intake

Intestinal peptides

Cholecystokinin—Cholecystokinin (CCK) is produced by I cells in the duodenum and jejunum, and serves a variety of functions, including that of a neurotransmitter in the CNS [72]. CCK secretion by the gut is stimulated by foods high in fat and protein, and aids digestion [73]. The CCK receptor, a seven-transmembrane GPCR, exists as two different isoforms, CCK-A and CCK-B. CCK-A is expressed in the pyloric sphincter and in vagal afferents. It appears to be responsible for the effect of CCK signaling on satiety, and CCK-A agonists suppress appetite [74,75]. In rodents, deficiency of CCK-A or receptor blockade produces hyperphagia and obesity [76]. In humans also, treatment with the CCK-A receptor antagonist, loxiglumide, drives increased caloric intake [77]. However, targeted antagonism of CCK-B appears to have no effect on CCK-mediated appetite reduction [78]. With chronic administration, tolerance to CCK develops [79], eliminating its ability to reduce weight [80]. Moreover, intermittent CCK reduces the size, but increases the frequency, of meals [81]. In that context, the selective CCK-A agonist GI 181771X (GlaxoSmithKline) failed to induce weight loss in Phase II trials [82]. However, CCK potentiates appetite and weight reduction by leptin [83], suggesting that combination therapy may have utility. It is noteworthy that chronic CCK administration in animals produced pancreatitis [84,85], suggesting limited utility of this therapeutic approach in humans.

Glucagon-like peptide 1—Glucagon-like peptide 1 (GPL-1) is produced by enteroendocrine L cells in the ileum and proximal colon. It is generated after processing of preproglucagon by prohormone convertase-1 [86]. Its secretion is stimulated by nutrients and neural and endocrine factors [87] after ingestion of a meal, particularly one rich in fat and carbohydrates [88]. The GLP-1 receptor (GLP-1R) is a GPCR expressed in the heart, kidney, lung, pancreas, CNS and PNS, including the nucleus tractus solitarius (NTS) of the DVC, and the ARC [86]. GLP-1 is an incretin, which are gut hormones that increase secretion of insulin by pancreatic β-cells [87]. GLP-1 is anorexigenic. Its administration induces satiety and weight loss in animals and humans [89–92]. In rats, GLP-1 effectiveness was lost after monosodium glutamate-induced lesions in the ARC [93], subdiaphragmatic vagotomy and transection of brainstem–hypothalamic connections [94], suggesting that hypothalamic and vagal signaling are essential for mediating the satiating effects of GLP-1. Moreover, GLP-1 antagonizes the orexigenic effects of NPY [95].

Glucagon-like peptide 1 has a characteristic short circulating half-life, reflecting rapid proteolysis by dipeptidyl peptidase IV (DPP-IV) [96], limiting its therapeutic utility in patients. This pharmacokinetic limitation has been abrogated by employing two different approaches. GLP-1 analogues resistant to DPP-IV degradation have been developed, including liraglutide (Victoza®; Novo Nordisk) and exenatide (Byetta®; Amylin/Eli Lilly), comprising exendin-4, a peptide extracted from the salivary gland of the *Heloderma suspectum*(gila monster). Furthermore, orally active DPP-IV inhibitors, vildagliptin (Novartis) and sitagliptin (Januvia®; Merck) have been developed. A meta-analysis examining these approaches in Type 2 diabetic patients revealed that, compared with

patients receiving insulin therapy, patients receiving GLP-1 analogues lost an average of 4.76 kg [97]. Indeed, weight loss induced by GLP-1 analogues was dose dependent, progressive and did not plateau by 30 weeks. Further to this, more weight was lost in patients receiving exenatide compared with liraglutide [97]. Moreover, DPP-IV inhibitors were less effective in inducing weight loss compared with GLP-1 analogues [97]. Similarly, in nondiabetic obese individuals, liraglutide induced a mean of approximately 6.0 kg in weight loss and >35% of the subjects treated with the highest dose achieved a reduction of ≥10% baseline weight [303]. As a result, liraglutide was approved by the EMA in 2009 and the US FDA in 2010 for the treatment of Type 2 diabetes, and is in trials to win FDA approval for the treatment of obesity. Recently, long-acting exenatide (exenatide-LAR) was shown to improve bodyweight during a 15-week trial in diabetic patients [98]. Following 2 years of weekly treatment, exenatide-LAR induced average reductions in bodyweight of 5.8 lbs [304]. To improve convenience and patient compliance, nasal and transdermal formulations of exenatide are being developed [305]. In that context, oral formulations of GLP-1 are being developed, and oral administration induces a rapid dose-dependent rise in circulating peptides, which are active [99]. With respect to adverse events, severe hypoglycemia was rare, but mild-to-moderate hypoglycemia was more than twice as common in patients receiving GLP-1 analogues [97]. In patients receiving exenatide, nausea and vomiting were the most common adverse effects [97]. Mild-to-moderate nausea was also the most common adverse effect reported with weekly treatment of exenatide-LAR [98]. Furthermore, exenatide should not be used in patients with renal disease, and kidney function should be monitored in patients receiving this medication [100].

Oxyntomodulin—Oxyntomodulin (OXM), a product of the gut, is also produced from processing of preproglucagon. OXM is secreted post-prandially along with GLP-1 by the L cells of the colon. It demonstrates weak activity as an incretin, but induces potent appetite suppression. In rats, ICV or intraperitoneal administration of OXM produced diminished feeding and weight gain [101,102]. In humans, intravenous infusion of OXM suppressed appetite and feeding, without a significant change in circulating insulin levels [103]. OXM may mediate its effects via activation of central GLP-1Rs. The anorectic effects of OXM are abolished both in GLP-1R knock out mice [104] and with administration of the GLP-1R antagonist exendin (9–39), even with concomitant ICV OXM administration or OXM injection into the PVN [101]. Another OXM receptor, however, may exist: compared with GLP-1, OXM binds GLP-1R with 100-fold lower affinity, but exerts the same degree of anorexia at equimolar concentrations [102]. Furthermore, intra-ARC administration of exendin (9–39) blocks the anorectic effects of OXM, but has no effect on GLP-1 activity [102]. Perhaps OXM stimulates ARC neurons directly, while GLP-1 does so indirectly through connections with the brainstem. The role of OXM in the ARC may be to stimulate POMC neurons, as the incubation of POMC neurons with OXM *ex vivo* stimulates α-MSH release [102]. Intravenous infusion of OXM (3.0 pmol/kg/min) reduced food intake by 19% compared with saline-infused subjects. Furthermore, OXM infusion reduced 12-h food intake by 11%, without affecting 24-h food consumption [103]. Subcutaneous injection of OXM (three-times daily, 30 min before each meal for 4 weeks) significantly reduced food consumption at the beginning and end of the 4-week trial, inducing an average weight loss of 2.3 kg [105]. In overweight and obese subjects, OXM administered before meals increased activity-related energy expenditure by 26% and total energy expenditure by 9.5% in addition to reducing food consumption [106]. Inducing an increase in physical activity is noteworthy, as weight loss can be achieved by promoting greater energy expenditure than energy intake. Many stimulants are well-characterized drugs that effectively increase physical activity, suppress appetite and promote weight loss. However, stimulants are also well known to pose serious risks such as addiction, hypertension and cardiovascular damage. Therefore, OXM might represent a safer means of stimulating an increase in energy

expenditure. However, as injections of OXM are required to induce weight loss, this is considered to be a barrier to therapy. Regarding adverse effects, this agent rarely induced mild nausea [105,106].

Peptide YY—Peptide YY (PYY) belongs, along with NPY, to the pancreatic polypeptide family, which bind to the GPCRs Y1–Y6 [42]. However, in contrast to NPY, PYY is potently anorexigenic. PYY is expressed throughout the small intestine, with the highest concentration found in L cells of the terminal ileum and colon, which secrete the peptide in response to a meal [107]. PYY stimulates gastrointestinal absorption of fluids and electrolytes [108], reduces gastric and pancreatic secretions and delays gastric emptying [109]. In rodents, administration of PYY induces a dose-dependent decrease in food intake [110–112]. PYY-deficient mice display hyperphagia and obesity [113]. Obese humans and rodents have lower circulating levels of postprandial PYY compared with lean controls [114]. Notably, however, obese subjects achieve a progressive rise back to normal plasma PYY levels following bariatric surgery. This phenomenon has been implicated in the success of bariatric surgery in producing long-term weight loss. Regarding PYY, obesity engenders a state of deficiency rather than resistance, which is the converse of obesity's effects on leptin. Thus, PYY replacement therapy is an attractive concept for treatment. PYY circulates as two major forms: $PYY_{1–36}$ and $PYY_{3–36}$. The more common $PYY_{3–36}$ exhibits high affinity for Y2R, and some affinity for the Y1R and Y5R [42]. Peripheral PYY administration induces appetite suppression by activating Y2R in the ARC. ICV administration, however, stimulates food intake, presumably due to PYY activation of orexigenic Y1R and Y5R in second-order neurons of the PVN [115]. Therefore, PYY conceivably suppresses appetite by activating presynaptic Y2R, which inhibits the activity of NPY/AgRP neurons. Vagal afferent signaling, too, is implicated, as bilateral subdiaphragmatic vagotomy or transecting brainstem–hypothalamic connections attenuates the anorectic effects of PYY [94]. Continuous infusion of PYY in healthy subjects reduced hunger and caloric intake by 36% [112], and obese patients behaved similarly [116]. Indeed, infusion of PYY reduced food consumption in a dose-dependent manner, with a maximum inhibition of 35% [117]. Unfortunately, continuous intravenous infusion is not a tractable approach for weight-loss therapy, and an intranasal formulation of PYY (Nastech/Merck) was ineffective in inducing weight loss [118]. Moreover, PYY produces nausea and vomiting in a dose-dependent manner, limiting its therapeutic utility in appetite suppression [117,118].

Ghrelin—Ghrelin is the only known circulating orexigenic hormone. Ghrelin is cleaved from preproghrelin and is mainly produced in the gastric fundus. It has been reported to stimulate the release of growth hormone by activating the growth hormone secretagogue receptor (GHS-R) [119]. As ghrelin deficiency does not translate into defective growth in mice, however, its physiological relevance on growth hormone release is unclear [120]. Ghrelin plays a role in energy balance. In rodents, ICV or peripheral administration induces a dose-dependent increase in food intake and bodyweight [121,122]. Ghrelin also regulates long-term energy homeostasis. Obese patients display reduced circulating ghrelin levels and anorexic patients display exaggerated circulating ghrelin levels. Weight gain correlates with a decline in ghrelin levels [123–125]. The receptor GHS-R1a is expressed throughout the CNS, notably within certain hypothalamic nuclei, the pituitary gland and the hippocampus. GHS-R1a is also expressed, albeit at lower levels, in the adrenal glands, heart, pancreas, spleen and thyroid [126,127]. Ghrelin is believed to induce hunger and feeding by activating NPY/AgRP neurons in the ARC. Vagal stimulation is also important. In rats with mechanical or chemical disruption of vagal signaling, ghrelin administration fails to stimulate feeding or activate NPY-expressing neurons [128]. In fact, ghrelin appears to function at several sites. Ghrelin induces food intake when injected into other CNS sites

expressing GHS-R, including the mesolimbic reward pathway, the hippocampus and the dorsal raphe nucleus [129,130]. A variety of therapeutic approaches to blocking ghrelin's action are being explored as a strategy for treating obesity. A first-generation ghrelin vaccine, CYT009-GhrQb, was discontinued because patients did not lose weight, even though they showed a strong ghrelin antibody response [306]. The next generation of ghrelin vaccine has been developed that decreases feeding, adiposity and bodyweight in rodents [131]. Furthermore, a ghrelin-neutralizing RNA Spiegelmer®, NOX-B11 (NOXXON Pharma Ag), which is an aptamer that binds to and inactivates ghrelin, blocked the orexigenic activity of exogenous ghrelin administration but did not alter food intake in rats [132]. Furthermore, ghrelin antagonists, produced by Elixir Pharmaceuticals, are in preclinical testing [307]. Moreover, ghrelin *O*-acyltransferase (GOAT) is a membrane-bound enzyme that adds octanoate to ghrelin, which is required for receptor binding, and inhibition of GOAT may be an effective strategy to inhibit ghrelin activity [133].

Pancreatic hormones

Pancreatic polypeptide—Pancreatic polypeptide (PP) is homologous to PYY, possibly originating as a duplication of the *PYY* gene [134]. PP levels in the circulation rise after eating, increasing proportionally to caloric intake, and remain elevated for up to 6 h [135]. PP secretion is induced by vagal stimulation and peripheral hormones, including ghrelin [136]. PP administration to obese mice decreases appetite [137] and repeated administration limits their weight gain [138]. PP administration to lean mice also suppresses feeding associated with delayed gastric emptying [138]. Similarly, overexpression of PP in transgenic mice suppresses eating, gastric emptying and weight gain [139]. Moreover, fasting- and food-induced PP levels are lower in obese patients [140], while PP responses are exaggerated in patients with anorexia nervosa [141]. PP binds with highest affinity to the Y4- and Y5-receptors [42]. As with PYY, the route of PP administration affects its impact on appetite. In rats, ICV administration of PP increases feeding [142], reflecting activation of orexigenic Y5R [64]. By contrast, peripheral administration of radiolabeled PP reveals significant accumulation in the area postrema (AP) of the DVC, which expresses Y4-receptors [143,144]. Vagotomy abolishes PP's anorectic effects in mice [138]. Peripheral administration of PP increases vagal activity and induces changes in the levels of hypothalamic neuropeptides, including decreasing NPY and orexin, and increasing the anorexigenic peptide, urocortin [138]. In healthy subjects, intravenous infusion of PP (10 pmol/kg/min) reduced appetite and caloric intake by 22%, an effect that was sustained over 24 h [145]. PP has a short half-life, and extended-duration formulations of Y2R or Y4R agonists may be more efficacious in long-term appetite control and weight loss [146]. Obinepitide (7TM Pharma), a Y2/Y4-receptor agonist, and TM30339 (7TM Pharma), a selective Y4-receptor agonist, are in Phase I/II clinical trials [308,309].

Amylin—Amylin, or islet amyloid polypeptide, is secreted with insulin by β-cells [147], and patients with Type 1 diabetes are deficient in both hormones. Like insulin, fasting plasma levels of amylin are low and increase in response to eating [148,149]. Amylin regulates post-prandial glucose levels together with insulin. Beyond glucose homeostasis, amylin has anorectic characteristics, and ICV administration reduced food intake in rodents, while constant infusion over 10 days reduced feeding and adiposity [150]. Conversely, pharmacologic antagonism of amylin signaling increased rodent appetite and adiposity [151], and amylin-deficient mice gain excess weight [152,153]. Amylin is homologous to calcitonin gene-related peptide, calcitonin and adrenomedullin [154,155], and amylin receptors appear when calcitonin receptors are coexpressed with receptor activity-modifying proteins [156,157]. Amylin receptors are expressed in selective regions of brain, including the AP [158]. The effects of amylin on gastric emptying and appetite are attenuated by vagotomy or injury of the AP/NTS, suggesting that vagal signaling is essential in mediating

the appetite suppression induced by amylin [159–161]. Pramlintide, a synthetic amylin analogue (Symlin®; Amylin) [162] has a pharmacokinetic and pharmaco-dynamic profile that is similar tothat of amylin [163]. Pramlintide is approved to treat diabetes and, unlike traditional diabetic medications, elicits weight loss in diabetic patients. Thus, subcutaneous injection of pramlintide with meals reduced bodyweight over 52 weeks of treatment in Type 2 diabetic patients [164,165]. Similarly, pramlintide produced bodyweight reductions in Type 1 diabetic patients [166]. Finally, a pooled *post hoc* analysis in Type 2 diabetic subjects demonstrated that pramlintide, at 120 μg twice daily or 150 μg three-times daily, induced an average weight loss of 2.6 kg over 52 weeks of therapy [167]. The only adverse effects associated with pramlintide were a transient increase in mild-to-moderate nausea and headache [164–167].

Adipose tissue hormones

Leptin—Leptin, an adipose tissue-derived hormone, has been labeled the ‘obese gene’ (*ob*), since mice harboring mutations develop morbid obesity [168]. Administration of leptin to *ob/ob* mice decreases consumption, increases energy expenditure and is associated with a 30% decrease in weight following 2 weeks of therapy [169,170]. Similarly, congenital leptin deficiency in humans manifests as early-onset obesity, which is treated with leptin replacement [171,172]. Circulating levels of leptin reflect both the degree of adiposity [173] and the feeding state [174]. Typically, obese patients exhibit elevated circulating leptin levels [173], which can be confirmed in rodent models of obesity. Elevated circulating leptin in obesity reflects leptin receptor resistance. Leptin receptors, members of the gp130 family of cytokine receptors, are expressed in the hypothalamus [175]. Leptin receptors activate janus kinase [176], which, in turn, activates signal transducer and activator of transcription-3, increasing the expression of POMC, while reciprocally suppressing the expression of AgRP [177]. Similarly, activated janus kinase phosphorylates insulin receptor substrate proteins, stimulating the phosphoinositide 3-kinase pathway, which also suppresses NPY and AgRP, while increasing POMC. Furthermore, 5′-AMP-activated protein kinase, an energy-sensing protein, which is active in low energy states and stimulates feeding, is inhibited in multiple areas of the hypothalamus by leptin receptor activation [178]. Leptin regulation of appetite is specifically related to signaling in the ARC. NPY/AgRP and POMC/CART neurons in the hypothalamus express leptin receptors [179,180] and ICV leptin fails to reduce food intake in rats if the ARC is damaged [181]. Indeed, leptin inhibits NPY/AgRP signaling and downregulates the expression of these neuropeptides, while it upregulates POMC expression and stimulates POMC/CART signaling in the ARC [182–184]. Targeting leptin as an therapeutic endocrine approach to obesity and weight loss has been disappointing, probably reflecting receptor resistance in obesity [185].

Adiponectin—Adiponectin is secreted from adipose tissue into the bloodstream and is very abundant in plasma relative to many hormones. Adiponectin promotes insulin sensitivity and the survival of pancreatic β-cells and cardiomyocytes [186]. Similar to leptin, it acts in the brain to mediate weight loss. However, it has yet to enter clinical trials.

Combination therapy with pramlintide & leptin—The ability of amylin to reduce appetite and weight in obese rats is potentiated by coadministration of leptin. This effect is specific to amylin, and synergy is not observed with other peptides, including PYY and GLP-1/exendin-4 analogues. This synergy appears to reflect the ability of amylin to restore leptin receptor signaling in the hypothalamus in the setting of obesity [187]. In overweight and obese patients, coadministration of pramlintide and leptin by subcutaneous injection twice daily produced approximately 13 kg of weight loss, while monotherapy with either agent only resulted in approximately 8 kg of loss. Importantly, patients on combination therapy continued to lose weight, while those on mono-therapy achieved a plateau over the

duration of the study [187]. In a Phase II study, overweight and obese individuals treated with combination therapy twice daily lost approximately 11% of bodyweight, which was significantly greater than patients receiving either agent alone (approximately 5.0%) [310]. In a continuation of this study, patients receiving cotherapy exhibited sustained weight loss, while those receiving placebo regained almost all their weight [311]. Based on these results, pramlintide/leptin cotherapy is advancing into Phase III trials.

Oleoyl-estrone—Oleoyl-estrone (OE) is packaged in lipoproteins derived from adipose tissue for secretion in the circulation. Like leptin, OE levels are associated with adiposity [188], but in contrast to leptin, obese patients exhibit reduced circulating OE. OE induces dose-dependent decreases in appetite and weight [189] with a preservation of body protein and wasting of fat stores in rodents [190]. Moreover, weight loss is maintained for 26 days following 2 weeks of constant OE infusion in lean rats, while obese rats regain weight immediately following cessation of OE infusion, reflecting a deficient leptinergic system [191]. Importantly, oral administration of OE induced loss of adipose tissue associated with a decrease in food intake, without changing the metabolic rate [189,192]. Although the underlying mechanism of action is not yet clear, the loss of weight can be sufficiently explained owing to the decrease in food consumption [193]. These observations underscore the principal advantage of OE, which is oral bioavailability, in contrast to peptide hormones, which require intravenous or subcutaneous administration. In humans, oral OE (150–300 μmol/day) administered to morbidly obese patients over ten consecutive 21-day trial periods followed by 2-month recovery periods induced a weight loss of 38.5 kg over 27 months [194]. While these data were promising, subsequent randomized clinical trials failed to demonstrate significant placebo-adjusted weight loss in obese patients [312].

Modulators of monoamine neurotransmission

Monoamine neurotransmitters, such as norepinephrine, serotonin and dopamine, are involved in regulating an array of neuronal functions, including appetite control [195]. Drugs that target monoamine neurotransmitter levels are effective in generating weight loss in patients. However, because of the variety of neuronal pathways that utilize these neurotransmitters, these drugs carry risks of addiction, tolerance, hypertension and cardiovascular adverse effects [196].

Bupropion is a dopamine and norepinephrine reuptake inhibitor, and is used as an antidepressant and a smoking cessation aid. Naltrexone is an opioid receptor antagonist and is used in treating opiate and alcohol addiction. The combination of the two drugs, marketed as Contrave® (Orexigen® Therapeutics), tries to synergize their mechanisms of action: bupropion stimulates hypothalamic POMC neurons and downstream α-MSH neurons, both anorexigenic, while naltrexone blocks the autoinhibition of the POMC neurons by endogenous β-endorphins [197]. Phase III clinical trials have demonstrated that patients on a diet and exercise program achieved greater weight loss over 56 weeks with bupropion/naltrexone (6.1 kg) than with placebo (1.4 kg) [313]. However, in February 2011, the FDA rejected approval of the bupropion/naltrexone combination due to concerns over potential cardiovascular risks [314].

Phentermine is a norepinephrine reuptake inhibitor. Topiramate is an antiepileptic and anticonvulsant. Individually, phentermine and topiramate have demonstrated efficacy in weight loss. However, the combination of topiramate and phentermine, marketed as Qnexa® (Vivus), was rejected by the FDA as a weight-loss drug due to concerns over adverse effects, including suicidal thoughts, heart palpitations, memory lapses and birth defects [315].

5-hydroxytryptamine receptor subtype 2C ($5HT_{2C}$) binds serotonin and acts in the regulation of feeding behavior, among other roles [198]. Lorcaserin (ADP-356; Arena) is a selective $5HT_{2C}$ agonist that proved to be effective in inducing weight loss in Phase II/III testing [199]. However, the FDA rejected approval for lorcaserin owing to marginal efficacy in weight loss and the risk of breast tumors in female rats [316].

Expert commentary

A host of technical, institutional and economic issues pose grave challenges to the development and deployment of safe and effective anti-obesity medications. The morbidity and mortality risks accompanying anti-obesity medications have figured prominently in the development of therapeutic agents in this field. Demonstrated safety appears as elusive a goal as it is undeniably a prerequisite for physicians who would prescribe these drugs for their patients, especially in light of the established safety and efficacy of many of the drugs used to treat the comorbidities of obesity. In addition, current drug formulations are often delivered via injection, which represents a serious impediment to patient compliance. Developing orally active drugs is essential to success in this field. Furthermore, most physicians prefer to limit pharmacological therapy to comorbidities, and address obesity through lifestyle modification programs, only employing anti-obesity drugs as a last resort. In that model, patients struggle unsuccessfully for months or years to achieve and maintain adequate weight loss. Earlier administration of anti-obesity pharmacotherapy could provide significant benefit in the reduction of both weight and the risk for the development of comorbidities. Therefore, educating both patients and physicians about the safety and efficacy of these new drugs will be paramount.

Regulatory guidelines for anti-obesity therapy represent a significant obstacle to developing drugs for this application. The FDA mandates that weight control by new drugs must be demonstrated over 1 year to classify a product as efficacious. These efficacy guidelines suggest that: placebo-subtracted weight loss induced by the drug must be ≥ 5%; and the percentage of drug-treated subjects losing ≥ 5% of baseline bodyweight must be ≥ 35% and double the percentage from the placebo-treated subjects. Moreover, at least 3000 subjects must be assigned to the experimental drug with no fewer than 1500 subjects assigned to placebo for a 1-year period to satisfy safety concerns [200,317]. These regulatory guidelines promote drug safety and efficacy and are therefore essential for the responsible and worthwhile development of pharmacotherapy. They nonetheless demand an enormous investment of time and resources from biopharmaceutical companies, and have contributed to the wane of approved anti-obesity drugs that are currently available to physicians and their patients.

Beyond regulatory considerations, there are also financial barriers for patients to consider anti-obesity therapy. Indeed, obesity is not classified as a disease itself, a position propagated by the FDA and its regulatory guidelines. Unfortunately, this position provides insurance companies with a basis to consider anti-obesity drugs with cosmetic procedures as exclusions, and decline patients reimbursement for anti-obesity medications. Thus, patients without an indication for another comorbid condition may have to pay out-of-pocket for anti-obesity therapy. Such costs could represent a major obstacle to patient care, especially in low-income populations with disproportionately high obesity rates. In that context, a 1-month supply of orlistat, for example, costs approximately US$120–140, a major hurdle for patients of low economic status.

Five-year view

Anti-obesity pharmacotherapeutics, leveraging a variety of pathophysiological mechanisms, are in preclinical and clinical development, with several showing great promise to be superior alternatives to orlistat. In the context of the pandemic into which obesity has evolved, recent efforts have focused on the development of combination therapeutics for the treatment of obesity, and based on the positive results achieved with these agents and the effectiveness of combination drug therapy in treating a variety of other pathologies, new combinations of anti-obesity drugs can be expected. Agents that target gut, pancreatic and adipose hormone and neuropeptide signaling will also continue to be developed. Furthermore, new delivery methods, including oral, intranasal and transdermal formulations, will make these drugs more attractive to patients and physicians. In addition, a better understanding of how the body regulates appetite will probably result in the discovery of new therapeutic targets. For example, an obstacle such as obesity-related leptin resistance may be circumvented as we further define mechanisms by which central leptin resistance develops in obesity. Despite this progress, however, the aforementioned scientific, regulatory and economic hurdles must be overcome to permit the rapid entry of anti-obesity pharmacotherapeutics into mainstream clinical care.

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Key issues

- Obesity has evolved into a global pandemic associated with comorbidities including Type 2 diabetes and cardiovascular disease. The health and economic impacts of chronic obesity exceed those of smoking or alcohol abuse.
- Safe and effective therapies to treat obesity and induce long-term weight loss represent an urgent unmet clinical need. Bariatric surgery is reserved for morbidly obese patients and those with serious comorbidities, while the sole anti-obesity drug that is US FDA-approved for long-term use, orlistat, has limited efficacy associated with substantial gastrointestinal side effects.
- Elucidating central and peripheral mechanisms regulating appetite has produced anti-obesity drug development programs targeting these pathways.
- Supplementation of hormonal regulators of appetite (glucagon-like peptide-1, oxyntomodulin, peptide YY, pancreatic polypeptide and amylin) reduces appetite associated with weight loss. Unfortunately, these regulatory peptides require administration by injection, which is a major drawback.
- New delivery methods for these peptide hormones, including oral, intranasal and transdermal formulations, will make these drugs more attractive to patients and physicians. Orally active drugs targeting hormone and neuropeptide receptors are in early development.
- Substantial scientific, regulatory and economic barriers to developing anti-obesity pharmacotherapeutics still remain.

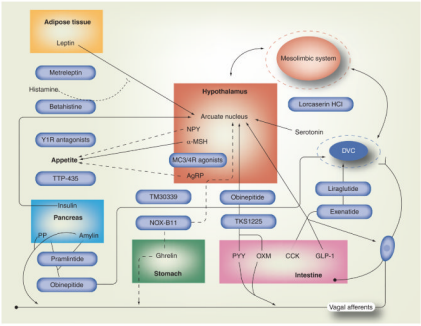

Figure 1. Satiety regulation by endogenous hormones and therapeutic intervention

Appetite is regulated by integrated neuronal circuits between the hypothalamus, mesolimbic system and DVC. Endogenous hormones regulate appetite by directly signaling to the arcuate nucleus in the hypothalamus or indirectly to the DVC in the brainstem, which then communicates with the hypothalamus. Appetite is also affected by reward mechanisms predominately regulated by neuronal signaling in the mesolimbic system, which has projections to the hypothalamus. Secretion of appetite-stimulating neurohormones, NPY and AgRP, is activated by ghrelin and inhibited by leptin, insulin, GLP-1, OXM and PYY. The α-MSH released from POMC/CART neurons in the arcuate nucleus is appetite-suppressing. Leptin, GLP-1, OXM and serotonin act on POMC/CART neurons to promote α-MSH-mediated suppression of appetite. CCK, GLP-1, PP and amylin induce satiety by activating appetite-suppressing neurons in the DVC directly or indirectly through vagal afferents. Hormones are color-coded by origin. Drugs targeting specific pathways are represented by blue capsules. Solid lines: appetite-suppressing; dashed lines: appetite-stimulating. α-MSH: α-melanocyte-stimulating hormone; AgRP: Agouti-related protein; CART: Cocaine- and amphetamine-regulated transcript; CCK: Cholecystokinin; DVC: Dorsal vagal complex; GLP-1: Glucagon-like peptide-1; NPY: Neuropeptide Y; OXM: Oxyntomodulin; POMC: Pro-opiomelanocortin; PP: Pancreatic polypeptide; PYY: Peptide YY.

Table 1

Therapeutic intervention targeting central appetite regulation signaling.

Drug	Company	Clinical trial status	Mechanism of action	Effects	Ref.
TTP-435	TransTech Pharma	Phase II	AgRP inhibitor, increasing MC3/4R signaling	Reduced food intake, bodyweight and insulin levels in animal models	[301,318]
RM-493	Rhythm	Preclinical	MC3/4R agonist, mimicking the effect of α-MSH	Reduced food intake, bodyweight and insulin resistance in preclinical studies	[319]
Spiegelmer® (NOX-B11)	Pfizer	Preclinical	Bind to and inhibit ghrelin	Reduced food intake and c-Fos induction in arcuate nucleus in rats and mice. However, other fasting-related signaling might mask the loss of the ghrelin effect	[201, 320]
GI 181771X	GlaxoSmithKine	Terminated	CCK-A agonist, mimicking the effect of CCK	Clinical trials failed	[82]
Sitagliptin (MK-0431)	Merck	Approved for diabetes	DDP-IV inhibitor, increasing GLP-1 signaling	Reduced weight gain and potentiated the secretion of insulin † Side effects include rare nausea, common cold-like symptoms and pancreatitis	[97,321]
Vildagliptin (LAF237)	Novartis	Phase III	DDP-IV inhibitor, increasing GLP-1 signaling	Reduced hyperglycemia † Skin lesions and kidney impairment in animal models. Additional safety data from clinical trials are required	[97,322]
Pramlintide	Amylin	Approved for diabetes	Amylin analog	Decreased blood glucose level and bodyweight † Side effects include nausea, hypoglycemia, vomiting, headache, abdominal pain and fatigue	[62,323]
Exenatide	Amylin/Eli Lilly	Approved for diabetes	GLP1R agonist, GLP-1 mimicking	Decreased blood glucose level and bodyweight † Side effects include gastrointestinal symptoms, acute pancreatitis, dizziness and headache. May increase risks of sulfonylurea-	[97,98,100, 304,305,324]

Drug	Company	Clinical trial status	Mechanism of action	Effects	Ref.
				induced hypoglycemia and thryroid cancer	
Liraglutide (NN2211)	Novo Nordisk	Approved for diabetes	GLP1R agonist, GLP-1 mimicking	Maintained normal blood glucose and bodyweight † Side effects including increased risks of C-cell carcinoma and thyroid C-cell focal hyperplasia were observed in rats and mice	[97,303, 325–327]
NN9924	Novo Nordisk	Phase I	GLP1R agonist, GLP-1 mimicking	Variant of liraglutide	[328]
TKS1225	Thiakis/Wyeth/Pfizer	Phase I	GLP1R agonist, OXM mimicking	Reduced insulin resistance, appetite and bodyweight preclinical models	[329,330]
Histalean (Betahistine)	OBEcure Ltd.	Phase II	H1 receptor agonist H3 receptor antagonist	Weight loss and decreased appetite † Side effects include headache and nausea	[331,332]
SCH-497079	Schering–Plough	Phase II	Histamine receptor antagonist	No study results posted	[333,334]
Metreleptin	Amylin/Takeda	Phase III	Leptin receptor agonist	Weight loss † Side effects include nausea and injection site adverse events	[310,311,335]
BMS-830216	Bristol-Myers Squibb	Phase I/II	MCH receptor antagonist	The Phase I/II studies is anticipated to be completed in 2011. No study results posted	[302,336]
ALB-127158	AMRI	Phase I	MCH1 antagonist	The Phase I study is anticipated to be completed in 2011. No study results posted	[337]
Qnexa® (phentermine/topiramate)	Vivus	Phase III	Norepinephrine-releasing agent GABA receptor activator	Weight loss Currently under review for approval. Possible side effects include suicidal thoughts, heart palpitations, memory lapses and birth defects	[338]
Empatic™ (zonisamide SR/ bupropion SR)	Orexigen	Phase II	Norepinephrine/dopamine reuptake inhibitor GABA receptor activator	Weight loss and reduced metabolic syndrome † Side effects include birth defects. Possible side effects in cognitive function, thoughts of	[339]

Drug	Company	Clinical trial status	Mechanism of action	Effects	Ref.
				suicide or depression were not significantly different from placebo	
Contrave® (bupropion SR/ naltrexone SR)	Orexigen	Rejected for approval in February 2011	Norepinephrine/dopamine reuptake inhibitor GABA receptor activator	Weight loss, decreased appetite and reduced metabolic syndrome † Side effects include headaches and constipation. Concerns are cardiovascular safety and psychological issues	[340,341]
Taranabant (MK-0364)	Merck	Phase III terminated	Cannabinoid receptor inverse agonist	Study stopped due to high level of control side effects, mainy depression and anxiety	[202,342]
Lorcaserin HCI	Eisai	Rejected for approval in October 2010	Selective 5HT2c receptor agonist	Limited weight loss efficiacy and possible increase in cancer risk † Side effects include headache, infection, sinusitis, nausea, depression, anxiety and suicidal thoughts. Possible concerns of cancer risk	[199,316,343]
Tesofensine (NS2330)	NeuroSearch	Phase III	Serotonin-norepinephrine/dopamine reuptake inhibitor	Weight loss † Side effects include dry mouth, headache, nausea, insomnia, diarrhea and constipation	[344,345]
TM30339	7TM Pharma	Phase I/II	Y4R agonist in DVC, Y2R agonist in arcuate nucleus	Weight loss and reduced metabolic syndrome. The study is ongoing and no study results posted	[309,346]
Obinepitide	7TM Pharma	Phase II	Y4R agonist in DVC, Y2R agonist in arcuate nucleus	Weight loss and reduced metabolic syndrome. No study results posted	[308,347]
PYY (3-36)	Merck	Phase II	Y4R agonist in DVC, Y2R agonist in arcuate nucleus	The Phase II trial does not meet weight loss end point	[42,94,112– 118, 348]
MK-0557	Merck	Phase II	Y5 receptor antagonist, NPY blocker	No significant weight loss compared with placebo	[65,349]
Velneperit (S-2367)	Shionogi USA	Phase II	Y5 receptor antagonist, NPY blocker	Reduced bodyweight † Side effects include nasopharyngitis, upper	[350,351]

Drug	Company	Clinical trial status	Mechanism of action	Effects	Ref.
				respiratory infection, sinusitis and headache	

† Adverse effect(s) of the drug.

α-MSH: α-melanocyte stimulating hormone; AgRP: Agouti-related protein; CCK: Cholecystokinin; DPP-IV: Dipeptidyl peptidase IV; DVC: Dorsal vagal complex; GABA: γ-aminobutyric acid; GLP-1: Glucagon-like peptide 1; GPL1R: Glucagon-like peptide 1 receptor; MC3/4R: Melanocortin 3/4 receptor; MCH: Melanin-concentrating hormone; NPY: Neuropeptide Y; OXM: Oxyntomodulin; Y2R: Neuropeptide Y receptor subtype 2.