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Anti-Obesity Pharmacotherapy: New Drugs and Emerging Targets

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Abstract

Obesity is a growing pandemic and related health and economic costs are staggering. Pharmacotherapy partnered with lifestyle modifications form the core of current strategies to reduce the burden of this disease and its sequelae. However, therapies targeting weight loss have a significant history of safety risks, including cardiovascular and psychiatric events. Here, evolving strategies for developing anti-obesity therapies, including targets, mechanisms, and developmental status are highlighted. Progress in this field is underscored by Belviq® (lorcaserin) and Qsymia® (phentermine/topiramate), the first agents in more than 10 years to achieve regulatory approval for chronic management weight in obese patients. On the horizon, novel insights in metabolism and energy homeostasis reveal cGMP signaling circuits as emerging targets for anti-obesity pharmacotherapy. These innovations in molecular discovery may elegantly align with practical off-the-shelf approaches leveraging existing approved drugs that modulate cGMP levels for the management of obesity.

Keywords

obesity; lorcaserin; Belviq; phentermine; topiramate; Qsymia; cyclic GMP

Introduction

Obesity is a global public health problem. The obesity epidemic has been growing in developed nations, including the US, for decades.[1] Moreover, this epidemic has spread to developing nations.[1] Growing affluence has been accompanied by the emergence of overweight and obesity, so much so that the proportions of underweight and overweight have inverted.[1] The worldwide burden is estimated at 1.5 billion overweight and 500 million obese.[2] The negative consequences of obesity have been quantified as exceeding those of either alcohol abuse or smoking.[2] Obesity-associated comorbidities, including major diseases like cardiovascular disease, cancer, and diabetes, are legion.[3] Overweight and obesity constitute the fifth leading risk for global deaths.[2] In June 2013, the American Medical Association officially recognized obesity as a disease.[4]

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The evidence has been readily available and mounting demonstrating the profound impact of obesity on morbidity, mortality, health care costs, and professional and personal quality of life.[2] The awareness of this crisis has done little to reverse the obesity trends among the global population. Neither has the awareness that healthier habits for eating and exercise can be curative proved particularly effective. To blame are a host of factors: the lack of access to healthy, affordable foods or safe places for physical activity, particularly in lower-income neighborhoods and communities; the inferiority of freshly prepared foods vs. fast foods or prepackaged foods in preservation, portability, and palatability; the marketing of mostly unhealthy products by the food and beverage industry; modern cultural habits increasing sedentary behaviors, degrading eating cadences and locations, and incurring excess stress levels and sleep debt.[2, 5]

Amid the waves of reports publicizing these threats, there are glimmers of hope. Among the most troubling obesity-related trends has been the three-fold increase in childhood obesity rates in the last 30 years.[6] Consequently, children are increasingly being diagnosed with traditionally adult-onset diseases like heart disease and type 2 diabetes.[6] Furthermore, the likelihood and severity of obesity in adulthood is dramatically heightened by obesity in childhood.[6] This problem has been met with an extensive fight to limit and reverse this disease. Public programs have developed health promotional campaigns, focused on raising a new generation of children with healthier habits regarding diet and physical activity, and changing the complexion of school foods and beverages from high-calorie/-fat/-sodium junk foods and sugar-rich sodas to more fresh fruits and vegetables, whole grains, and healthier beverages. Curbing the consumption of sugary high-calorie drinks are public policy measures such as container size limits and sugar taxes.[7] Recent data suggest that these efforts are succeeding modestly in trimming the growth of the overweight population; however, the overall rates of overweight adults and children remain stubbornly large.[8]

Bariatric surgery reduces the size of the stomach, increases the feeling of fullness, and reduces the amount of food intake.[9] Different types of bariatric surgery include: Roux-en-Y gastric bypass; biliopancreatic diversion with duodenal switch; vertical sleeve gastrectomy; and adjustable gastric banding. Bariatric surgery has demonstrated efficacy in inducing sustained weight loss and improvements in blood pressure, glycemic control, and lipid profiles. Improvements and innovations in surgical techniques have reduced invasiveness, surgical risk, and recovery times. And evolving guidelines have lowered the BMI thresholds and expanded the patient population eligible for this treatment option, which has traditionally been indicated for only the extremely obese. Notably, bariatric surgery has been increasingly prominent in diabetes management, with a dramatic effect on glycemic control independent of weight loss.[10] Nonetheless, bariatric surgery still has serious risks of surgical and metabolic complications, and remains very expensive, making it less than ideal for the majority of the obese population.

Given the failure of lifestyle modifications to effect meaningful change and the limitations of bariatric surgery, anti-obesity drugs as adjuncts in obesity therapy is vital. The goal is not to hunt for a magic pill, as the long history of weight loss drugs has seen the rise and fall of countless agents that proved highly effective but ultimately dangerous. The goal is to employ a safe and effective drug regimen, in combination with improved diet and exercise,

to achieve a meaningful and sustainable reduction in body weight and enjoy the consequent benefits.

For regulatory agencies such as the US Food and Drug Administration (FDA), caution is key. Efficacy must go hand-in-hand with safety. The FDA's efficacy benchmarks require that the difference in mean weight loss between the drug and placebo groups is at least 5% over at least one year and statistically significant; and that the proportion of subjects who lose at least 5% of baseline body weight in the active-product group is at least 35% and is approximately double the proportion in the placebo-treated group.[6] Moreover, the obese population is heterogeneous, with variations in degree and duration of overweight, age, and associated comorbidities. A weight-loss drug must be compatible with the profile of an individual obese patient to be truly meaningful in terms of efficacy, safety, and durability. These necessary but demanding requirements have resulted in very limited pharmacotherapeutic options. As of September 2013, only three drugs were approved by the FDA as adjunctive therapy for chronic weight management: orlistat (Alli®, GlaxoSmithKline; Xenical®, Roche), approved in 1999; lorcaserin (Belviq®, Arena Pharmaceuticals), approved in 2012; and phentermine/topiramate extended-release (Qsymia®, Vivus), also approved in 2012. Nonetheless, drug development programs have been investigating the molecular mechanisms underlying the regulation of appetite and metabolism, and translating their discoveries into new pharmacotherapeutic agents and molecular targets to address the dual mandate of safety and efficacy.

Safety Issues with Weight Loss Drugs

Drugs can be very effective in inducing weight loss. The history of dietary supplements is full of success stories in terms of efficacy, but this success is matched by tragedy with regard to safety. Perhaps the most infamous is the combination drug Fen-Phen. A combination of the amphetamine analogs fenfluramine and phentermine, Fen-Phen's effectiveness helped it to achieve extensive popularity in the 1990s. Unfortunately, it also caused pulmonary hypertension and valvular heart disease, which forced its withdrawal from the market and birthed a legal and financial disaster.[11] Other amphetamine analogs and sympathomimetics have had similarly grave risks, including addiction, myocardial toxicity, and sudden death.[12] Aminorex caused chronic pulmonary hypertension with 50% mortality.[6] Phenylpropanolamine caused intracranial bleeding and strokes.[13] Ephedrine caused heart attacks, hypertension, palpitations, strokes, and sudden death.[14] Sibutramine caused increased cardiovascular events.[15] Rimonabant, the endocannabinoid receptor CB1 inverse agonist, caused increased depression and suicide.[Topol, 2010 #860] These unsafe drugs have had their regulatory approval withdrawn, though their unregulated use may continue to some extent.

As of September 2013, there is only one drug, orlistat, that is FDA- and EMA (European Medicines Agency)-approved for chronic weight management. Orlistat is also the only FDA-approved weight loss drug that is available without a prescription. It was approved in 1999 for prescription sale and 2007 for over-the-counter sale. Orlistat inhibits gastrointestinal lipases to reduce fat absorption. Consequently, its most common adverse

effect is steatorrhea. Despite its approved status, orlistat has had a number of safety issues, including hepatotoxicity, nephrotoxicity, pancreatitis and kidney stones.[6]

In 2010, the FDA rejected two proposed weight loss drugs, lorcaserin and phentermine/topiramate extended-release (ER) over safety and efficacy issues. Major concerns over lorcaserin included limited efficacy, carcinogenesis, cardiovascular events, cognitive impairment, and psychiatric disorders. Major concerns over phentermine/topiramate included cardiovascular events, fetal toxicity, and suicidal ideation. In 2012, the FDA reversed its position and granted approval to both lorcaserin and phentermine/topiramate. Nonetheless, the FDA has required postmarketing safety studies to address the original cardiovascular concerns. Furthermore, the EMA has rejected both lorcaserin and phentermine/topiramate. The EMA rejected lorcaserin due to its opinion that its benefits did not outweigh its risks, particularly the potential risk for tumors[16], and phentermine/topiramate due to concerns over the potential cardiovascular and central nervous system effects associated with long-term use, teratogenic potential, and use by patients for whom it is not indicated.[17]

Despite their limitations, lorcaserin and phentermine/topiramate represent the first new anti-obesity drug approvals in 13 years. In this article, we discuss these two new drugs in more detail. We also discuss other promising weight-loss agents that are currently in development and undergoing clinical trials, as well as future directions in medical weight loss strategies.

Orlistat (Alli®, Xenical®)

Orlistat is a gastrointestinal lipase inhibitor. It was approved by the FDA for prescription sale in 1999 and over-the-counter sale in 2007. Because of the safety-related withdrawals of other drugs from the market, orlistat had been the sole drug approved by the FDA for adjunctive use in long-term weight management until the 2012 approvals of lorcaserin and phentermine/topiramate. Moreover, orlistat remains the only obesity drug approved by the EMA. Orlistat acts by binding and inhibiting lipases that are produced by the pancreas and stomach and active in the small intestine to break down dietary triglycerides into free fatty acids, which can be absorbed via fatty acid transporters expressed by the intestinal epithelial cells. Thus, by inhibiting these lipases, orlistat acts to reduce systemic fat absorption. Unsurprisingly, a major adverse effect is steatorrhea. In obese patients started on a controlled-energy diet, orlistat (120 mg t.i.d.) versus placebo induced more weight loss (3%) after one year, produced less weight regain after two years, and was associated with improvements in fasting low-density lipoprotein cholesterol and insulin levels.[18] Though orlistat has remained approved and has modest but demonstrated efficacy, it has garnered attention by the FDA and Public Citizen, a non-profit consumer rights advocacy group, because of safety issues. Risks include severe liver damage, acute pancreatitis, acute renal failure, and pre-cancerous colon lesions.[19] In summary, the modest efficacy, undesirable adverse effects, and serious health risks combine to highlight the deficiencies of orlistat and underscore the pressing need for other obesity drug options.

Lorcaserin (Belviq®)

Serotonin, or 5-hydroxytryptamine (5-HT), is an important neurotransmitter that regulates food intake behaviors in both invertebrates and vertebrates.[20, 21] In more complex animals including humans, serotonin mediates multiple processes in the central nervous system (CNS) through 14 distinct 5-HT receptors belonging to seven families.[21] The serotoninergic neurons project axons into almost all brain areas and the spinal cord to release 5-HT to activate serotonin-sensitive neurons in virtually all regions of the CNS, mainly from the raphe nuclei of the midbrain.[21] It is notable that the majority of the serotonin-sensitive neurons are heteroreceptors, which release different neurotransmitters from those that activate them[21] One of the physiological processes that serotonin regulates is postprandial satiety through hypothalamic serotonin 5-HT_{2C}, and possibly 5-HT_{1A}, 5-HT_{1B}, and 5-HT_6 receptors.[22]

These receptors receive serotonin secreted from serotoninergic neurons that project from the brain stem into the hypothalamus to orchestrate feeding behavior through the melanocortin (MC) system.[22] Specifically, serotonin regulates appetite and body weight through MC4R in the arcuate nucleus. Activation of 5-HT_{2C} and 5-HT_{1B} receptors by serotonin increases the anorexigenic α-melanocyte-stimulating hormone (α-MSH) and decreases the orexigenic agouti-related peptide (AgRP) in the presynaptic area in the arcuate nucleus (ARC) and promotes satiety through MC4R-expressing neurons.[23, 24] Silencing *Mc4r* in mice eliminates the appetite-suppressing effects mediated by 5-HT_{2C} and 5-HT_{1B} agonists, while expression of *Mc4r* in the ARC restores the ability of 5-HT compounds to regulate appetite.[24, 25]

Genetic manipulation of 5-HT receptors revealed that ablation of 5-HT receptors resulted in hyperphagia and obesity.[22] Elimination of the G_i-coupled 5-HT_{1B} receptor (*Htr1b*) in mice only exhibited a limited increase in food consumption and body weight.[25, 26] However, genetic inactivation of the G_q-coupled receptor 5-HT_{2C}R (*Htr2c*) leads to hyperphagia and obesity, accompanied by partial leptin and insulin resistance.[27] Reinstating 5-HT_{2C}R on pro-opiomelanocortin (POMC) neurons in *Htr2c*$^{-/-}$ mice is sufficient to mediate the serotonin effects on appetite and correct the hyperphagic and obese phenotypes.[27] Additionally, pharmacologic or genetic inactivation of the 5-HT_3 receptor in the nucleus tractus solitarius (NTS) of the dorsal vagal complex (DVC) promotes food intake in *Agrp*^{DTR} mice, whose orexigenic AgRP neurons were ablated by diphtheria toxin (DT).[28] Accordingly, central serotonergic neurons may be a potential target to modulate food intake and energy homeostasis.

Lorcaserin (previously known as APD-356), marketed as Belviq® by Arena Pharmaceuticals, is a selective 5-HT_{2C} receptor agonist that specifically activates 5-HT_{2C} receptors over other 5-HT receptor subtypes. This characteristic of lorcaserin limits the risk of hallucinations due to 5-HT_{2A} activation and the risk of cardiovascular side effects, including valvulopathy and pulmonary hypertension, through 5-HT_{2B} receptors.[25] This preferential affinity to 5-HT_{2C} receptors provides lorcaserin the efficacy of previous serotonergic anti-obesity treatments without the undesirable safety concerns that led to their withdrawal.[29, 30] Lorcaserin has a half-life of about 11 hours and a median time to

maximum concentration of 1.5-2 hours.[25] Lorcaserin is metabolized by multiple hepatic pathways to inactive metabolites and excreted in the urine. This drug inhibits CYP2D6 metabolism and cannot be cleared by hemodialysis.[25]

Preclinical studies demonstrated that chronic administration of lorcaserin at doses of 4.5, 9 and 18 mg/kg reduced food consumption and prevented diet-induced obesity in mice.[25] In a multi-center, randomized, 52-week, placebo-controlled, double-blinded trial, lorcaserin at a dose of 10 mg twice daily mediated an average weight loss of 5.8 ± 0.2 kg (5.8%) in 883 patients within one year, while placebo induced an average weight loss of 2.2 ± 0.1 kg (2.2%) in 716 patients. There was no significant difference in adverse events between lorcaserin and placebo groups.[31] The effect of lorcaserin on body weight management was also examined in an 8-week, double-blinded, placebo-controlled trial. Lorcaserin induced significant reduction of body weight and food intake in comparison with placebo and baseline.[25] In a number of phase III trials, including the BLOOM-DM (behavioral modification and lorcaserin for overweight and obesity management in diabetes mellitus) and BLOSSOM (behavioral modification and lorcaserin second study for obesity management) study, subjects in the lorcaserin groups achieved significantly greater weight loss than the ones in the placebo groups.[32, 33]

Lorcaserin, similar to other 5-HT receptor agonists but to a lesser extent, has safety concerns regarding psychiatric and cardiovascular risks. The most common adverse events in non-diabetic patients include headache, dizziness, fatigue, nausea, dry mouth, and constipation. In diabetic patients, hypoglycemia, headache, back pain, cough, and fatigues are the major complaints.[31-33] Potential life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions might take place if lorcaserin is used in combination with drugs that impair metabolism of serotonin or increase presynaptic serotonin concentration.[25] In very rare cases, lorcaserin induces changes in echocardiography, and possibly valvular heart diseases. Other potential side effects include cognitive impairment, psychiatric disorders, priapism, bradycardia, hematological changes, prolactin elevation and pulmonary hypertension.[25] The effect of lorcaserin on breast cancer risk is unclear. Given that lorcaserin increases breast cancer risk in rats, long-term postmarketing safety monitoring is required to evaluate the potential risks and safety concerns as well as unexpected adverse events.

Phentermine/Topiramate Extended-Release (Qsymia®)

Many etiologies contribute to obesity in humans. This disease is caused by a confluence of a variety of factors including energy balance, neuroendocrine axes and psychological factors. Given this complex etiology, it is unlikely that monotherapy will be sufficient to reverse the disease. It is therefore not surprising that combination therapies have been evaluated clinically, and show substantial promise in the treatment of obesity. One such cocktail therapy that has recently been approved for treatment of obesity is **phentermine/topiramate** extended-release, which is being marketed in the US as Qsymia® by Vivus.

Phentermine has been used in the US since 1959 for short-term management of obesity.[25] Its mechanism of action is believed to be dependent on modulation of catecholamines in the

satiety centers of the hypothalamus, reducing appetite.[25] Topiramate has also been approved by the FDA, although it is primarily used to treat convulsive disorders and migraines. Interestingly, it was observed that patients receiving topiramate lost weight, and this generated interest in evaluating this compound as a potential obesity drug.[34-36] Topiramate enacts its effects at least partially through antagonism of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate/kainate (AMPA/KA) receptors, although induction of gamma-aminobutyric acid (GABA) receptor-mediated inhibitory currents and modification of voltage-gated calcium and sodium channels may also play a role.[37] Animal studies suggest that topiramate induces weight loss not only by decreasing food intake but also by increasing energy expenditure, possibly through decreased efficiency of nutrient utilization.[38-40] Although the exact mechanisms by which topiramate regulates appetite and induces weight loss in humans is unknown, significant clinical evidence exists to support its use as an obesity drug.[34-36]

The FDA approved the combination of phentermine/topiramate in 2012, largely on the strength of evidence from three clinical trials, known as the CONQUER, EQUIP, and SEQUEL trials.[41-43] Data from these three trials showed phentermine/topiramate to be efficacious in inducing and maintaining weight loss. Across the three trials, approximately 75% of treated subjects exhibited a 5% weight loss, and approximately 50% exhibited a 10% weight loss. These benchmarks represent important efficacy thresholds in evaluation of obesity pharmacotherapies. Importantly, this weight loss was accompanied by improvement in weight-related comorbidities, including serum lipid profile, waist circumference, and blood pressure. It is unclear whether sustained weight loss requires indefinite treatment with phentermine/topiramate, but it has been speculated that discontinuation of the drug may lead to weight regain.[25]

Although drug interactions are rare for phentermine/topiramate, adverse events observed in clinical trials include paresthesias, headaches, constipation, dry mouth, upper respiratory tract infection, nasopharyngitis, dizziness, insomnia, depression, anxiety, blurry vision and irritability.[41-43] Given this lengthy list of events, it is not surprising that one clinical trial of phentermine/topiramate reported a drop-out rate of approximately 19% (although another trial reported this number to be as low as 4%).[42, 43] A more serious potential adverse event involves the risk of cardiovascular events. Although patients treated with phentermine/topiramate in clinical trials exhibited a slight increase in heart rate, the risk of cardiovascular events is unclear at this time, and is being monitored by Vivus in post-marketing studies.[41-44]

In addition to adverse events observed in clinical trials, several other safety issues cloud the use of phentermine/topiramate. Given the addictive potential of amphetamines, there was some concern regarding wide-spread use of phentermine. However, a study investigating the addictive potential of phentermine showed only minimal addictiveness, allaying these concerns.[45] Importantly, phentermine/topiramate is also a teratogen, classified as a pregnancy category X.[25] Amid these concerns, the FDA approved the combinatorial therapy with a Risk Evaluation and Mitigation Strategy (REMS).[25] As with the cardiovascular risks, Vivus is engaged in a rigorous post-marketing surveillance program to evaluate these teratogenic risks.[25, 44]

Weight regain remains a significant limitation among patients attempting to lose weight. Although such interventions as lifestyle modification, pharmacotherapy or bariatric surgery are effective in inducing weight loss initially, most will eventually regain their lost weight. Given the importance of weight maintenance in the long-term disease prognosis for obese patients, the mechanisms underlying weight regain remain important and actively-researched questions. In the context of the substantial problem of weight regain, persistence of the weight loss response is desirable in any potential obesity therapy. Importantly, topiramate appears to possess this important characteristic. In several clinical trials, cohorts of patients treated with topiramate maintained weight loss as far out as one year, even after the placebo group had exhibited marked weight regain.[34, 35] Importantly, one of the clinical trials evaluating the combination of phentermine/topiramate showed a sustained weight loss at two years of follow up.[43]

The persistent and robust clinical effects of phentermine/topiramate may be attributable to the complementary effects of these two compounds. The chronology of weight loss induced by both compounds may represent the source of this complementarity. Phentermine induces weight loss in the short-term, while topiramate has been shown to be a longer-term agent. In addition to chronology, complementary effects may exist in the mechanisms by which the compounds induce weight loss. Interestingly, several studies have documented the ability of topiramate to reduce calorie intake.[46, 47] These studies have suggested that this effect may be due to topiramate's ability to inhibit compulsive food cravings and addictive behavior. This observation is based largely on the clinical efficacy of topiramate in treating binge eating disorder through antagonism of AMPA/KA receptors.[46-48] These beneficial psychological effects may behave synergistically with neuroendocrine mechanisms of inducing weight loss. This makes phentermine/topiramate unique in obesity therapeutics in that it targets not only the neuroendocrine milieu of obesity but also the psychological factors of binge eating underlying the disease. These various complementary effects make this regimen unique among its peers, and may represent an important paradigm in future development of combinatorial therapies.

Obesity Drugs in the Pipeline

A fundamental trait shared by many obesity drugs in development is the targeting of endogenous endocrine circuits regulating energy homeostasis. Most of these endocrine circuits are anorexigenic. Peripheral peptide hormones are released postprandially, and travel in the circulation to their cognate receptors, which are expressed in the homeostatic regulatory centers in the CNS, notably the ARC of the hypothalamus and the DVC in the medulla. The ARC is home to neurons expressing the key orexigenic (stimulating appetite) neurotransmitters, AgRP and neuropeptide Y (NPY); and anorexigenic (suppressing appetite) neurotransmitters, POMC and cocaine- and amphetamine-regulated transcript (CART).

POMC itself is cleaved to yield several hormones, including α-MSH, which binds melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors to transmit the anorexigenic signal. Rhythm has developed the MC4R agonist **RM-493**. In preclinical studies, obese primates treated for eight weeks lost an average of 13.5% of their body weight, with

significant improvements in both insulin sensitivity and cardiovascular function. However, in a trial with obese human subjects, Merck's MC4R agonist MK-0493 induced only a small, statistically-insignificant weight reduction compared to placebo after 12 weeks in a fixed-dose study or after 18 weeks of stepped-titration dosing.[Krishna, 2009 #758] As Merck's MK-0493 was promising at the preclinical stage but only tested in rodents, that Rhythm's RM-493 preclinical success was in primates may be more predictive of the results in humans. Rhythm initiated phase II trials of RM-493 in December 2012, with completion scheduled for October 2013.[6] Due to the role of melanocortins in cardiovascular and sexual function, the potential off-target adverse effects of melanocortin signaling in obesity treatment warrant scrutiny.[49] For example, phase I/II trials with the α-MSH analog, Melanotan II, caused dose-dependent penile erections. [Wessells, 2000 #873]

NPY activates G protein-coupled receptors (GPCRs) Y1 and Y5 to stimulate appetite.[50] Shionogi's **S-2367** (Velneperit) is a Y5 receptor inhibitor that has completed phase II trials in the US and is in a phase III trial in Japan initiated in August 2013 and scheduled for completion in March 2014. In combination with a reduced-calorie diet, 800 mg daily S-2367 versus placebo induced at least 5% weight loss, waist circumference reduction, and improved lipid panels in obese patients over the course of one year.[51] It should be noted that neuropeptide Y5 receptor antagonism with Merck's MK-0557 failed to induce clinically meaningful weight loss in overweight and obese adults in a 52-week weight-loss study, despite its success in preclinical and proof-of-concept/dose-ranging studies.[Erondu, 2006 #760] The investigators concluded that neuropeptide Y5 receptor antagonism was insufficient as monotherapy for anti-obesity drug therapy, but discussed its potential in combination therapy.

Modulation of monoamine neurotransmitters, such as dopamine, norepinephrine, and serotonin, can be highly effective in suppressing appetite, but adverse effects like cardiovascular events and addiction are major concerns with their use in weight management.[52] Orexigen Therapeutics has developed the combination drug **bupropion/naltrexone** (Contrave), which combines bupropion, a dopamine and norepinephrine reuptake inhibitor, and naltrexone, an opioid receptor antagonist. Bupropion increases dopamine activity and POMC neuronal activation, thereby reducing appetite and increasing energy expenditure. Naltrexone blocks opioid receptors on the POMC neurons, preventing feedback inhibition and further increasing POMC activity. In a comparison of combined bupropion (400 mg/d, sustained-release) and naltrexone (48 mg/d) therapy for obesity versus monotherapy or placebo, weight loss was 1.2 kg (1.1%) for placebo, 1.6 kg (1.7%) for naltrexone monotherapy, 3.1 kg (3.1%) for bupropion monotherapy, and 6.9 kg (7.5%) for naltrexone/bupropion combination therapy, which demonstrated their synergy.[Greenway, 2009 #769] In addition, bupropion/naltrexone may regulate activity in the dopamine reward system of the brain that helps control food cravings and overeating behaviors.[53] In phase III clinical trials, bupropion/naltrexone vs. placebo induced greater weight loss on a diet and exercise program over 56 weeks.[6] In 2011, the FDA rejected bupropion/naltrexone, and requested a large cardiovascular risk trial to address long-term adverse effects before it could approve the drug.[6] Orexigen has begun the requested long-term clinical trial, and its

New Drug Application has been submitted and reviewed by the FDA, with potential approval in late 2013 or early 2014.

Amylin, also called islet amyloid polypeptide (IAPP), is synthesized by pancreatic β-cells and secreted with insulin postprandially.[54] Amylin acts synergistically with insulin to regulate plasma glucose levels. Amylin's fasting plasma concentration is low, and rises following food intake.[55] Amylin also functions as an anorectic, mediating appetite suppression via activation of amylin receptors in the area postrema (AP) of the DVC[54] and vagal signaling.[56, 57] The amylin analog, **pramlintide** (Symlin), from Amylin Pharmaceuticals/Bristol-Myers Squibb/AstraZeneca is already approved for diabetic adjunctive treatment.[6] Notably, 120 μg b.i.d. or 150 μg q.d. pramlintide also induced an average weight loss of 2.6 kg over one year in type 2 diabetics with minimal adverse effects.[58] Amylin Pharmaceuticals's second-generation amylin analog, **davalintide** (AC2307), is in phase II trials for an obesity indication.

Leptin is a hormone made by adipose tissue and secreted into the circulation in proportion to its mass. Leptin activates leptin receptors, which are expressed throughout the body, with high expression in the hypothalamic ARC. Hypothalamic leptin receptor activation drives increased POMC expression and signaling and inhibits NPY/AgRP expression and signaling, thereby suppressing appetite.[6] Conversely, a decreased fat mass results in lower plasma leptin concentrations, leading to increased appetite. Thus, leptin is a key hormone in the regulation of energy homeostasis. Patients with congenital leptin deficiency develop early-onset obesity and are responsive to leptin replacement therapy.[59, 60] Unfortunately, patients with diet-induced obesity develop leptin receptor resistance.[61] These patients have high plasma leptin concentrations reflecting their high adiposity, but this high leptin level is ineffective in driving appetite reduction. While leptin monotherapy appears intractable as a therapeutic option, the resensitization of the leptin receptor to its cognate hormone is an active strategy in obesity drug development. Intriguingly, the pancreatic hormone amylin restores leptin receptor responsiveness to leptin in the setting of obesity.[62] Combination therapy comprising Amylin Pharmaceuticals' leptin analog, **metreleptin**, and its amylin analog, pramlintide, induced a greater and more durable weight reduction vs. monotherapy in overweight and obese patients in phase II trials[63] Unfortunately, Amylin Pharmaceuticals and Takeda Pharmaceutical Company were forced to suspend the trials due to a laboratory finding involving antibody-mediated metreleptin neutralization.[64] Fortunately, other preclinical studies suggest that leptin resensitization is achievable with combination therapy comprising leptin analogs and other pharmacotherapeutic agents, namely exendin-4 or fibroblast growth factor 21.[65]

Glucagon-like peptide 1 (GLP-1) is derived from cleavage of the preproglucagon gene product which is synthesized by enteroendocrine L cells in the ileum and proximal colon.[66] GLP-1 is secreted following food intake and mediates a variety of functions: increased insulin secretion, decreased glucagon secretion, decreased gastric secretion and motility, increased satiety, and decreased food intake. Indeed, GLP-1 administration in preclinical and clinical testing induced satiety and weight loss.[67-70] However, dipeptidyl peptidase-4 (DPP-4) degrades endogenous GLP-1 in under two minutes.[71] Consequently, degradation-resistant GLP-1 analogs have been developed to increase the practicality of GLP-1

pharmacotherapy. **Liraglutide** (Victoza) from Novo Nordisk is a GLP-1 analog that contains an amino acid substitution and a fatty acid attachment, which stabilize it against degradation by DPP-4. Its 13-hour half-life makes it suitable for once-daily administration. **Exenatide** (Byetta) from Amylin Pharmaceuticals/Bristol-Myers Squibb/AstraZeneca is an analog of exendin-4, a Gila monster salivary hormone with functions similar to GLP-1. As with the amylin analog pramlintide, liraglutide and exenatide are FDA-approved for adjunctive therapy in type 2 diabetes.[72-75] The potential of these drugs to treat both diabetes and obesity would be a major synergistic benefit considering the overlap in patient population and the close association between these diseases. Liraglutide and exenatide induced significant weight loss in diabetics. This weight loss was dose-dependent, progressive, and durable over 30 weeks. In studies with non-diabetic obese patients, liraglutide drove a 6-kg (8%) weight loss, and >35% of the patients on the highest dose achieved weight loss of over 10%. Novo Nordisk completed these phase III trials for liraglutide for an obesity indication in non-diabetic obese patients in September 2010, and in diabetic obese patients in January 2013. Novo Nordisk expects regulatory filings in the EU and US to begin by the start of 2014. Bristol-Myers Squibb is scheduled to complete its phase III obesity trials on exenatide in February 2014. Furthermore, Novo Nordisk/ Emisphere utilized Emisphere's proprietary oral SNAC (sodium N-[8-(2-hydroxybenzoyl) amino] caprylate) technology to develop the long-acting oral GLP-1 analog, **NN9924**, which is in phase I trials in the UK.[6]

Like GLP-1, oxyntomodulin (OXM) is an anorexigenic peptide hormone produced from the processing of preproglucagon and secreted postprandially with GLP-1 by the L cells in the colon. Injections of OXM in humans caused a significant reduction in weight and appetite, as well as an increase in energy expenditure. OXM is a dual agonist of the GLP-1R and the glucagon receptor, and may exert its anorectic effects via activation of central GLP-1Rs and stimulation of POMC neurons in the ARC.[6, 76] Like GLP-1, rapid degradation makes endogenous OXM impractical for pharmacotherapy, but long-acting OXM analogs are in development. **TKS1225** from Thiakis/Wyeth/Pfizer is in phase I trials. **OXY-RPEG** from PROLOR Biotech has been engineered with its proprietary reversible pegylation technology to increase its half-life, with an added benefit of increased potency. In preclinical testing, OXY-RPEG was significantly superior to twice daily injections of OXM in the reduction of food intake and the degree and durability of weight loss.[6]

The Emerging Role of Cyclic GMP Signaling in Anti-Obesity Pharmacotherapy

Cyclic nucleotides, including 3′-5′-cyclic guanosine monophosphate (cGMP) and 3′-5′-cyclic adenosine monophosphate (cAMP), are second messengers important in many biological processes. The canonical role of cAMP in carbohydrate and lipid metabolism is well established, reflecting sophisticated studies of insulin and glucagon.[79] Specifically, binding of glucagon to an adrenergic receptor activates adenylyl cyclase, which results in an increase in intracellular cAMP and elicits sequential downstream signaling that promotes gluconeogenesis and lipolysis in the liver.[80] On the contrary, insulin, through its receptor on the plasma membrane of hepatocytes, activates cyclic nucleotide phosphodiesterases (PDEs)

that convert cAMP to AMP and consequently terminates cAMP signaling.[81] Reciprocally, hydrolysis of cAMP by PDEs in pancreatic β-cells depletes intracellular cAMP levels and inhibits insulin secretion.[82]

The role of cAMP in the regulation of energy homeostasis has been extended via its intimate relationship with AMPK (AMP-activated protein kinase) signaling. Intracellular cAMP activates the AMPK signaling pathway by its metabolite AMP and by elevated cytosolic Ca_2^+ concentrations through Epac1 (exchange protein activated by cyclic AMP) signaling and thereby activation of CaMkkβ (calmodulin-dependent protein kinase kinase-beta).[83] AMPK regulates energy balance at both cellular and whole-body levels.[84] AMPK inhibits both fatty acid and cholesterol synthesis by inactivation of acetyl-CoA carboxylase and HMG-CoA reductase.[84] AMPK opposes gluconeogenesis by inhibiting transcription of critical gluconeogenic enzymes. Activation of AMPK facilitates fatty acid oxidation and mitochondria biogenesis, which promotes energy expenditure.[85] Interestingly, activation of AMPK in the hypothalamus promotes food intake behavior.[86] In some cells, an increase in intracellular cGMP concentration increases cAMP levels by inhibiting PDEs that degrades cAMP.[87] Indeed, inhibition of PDE4, PDE5, PDE9, and PDE10 decreases the adiposity in mice fed a high fat diet or in *ob/ob* mice. Recently, emerging evidences suggest that cGMP may regulate energy balance directly.[88]

cGMP is an important second messenger generated by the family of guanylyl cyclases (GCs).[87] There are two forms of guanylyl cyclases: cytosolic (soluble) and membrane-bound (particulate). Soluble GCs are activated by nitric oxide (NO), while particulate GCs are activated upon binding by their cognate ligands, such as the natriuretic peptides (ANP and BNP for GC-A [GUCY2A], and CNP for GC-B [GUCY2B]) and the intestinal peptides (guanylin and uroguanylin for GC-C [GUCY2C]).[87] As a critical second messenger, cGMP regulates a variety of physiological processes and its intracellular concentration is meticulously balanced by the activity of guanylyl cyclases that produce cGMP and phosphodiesterases that hydrolyze cGMP.[87] The role of cGMP in regulation of energy balance is highlighted by its role in mitochondrial biogenesis[89] and protection of mitochondrial function from oxidative damage.[90]

Mammalian adipose tissue is mainly composed of two types: white adipose tissue (WAT) and brown adipose tissue (BAT).[91] WAT extracts fat from the circulation and stores the excess energy in the form of triglycerides. WAT is also responsible for production of hormones, such as leptin, estrogen, resistin, and inflammatory cytokines.[92] BAT is the major tissue that dissipates energy in the form of heat through a process known as non-shivering thermogenesis. BAT generates heat and increases energy expenditure through the mitochondrial transmembrane protein, UCP1, which dissipates the energy generated in oxidative phosphorylation in mitochondria into heat by allowing protons that have been pumped into the inter-membrane space to leak back to the mitochondria matrix.[93] As a consequence, increasing BAT function or differentiating WAT into BAT may promote energy expenditure and offset the positive energy balance associated with over-nutrition to reduce obesity.[94]

In BAT, cGMP signaling has been shown to induce adipogenic and thermogenic programs during brown fat cell differentiation through PKG-mediated inhibition of RhoA and Rho-associated kinase (ROCK), and thereby activation of phosphoinositide 3-kinase-AKT signaling.[95] Additionally, increasing cGMP levels through cell-permeable cGMP or **sildenafil**-mediated PDE5 inhibition enhanced BAT differentiation.[96] Conversely, cGMP signaling, activated by binding of natriuretic peptides (ANP and BNP) to guanylyl cyclase A (GUCY2A), triggers lipolytic pathways and mobilizes the fat stored in WAT.[97] Notably, ANP-mediated lipolysis is resistant to hyperinsulinemia and independent of impaired β-adrenergic receptor signaling.[97] Therefore, "browning" of the WAT via cGMP pathways may be a promising strategy to increase BAT-mediated energy expenditure and decrease WAT-mediated fat storage. Moreover, the ready availability of approved PDE5 inhibitors, such as sildenafil, may significantly facilitate implementing this strategy. In addition to BAT, skeletal muscle is another site for thermogenesis and energy expenditure. Activation of guanylyl cyclase A (GUCY2A) by natriuretic peptides in skeletal muscle increases cGMP accumulation and promotes energy utilization through PKG-dependent mitochondrial biogenesis.[6]

Guanylyl cyclase C (GUCY2C) is another member of the particulate guanylyl cyclase family, whose expression has been historically restricted to the intestinal epithelium.[87] GUCY2C is activated by the endogenous hormones guanylin (GUCA2A) and uroguanylin (GUCA2B) in a paracrine fashion in the intestine. GUCY2C signaling defends a variety of homeostatic mechanisms that are crucial to intestinal integrity, including electrolyte and fluid balance, proliferation and differentiation along the intestinal crypt-villus axis, DNA damage sensing and repair, and the barrier function of the intestinal lining.[98-101] The recent discovery of GUCY2C expression and function in the hypothalamus expands the homeostatic role of GUCY2C. Explicitly, hypothalamic GUCY2C induces satiety responses upon activation by endocrine uroguanylin released from the intestine postprandially.[102] Further, mice deficient in GUCY2C signaling (*Gucy2c*$^{-/-}$) have defective satiety responses after food intake, resulting in hyperphagia and excess weight gain.[102] These mice display obesity-associated disorders, including elevated adiposity, hypertriglyceridemia, hyperleptinemia, hyperinsulinemia, and impaired glycemic control, and develop metabolic disease including fulminant diabetes, left ventricular hypertrophy, and hepatic steatosis.[102]

This gut-brain axis regulating appetite, body weight, and metabolism through GUCY2C signaling[102] offers a target for the development of pharmacotherapeutic interventions to combat obesity. Targeting GUCY2C signaling would leverage an endogenous endocrine mechanism that sentinels energy homeostasis. Moreover, GUCY2C activation may be achievable with reformulations of existing GUCY2C peptide agonists, such as linaclotide (Linzess™, Ironwood Pharmaceuticals, Forest Laboratories) and plecanatide (Synergy Pharmaceuticals). Particularly, **linaclotide** was approved in 2012 by the FDA and EMA to treat disorders of gastrointestinal motility (chronic idiopathic constipation [CIC], irritable bowel syndrome with constipation).[103] In clinical trials, patients with chronic constipation improved after 12 or 26 weeks of treatment with 290 μg oral linaclotide, which had no systemic exposure, was well-tolerated, and had minimal adverse effects, diarrhea being the

most common.[6] A phase III trial will be initiated in the fourth quarter of 2013 to evaluate the safety and efficacy of plecanatide for the treatment of CIC in patients.

These developments offer new signaling circuits that can be leveraged for weight management. Intriguingly, since both thermogenesis and satiety are increased by activation of these cGMP pathways, stimulating them through drug administration could conceivably drive both of these physiologic processes in the same direction, and induce weight loss by mutual reinforcement. Moreover, practical, off-the-shelf approaches might be possible, given the existence of an established market for medications targeting cGMP pathways, with FDA- and EMA-approved drugs such as sildenafil and linaclotide.

Conclusion

Obesity is a global public health crisis. Obesity-related comorbidities are highlighted by three major causes of death: cardiovascular disease, cancer, and diabetes. In June 2013, the American Medical Association officially recognized obesity itself as a disease. Obesity profoundly impacts morbidity, mortality, health care costs, and professional and personal quality of life. Awareness of the obesity problem has done little to reverse the obesity trends among the global population. Recent data suggest that growth of the overweight and obese population in both children and adults have slowed. However, these populations remain substantial and growing. Given that the promotion of lifestyle modifications has proven inadequate, the adjunctive role of medical therapy is vital. The goal is to employ drug regimens in combination with improved eating habits and physical activity to achieve a meaningful, sustainable reduction in body weight. However, safety issues throughout the long history of weight loss drugs had decimated the field, leaving only the lipase inhibitor orlistat as the sole drug approved for chronic weight management until 2012, when two new anti-obesity drugs were approved by the FDA: lorcaserin and phentermine/topiramate extended-release. Concerns remain for these new entries, including limited efficacy, carcinogenicity, and cardiovascular risk. Nonetheless, they represent the first new approved chronic weight management drugs in 13 years. Moreover, a host of new obesity drugs are in the pipeline, and many epitomize newer strategies in obesity drug development designed to minimize risk and maximize efficacy: targeting endogenous endocrine circuits regulating energy homeostasis and metabolism; and combination therapy with monotherapeutic agents to elicit improved safety and efficacy, with potential synergy. These future drugs offer the potential of supplanting or even combining with the newly approved drugs. Finally, the modulation of cGMP signaling in medical weight management has emerged as an intriguing new paradigm for a well-characterized drug class. Discoveries in the molecular mechanisms regulating adipose metabolism and satiety signaling have opened the door for targeting cGMP signaling as a future anti-obesity strategy. These advances in the development of anti-obesity pharmacotherapy offer new armaments in the fight to reverse the decades-long rise of obesity.

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Abbreviations

AgRP	agouti-related peptide
AMPA/KA	alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate/kainite
AMP	AMP-activated protein kinase
ANP	atrial natriuretic peptide
ARC	arcuate nucleus

AP	area postrema
BAT	brown adipose tissue
BNP	brain natriuretic peptide
cAMP	3′-5′-cyclic adenosine monophosphate
CaMkkβ	calmodulindependent protein kinase kinase-beta
CART	cocaine- and amphetamine-regulated transcript
cGMP	3′-5′-cyclic guanosine monophosphate
CIC	chronic idiopathic constipation
CNS	central nervous system
DPP-4	dipeptidyl peptidase-4
DT	diphtheria toxin
DVC	dorsal vagal complex
EMA	European Medicines Agency
Epac1	exchange protein activated by cyclic AMP
ER	extended-release
FDA	US Food and Drug Administration (FDA)
GABA	gamma-aminobutyric acid
GCs	guanylyl cyclases
GLP-1	Glucagon-like peptide 1
GPCRs	G protein-coupled receptors
GUC2A	guanylin
GUCA2B	uroguanylin
5-HT	5-hydroxytryptamine
IAPP	islet amyloid polypeptide
MC	melanocortin
MC3R	melanocortin 3 receptors
MC4R	melanocortin 4 receptors
α-MSH	α-melanocyte-stimulating hormone
NMS	neuroleptic malignant syndrome
NO	nitric oxide
NPY	neuropeptide Y
NTS	nucleus tractus solitarius

OXM	oxyntomodulin
PDEs	phosphodiesterases
POMC	pro-opiomelanocortin
PP	pancreatic polypeptide
RMES	Risk Evaluation and Mitigation Strategy
ROCK	Rho-associated kinase
SNAC	sodium N-[8-(2-hydroxybenzoyl) amino] caprylate
WAT	white adipose tissue

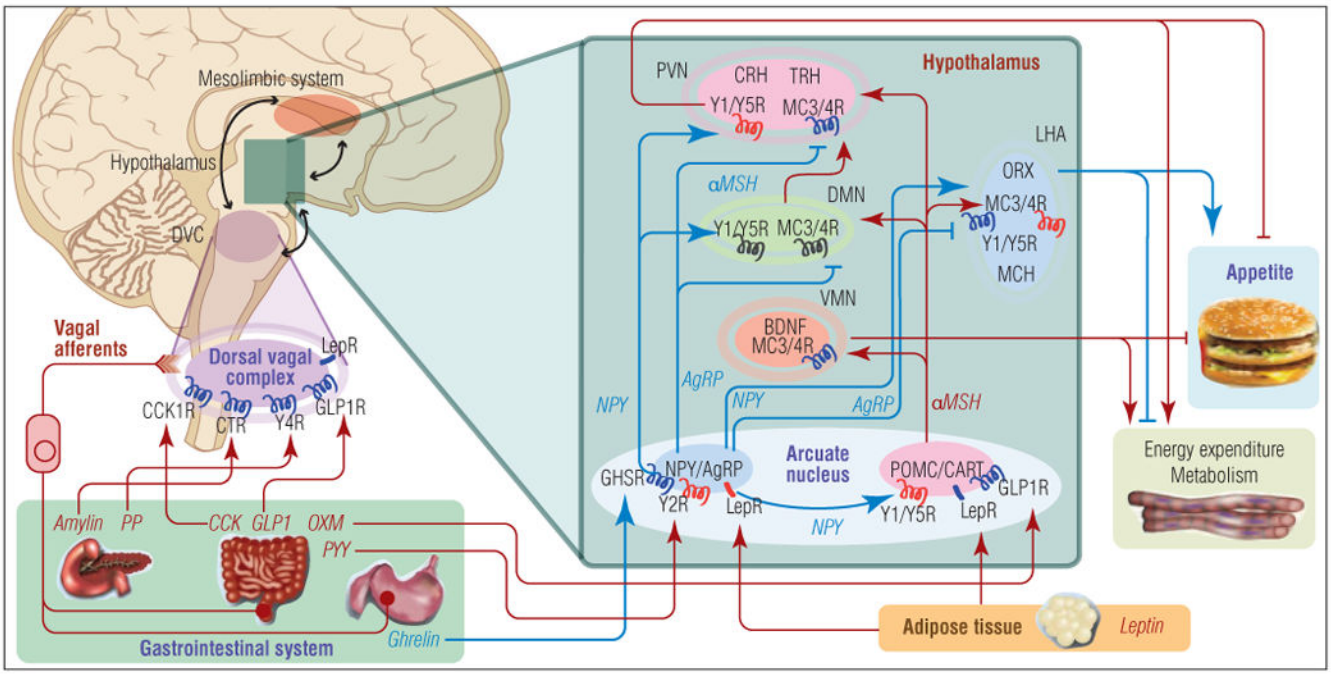

Figure 1. Central regulation of appetite and energy homoeostasis

The hypothalamus is the major site of integration of anorexigenic and orexigenic signaling. Peripheral satiety hormones, such as ghrelin from the stomach and leptin from adipose tissue, primarily bind and activate their cognate receptors directly in the hypothalamus, particularly in the arcuate nucleus, or in the dorsal vagal complex in the medulla, which communicates with the hypothalamus. Among the neurons in the arcuate nucleus there exist two populations of neurons: those expressing the orexigenic neuropeptide Y (NPY) or agouti-related peptide (AgRP); and those expressing the anorexigenic pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). Several satiety hormones induce their anorectic effects by either inhibiting the activity of NPY/AgRP neurons or activating POMC/CART neurons. These neurons in the arcuate nucleus project to second-order neurons in other hypothalamic nuclei, including the paraventricular nucleus (PVN), dorsomedial nucleus (DMN), ventromedial nucleus (VMN), and lateral hypothalamic area (LHA). These second-order hypothalamic neurons express anorexigenic neuropeptides (corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), brain-derived neurotrophic factor (BDNF)) and orexigenic neuropeptides (orexin (ORX), melanin-concentrating hormone (MCH)), which modulate appetite and energy homeostasis. Furthermore, the regulation of energy balance involves an integration of signaling from the hypothalamus, brainstem, and reward pathways of the mesolimbic system. Symbols: blue receptor = activating; red receptor = inhibiting; blue arrow = appetite-stimulating; red arrow = appetite-suppressing.

Figure 2a

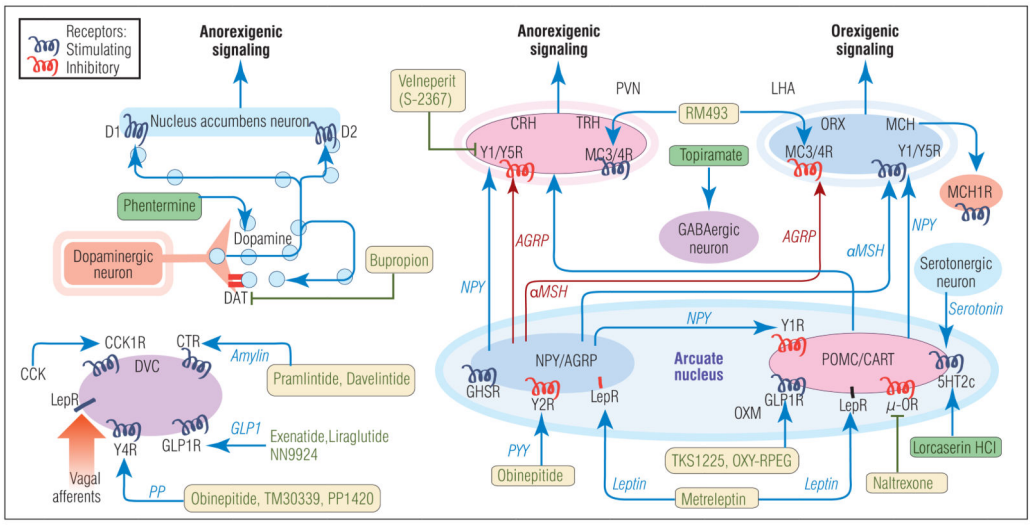

Figure 2b

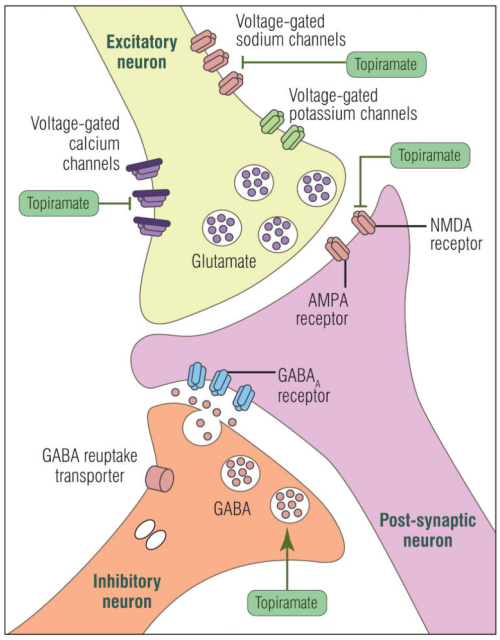

Figure 2c

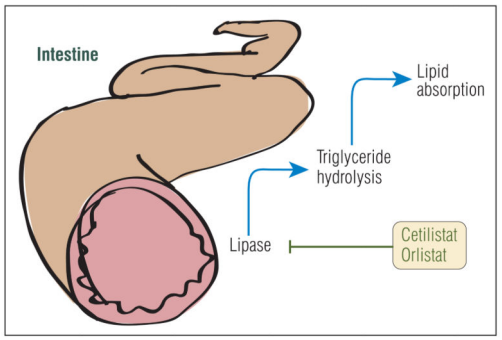

Figure 2. Molecular targets for anti-obesity pharmacotherapeutics

(2a) Phentermine stimulates the release of dopamine (DA) into the synapse from the presynaptic dopaminergic neurons from the ventral tegmental area (VTA). This released dopamine binds and activates dopamine receptors, including D1 and D2, on postsynaptic neurons in the nucleus accumbens. Dopamine is taken back up into the presynaptic neuron by the dopamine transporter (DAT), which is bound and inhibited by bupropion. Pramlintide and davalintide are amylin analogs that activate amylin receptors (CTR) in the dorsal vagal complex (DVC). Exenatide, liraglutide, and NN9924 are GLP-1 analogs that activate GLP-1

receptors (GLP-1R) in the hypothalamus and DVC. S-2367 binds and inhibits Y5 receptors in the hypothalamic paraventricular nucleus (PVN) to suppress neuropeptide Y (NPY) signaling. RM493 is a melanocortin 4 receptor (MC4R) agonist that binds and activates MC4R in the PVN and lateral hypothalamic area (LHA). Topiramate induces gamma-aminobutyric acid (GABA) receptor-mediated inhibitory currents. TKS1225 and OXY-RPEG are oxyntomodulin (OXM) analogs that bind and activate GLP-1R in the arcuate nucleus and DVC. Lorcaserin selectively binds and activates 5-HT2c serotonin receptors in the arcuate nucleus. Symbols: blue receptor = activating; red receptor = inhibiting. (2b) Topiramate's exact mechanism of action is unknown, but may involve its ability to block voltage-gated sodium channels in the presynaptic excitatory neuron; antagonize AMPA/NMDA glutamate receptors on postsynaptic neurons; and enhance the activity of inhibitory GABA neurons. (2c) Orlistat binds and inhibits gastric and pancreatic lipases in the intestine. These lipases hydrolyze dietary triglycerides into free fatty acids that can be absorbed by intestinal epithelial cells via fatty acid transporters. Thus, orlistat suppresses systemic lipid absorption.

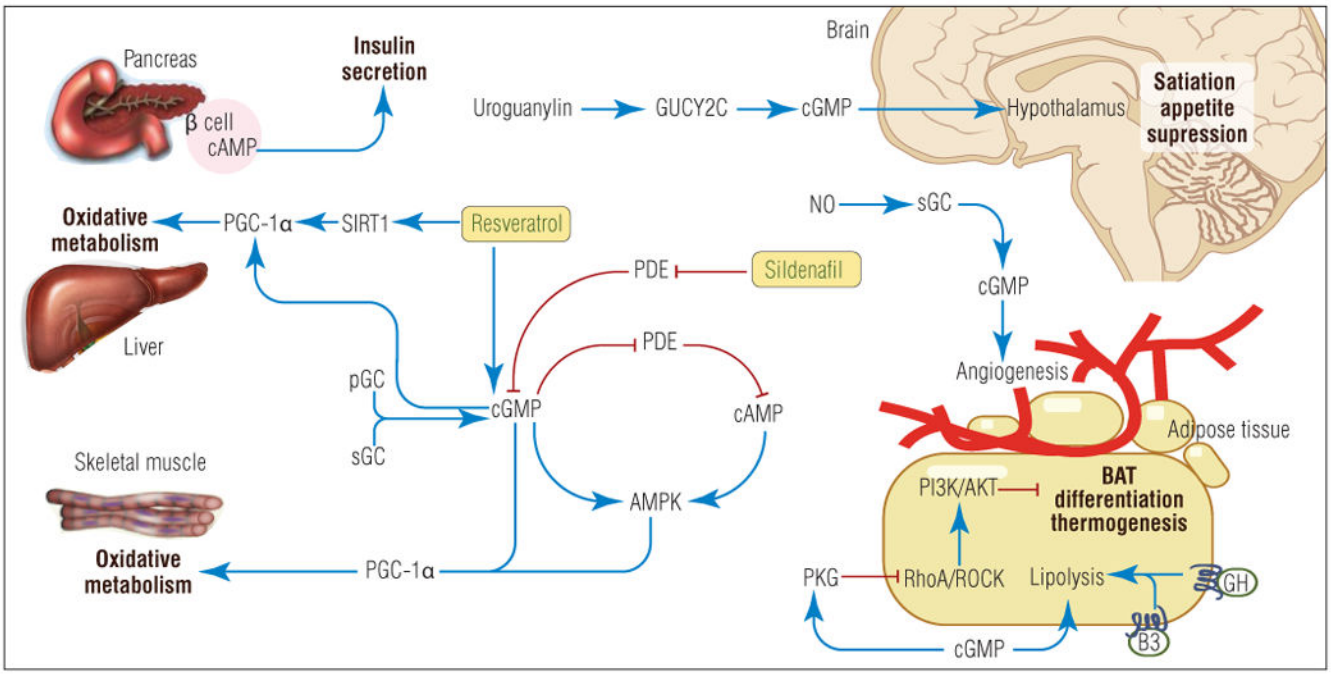

Figure 3. Cyclic AMP- and GMP-mediated signaling regulates metabolism and energy homeostasis

Increased cGMP levels, via activation of particulate or soluble guanylyl cyclases (pGC or sGC), activates peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), a master regulator of mitochondrial biogenesis and function. Cyclic GMP signaling also regulates the metabolic sensors SIRT1 and AMP-activated protein kinase (AMPK), which directly activate PGC-1α by deacetylation and phosphorylation, respectively. Resveratrol stimulates mitochondrial function by activating SIRT1 and stimulating cGMP production. Phosphodiesterases (PDE), which hydrolyze cAMP and cGMP and thereby terminate their signal, are the target for sildenafil, a PDE inhibitor specific for PDE5. Also, cAMP is required for glucose-induced insulin release by pancreatic β-cells. Furthermore, postprandial release of the intestinal hormone uroguanylin results in the endocrine activation of hypothalamic guanylyl cyclase C (GUCY2C) to produce cGMP, which stimulates satiety and suppresses appetite. Also, in adipose tissue, cGMP signaling promotes lipolysis, and induces adipogenic and thermogenic programs during brown fat cell differentiation through PKG-mediated inhibition of RhoA and Rho-associated kinase (ROCK), and thereby activation of phosphoinositide 3-kinase-AKT signaling.

Table 1

current anti---obesity medications

Mechanism of action	Drug	Effects and safety concerns	Efficacy	Status
Appetite suppressant. Stimulates anorexic signaling in hypothalamus or dopamine receptor in the hippocampus. Sympathomimetic agents similar to norepinephrine with central nervous system (CNS) stimulatory activity.	Phentermine	Appetite suppression and weight loss. *Side effects include dizziness, dry mouth, difficulty sleeping, irritability, nausea, vomiting, diarrhea, or constipation. This drug has withdrawal symptoms.	Weight loss greater than placebo was 3.6 kg [CI] 0.6---6.0 kg	FDA---approved in 1959
	Amphetamine	Anorexia and weight loss. *Side effects include nervousness, restlessness, excitability, dizziness, headache, fear, anxiety, and tremor. Blood pressure and heart rate may increase. Chronic use may lead to dependence. These drugs have withdrawal symptoms.	Weight loss greater than placebo was less than 1 kg [CI] 0.5---1.6 kg	Off---label usage Approved for ADHD
Serotonin, dopamine and norepinephrine reuptake inhibitor (SNRI) that potentiates the neurotransmitter activity in the central nervous system (CNS).	Lorcaserin (Belviq)	Limited weight loss efficacy and possible increase in cancer risk. *Side effects include headache, infection, sinusitis, nausea, depression, anxiety and suicidal thoughts. Possible concerns of cancer risk.	Mean body weight loss: Lorcaserin 5.8 ± 0.2 kg; Placebo 2.2 ± 0.1 kg	FDA---approved in 2012
	Desvenlafaxine (Pristiq)	Anorexia but effect on body weight is unclear. *Vision problem, headache, low libido, dry mouth, dizziness, insomnia, taste problems, vomiting, anxiety, Sexual dysfunction, depression, high blood pressure, stomach ache, numbness and tingling, fatigue, and involuntary quivering.	Mean body weight loss greater than placebo was 0.22---1.41 kg	Off---label usage Approved for depression
	Sibutramine (Meridia)	Limited weight loss efficacy. *Increased risk for cardiovascular events and stroke.		FDA---approved in 1997, but withdrawn in 2010 due to cardiovascular effects
Inhibits the neuronal uptake of dopamine, norepinephrine, and serotonin.	Bupropion (Wellbutrin, Zyban)	Modest weight loss. *Nausea, vomiting, dry mouth, headache, constipation, increased sweating, joint aches, sore throat, blurred vision, strange taste in the mouth, agitation and insomnia, tremer or dizziness may occur. Rare side effects includes cardiovascular	% weight loss greater than placebo: Bupropion SR 400 mg/d 5.1% [CI] 6.9---3.2% Bupropion SR 300 mg/d 2.2% [CI] 4.0---0.4%	Off---label usage Approved for depression

Mechanism of action	Drug	Effects and safety concerns	Efficacy	Status
		effects, hearing problems, severe headache, an increase in suicide risk, and respiratory problems.		
Reversible inhibitor of intestinal lipases.	Orlistat (Xenical)	Weight loss. *increased number of bowel movement and potential changes in the bowel function and microbiota.	Mean body weight loss greater than placebo was 4.2 kg	FDA---approved drug in 1999
Enhancing GABA singaling to promote anorexigenic signaling. Inhibiting voltage---gated channels and AMPA receptor in the orexigenic neurons.	Topiramate (Topamax)	Appetite suppression and weight loss. *Tiredness, drowsiness, dizziness, loss of coordination, tingling of the hands/feet, bad taste in the mouth, diarrhea. Mental problems such as confusion, slowed thinking, trouble concentrating or paying attention, nervousness, memory problems, or speech/language problems may also occur. Rare side effects include kidney stones, depression, suicidal thoughts/attempts, and vision loss.	Weight loss greater than placebo was 6.5 kg [CI] 4.8---8.3 kg	Off---label usage Approved for epilepsy
Glucagon---like peptide---1 (GLP---1) receptor agonist.	Exenatide (Byetta, Bydureon)	Decreased blood glucose level and body weight. * Side effects include GI symptoms, acute pancreatitis, dizziness and headache. It might increase risks of sulfonylurea---induced hypoglycemia and thyroid cancer.	Mean body weight change: Exenatide --- (2.49 ± 0.66) kg, placebo + (0.43 ± 0.63) kg	Off---label usage Approved for diabetes
	Liraglutide (Victoza)	Maintained normal blood glucose and body weight. *Increased risks of C---cell carcinoma and thyroid C---cell focal hyperplasia were observed in rats and mice.	Weight loss greater than placebo was 4.4 kg [CI] 2.9---6.0 kg	Off---label usage Approved for diabetes
Amylin analog.	Pramlintide (Symlin)	Decreased blood glucose level and body wieght. * Side effects include nausea, hypoglycemia, vomiting, headache, abdominal pain and fatigue.	%weight loss greater than placebo was 2.2 ± 0.7%	Off---label usage Approved for diabetes
Cocktail drug.	Phentermine/topiramate (Osymia)	See above effects from individual drugs	%weight loss from baseline was placebo −2.2%, (PHEN 7.5 mg/TPM 46 mg) CR −9.3%, and (PHEN 15 mg/TPM 92 mg) CR −10.7%	FDA---approved in 2012

Table 2
Anti-obesity medication under development

Target	Drug	Company	Mechanism of action	Status
Central neuropeptide signaling				
Melanocortin receptor	MK-0493	Merck	Selective MC4R agonist, increasing MC3/4R signaling	**Phase II completed**
	RM-493	Rhythm	Selective MC4R agonist, increasing MC3/4R signaling	**Phase II**
NPY	MK-0557	Merck	Y5 receptor antagonist, NPY blocker	**Phase II completed**
	Velneperit (S-2367)	Shionogi USA	Y5 receptor antagonist, NPY blocker	**Phase III**
Monoamine neurotransmission				
Dopamine / norepinephrine / serotonin	Contrave (bupropion / naltrexone)	Orexigen	Norepinephrine/dopamine reuptake inhibitor	**Phase III completed NDA submission**
Intestinal peptide hormone signaling				
GLP-1	Liraglutide (Victoza)	Novo Nordisk	GLP1R agonist, GLP-1 mimicking	**Phase III completed NDA submission**
	Byetta® (exenatide)	Amylin	GLP1R agonist, GLP-1 mimicking	**Phase III**
OXM	Qxyntomodulin (OXY-RPEG)	Prolor	GLP1R agonist, OXM mimicking	**Phase I recruiting**
	TKS1225	Thiakis / Wyeth / Pfizer	GLP1R agonist, OXM mimicking	**Phase I**
Pancreatic hormone signaling				
PP	PP1420	Wellcome Trust	Pancreatic polypeptide analog	**Phase I completed**
Amylin	Davalintide (AC2307)	Amylin	Amylin mimicking	**Phase II**
Adipose tissue hormone signaling				
Leptin	Metreleptin	Amylin / Takeda	Leptin receptor agonist	**Phase III recruiting**
Inhibition of lipase				
Pancreatic lipase	Cetilistat (ATL-962)	Alizyme / Takeda / Norgine	Pancreatic lipase inhibitor, inhibiting intestinal lipid absorption	**Phase III completed**