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REVIEW

The regulation of food intake by the gut-brain axis: implications for obesity

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Our understanding of the regulation of appetite has improved considerably over the last few decades. Recent work, stimulated by efforts aimed at curbing the current obesity epidemic, has unravelled some of the complex pathways regulating energy homeostasis. Key factors to this progress have been the discovery of leptin and the neuronal circuitry involved in mediating its effects, as well as the identification of gut hormones that have important physiological roles relating to energy homeostasis. Despite these advances in research, there are currently no effective treatments for the growing problem of obesity. In this article, we summarise the regulatory pathways controlling appetite with a special focus on gut hormones. We detail how recent findings have contributed to our knowledge regarding the pathogenesis and treatment of common obesity. A number of barriers still need to be overcome to develop safe and effective anti-obesity treatments. We outline problems highlighted by historical failures and discuss the potential of augmenting natural satiety signals, such as gut hormones, to treat obesity.

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INTRODUCTION

Over 60 years ago, while studying the effect of hypothalamic lesions on appetite, Brobeck[1] contemplated 'Why does the normal animal eat food? What determines how much it will eat? What changes in the internal environment set the animal to eating? and what changes are associated with satiety?'. The wealth of knowledge gained by recent research has revealed some of the complex control mechanisms relating to Brobeck's questions. Our simplistic views regarding appetite control are constantly being updated to accommodate the complexity of a diverse homeostatic system, which is influenced by a variety of stimuli in the modern world.[2]

Most of our knowledge regarding appetite control has stemmed from studying the genetics of obesity and altering signalling pathways implicated in obesity to investigate their impact on appetite and body weight regulation. The brain has emerged as the key regulator of appetite. It receives and integrates a variety of homeostatic signals regarding energy status with environmental, social and hedonistic influences to produce an overall response of hunger, which promotes food intake, or satiety, which limits food intake (Figure 1).[3,4] Although common obesity is unlikely to be a result of pre-existing pathological changes in these circuits, it may be propagated by inappropriate homeostatic responses to energy excesses in an obesogenic environment. Weight gain does not necessarily lead to diminished energy intake and weight loss through dieting is difficult to achieve and sustain. Therefore, this complex regulatory system controlling appetite and body weight is more responsive to a loss in energy stores and is tolerant towards energy gains. Work over the recent years has highlighted a number of redundancies in the appetite regulation system.[5] These redundancies are likely to contribute to the difficulty in achieving and sustaining meaningful weight loss on anti-obesity therapies.[6]

With energy availability being integral to our survival, it is not surprising that we have powerful hunger signals that are aimed at constantly replenishing and building energy reserves. However, the role for signals that limit food intake is less obvious. It is likely that short-term satiety signals, activated following the intake of a meal and emanating largely from the gut, improve digestive efficiency, nutrient utilisation and prevent large fluctuations in circulating nutrients by preventing consumption of large meals through their effects on the brain. What is evident is that these gut satiety signals are weak, especially in the current obesigenic environment where they are not powerful enough to limit excess energy intake. Nevertheless, understanding these signals and augmenting them pharmacologically may provide an important avenue to treat obesity.

At present, we are unable to tackle the growing obesity problem effectively. Currently, only one drug is licensed for the long-term treatment of obesity.[7] Despite its efficacy, the costs of and risks from bariatric surgery make it an impractical solution for this worldwide problem. In this review, we summarise our current understanding regarding the central nervous system (CNS) pathways regulating appetite and focus on the role of gut signals in this regard. We discuss the problems with current approaches to tackle obesity, lessons learnt from previous experiences and how our current knowledge may improve the future treatment of obesity. Given the breadth and size of this topic, it is difficult to present a comprehensive account of all the control mechanisms involved. Our eclectic efforts should not diminish the importance of processes that are not discussed in this review.

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THE HYPOTHALAMIC CONTROL OF APPETITE

The hypothalamus has a prominent role in coordinating the central control of appetite.[6] Neural, nutrient and hormonal signals converge directly and indirectly on the hypothalamus forming a network of communication between the gut, pancreas, liver, adipose tissue, brainstem and hypothalamus (Figure 1). The hypothalamus integrates these peripheral signals and modulates appetite in response to them via higher cortical centres, pertaining to food memory and reward, sympathetic and parasympathetic nervous system, influencing gastric motility and hormone secretion among other processes relevant to energy homeostasis.

Within the hypothalamus, the arcuate nucleus (ARC) is one of the main nuclei regulating appetite.[8] A semipermeable blood–brain barrier resulting from a highly fenestrated local capillary network is thought to allow peripheral signals, such as hormones and nutrients, to gain access to the CNS.[9,10] The ARC neuronal populations communicate with other hypothalamic nuclei implicated in the control of food intake, such as paraventricular nucleus, dorsomedial nucleus, lateral hypothalamus and ventromedial nucleus.[11,12] The involvement of specific hypothalamic neuronal populations, especially in the ARC, in appetite regulation has been highlighted in a number of studies. Two well-characterised neuronal populations within the ARC are known to regulate food intake. These are the orexigenic neuropeptide Y/agouti-related peptide neurons and anorexigenic pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript containing neurons.[13] Neuronal populations in other hypothalamic nuclei involved in cocoordinating food intake include orexigenic orexin and melanin concentrating hormone releasing neurons of the lateral hypothalamus, anorexigenic brain-derived neurotrophic factor and steroidogenic factor-1 releasing neurons in the ventromedial nucleus.[14–18]

The discovery of leptin's role in energy homeostasis along with the use of specific genetic manipulations has provided further insight into the specific role of neuronal populations, receptors and cellular pathways involved in altering energy homeostasis. It is now well regarded that these appetite modulating hypothalamic neurons functioned as metabolic sensing units that are capable of 'sensing' nutrients and hormones, including gut hormones.[19–21] Although, the contribution of pre-existing defects in these neuronal pathways to the development and propagation of common obesity is unclear; these studies have helped our understanding of appetite regulatory pathways.

THE BRAINSTEM SENSES ENERGY BALANCE AND MODULATES FEEDING ACTIVITY

Recent evidence has demonstrated that systems outside the hypothalamus are also important in regulating food intake. The caudal brainstem has a crucial role in ingestive behaviour and is regarded as being the second homeostatic integrator controlling food intake.[22] The DVC (dorsal vagal complex) in the caudal brainstem facilitates communication between the periphery and hypothalamus to control food intake. Neural, nutrient and hormonal signals from the gastrointestinal tract are sensed in the brainstem by mechanisms analogous to those seen in the hypothalamus.[23–25] Receptors and signalling systems influenced by gut hormones and implicated in energy homeostasis have been demonstrated in the vagus nerve and brainstem.[26] These appetite signals in the brainstem are relayed to the hypothalamus (Figure 1).[27–29] The hypothalamus integrates these and other signals to generate an efferent signal, which is transmitted via the brainstem to modulate appetite and gastrointestinal function.[23,30,31] The vagus has an important role in the transmission of afferent and efferent neural signals between gastrointestinal system and nucleus of the tractus solitarus in the DVC. Cessation of these signals results in altered meal patterns.[27]

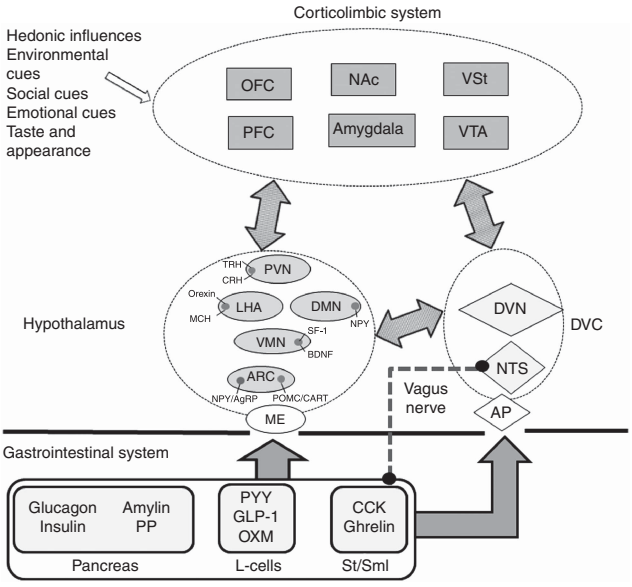

Figure 1. A gut-brain axis controls food intake and appetite in response to homeostatic and non-homoeostatic signals. The hypothalamus, brainstem and corticolimbic system form a complex neuronal network, which allows signals from the gut and external environment to be integrated. In response to chemical, mechanical, hormonal and nutritive changes, neural signals are conveyed from the gut to the brainstem via the vagus nerve. Gut hormone signals are also relayed directly to the hypothalamus and brainstem via the median eminence and area postrema, respectively, which forms an incomplete blood–brain barrier. Hedonistic, environmental, social and taste influences are processed via the corticolimbic system and modulate hypothalamic appetite centres. Integration of these signals by the brain produces overall feelings of hunger and satiety. AP, area postrema; ARC, arcuate nucleus; BDNF, brain-derived neurotrophic factor; CCK, choleycystokinin; CRH, corticotropin-releasing hormone; DMN, dorsomedial nucleus; DVC, dorsoventral vagal complex; DVN, dorsovagal neurons; GLP-1, glucagon like peptide-1; L-cells, enteroendocrine L cells of the gastrointestinal tract; LHA, lateral hypothalamic area; MCH, melanin-concentrating hormone; ME, median eminence; NAc, nucleus accumbens; NTS, nucleus of the tractus solitarius; NPY/AgRP, neuropeptide Y and agouti-related peptide; OFC, orbitofrontal cortex; OXM, oxyntomodulin; PFC, pre-frontal cortex; POMC/CART, pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript; PVN, paraventricular nucleus; PP, pancreatic polypeptide; PYY, peptide YY; SF-1, steroidogenic factor-1; St/SmI, stomach and small intestine; TRH, thyrotropin-releasing hormone; VMN, ventromedial nucleus; VSt, ventral striatum; VTA, ventral tegmental area.

THE CORTICOLIMBIC SYSTEM ALLOWS LEARNING, LIKING AND WANTING TO BE INTEGRATED WITH HOMEOSTATIC MECHANISMS

The homeostatic control of food intake is strongly influenced by hedonism, reward and mnemonic representations of food experiences.[4] These non-homeostatic factors are affected by the environment and processed via the corticolimbic system.

The corticolimbic system structures consist of structures including prefrontal cortex, nucleus accumbens, ventral striatum, hippocampus and amygdala. Histochemical and pharmacological studies, in the corticolimbic and hypothalamic systems, highlight the importance of connections between homeostatic and non-homeostatic centres in altering food intake.[4] These studies suggest that homeostatic appetite control systems in the hypothalamus are modulated by non-homeostatic influences from the corticolimbic system, allowing environmental cues to dominate homeostatic regulation.[4] Recent data propose that non-homeostatic systems may also be influenced by homeostatic signals, such as gut hormones. [32,33] This opens the possibility of

influencing both homeostatic and non-homeostatic systems in an obesogenic environment using single agents such as gut hormones. It has also been hypothesised that altered sensing of these homeostatic signals in common obesity may lead to altered motivation to consume foods.[34] Further work is needed to explore the cross-talk between the homeostatic and non-homeostatic systems.

ADIPOSITY SIGNALS MODULATE APPETITE BUT ARE WEAKENED IN OBESITY

The role of leptin and, to some extent, insulin as adiposity feedback signals influencing appetite has been demonstrated and is reviewed in detail elsewhere.[35] Resistance to the effects of adiposity signals, such as leptin and insulin, is an important feature of common obesity.[35] Leptin levels are elevated in obesity, with impaired hypothalamic leptin signalling, and fall on weight loss. It is unclear if resistance to leptin signalling and altered association of leptin with food intake and satiety are a cause or consequence of obesity. In post-obese subjects, increased post-prandial mean leptin levels are associated with increased post-meal satiety scores as compared with controls, suggesting that the development of obesity may lead to a change in leptin sensitivity.[36] Regardless of its aetiology, resistance to adiposity signals may contribute towards increased food intake despite excessive adiposity in obesity, difficulty in achieving weight loss and robust hunger responses elicited after weight loss in obese individuals.

SIGNALS FROM THE GUT INFORM THE BRAIN REGARDING ENERGY STATES

Food intake is the main source of energy in animals. Therefore, it is not surprising that one of the main organs responsible for intake and absorption of food has a key role in informing the brain regarding energy status and altering appetite. The gut-brain axis modulates short-term satiety and hunger responses to regulate the delivery of nutrients and transit of nutrients through the gastrointestinal tract, enabling efficient digestion and storage of energy (Figure 1). This axis also has a role in the regulation of blood glucose levels, adipocyte function and energy expenditure, ensuring maintenance of energy homeostasis following a meal.[37]

NEURAL SIGNALS FROM THE GUT TO THE BRAINSTEM

Gustatory fibres of cranial nerves VII, IX and X, olfactory fibres of cranial nerve I, and sensory fibres of cranial nerve V are directly or indirectly relayed to the DVC and corticolimbic system.[38] Afferent vagus nerve mechanoreceptors, sensitive to gastric and gut intraluminal distension, and chemoreceptors, sensitive to a variety of intraluminal chemical stimuli, relay information from the gastrointestinal tract to the DVC regarding the chemical, mechanical and nutritive properties of ingested food.[39]

GUT HORMONES

A number of gut hormones have been identified in the gastrointestinal system. They have a fundamental role in coordinating digestive process within the gastrointestinal system via autocrine and paracrine effects but also exert endocrine effects on other organ systems particularly the brain, where some of them have also been found to exist as neurotransmitters. Their role in food intake is reviewed here.

Cholecystokinin

Cholecystokinin was the first gut hormone shown to have a role in appetite regulation.[40,41] It is secreted post-prandially from I cells of the small intestine and promotes fat and protein digestion.[42–44] Its effects on increasing satiety following meal ingestion are via the CCK1 (cholecystokinin 1) receptors on the vagal afferents, brainstem and the hypothalamus.[45–47] Support for this comes from the hyperphagic and obese Otsuka Long-Evans Tokushima Fatty rat, which lacks the CCK1 receptor.[48] In contrast, CCK1 knockout mice do not display the same phenotype and the reasons for this are not entirely clear.[49]

Despite the convincing support for cholecystokinin's role in mediating post-prandial satiety, its potential as a therapeutic agent for obesity is limited. Repeated or chronic administration of cholecystokinin is ineffective in reducing long-term food intake.[50–52] It is possible that tachyphylaxis or short duration of cholecystokinin's anorectic effects may account for its failure in mediating long-term changes in food intake and weight loss.

Ghrelin

The 'hunger hormone' ghrelin is the only known orexigenic gut hormone.[53] It was first identified as an endogenous ligand to the growth hormone secretagogue receptor in the stomach.[54] It is secreted by the A cells of the gastric fundus and results in increased gastric motility, decreased fat utilisation and stimulation of growth hormone release.[53,55]

Plasma ghrelin levels are elevated before meals and decline post-prandially in proportion to calories ingested, supporting a role relevant to food intake.[56–58] Peripheral administration of ghrelin increases food intake in both rodents and humans.[59,60] These findings have been replicated in several studies confirming ghrelin as a potent appetite stimulator that has a role in meal initiation. Ghrelin mediates its effects on appetite via the growth hormone secretagogue receptor on vagal afferents and in the ARC to alter neuronal activity of neuropeptide Y/agouti-related peptide neurons.[61] Ghrelin's effects occur in other parts of the hypothalamus and brainstem as well.[62] A recent report suggested that it has a role in stress induced food reward.[63]

Ghrelin levels are inversely correlated with bodyweight and rise after weight loss.[64,65] Furthermore, ghrelin resistance in rodents on high-fat diets has also been described.[66] These observations suggest that ghrelin may not be important in initiating feeding in obesity.[55] However, the rise in ghrelin following weight loss may contribute to the poor dietary adherence and regain of lost weight in weight-loss interventions. Strategies to antagonise ghrelin either directly or by inhibition of ghrelin *O*-acyltransferase (an enzyme required to permit ghrelin to bind to growth hormone secretagogue receptor) are being developed as anti-obesity agents. This approach may lead to more fruitful weight-loss outcomes; however, a successful therapy is yet to emerge.

Peptide YY

Peptide YY (PYY) is a member of the pancreatic polypeptide (PP)-fold family, which also includes neuropeptide Y and PP. These related peptides have a similar PP-fold structural motif and bind to Y family of receptors. PYY is secreted by the L cells of the gastrointestinal tract. $PYY_{3–36}$ is the active form of PYY and binds preferentially to the Y_2 receptor. Its levels are low in the fasting state and rise post-prandially, for several hours, in proportion to calories ingested and especially after a protein-rich meal.[67–69] Blunted post-prandial rises in PYY are noted in obesity.[68] Exaggerated post-prandial PYY rises occur following Roux-en-Y gastric bypass (RYGB).[70] This increased response may have an important role in the initial weight loss noted by this effective surgical treatment for obesity.[71] The anorectic potential of peripherally administered $PYY_{3–36}$ has been demonstrated and confirmed in several rodent and human studies.[26,72–74] These anorectic effects of $PYY_{3–36}$ are mediated via the hypothalamus through direct effects on Y_2 receptors in the ARC and indirect effects via the Y_2 receptors on the vagus.[26] The net effect of this is to alter ARC neuronal activity.[75] Decreased gastric emptying by PYY may also have a part in promoting satiety. PYY is one of the hormones considered to mediate the 'ileal brake reflex'. This reflex

results in inhibition of proximal intestine and gastric motor activity with nutrient stimulation of the ileum. This reflex may serve to protect the distal intestine from large nutrient loads. The anorectic potential of PYY_{3-36} has stimulated considerable interest in developing therapies targeting Y_2 receptors for the treatment of obesity.

Pancreatic polypeptide

PP belongs to the PP-fold family of peptides. It is released post-prandially by PP cells in the pancreatic islets and binds to the Y receptor family.[26] Its highest affinity is to the Y_4 receptor subtype.[76] PP delays gastric emptying and also reduces appetite in rodents and humans.[77–79] It has been suggested that PP exerts its effects via Y_4 receptors in the ARC, area postrema in the brainstem and vagus.[26] Evidence for its central mode of action via hypothalamic centres implicated in energy homeostasis is further strengthened by functional imaging using manganese-enhanced magnetic resonance imaging following PP administration in mice.[80]

Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is formed from cleavage of the preproglucagon precursor.[81] It is secreted by the L cells of the gastrointestinal tract post-prandially in proportion to calories ingested and especially by glucose.[82] The secretion of GLP-1 from the L cells is stimulated by enteric neuronal signals, as well as via the G protein-coupled 119 receptor, which comes into direct contact with gut luminal contents.[83,84] $GLP\text{-}1_{7-36}$ and $GLP\text{-}1_{7-37}$ amide are the major bioactive forms of GLP-1 in the circulation. GLP-1 is degraded by the enzyme dipeptidyl peptidase-4.

GLP-1's incretin effects include increased glucose-dependent insulin release, decreased glucagon secretion and decreased gastric emptying.[85] Therefore, it has important effects on attenuating post-prandial glucose rise. GLP-1 is also one of the components of the 'ileal brake reflex' and has an anorectic effect on appetite.[86] Peripheral and central administration in animals and peripheral administration in humans results in reduced food intake.[26] GLP-1 mediates this effect via GLP-1 receptors in the ARC, paraventricular nucleus and superior optic nuclei of the hypothalamus, nucleus of the tractus solitarus and area postrema of the brainstem and vagus.[26,87]

GLP-1's incretin properties have been utilised for the treatment of type 2 diabetes. Exenatide (exendin-4) is a GLP-1 receptor agonist, originally isolated from the saliva of *Heloderma suspectum*, the Gila monster lizard.[88] It is resistant to dipeptidyl peptidase-4 cleavage. Its use in type 2 diabetes has led to improved glycaemic control as well as weight loss.[89] Other longer acting dipeptidyl peptidase-4-resistant analogues have been developed and are currently in trials for the treatment of obesity. In a recent study 2-year study, Liraglutide, a once-daily GLP-1 analogue, demonstrated sustained weight loss, increased efficacy compared with orlistat, improvement in metabolic risk factors without any major safety concerns.[90] Phase III trials for this promising anti-obesity agent are being undertaken.

A recent meta-analysis provides convincing evidence that GLP-1 receptor agonists leads to weight loss in obese patients with or without type 2 diabetes.[91] Furthermore, this meta-analysis also highlighted beneficial effects on blood pressure and total cholesterol. It is unclear if these benefits are a direct result of weight loss or whether there are possible off target effects on GLP-1 receptors present in the vascular system or CNS areas that are not directly involved in appetite control.[92,93]

Oxyntomodulin

Like GLP-1, oxyntomodulin is a product of preproglucagon precursor and is also secreted post-prandially by the L cell in proportion to caloric intake.[94] Oxyntomodulin exerts its effects mainly via the GLP-1 receptor, although it also has weak affinity to the glucagon receptor.[26,95] Oxyntomodulin has a 50 × fold lower affinity for the GLP-1 receptor as compared with GLP-1. Despite its lower receptor affinity, oxyntomodulin reduces food intake and body weight to a similar degree as GLP-1 in rats.[26] Oxyntomodulin also delays gastric emptying.[96] However, unlike GLP-1, oxyntomodulin increases energy expenditure and suppresses ghrelin.[26,97,98] It is also likely that oxyntomodulin has different pharmacological properties and different tissue-specific actions as compared with GLP-1. The anorectic effects of intraperitoneal oxyntomodulin, but not GLP-1, are inhibited by $exendin_{9-39}$ injected directly into the ARC.[99] Therefore, oxyntomodulin may exert its anorectic effects in the hypothalamus via different neuronal sub-populations or an unidentified receptor that may also bind to $exendin_{9-39}$ but not GLP-1. This observation is further strengthened by studying the pattern of neuronal activation following oxyntomodulin or GLP-1 administration in mice using manganese-enhanced magnetic resonance imaging. The pattern of hypothalamic neuronal activation is distinct for these two hormones, suggesting that they act differently to mediate their anorectic effects.[87] The potential of this anorectic gut hormone as an anti-obesity agent is currently being investigated.

Glucagon

Glucagon is a pancreatic hormone produced from the preproglucagon precursor molecule in the α cells of the pancreas. Its effects occur via the glucagon receptor, which is mainly expressed in the liver and kidney, although found in a wide range of other tissues as well.[100] Its main effect is to maintain blood glucose levels during fasting and exercise by promoting hepatic glycogenolysis and gluconeogenesis. However, it also has anorectic properties and promotes satiety. Glucagon levels rise post-prandially, especially after a protein diet.[101] Glucagon administration in man and rodents results in a reduction of meal size, food intake and body weight.[101–103] Blockade of glucagon increases meal size.[104] Glucagon's satiating effect is most marked when glucagon is infused in to the hepatic portal vein.[101] The vagus nerve has been implicated in transducing glucagon signalling to the brainstem to mediate its satiating effects.[101] In addition to its satiating effects, glucagon can also increase energy expenditure.[105]

Glucagon's anti-obesity potential is severely limited by its detrimental effects on glucose homeostasis. However, co-agonism of glucagon and GLP-1 receptors decreases food intake and increases energy expenditure with no unfavourable effects on glucose homeostasis in rodents.[106,107] This raises the possibility of utilising dual agonism of glucagon and GLP-1 in the treatment of obesity. Studies utilising this approach are currently underway.

Amylin

Amylin is co-secreted with insulin by pancreatic β cells. In humans, it binds to AMY receptor subtypes, which are complexes of calcitonin receptors with receptor activity-modifying proteins; however, in rodents amylin receptors have not been well characterised.[108] It inhibits gastric secretion, delays gastric emptying improves post-prandial glucose rises and reduces food intake.[26] Its satiety effects occur via activation of the serotonin-histamine-dopaminergic system and is independent of the vagus.[101] An analogue of amylin is currently being used as adjunctive therapy in diabetes mellitus. Its use is associated with improved glycaemic control and significant weight loss, prompting consideration for its use as an anti-obesity therapy.[109]

Other gut hormones

A number of other gut hormones have been implicated in the control of food intake. Neurotensin, first identified as a CNS neurotransmitter, is largely found in the enteroendocrine N cells of the gastrointestinal tract and regulates a number of digestive processes.[110] Neurotensin and xenin, a gut hormone with

structural homology to neurotensin, have been shown to have anorexogenic potential in rodents.[111,112] However, neurotensin's effect on reducing food intake in rodents does not occur chronically, which limits its potential as an anti-obesity therapy.[113]

Obestatin is a novel gut hormone that is derived from the preproghrelin precursor and was considered to have opposite effects on food intake to ghrelin.[114] Although several studies demonstrated its anorexigenic potential, other studies did not support this.[115] Hence, its effects on energy homeostasis require further validation.

Glucagon-like peptide-2 is another product of preproglucagon cleavage in the intestinal L cells.[116] Central administration of glucagon-like peptide-2 into rats reduces food intake.[117] Peripheral administration in rodents and humans does not alter energy intake.[118,119] Therefore, it is unlikely to be of much value as an anti-obesity agent.

IMPLICATIONS FOR TREATMENT OF OBESITY: WHY HAVE CURRENT THERAPIES FAILED?

Lifestyle interventions are the cornerstone of obesity management. These interventions include dietary therapy, exercise and behaviour modification. They can achieve a weight loss of up to 10% bodyweight.[120] However poor adherence and regain of lost weight, due to relapse of lifestyle factors, lead to substantial weight regain. Dropout rates for diets range from 35 to 50% within a year and are predominantly due to the diet becoming hard to follow and frustration at inability to lose further weight.[121] Patients treated through lifestyle measures tend to regain 30 to 35% of their lost weight within a year.[120] These issues are a familiar problem in obesity management and highlight a homeostatic system that is engineered to defend weight losses with robust hunger responses and diminished energy expenditure. Environmental stimuli and lack of reward on stringent diets make lifestyle interventions even harder to follow. Studies in rodents have highlighted decreased reward value from palatable foods in obesity, leading to increased compulsive eating of palatable foods.[122] The dopamine system has been implicated in this addiction like adaptation to palatable foods in obesity. Therefore, difficulties in losing further weight, poor perception of satiety after weight loss and diminished reward on dietary therapies are unfortunately to be expected with weight-loss interventions.

At present, orlistat is the only available drug for the long-term treatment of obesity. When combined with lifestyle interventions, it results in a mild supplementary weight loss of 2.9 kg above placebo.[123] However, no further weight loss is noted thereafter, again reflecting the emergence of multiple compensatory mechanisms, which diminish weight-loss strategies.[124] Moreover, as for other interventions, there is a marked regain of weight following discontinuation of treatment. Orlistat causes a number of problematic gastrointestinal side effects. These side effects along with limited efficacy and possible cost implications lead to substantial discontinuation of therapy. In trial settings this may be 15–30%, but in non-trial settings up to 98% has been reported.[125] This further underscores its efficacy as an anti-obesity agent.

DIFFICULTIES IN DRUG DEVELOPMENT IN OBESITY

The above problems highlight the need for drugs that can target the multiple compensatory mechanisms counteracting the effects of weight loss. Although a number of potential targets modulating satiety, hunger, reward and energy expenditure have emerged, developing a safe and effective drug for weight loss remains a big challenge.

Problems with demonstrating safety

Neurotransmitters involved in the neuroendocrine regulation of energy homeostasis are spatially distributed in the CNS and peripheral system. Therefore, it is not surprising that altering neurotransmitter signalling in a widespread system may lead to unwanted side effects. The use of amphetamine derivatives fenfluramine and dexfenfluramine highlight concerns regarding this. These serotonergic agents lacked the psychostimulant properties associated with amphetamines but were effective in promoting substantial weight loss.[126] This efficacy, coupled with FDA (Food and Drug Administration, US) approval for short-term and longer term use of these agents, lead to widespread prescribing and off-label use of products containing these agents in the 1990s. The emergence of cardiac valvulopathy resembling serotonin mediated carcinoid syndrome caused a grave concern given its prevalent use.[127] This prompted investigations into its role in valvulopathies and 20 years after its introduction the FDA estimated a 32.8% incidence of valvular heart disease in those taking fenfluramine. Despite initial warnings issued by the FDA in 1997, these drugs were often not discontinued. By the time it was withdrawn later that year, over 4 million individuals were exposed to fenfluramine and 2 million to dexfenfluramine. Massive litigation eventually culminated in a $5 billion settlement by Wyeth to 475 000 individuals claiming compensation.

Another example is Rimonanbant, a selective CB1 receptor antagonist. This drug emerged on the European market in 2006 after promising initial results and was used extensively as a treatment for obesity.[128] Post-marketing surveillance resulting from its use in obesity indicated increased psychiatric adverse effects, such as depression and suicide.[129] After issuing an advisory in 2008, rimonanbant was eventually withdrawn from the European market in 2009.

Sibutramine (Reductil), a serotonin and noradrenalin reuptake inhibitor, was licensed for the treatment of obesity in 1997. Cardiovascular concerns emerged because of its sympatheticomimetic effects and it was noted to increase blood pressure and pulse rate in some patients.[130] Hence, it was not indicated for patients with a history of cardiovascular disease. Following the emergence of data from Sibutramine Cardiovascular Outcome Trial (SCOUT), it was withdrawn from the European market by the European Medicines Agency.[131] This large study showed a 16% increased rate of serious non-fatal cardiovascular events, such as stroke or myocardial infarction, with sibutramine as compared with placebo. Under pressure from the FDA, this drug was eventually withdrawn from the US market by its manufacturers.

These examples illustrate the potential of adverse events from agents modulating neurotransmission. Subtle and unpredictable side effects from these agents may only become apparent in large, long-term studies. In light of these historical concerns, the FDA has adopted a rigorous approach on approving emerging drugs for the treatment of obesity. In 2010, the FDA rejected Phentermine/Topiramate (Qnexa-Vivus Inc., Mountain View, CA, USA), Bupropion/Naltrexone (Contrave-Orexigen Therapeutics, La Jolla, CA, USA) and Lorcaserin Hydrochloride (Lorqess-Arena Pharmaceuticals, San Diego, CA, USA) primarily over safety concerns. Both Lorcaserin and Phentermine/Topiramate have refilled their applications to the FDA, with Phentermine/Topiramate being recommended for approval by an FDA advisory panel earlier this year. Orexigen is attempting to address the cardiovascular safety concerns highlighted by the FDA for Bupropion/Naltrexone by conducting a cardiovascular outcomes trial. Although these potential anti-obesity drugs may eventually obtain approval for their use, such stringency by drug regulatory authorities, on a background of previous failures, could be a potential deterrent for pharmaceutical companies looking to develop new anti-obesity agents.

The complexity of the biological systems regulating energy homeostasis

The discovery of leptin as an adiposity factor involved in appetite regulation in 1994 was heralded by many as a finding which

would revolutionise the treatment of obesity. Amgen Inc. (Thousand Oaks, CA, USA) embraced this discovery, investing millions with the hope of using leptin as an anti-obesity agent. However, most human trials with leptin in common obesity have been disappointing. Over the last decade, and as mentioned earlier, it has become increasingly apparent that obesity is a leptin-resistant state with hyperleptinaemia. Therefore, simply replacing leptin may not be a useful strategy to reduce appetite in obese individuals. The mechanisms regulating energy homeostasis and metabolism are complex. Our current views regarding these processes are often too simplistic to predict the long-term efficacy and consequences of altering biological systems in obesity.

Unexpected biological outcomes

The emergence of ciliary neurotrophic factor as a nerve growth factor involved in producing an anorectic response was also very promising. In trials for the treatment of motor neuron disease, ciliary neurotrophic factor caused marked weight loss. Subsequent investigations highlighted that ciliary neurotrophic factor may mediate its effect on energy homeostasis by stimulating increased neurogenesis in pathways linked to energy homeostasis, resulting in increased leptin responsive neurons and leptin-like signalling.[132,133] This effect was preserved in leptin-resistant obesity states raising hopes that this may be an effective treatment in common obesity. Axokine (Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA), a modified version of ciliary neurotrophic factor, was investigated as a treatment for weight loss. Initial results were encouraging.[134] However, a phase III study resulted in the development of neutralising antibodies in 70% of participants after 3 months of therapy, compromising its efficacy and raising concerns about disrupting neuronal regeneration processes in individuals treated with this agent. These scenarios are a common concern when translating successes from the lab to patients. It is difficult to assess the biological responses of potential anti-obesity agents comprehensively in rodents and small duration, short-term studies in humans.

WHERE NEXT?

Lessons from an effective but invasive and costly treatment

Bariatric surgical procedures are currently the most effective weight-loss treatment for obesity. Weight loss, sustainance of weight decline, incidence of obesity-related diseases and quality of life significantly improve with bariatric surgery, as compared with other conventional therapies.[135] There are several type of bariatric surgical procedures. These include restrictive procedures such as gastric banding, malabsorbptive procedures such as biliopancreatic diversion and mixed procedures such as RYGB that restric caloric intake and incorporate an element of gastrointestinal bypass. Appetite, weight loss and amelioration of type 2 diabetes are more effective with mixed procedures such as RYGB. A rise in post-prandial gut hormone secretion is noted immediately after duodenal switch in RYGB surgery.[70] This may account for the reduced hunger and altered food preference, despite substantial weight loss, in patients undergoing RYGB surgery. Unfortunately, the cost, operative risks and limited availability of the procedure, even in developed countries, makes bariatric surgery an impractical option for the treatment of obesity. This form of treatment is usually reserved for severely obese, particularly those with obesity exacerbated health conditions. However, they illustrate the therapeutic potential of altering gut signals in managing obesity. Hence, mimicing this model, by using these naturally occuring satiety signals as anti-obesity treatments, is likely to be a successful strategy to combat obesity and may circumvent safety problems associated with past failures in obesity therapy.

Combination therapy

Given the redundancies in the appetite regulation pathways and multiple compensatory mechanisms elicited on weight loss, combination therapy using multiple agents may offer better weight-loss outcomes. Furthermore, this strategy may also allow lower doses for each agent to be used, thereby reducing the emergence of potential side effects. This rationale has been used in the treatment of other common complex diseases, such as hypertension and diabetes. Buproprion/naltrexone (Contrave) and phentermine/ topiramate (Qnexa), discussed earlier in this review, as well as bupropion/zonisamide (Empatic) are based on this approach.[136] Early results from combinatorial gut hormone approaches using GLP-1 receptor agonists and PYY_{3-36} show additive weight-loss benefits in rodents and short human studies.[33,137,138] Other combination gut hormone approaches that are currently being investigated include PP/PYY_{3-36} (Obinepeptide), GLP-1/Glucagon co-agonism and metreleptin/ pramlintide.[136]

CONCLUSIONS

Metabolism and continuous availability of energy is integral to our survival. The gut-brain axis represents a holistic control system where the peripheral and central systems link and feedback to each other continuously to control energy homeostasis. This cross-talk allows us to adapt to changes in the environment and maintain energy homeostasis; ensuring energy is constantly available for the body's needs. Our perception of hunger and satiety is modulated through this network depending on energy status, environmental stimuli, as well as other needs and behaviours.

The sensitivity and nature of these signals controlling energy homeostasis is biased towards promoting weight gain and preventing weight loss. Modulating these signals by pharmacological means would help tackle the obesity problem. So-far efforts in this regard have been unsuccessful. The complexity, diversity and redundancy of pathways regulating food intake present a number of obstacles to effective and safe drug development. Nevertheless, our efforts to delineate the mechanisms that control food intake, as well as lessons from failures and successes, have provided an important framework that will enable us to identify and study targets for drug development. Gut hormones have been shown to have a fundamental role in energy homeostasis. The use of gut hormones as anti-obesity treatments is an attractive option and shows considerable promise. Although it is unlikely that we will ever have a miracle cure to a problem that has societal and environmental origins, judicious use of combinatorial gut hormone regimens is likely to help our currently futile efforts to tackle this growing problem.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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