

Approaches to the Pharmacological Treatment of Obesity

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Abstract and Introduction

Abstract

Obesity is a global health crisis resulting in major morbidity and premature death. The need for safe and efficacious drug therapies is great, and presently unmet. The two drugs currently licensed in the USA for the long-term treatment of obesity, orlistat and sibutramine, provide only modest weight-loss benefits and are associated with high attrition rates owing to side effects. This review summarizes current concepts in the neuroendocrine control of energy homeostasis and major pharmacological treatments for obesity in the pipeline.

Definition & Scope of the Problem

Obesity is a rapidly increasing global health problem of critical concern. The causes of this epidemic are complex and multifactorial, but fundamentally lead to an excess calorie intake over energy expenditure. Modern lifestyles, incorporating altered eating patterns, access to cheap, highly palatable, energy-dense yet nutritionally poor foods, sedentary habits and labor-saving devices, have hugely accelerated the problem during the latter part of the 20th Century. Even small excesses in daily caloric intake very easily translate into unhealthy weight gain over a lifetime. As more of the world's population becomes urbanized and incomes rise, the problem will undoubtedly continue to grow.

Obesity is defined as a BMI of 30 kg/m² or more, calculated as an individual's weight divided by the square of their height. Overweight is defined as a BMI greater than 25 kg/m². In 2005, the WHO estimated that 1.6 billion adults worldwide were overweight and at least 400 million obese. By 2015, this is projected to rise to 2.3 billion and over 700 million, respectively.^[201] Furthermore, with the alarming rise in childhood obesity rates (an estimated 15% of juveniles are obese), the devastating chronic health consequences of obesity are likely to start occurring earlier. In 2005, Olshansky and associates predicted a reversal of 20th Century gains in life expectancy, owing to the adverse health consequences of obesity in the coming decades.^[1]

Health Consequences

Overweight and obesity are independently linked to an increased risk of cardiovascular disease, as well as contributing to other established risk factors such as hypertension, dyslipidemia impaired glucose metabolism.^[2-4] This has been supported by an increased understanding of the role of excess adipose tissue, particularly intra-abdominal visceral fat, as a producer of free fatty acids (FFAs) and proinflammatory cytokines that cause insulin resistance, abnormal lipid metabolism, endothelial dysfunction, prothrombotic and proatherosclerotic effects.^[5]

Overweight and obesity are the most important risk factors for the development of Type 2 diabetes, with all of its attendant risks of macrovascular disease, limb loss, blindness and renal

failure. Furthermore, obesity has been linked to the development of numerous cancers, obstructive sleep apnea, musculoskeletal disorders, infertility and depression, as well as many other morbidities.^[6,7] Longer-term follow-up studies of patients undergoing bariatric surgery, which is presently the most effective treatment for obesity in terms of producing significant and sustained weight reduction, have provided compelling evidence that weight loss can ameliorate many obesity-related conditions and improve life expectancy.^[8-11] In 2007, a retrospective cohort study of obese subjects who were undergoing weight-loss surgery showed a 40% reduction in all-cause mortality, a 92% reduction in diabetes deaths, a 56% reduction in coronary artery disease deaths and a 60% reduction in cancer deaths.^[12]

Understanding the Neuroendocrine Control of Energy Homeostasis

Understanding the complex physiology of energy balance is vital for the development of safer and more effective long-term weight-loss pharmacotherapy, as an alternative to risk-laden surgical procedures. We have observed many advances in this field of research over the past two decades, and the following section provides a brief overview. The crucial areas of the brain co-ordinating energy and bodyweight homeostasis are the brainstem and hypothalamus. Peripheral neural and endocrine signals bringing information regarding energy availability are integrated with signals from higher brain centres (for example, regarding reward, stress or mood) to regulate appetite and control energy expenditure. Insulin from the pancreas and circulating humoral factors from adipose tissue (adipokines such as leptin) interact with CNS circuits to relay information regarding long-term energy stores.^[13,14] Gastrointestinal hormones, which also act in a neuroendocrine fashion, are released on a meal-to-meal basis and signal short-term nutrient availability (this is summarised in Figure 1). Upon meal ingestion, vagal afferents are triggered by stretch receptors, nutrient chemoceptors and receptors for locally released gut hormones. These neurones converge in the nucleus of the tractus solitarius (NTS) of the brainstem. Close to this is the area postrema (AP), a region relatively deficient in blood–brain barrier and a second site for circulating hormones to influence these neuronal circuits. A gut–brain reflex circuit is completed by vagal efferents projecting back from the NTS to the gastrointestinal tract, to modulate digestive functions. In addition, projections from the brainstem carry signals upwards to the hypothalamus, which is the seat of homeostatic energy balance.^[15] The arcuate nucleus (ARC) of the hypothalamus contains two populations of neurones, which have opposing effects on food intake. Orexigenic neurones (i.e., those stimulating food intake) in the medial ARC express neuropeptide Y (NPY) and Agouti-related protein (AgRP). Laterally located anorexigenic neurones (i.e., those inhibiting food intake) express α -melanocyte-stimulating hormone (α -MSH) derived from pro-opiomelanocortin (POMC), and cocaine- and amphetamine-regulated transcript (CART).^[16] The relative tone of these two sets of opposing neurones is delicately altered by numerous neuroendocrine inputs. Signals arrive from the brainstem conveying a huge amount of information from the gastrointestinal tract as already described. The median eminence, an area deficient in blood–brain barrier that is close to the ARC, provides access for circulating factors such as leptin and gut hormones to directly affect the activity of appetite-regulatory neurones. There is additional influence from the many interconnections with higher brain centres inputting information such as reward drives and mood. In turn, the ARC projects neurones to the paraventricular nucleus (PVN) of the hypothalamus where responsive effects on energy expenditure arise, including changes in basal metabolic rate (via the thyroid axis), sympathetic outflow and thermoregulation.^[16]

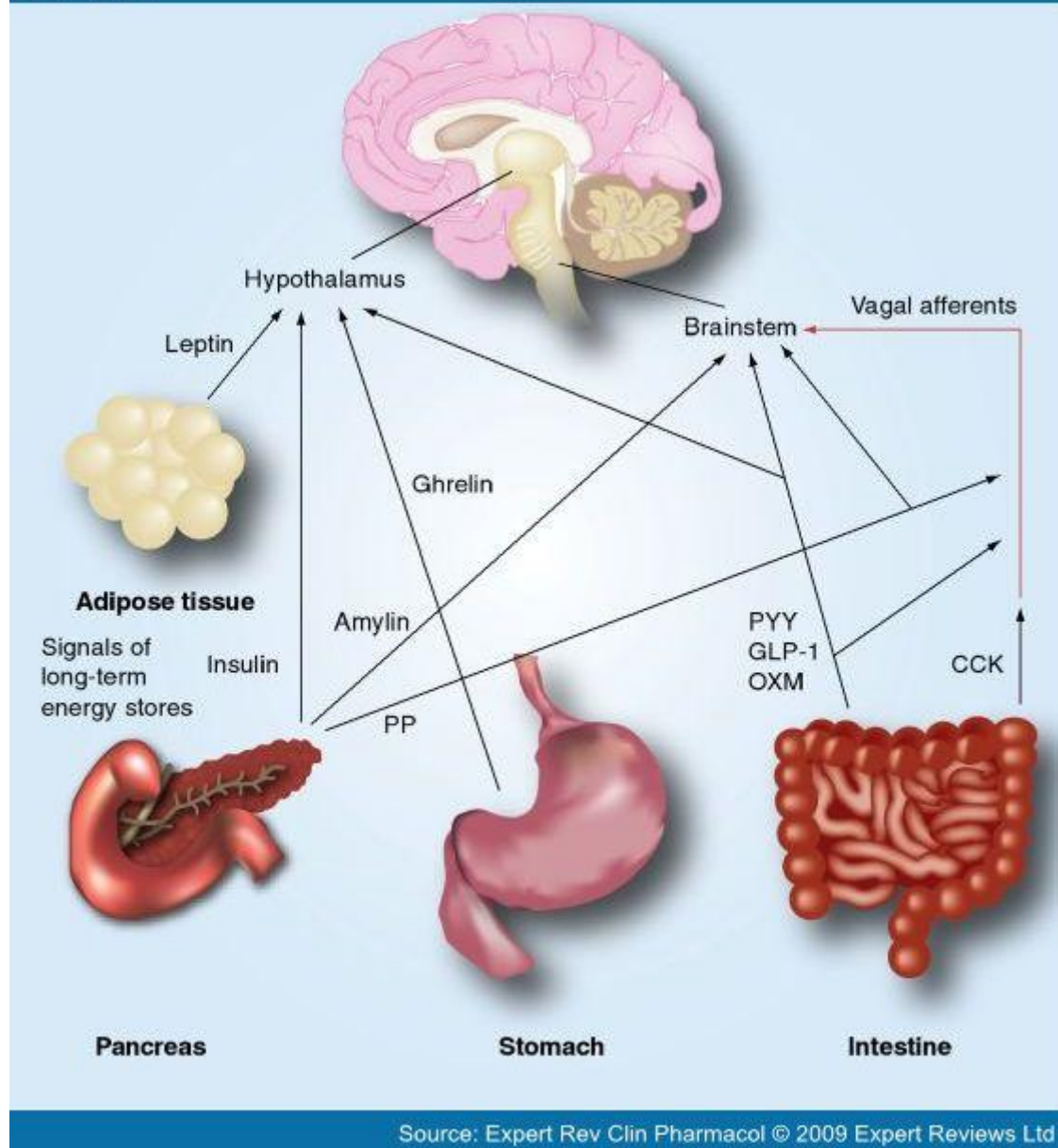


Figure 1. Circulating factors are able to directly influence neuronal transmission in the brainstem and hypothalamus as well as activating vagal afferents.

Leptin and insulin are signals of long term energy stores. Gastrointestinal peptide hormones tract which signal short term nutrient availability on a meal-to-meal basis. Stomach-derived ghrelin is the only gut hormone released during fasting and is a meal initiator. The remaining gut hormones are released post prandially: pancreatic polypeptide and amylin from the pancreas, and cholecystikinin, peptide YY and the incretins glucagon-like peptide-1 and oxyntomodulin from the intestine. CCK: Cholecystikinin; GLP: Glucagon-like peptide; OXM: Oxyntomodulin; PP: Pancreatic polypeptide; PYY: Peptide YY.

Monogenic forms of obesity, although very rare, have helped delineate some of the central pathways involved in appetite regulation. For example, humans with homozygous deficiency of POMC or the melanocortin-4 receptor (which is the receptor for α -MSH from anorexigenic neurones) develop severe, early onset obesity.^[17] Interestingly, NPY knockout mouse models do not exhibit a lean phenotype as expected, but do display normal food intake^[18] – most likely owing to the activation of numerous compensatory pathways protecting against starvation. These

findings lend support to the generally held view that organisms possess an evolutionarily programmed tendency to protect against weight loss more than weight gain.

Understanding the genetic contribution of more common forms of obesity is an area of intense recent research, with the hope that this may help to identify novel pharmacological approaches. Observationally, it is clear that some people are protected more than others against the obesogenic effects of our modern lifestyles. In fact, twin studies suggest that 70% of variation in adiposity within the population is due to genetic factors.^[19] Thus, the commonly held view that obesity is simply a consequence of the individual's decision to eat too much and exercise too little is an oversimplification. The salient question that remains largely unanswered is: what biologically determined factors make it difficult for some more than others to maintain a normal bodyweight? We are a long way from explaining the high heritability of the condition and, as is true of many common and complex diseases, a large number of genetic factors are likely to be interplaying. The advent of high-powered genome-wide association studies is helping to pave the way to identifying new candidate genes, with the *FTO* gene in obesity as a recent example.^[20] The obesity high-risk *FTO* allele is common in Caucasians, and homozygous adults are 2–3 kg heavier, with higher BMI and reduced satiety observable from childhood. *FTO* codes for the enzyme 2-oxoglutarate-dependent nucleic acid demethylase,^[21] which is particularly highly expressed in the hypothalamus, although the exact molecular mechanism underlying the *FTO* association with obesity remains to be elucidated.

What are the Current Treatment Options?

Lifestyle

Although not yet matched by a robust evidence base, many government policy-makers support the introduction of societal interventions as a means of encouraging people away from obesogenic environments and behavior patterns. Such efforts are important, but seem largely impractical as an immediate means of tackling the obesity crisis as it stands. Dietary and exercise advice remains the mainstay of the medical management of obesity and should be encouraged alongside all other treatment adjuncts. Sustained caloric restriction (to 1500 kcal/day for women and 1800 for men), regardless of dietary macronutrient composition or regimen,^[22] has fairly similar effects on weight loss, ranging from 3–5 kg over 2 years.^[23] The addition of physical exercise facilitates weight loss by increasing energy expenditure and increasing basal metabolic rate through an increase in muscle mass. Unfortunately, lifestyle interventions alone rarely result in long-term weight loss and the majority of dieters return to baseline weight within 3–5 years. This even holds true for participants in weight-loss trials who are offered education and intensive support to help prevent weight regain,^[24,25] and adds support to the concept that appetite may be consciously overridden in the short-term but in the longer term this is superseded by a biologically determined 'set-point'.

Pharmacotherapy

In the midst of the obesity-related health crisis, the case for safe and efficacious pharmacotherapies is clear. Unfortunately, drugs currently available for long-term weight management are limited in number and efficacy. There are many more examples of drugs used historically for weight loss that have been removed owing to significant side effects, including hypertension, severe mood disturbance, serious cardiac pathology and increased mortality. This has often been due to the use of centrally acting adrenergic stimulants, which suppress appetite and increase energy expenditure through generalized sympathetic activation. At present, there remain three sympathomimetic amphetamine-like drugs still approved by the US FDA as weight-loss adjuncts; phentermine, diethylpropion and phendimetrazine. This drug class has been

associated with side effects including systemic and pulmonary hypertension, as well as the obvious potential for abuse and addiction. They are approved for short-term use only and so they have limited use in the long-term management of obesity.^[26] FDA guidance for the approval of weight-loss therapies intended for long-term use recommends a 5% placebo-corrected weight reduction that should be maintained for at least 12 months after treatment initiation. Small, sustained reductions in weight can significantly improve cardiovascular risk factors, particularly glucose tolerance, in overweight and obese individuals. The target adult population for drug therapy is set at BMI above 30 (or >27 with comorbidities). This opens up a potentially huge market for weight-loss drugs. However, there are currently only two drugs licensed in the USA for the long-term treatment of obesity. The first is orlistat (Xenical; Roche) and the second sibutramine (Meridia/Reductil; Abbott). Orlistat irreversibly inhibits intestinal lipases by covalently binding to a serine residue on the active site. Lipases are required to hydrolyze dietary triglycerides into absorbable FFAs. With orlistat, up to 30% of ingested fat is not absorbed. This is the reason for the most common adverse events reported with the drug—gastrointestinal discomfort and fecal urgency. In fact, some claim that the benefit of the drug is best seen in patients who learn to switch to a low-fat diet in order to avoid such side effects. In the longer term, there is also the risk of deficiency of fat-soluble vitamins. Between 1999 and 2008, six cases of liver failure in patients taking orlistat were reported to the FDA's Adverse Event Reporting System. Analysis of these and other reports of liver injury associated with orlistat use is being undertaken by the agency, although as yet no clear link has been identified.^[203] In terms of efficacy, meta-analysis of clinical trials indicate a mean weight loss for orlistat-treated patients of 2.89 kg compared with placebo-treated patients over 12 months.^[27] This mix of modest weight loss and often intolerable side effects leads to high attrition rates in users. One survey of 17,000 orlistat users in Canada reported rates of ongoing use of less than 10% at 1 year and 2% at 2 years.^[28] In 2007, GlaxoSmithKline (GSK) under licence from Roche released a low-dose, over-the-counter formulation of orlistat (Alli). Initial US sales in that year reached \$119.6 million but fell to \$76.7 million in 2008. European trends are following a similar pattern.^[202] Sibutramine belongs to the class of selective serotonin and noradrenaline reuptake inhibitors that elevate synaptic concentrations of 5-hydroxytryptamine (5-HT).^[29] It may also increase energy expenditure through sympathetic activation^[30] and the elevated heart rate and blood pressure seen with the drug may be a cause for concern. Analysis from the ongoing Sibutramine Cardiovascular Outcomes (SCOUT) trial, which is a prospective randomized, double-blind, placebo controlled trial in cardiovascular high-risk, overweight and obese subjects, has raised some concerns about a possible increased incidence of cardiovascular events in such patients taking the drug. Further FDA guidance is awaited.^[204] Meta-analysis of earlier clinical trials reveals that after 1 year, an average of 4.2 kg more weight is lost by patients taking sibutramine, with an associated 20–30% increased probability of losing at least 5% of their bodyweight.^[27]

Surgery

At present, the most effective means of significant and sustained weight loss for obese patients is bariatric surgery. Gastric banding is a restrictive procedure that involves the insertion of an adjustable band around the upper portion of the stomach to limit the amount of food that can be ingested. Roux-en-Y gastric bypass involves the formation of a small stomach pouch and bypass of the proximal small bowel. Although malabsorption is not a major feature of modern gastric bypass surgery,^[31] patients undergoing this type of procedure lose much more weight (in the order of 30%) than those undergoing gastric banding alone (20% loss).^[32] They also experience a prompt reduction in appetite and improvement in glucose metabolism, well before the advantages of weight loss through restricted intake have had time to accrue. These added advantages of bypass surgery are thought to be due to an alteration in the release profile of gut hormones. Postprandial levels of glucagon-like peptide (GLP-1) and peptide tyrosine tyrosine (PYY), which are appetite-inhibiting gut hormones, are elevated following gastric bypass surgery

but not after gastric banding. GLP-1 also acts at pancreatic β -cells to augment glucose-dependent insulin release,^[32–35] referred to as the incretin effect. However, bypass surgery is costly, in many cases irreversible and associated with significant risks, including a 0.5% mortality rate.^[36] There is, therefore, a huge incentive to provide safe pharmacological alternatives.

Other Pharmaceutical Strategies for the Treatment of Obesity

The shortcomings of presently available therapies has led to massive interest in finding new therapeutic approaches. Table 1 summarizes the major therapeutic advances so far, and the following sections highlight some of the more promising future candidates.

Table 1. Major obesity drugs on the market and selected drugs in development.

| Drug | Manufacturer | Mechanism | Phase of development | Side effects |
|--|--|--|---|--|
| Currently available on the market | | | | |
| Orlistat | Roche | Lipase inhibitor – inhibits intestinal fat absorption | Launched 1998 Available without prescription since 2007 | Fecal urgency, diarrhea and abdominal pain Case reports of liver injury under investigation |
| Sibutramine | Abbott | Selective serotonin and noradrenaline reuptake inhibitor – induces satiety | Launched 1999 | Headache, dry mouth, constipation, elevated pulse rate, insomnia |
| Phentermine | Gate Pharmaceuticals Medeva Pharmaceuticals Available as generic | Amphetamine-like drug – generalized sympathetic activation inducing satiety | Launched 1970 Only approved for short-term weight management | Tremor, elevated pulse rate and blood pressure, insomnia, potential for addiction |
| Peripherally acting anti-obesity drugs and targets in development | | | | |
| Cetilistat | Allizyme | Lipase inhibitor | Phase III | Fecal urgency, diarrhea and abdominal pain |
| Fatostatin | | Sterol regulatory element binding protein inhibitor – downregulates genes expression | Animal testing | |

| | | | | |
|--|--|---------------------------|--|--|
| | | required for adipogenesis | | |
|--|--|---------------------------|--|--|

Centrally acting anti-obesity drugs and targets in development

| | | | | |
|------------|-----------------------|--|-----------|---|
| Lorcaserin | Arena Pharmaceuticals | Highly selective 5HT _{2c} agonist - activates hypothalamic and mesolimbic appetite suppressing pathways | Phase III | Headache, dizziness, nausea. No reports of cardiac valvular dysfunction to date |
| Qnexa | Vivus | Combination topiramate (an antiepileptic which inhibits excitatory neurotransmission via voltage-gated sodium channels) plus phentermine | Phase III | Paraesthesia, dry mouth, taste disturbance |
| Contrave | Orexigen Therapeutics | Combination bupropion (dopamine and noradrenaline reuptake inhibitor) and naltrexone (opioid antagonist) | Phase III | Nausea, headaches, constipation |

Gut hormone analogs as anti-obesity drugs

| | | | | |
|-------------|------------------|--|--|---|
| Exenatide | Amylin Eli Lilly | Long-acting GLP-1 analog – incretin mimetic and hypothalamic anorectic agent | Launched in 2005 as a treatment for Type 2 diabetes. Currently in Phase II/III trials for the treatment of obesity | Nausea and gastrointestinal disturbance, case reports of pancreatitis |
| Liraglutide | NovoNordisk | Long-acting GLP-1 analog | Approved in 2009 as a treatment for Type 2 diabetes. Currently in | Nausea and gastrointestinal disturbance, reports of medullary thyroid |

| | | | | |
|-----------------------|------------|-------------------------------------|--|--------------------|
| | | | Phase II/III trials for the treatment of obesity | tumours in animals |
| Pramlintide-metreptin | Amylin | Synthetic amylin and leptin analogs | Phase II/III | Nausea |
| TM30338 | 7TM Pharma | Dual Y2 and Y4 agonist | Phase II | Nausea |

Peripherally Acting Approaches

Pharmacological approaches to the treatment of obesity can broadly be classified into peripherally and centrally acting drugs. The company Alizyme has moved into Phase III clinical trials of its lipase inhibitor, cetilistat, which had comparable efficacy to orlistat at inducing weight loss but with a more favorable gastrointestinal side effect profile at Phase II testing.^[37] There are few other imminent developments in obesity pharmacotherapy utilizing peripheral mechanisms, such as the inhibition of nutrient absorption or the regulation of fatty acid metabolism. However, this is the focus of early-stage research at present and may hold promise for the future.^[38,39] One such example is fatostatin, a recently discovered molecule that inhibits sterol regulatory element-binding proteins (SREBPs), which are major transcription factors regulating genes encoding enzymes required for lipogenesis. Pharmacological studies in genetically obese *ob/ob* strains revealed a reduction of bodyweight, visceral adiposity and blood glucose in fatostatin-treated mice.^[40]

Centrally Acting Approaches

There are many more anti-obesity agents currently undergoing late-stage clinical trials which are centrally-acting drugs that interact with appetite-regulatory neurotransmission. Intensive monitoring for side effects with these types of drugs has gained even greater importance with the lessons learned from cannabinoid receptor antagonists. Endocannabinoids are endogenous lipid-based neurotransmitters synthesized from arachidonic acid which activate cannabinoid receptors (CBs). In the CNS, CB1 receptor activation alters the release of a variety of neurotransmitters, including dopamine in the mesolimbic system, and affects appetite and energy expenditure in the hypothalamus by changing the relative expression of orexigenic and anorexigenic neuropeptides to increase appetite.^[41] The CB1 receptor antagonist rimonabant, developed by Sanofi-Aventis, received European approval as an anti-obesity agent following the results of the four Phase III studies that comprised the Rimonabant in Overweight/Obesity (RIO) program. Subjects taking the drug lost an average of 4.5 kg relative to placebo in 1 year, with concomitant significant improvements in visceral fat, abdominal circumference and all other measures of the metabolic syndrome.^[42] However, postmarketing surveillance unveiled serious concerns regarding the association between rimonabant and psychiatric side effects, including depression and suicide, and neurological side effects, such as the risk of convulsions. In June 2007, the FDA's Endocrine and Metabolic Drugs Advisory Committee (EMDAC) concluded that the safety of rimonabant had not been adequately demonstrated by the manufacturer Sanofi-Aventis and the full application for approval was subsequently withdrawn. Later that year, the European Medicines Agency (EMA) concurred that the benefits of rimonabant no longer outweighed its risks and marketing authorization was suspended across the EU. All drug manufacturers have since ceased further development of centrally acting CB1 receptor antagonists.

5-HT_{2c} Agonists

The serotonin 5-HT₂ family of receptors mediate a wide range of physiological functions including appetitive behavior, mood and smooth muscle function.^[43] Early, less selective serotonergic appetite suppressants such as fenfluramine and dexfenfluramine, were removed from the market in the 1990s after a link was established with the development of valvular heart disease, found to be mediated via the 5-HT_{2B} subtype.^[44] Lorcaserin is a serotonin receptor agonist with 104-fold selectivity for the 5-HT_{2C} over the 5-HT_{2B} receptor^[45] and which therefore holds promise as an appetite suppressant with a safer side-effect profile. 5-HT_{2C} receptors are widely distributed throughout the CNS, including higher centers involved in reward and mood, as well as areas involved in the homeostatic regulation of appetite such as the hypothalamus and NTS.^[43] The 5-HT_{2C} knockout mouse is obese and hyperphagic and resistant to the weight-lowering effects of other serotonin agonists.^[46] Chronic daily treatment with lorcaserin in diet induced obese rats produce dose-dependent reductions in food intake and bodyweight.^[44] Lorcaserin has since made its way through to Phase III human testing in the Behavioral modification and lorcaserin for Overweight and Obesity Management (BLOOM) trial. First-stage results report a 5.77-kg weight loss in the Lorcaserin group over 1 year compared with 2.14-kg weight loss in the placebo group. It was also revealed that 47.5% of patients on the drug lost at least 5% of their bodyweight, compared with 20.3% of those on placebo, and that 22.6% lost at least 10% of their bodyweight compared with 7.7% on placebo.^[205] Notably, no excess valvular cardiac disease has been reported during 2 years of its use. The BLOOM trial discontinuation rates owing to adverse events in the lorcaserin and placebo groups were similar, with 7.1 versus 6.7% for year 1 and 3.0 versus 3.0% for year 2, respectively.

Qnexa

The pharmaceutical company Vivus is developing Qnexa, a combination of low-dose phentermine and the anticonvulsant agent topiramate, for the long-term treatment of obesity. Topiramate is a sulphamate-substituted fructose approved for the treatment of refractory seizures and for migraines. It inhibits excitatory neurotransmission by blocking voltage-gated sodium channels and other actions on GABA and glutamate systems. The exact mechanism by which it promotes weight loss remains unclear, although dose-ranging studies reveal that it does so in a dose-dependent fashion.^[47] The Phase III EQUATE trial evaluated Qnexa versus placebo in 756 obese subjects over 28 weeks. Patients taking full-dose and mid-dose Qnexa achieved an average weight loss of 9.2 and 8.5% respectively, as compared with 1.7% reported for the placebo group.^[206] There were also significant improvements in HbA1c in the group taking Qnexa mediated via its weight-loss effects. In the high-dose group, 20% reported paraesthesia, 18% dry mouth and 15% altered taste versus 3, 0, and 0%, respectively, in the placebo group, but there was no difference in reports of mood disturbance.

Contrave

Contrave is a combination of bupropion, a dopamine and noradrenaline reuptake inhibitor, with naltrexone, an opioid antagonist used to treat various addictive disorders. These two agents are reported to synergistically block b-endorphin-mediated inhibition of POMC neurones, leading to increased hypothalamic anorexigenic neuronal activity. They have each on their own been shown to reduce appetite and bodyweight in humans.^[48,49] Contrave's developers, Orexigen, have published results from the NB-302 trial, a 56-week, double-blind, placebo-controlled trial, conducted in 793 patients also receiving intensive dietary and exercise advice. It revealed that over the course of the study, the Contrave group lost 9.2–11.4 kg compared with 7.3 kg in the placebo group and that 41.5% lost at least 10% of their weight in the treatment arm compared with 20.2% on placebo.^[207] The overall discontinuation rate owing to adverse events was 25.9% for patients taking Contrave versus 13.0% for those taking placebo, but the drug was not

associated with an increased incidence of depressive symptoms. Overall, 4.6 % discontinued the drug owing to nausea – an effect that is attenuated with adequate dose titration.

Reuptake Inhibitors

Tesofensine is an inhibitor of presynaptic noradrenaline, dopamine and serotonin uptake under development by NeuroSearch who have completed a 24 week Phase II, randomized, double-blind, placebo-controlled trial, testing it in 203 obese patients.^[50] Patients receiving tesofensine lost 6.7–12.8 kg of weight compared with a 2.2-kg loss in the placebo group. A total of 74% of patients receiving high-dose tesofensine and 35% receiving medium dose lost more than 10% of their bodyweight, compared with 7% in the placebo group. However, 20% of patients withdrew from the trial due to adverse events in the high dose group, compared with 8% in both the medium-dose and placebo groups. Dose-dependent reports of nausea, dry mouth and insomnia were reported and there were increased reports of agitation and mood disturbance, which are a cause for concern following the market withdrawal of cannabinoid receptor antagonists for similar reasons. These side effects will be carefully monitored in future planned Phase III studies.

Expert Commentary

Gut Hormones in the Treatment of Obesity

The discovery of leptin and gut hormones as major neuroendocrine regulators of bodyweight is leading the way to the development of attractive therapeutic approaches to the long-term manipulation of energy homeostasis in favor of appetite reduction and weight loss. It is hoped that this may be associated with a relative paucity of central or unexpected side effects. The rest of this article will concentrate on these therapeutic strategies.

Leptin

Leptin is a circulating 167-amino acid peptide that is the product of the *ob* gene that is exclusively expressed in adipose tissue. Plasma leptin concentrations are highly correlated with adipose tissue mass.^[51] Peripheral and intracerebroventricular injections of leptin reduce food intake and bodyweight in both wildtype and leptin-deficient (*ob*) mice, but not in leptin-receptor-deficient (*db*) mice.^[52–54] The leptin receptor is expressed throughout the CNS, particularly in the hypothalamus.^[55] It is now understood that by modulating neural activity in hypothalamic neurones that regulate energy balance, leptin acts in an important negative feedback loop to homeostatically maintain adiposity. Congenital leptin deficiency in humans is associated with massive early-onset obesity which is reversible with leptin replacement treatment.^[56] However, the majority of cases of human obesity are associated with elevated circulating leptin levels and hence leptin-resistance, such that the utility of leptin as monotherapy for the treatment of obesity is limited.^[57] More recent studies have investigated the synergistic use of leptin alongside other antiobesity agents to induce clinically significant weight loss in obese individuals.^[58] Understanding the molecular mechanisms underpinning leptin resistance may open the way to other potential anti-obesity treatments. The leptin receptor signals via the JAK-kinase signal transducers and activators of transcription (JAK-STAT) pathway.^[59] This type of signaling is limited by the activation of suppression of cytokine signaling (SOCS) proteins, which inhibit JAK kinase. Mice deficient in SOCS3 are resistant to diet-induced obesity and remain leptin sensitive^[60] and in the future, chemical inhibitors of these proteins may have potential as anti-obesity drugs.

Peptide Tyrosine Tyrosine

Along with pancreatic polypeptide (PP) and NPY, PYY is a member of the PP-fold family of peptides – so named due to a common hair-pin fold motif necessary for receptor binding. PP-fold

proteins mediate their effects through a set of G-protein coupled Y receptors – Y1, Y2, Y4, Y5 and Y6. The receptors are distributed widely in the periphery as well as the CNS, and there is a degree of cross-reactivity between all of the PP peptides at each of the receptors, producing an overlapping system that is difficult to untangle. However, there is evidence that each of the PP-fold peptides bind more selectively to specific receptor subtypes and have distinct effects on energy homeostasis.^[61] PYY is released from L-cells of the gastrointestinal tract, in proportion to the number of calories ingested. Circulating levels rise approximately 15 min after a meal has been ingested and remain elevated for 2 h.^[62] Fasted humans infused intravenously with PYY_{3–36} to mimic postprandial concentrations consume 35% fewer calories at a subsequent buffet meal.^[63] Importantly, in contrast to the problem of leptin resistance, obese subjects remain just as sensitive to the anorectic effects of the hormone.^[64] The prospective finding of a negative correlation between peak postprandial PYY concentrations and bodyweight suggests that altered PYY physiology has a role to play in the pathogenesis of obesity.^[65,66] Furthermore, fasting levels of PYY are chronically elevated in a number of anorexia-driven weight-losing enteropathies in humans.^[67,68] PYY knockout mice display hyperphagia and increased adiposity, which is reversed upon exogenous replacement of PYY_{3–36}.^[69] Some of the satiety effects of PYY are because it slows gastric emptying, the 'ileal brake' effect, leading to a more prolonged feeling of fullness. However, PYY released into the bloodstream more importantly exerts its appetite-regulatory effects in a neurohumoral manner along the gut–brain axis. The major site of action of circulating PYY_{3–36} is most likely to be the hypothalamus via the nearby median eminence. Studies reveal that c-fos expression (a marker of neuronal activation) is increased in the hypothalamus following the peripheral administration of PYY, which increases POMC and decreases NPY mRNA expression in the ARC.^[64,70,71] Acute stress induces anorexia by downregulating arcuate NPYergic activity in a very similar manner.^[72] Exploiting the anorectic action of PYY_{3–36} still holds promise for the development of novel anti-obesity therapies. Similar to the other satiety-inducing gut hormones, the most commonly reported adverse effect with PYY, which is dose related, is nausea. This probably represents part of the spectrum of the expected effects of these hormones, from a pleasant sensation of fullness through to feeling 'overfull' and eventually nauseous. Phase II clinical trials of nasal PYY (Nastech/Merck) taken with each meal were terminated after 24 weeks since it was no better than currently available sibutramine at reducing weight, and because there were significant problems with nausea.^[208] However, in this study the maximum plasma PYY concentrations achieved of 105 pmol/l were much higher than normal postprandial levels of 50 pmol/l. Furthermore, the time taken to reach peak levels of 18–26 min was greatly shorter than the more gentle and sustained natural post-prandial rise.^[73] Thus the high incidence of nausea and failure of nasal PYY to induce longer-term appetite reduction and weight loss may possibly have been due to the pharmacokinetics of this mode of delivery. Future studies investigating the chronic use of steady-state preparations of PYY are warranted. A more detailed understanding of the Y-receptor system and the highly complicated neuronal circuitry involved in the appetite regulatory effects of PYY is vital for the development of optimally targeted antiobesity drugs of this nature. At physiologic concentrations, PYY activates hypothalamic presynaptic (autoinhibitory) Y2 receptors, as evidenced by the lack of anorectic effect of PYY in Y2 receptor knockout mice, and the attenuation of the anorectic effect of peripherally administered PYY when a Y2 receptor antagonist is concomitantly given.^[63] Recent functional magnetic resonance imaging studies in humans point to the fact that PYY may also interact with even higher brain centers, such as those involved in the reward processing of food, to alter meal preference and palatability.^[74] In B6.V- Lepob/J obese mice under chronic stress (who have very high circulating NPY levels), there is evidence that pharmacological inhibition or fat-targeted knockdown of peripheral Y2 receptors is anti-adipogenic, reducing abdominal obesity and metabolic abnormalities,^[75] highlighting the complicated interplay between the Y-receptor superfamily and the PP-fold peptides.

Pancreatic Polypeptide

Pancreatic polypeptide is synthesized and secreted from PP cells within the islets of Langerhans in the pancreas. PP is released postprandially largely under vagal control in proportion to calories ingested and levels remain elevated for 6 h.^[76] Chronic administration of PP to rodents reduces food intake, increases energy expenditure and results in a loss of bodyweight.^[77-79] PP-overexpressing mice display a lean and hypophagic phenotype, reversible with the administration of antibodies against PP.^[80] In fasted healthy lean human volunteers, an infusion of PP mimicking normal postprandial levels reduces caloric intake over the subsequent 24 h period by 25%.^[81] PP probably acts both via the vagus nerve and directly at the brainstem to produce its appetite regulatory effects via the Y4 receptor, for which it shows particularly high affinity.^[61] The anorexigenic effect of intra-peritoneally administered PP in rodents is abolished by vagotomy.^[78] Direct injection of PP into the dorsal vagal complex (DVC) of rats stimulates efferent vagal activity, suggesting that circulating PP also acts directly on the brainstem.^[82] This occurs via the nearby area AP, which is rich in Y4 receptors.^[83] The hypothalamus has also been demonstrated to play a role in PP's appetite-modulatory effects. The Y4 receptor is expressed in both the ARC and PVN of the hypothalamus. Peripheral injection of PP results in a downregulation of hypothalamic NPY expression.^[78] This may occur in direct response to circulating PP or secondary to incoming nervous signals from the brainstem. These initial insights into the satiety-inducing effects of PP and PYY have driven the development of synthetic analogs as potential anti-obesity agents. 7TM Pharmaceuticals (Copenhagen) have developed two such analogs. TM-30339 is a selective Y4-receptor agonist which demonstrated significant weight loss when administered chronically to diet-induced obese mice. Phase I/IIa trials are currently underway in healthy obese individuals over a 28 day study period to assess safety, tolerability and the effective dose to induce weight loss.^[209] TM-30338, named Obinipitide, is a dual Y2-Y4 receptor agonist already shown to be safe and well tolerated in humans during Phase I/II clinical trials. In obese volunteers given once daily subcutaneous injections, the compound significantly reduced food intake for up to 9 h after dosing and is scheduled for further Phase II testing.^[210]

Amylin

Amylin (islet amyloid polypeptide) is a 37-amino acid peptide coreleased from pancreatic β -cells in a 1:100 molar ratio with insulin. In a similar fashion to other gut hormones, amylin's release is rapidly stimulated by nutrient ingestion, peaking at 60 min and remaining elevated for 4 h.^[84] Amylin's effects are to potently inhibit glucagon release^[85] and to slow gastric emptying.^[86] It has no identified specific receptor of its own, and amylin mediates its effects via the calcitonin receptor, with tissue-specific sensitivities accorded by the differential expression of calcitonin receptor activity-modifying proteins.^[87] Chronically administered amylin reduces appetite in humans.^[88] The weight of evidence suggests that it acts directly at the brainstem. In rats, direct injection of amylin into the AP is strongly anorectic, while the reduction in food intake seen after peripheral administration is abolished with either NTS lesioning or direct injection of the amylin antagonist AC187 into the AP.^[89,90] The endogenous form of amylin has the tendency to form amyloid fibrils which, with long-term administration, could deposit in tissues and cause organ damage. Amylin Pharmaceuticals have developed a nonamyloidogenic, stable, subcutaneously delivered analog called pramlintide, which is already licensed in the USA as an adjunct to insulin for the treatment of both Type 1 and Type 2 diabetes. They have also studied the effects of pramlintide as a weight-loss treatment in nondiabetic obese subjects, replicating the weight-loss benefits seen in diabetic cohorts.^[91] Their second generation amylin analog, davalintide, has now been entered into Phase II clinical trials to study its safety, tolerability and efficacy as a weight-loss agent in healthy overweight and obese volunteers. Amylin Pharmaceuticals' combination treatment of pramlintide with recombinant human leptin, metreleptin, was developed following the observation in rodent studies that amylin increases leptin responsiveness in diet-induced

obesity.^[92] Phase II data is available for placebo-controlled testing of pramlintide and metreleptin alone and in combination. A total of 177 obese patients were studied following a 4-week lead-in period with either low-dose or high-dose injections of pramlintide alone alongside dietary restriction. Over the entire 24-week study period, subjects treated with pramlintide/metreleptin lost 11.5 kg from baseline, significantly more than the 7.4-kg lost by subjects treated with metreleptin alone or 7.9-kg loss with pramlintide alone.^[58] Nausea led to four withdrawals from the study during the lead-in period and one withdrawal in the pramlintide/metreleptin arm. Wider-scale clinical testing of the combination therapy is anticipated.

Glucagon-like Peptide-1

Glucagon-like peptide-1 is secreted from intestinal L-cells along with PYY and oxyntomodulin (OXM). It is rapidly released postprandially and levels remain elevated for several hours. Alongside OXM and glucose-dependent insulinotropic polypeptide (GIP), it is an incretin hormone which stimulates postprandial insulin release. In addition to its pancreatic glucoregulatory effects, the active form of GLP-1, GLP_{7-36amide}, also inhibits food intake in a number of species when given centrally or peripherally. Chronic peripheral administration causes significant weight loss in mice, which is inhibited by the coadministration of the specific GLP-1 receptor antagonist exendin₉₋₃₉.^[93] Unexpectedly, the GLP-1 receptor knockout mouse displays normal food intake and bodyweight (although it is glucose intolerant).^[94] However, as is true of many neuropeptide and receptor knockout strains, the lack of an obese phenotype is probably owing to developmental compensatory mechanisms. In fasted wild-type rats, direct intracerebroventricular (ICV) administration of GLP-1 strongly inhibits feeding, an effect that is abolished by the coadministration of exendin₉₋₃₉. Furthermore, ICV exendin₉₋₃₉ on its own doubles food intake in satiated rats, suggesting that endogenous GLP-1 physiologically regulates appetite.^[95] In normal-weight humans, GLP-1 dose-dependently reduces appetite and acutely reduces food intake by 12%. These appetite inhibitory effects are preserved in obese and diabetic human studies.^[96,97] Circulating GLP-1 is likely to exert its appetite regulatory effects both via vagal afferents and direct interaction with the brainstem and hypothalamus. GLP-1 administered either directly into the CNS or peripherally strongly induces c-fos expression in the PVN.^[93,98] Peripheral administration in addition activates the brainstem. GLP-1 receptor mRNA is found in high levels in the hypothalamic ARC, PVN and supraoptic nuclei. A further observation is that vagotomy and lesioning to disconnect the brainstem from the hypothalamus attenuates peripherally delivered GLP-1's anorectic effects.^[99] Short plasma half-life is a feature shared by all peptide gut hormones. In the case of GLP-1, the half-life is 2 min. Complete deactivation occurs following N-terminal cleavage by the enzyme dipeptidyl-peptidase (DPP)-IV.^[100] Exendin_{1-39amide}, a peptide purified from the saliva of the Gila monster *Heloderma suspectum*, was developed by Amylin Pharmaceuticals, in conjunction with Eli Lilly, into the drug exenatide. Better known by its trade name Byetta, exenatide is a long-acting GLP-1 agonist licensed as an adjunct to oral treatments for Type 2 diabetes. In addition to improved glycemic control, meta-analysis of clinical trials reveals an average weight loss of 2.13 kg in exenatide treated groups above placebo, and a 4.76-kg weight loss compared with insulin.^[101] Eli Lilly have reported results from a 24-week, double-blinded, randomized, control trial of high-dose exenatide in obese, nondiabetic subjects as an adjunct to dietary and exercise intervention. Individuals who received exenatide lost 5.06 kg compared with a 1.61-kg loss in the placebo group. Only exenatide-treated subjects (9.6%) lost more than 10% of their bodyweight. As with other peptide hormone treatments, Byetta needs to be delivered by twice-daily subcutaneous injection, a mode that will be unfamiliar and unattractive to many. Amylin and Eli Lilly are seeking approval for their once-weekly formulation of exenatide LAR, which was demonstrated to produce significantly improved glycemic control compared with the twice daily version with similar weight-loss effects in the long term.^[102] In early 2009, Alta Therapeutics Corp granted Amylin and Eli Lilly exclusive worldwide rights to develop transdermal exenatide using its Passport Transdermal Delivery System. A

once-daily transdermal exenatide patch is now in Phase I testing for Type 2 diabetes. The most common side effect with exenatide is nausea. In comparative studies, the incidence ranged from 33 to 57% in exenatide groups compared with 0.4–9% in patients treated with insulin analogs.^[103] In general, this side effect can be ameliorated by early dose titration and eventually mitigates with continued use. There is evidence to support the notion that the drug continues to exert its therapeutic benefits on both glycaemic control and bodyweight after side effects have subsided.^[104] In October 2007, the FDA issued an alert that acute pancreatitis should be included on exenatide's product label precautions section. This followed 30 postmarketing reports of acute pancreatitis in patients taking Byetta. Among these were 22 examples of symptomatic improvement following discontinuation of the drug, six cases where the symptoms started at the point of dose escalation, and three examples of a resurgence of symptoms after the drug was reintroduced. It has been noted that the obese, Type 2 diabetic population is at an already increased risk of developing gallstone or hypertriglyceridemia-related pancreatitis. In fact, the drug's manufacturers have reported retrospective data negating an increased incidence of pancreatitis in patients taking Byetta.^[212]

A second GLP-1 analog has recently been introduced: liraglutide (Victoza; Novo Nordisk). Liraglutide is 97% identical to the native human peptide. It is coupled to a 16-carbon fatty acid side chain, which promotes binding to albumin, thereby lengthening its half-life in a similar fashion to insulin detemir. It is argued that its 97% homology to the native human peptide reduces the drug's immunogenicity (around 40% of patients taking exenatide produce antibodies to it, although in practice this is rarely of clinical consequence). Victoza is already approved in the EU for the treatment of Type 2 diabetes, with evidence of improved glycemic control compared with exenatide and a similar weight loss profile.^[105] NovoNordisk have reported results from their 32-week open-label extension study of liraglutide in obese non-diabetic subjects following on from the 20-week, double-blind, placebo-controlled Phase II study comparing liraglutide with open-label orlistat. At 52 weeks, high-dose liraglutide led to a 5.5–6.0-kg placebo-adjusted weight loss. A total of 75% of subjects receiving high-dose liraglutide lost greater than 5% bodyweight, and 35% lost over 10%. A 10% drop-out rate owing to side effects, largely nausea, is comparable to that seen with exenatide.^[213] There was no increased incidence of pancreatitis in trial participants compared with controls. However, a slightly increased incidence of medullary thyroid tumors has been reported in two nonhuman species in clinically relevant liraglutide doses, which is worrisome.^[214]

Other long-acting GLP-1 analogs in the pipeline include lixisenatide by Zealand Pharma (currently undergoing Phase III testing^[215]); CJC-1134-PC from ConjuChem Biotechnologies Inc., which is a conjugate of exendin-4 and recombinant human albumin; albiglutide by GSK and taspoglutide by Roche. In a separate development, Emisphere have formulated orally administered PYY and GLP-1 using a sodium *N*-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) carrier. Early studies revealed that peptides delivered orally in this way are rapidly absorbed from the gastrointestinal tract and reach concentrations several-fold higher than those seen naturally postprandially. Oral GLP-1 (2-mg tablet) alone and the combination of oral GLP-1 (2-mg tablet) plus PYY_{3–36} (1-mg tablet) induced a significant reduction in calorie intake.^[216]

Oxyntomodulin

Oxyntomodulin (OXM) is a 37-amino acid cleavage product of preproglucagon. It is released from intestinal L-cells in proportion to calories ingested, with circulating levels peaking at 30 min and remaining elevated for several hours. OXM's gastrointestinal effects are to inhibit gastric secretion, gastric emptying and pancreatic exocrine secretion.^[106] When administered chronically to rodents, OXM inhibits food intake and reduces bodyweight.^[107,108] Intravenous infusion in lean human volunteers reduces appetite without increasing nausea or affecting food

palatability.^[109] Caloric intake at a subsequent buffet meal is reduced by 19%. Chronic administration over 4 weeks to healthy overweight and obese volunteers resulted in a 2.3-kg weight loss compared with 0.5-kg weight reduction in placebo-treated controls.^[110] Part of this weight loss is mediated via an increase in energy expenditure. Thrice daily subcutaneous administration of OXM to obese volunteers induced a 26% rise in activity-related energy expenditure over 4 days.^[111] This finding is supported by pair-fed rat feeding studies – where rats receiving OXM display a greater reduction in bodyweight gain than identically fed, saline-treated controls.^[112] No specific receptor has been identified for OXM. Its biological effects are thought to be mediated by the GLP-1 receptor, for which it displays a 50-fold lower binding affinity compared with GLP-1.^[113] The anorectic effects of OXM are abolished in the GLP-1 receptor knockout mouse. As expected, OXM is a less potent incretin than GLP-1, although it is equipotent at reducing food intake.^[98] This raises the possibility of interaction with other receptors or the existence of a hitherto unidentified OXM receptor in the CNS. In support of this, manganese-enhanced MRI scanning of mouse brains following the peripheral administration of OXM reveals neuronal activation in the ARC, PVN and supraoptic hypothalamic nuclei, whereas GLP-1 activates the PVN and ventromedial hypothalamus.^[114] Thiakis Ltd., a spin-out biotechnology company from Imperial College London UK, has developed TKS1225, a long-acting synthetic analog of OXM as a potential anti-obesity agent. This was recently acquired by Wyeth Pharmaceuticals, and is currently in Phase I development.^[216]

Cholecystokinin

Cholecystokinin (CCK) was the first gut hormone demonstrated to have appetite regulatory effects, acting primarily to promote meal termination rather than induce longer-term satiety, largely via the vagus nerve.^[115–117] Acute administration in both lean and obese humans reduces food intake, however there is a tendency to tachyphylaxis (an attenuation of the hormone's appetite-inhibitory effects) with repeated doses. In rats, continuous intraperitoneal infusion produces tolerance after 24 h.^[118] Acute studies in rats reveal that CCK acts to initiate early meal termination but that this is ultimately compensated for by an increase in meal frequency.^[119] GSK abandoned its CCK-1 agonist (GI 181771X) program after Phase II trials failed to produce significant weight loss, most probably owing to the development of tolerance in the chronic setting. Recent studies have suggested a synergistic weight loss effect in combination with leptin,^[120] which may reopen doors to the development of another anti-obesity therapy.

Ghrelin

Ghrelin was discovered after a search for the endogenous ligand of the GH secretagogue receptor which is widely expressed in the CNS, gastrointestinal tract, liver, pancreas, kidney and adipose tissue. Ghrelin is a 28 amino acid peptide principally secreted from the X/A-like cells of gastric oxyntic glands.^[121] A post-translational octanoylation of ghrelin's third serine residue by the enzyme ghrelin O-acyltransferase (GOAT) is essential for receptor binding.^[122] Ghrelin is the only known gut hormone that is a potent stimulator of appetite. Ghrelin secretion from the stomach correlates with hunger. Levels rise prior to meals, ultimately acting as a meal initiator, and fall afterwards in proportion to calories ingested.^[123–125] With regular meal times, ghrelin spikes become entrained. In general, plasma ghrelin levels correlate inversely with bodyweight. However, in obese humans an attenuated postprandial reduction in ghrelin has been reported.^[126] By contrast, diet-induced weight loss results in an increase in ghrelin levels, which would theoretically counter further attempts to calorie restrict and may in part explain why sustained dieting is so frequently unsuccessful. In rats, both peripheral and direct CNS administration of ghrelin acutely and potently increases food intake, and chronic administration produces weight gain.^[127,128] In healthy lean humans, intravenous infusion increases buffet meal energy intake by 28%.^[129] Ghrelin causes an upregulation of NPY and AgRP expression in the

ARC.^[130] Ablation of the ARC eliminates ghrelin's orexigenic effects.^[131] However, *c-fos* expression is also observed in the brainstem following peripheral injection of ghrelin and there is also evidence for vagal involvement, since vagotomy attenuates its appetite stimulatory effects as well.^[132] Interestingly, functional MRI studies in humans suggest that ghrelin may also modulate neuronal activity in higher brain centers which are involved in the reward processing of food, such as the orbitofrontal cortex.^[133] It remains unclear as to whether this is mediated via upward projections from the hypothalamus. In the arena of antiobesity pharmacotherapy, GHS-R1a (ghrelin receptor) antagonists have been developed which acutely reduce food intake in lean, diet-induced obese and *ob/ob* mice, and chronic administration results in weight loss in the *ob/ob* strains.^[134,135] Several pharmaceutical companies have ghrelin antagonist programs, but not all have yielded expected results. As an example, Ipsen Group's full GHS-R1a antagonist BIM-28163 actually increased food intake and bodyweight *in vivo*.^[136] Attempts to develop drugs based on the effects of ghrelin have taken a few other turns. NOXXON Pharma AG has developed spiegelmers, stable L-enantiomer RNA-based aptamers, which irreversibly bind to and deactivate octanoylated ghrelin. NOX-B11 reduced food intake in rats and the related NOX-B11-2 caused weight loss when administered chronically to diet-induced obese mice.^[137,138] Pfizer has been granted exclusive licence to take forward development of NOX-B11. Cyto Biotechnology AG created a ghrelin 'vaccine' using ghrelin immunoconjugates to induce an immune response to the endogenous peptide. Promising results in animal studies unfortunately did not translate to any weight loss in human Phase I/II trials. In the future, GOAT inhibition may provide a useful therapeutic target, since ghrelin is the only known protein to require octanoylation for receptor activity.^[139]

Five Year View

The stage is set for the continued rise in the prevalence of obesity and its associated morbidities. While lifestyle interventions at personal and societal levels are of the utmost importance, the need for better tolerated and more efficacious pharmacotherapies is undoubted. Important historical lessons have been learned from drugs designed to interact with receptors and neurotransmitters involved in the complicated circuitry of energy homeostasis and appetitive behavior, which overlap with several other higher functions, resulting in unwanted effects such as mood disturbance. A more detailed understanding of the physiological control of energy balance and the pathophysiology of obesity will continue to inform the development of highly selective, better targeted compounds. Energy homeostasis is of such critical physiological importance that there exists much redundancy and compensatory mechanisms within the system. This is compounded by the tendency to protect against weight loss much more avidly than weight gain. As more drugs become available, a polypharmacy approach, possibly alongside shifting dosing schedules, will develop to overcome these problems. This may be further aided by the greater understanding of the genetic influences on obesity, such as receptor polymorphisms, which would allow for individually tailored combinations. As natural activators of satiety circuits on a daily basis, gut hormones are likely to be an ongoing area of intense research in the field of anti-obesity drug development. There is impetus towards the realistic goal of using combination gut hormone therapy to produce a 'medical bypass' – achieving the outstanding weight loss and health benefits of gastric bypass surgery without its associated risks. Future advances in this field will include the development of long acting peptide hormone analogs to overcome the problem of the very short plasma half-life of endogenous peptide hormones, and the introduction of new forms of delivery: slow-release injectable depots, protease-resistant oral formulations, inhalation devices and transdermal patches.

Sidebar

Key Issues

- Obesity is a global health crisis associated with multiple morbidities and early mortality. There is evidence to show that weight loss will reverse such consequences and prolong life.
- A better understanding of the complex physiological systems regulating energy homeostasis is crucial for the production of more efficacious and better tolerated weight-loss drugs.
- Currently approved drugs for the long-term treatment of obesity, orlistat and sibutramine, produce only modest weight loss and a series of side effects that result in high attrition rates.
- Qnexa, Contrave and lorcaserin, all of which interact with appetitive neurotransmission in the CNS, are anti-obesity drugs currently in late-stage clinical trials.
- Gastric bypass surgery is currently the most effective long-term treatment for obesity but is risk-laden and costly. Many of the weight-loss effects of bypass have been shown to be mediated via postoperative elevations in appetite-inhibitory gut hormones. Combination therapy with anorexigenic gut hormones or their analogs in an attempt to mimic the effects of surgery is a promising approach.

References

1. Olshansky SJ, Passaro DJ, Hershow RC *et al.* A potential decline in life expectancy in the United States in the 21st Century. *N. Engl. J. Med.* 352(11), 1138–1145 (2005).
2. Dhaliwal SS, Welborn TA. Central obesity and multivariable cardiovascular risk as assessed by the Framingham prediction scores. *Am. J. Cardiol.* 103(10), 1403–1407 (2009).
3. Dyer AR, Elliott P, Shipley M. Body mass index versus height and weight in relation to blood pressure. Findings for the 10,079 persons in the INTERSALT Study. *Am. J. Epidemiol.* 131(4), 589–596 (1990).
4. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17(9), 961–969 (1994).
5. Nieves DJ, Cnop M, Retzlaff B *et al.* The atherogenic lipoprotein profile associated with obesity and insulin resistance is largely attributable to intra-abdominal fat. *Diabetes* 52(1), 172–179 (2003).
6. Field AE, Coakley EH, Must A *et al.* Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch. Intern. Med.* 161(13), 1581–1586 (2001).
7. Kopelman PG. Obesity as a medical problem. *Nature* 404(6778), 635–643 (2000).
8. Adams TD, Stroup AM, Gress RE *et al.* Cancer incidence and mortality after gastric bypass surgery. *Obesity (Silver Spring)* 17(4), 796–802 (2009).
9. Brancatisano A, Wahlroos S, Matthews S, Brancatisano R. Gastric banding for the treatment of Type 2 diabetes mellitus in morbidly obese. *Surg. Obes. Relat. Dis.* 4(3), 423–429 (2008).
10. Busetto L, Mirabelli D, Petroni ML *et al.* Comparative long-term mortality after laparoscopic adjustable gastric banding versus nonsurgical controls. *Surg. Obes. Relat. Dis.* 3(5), 496–502 (2007).
11. Sjostrom L, Narbro K, Sjostrom CD *et al.* Effects of bariatric surgery on mortality in Swedish obese subjects. *N. Engl. J. Med.* 357(8), 741–752 (2007).
12. Adams TD, Gress RE, Smith SC *et al.* Long-term mortality after gastric bypass surgery. *N. Engl. J. Med.* 357(8), 753–761 (2007).

13. Porte D Jr, Baskin DG, Schwartz MW. Leptin and insulin action in the central nervous system. *Nutr. Rev.* 60(10 Pt 2), S20–S29 (2002).
14. Levin BE. Factors promoting and ameliorating the development of obesity. *Physiol. Behav.* 86(5), 633–639 (2005).
15. Schwartz GJ. The role of gastrointestinal vagal afferents in the control of food intake: current prospects. *Nutrition* 16(10), 866–873 (2000).
16. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 404(6778), 661–671 (2000).
17. O'Rahilly S, Farooqi IS, Yeo GS, Challis BG. Minireview: human obesity-lessons from monogenic disorders. *Endocrinology* 144(9), 3757–3764 (2003).
18. Erickson JC, Clegg KE, Palmiter RD. Sensitivity to leptin and susceptibility to seizures of mice lacking neuropeptide Y. *Nature* 381(6581), 415–421 (1996).
19. Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am. J. Clin. Nutr.* 87(2), 398–404 (2008).
20. Dina C, Meyre D, Gallina S *et al.* Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat. Genet.* 39(6), 724–726 (2007).
21. Gerken T, Girard CA, Tung YC *et al.* The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science* 318(5855), 1469–1472 (2007).
22. Summerbell CD, Cameron C, Glasziou PP. WITHDRAWN: advice on low-fat diets for obesity. *Cochrane Database Syst. Rev.*(3), CD003640 (2008).
23. Shai I, Schwarzfuchs D, Henkin Y *et al.* Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N. Engl. J. Med.* 359(3), 229–241 (2008).
24. Wing RR, Tate DF, Gorin AA, Raynor HA, Fava JL. A self-regulation program for maintenance of weight loss. *N. Engl. J. Med.* 355(15), 1563–1571 (2006).
25. Weiss EC, Galuska DA, Kettel KL, Gillespie C, Serdula MK. Weight regain in U.S. adults who experienced substantial weight loss, 1999–2002. *Am. J. Prev. Med.* 33(1), 34–40 (2007).
26. Ioannides-Demos LL, Proietto J, Tonkin AM, McNeil JJ. Safety of drug therapies used for weight loss and treatment of obesity. *Drug Saf.* 29(4), 277–302 (2006).
27. Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *BMJ* 335(7631), 1194–1199 (2007).
28. Padwal R, Kezough A, Levine M, Etminan M. Long-term persistence with orlistat and sibutramine in a population-based cohort. *Int. J. Obes.(Lond.)* 31(10), 1567–1570 (2007).
29. Ledonne A, Sebastianelli L, Federici M, Bernardi G, Mercuri NB. The anorexic agents, sibutramine and fenfluramine, depress GABA(B)-induced inhibitory postsynaptic potentials in rat mesencephalic dopaminergic cells. *Br. J. Pharmacol.* 156(6), 962–969 (2009).
30. Sharma B, Henderson DC. Sibutramine: current status as an anti-obesity drug and its future perspectives. *Expert. Opin. Pharmacother.* 9(12), 2161–2173 (2008).
31. Pilkington TR, Gazet JC, Ang L, Kalucy RS, Crisp AH, Day S. Explanations for weight loss after ileojejunal bypass in gross obesity. *Br. Med. J.* 1(6024), 1504–1505 (1976).
32. Maggard MA, Shugarman LR, Suttorp M *et al.* Meta-analysis: surgical treatment of obesity. *Ann. Intern. Med.* 142(7), 547–559 (2005).
33. Le Roux CW, Welbourn R, Werling M *et al.* Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. *Ann. Surg.* 246(5), 780–785 (2007).
34. Borg CM, Le Roux CW, Ghatei MA, Bloom SR, Patel AG, Aylwin SJ. Progressive rise in gut hormone levels after Roux-en-Y gastric bypass suggests gut adaptation and explains altered satiety. *Br. J. Surg.* 93(2), 210–215 (2006).

35. Le Roux CW, Aylwin SJ, Batterham RL *et al.* Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. *Ann. Surg.* 243(1), 108–114 (2006).
36. Marsk R, Freedman J, Tynelius P, Rasmussen F, Naslund E. Antiobesity surgery in Sweden from 1980 to 2005: a population-based study with a focus on mortality. *Ann. Surg.* 248(5), 777–781 (2008).
37. Bryson A, de la MS, Dunk C. Reduction of dietary fat absorption by the novel gastrointestinal lipase inhibitor cetilistat in healthy volunteers. *Br. J. Clin. Pharmacol.* 67(3), 309–315 (2009).
38. Loftus TM, Jaworsky DE, Frehywot GL *et al.* Reduced food intake and bodyweight in mice treated with fatty acid synthase inhibitors. *Science* 288(5475), 2379–2381 (2000).
39. Thupari JN, Landree LE, Ronnett GV, Kuhajda FP. C75 increases peripheral energy utilization and fatty acid oxidation in diet-induced obesity. *Proc. Natl Acad. Sci. USA* 99(14), 9498–9502 (2002).
40. Kamisuki S, Mao Q, bu-Elheiga L *et al.* A small molecule that blocks fat synthesis by inhibiting the activation of SREBP. *Chem. Biol.* 16(8), 882–892 (2009).
41. de Kloet AD, Woods SC. Minireview: Endocannabinoids and their receptors as targets for obesity therapy. *Endocrinology* 150(6), 2531–2536 (2009).
42. Van GL, Pi-Sunyer X, Despres JP, McCarthy C, Scheen A. Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program. *Diabetes Care* 31(Suppl. 2), S229–S240 (2008).
43. Roth BL, Willins DL, Kristiansen K, Kroeze WK. 5-Hydroxytryptamine₂-family receptors (5-hydroxytryptamine_{2A}, 5-hydroxytryptamine_{2B}, 5-hydroxytryptamine_{2C}): where structure meets function. *Pharmacol. Ther.* 79(3), 231–257 (1998).
44. Thomsen WJ, Grottick AJ, Menzaghi F *et al.* Lorcaserin, a novel selective human 5-hydroxytryptamine_{2C} agonist: *in vitro* and *in vivo* pharmacological characterization. *J. Pharmacol. Exp. Ther.* 325(2), 577–587 (2008).
45. Smith BM, Smith JM, Tsai JH *et al.* Discovery and structure-activity relationship of (1R)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzazepine (lorcaserin), a selective serotonin 5-HT_{2C} receptor agonist for the treatment of obesity. *J. Med. Chem.* 51(2), 305–313 (2008).
46. Tecott LH, Sun LM, Akana SF *et al.* Eating disorder and epilepsy in mice lacking 5-HT_{2C} serotonin receptors. *Nature* 374(6522), 542–546 (1995).
47. Bray GA, Hollander P, Klein S *et al.* A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obes. Res.* 11(6), 722–733 (2003).
48. Lee MW, Fujioka K. Naltrexone for the treatment of obesity: review and update. *Expert Opin. Pharmacother.* 10(11), 1841–1845 (2009).
49. Gadde KM, Parker CB, Maner LG *et al.* Bupropion for weight loss: an investigation of efficacy and tolerability in overweight and obese women. *Obes. Res.* 9(9), 544–551 (2001).
50. Astrup A, Madsbad S, Breum L, Jensen TJ, Kroustrup JP, Larsen TM. Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial. *Lancet* 372(9653), 1906–1913 (2008).
51. Maffei M, Halaas J, Ravussin E *et al.* Leptin levels in human and rodent: measurement of plasma leptin and *ob* RNA in obese and weight-reduced subjects. *Nat. Med.* 1(11), 1155–1161 (1995).
52. Pelleymounter MA, Cullen MJ, Baker MB *et al.* Effects of the obese gene product on bodyweight regulation in *ob/ob* mice. *Science* 269(5223), 540–543 (1995).
53. Halaas JL, Gajiwala KS, Maffei M *et al.* Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* 269(5223), 543–546 (1995).

54. Halaas JL, Boozer C, Blair-West J, Fidahusein N, Denton DA, Friedman JM. Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proc. Natl Acad. Sci. USA* 94(16), 8878–8883 (1997).
55. Tartaglia LA, Dembski M, Weng X *et al.* Identification and expression cloning of a leptin receptor, OB-R. *Cell* 83(7), 1263–1271 (1995).
56. Farooqi IS, Jebb SA, Langmack G *et al.* Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N. Engl. J. Med.* 341(12), 879–884 (1999).
57. Heymsfield SB, Greenberg AS, Fujioka K *et al.* Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA* 282(16), 1568–1575 (1999).
58. Ravussin E, Smith SR, Mitchell JA *et al.* Enhanced weight loss with pramlintide/metreleptin: an integrated neurohormonal approach to obesity pharmacotherapy. *Obesity (Silver Spring)* 17(9), 1736–1743 (2009).
59. Vaisse C, Halaas JL, Horvath CM, Darnell JE Jr, Stoffel M, Friedman JM. Leptin activation of Stat3 in the hypothalamus of wild-type and *ob/ob* mice but not *db/db* mice. *Nat. Genet.* 14(1), 95–97 (1996).
60. Bjorbaek C, Elmquist JK, Frantz JD, Shoelson SE, Flier JS. Identification of SOCS-3 as a potential mediator of central leptin resistance. *Mol. Cell* 1(4), 619–625 (1998).
61. Berglund MM, Hipskind PA, Gehlert DR. Recent developments in our understanding of the physiological role of PP-fold peptide receptor subtypes. *Exp. Biol. Med. (Maywood)* 228(3), 217–244 (2003).
62. Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR. Human distribution and release of a putative new gut hormone, peptide YY. *Gastroenterology* 89(5), 1070–1077 (1985).
63. Batterham RL, Cowley MA, Small CJ *et al.* Gut hormone PYY(3–36) physiologically inhibits food intake. *Nature* 418(6898), 650–654 (2002).
64. Batterham RL, Cohen MA, Ellis SM *et al.* Inhibition of food intake in obese subjects by peptide YY3–36. *N. Engl. J. Med.* 349(10), 941–948 (2003).
65. Le Roux CW, Batterham RL, Aylwin SJ *et al.* Attenuated peptide YY release in obese subjects is associated with reduced satiety. *Endocrinology* 147(1), 3–8 (2006).
66. Guo Y, Ma L, Enriori PJ *et al.* Physiological evidence for the involvement of peptide YY in the regulation of energy homeostasis in humans. *Obesity (Silver. Spring)* 14(9), 1562–1570 (2006).
67. Adrian TE, Savage AP, Bacarese-Hamilton AJ, Wolfe K, Besterman HS, Bloom SR. Peptide YY abnormalities in gastrointestinal diseases. *Gastroenterology* 90(2), 379–384 (1986).
68. Adrian TE, Savage AP, Fuessl HS, Wolfe K, Besterman HS, Bloom SR. Release of peptide YY (PYY) after resection of small bowel, colon, or pancreas in man. *Surgery* 101(6), 715–719 (1987).
69. Batterham RL, Heffron H, Kapoor S *et al.* Critical role for peptide YY in protein-mediated satiation and body-weight regulation. *Cell Metab.* 4(3), 223–233 (2006).
70. Challis BG, Pinnock SB, Coll AP, Carter RN, Dickson SL, O'Rahilly S. Acute effects of PYY3–36 on food intake and hypothalamic neuropeptide expression in the mouse. *Biochem. Biophys. Res. Commun.* 311(4), 915–919 (2003).
71. Vincent RP, Le Roux CW. The satiety hormone peptide YY as a regulator of appetite. *J. Clin. Pathol.* 61(5), 548–552 (2008).
72. Heilig M. The NPY system in stress, anxiety and depression. *Neuropeptides* 38(4), 213–224 (2004).
73. Gantz I, Erondou N, Mallick M *et al.* Efficacy and safety of intranasal peptide YY3–36 for weight reduction in obese adults. *J. Clin. Endocrinol. Metab.* 92(5), 1754–1757 (2007).

74. Batterham RL, Ffytche DH, Rosenthal JM *et al.* PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. *Nature* 450(7166), 106–109 (2007).
75. Kuo LE, Kitlinska JB, Tilan JU *et al.* Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome. *Nat. Med.* 13(7), 803–811 (2007).
76. Track NS, McLeod RS, Mee AV. Human pancreatic polypeptide: studies of fasting and postprandial plasma concentrations. *Can. J. Physiol. Pharmacol.* 58(12), 1484–1489 (1980).
77. Asakawa A, Inui A, Ueno N, Fujimiya M, Fujino MA, Kasuga M. Mouse pancreatic polypeptide modulates food intake, while not influencing anxiety in mice. *Peptides* 20(12), 1445–1448 (1999).
78. Asakawa A, Inui A, Yuzuriha H *et al.* Characterization of the effects of pancreatic polypeptide in the regulation of energy balance. *Gastroenterology* 124(5), 1325–1336 (2003).
79. Liu YL, Semjonous NM, Murphy KG, Ghatei MA, Bloom SR. The effects of pancreatic polypeptide on locomotor activity and food intake in mice. *Int. J. Obes. (Lond.)* 32(11), 1712–1715 (2008).
80. Ueno N, Inui A, Iwamoto M *et al.* Decreased food intake and bodyweight in pancreatic polypeptide-overexpressing mice. *Gastroenterology* 117(6), 1427–1432 (1999).
81. Batterham RL, Le Roux CW, Cohen MA *et al.* Pancreatic polypeptide reduces appetite and food intake in humans. *J. Clin. Endocrinol. Metab.* 88(8), 3989–3992 (2003).
82. McTigue DM, Hermann GE, Rogers RC. Effect of pancreatic polypeptide on rat dorsal vagal complex neurons. *J. Physiol.* 499(Pt 2), 475–483 (1997).
83. Dumont Y, Moyse E, Fournier A, Quirion R. Distribution of peripherally injected peptide YY ([¹²⁵I] PYY (3–36)) and pancreatic polypeptide ([¹²⁵I] hPP) in the CNS: enrichment in the area postrema. *J. Mol. Neurosci.* 33(3), 294–304 (2007).
84. Butler PC, Chou J, Carter WB *et al.* Effects of meal ingestion on plasma amylin concentration in NIDDM and nondiabetic humans. *Diabetes* 39(6), 752–756 (1990).
85. Silvestre RA, Rodriguez-Gallardo J, Jodka C *et al.* Selective amylin inhibition of the glucagon response to arginine is extrinsic to the pancreas. *Am. J. Physiol. Endocrinol. Metab.* 280(3), E443–E449 (2001).
86. Young AA, Gedulin BR, Rink TJ. Dose-responses for the slowing of gastric emptying in a rodent model by glucagon-like peptide (7–36) NH₂, amylin, cholecystokinin, and other possible regulators of nutrient uptake. *Metabolism* 45(1), 1–3 (1996).
87. Chen WJ, Armour S, Way J *et al.* Expression cloning and receptor pharmacology of human calcitonin receptors from MCF-7 cells and their relationship to amylin receptors. *Mol. Pharmacol.* 52(6), 1164–1175 (1997).
88. Aronne L, Fujioka K, Aroda V *et al.* Progressive reduction in bodyweight after treatment with the amylin analog pramlintide in obese subjects: a Phase 2, randomized, placebo-controlled, dose-escalation study. *J. Clin. Endocrinol. Metab.* 92(8), 2977–2983 (2007).
89. Lutz TA, Mollet A, Rushing PA, Riediger T, Scharrer E. The anorectic effect of a chronic peripheral infusion of amylin is abolished in area postrema/nucleus of the solitary tract (AP/NTS) lesioned rats. *Int. J. Obes. Relat Metab Disord.* 25(7), 1005–1011 (2001).
90. Mollet A, Gilg S, Riediger T, Lutz TA. Infusion of the amylin antagonist AC 187 into the area postrema increases food intake in rats. *Physiol. Behav.* 81(1), 149–155 (2004).
91. Smith SR, Aronne LJ, Burns CM, Kestey NC, Halseth AE, Weyer C. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care* 31(9), 1816–1823 (2008).

92. Trevaskis JL, Lei C, Koda JE, Weyer C, Parkes DG, Roth JD. Interaction of leptin and amylin in the long-term maintenance of weight loss in diet-induced obese rats. *Obesity (Silver Spring)* DOI:10.1038/oby.2009.187 (2009) (Epub ahead of print).
93. Turton MD, O'Shea D, Gunn I *et al.* A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* 379(6560), 69–72 (1996).
94. Gallwitz B, Schmidt WE. [GLP-1 receptor gen 'knock out' causes glucose intolerance, but no alterations of eating behavior]. *Z. Gastroenterology* 35(8), 655–658 (1997).
95. Meeran K, O'Shea D, Edwards CM *et al.* Repeated intracerebroventricular administration of glucagon-like peptide-1-(7–36) amide or exendin-(9–39) alters bodyweight in the rat. *Endocrinology* 140(1), 244–250 (1999).
96. Verdich C, Flint A, Gutzwiller JP *et al.* A meta-analysis of the effect of glucagon-like peptide-1 (7–36) amide on ad libitum energy intake in humans. *J. Clin. Endocrinol. Metab.* 86(9), 4382–4389 (2001).
97. Naslund E, King N, Mansten S *et al.* Prandial subcutaneous injections of glucagon-like peptide-1 cause weight loss in obese human subjects. *Br. J. Nutr.* 91(3), 439–446 (2004).
98. Baggio LL, Huang Q, Brown TJ, Drucker DJ. Oxyntomodulin and glucagon-like peptide-1 differentially regulate murine food intake and energy expenditure. *Gastroenterology* 127(2), 546–558 (2004).
99. Abbott CR, Monteiro M, Small CJ *et al.* The inhibitory effects of peripheral administration of peptide YY(3–36) and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal-brainstem-hypothalamic pathway. *Brain Res.* 1044(1), 127–131 (2005).
100. Kieffer TJ, McIntosh CH, Pederson RA. Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 *in vitro* and *in vivo* by dipeptidyl peptidase IV. *Endocrinology* 136(8), 3585–3596 (1995).
101. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in Type 2 diabetes: systematic review and meta-analysis. *JAMA* 298(2), 194–206 (2007).
102. Kim D, MacConell L, Zhuang D *et al.* Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and bodyweight in subjects with Type 2 diabetes. *Diabetes Care* 30(6), 1487–1493 (2007).
103. Barnett AH, Burger J, Johns D *et al.* Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with Type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. *Clin. Ther.* 29(11), 2333–2348 (2007).
104. Ratner RE, Maggs D, Nielsen LL *et al.* Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with Type 2 diabetes mellitus. *Diabetes Obes. Metab.* 8(4), 419–428 (2006).
105. Buse JB, Rosenstock J, Sesti G *et al.* Liraglutide once a day versus exenatide twice a day for Type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 374(9683), 39–47 (2009).
106. Stanley S, Wynne K, Bloom S. Gastrointestinal satiety signals III. Glucagon-like peptide 1, oxyntomodulin, peptide YY, and pancreatic polypeptide. *Am. J. Physiol. Gastrointest. Liver Physiol.* 286(5), G693-G697 (2004).
107. Dakin CL, Gunn I, Small CJ *et al.* Oxyntomodulin inhibits food intake in the rat. *Endocrinology* 142(10), 4244–4250 (2001).
108. Dakin CL, Small CJ, Batterham RL *et al.* Peripheral oxyntomodulin reduces food intake and bodyweight gain in rats. *Endocrinology* 145(6), 2687–2695 (2004).
109. Cohen MA, Ellis SM, Le Roux CW *et al.* Oxyntomodulin suppresses appetite and reduces food intake in humans. *J. Clin. Endocrinol. Metab.* 88(10), 4696–4701 (2003).

110. Wynne K, Park AJ, Small CJ *et al.* Subcutaneous oxyntomodulin reduces bodyweight in overweight and obese subjects: a double-blind, randomized, controlled trial. *Diabetes* 54(8), 2390–2395 (2005).
111. Wynne K, Park AJ, Small CJ *et al.* Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised controlled trial. *Int. J. Obes. (Lond.)* 30(12), 1729–1736 (2006).
112. Dakin CL, Small CJ, Park AJ, Seth A, Ghatei MA, Bloom SR. Repeated ICV administration of oxyntomodulin causes a greater reduction in bodyweight gain than in pair-fed rats. *Am. J. Physiol. Endocrinol. Metab.* 283(6), E1173–E1177 (2002).
113. Fehmman HC, Jiang J, Schweinfurth J, Wheeler MB, Boyd AE, III, Goke B. Stable expression of the rat GLP-I receptor in CHO cells: activation and binding characteristics utilizing GLP-I(7–36)-amide, oxyntomodulin, exendin-4, and exendin(9–39). *Peptides* 15(3), 453–456 (1994).
114. Chaudhri OB, Parkinson JR, Kuo YT *et al.* Differential hypothalamic neuronal activation following peripheral injection of GLP-1 and oxyntomodulin in mice detected by manganese-enhanced magnetic resonance imaging. *Biochem. Biophys. Res. Commun.* 350(2), 298–306 (2006).
115. Pi-Sunyer X, Kissileff HR, Thornton J, Smith GP. C-terminal octapeptide of cholecystokinin decreases food intake in obese men. *Physiol. Behav.* 29(4), 627–630 (1982).
116. Lieveise RJ, Jansen JB, Masclee AM, Lamers CB. Satiety effects of cholecystokinin in humans. *Gastroenterology* 106(6), 1451–1454 (1994).
117. Lieveise RJ, Jansen JB, Masclee AA, Lamers CB. Satiety effects of a physiological dose of cholecystokinin in humans. *Gut* 36(2), 176–179 (1995).
118. Crawley JN, Beinfeld MC. Rapid development of tolerance to the behavioural actions of cholecystokinin. *Nature* 302(5910), 703–706 (1983).
119. West DB, Fey D, Woods SC. Cholecystokinin persistently suppresses meal size but not food intake in free-feeding rats. *Am. J. Physiol.* 246(5 Pt 2), R776–R787 (1984).
120. Matson CA, Reid DF, Cannon TA, Ritter RC. Cholecystokinin and leptin act synergistically to reduce bodyweight. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 278(4), R882–R890 (2000).
121. Date Y, Kojima M, Hosoda H *et al.* Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology* 141(11), 4255–4261 (2000).
122. Yang J, Brown MS, Liang G, Grishin NV, Goldstein JL. Identification of the acyltransferase that octanoylates ghrelin, an appetite-stimulating peptide hormone. *Cell* 132(3), 387–396 (2008).
123. Tschop M, Wawarta R, Riepl RL *et al.* Post-prandial decrease of circulating human ghrelin levels. *J. Endocrinol. Invest.* 24(6), RC19–RC21 (2001).
124. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes* 50(8), 1714–1719 (2001).
125. Cummings DE, Frayo RS, Marmonier C, Aubert R, Chapelot D. Plasma ghrelin levels and hunger scores in humans initiating meals voluntarily without time- and food-related cues. *Am. J. Physiol. Endocrinol. Metab.* 287(2), E297–E304 (2004).
126. Tschop M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. *Diabetes* 50(4), 707–709 (2001).
127. Wren AM, Small CJ, Ward HL *et al.* The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. *Endocrinology* 141(11), 4325–4328 (2000).

128. Wren AM, Small CJ, Abbott CR *et al.* Ghrelin causes hyperphagia and obesity in rats. *Diabetes* 50(11), 2540–2547 (2001).
129. Wren AM, Seal LJ, Cohen MA *et al.* Ghrelin enhances appetite and increases food intake in humans. *J. Clin. Endocrinol. Metab.* 86(12), 5992 (2001).
130. Kamegai J, Tamura H, Shimizu T, Ishii S, Sugihara H, Wakabayashi I. Chronic central infusion of ghrelin increases hypothalamic neuropeptide Y and Agouti-related protein mRNA levels and bodyweight in rats. *Diabetes* 50(11), 2438–2443 (2001).
131. Tamura H, Kamegai J, Shimizu T, Ishii S, Sugihara H, Oikawa S. Ghrelin stimulates GH but not food intake in arcuate nucleus ablated rats. *Endocrinology* 143(9), 3268–3275 (2002).
132. Williams DL, Grill HJ, Cummings DE, Kaplan JM. Vagotomy dissociates short- and long-term controls of circulating ghrelin. *Endocrinology* 144(12), 5184–5187 (2003).
133. Malik S, McGlone F, Bedrossian D, Dagher A. Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metab.* 7(5), 400–409 (2008).
134. Asakawa A, Inui A, Kaga T *et al.* Antagonism of ghrelin receptor reduces food intake and bodyweight gain in mice. *Gut* 52(7), 947–952 (2003).
135. Beck B, Richy S, Stricker-Krongrad A. Feeding response to ghrelin agonist and antagonist in lean and obese Zucker rats. *Life Sci.* 76(4), 473–478 (2004).
136. Halem HA, Taylor JE, Dong JZ *et al.* A novel growth hormone secretagogue-1a receptor antagonist that blocks ghrelin-induced growth hormone secretion but induces increased bodyweight gain. *Neuroendocrinology* 81(5), 339–349 (2005).
137. Kobelt P, Helmling S, Stengel A *et al.* Anti-ghrelin Spiegelmer NOX-B11 inhibits neurostimulatory and orexigenic effects of peripheral ghrelin in rats. *Gut* 55(6), 788–792 (2006).
138. Shearman LP, Wang SP, Helmling S *et al.* Ghrelin neutralization by a ribonucleic acid-SPM ameliorates obesity in diet-induced obese mice. *Endocrinology* 147(3), 1517–1526 (2006).
139. Yang J, Zhao TJ, Goldstein JL, Brown MS. Inhibition of ghrelin O-acyltransferase (GOAT) by octanoylated pentapeptides. *Proc. Natl Acad. Sci. USA* 105(31), 10750–10755 (2008).

Websites

201. World Health Organisation factsheet number 311 – obesity and overweight
www.who.int/mediacentre/factsheets/fs311/en/index.html
202. Datamonitor's pipeline & commercial insight. Obesity: still a tough nut to crack
www.datamonitor.com/store/news/obesity_still_a_tough_nut_to_crack?productid=82C897C3-D425-4684-A8FC-0C080B472886
203. US FDA. Orlistat (marketed as Alli and Xenical): early communication about an ongoing safety review, updated 24 August 2009
www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm180025.htm
204. US Food and Drug Administration Early Communication about an Ongoing Safety Review of Meridia (sibutramine hydrochloride) Link. (Accessed November 2009).
205. Smith SR, Weissman NJ, Stubbe S, Anderson CM, Shanahan W. Lorcaserin reduces bodyweight in obese and overweight subjects: behavioral modification and lorcaserin for overweight and obesity management, the BLOOM trial. *American Diabetes Association's 69th Scientific Sessions*. New Orleans, LA, USA, June 5–9, 2009
www.aievolution.com/ada0901/index.cfm?do=abs.viewAbs&abs=7912
206. Vivus Pharmaceuticals: results from Phase 3 EQUATE trial of VIVUS' Qnexa highlighted at European Congress on Obesity
<http://ir.vivus.com/releasedetail.cfm?ReleaseID=382339>

207. Orexigen Therapeutics: Orexigen[®] Therapeutics presents additional NB-302 Contrave[®] data at *American Diabetes Association (ADA) 69th Scientific Sessions* <http://ir.orexigen.com/phoenix.zhtml?c=207034&p=irol-newsArticle&ID=1296807&highlight>
208. MDRNA: MDRNA announces Phase 2 trial of PYY(3–36) does not meet weight loss endpoint <http://phx.corporate-ir.net/phoenix.zhtml?c=83674&p=irol-newsArticle&ID=1182214&highlight>
- 7TM Pharma: TM30339 www.7tm.com/R-D/Metabolic_Disorders/TM30339.aspx
209. 7TM Pharma: obinepitide www.7tm.com/R-D/Metabolic_Disorders/Obinepitide.aspx
210. The Endocrine Society. Exenatide promotes weight loss when added to diet and exercise. *ScienceDaily* 11 June 2009
www.sciencedaily.com/releases/2009/06/090611112555.htm
211. Eli Lilly and Co Pharmaceuticals: interim study results presented at ADA 2009: exenatide not associated with increased rate of acute pancreatitis compared to other antidiabetic drugs <http://newsroom.lilly.com/releasedetail.cfm?ReleaseID=388389>
212. Novo Nordisk: Significant weight loss sustained in obese people treated with liraglutide for one year www.novonordisk.com/science/pipeline/liraglutide-press-releases.asp
213. Endocrine today newsletter: FDA vote split for liraglutide use in patients with Type 2 diabetes www.endocrinetoday.com/view.aspx?rid=38572
214. Zealand Pharma product pipeline www.zp.dk/%7BD566D263-F216-4A37-A38F-8C33A4ECC4E0%7D
215. Emisphere Technologies: oral GLP-1, GLP-1 analogues and combined PYY and GLP-1 for Type 2 diabetes www.emisphere.com/oral_GLP-1.html
216. Wyeth Pharmaceuticals acquires thiakis Limited (December 2008): acquires portfolio of synthetic oxyntomodulin peptides, including early clinical candidate for medical obesity
www.wyeth.com/news?nav=display&navTo=/wyeth_html/home/news/pressreleases/2009/1229603323725.html

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