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Gut hormones: the future of obesity treatment?

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Obesity is a major worldwide health problem. The treatment options are severely limited. The development of novel anti-obesity drugs is fraught with efficacy and safety issues. Consequently, several investigational anti-obesity drugs have failed to gain marketing approval in recent years. Anorectic gut hormones offer a potentially safe and viable option for the treatment of obesity. The prospective utility of gut hormones has improved drastically in recent years with the development of longer acting analogues. Additionally, specific combinations of gut hormones have been demonstrated to have additive anorectic effects. This article reviews the current stage of anti-obesity drugs in development, focusing on gut hormone-based therapies.

Introduction

Obesity is a leading cause of preventable mortality worldwide. Current strategies for obesity management include lifestyle changes, pharmacological intervention and bariatric surgery. Bariatric surgical procedures most successfully achieve sustained weight loss. However, due to the expensive and highly invasive nature of these procedures, they are generally only available to the morbidly obese. In England, approximately 2% of the population is morbidly obese (BMI > 40 kg m^{-2}) but a further 60% is considered to be overweight or obese (BMI 25–40 kg m^{-2}) [1]. For the majority of the overweight population the only options are therefore pharmacological and/or lifestyle interventions. However, long term compliance with such interventions is low and the efficacy of currently available drugs is limited, leading to relatively low successful treatment rates [2].

Pharmacotherapy for obesity is limited by efficacy and safety issues. Orlistat, a gastric and pancreatic lipase inhibitor, is the only prescription medicine for obesity currently licensed in the UK. The European Medicines Agency (EMEA) and the Food and Drugs Administration (FDA) currently recommend that for a new anti-obesity drug to be approved it should result in a statistically significant placebo adjusted weight loss of greater than 5% at the end of a 12 month period. Less than 30% of patients on Orlistat achieve this magnitude of weight loss [3]. More effective pharmacotherapy is therefore urgently needed. Analysis of certain drugs in development have demonstrated improved efficacy. The SEQUEL study of Qnexa® (a combination of the anticonvulsant topiramate, a weak carbonic anhydrase inhibitor, and the appetite suppressant phentermine, an amphetamine derivative) reports 79% of treated patients achieving >5% weight loss [4]. However, the development of novel drug treatments is also burdened with safety concerns. A number of investigational drugs that are in late phase clinical trials, including Qnexa®, and also Contrave® and lorcaserin, have recently failed to gain marketing approval because of such concerns [5–7]. The ability to predict efficacy and potential side effects and the frequency with which such side effects occur are consequently major hurdles to the development of novel anti-obesity drugs.

Animal models have proven useful in the study of obesity and the identification of novel anti-obesity drug targets. Drug-induced weight loss in such models commonly reflects effects in humans. However, their ability to predict potential side effects remains in question. Some of the most common side effects associated with previous and putative anti-obesity drugs are nausea, cardiovascular events and psychological sequelae [8]. Unlike humans, rodents lack an emetic response. Consequently, strategies

such as behavioural studies, measuring pica, conditioned taste aversion or conditioned gaping have to be used to evaluate potential drug induced nausea in pre-clinical studies in rodents [8, 9]. However, it is unclear how predictive the results of these tests are of the effects in humans. To help predict potential cardiovascular side effects in the clinic, the application of radio-telemetry technology to assess comprehensively changes in cardiovascular parameters, such as blood pressure, heart rate and electrical activity, during pre-clinical drug assessment can be utilized. Psychological side effects are possibly the most difficult to evaluate pre-clinically, although tests such as the forced swim test can be employed to help evaluate potential depression-like side effects (similar to those that resulted in the recent market withdrawal of rimonabant) [10]. In addition, both cardiovascular and psychological side effects tend to develop after chronic treatment and can therefore be difficult to identify during pre-clinical testing.

The history of the obesity drug market suggests that greater emphasis on investigating potential side effects is required in the early pre-clinical stages of drug development. Recent research has identified a number of potentially safer targets. This article focuses on anti-obesity drugs currently in development and, in particular, the potential utility of gut hormones as anti-obesity agents.

Anti-obesity drugs currently in late phase development

The extent of the obesity problem and the lack of licensed pharmacotherapies have created a large potential market for the development of new treatment options. Consequently, there are currently a number of drugs for obesity in late stage development (summarized in Table 1). However approval for some of these agents has been delayed due to safety concerns.

Qnexa®

Qnexa® is an investigational, once daily, oral, controlled release combination therapy. It consists of topiramate, a drug originally approved for migraine prophylaxis and used as an anti-convulsant which demonstrated unexpected weight loss as a side effect [11], and phentermine, an amphetamine derivative which has been available in the US for more than 30 years as a short term treatment for obesity. Developed by Vivus Inc, Qnexa® has undergone multiple phase III trials demonstrating weight loss that meets the criteria set forth by the FDA for a novel anti-obesity drug [4]. The FDA stated associations with an elevated heart rate and potential teratogenic effects [5], as reasoning for non-approval of a New Drug Application (NDA) for Qnexa® submitted in December 2009. In October 2011, Vivus submitted a NDA for Qnexa® to the FDA seeking approval for an initial indication for the treatment of obesity, with a contraindication for women of childbearing potential [12]. The FDA Endocrinologic and Metabolic Drugs Advisory Committee have since recommended Qnexa® be granted marketing approval by the FDA for the treatment of obesity in adults [13].

Contrave®

Contrave® is a controlled release combination therapy of bupropion, an inhibitor of dopamine and norepinephrine

Table 1

Anti-obesity drugs in late phase development

Drug	Target	Status
Qnexa® (topiramate and phentermine) Vivus	Carbonic anhydrase inhibitor, Sympathomimetic agent	FDA complete response letter received. Concerns over elevated heart rate and teratogenic potential. NDA submitted in October 2011 seeking approval for reduced market population.
Contrave® (bupropion and naltrexone) Orexigen Therapeutics Inc	Dopamine and norepinephrine re-uptake inhibitor, μ-opioid antagonist	FDA complete response letter received. Concerns over long term cardiovascular risk. Further trials in the pipeline
Lorcaserin Arena Pharmaceuticals	5-HT2C receptor agonist	FDA complete response letter received. Concerns over efficacy and safety: carcinogenicity and valvulopathy. Further trials on going
Liraglutide Novo Nordisk	GLP-1 analogue	Phase III clinical trials
Cetilistat Norgine B.V.	Pancreatic lipase inhibitor	Phase III clinical trials
Empatic® (zonisamide and bupropion) Orexigen Therapeutics Inc.	Anti-epileptic, dopamine and norepinephrine re-uptake inhibitor	Phase II clinical trials
Pramlinitide/Metreleptin Amylin Pharmaceuticals	Amylin analogue and leptin analogue	Phase II clinical trials
Velneperit Shionogi & Co. Ltd	NPY5R antagonist	Phase II clinical trials
Tesofensine NeuroSearch A/S	Triple monoamine re-uptake inhibitor: serotonin, dopamine and norepinephrine	Phase II clinical trials
Obinepitide 7TM Pharma	PP and PYY_{3-36} analogues	Phase II clinical trials

re-uptake, and naltrexone, a μ-opioid antagonist. Developed by Orexigen Therapeutics Inc, Contrave® has completed a number of phase III trials successfully demonstrating appropriate efficacy [14]. However its approval has been prevented by cardiovascular safety concerns [6]. In September 2011, Orexigen announced that following a meeting with FDA's Office of New Drugs, a suitable cardiovascular outcomes trial that would address these concerns is feasible and likely forthcoming [15]. A Special Protocol Assessment (SPA) for the Contrave® outcomes trial was agreed with the FDA in January 2012. Initiation of this outcomes trial is imminent [16].

Lorcaserin

Lorcaserin is a selective 5-HT_{2C} receptor agonist developed by Arena Pharmaceuticals. In September 2010, an FDA advisory panel voted to recommend against granting approval to market the drug based on concerns regarding both efficacy and safety [7]. In phase III trials lorcaserin demonstrated only a 3.1% placebo adjusted weight loss. There are also concerns regarding unexplained pre-clinical carcinogenicity signals and rates of valvulopathy in rats. The carcinogenicity of lorcaserin has since been reviewed by Arena and an increased incidence of malignant tumours was only associated with doses greater than those demonstrated to reduce significantly food intake [17, 18]. Phase III trials are continuing. Another 5-HT_{2C} receptor agonist is also being developed by Proximagen Group plc for the treatment of obesity and is currently in phase II trials.

It seems likely that Qnexa®, Contrave® and lorcaserin will eventually be approved, and thus that more efficacious drugs are on the horizon. However, the development of safe drugs remains the biggest hurdle in the anti-obesity drug market.

The utility of gut hormones as anti-obesity drugs

Anorectic gut hormones such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and oxyntomodulin (OXM) are released from intestinal L-cells in response to the ingestion of nutrients and act on central appetite centres to control eating [19]. In states of obesity, endogenous production of gut hormones is insufficient to maintain energy homeostasis and thus a suitable intervention is required. It is widely acknowledged that obese patients do not respond successfully to exogenous leptin therapy, and that this is likely due to a saturable transport mechanism that is already at capacity in many obese individuals [20–22]. However, the obese do maintain their sensitivity to anorectic gut hormones [23–26]. Unlike many past and present treatment strategies, gut hormones are an important component of the physiological systems regulating appetite and lack severe adverse side effects, thus making them an attractive target for the treatment of obesity.

Glucagon-like peptide-1

GLP-1 is a 30 amino acid peptide produced by post translational enzymatic cleavage of the pre-proglucagon gene product, and is released from enteroendocrine L-cells in response to nutrient ingestion. Its biological activities include the stimulation of glucose-dependent insulin secretion and the inhibition of glucagon secretion, gastric emptying and food intake [27]. $GLP\text{-}1_{7–36}$ is the major circulating bioactive form of GLP-1. GLP-1 treatment robustly reduces acute food intake in animals and man [28–30]. However, like other pre-proglucagon gene products, GLP-1 has a short half-life *in vivo* due to enzymatic degradation by dipeptidyl peptidase-IV (DPP-IV) [31, 32]. Exogenous GLP-1 dosing is therefore not an ideal pharmacotherapy.

The incretin effects of GLP-1 have formed the basis of a number of anti-diabetic drugs. Two long acting GLP-1 analogues, exenatide and liraglutide, are widely used for the treatment of type II diabetes. In clinical trials both induced similar weight loss. However liraglutide appears to be better tolerated by patients and thus may be a more viable treatment option for weight management [33]. Liraglutide, developed by Novo Nordisk, is an acylated analogue of human GLP-1, with a considerably extended half-life *in vivo*. It was approved for clinical use in Europe in 2009 and in the USA in 2010 as a treatment for type II diabetes. Liraglutide is currently undergoing phase III clinical trials as an anti-obesity therapy [34].

However, safety concerns have arisen from post marketing surveillance of GLP-1 analogues which may impede their development as anti-obesity therapies. These include an apparent increased incidence of acute pancreatitis in patients treated with exenatide or liraglutide compared with other treatment strategies for type II diabetes [35, 36]. In contrast, rodent models provide no evidence of such an effect [37, 38]. Furthermore, rodent studies have suggested that liraglutide causes dose-dependent and treatment duration-dependent thyroid C-cell hyperplasia and tumours [39]. However, 2 year treatment with liraglutide in humans has not resulted in any increase in clinical signs of C-cell hyperplasia or tumours, as assessed by circulating concentrations of calcitonin [40]. These studies suggest potential inter-species differences, an obvious limitation of the use of animal models in the development of pharmacotherapies for human obesity. An additional concern is the development of treatment specific antibodies. Suitability for lifetime use is an advantageous property of any anti-obesity drug. Should treatment induce an immune response, this would limit the drug's long term efficacy and safety profile. Liraglutide is associated with a reduced frequency and lower levels of treatment-associated antibodies compared with exenatide [41], which is predicted to make it a safer and more efficacious option for development as an anti-obesity drug.

Oxyntomodulin

Oxyntomodulin (OXM), a 37-amino acid peptide secreted from L-cells, is another pre-proglucagon product demonstrated to reduce food intake in animal models and in humans [24, 42–46]. In comparison with other exogenously administered gut hormone peptides, OXM is thought to have a lower incidence of treatment-associated nausea [45, 47]. No OXM specific receptor has been identified to date. OXM has weak affinity for the glucagon receptor (GCGR) and also binds to the glucagon-like peptide-1 receptor (GLP-1R), though at a much lower affinity than GLP-1. In mice, the anorectic effect of OXM is blocked by the GLP-1R antagonist exendin$_{9-39}$ and is absent in GLP-1R knockout models but not in GCGR knockout models. The anorectic effects of OXM are thus thought to be mediated primarily through GLP-1R [44]. Despite its relatively weak affinity for GLP-1R, OXM has a more potent anorectic effect in acute food intake studies compared with GLP-1 at similar doses [48] and is thus a strong target for obesity therapeutics.

Oxyntomodulin has a short circulating half-life due to breakdown by DPP-IV and/or neutral endopeptidases (NEP), thus limiting the utility of the exogenous molecule as an anti-obesity agent. The *in vivo* bioactivity of OXM is increased by inhibitors of DPP-IV [49]. Furthermore, NH_2-terminal modification of proglucagon-derived peptides, such as OXM and GLP-1, can reduce their susceptibility to enzymatic degradation by DPP-IV and extend their efficacy *in vivo* [49–51]. OXM bioactivity can also be prolonged by the substitution of short amino acid sequences in the mid-section and octapeptide junction regions that reduce its susceptibility to NEP degradation. Moreover, acylation of the OXM C-terminal may improve bioactivity by increasing peptide binding to albumin, thereby impairing degradation and clearance [49]. It has been suggested that OXM stimulates energy expenditure via the glucagon receptor [46]. A study in diet-induced obese mice comparing the effects of a long-acting protease resistant dual GLP-1R/GCGR agonist and a selective GLP-1R agonist, with matched potency and pharmacokinetics, demonstrated that the dual agonist was the more effective anti-obesity agent [52]. Utilizing the mechanisms by which OXM exerts its effects on appetite and energy expenditure may thus be a promising approach for the development of novel anti-obesity drugs. Additionally, a long acting OXM analogue, OAP-189 (formally TKS1225), is currently in phase I clinical trials with Pfizer as a treatment for obesity [53].

Peptide tyrosine tyrosine

Peptide tyrosine tyrosine (PYY), a member of the PP-fold family of peptides, is secreted from intestinal L-cells in response to food ingestion. Two major forms are found in the circulation, PYY$_{1-36}$ and a truncated form, PYY$_{3-36}$ [54], produced by enzymatic cleavage of PYY$_{1-36}$ by DPP-IV [55]. PYY$_{1-36}$ has agonist activity at Y_1, Y_2 and Y_5 receptors, whereas PYY$_{3-36}$ is a selective Y_2 receptor agonist. There is little evidence to suggest PYY$_{1-36}$ has a role in energy intake [56] but PYY$_{3-36}$ is widely accepted as an anorexigenic hormone that can reduce food intake in lean and obese animals and in humans [23, 57–62].

The utility of exogenous PYY$_{3-36}$ as a treatment for obesity is limited by its rapid metabolism [63]. Furthermore, the supraphysiological doses likely required for periodic administration of PYY$_{3-36}$ to reduce food intake are associated with nausea [64]. As with GLP-1 and OXM, long-acting PYY$_{3-36}$ analogues may be more useful than the endogenous molecule. The mechanisms by which PYY$_{3-36}$ is rapidly degraded are not fully characterized. However, endopeptidases have been implicated in the degradation of PYY$_{1-36}$ [65], and thus similar mechanisms may be involved in the degradation of PYY$_{3-36}$. It is likely that metalloendopeptidases such as meprin β are involved in the degradation of PYY$_{3-36}$. Meprin β is proposed to cleave PYY$_{3-36}$ at the conserved sites, Glu_{10}-Asp_{11}, Asp_{11}-Ala_{12} and Ala_{12}-Ser_{13}. Co-administration of PYY$_{3-36}$ and actinonin, an inhibitor of meprin β, to mice prolongs its anorectic effects [66]. Alternative strategies to prolong the anorectic actions of PYY$_{3-36}$ have been investigated, including the use of polyethylene glycol (PEG)ylated conjugates and reversible PEGylation [67–69]. The latter method involved coupling PYY$_{3-36}$ to a 40 kDa PEG group via a spontaneously cleavable linker which was gradually hydrolyzed, releasing unmodified PYY$_{3-36}$ into the circulation. This type of modification avoids the need for repeat administrations or supraphysiological dosing and has been shown to induce a similar reduction in food intake in mice to that seen when PYY$_{3-36}$ is continuously infused [69].

Pancreatic polypeptide

Pancreatic polypeptide (PP), another member of the PP-fold family of peptides, is secreted postprandially from pancreatic islet PP cells. It has a high affinity for the Y_4 receptor, via which it is thought to reduce food intake [70]. Peripheral administration of PP in rodents and humans reduces food intake [71–73]. However, PP also has a short half-life *in vivo*, limiting its potential as a treatment for obesity.

Longer acting PP analogues have been synthesized and have shown therapeutic promise. Lipidation of human PP (hPP) with palmitic acid increases its anorectic efficacy in mice [74]. PP 1420 is a peptidase resistant analogue of hPP, shown in phase I clinical trials to be well tolerated and to have a longer circulating half-life compared with the endogenous hormone [75].

Gut hormone combination therapies

The maintenance of energy balance involves a number of central and peripheral signals. Simultaneously targeting more than one of these components may improve the

efficacy of anti-obesity drugs and in doing so, may better mimic the physiological control of appetite. Bariatric surgery elevates a number of anorectic gut hormones which are thought, in combination, to contribute to the weight loss observed following this surgery. The effects of administering various gut hormone combinations have therefore been investigated.

$PYY_{3–36}$ potently reduces appetite, but is strongly associated with treatment-induced nausea. A combined infusion of oxyntomodulin and $PYY_{3–36}$, at doses not associated with nausea, has an additive anorectic effect in humans [76]. Although this method of administration is impractical for an obesity treatment, it highlights that these hormones work through different mechanisms that can be simultaneously exploited. Utilizing long acting gut hormone analogues in combination might therefore provide the prolonged action without the side effects required for a successful anti-obesity agent.

$PYY_{3–36}$ and PP given in combination showed no additive effect compared with either treatment alone when administered intraperitoneally to mice or intravenously to humans [77]. However, obinepitide (TM30338), from 7TM Pharma, is a synthetic analogue of human PYY and PP that has been reported to have improved anorectic effects. It acts as a dual Y_2 and Y_4 receptor agonist and is designed to be administered as a once or twice daily subcutaneous injection. 7TM Pharma reported that obinepitide was safe and well tolerated and resulted in prolonged reductions in food intake compared with either hormone alone in phase I/II clinical trials [78]. The utility of combined PYY and PP treatment consequently requires further investigation.

Perhaps the most promising combination of gut hormones is that of $GLP\text{-}1_{7–36}$ and $PYY_{3–36}$. This combination has been shown to have an additive anorectic effect in both mice and humans [79]. The administration of $GLP\text{-}1_{7–36}$ and $PYY_{3–36}$ in combination at doses that do not reduce food intake individually significantly reduces food intake in genetically obese mice and in humans [79]. Most interestingly, a $GLP\text{-}1_{7–36}$ and $PYY_{3–36}$ oral combination therapy utilizing sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) delivery technology to mimic endogenous secretion of the peptides also has an additive anorectic effect in humans [80].

Oral administration is considered the most convenient and economical method of drug delivery and tends to encourage a higher rate of compliance than other administration routes [81]. However, gut hormone peptides are subject to rapid degradation in the digestive environment of the upper gastrointestinal (GI) tract and are poorly absorbed, severely limiting their oral bioactivity. SNAC technology, mentioned above, is an emerging strategy for the oral delivery of drugs. It is based on Emisphere's Eligen® Technology which facilitates the transport of compounds with low oral bioavailability, such as gut hormones, across biological membranes. SNAC is hydrophobic and forms non-covalent bonds with peptides, increasing their lipophilicity, and therefore improving their absorption across the GI epithelium. Upon crossing the GI epithelium, the drug should disassociate from the SNAC molecule, leaving it free to pass directly into the circulation and exercise its intended pharmacological action. Such a delivery system could be utilized to provide a pharmacological profile that closely resembles the physiological release of gut hormones. Additionally, the SNAC carrier is readily and safely eliminated by normal excretion pathways. Emisphere's Eligen® Technology has been successfully employed in the development of oral forms of heparin [82], insulin [83] and parathyroid hormone [84], and initial results suggest it may have utility as a delivery agent for gut hormones such as $GLP\text{-}1_{7–37}$ and $PYY_{3–36}$ [85, 86]. The development of anti-obesity drugs that can be delivered orally and are as efficacious as injectables would be of great clinical significance.

Targeting nutrient sensing receptors

An emerging field of anti-obesity research is the study of nutrient sensing receptors. Many nutrient sensing receptors present in the GI tract have been localized to the L-cells of the distal small intestine and colon. Stimulation of specific nutrient receptors, such as the sweet taste receptor, in immortalized and primary L-cell cultures has been shown to cause gut hormone release [87, 88]. However, there is currently very little *in vivo* data on these systems and thus the physiological relevance of these effects are unclear. The use of receptor knockout models will aid the investigation of the potential of these receptors as anti-obesity targets. Theoretically, directly targeting these nutrient sensing receptors to stimulate endogenous gut hormone release might provide a relatively physiological means of suppressing appetite and reducing energy intake. Stimulating the L-cell directly requires the specific receptor agonist or agonists used to avoid absorption and degradation in the upper GI tract. Several mechanisms have been developed for colon-targeted drug delivery including systems that are pH and time-dependent, pressure-controlled and microbiota activated. While each of these systems has limitations, the combination of two or more systems may improve the accuracy of site specific drug targeting [89]. The oral administration of nutrient sensing receptor agonists which stimulate the endogenous release of gut hormones may be an effective long term treatment for obesity, minimizing administration site-specific side effects and the potential risk of antibody development which can be linked to exogenous gut hormone treatment [41, 90].

The future of anti-obesity drug development

It is likely that Qnexa® and Contrave® will be approved for the treatment of obesity in the foreseeable future.

However, the development of safe drugs remains the biggest hurdle in the anti-obesity drug market. With the development of long acting gut hormone analogues and the additive anorectic effects seen with specific gut hormone combinations, the potential utility of gut hormones as a treatment for obesity remains high. Finally, with research into drug delivery mechanisms growing, it is possible that orally delivered gut hormone analogues represent the next generation of anti-obesity drugs.

Competing Interests

There are no competing interests to declare.

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