Emerging drugs for obesity therapy

Novos fármacos para o tratamento da obesidade

Maria Teresa Zanella[1], Fernando Flexa Ribeiro Filho[1]

ABSTRACT

Central obesity have an important impact on the development of risk factors for coronary heart disease, including dislipidemia, glucose intolerance, insulin resistance and hypertension. These factors contribute to building cardiovascular (CV) disease as a major cause of death. The approach to obesity therapy should be designed to reduce CV risk and mortality. Diet and lifestyle changes remain the cornerstones of therapy for obesity, but the resultant weight loss is often small and long-term success is uncommon and disappointing. Drug therapy is considered for individuals with a body mass index greater than 30 kg/m^2 or ranging from 25 to 30 kg/m^2 if they have comorbid conditions. Antiobesity agents can be helpful to some patients in achieving and maintaining meaningful weight loss, but yet our pharmaceutical tools are of limited effectiveness considering the magnitude of the problem. At the present, only two drugs, orlistat and sibutramine, are approved for long-term treatment of obesity and promote no more than 5 to 10% of weight loss. Rimonabant, a cannabinoid-1 receptor antagonist, was withdrawn from the market because of concerns about its safety, including risk of suicidal and seizures, although very effective in promoting clinically meaningful weight loss, reduction in waist circumference, and improvements in several metabolic risk factors, rimonabant, a cannabinoid-1 receptor antagonist was withdrawn from the market because it concerns about its safety, including risk of suicidal and seizures. Fortunately, recent fundamental insights into the neuroendocrine mechanisms regulating body weight provide an expanding list of molecular targets for novel, rationally designed antiobesity drugs. In this review, the therapeutic potential of some antiobesity molecules in the development will be analyzed based on an understanding of energy homeostasis. Arq Bras Endocrinol Metab. 2009;53(2):271-280.

Keywords

Obesity therapy; antiobesity drugs; antiobesity molecules, weight loss

[1] Endocrinology Division, Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brasil; Clinical Research Center of Hypertension and Cardiovascular Metabology, Fundação Oswaldo Ramos, São Paulo, SP, Brasil

RESUMO

Obesidade e, particularmente, a obesidade central têm influência importante na predisposição a fatores de risco para doença coronariana, incluindo dislipidemia, intolerância à glicose, resistência à insulina e hipertensão. Tais fatores contribuem para tornar as doenças cardiovasculares (DC) causas frequentes de morte. Os métodos de tratamento da obesidade deveriam ser voltados à redução do risco e da mortalidade devido às doenças cardiovasculares. Dietas e mudanças no estilo de vida continuam sendo fatores-chave no tratamento à obesidade, mas a perda de peso resultante é geralmente pequena e o sucesso em longo prazo costuma ser incomum e frustrante. O tratamento com medicamentos é indicado para indivíduos com índice de massa corpórea superior a 30 kg/m^2 ou entre 25 e 30 kg/m^2, se apresentarem comorbidades. Agentes antiobesidade podem ajudar alguns pacientes a alcançar e manter uma perda de peso significativa, mas, ainda assim, os agentes farmacológicos são pouco efetivos considerando-se a magnitude do problema. Atualmente, apenas duas drogas, orlistat e sibutramina, são consideradas efetivas para tratamentos em longo prazo, promovendo não mais do que 5% a 10% de perda de peso. Embora seja muito eficaz ao promover perda de peso significativa do ponto de vista clínico, redução da circunferência da cintura e melhora no perfil metabólico, o rimonabanto, um antagonista do receptor canabinoide 1, foi retirado do mercado por fatores relacionados à segurança, incluindo a ocorrência de suicídios e convulsões. Felizmente, conhecimentos fundamentais recentes sobre mecanismos neuroendócrinos que regulam o peso corporal forneceram uma lista considerável de alvos moleculares para novas drogas antiobesidade produzidas racionalmente. Nesta revisão de literatura, a eficácia terapêutica de algumas moléculas antiobesidade será analisada com base no entendimento da homeostase energética. Arq Bras Endocrinol Metab. 2009;53(2):271-280.

Descritores

Tratamento da obesidade, novas moléculas antiobesidade; drogas antiobesidade; perda de peso

Correspondence to:
Maria Teresa Zanella
Departamento de Medicina da Universidade Federal de São Paulo, Hospital do Rim e Hipertensão
Rua Leandro Dupret, 365
04025-011 – São Paulo, SP, Brasil
tereza.zanella@hrim.com.br

Received in Feb/19/2009
Accepted in Mar/09/2009

INTRODUCTION

Obesity has reached an epidemic proportion worldwide. Once considered a problem only in high-income countries, the prevalence of obesity is now dramatically on the rise in low and middle-income countries, like Brazil.

There is growing evidence that obesity, and particularly central obesity, has an important impact on predisposing risk factors for coronary heart disease, including dislipidemia, glucose intolerance, insulin resistance and hypertension. All these risk factors have been contributing markedly to build cardiovascular disease as a major cause of death in the United States and many other countries. Thus, the approach to obesity therapy should be designed to reduce the risk of cardiovascular events and mortality.

Diet and lifestyle changes remain the cornerstones of therapy for obesity, but the resultant weight loss is often small and long-term success is extremely uncommon and disappointing. Drug therapy has been considered for individuals with a body mass index (BMI) greater than 30 kg/m^2, or of 25 to 30 kg/m^2 if they have comorbid conditions. Antiobesity agents can be useful to some patients in achieving and maintaining meaningful weight loss, but yet our pharmaceutical tools are of limited effectiveness in the face of the magnitude of the problem. At present, only two drugs, orlistat and sibutramine, are approved for long-term use in the treatment of obesity and each of these typically promotes 5% to 10% of loss of body weigh (1,2). Although very effective in promoting clinically meaningful weight loss, reduction in waist circumference and improvements in several metabolic risk factors, rimonabant, a cannabinoid-1 receptor antagonist was withdrawn from the market due to concerns about its safety, including risk of suicidal and seizures. Fortunately, recent fundamental insights into the neuroendocrine mechanisms regulating body weight provide an expanding list of molecular targets for novel, rationally designed antiobesity drugs. In this review, the therapeutic potential of some antiobesity molecules in the development will be analyzed based on an understanding of energy homeostasis.

NEUROENDOCRINE REGULATION OF BODY WEIGHT

In most humans, body weight remains stable for long periods of time, despite large fluctuations in food intake and physical activity because energy intake and expenditure are matched through a neuroendocrine complex mechanism of energy homeostasis. The importance of this control system was illustrated in a careful study of 18 obese and 23 never-obese subjects who were monitored during caloric restriction and caloric excess (3). Weight loss of 10% to 20% was associated with a decrease in total and resting energy expenditure which retards further weight loss and acts coordinately favoring weight regain. Similarly, weight gain was associated with an increase in energy expenditure which retarded further weight gain. These observations reflect a system in which information about the status of energy reserves is transmitted to the brain by adiposity and satiety signals in order to modify either anabolic or catabolic pathways. Consequently, food intake is altered in line with signaled energy requirements. This complex mechanism tends to maintain body weight and supports the theory that behavior is not the only determinant of obesity (4). Unfortunately, for those who diet, this homeostatic system defends against weight loss more efficiently than against weight gain. Body weight reduction induces decreases in circulating concentrations of leptin, nervous system tone and circulating thyroxine and triiodothyronine changes that decrease energy expenditure and acts synchronically to favor weight regain. Thus, understanding the mechanisms that regulate energy homeostasis is essential for understanding novel obesity therapies in development, which target anabolic or catabolic regulatory networks to reduce food intake or increase energy expenditure to promote weight loss.

Energy homeostasis is maintained by adapting meal size to current energy requirements (Figure 1). This control is achieved by communication between the digestive system and central nervous system (CNS). The status of body energy stores is communicated to the central nervous system by the adiposity-associated hormones leptin, insulin and selected gastrointestinal (GI) peptides, such as ghrelin (5). Information on meal quality and content is relayed from the gastrointestinal tract to the brain via satiety signals which are primarily integrated by the hypothalamus to determine meals size.

Acting in the brain, leptin and, in a less extent, insulin decrease food intake and increase energy expenditure, promoting weight loss, thus being considered catabolic adiposity signals. Acting on the same neuronal targets, ghrelin exerts the opposite effects and is thus termed an anabolic hormone. Weight loss evokes proportionate decreases in leptin and insulin and an

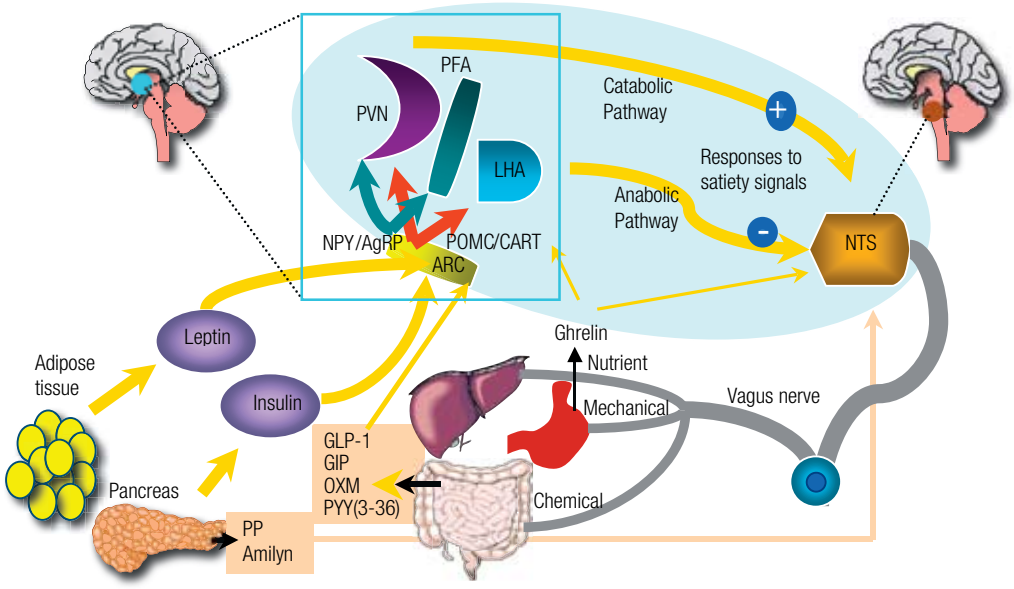

Figure 1. Signals such as leptin and insulin are secreted in proportion to the size of the fat mass and circulate in the blood. They enter the brain and act at the level of the hypothalamus. Neuroendocrine signals from the stomach, the gastrointestinal system and the liver are sent to the hindbrain, providing information about the food that is eaten: its taste and chemical content, and how much the stomach is distended.

increase in ghrelin. These catabolic and anabolic signals induce corresponding alterations in catabolic and anabolic neuropeptides and neurotransmitters in brain centers responsible for energy homeostasis.

In the central nervous system, the hypothalamus is one of the most important centers for energy balance, especially its arcuate nucleus (ARC). Leptin is primarily secreted from adipose tissue and its circulating levels are positively correlated to adiposity (6). Hypothalamic insulin and leptin receptors are located in ARC, on neuropeptide Y (NPY) and proopiomelanocortin (POMC) neurons that project from the ARC to other hypothalamic regions such as the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA). Leptin and insulin stimulate POMC neurons, promoting the release of the anorexigenic neuropeptides corticotrophin-releasing hormone (CRH) and cocaine-and-amphetamine-regulated transcript (CART) in the PVN, and inhibiting the release of orexigenic neuropeptides orexin and melanocortin-concentrating hormone (MCH) in the LHA, via the release of melanocyte-stimulating hormone (α-MSH) and (CART), lead to suppression of food intake. NPY neurons release agouti-related protein (AgRP) and gamma-aminobutyric acid (GABA); both tonically inhibit POMC neurons via NPY Y_1 receptors. NPY/AgRP neurons inhibit the release of the anorexigenic neuropeptides CRH and CART in the PVN, promote the release of the orexigenic neuropeptides orexin and MCH in the LHA, via release of NPY, and inhibit POMC neuronal activity via release of AgRP and GABA, thus promoting food intake (7). Leptin and insulin inhibit NPY/AgRP neurons via leptin and insulin receptors, thereby decreasing GABAergic inhibitory input to POMC cells, which ultimately increases the release of CRH and CART via the PVN. In summary, activation of leptin receptors in ARC stimulates POMC neurons and inhibits NPY neurons (6). When leptin levels are high after a meal, for example, it activates POMC neurons that suppress feeding and inhibits NPY neurons. As energy and leptin levels decrease, NPY neurons are disinhibited, thus stimulating feeding and inhibiting POMC neurons. Insulin parallels the actions of leptin in the ARC (8).

The cannabinoid and serotonin (5-HT) systems, among other neurotransmitter systems, modulate the hypothalamic melanocortin and NPY feeding networks. It has been shown that administration of cannabinoid-1 receptor (CB_1) agonists and antagonists causes hyperphagia and hypophagia, respectively (9). These effects are mediated by modulation of the hypothalamic feeding pathways. Serum endocannabinoid levels are elevated in obesity (10), which implies a role for CB_1 activation in weight gain. These observations lead to development of rimonabant, a cannabinoid-1

receptor antagonist, for the treatment of obesity. This agent was shown to be very effective in promoting weight loss and improvements in the metabolic profile in patients with metabolic syndrome (11). However, increased incidence of mood-related disorders lead to the withdrawn of ribonabant from the market. The development of other cannabinoid-1 receptor antagonists agents for obesity therapy has been also discontinued.

Enhanced 5-HT release causes hypophagia, whereas inhibition of 5-HT release causes hyperphagia. These effects are mediated by 5-HT2C and 5-HT1B receptors, located on hypothalamic POMC and NPY neurons, respectively. Acting through 5-HT1B receptors, 5-HT hyperpolarizes and inhibits NPY/Agrp neurons, thereby decreasing GABAergic inhibitory input to POMC cells. 5-HT also directly activates POMC neurons through its effects on 5-HT2C receptors. These processes lead to a reciprocal increase in α-MSH and decrease in AgRP release at melanocortin target sites (12).

In addition to digesting and assimilating nutrients, the gastrointestinal system play a key-role sensing and signaling the physiology of energy homeostasis. The gut, the pancreatic islets of Langerhans, and elements in the portal vasculature, communicate with the controllers of energy balance in the brain by means of neural and endocrine pathways. Short-term alterations in nutrient status are communicated to the brain through satiety signals from the gastrointestinal (GI) tract. In response to volumetric and caloric cues, GI peptides (as cholecystokinin, peptide YY3-36, pancreatic polypeptide and glucagon-like peptide-1) are released in the gut during feeding (13) and, binding to specific receptors on the vagus nerve, convey information to the brain. These satiety signals, and those from the hypothalamic feeding networks, are integrated centrally to determine meal size. Amylin, which is a peptide co-secreted with insulin from the pancreas in response to meals, also promotes satiety (14). The sensitivity of the brain response to afferent GI satiation signals is enhanced by long-acting catabolic adiposity hormones, leptin and insulin, which also contribute to regulating meal size (5). In the opposite way, secretion of the orexigenic peptide ghrelin, primarily from the stomach, occurs shortly before, rather than after, meals, and by increasing hunger it appears to promote meal initiation. Ghrelin also increases with weight loss and, acting on the hypothalamus, hindbrain, vagus nerve, and mesolimbic reward centers, promote increases in food intake and body weight.

EXPERIMENTAL DRUGS

Considering the lack of successful weight-loss treatments and the public-health implications of the obesity pandemic state, the development of safe and effective drugs should be a priority. There are several pharmacological agents in development that results in weight loss, either by a reduction in food intake, or by increasing energy expenditure.

Central stimulators agents of catabolic pathways

Leptin

Leptin is a peptide produced primarily in adipose tissue. In mice and in few humans with leptin deficiency, the administration of physiological doses of leptin decreases food intake and causes weight loss (15). When first identified, it was hoped that leptin would provide an effective antiobesity therapy. However, shortly it was discovered that obese patients are leptin-resistant and have elevated circulating leptin levels, which can be reduced with weight loss. In a study with 47 obese women and men given placebo or varying doses of recombinant human leptin for 24 weeks (and advised to eat 500 kcal less than requirement each day), there was a weakly dose-dependent decrease in body weight, ranging from -1.3 kg in the placebo group to -1.4 kg in the 0.03 mg/kg group and to -7.1 kg in the 0.30 mg/kg group (16). These results suggest that leptin resistance can be overcome with high doses of leptin, but it is not known whether the effect can be sustained or not. One small study suggested that leptin therapy may prevent regaining weight after significant weight loss by preventing the weight gain associated to the decrease in energy expenditure (15). Thus, leptin could be developed as an adjunctive therapy to a primary weight loss agent to reduce the counter-regulatory neuroendocrine effects of low leptin levels.

Mechanisms of insulin and leptin resistance

The intracellular signaling mechanisms involved in hypothalamic leptin and insulin resistance are under active investigation. Experimental studies in animals with diet-induced obesity have identified some potential mediators of leptin resistance in brain areas critical to energy homeostasis. Leptin receptor activation engages two intracellular proteins that terminate receptor signaling – namely, suppressor of cytokine signaling-3 (SOCS3) and protein tyrosine phosphatase-1B (PTP1B) – and inhibition of either of these autoinhibitory factors could theo-

retically increase leptin sensitivity (17,18). It has been shown that SOCS3 activity is increased in obesity, which suggests an etiological role in leptin resistance. However, the inhibition of SOCS3 as a strategy to treat obesity deserves caution since SOCS3 regulates more than just leptin signaling, and homozygous global knockout mice die *in utero* (19). Also, potentially, PTB1B might be a viable antiobesity drug target, since PTP1B knockout mice are hypersensitive to insulin and leptin and resistant to obesity when fed a high-fat diet (20). In addition, it has been shown that selective blockade of PTP1B expression, induced by infusion of an antisense oligonucleotide, in rat hypothalamic areas surrounding the third ventricle, results in decreases in food intake, reductions in body weight and adiposity after high-fat diet. These effects were associated with increases in leptin and insulin action in hypothalamus (21). However, translating these promising findings into clinical utility is related to the difficulty of inhibiting PTP1B selectively in body-weight regulatory circuits without interfering in other important functions of this enzyme.

It is well known that obesity is associated with a state of abnormal inflammatory response. The Toll-like receptor 4 (TLR4) is a subclass of Toll-like receptors which play an important role in inflammation and immunity. TLR4 can be activated by saturated fatty acids (22) and has been recognized as a mediator in the crosstalk between inflammatory and metabolic signals. The activation of TLR4 signaling leads to up regulation of intracellular inflammatory pathways that induce insulin resistance (23). Furthermore, mice with a loss-of-function mutation in TLR4 are protected against the development of diet-induced obesity and insulin resistance (24). More recently it was shown that in animal models of diet-induced obesity, TLR4 acts as a predominant molecular target for saturated fatty acids in the hypothalamus and, triggering the intracellular signaling network, induces an inflammatory response which determines the resistance to the anorexigenic hormones insulin and leptin (25). Thus, a selective interference with TLR4 or even with the inflammatory response to its activation may emerge, in the future, as an important strategy for the treatment of obesity and insulin resistance.

Melanocortin-4 receptor agonists

In the leptin-melanocortin pathway, POMC is the first key intermediary downstream of leptin-receptor signaling. By enhancing energy expenditure and suppressing appetite, melanocortin peptides derived from POMC play a primary role in the hypothalamic regulation of body weight. Cleavage of POMC by prohormone convertase-1 produces, among other peptides, α-MSH, which activates melanocortin-3 and -4 receptors (MC3R, MC4R). These receptors were recognized as possible targets for antiobesity therapies because of their specific roles in energy homeostasis and their position downstream the locus of leptin resistance.

In a study in normal-weight adults, the 6-week intranasal administration of the MSH/ACTH (4-10) core fragment of POMC resulted in a distinct reduction of body weight and body fat, accompanied by significant decreases in leptin and insulin plasma concentrations (26). However, in overweight individuals, MSH/ACTH (4-10) did not induce any significant reduction in body weight, body fat, and plasma levels of insulin and leptin as compared to the effects of placebo. The authors conclude that, contrasting with normal-weight humans, overweight subjects are not susceptible to the effects of melanocortin administration on hypothalamic weight regulatory systems. The hypothesis is that in overweight subjects, a decreased sensitivity to ACTH/MSH peptides may derive from alterations at the level of the melanocortin receptors or at subsequent steps in the processing of the body fat signal (27).

Subtype-selective serotonin-receptor agonists

Three of the pharmacological agents that have been used clinically to treat obesity – sibutramine, fenfluramine, and dexfenfluramine (d-FEN) – all increase signaling by the neurotransmitter serotonin [5-hydroxytryptamine (5-HT)]. Anorectic medications targeting the 5-HT system are typically derived from β-phenethylamine (the skeletal structure of the neurotransmitters dopamine, noradrenalin and adrenaline), and mediate their effects by influencing noradrenergic, dopaminergic and serotonergic neurotransmission. Increasing the availability of 5-HT by affecting its release and reuptake in the synaptic cleft, or the direct activation of the 5-HT receptors, reduces food consumption, whereas decreasing 5-HT receptor activation produces the opposite effect.

Serotonin is a monoaminergic neurotransmitter that acts through a family of at least fourteen 5-HT receptor subtypes to modulate numerous sensory, motor, and behavioral processes. Serotonin 5-HT1B and 5-HT2C receptors have been specifically recognized as mediators of serotonin-induced satiety, probably acting through

the hypothalamic melanocortin system. Acting through 5-HT1B receptors, 5-HT hyperpolarizes and inhibits NPY/AGRP neurons, thus decreasing GABAergic inhibitory input to POMC cells. Serotoninergic agents also activate hypothalamic POMC neurons through 5-HT2C receptors which subsequently activates MC3R and MC4R, reducing food intake (28). Sibutramine, dexfenfluramine, fluoxetine and the 5-HT2C receptor agonist chlorophenylpiperazine (mCPP) have showed to modify appetite in both lean and obese humans, resulting in reduced caloric intake. In addition to its serotoninergic action, it has been shown in lipopolysaccharide (LPS)-stimulated microglia and astrocyte cultures that mCPP attenuates the expression of pro-inflammatory cytokines, such as IL-1beta and TNF-alpha, and inhibits both the activation of the nuclear factor-kappa B and phosphorylation of p38 mitogen-activated protein kinase (29). Considering that the activation of TLR4 by saturated fatty acids is implicated in the up regulation of intracellular inflammatory pathways involved in the hypothalamic leptin and insulin resistance (27), this cerebral anti-inflammatory action of mCPP, theoretically, can contribute to the anorexigenic action of this compound. However, this potential drug mechanism of action has to be proven yet.

Several 5-HT_{2C} receptor agonists are in development. Lorcaserin (APD356) is a selective 5-HT_{2C} receptor agonist for obesity, which is currently undergoing the final phase III of clinical trials. Phase IIb data for this compound demonstrated average weight loss of 1.8, 2.6 and 3.6 kg following a 12-week administration of 10, 15 or 20 mg daily, respectively, compared with 0.3 kg for the placebo group (30). Lorcaserin does not cause heart valve damage in the same way as previously withdrawn serotonergic drugs. After 12 months of observation, the echocardiograms of the participants of the first of three Phase III clinical trials ("BLOOM") did not meet the trial-stopping criteria developed by an independent Echocardiographic Data Safety Monitoring Board (EDSMB), and so the trial continues (31). Also in development is the 5-HT_{2C} agonist WAY-163909 (32).

CENTRAL INHIBITORS AGENTS OF ANABOLIC PATHWAYS

Neuropeptide Y (NPY)

NPY is a hypothalamic anabolic neuropeptide inhibited by the anorexigenic hormones insulin and leptin. It has been shown that chronic NPY administration powerfully increases food intake and body weight. NPY, however, is the most abundant central neuropeptide, with pleiotropic functions that act through at least five receptors subtypes (Y1, Y2, Y4, Y5, and Y6). It imposes a difficulty to target them for obesity without eliciting unacceptable side effects. Some studies identified the Y5 receptor as one of the isoforms responsible for the orexigenic effects of NPY that could be targeted to promote weight loss. The NPY Y_5 receptor is located on POMC neurons in the ARC and preclinical data have shown marked hyperphagia on administration of selective Y_5 receptor agonists. Compounds targeting the NPY system, S-2367 and MK-0577, are NPY Y_5 receptor antagonists. However, in a clinical trial with obese patients, administered S-2367 (1,600 mg, 12 weeks) promoted a weight loss of 3.6 kg. However in a 1-year phase, two trials of MK-0577 were abandoned because of lack of efficacy (33).

Melanin-concentrating hormone (MCH)

Another leptin-inhibited orexigenic hypothalamic neuropeptide is melanin-concentrating hormone (MCH). This peptide acts downstream of at least some levels of leptin resistance and is expressed in neurons of the lateral hypothalamic area. The feeding effects of MCH are mediated by, the MCH1 receptor (MCHR1) (34). Medicinal blockade of MCH signaling has been explored as an antiobesity modality. However, MCH regulates many functions beyond feeding, such as locomotor activity, anxiety, aggression, sensory processing and learning; it is not easy to design anti-MCH agents that selectively modulate energy homeostasis without eliciting undesirable side effects. MCHR1 antagonism has yet to be proven as an effective treatment for obesity.

GASTROINTESTINAL PEPTIDES THAT REGULATE FOOD INTAKE

Many of the circulating gastrointestinal peptides have direct access to regions of the brain involved in the regulation of food intake, including the arcuate nucleus (ARC) of the hypothalamus and the area postrema. These peptides may also function outside of the CNS to influence the activity of neurons such as the vagal nerve, which projects to the nucleus of the solitary tract (NTS) in the brain stem (Figure 1).

Peptide YY (PYY)

The gut hormone peptide YY (PYY) suppresses appetite and decreases food intake apparently by activating

autoinhibitory receptors on orexigenic NPY/AGRP neurons in the hypothalamus, and thereby derepressing anorexigenic POMC neurons. It has been shown, in a trial of obese and lean adults, that short-term intravenous PYY_{3-36} administration decreased appetite and caloric intake by approximately 30% in both groups, suggesting that PYY might be a useful therapy for weight loss (35). Also, the observation that the anorectic efficacy of exogenous PYY_{3-36} is fully intact in obese people, encouraged long-term studies to determine whether chronic administration of PYY_{3-36} or related peptidomimetics could promote weight loss. However, in a 12-week trial of 133 obese patients who were randomly assigned to intranasal PYY (200 or 600 mcg three times a day before meals) or placebo, in conjunction with diet and exercise, weight loss was similar in the placebo and 200 mcg PYY groups (2.8 and 3.7 kg, respectively) (36). Weight loss could not be assessed in the 600 mcg PYY group, because 60% of patients dropped out due to nausea and vomiting.

Pancreatic polypeptide (PP)

A 36-amino-acid peptide that is primarily expressed in the duodenal endocrine cells of the pancreas and distal gut belongs to the same peptide family as PYY. Plasma PP concentrations are primarily regulated by food intake. Like $PYY_{(3-36)}$ PP is released postprandially, but in a biphasic manner, in proportion to calories ingested. In normal-weight individuals, PP infusion rapidly diminishes appetite after just two hours, and causes a prolonged decrease in food intake over the following 24 hours (37). As with $PYY_{(3-36)}$, levels of PP are lower in obese subjects. Circulating PP is thought to mediate its anorectic effects through the highly expressed Y_4 receptors located in the area postrema. A synthetic analogue (TM30338) of both $PYY_{(3-36)}$ and PP, which acts as an agonist of both the Y_2 and Y_4 receptors, is under development. Recently, reported data indicate that once-a-day subcutaneous dosing of TM30338 in obese human subjects inhibited food intake, at a statistically significant level, up to at least nine hours after dosing (38).

Glucagon-like peptide-1 (GLP-1)

Exendin-4 (39) exenatide (Byetta; Amylin/Lilly), is a naturally occurring agonist of the GLP-1 receptor isolated from the lizard *Heloderma suspectum* and has longer biological activity than GLP-1. This protease-resistant GLP-1 congener increases insulin secretion and possibly sensitivity, being already marketed to treat diabetes. In clinical trials, beyond reductions in hemoglobin A1C, exenatide promotes a modest but progressive weight loss (40) which is especially remarkable because improvements in glycemic control achieved with other agents typically promote weight gain. The mechanisms mediating anorectic effects of GLP-1 are not fully known but they appear to play an important role for the vagus nerve. Other GLP-1 analogue, liraglutide, is also reported to produce weight loss and reduce food intake. Although GLP-1 receptor agonists are not currently approved for obesity treatment, the impressive effects of exenatide on body weight demands consideration of such agents for this indication.

Oxyntomodulin

Oxyntomodulin is a peptide produced in L-cells of the GI tract from the proglucagon gene product. Chronic oxyntomodulin injections in animals decrease body weight more than expected from the reduction in food intake, suggesting an additional effect of increasing energy expenditure. When self-administered three times a day 30 minutes before meals in obese volunteers the group (n = 14) treated with oxyntomodulin lost 2.3 ± 0.4 kg, compared to 0.5 ± 0.5 kg in those treated with placebo. Food intake was reduced by 250 kcal (35% ± 9%) in the last meal (41).This modest but favorable results provide justification for larger, longer term trials of oxyntomodulin as a potential antiobesity agent.

Amylin

Amylin, a 37-amino acid peptide that is stored in pancreatic β-cells and is co-secreted with insulin postprandially from pancreatic β-cells, inhibits gastric emptying, gastric acid output, and glucagon secretion. It can also dose-dependently decrease meal size and food intake through vagus-independent actions on the hindbrain area postrema. Pramlintide is a stable, soluble, nonaggregating, equipotent amylin analog that is administered by mealtime subcutaneous injection. It is marketed for diabetes treatment, but it also causes mild progressive weight loss for at least 16 week in humans (42). Pramlintide does not cause hypoglycemia in the absence of therapies with other hypoglycemic agents, since its effects are glucose-dependent and are overridden as serum glucose levels fall. It has been shown that

supraphysiologic doses of pramlintide do not provoke hypoglycemia in normal subjects.

The effects of pramlintide were assessed in non diabetic obese patients. In a randomized, double-blind, placebo-controlled study, 204 obese subjects self-administered pramlintide (nonforced dose escalation < or = 240 mg) or placebo via subcutaneous injection three times a day before meals for 16 week, without concomitant lifestyle intervention (43). The drug was generally well tolerated, and the withdrawal rates were similar to placebo (25%) and pramlintide-treated groups (29%). Subjects completing 16 week of pramlintide treatment experienced placebo-corrected reductions in body weight of 3.7% ± 0.5% and in waist circumference of 3.6 ± 1.1 cm; approximately 31% of subjects treated with pramlintide achieved 5% or greater weight loss compared to 2% in the placebo group. These results support continued evaluation of pramlintide as a potential treatment for obesity.

AGENTS ACTING THROUGH PERIPHERAL MECHANISMS

Lipase inhibitors

Lipase inhibitors inhibit gastric and pancreatic lipases in the lumen of the gastrointestinal tract to decrease systemic absorption of dietary fat. Krista (Xenia; Roche), or tetra-hydrolipstatin, is indicated for the management of obesity (including weight loss and weight maintenance) when used in conjunction with a diet of reduced calories. The only other lipase inhibitor currently in clinical development for the treatment of obesity is ATL-962 (Cetilistat; Alizyme). Clinical data available indicate that ATL-962 has comparable efficacy to orlistat (Phase IIb clinical trial showed 3 kg weight loss over placebo in three months) but with a favorable side-effect profile (90% fewer severe gastrointestinal side effects) compared with that reported for orlistat.

Lipid metabolism modulators

Human growth hormone (hGH) has lipolytic/antilipogenic properties. As an inhibitor of lipoprotein lipase, it can increase circulation of free fatty acids and ultimately reduce fat-cell mass (44). Levels of human growth hormone are typically suppressed in the obese state and with increasing age. It has been shown that hGH therapy reduces abdominal fat both in men and postmenopausal women (45,46). However, clinical applications of hGH for long-term obesity treatment have not been successful because of its diabetogenic and other unwanted side effects. The lipolytic domain of the hGH molecule has been identified as the carboxyl terminus of the intact hormone (residues 177-191). $hGH_{(177–191)}$ inhibits the activity of acetyl co-enzyme A carboxylase in adipocytes and hepatocytes, which reduces glucose incorporation into lipid in both isolated cells and tissues, and thereby enhances the breakdown of stored fats, and inhibits the synthesis of new fat (47) without the diabetogenic effects associated with the amino-terminal region of the molecule. The fragment $hGH_{(177–191)}$ is currently under development by Metabolic Pharmaceuticals as AOD9604, an orally available peptide (due to cyclization) described as a lipid-metabolism modulator. Results of a Phase IIb clinical trial showed that administration of 1 mg AOD9604 once a day led to weight loss of 2.0 kg more than placebo over the course of 12 weeks.

Compounds that aim at reducing body weight by increasing energy expenditure have also been explored. β3-adrenergic receptor agonists cause lipolysis and increase thermogenesis. However, several phase 2 trials with β3-adrenergic receptor agents have been discontinued because of poor drug efficacy and safety profiles (48).

Thyroid hormone increases thermogenesis via thyroid hormone receptor β subtype. Thyroid hormone receptor agonists have been investigated as potential therapeutic targets, but with limited success, as it was proved the difficulty in developing selective compounds with good safety profiles.

COMBINATION THERAPIES

Body weight is defended by redundant regulatory systems so that weight loss resulting from an intervention that only stimulates metabolic rate should elicit an adaptive increase in food intake. On the other hand, pharmacological antagonism of anabolic signals is theoretically limited in its ability to promote major weight reduction because changes in other pathways could compensate for the loss of an orexigen mechanism. Therefore, as in other chronic diseases (e.g., hypertension, diabetes), combination therapies targeting several points in the network may be necessary to achieve effective control of body weight.

Qnexa (VI-0521), a pharmaceutical combination containing low doses of the amphetamine-derived compound and a catecholamine releaser, phentermine with and the anticonvulsant agent topiramate, is being

developed for obesity. Topiramate is a sulphamate-substituted fructose that is approved as an anti-epileptic/antimigraine agent and which has multifactorial effects on the CNS, involving blockade of voltage-dependent sodium channels and action on the GABA (γ-amino butyric acid) and glutamate systems (49). Phase II data for Qnexa demonstrated a placebo-adjusted non-plateaued weight loss of 9.2 kg after 24 weeks, and the proportion of patients achieving 10% or more total body weight loss was greater than the sum of phentermine and topiramate comparator agents administered alone. Subjects with an average BMI of 38 received daily doses of Qnexa (or placebo/one of the active ingredients separately), and were asked to reduce caloric intake by 500 calories per day.

Contrave, a combination of the centrally acting medications bupropion, a dopamine and noradrenalin-reuptake inhibitor that has demonstrated dose-related weight loss (50), and naltrexone, an opioid-receptor antagonist used to treat narcotic and alcohol dependency. Bupropion and naltrexone have been reported to synergistically stimulate the pro-opiomelanocortin (POMC) system that is associated with reducing food intake by blocking a β-endorphin-mediated inhibition of POMC neurons. Phase II data for Contrave (bupropion 150 mg b.i.d., naltrexone 50 mg q.d., 24 weeks) demonstrated a 6.6% non-plateaued weight loss after 24 weeks in subjects with a BMI ranging from 30 to 40, in comparison with 3.8% (bupropion alone), 2.2% (naltrexone alone) and 0.9% (placebo), respectively (51). Although nausea (40%) led to withdrawals, it is thought that dosage adjustment of the components might diminish it.

Excalia is a combination of bupropion and zonisamide, an anticonvulsant; both enhance the release of α-MSH and CART and increase 5-HT levels. In a short-term, open-label, preliminary trial, combination treatment of zonisamide and bupropion resulted in more weight loss than treatment with zonisamide alone (52). Finally, combination therapy with sibutramine and leptin has been shown, in preclinical studies, to cause a synergistic decrease in body weight (53).

CONCLUSIONS

Despite the incredible gains in our understanding of energy homeostasis, much remains unknown regarding the complex central and peripheral mechanisms that underlie obesity. Like many drugs for chronic disease, medication is not a cure, but an indutor of a pharmacologic effect that occurs while it is taken. Moving forward, treatment with a combination of agents may result in better outcomes in obesity therapy while more efficacious drugs are not available.

Disclosure: No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ. 2007;335(7631):1194-9.
2. Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. Lancet. 2007;369(9555):71-7.
3. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995;332(10):621-8.
4. Schwartz MW, Woods SC, Seeley RJ, Barsh GS, Baskin DG, Leibel RL. Is the energy homeostasis system inherently biased toward weight gain? Diabetes. 2003;52(2):232-8.
5. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. Nature. 2006;443(7109):289-95.
6. Ahima RS, Flier JS. Leptin. Annu Rev Physiol. 2000;62:413-37.
7. Broberger C, Landry M, Wong H, Walsh JN, Hökfelt T. Subtypes Y1 and Y2 of the neuropeptide Y receptor are respectively expressed in pro-opiomelanocortin- and neuropeptide-Y-containing neurons of the rat hypothalamic arcuate nucleus. Neuroendocrinology. 1997;66(6):393-408.
8. Niswender KD, Baskin DG, Schwartz MW. Insulin and its evolving partnership with leptin in the hypothalamic control of energy homeostasis. Trends Endocrinol Metab. 2004;15(8):362-9.
9. Kirkham TC, Tucci SA. Endocannabinoids in appetite control and the treatment of obesity. CNS Neurol Disord Drug Targets. 2006;5(3):272-92.
10. Engeli S, Bohnke J, Feldpausch M, Gorzelniak K, Janke J, Bátkai S, et al. Activation of the peripheral endocannabinoid system in human obesity. Diabetes. 2005;54(10):2838-43.
11. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet. 2007;370(9600):1706-13.
12. Heisler LK, Jobst EE, Sutton GM, Zhou L, Borok E, Thornton-Jones Z, et al. Serotonin reciprocally regulates melanocortin neurons to modulate food intake. Neuron. 2006;51(2):239-49
13. Woods SC. Gastrointestinal satiety signals I. An overview of gastrointestinal signals that influence food intake. Am J Physiol Gastrointest Liver Physiol. 2004;286(1):G7-13.
14. Woods SC, Lutz TA, Geary N, Langhans W. Pancreatic signals controlling food intake; insulin glucagons, and amylin. Philos Trans R Soc Lond B Biol Sci. 2006;361(1471):1219-35.
15. Rosenbaum M, Goldsmith R, Bloomfield D, Magnano A, Weimer L, Heymsfield S, et al. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. J Clin Invest. 2005;115(12):3579-86.
16. Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA. 1999;282(16):1568-75.
17. Bjorbaek C, Elmquist JK, Frantz JD, Shoelson SE, Flier JS. Identification of SOCS-3 as a potential mediator of central leptin resistance. Mol Cell. 1998;1(4):619-25.
18. Zabolotny JM, Bence-Hanulec KK, Stricker-Krongrad A, Haj F, Wang Y, Minokoshi Y, et al. PTP1B regulates leptin signal transduction in vivo. Dev Cell. 2002;2(4):489-95.

19. Marine JC, McKay C, Wang D, Topham DJ, Parganas E, Nakajima H, et al. SOCS3 is essential in the regulation of fetal liver erythropoiesis. Cell. 1999;98(5):617-27.
20. Elchebly M, Payette P, Michaliszyn E, Cromlish W, Collins S, Loy AL, et al. Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. Science. 1999;283(5407):1544-8.
21. Picardi PK, Calegari VC, Prada PO, Moraes JC, Araújo E, Marcondes MC, et al. Reduction of hypothalamic protein tyrosine phosphatase improves insulin and leptin resistance in diet-induced obese rats. Endocrinology. 2008;149(8):3870-80.
22. Lee JY, Ye J, Gao Z, Youn HS, Lee WH, Zhao L, et al. Reciprocal modulation of Toll-like receptor-4 signaling pathways involving MyD88 and phosphatidylinositol 3-kinase/AKT by saturated and polyunsaturated fatty acids. J Biol Chem. 2003;278(39):37041-51.
23. Takeda K, Kaisho T, Akira S. Toll-like receptors. Annu Rev Immunol. 2003;21:335-76.
24. Tsukumo DM, Carvalho-Filho MA, Carvalheira JB, Prada PO, Hirabara SM, Schenka AA, et al. Loss-of-function mutation in Toll-like receptor 4 prevents diet-induced obesity and insulin resistance. Diabetes. 2007;56(8):1986-98.
25. Milanski M, Degasperi G, Coope A, Morari J, Denis R, Cintra DE, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. J Neurosci. 2009;29(2):359-70.
26. Fehm HL, Smolnik R, Kern W, McGregor GP, Bickel U, Born J. The melanocortin melanocyte-stimulating hormone adrenocorticotropin(4-10) decreases body fat in humans. J Clin Endocrinol Metab. 2001;86(3):1144-8
27. Hallschmid M, Smolnik R, McGregor G, Born J, Fehm HL. Overweight humans are resistant to the weight-reducing effects of melanocortin4-10. J Clin Endocrinol Metab. 2006;91(2):522-5.
28. Heisler LK, Jobst EE, Sutton GM, Zhou L, Borok E, Thornton-Jones Z, et al. Serotonin reciprocally regulates melanocortin neurons to modulate food intake. Neuron. 2006;51(2):239-49
29. Hwang J, Zheng LT, Ock J, Lee MG, Suk K. Anti-inflammatory effects of m-chlorophenylpiperazine in brain glia cells. Int Immunopharmacol. 2008;8(12):1686-94.
30. Arena Pharmaceuticals Announces Positive Phase 2b Clinical Trial Results of Novel Anti-Obesity Compound. Disponível em: http://www.invest.arenapharm.com/releasedetail.cfm?ReleaseID=320421
31. Arena Pharmaceuticals' Lorcaserin for Obesity Passes Major Safety Milestone. Disponível em: http://www.invest.arenapharm.com/releasedetail.cfm?ReleaseID=320197.
32. Dunlop J, Sabb AL, Mazandarani H, Zhang J, Kalgaonker S, Shukhina E, et al. WAY-163909 [(7bR, 10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1h i]indole], a novel 5-hydroxytryptamine 2C receptor-selective agonist with anorectic activity. J Pharmacol Exp Ther. 2005;313:862-9.
33. Erondu N, Gantz I, Musser B, Suryawanshi S, Mallick M, Addy C, et al. Neuropeptide Y5 receptor antagonism does not induce clinically meaningful weight loss in overweight and obese adults. Cell Metab. 2006;4(4):275-82.
34. Pissios P, Bradley RL, Maratos-Flier E. Expanding the scales: the multiple roles of MCH in regulating energy balance and other biological functions. Endocr Rev. 2006;27(6):606-20.
35. Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, et al. Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med. 2003;349(10):941-8.
36. Gantz I, Erondu N, Mallick M, Musser B, Krishna R, Tanaka WK, et al. Efficacy and safety of intranasal peptide YY3-36 for weight reduction in obese adults. J Clin Endocrinol Metab. 2007;92(5):1754-7.
37. Batterham RL, Le Roux CW, Cohen MA, Park AJ, Ellis SM, Patterson M et al. Pancreatic polypeptide reduces appetite and food intake in humans. J Clin Endocrinol Metab. 2003;88(8):3989-92.
38. 7TM Pharma. 7TM Pharma's new first-in-class anti-obesity drug completes Phase I/II clinical studies. Press release [online] 2006. Disponível em: <http://www.demo.7tm.com/news>.
39. Davidson MB, Bate G, Kirkpatrick P. Exenatide. Nat Rev Drug Discov. 2005;4(9):713-4.
40. Bhushan R, Elkind-Hirsch KE, Bhushan M, Butler WJ, Duncan K, Marrioneaux O. Exenatide use in the management of metabolic syndrome: a retrospective database study. Endocr Pract. 2008;14(8):993-9.
41. Wynne K, Park AJ, Small CJ, Patterson M, Ellis SM, Murphy KG, et al. Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. Diabetes. 2005;54(8):2390-5.
42. Hollander P, Maggs DG, Ruggles JA, Fineman M, Shen L, Kolterman OG, et al. Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. Obes Res. 2004;12(4):661-8.
43. Aronne L, Fujioka K, Aroda V, Chen K, Halseth A, Kesty NC, et al. Progressive reduction in body weight after treatment with the amylin analog pramlintide in obese subjects: a phase 2, randomized, placebo-controlled, dose-escalation study. J Clin Endocrinol Metab. 2007;92(8):2977-83.
44. Ridderstrale M, Tornqvist H. Effects of tyrosine kinase inhibitors on tyrosine phosphorylations and the insulin-like effects in response to human growth hormone in isolated rat adipocytes. Endocrinology. 1996;137(11):4650-6.
45. Franco C, Brandberg J, Lönn L, Andersson B, Bengtsson BA, Johannsson G. Growth hormone treatment reduces abdominal visceral fat in postmenopausal women with abdominal obesity: a 12-month placebo-controlled trial. J Clin Endocrinol Metab. 2005;90(3):1466-74.
46. Halpern A, Mancini MC, Cercato C, Villares SM, Costa AP. Effects of growth hormone on anthropometric and metabolic parameters in android obesity. Arq Bras Endocrinol Metabol. 2006;50(1):68-73.
47. Wu Z, Ng FM. Antilipogenic action of synthetic C-terminal sequence 177-191 of human growth hormone. Biochem Mol Biol Int. 1993;30(1):187-96.
48. Arch JR. Beta(3)-adrenoceptor agonists: potential, pitfalls and progress. Eur J Pharmacol. 2002;440(2-3):99-107.
49. Rosenfeld WE. Topiramate: a review of preclinical, pharmacokinetic, and clinical data. Clin Ther. 1997;19(6):1294-308.
50. Anderson JW, Greenway FL, Fujioka K, Gadde KM, McKenney J, O'Neil PM. Bupropion SR enhances weight loss: a 48-week double-blind, placebo- controlled trial. Obes Res. 2002;10(7):633-41.
51. Greenway FL, et al. Bupropion and naltrexone for the treatment of obesity; Am. Diabetes Assoc. 66th Scientific Sessions Abs1706-P; 2006.
52. Gadde KM, Yonish GM, Foust MS, Wagner HR. Combination therapy of zonisamide and bupropion for weight reduction in obese women: a preliminary, randomized, open-label study. J Clin Psychiatry. 2007;68(8):1226-9.
53. Boozer CN, Leibel RL, Love RJ, Cha MC, Aronne LJ. Synergy of sibutramine and low-dose leptin in treatment of diet-induced obesity in rats. Metabolism. 2001;50(8):889-93.