

Current and Investigational Antiobesity Agents and Obesity Therapeutic Treatment Targets

Harold E. Bays

Abstract

BAYS, HAROLD E. Current and investigational antiobesity agents and obesity therapeutic treatment targets. *Obes Res.* 2004;12:1197–1211.

Public health efforts and current antiobesity agents have not controlled the increasing epidemic of obesity. Investigational antiobesity agents consist of 1) central nervous system agents that affect neurotransmitters or neural ion channels, including antidepressants (bupropion), selective serotonin 2c receptor agonists, antiepileptic agents (topiramate, zonisamide), some dopamine antagonists, and cannabinoid-1 receptor antagonists (rimonabant); 2) leptin/insulin/central nervous system pathway agents, including leptin analogues, leptin transport and/or leptin receptor promoters, ciliary neurotrophic factor (Axokine), neuropeptide Y and agouti-related peptide antagonists, pro-opiomelanocortin and cocaine and amphetamine regulated transcript promoters, α -melanocyte-stimulating hormone analogues, melanocortin-4 receptor agonists, and agents that affect insulin metabolism/activity, which include protein-tyrosine phosphatase-1B inhibitors, peroxisome proliferator activated receptor- γ receptor antagonists, short-acting bromocriptine (ergometrin), somatostatin agonists (octreotide), and adiponectin; 3) gastrointestinal-neural pathway agents, including those that increase cholecystokinin activity, increase glucagon-like peptide-1 activity (extendin 4, liraglutide, dipeptidyl peptidase IV inhibitors), and increase protein YY3-36 activity and those that decrease ghrelin activity, as well as amylin analogues (pramlintide); 4) agents that may increase resting metabolic rate (“selective” β -3 stimulators/agonists, uncoupling protein homologues, and thyroid receptor agonists); and 5) other more diverse agents, including melanin concentrating hormone antagonists, phytosterol analogues, functional oils, P57, amylase inhibitors, growth hormone fragments, synthetic analogues of dehydroepiandrosterone sulfate, antagonists of adipocyte 11 β -hydroxysteroid dehydrogenase type 1 activity, corticotropin-

releasing hormone agonists, inhibitors of fatty acid synthesis, carboxypeptidase inhibitors, indanones/indanols, aminosterols, and other gastrointestinal lipase inhibitors (ATL962). Finally, an emerging concept is that the development of antiobesity agents must not only reduce fat mass (adiposity) but must also correct fat dysfunction (adiposopathy).

Key words: adiposopathy, insulin, leptin, treatment target

Introduction

Obesity is the most common metabolic disease in developed nations. Despite public health education and initiatives, its prevalence continues to increase, with >30% of adults in the United States being obese and >60% of adults being overweight or obese (1). The World Health Organization has estimated that worldwide, over one billion adults are overweight, with at least 300 million of them being obese (2). The increasing prevalence of obesity among children and adolescents is also of great concern (3) and suggests a likelihood of worsening obesity trends in future adults. Obesity leads to, or significantly increases the risk of, comorbidities involving various body systems including 1) cardiovascular [hypertension, congestive cardiomyopathy, varicosities, pulmonary embolism, coronary heart disease (CHD)¹], 2) neurological (stroke, idiopathic intracranial hypertension, neuralgia parasthetica), 3) respiratory (dyspnea, obstructive sleep apnea, hypoventilation syndrome, Pickwickian syndrome, asthma), 4) musculoskeletal (immobility, degenerative osteoarthritis, low back pain), 5) skin (striae distensae or “stretch marks,” venous stasis of the

Received for review November 18, 2003.

Accepted in final form May 28, 2004.

Address correspondence to Dr. Harold E. Bays, FACP Louisville Metabolic and Atherosclerosis Research Center, 3288 Illinois Ave., Louisville, KY 40213.

E-mail: HBaysMD@aol.com

Copyright © 2004 NAAASO

¹ Nonstandard abbreviations: CHD, coronary heart disease; GI, gastrointestinal; 5-HT, 5-hydroxytryptamine (serotonin); CNS, central nervous system; GABA, γ -aminobutyric acid; CB, cannabinoid; BBB, blood-brain barrier; JAK/STAT, janus kinase/signal transducer and activator of transcription; CNTF, ciliary neurotrophic factor; NPY, neuropeptide Y; AgRP, agouti-related peptide; POMC, pro-opiomelanocortin; CART, cocaine and amphetamine regulated transcript; PYY, protein YY3-36; MC, melanocortin; α MSH, α -melanocyte-stimulating hormone; CRH, corticotropin-releasing hormone; PI3K, phosphatidylinositol 3 kinase; IRS-1, insulin receptor substrate; PTP, protein-tyrosine phosphatase; PPAR, peroxisome proliferator activated receptor; CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; DPP IV, dipeptidyl peptidase IV; RMR, resting metabolic rate; UCP, uncoupling protein; BAT, brown adipose tissue; MCH, melanin-concentrating hormone; DHEAS, dehydroepiandrosterone sulfate.

lower extremities, lymphedema, cellulitis, intertrigo, carbuncles, acanthosis nigricans, skin tags), 6) gastrointestinal (GI; gastro-esophageal reflux disorder, nonalcoholic fatty liver/steatohepatitis, cholelithiasis, hernias, colon cancer), 7) genitourinary (stress incontinence, obesity-related glomerulopathy, breast and uterine cancer), 8) psychological (depression and low self-esteem, impaired quality of life), and 9) endocrine (metabolic syndrome, type 2 diabetes, dyslipidemia, hyperandrogenemia in women, polycystic ovarian syndrome, dysmenorrhea, infertility, pregnancy complications, male hypogonadism) (4).

Therefore, it has been a therapeutic and research goal to develop strategies to reduce the worldwide obesity epidemic (5,6) and a research goal to develop safe and effective antiobesity drugs, analogous to what has occurred with hypertension, dyslipidemia, and diabetes (7).

Current Therapies

Amphetamines (dextroamphetamine) have been used as antiobesity drugs, but can cause unacceptable tachycardia and hypertension. They also have a high rate of abuse potential and do not have a U.S. Food and Drug Administration indication for the treatment of obesity. Other sympathomimetic adrenergic agents, including phentermine, benzphetamine, phendimetrazine, mazindol, and diethylpropion, have less abuse potential than amphetamines; but these agents may have adverse cardiovascular side effects, and their indicated use is only short term (~12 weeks) (8) for the treatment of what is commonly a chronic metabolic disease. In 2000, the appetite suppressant phenylpropanolamine was removed from the over-the-counter market in the United States because of unacceptable risks of stroke, especially in adult women.

Sibutramine is a noradrenaline and serotonin (5-HT) reuptake inhibitor drug that has an indication for treatment of obesity by primarily increasing satiety (although some thermogenic effects may exist as well) (9). Sibutramine-associated weight loss occurs within the first 6 months of treatment, may be maintained for at least 2 years (10,11), and may have favorable effects on CHD risk factors, such as increasing high-density lipoprotein-cholesterol and decreasing triglyceride blood levels (12), as well as improving glucose control in patients with diabetes (13,14). However, because patients administered sibutramine may experience increases in blood pressure and heart rate, sibutramine's use is contraindicated in patients with uncontrolled hypertension, CHD, cardiac dysrhythmias, congestive heart failure, or stroke (15).

Orlistat, a gastrointestinal lipase inhibitor that impairs the absorption of dietary fat, has been shown to result in significant and sustained weight reduction for at least 2 years (16) and to favorably affect CHD risk factors. Orlistat may improve lipid blood levels (17,18), improve glucose metabolism in obese patients with and without diabetes (19–21),

and reduce high blood pressure (22). Orlistat use frequently results in adverse events including flatus, oily stools, fecal urgency or fecal incontinence, and abdominal pain, particularly among patients who do not follow the recommended low-fat diet. Daily multivitamin supplementation is recommended to prevent the potential of impaired absorption of fat-soluble vitamins (A, D, E, and K) that may theoretically occur with long-term use.

Antiobesity Agents that Affect Neurotransmitters and/or Neural Ion Channels (Table 1)

From a public health standpoint, diet, exercise, lifestyle, and behavior modifications (23,24) should be the first steps in obesity management. Avoidance of drugs known to potentially contribute to obesity is another step.

Various drugs and drug classes are known to affect body weight. Steroid hormones (glucocorticoids, estrogens, progestins), diabetes therapies (insulin, sulfonylureas, thiazolidinediones), highly active antiretroviral protease inhibitors, β -adrenergic blockers (most commonly described with nonselective β -blockers such as propranolol), some α -adrenergic blockers, and certain antihistamines (diphenhydramine) may increase body weight. Agents that affect the central nervous system (CNS) may either increase or decrease body weight. CNS drugs associated with increased body weight include some antidepressants [tricyclic antidepressants, irreversible monoamine oxidase (MAO) inhibitors, mirtazapine, and some selective serotonin reuptake inhibitors (such as paroxetine)], antiserotonin agents (pizotifen), some antiseizure drugs (valproate, gabapentin, and carbamazepine), some psychotropic drugs (clozapine, olanzapine, risperidone, quetiapine, thioridazine, divalproex, and chlorpromazine) (25), and lithium. CNS drugs that may decrease body weight are described later.

The weight gain and metabolic effects associated with some of these CNS drugs may be of potential clinical significance, and monitoring for significant weight gain, dyslipidemia, and diabetes has been recommended (25). For example, while it has been suggested that caloric intake may be decreased with dopamine antagonists such as risperidone in some patients with Prader-Willi syndrome (26), most studies have suggested that certain psychotropic drugs (including risperidone) are not only associated with weight gain, but also may be a particular concern in adolescents, perhaps increasing the risk of type 2 diabetes (27,28).

Thus, it is clinically useful to know the potential for weight gain or loss when using CNS drugs in the obese patient (Figure 2). Bupropion is an aminoketone unrelated to tricyclic antidepressants or selective serotonin reuptake inhibitors that seems to be a weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine and is currently indicated for the treatment of depression and smoking ces-

sation. It also has been shown to be effective in promoting weight loss in clinical trials in patients with or without depression (29,30). However, the antiobesity effects have been variable among individual patients, and bupropion does not currently have a specific indication for weight loss.

Other noradrenaline reuptake inhibitors are also sometimes used as antidepressant agents. GW320659 is a noradrenaline reuptake inhibitor that has undergone evaluation as both an antiobesity agent and a potential treatment for attention deficit hyperactivity disorder (31,32).

Dexfenfluramine and fenfluramine were dual 5-HT reuptake inhibitors and serotonin-releasing agents that were not indicated for treatment of depression, but had previously been used for suppression of appetite as antiobesity drugs. They were subsequently withdrawn from the market because of the onset of heart valve abnormalities thought to be related to the stimulation of peripheral (heart) 5-hydroxytryptamine (5-HT) 2b receptors (7,33,34). Investigational "selective" 5-HT 2c receptor agonists under development may induce satiety by selective effects on the hypothalamus while avoid toxicities to the heart.

Topiramate is a derivative of the naturally occurring sugar monosaccharide D-fructose and was originally developed as a diabetes treatment. Studies have suggested some potentially favorable effects on glucose tolerance and insulin sensitivity in animals administered topiramate and some glucose lowering in obese type 2 diabetic patients. However, direct antihyperglycemic effects of topiramate (independent of weight loss) have not been proven clinically, and topiramate's indicated use has been as an antiseizure drug. Topiramate modulates neuronal sodium and calcium channels, enhances γ -aminobutyric acid (GABA)-coupled ion channel flux, and blocks glutamate receptors. Topiramate has been shown to be efficacious in treating binge-eating disorder (35) and may increase energy expenditure in rats (36), but the potential for increased energy expenditure in humans has yet to be proven. A 6-month clinical trial of topiramate showed weight loss compared with placebo, but 21% of topiramate subjects withdrew because of adverse events (compared with 11% of placebo-administered patients) (37). In another trial, after >1 year (60 weeks) of treatment, topiramate continuously and significantly reduced mean body weight and significantly reduced mean visceral abdominal fat (38). The most common adverse effects of topiramate include cognitive dysfunction and (mostly transient) paresthesias, which may be related to the fact that topiramate is a weak inhibitor of carbonic anhydrase (types 2 and 4). A controlled-release formulation is currently in development that may maintain weight loss benefits with reduced risk of adverse side effects.

Zonisamide is also an antiseizure drug being evaluated for potential benefits in treatment of obesity. Zonisamide has serotonergic and dopaminergic activity and may also block neuronal sodium and calcium channels. In a small

16-week trial of 60 subjects (92% women) administered a hypocaloric diet, Zonisamide was shown to result in greater weight loss compared with placebo, with few adverse effects (39).

As noted before, antipsychotic drugs functioning as dopamine antagonists may be associated with weight gain and potentially increase the risk of abnormalities in glucose metabolism. However, not all antipsychotic drugs that have dopamine antagonist activity are necessarily associated with weight gain (e.g., ziprasidone and aripiprazole) (25). Ecopipam is a dopamine antagonist that was being evaluated as a weight loss agent in obese subjects, including patients with diabetes (31). It is no longer in development as an antiobesity agent.

Finally, cannabinoid (CB) receptors may control neurotransmitters, including 1) glutamate and possibly other excitatory amino acids, 2) GABA and glycine and possibly other inhibitory amino acids, and 3) noradrenaline, 5-HT, dopamine, acetylcholine, neuropeptides, and possibly other monoamines (40). Rimonabant is an example of a CB antagonist that blocks the CB-1 receptor that may be involved with appetite. It was developed through the observation that cannabis smokers may experience increased appetite ("munchies") (41). Rimonabant may increase satiety and cause weight reduction. It is currently under development as an antiobesity agent and is being studied in phase III clinical trials of over 6000 patients, including patients with type 2 diabetes (42). Early results suggest favorable effects on lipids such as triglyceride, high-density lipoprotein-cholesterol levels, and small dense low-density lipoprotein particles, and a reduction in the number of patients meeting the criteria for the metabolic syndrome (43).

Investigational Antiobesity Agents that Affect the Leptin/Insulin/CNS Pathways

Leptin (derived from Greek *leptos*, meaning thin) is a hormone produced predominantly by fat cells that normally circulates and crosses the blood-brain barrier (BBB) (Table 2). In obese humans, leptin blood levels generally correlate with the amount of fat stored in the body. Leptin stimulates cytokine or cytokine-like receptors and is sometimes characterized as a cytokine. An important effect of leptin receptor stimulation is the promotion of the janus kinase/signal transducer and activator of transcription (JAK/STAT) cascade, which is one of the major mechanisms by which cytokine receptors transduce intracellular signals and is a pathway that mediates important leptin-induced CNS effects.

The CNS (especially the hypothalamus) may influence caloric balance due to actions on 1) feeding through effects on the CNS neuroendocrine system involved with appetite and behavior, 2) autonomic nervous system activity through effects on energy expenditure, and 3) hormone secretion

Table 1. Examples of antiobesity agents in development

CNS agents that affect neurotransmitters or neural ion channels

- Antidepressants (bupropion)
- Noradrenaline reuptake inhibitors (GW320659)
- Selective 5HT 2c receptor agonists
- Antiseizure agents (topiramate, zonisamide)
- Some dopamine antagonists
- CB-1 receptor antagonists (rimonabant)

Leptin/insulin/CNS pathway agents

- Leptin analogues
- Leptin transport and/or receptor promoters
- CNTF (Axokine)
- NPY antagonists
- AgRP antagonists
- POMC promoters
- CART promoters
- α MSH analogues
- MC4 receptor agonists
- Agents that affect insulin metabolism/activity [PTP-1B inhibitors, PPAR γ receptor antagonists, short-acting bromocriptine (ergoset), somatostatin agonists (octreotide), and adiponectin/Acrp30 (Famoxin or *Fatty Acid Metabolic OXidation INducer*)]

Gastrointestinal-neural pathway agents

- Agents that increase CCK and PYY activity
- Agents that increase GLP-1 activity (extendin 4, liraglutide, DPP IV inhibitor)
- Agents that decrease ghrelin activity
- Amylin (pramlintide)

Agents that may increase RMR

- “Selective” β -3 stimulators/agonist
- UCP homologues
- Thyroid receptor agonists

Other agents

- MCH antagonists
- Phytosterol analogues
- Functional oils
- P57
- Amylase inhibitors
- Growth hormone fragments
- Synthetic analogues of DHEAS (fluasterone)
- Antagonists of adipocyte 11 β -hydroxysteroid dehydrogenase type 1 activity
- CRH agonists
- Carboxypeptidase inhibitors
- Inhibitors of fatty acid synthesis (cerulenin and C75)
- Indanones/indanols
- Aminosterols (Trodusquemine/trodulamine)
- Other gastrointestinal lipase inhibitors (ATL962)

CNS, central nervous system; 5HT 2c, 5-hydroxytryptamine 2c; CB, cannabinoid; CNTF, ciliary neurotrophic factor; NPY, neuropeptide Y; AgRP, agouti-related peptide; POMC, proopiomelanocortin; CART, cocaine and amphetamine regulated transcript; α -MSH, alpha melanocyte-stimulating hormone; MC4R, melanocortin-4 receptor; PTP, protein-tyrosine phosphatase; PPAR, peroxisome proliferator activated receptors; Acrp30, adipocyte complement-related protein of 30kDa; CCK-A, Cholecystokinin-A; GLP-1, glucagon-like peptide-1; PYY, Protein YY3-36; DPP, dipeptidyl peptidase; RMR, resting metabolic rate; UCP, uncoupling protein; MCH, melanin concentrating hormone; DHEAS, dehydroepiandrosterone sulfate; CRH, corticotropin releasing hormone.

Table 2. Examples of select endocrine and metabolic factors released from fat cells

Examples of hormones released from fat cells*

Leptin
 Adiponectin (adipoQ, adipocyte complement-related protein of 30 kDa)
 Resistin

Examples of cytokines released from fat cells*

Tumor necrosis factor- α
 Interleukin-6

Examples of other enzymes, molecules, or factors described as being released from fat cells

Acylation-stimulating protein (ASP)
 Adipophilin
 Adipsin
 Agouti protein
 Angiotensinogen
 Apolipoprotein E
 Endothelin-1
 Fasting-induced adipose factor (FIAF)
 Cholesteryl ester transfer protein (CETP)
 Estrogen
 Free fatty acids
 Galectin-12
 Insulin-like growth factor (IGF-1)
 Lactate
 Lipoprotein lipase
 Macrophage inhibitory factor (MIF)
 Metallothionein
 Monobutyrin
 Nitric oxide synthase
 Phospholipid transfer protein
 Plasminogen activator inhibitor (PAI-1)
 Prostaglandins I₂ & F₂ prostacyclins
 Retinol-binding protein
 Tissue factor
 Transforming growth factor β (TGF β)

* Cytokines are proteins that are secreted by one cell for the purpose of autocrine effect or paracrine effects, and are often involved in the inflammatory and immune processes. Adipocyte hormones are sometimes referred to as cytokines, as they may have potential autocrine or paracrine effects or, at least, may result in subsequent actions that result in autocrine or paracrine effects.

through effects on secretion of growth hormone, thyroid-related hormones, cortisol, insulin, sex steroids, etc. (44). Thus, decreased leptin/insulin activity in the CNS may promote obesity through increased caloric balance as a

result of effects on 1) the CNS neuroendocrine system, 2) decreased energy expenditure through targeted sympathetic nervous system effects on fat, muscle, and liver, and 3) effects on secretion of hormones, all resulting in positive caloric balance and weight (fat) gain (Figure 1).

Leptin, in some respects, may be considered a counter-regulatory hormone that acts in a similar way to that of a thermostat by signaling the hypothalamus when the body has too little, sufficient, or too much fat. In fact, direct administration of leptin into the CNS reduces caloric balance, with subsequent weight loss that may be caused entirely by loss of fat (45). Thus, with excessive fat, leptin's signaling to the hypothalamus should theoretically result in decreased food intake through effects on the brain and increased energy expenditure through effects on the sympathetic nervous system. This may, in fact, occur in lean individuals, particularly if they engage in routine physical exercise. However, this counterregulatory effect clearly fails to prevent excessive fat accumulation in obese patients, presumably because obese patients with elevated leptin blood levels have leptin insensitivity or other circumstances that overcome or overwhelm leptin's antiobesity signaling effects. Administration of more leptin may seem like a reasonable solution. Unfortunately, while some clinical trials have suggested modest benefit with peripheral leptin or leptin analogue administration, other studies have been disappointing (46,47).

Nonetheless, other leptin analogues or agonists are undergoing development that may prove to be more effective than previous preparations or native leptin (48). Leptin promoters are also in development that may increase peripheral leptin levels through increased gene expression. However, simply increasing leptin blood levels might not be expected to overcome significant "resistance" to leptin as might occur through 1) impaired leptin transport across the BBB, 2) impaired leptin receptor-stimulated functions, or 3) impaired response to leptin-induced hormones/factors. Instead, agents that target leptin resistance may prove to be promising targets in improving leptin's CNS activity.

Reducing leptin resistance may theoretically be achieved through improving leptin's transport across the BBB. Although obese patients frequently have elevated leptin blood levels, they may not necessarily have elevated leptin cerebral spinal fluid levels, likely because of 1) decreased transport capacity, 2) partial saturation of the transport mechanism, and/or 3) inability of the leptin transporter to be up-regulated, all resulting in a limitation of how much circulating leptin crosses the BBB. Currently, it is not entirely clear exactly how leptin crosses the BBB. Some evidence supports an uncharacterized leptin transporter in the brain capillary endothelium. Leptin BBB transport may also be augmented through leptin receptor variants or through leptin receptors themselves. Either way, increasing

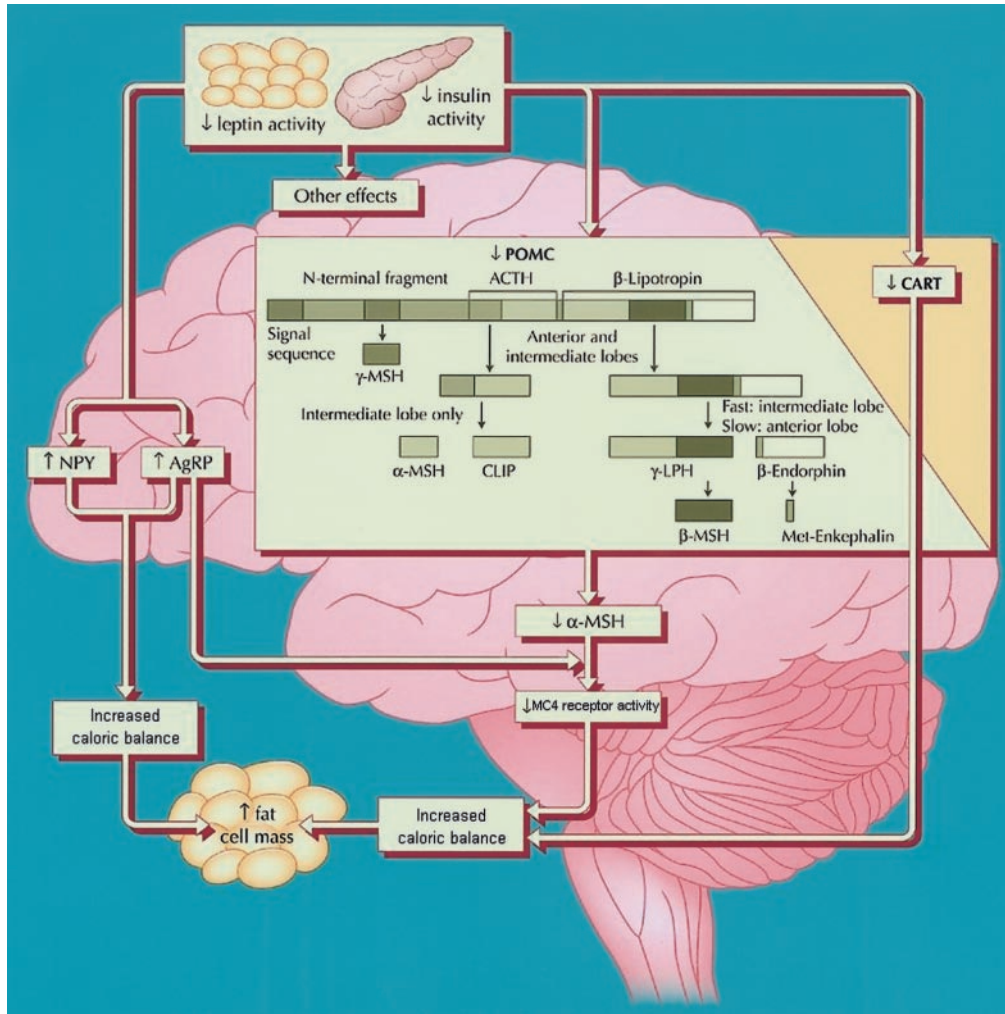


Figure 1: Simplified and illustrative select antiobesity drug targets of the leptin/insulin/CNS pathways. Although circulating levels may be increased, CNS leptin and insulin activity may be decreased in obese patients. Decreased CNS leptin and insulin activity may increase NPY/AgRP, decrease POMC and CART, and have other effects (such as decreased α MSH and decreased MC4 receptor activity), leading to positive caloric balance (fat weight gain). Targets of antiobesity agents include the following: (1) Leptin analogues, leptin gene promoters, leptin-like agonists (Axokine), leptin BBB transport enhancers, and leptin receptor facilitators; (2) NPY and AgRP antagonists; (3) POMC and CART promoters (CART peptides); (4) α MSH analogues; (5) MC4 receptor agonists; and (6) agents that favorably affect insulin metabolism/activity. Through these pathways and other effects, CNS leptin and insulin activity may affect feeding, targeted sympathetic nervous system activity (and thus, influence energy expenditure), and secretion of various neuroendocrine factors/hormones. *NPY, AgRP, POMC, and CART are found in the arcuate nucleus of the hypothalamus.

leptin BBB transport, or otherwise increasing CNS leptin receptor activity, may prove to be an important antiobesity target.

Leptin-like effects may also be increased through ciliary neurotrophic factor (CNTF). CNTF was first characterized as a trophic factor for motor neurons in the ciliary ganglion and spinal cord. During its evaluation for potential treatment of amyotrophic lateral sclerosis, CNTF was serendipitously found to result in weight loss. Axokine (Regeneron Pharmaceuticals, Tarrytown, NY) is a second-generation variant of CNTF that seems to activate leptin-like post-receptor mechanisms in leptin-resistant animals through

CNTF receptors in the hypothalamus and is under development as an antiobesity agent. Axokine has been shown to promote weight reduction in early clinical trials (49). A much larger phase III study showed that Axokine was generally well tolerated, with the main adverse events being mild injection site reactions, nausea, and cough. The weight loss achieved by Axokine was limited by the development of Axokine antibodies. Nonetheless, in the >30% of the 1467 subjects administered Axokine who did not develop Axokine antibodies, weight loss occurred that was similar to what has been described with existing antiobesity drugs (50). Axokine is currently being evaluated to determine

what type of patients might best achieve weight loss with this agent, as well as its efficacy in specific patient populations, including those with type 2 diabetes (51).

Other antiobesity agents undergoing development include those that affect satiety as agonists and antagonists of hypothalamic hormones involved with food intake signaling. Decreased brain leptin/insulin activity may stimulate the neuropeptide Y (NPY)/agouti-related peptide (AgRP) axis and, conversely, decrease the proopiomelanocortin (POMC)/cocaine and amphetamine regulated transcript (CART) axis, thus increasing feeding and decreasing energy expenditure. This promotes positive caloric balance and weight (fat) gain (Figure 1). Conversely, agents that inhibit NPY and AgRP and/or stimulate the POMC and CART pathways may help create negative caloric balance and may decrease weight (fat).

NPY is a neuropeptide produced in the hypothalamus that is the most abundant neuropeptide in the brain in mammals and humans. As many as six G-protein-coupled NPY receptor subtypes have been described (Y1, Y2, Y3, Y4, Y5, Y6) (52). NPY shares structural homology with peptide YY (PYY) from the intestine and pancreatic polypeptide from the pancreas (53). Both Y1 and Y2 NPY receptors seem to be involved in feeding and may interact with one another (53), and these receptors are among the most promising antiobesity targets. NPY receptor antagonists have been evaluated and have been shown to inhibit NPY-induced feeding in animals (52,53). In humans, at least one such agent has been discontinued because of elevated liver enzymes (54). Newer NPY antagonists are in the pipeline of pharmaceutical companies and are at variable stages of development as antiobesity agents.

AgRP (also found in the hypothalamus) antagonizes melanocortin (MC) receptors, such as the MC4 (and MC3) receptors, which are found only in the brain (55) (Figure 1). Stimulation of MC4 receptors normally results in inhibition of feeding. In fact, impaired MC4 activity through MC4 receptor mutations has been described to account for 0.5% to 5.8% of severe cases of obesity (56). AgRP blocks α -melanocyte-stimulating hormone (α MSH)'s effects on MC4 receptors, resulting in weight gain (and, interestingly, decreased black and increased yellow fur pigment in mutant *agouti* strains of overweight mice that hypersecrete AgRP, which blocks the stimulation of melanin by α MSH). Inhibiting the antagonist effects of AgRP might be a promising target in the development of antiobesity agents.

POMC precursor production is a process that may be regulated by various hypothalamic hormones, neurotransmitters, and neuropeptides, including sex steroids, glucocorticoids, opioids, dopamine, GABA, corticotropin releasing hormone (CRH), and even NPY (57). POMC is cleaved to various derivatives, including an α MSH segment that stimulates MC4 receptors and promotes negative caloric balance

(weight loss) (Figure 1). Thus, POMC promoters, α MSH analogues, and MC4 receptor agonists may all prove to be promising antiobesity agents.

While leptin's CNS signaling is perhaps more effective in affecting caloric balance, insulin is also an important circulating hormone with CNS signaling that affects adiposity (58). Both leptin and insulin 1) have blood concentrations that frequently correspond to adiposity, 2) enter the CNS by a receptor-mediated, saturable transport process across brain capillary endothelial cells (59), and 3) have receptors located in similar hypothalamic areas. The direct action of increased leptin and insulin activity to the brain is to decrease feeding and increase energy expenditure. Conversely, diminished CNS insulin (or leptin) activity in the brain may promote positive caloric balance and weight (fat) gain (Figure 1). Thus, there is substantial analogy, redundancy, and, in fact, interaction ("cross-talk") between CNS leptin and insulin receptors and activity (58,60).

With regard to signaling, increased leptin receptor activity seems to propagate pathways, such as 1) the JAK/STAT3 pathway, which may mediate leptin's action in the hypothalamus through effects on NPY and POMC and possibly other factors (61); 2) the mitogen-activated protein kinase pathway (60), which may have various effects on cell (adipose) growth and differentiation, inflammatory responses (62,63), and increases in plasminogen activation inhibitor-1 (64); and 3) the phosphatidylinositol 3 kinase (PI3K) pathway (60), which may affect glucose transport and endothelial nitric oxide production (65). Similarly, both the mitogen-activated protein kinase and PI3K pathways are part of insulin's cascade effect (65), and insulin may modulate leptin's signal transduction through JAK/STAT3. Thus, just as with leptin, CNS insulin activity may affect feeding (66), autonomic nervous system activity, and hormonal secretions.

Leptin binds to the extracellular portion of the leptin receptor, stimulating intracellular tyrosine kinase enzyme (JAK2) and promoting the JAK/STAT3 cascade. In an analogous way, insulin binds to the extracellular domain of the insulin receptor, which activates intracellular tyrosine kinase, which, in turn, mediates phosphorylation of the insulin receptor substrate (IRS-1) protein required for the propagation of subsequent cascade signaling to enzymes including PI3K, which, as noted before, is a kinase that may elicit cell growth and proliferation, differentiation, cell survival, protein synthesis, and lipid metabolism and which is also a crucial component of insulin signaling, glycogen synthesis, and glucose transport (through glucose transporter-4).

Leptin resistance associated with obesity results in elevated leptin blood levels. Similarly, insulin resistance results in hyperinsulinemia, which also may occur early in the onset of obesity. Acarbose is an antidiabetes treatment that improves glucose metabolism, but does not seem to affect fasting insulin levels (67). While it may not have significant

benefits in improving weight maintenance after weight loss in obese patients, acarbose has been associated with modest weight loss in some clinical trials (68). Metformin also improves glucose metabolism, but results in reduction in insulin levels when administered to patients with insulin resistance. Metformin is commonly associated with weight loss, at least partially because of a decrease in caloric intake (69). In contrast to agents that increase insulin sensitivity with no increase (or perhaps even a decrease) in insulin levels, antidiabetes drug treatments that may increase insulin levels or increase insulin production (such as insulin administration or sulfonylureas) are often associated with weight gain (70). Even without pharmacologically induced hyperinsulinemia, elevated blood levels of insulin (a growth factor), as occurs with insulin resistance, are associated with excessive body weight—particularly central obesity (71). Thus, improving glucose metabolism through increased insulin sensitivity (which may improve peripheral and central glucose metabolism) and decreased insulin levels (which may have advantages with respect to minimizing weight gain) has been, and may continue to be, a useful treatment strategy in treating obese patients with type 2 diabetes and insulin resistance.

Dysfunctional adipose tissue (adiposopathy) is a contributing cause of insulin resistance in skeletal muscle and liver (72), which results in an increase in insulin blood levels. Because adipose tissue may remain relatively sensitive to insulin in an environment of muscle and liver insulin insensitivity, increased insulin blood levels may further promote adiposity, potentially further worsen adiposopathy, and in turn, potentially further worsen insulin resistance. The hyperinsulinemia followed by worsening insulin resistance, followed by even greater hyperinsulinemia, may promote an “obesity metabolic cycle.” Agents that improve insulin sensitivity and decrease insulin blood levels may prove to be promising useful antiobesity treatments, particularly in patients with type 2 diabetes or insulin resistance.

An illustrative example would be patients with type 2 diabetes who have impaired insulin-stimulated glucose transport largely because of a marked reduction in IRS-1 protein activity. Inactivation of IRS-1 may occur through protein-tyrosine phosphatase (PTP)-1B, which is a key enzyme involved in regulation of the reversible tyrosine phosphorylation. PTP-1B inactivates insulin receptors by removing phosphates from active insulin receptors and IRS-1. The effects of insulin are reduced, contributing to insulin resistance/intolerance, promoting the metabolic syndrome, and potentially leading to type 2 diabetes itself. Interestingly, PTP-1B may also dephosphorylate JAK/STAT3, decreasing leptin’s effects and potentially contributing to leptin resistance as well (73).

PTP-1B levels have reportedly been found to be increased in patients with insulin resistance. Reducing the production or activity of PTP-1B may increase insulin sen-

sitivity, reduce insulin levels, and, thus, reduce the obesity metabolic cycle of hyperinsulinemia-stimulated fat increase and may even increase energy expenditure, which would all be favorable effects in obese patients. A novel approach in accomplishing this may be through the development of an antisense inhibitor of the gene encoding for PTP-1B (74).

Peroxisome proliferator activated receptor (PPAR) activity may also affect body weight. PPARs are nuclear receptors involved in fat and glucose metabolism. PPAR α receptors are preferentially found in the liver and have historically been the targets of lipid-altering drugs (fibrates), whereas PPAR γ receptors are predominantly found in adipose tissue and have historically been the targets of type 2 diabetes treatments (thiazolidinediones) (75). However, this functional delineation of nuclear receptor types may not be so distinct. Animal studies have suggested that non-PPAR γ agonists (i.e., PPAR agonists without γ activity, such as PPAR α and δ agents) may also result in increased insulin sensitivity and weight loss (75,76).

Although PPAR γ activation may reduce insulin resistance, it also promotes the differentiation and proliferation of adipocytes from fibroblasts, thus causing an increase in fat that, at least partially, explains some of the weight gain observed with these insulin-sensitizing drugs. It is theoretically possible that impairing, or in fact reversing, adipocyte differentiation through PPAR γ antagonism may be the target for future antiobesity drug development. Mice treated with PPAR γ antagonists have shown decreases in triglyceride content in white adipose tissue, skeletal muscle, and liver. PPAR γ antagonists have also been shown to potentiate leptin’s effects, and adiponectin levels may be stimulated, resulting in increase fatty acid combustion and increased energy expenditure. Finally, high-fat diet-induced obesity and insulin resistance may be decreased as well (77).

However, there are reasons to be cautious about antagonizing the potential beneficial effects of PPAR γ -stimulated adipose tissue differentiation and development. An emerging concept of the pathogenesis of type 2 diabetes is that dysfunctional adipose tissue (adiposopathy) may contribute to the pathogenesis of type 2 diabetes through excessive release of free fatty acids that may be “lipotoxic” to liver, muscle, and, perhaps, pancreatic β cells, resulting in hepatic and muscle insulin resistance, and, perhaps, diminished β cell function (72). Adiposopathy may also increase adipocyte cytokine release (Table 2), which may contribute to glucose intolerance, the metabolic syndrome, and type 2 diabetes (75). These abnormalities associated with adiposopathy may be corrected with PPAR γ agonism (72). Thus, the ensuing fat weight gain that frequently occurs with PPAR γ agents (thiazolidinediones) could be viewed as a beneficial effect of the drugs through the recruitment and differentiation of adipose cells into a more healthy adipose organ, resulting in reduced circulating free fatty acids, im-

proved glucose metabolism, and decreased inflammatory response (72). Antagonism of these PPAR γ effects has the potential to negate these beneficial effects and/or conceivably worsen adiposopathy, which would theoretically worsen fatty acid and glucose handling by fat cells, with potentially undesirable metabolic consequences.

This is an illustrative example of an important principle that the development of any effective antiobesity agent must not only reduce fat mass (adiposity) but must also correct fat dysfunction (adiposopathy) to maximize metabolic health.

Other potential antiobesity drugs that may improve insulin sensitivity and thus be promising antiobesity targets include short-acting bromocriptine (ergoset—a dopamine receptor agonist) (78) and octreotide, a synthetic somatostatin analogue that may 1) inhibit gastrointestinal gastrin and serotonin, 2) inhibit secretion of growth hormone, insulin, and glucagons, 3) modulate biliary and gastrointestinal motility, and 4) act as a neurotransmitter. Clinical trials of octreotide have shown efficacy in pediatric hypothalamic obesity (79,80).

Finally, adiponectin (adipocyte complement-related protein of 30 kDa) is a hormone produced by fat cells that is associated with fatty acid oxidation and energy release, increased insulin sensitivity, and possible antiatherogenic properties because of favorable effects on endothelial inflammation (Table 2). Adiponectin blood levels are decreased in obesity and type 2 diabetes. Increasing the activity of adiponectin may be a potential target as an antiobesity agent, with anticipated favorable effects on body weight, glucose metabolism, lipid blood levels, and reduction in atherosclerosis (81).

Investigational Antiobesity Agents that Affect the GI Pathways

Food intake may also be influenced by neural and hormonal actions of the GI tract, including the vagus neural pathways (e.g., stretch and chemoreceptors) and various endocrine factors (the gut is also among the most active of endocrine organs). Examples of hormones located in the GI system that are thought to be most promising as potential antiobesity targets include cholecystokinin (CCK), glucagon-like peptide-1 protein (GLP-1), PYY, and ghrelin (Figure 2).

CCK is produced in gall bladder, pancreas, and stomach and concentrated in the small intestine. It is released mainly in response to dietary fat and functions to regulate gallbladder contraction, pancreatic exocrine secretion, gastric emptying, and gut motility. CCK also has central nervous system effects that may increase satiety and decrease appetite. CCK-A (“alimentary”) receptors are alternatively termed CCK-1 receptors, in part, because some of these receptors can also be found in the brain. Similarly, CCK-B (“brain”) receptors are alternatively termed CCK-2 receptors because

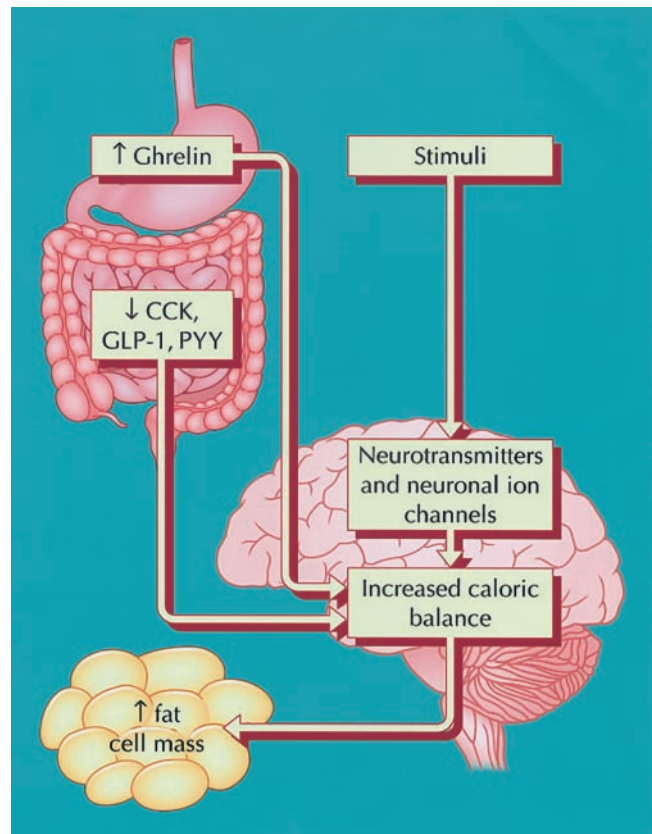


Figure 2: Simplified and illustrative select antiobesity drug targets of the gastrointestinal/CNS and neurotransmitter/neuronal ion channel pathways. Postprandial increase in CCK, GLP-1, PYY, and fasting decrease in ghrelin activity may decrease feeding. Submaximal activity or decreased effectiveness of CCK, GLP-1, PYY, or an increase in ghrelin may result in positive caloric balance (fat weight gain). Targets of antiobesity agents include the following: (1) ghrelin antagonism (or gastric bypass); (2) CCK agonism; (3) GLP-1 agonism (extendin 4, liraglutide, DPP IV inhibitors); and (4) PYY agonism. CNS drugs that may decrease appetite through a variety of effects on neurotransmitters, neuronal ion channels, and possibly other pathways, include the following: some antidepressants (bupropion), some noradrenaline reuptake inhibitors, selective 5HT receptor agonists, some antiseizure drugs (topiramate, zonisamide), some dopamine antagonists, and CB 1 receptor antagonists (rimonabant).

some of these receptors are also found in the GI/alimentary system. CCK receptor agonism inhibits gastric emptying and primarily increases central signaling of satiety through vagal afferent signals to the brain resulting in short-term inhibition of food intake. Increasing CCK activity is being evaluated as a potential antiobesity and antidiabetes treatment target (82) (Figure 2).

GLP-1 is an insulinotropic peptide gut hormone (incretin hormone) produced mainly in the distal ileum and colon that delays gastric emptying, inhibits glucagon secretion, stimulates glucose-induced insulin secretion (possibly through

restored pancreatic β cell sensitivity to exogenous secretagogues), increases insulin sensitivity, delays or prevents the decay in pancreatic β cell insulin production, improves glucose blood levels in patients with diabetes, and increases satiety. Thus, GLP-1 is another promising target for antidiabetes and antiobesity agents (83). GLP-1 agonism may be achieved through direct administration of analogues. Exendin-4 (exenatide) is a potent and long-acting GLP-1 analogue [originating in the saliva of *Heloderma suspectum* (Gila monster lizard)] that may not only inhibit gastric emptying and increase central signaling of satiety, but may also have favorable effects in the treatment of type 2 diabetes (84). Liraglutide is also a long-acting derivative of GLP-1 (85) (Figure 2).

Normally, the enzyme dipeptidyl peptidase IV (DPP IV) rapidly inactivates GLP-1. DPP IV inhibitors increase endogenous GLP-1 levels and are being evaluated as an antidiabetes agent in overweight patients with diabetes (83,86,87); however, it remains to be shown that these oral agents result in the same degree of weight loss as achieved with the GLP-1 injectable analogues.

PYY is a hormone shown to have postprandial secretion by intestinal cells that may signal satiety in the hypothalamus possibly through a decrease in NPY and an increase in POMC activity. Administration of PYY before meals has been shown to result in decreased food consumption after meals in humans (88), presumably because it provides the same sense of satiety as a postprandial snack. It has, thus, been characterized as a “third-helping hormone,” in that it has been shown to result in diminished postprandial “snacking” after meals (Figure 2).

The peptide hormone ghrelin is synthesized in the stomach (as well as intestine, pituitary, and possibly hypothalamus) and may activate the growth hormone secretagogue receptor. (The “gh” portion of ghrelin originates from growth hormone.) With decreased food intake in animals and humans, ghrelin secretion may increase and stimulate food intake. Thus, the “drive to eat” after dieting may be partially because of ghrelin secretion. Reducing ghrelin activity may reduce the “drive to eat,” and, in fact, it has been suggested that it is the reduction in ghrelin that partially accounts for the effectiveness of gastric bypass surgery. Therefore, ghrelin antagonism may potentially decrease or at least blunt the increased appetite that may occur with decreased feeding and, thus, be a potential adjunctive treatment for obesity (89,90) (Figure 2).

Finally, amylin is a peptide secreted by the pancreas in response to nutrients and other insulinogenic stimuli. Amylin is a neuroendocrine hormone (91) that may be a promising antiobesity or antidiabetes treatment target. Pramlintide is a subcutaneously administered synthetic analogue of amylin that is currently in development as a possible ben-

eficial adjunct to insulin. It has been shown to improve blood sugar control and reduce weight among patients with type 2 diabetes (92–94).

Investigational Antiobesity Agents that May Increase Resting Metabolic Rate

Increasing energy expenditure through physical activity, or through an increase in resting metabolic rate (RMR) and/or thermogenesis, is another important part of the equation in achieving weight reduction in obese patients. Unfortunately, long-term compliance and commitment to routine physical exercise frequently does not occur. Therefore, the target of some investigational antiobesity drugs is to increase RMR and/or thermogenesis.

β -Adrenergic agonists selective for β_3 receptors in adipose tissue may increase heat production through effects on fat cell mitochondria and, thus, theoretically increase RMR and reduce body fat (95). Unfortunately, early clinical trials have suggested that “selective” β_3 receptor agonists have not always been so “selective” and stimulate other β receptors, including the β_1 receptors in the heart, resulting in tachycardia. Nonetheless, studies continue in pursuit of selective agents that can promote fatty acid oxidation, especially in adipose tissue, while avoiding adverse cardiovascular effects.

Similarly, uncoupling protein (UCP) homologues are being developed that may increase thermogenesis. The mitochondria are the intracellular furnaces where fuels derived from fatty acids and glucose are oxidized (45). Energy is either stored (through creation of ATP through a respiration process coupled with oxygen consumption) or released as heat (not linked to ATP production and not coupled to oxygen consumption). UCP-1 is found in brown adipose tissue (BAT) (whose color is caused by the rich vascularization and densely packed mitochondria). BAT is present in small amounts at birth but is an important contributor to thermogenic responses and thermoregulation, as might be beneficial after birth when emerging from a warm, isothermic uterine environment to the colder outside world. In adults, UCP-1-associated BAT is negligible. However, the UCP-2, as found in adult white adipose tissue, is ubiquitous, whereas UCP-3 is found in skeletal muscle (96). UCPs serve as transporters of cations and, perhaps, anions across the mitochondrial membranes, reducing ADP phosphorylation, decreasing ATP energy storage, and increasing energy expenditure in the form of heat (referred to as “uncoupling”), and thus may increase thermogenesis. UCP-acting agents may be antiobesity targets.

Thyroid hormone is also known to increase thermogenesis. However, because of its potential adverse side effects at superphysiologic doses (cardiovascular toxicity, myopathy, and potential acceleration of osteoporosis), thyroid hormone is contraindicated as a treatment specifically for obesity

alone. Agents that target certain actions at the thyroid hormone receptor, while at the same time avoiding the undesirable side effects of current thyroid hormone drugs, are under development as an adjunct in the treatment of obesity and, potentially, dyslipidemia (97). However, an efficacy focus of thyroid receptor agonists would be to ensure that weight loss is predominantly fat, rather than lean body tissue loss, including muscle and bone.

Finally, other previously mentioned agents (such as adiponectin) may increase energy expenditure in animals (98) but have yet to be proven to do so in humans, or at least, yet to be proven to do so to a clinically significant extent.

Other Investigational Antiobesity Agents

Melanin-concentrating hormone (MCH) may increase food intake by its interaction with the G-protein-coupled receptor (somatostatin-like receptor). MCH receptor (somatostatin-like receptor) antagonism has been shown to inhibit food intake in rats and may also have antidepressant and anxiolytic effects as well. Thus, MCH receptor antagonism may prove to be an important target for antiobesity drug development (99).

Certain “natural” or nutraceutical analogues also have been suggested to have favorable effects on weight reduction. These include phytosterol analogues (including disodium ascorbyl phytostanol phosphate) (75,100), functional oils/medium-chain fatty acids (75,101–105), P57 [a cactus extract that is consumed by African tribesmen to decrease hunger during long hunting trips] (106), and various amylase inhibitors that may be derived from wheat and beans (107,108).

Last, a remaining diverse group of antiobesity drugs are currently under development. Administration of growth hormone to growth hormone-deficient patients may result in an increase in lean body mass with reduction in fat mass. Particularly in patients with Prader-Willi syndrome, growth hormone administration has been shown to result in sustained fat use and physical strength (109). However, the beneficial effects of intact growth hormone on obesity may be limited (110). Intact growth hormone may also induce insulin resistance. It is, therefore, possible that the development of growth hormone fragments (with predominant activity directed at fat) may preserve or potentially improve lean body mass benefits without adversely affecting glucose metabolism (111,112).

Other novel agents under investigation as antiobesity treatment targets include steroid drugs, including fluasterone, which is a synthetic analogue of the adrenal steroid hormone dehydroepiandrosterone (DHEAS). DHEAS has been proposed, but not proven, to increase mitochondrial respiration, augment thyroid hormone function, and possibly influence peroxisome proliferation (113); its questionable and potential benefits in patients await the outcomes of long-term clinical trials (114). Other novel agents are the

antagonist of adipocyte 11β -hydroxysteroid dehydrogenase type 1 activity (pharmaceutical agents or possibly through magnolia officinalis bark extract), which is an enzyme suggested to contribute to visceral obesity, as well as the metabolic syndrome (115,116); agonists of the catabolic corticotropin releasing hormone or factor (CRH) molecule (animal studies have shown that human CRH increases thermogenesis, increases fat oxidation, and decreases food intake) (117); agents that decrease carboxypeptidase activity (an enzyme necessary for proteolytic processing and, thus, biosynthesis of insulin, MC, and NPY) (118,119); inhibitors of fatty acid synthesis (cerulenin and C75) (120,121); and a diverse variety of compounds, including indanones/indanols (122), aminosterols (Trodoxamine, formerly known as trodulamine), and other gastrointestinal lipase inhibitors (ATL962) (123).

In conclusion, this review has focused on the existing and some of the more promising investigational antiobesity agents and targets. However, examples of other molecules, enzymes, and assorted factors being evaluated in relation to obesity research include adrenomedullin, adenosine monophosphate-activated protein kinase, apolipoprotein A-IV, attractin, beacon, bombesin, bombesin M gene associated peptide, calcitonin receptor-stimulating peptide, dynorphin, endorphin, enterostatin, fatty acid synthase, feeding circuit-activating peptides, galanin, galanin-like peptide, gastric inhibitory polypeptide, gastrin releasing peptide, glucagons, growth hormone releasing factor, high mobility group protein isoform I-C, HS014, JKC363, myostatin, neuromedin B and U, neurotensin, neuropeptide B and W, orexins, oxytocin, oxynomodulin, pituitary adenylate cyclase-activating polypeptide, perilipin, protein kinase A, resistin, secretin, somatostatin, thyroid-releasing hormone, tubero-infundibular peptide, and urocortin (124,125). Because studies in antiobesity research are in such a state of infancy, it is difficult to determine which of these single treatment targets, or which combination of treatment targets, has the best potential to effectively manage the worldwide epidemic of obesity. Therefore, it is impossible to predict at this point which agent or agents will eventually prove to revolutionize obesity treatment, as occurred when diuretics were introduced to treat hypertension, when insulin was introduced to treat diabetes, and when statins were introduced to treat dyslipidemia (7). However, given that medical science has almost always risen to and met epidemic challenges, there is no reason to believe that such a therapy or therapies are not forthcoming.

Acknowledgments

There was no outside funding/support for this review. Dr. Bays has served as a Clinical Investigator for (and has received research grants from) pharmaceutical companies such as AstraZenca, Aventis, Bayer, Boehringer Ingelheim,

Boehringer Mannheim, Bristol Myers Squibb, Fujisawa, Ciba Geigy, GelTex, Glaxo, Genetech, Hoechst Roussel, KOS, Lederle, Marion Merrell Dow, Merck, Merck Schering Plough, Miles, Novartis, Parke Davis, Pfizer, Purdue, Roche, Rorer, Regeneron, Reliant, Sandoz, Sankyo, Sanofi, Shering Plough, Searle, SmithKline Beacham, Takeda, TAP, UpJohn, Upsher Smith, Warner Lambert, and Wyeth-Ayerst. He has also served as a consultant, speaker, and/or advisor to and for pharmaceutical companies such as AstraZeneca, Aventis, Bayer, Bristol Myers Squibb, KOS, Merck, Merck Schering Plough, Novartis, Ortho-McNeil, Parke Davis, Pfizer, Roche, Sandoz, Sankyo, Sanofi, Shering Plough, SmithKline Beacham, Takeda, UpJohn, and Warner Lambert.

References

- Flegal KM, Carroll MD, Ogden CL, Johnson CL.** Prevalence and trends in obesity among US adults, 1999–2000. *JAMA*. 2002;288:1723–7.
- World Health Organization.** Obesity and overweight facts. http://www.who.int/hpr/NPH/docs/g_s_obesity.pdf (accessed July 2004).
- Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM.** Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA*. 2004;291:2847–50.
- Kushner R, Roth J.** Assessment of the obese patient. *Endocrinol Metab Clin North Am*. 2003;32:915–33.
- International Obesity Taskforce.** <http://www.iof.org> (accessed July 2004).
- World Health Organization.** Controlling the global obesity epidemic: nutrition. <http://www.who.int/nut/obs.htm> (accessed July 2004).
- Bays HE, Dujovne CA.** Anti-obesity drug development. Expert opinion. *Invest Drugs*. 2002;11:1189–204.
- Yanovski SZ, Yanovski JA.** Obesity. *N Engl J Med*. 2001;346:591–602.
- Conoley IP, Liu YL, Frost I, Reckless IP, Heal DJ, Stock MJ.** Thermogenic effects of sibutramine and its metabolites. *Br J Pharmacol*. 1999;126:1487–95.
- Wirth A, Krause J.** Long-term weight loss with sibutramine. *JAMA*. 2001;286:1331–9.
- James WP, Astrup A, Finer N, et al.** Effect of sibutramine on weight maintenance after weight loss: a randomized trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet*. 2000;356:2119–25.
- Dujovne CA, Zavoral JH, Rowe E, Memdel CM.** Effects of sibutramine on body weight and serum lipids. *Am Heart J*. 2001;142:489–97.
- Fujioka K, Seaton TB, Rowe E, et al.** Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. *Diabet Obes Metab*. 2000;2:175–87.
- Finer N, Bloom SR, Frost GS, Banks LM, Griffiths J.** Sibutramine is effective for weight loss and diabetic control in obesity with type 2 diabetes: a randomized, double-blind, placebo controlled study. *Diabet Obes Metab*. 2000;2:105–12.
- Kim SH, Lee YM, Jee SH, Nam CM.** Effect of sibutramine on weight loss and blood pressure: a meta-analysis of controlled trials. *Obes Res*. 2003;11:1116–23.
- Davidson M, Hauptman J, Digirolamo M, et al.** Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat. *JAMA*. 1999;281:235–42.
- Sjöström L, Rissanen A, Andersen T, et al.** Randomized placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet*. 1998;352:167–72.
- Mittendorfer B, Ostlund R, Patterson BW, et al.** Orlistat inhibits daily cholesterol absorption. *Obes Res*. 2000;8(Suppl 1):43S.
- Heysfield SB, Segal KR, Hauptman J, et al.** Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med*. 2000;160:1321–6.
- Kelley DE.** Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care*. 2002;25:1033–41.
- Lindgarde F.** The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: The Swedish Multimorbidity Study. *J Intern Med*. 2000;248:245–54.
- Rossner S, Sjöström L, Noack R, Meinders AE, Noseda G.** Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. *Obes Res*. 2000;8:49–61.
- Stone NJ, Kushner R.** Effects of dietary modification and treatment of obesity. *Med Clin North Am*. 2000;84:95–122.
- Wadden TA, Foster GD.** Behavioral treatment of obesity. *Med Clin North Am*. 2000;84:441–61.
- Consensus Statement.** Consensus development conference on antipsychotic drugs and obesity and diabetes. *Obes Res*. 2004;12:362–8.
- Durst R, Rubin-Jabotinsky K, Raskin S, Katz G, Zislin J.** Letter to the editor: risperidone in Prader-Willi syndrome. *J Am Acad Child Adolesc Psychiatr*. 2000;39:545–6.
- Ratzoni G, Gothelf D, Brand-Gothelf A, et al.** Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. *J Am Acad Child Adolesc Psychiatry*. 2002;41:1272.
- Bloch Y, Vardi O, Mendlovic S, Levkovitz Y, Gothelf D, Ratzoni G.** Hyperglycemia from olanzapine treatment in adolescents. *J Child Adolesc Psychopharmacol*. 2003;13:97–102.
- Jain AK, Kaplan RA, Gadde KM, et al.** Bupropion SR vs. placebo for weight loss in obese patients with depressive symptoms. *Obes Res*. 2002;10:1049–56.
- 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;10:633–41.

31. **The Kretzman Obesity Newsletter, January 2002, Volume 9, Number 0.** *What's going on in obesity research.* Available at: <http://home.net/~brentzman/articles/kretzman.obesity.newsletter/2002/newsletter.25.00.html> (accessed July 2004).
32. **GlaxoSmithKline.** GlaxoSmithKline annual report 2001—operational activities, research and development. <http://www.gsk.com/financial/reports/ar2001/annual-report-01/gskrep9.html> (accessed July 2004).
33. **Centers for Disease Control and Prevention.** Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services Interim Public Health Recommendations. *MMWR.* 1997;46:45.
34. **Bengel D, Isaacs KR, Heils A, Lesch KP, Murphy DL.** The appetite suppressant d-fenfluramine induces apoptosis in human serotonergic cells. *Neuroreport.* 1998;9:2989–93.
35. **McElroy SL, Arnold LM, Shapira NA, et al.** Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. *Am J Psychiatry.* 2003;160:255–61.
36. **Picard F, Deshaies Y, Lalonde J, Samson P, Richard D.** Topiramate reduces energy and fat gains in lean (Fa/?) and obese (fa/fa) Zucker rats. *Obes Res.* 2000;8:656–63.
37. **Bray GA, Hollander P, Klein S, et al.** A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obes Res.* 2003;11:722–33.
38. **Van Der Merwe T, Vercruyse F, Perry B, Fitchet M.** A randomized, placebo-controlled study of the long-term effect of topiramate on body composition. Posters and Abstracts of the 18th International Diabetes Federation Congress, Paris, France, August 24–29, 2003.
39. **Gadde KM, Franciscy DM, Wagner HR 2nd, Krishnan KR.** Zonisamide for weight loss in obese adults: a randomized controlled trial. *JAMA.* 2003;289:1820–5.
40. **Baker D, Pryce G, Giovannoni G, Thompson A J.** The therapeutic potential of cannabis. *Lancet Neurol.* 2003;2:291–8.
41. **Sapa AP.** Pot teaches a munchies lesson. <http://www.planetsave.com/ViewStory.asp?ID=2909> (accessed July 2004).
42. **SPG Media Limited.** Rimobant selective CB1 endocannabinoid receptor antagonist for the treatment of obesity. <http://www.drugdevelopment-technology.com/projects/rimobant/> (accessed July 2004).
43. **Anthenelli RM, Despres JP.** Effects of rimobant in the reduction of major cardiovascular risk factors. Results from the STRATUS-US Trial (Smoking Cessation in Smokers Motivated to Quit) and the RIO-LIPIDS Trial (Weight Reducing and Metabolic Effects in Overweight/Obese Patients with Dyslipidemia). Session Late Breaking Clinical Trials II Annual Scientific Session, New Orleans, LA, March 9, 2004.
44. **Spiegelman BM, Flier JS.** Obesity and the regulation of energy balance. *Cell.* 2001;104:531–43.
45. **Woods SC, Seeley RJ, Porte D, Schwartz MW.** Signals that regulate food intake and energy homeostasis. *Science.* 1998;280:1378–83.
46. **Heysfield SB, Greenberg AS, Fujioka D, et al.** Recombinant leptin for weight loss in obese and lean adults. *JAMA.* 1999;282:1568–75.
47. **Mantzoros CS, Flier JS.** Editorial: leptin as a therapeutic agent—trials and tribulations. *J Clin Endocrinol Metab.* 2000;85:4033–9.
48. **Hukshorn CJ, Saris WH, Westerterp-Plantenga MS, Farid AR, Smith FJ, Campfield LA.** Weekly subcutaneous pegylated recombinant native human leptin (PEG-OB) administration in obese men. *J Clin Endocrinol Metab.* 2000;85:4003–9.
49. **Ettinger MP, Littlejohn TW, Schwartz SL, et al.** Recombinant variant of ciliary neurotrophic factor for weight loss in obese adults. *JAMA.* 2003;289:1826–32.
50. **Regeneron Pharmaceuticals.** Axokine. Press release. Regeneron announces results of phase III obesity study (3/31/2003) and Regeneron moving forward with AXOKINE phase III program for treatment of obesity (9/9/2003). http://www.regeneron.com/company/press_detail.asp?v_c_id=182 (accessed July 2004).
51. **Glicklich A, Bays H, Russell T, Weinstein S, Hollander P.** AXOKINE promotes weight loss in overweight and obese patients with type 2 diabetes mellitus. Poster Abstract 471-P. NAASO's 2003 Annual Meeting. Ft. Lauderdale, FL, October 11–15, 2003.
52. **Balasubramaniam A.** Clinical potentials of neuropeptide Y family of hormones. *Am J Surg.* 2002;4:430–4.
53. **Wieland HA, Hamilton BS, Drist B, Doods HN.** The role of NPY in metabolic homeostasis: implications for obesity therapy. *Invest Drugs.* 2000;9:1327–46.
54. **Woolley GH, Hunt KJ.** Incorporating pharmacotherapy into obesity management. Therapeutics Report Newsletter. 1999;6. Available at: <http://www.brucewoolley.com/TherapeuticsReport/1999/Apr99.html> (accessed July 2004).
55. **Proietto J, Fam BC, Ainslie DA, Thornburn AW.** Novel anti-obesity drugs. *Invest Drugs.* 2000;9:1317–26.
56. **Damcott C, Sack P, Shuldiner AR.** The genetics of obesity. *Endocrine Metab Clin.* 2003;32:761–86.
57. **Wardlaw SL.** Obesity as a neuroendocrine disease: lessons to be learned from proopiomelanocortin and melanocortin receptor mutations in mice and men. *J Clin Endocrinol Metab.* 2001;86:1442–6.
58. **Porte D, Baskin DG, Schwartz MW.** Leptin and insulin action in the central nervous system. *Nutr Rev.* 2002;60:S20–9.
59. **Banks WA.** The source of cerebral insulin. *Eur J Pharmacol.* 2004;19:5–12.
60. **Zabeau L, Lavens D, Peelman F, Eyckerman S, Vanderkerckhove J, Tavernier J.** The ins and outs of leptin receptor activation. *FEBS Lett.* 2003;546:45–50.
61. **Meister B.** Control of food intake via leptin receptors in the hypothalamus. *Vitamin Horm.* 2000;59:265–304.
62. **Ono K.** The P38 signal transduction pathway: activation and function. *Cell Signal.* 2000;12:1–13.
63. **Stambe C, Atkins RC, Tesch GH, et al.** Blockade of p38 alpha MAPK ameliorates acute inflammatory renal injury in rat anti-GBM glomerulonephritis. *J Am Soc Nephrol.* 2003;14:338–51.
64. **Chang H, Shyu KG, Lin S, et al.** The plasminogen activator inhibitor-1 gene is induced by cell adhesion through the MEK/ERK pathway. *J Biomed Sci.* 2003;10:738–45.

65. **Reusch JEB.** Current concepts in insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome. *Am J Cardiol.* 2001;90:19G–26G.
66. **Gerozissis K.** Brain insulin and feeding: a bi-directional communication. *Eur J Pharmacol.* 2004;490:59–70.
67. **Fischer S.** Influence of treatment with acarbose or glibenclamide on insulin sensitivity in type 2 diabetic patients. *Diabetes Obes Metab.* 2003;5:38–44.
68. **Hauner H.** Effect of acarbose on weight maintenance after dietary weight loss in obese subjects. *Diabetes Obes Metab.* 2001;3:423–7.
69. **Schultes B, Oltmanns KM, Kern W, Horst LF, Born J, Peters A.** Modulations of hunger by plasma glucose and metformin. *Endocr Soc.* 2003;88:1133–41.
70. **Mudaliar S, Edelman SV.** Insulin therapy in type 2 diabetes. *Endocrinol Metab Clin.* 2001;30:935–82.
71. **Howard BV, Ruotolo G, Robbins DC.** Obesity and dyslipidemia. *Endocrinol Metab Clin.* 2003;32:855–67
72. **Bays H, Mandarin L, DeFronzo RA.** Role of the adipocyte FFA, and ectopic fat in pathogenesis of type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2004;89:463–78.
73. **Cheng A, Uetani N, Simoncic PD, et al.** Attenuation of leptin action and regulation of obesity by protein tyrosine phosphatase 1B. *Dev Cell.* 2002;2:497–503.
74. **Goldstein BJ.** Protein-tyrosine phosphatase 1B (PTP1B): a novel therapeutic target for type 2 diabetes mellitus, obesity, and related states of insulin resistance. *Curr Drug Targets Immune Endocr Metabol Disord.* 2001;3:265–75.
75. **Bays HE, Stein EA.** Pharmacotherapy for dyslipidemia—current therapies and future agents. *Pharmacotherapy.* 2003; 4:1901–38.
76. **Bodkin NL, Pill J, Meyer K, Hansen BC.** The effects of K-111, a new insulin-sensitizer on metabolic syndrome in obese prediabetic rhesus monkeys. *Horm Metab Res.* 2003; 35:617–24.
77. **Kadowaki T.** PPAR gamma agonists, antagonists. *Nippon Yakurigaku Zasshi.* 2001;118:321–6.
78. **Cincotta AH, Meier AH.** Bromocriptine (Ergoset) reduces body weight and improves glucose tolerance in obese subjects. *Diabetes Care.* 1996;19:667–70.
79. **Boehm BO.** The therapeutic potential of somatostatin receptor ligands in the treatment of obesity and diabetes. *Invest Drugs.* 2003;12:1501–9.
80. **Lustig RH, Hinds PS, Ringwald-Smith K, et al.** Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab.* 2003;88: 2586–92.
81. **Havel PJ.** Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism. *Diabetes.* 2004;53:143–51.
82. **Szewczyk JR, Laudeman C.** CCK1R agonists: a promising target for the pharmacological treatment of obesity. *Curr Top Med Chem.* 2003;3:837–54.
83. **Albu J, Raja-Khan N.** The management of the obese diabetic patient. *Clin Office Pract.* 2003;30:465–91.
84. **DeFronzo R, Ratner R, Han J, Kim D, Fineman M, Baron A.** Effects of exenatide (synthetic exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Program and abstracts of the 64th Scientific Sessions of the American Diabetes Association; June 4–8, 2004; Orlando, FL. Late breaking abstract 6.
85. **Sturis J, Gotfredsen CF, Romer J, et al.** GLP-1 derivative liraglutide in rats with beta-cell deficiencies: influence of metabolic state on beta-cell mass dynamics. *Br J Pharmacol.* 2003;140:123–32.
86. **Ahren B, Simonsson E, Larsson H, et al.** Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4 week study period in type 2 diabetes. *Diabetes Care.* 2002; 25:869–75.
87. **Chakrabarti R, Rajagopalan R.** Diabetes and insulin resistance associated disorders: disease and therapy. *Curr Sci.* 2002;83:1533–8.
88. **Batterham RL, Cowley MA, Small CJ, et al.** Gut hormone PYY 3–36 physiologically inhibits food intake. *Nature.* 2002;418:650–3.
89. **Cummings DE, Weigle DS, Frayo RS, et al.** Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med.* 2002;346:1623–30.
90. **Stoeckli R, Chanda Robin, Langer I, Keller U.** Changes of body weight and plasma ghrelin levels after gastric banding and gastric bypass. *Obes Res.* 2004;12:346–50.
91. **Young AA.** Amylin as a neuroendocrine hormone. *Scientific World J.* 2001;18:24.
92. **Maggs D, Shen L, Brown D, Kolterman O, Weyer C.** Effect of pramlintide on A1C and body weight in insulin-treated African Americans and Hispanics with type 2 diabetes: a pooled post hoc analysis. *Metabolism.* 2003;12:1638–42.
93. **Hollander P, Ratner R, Fineman M, et al.** Addition of pramlintide to insulin therapy lowers HbA1c in conjunction with weight loss in patients with type 2 diabetes approaching glycaemic targets. *Diabetes Obes Metab.* 2003;5:408–14.
94. **Hollander P, Maggs DG, Ruggles JA, et al.** Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. *Obes Res.* 2004;12:661–8.
95. **Hu B, Jennings LL.** Orally bioavailable beta 3-adrenergic receptor agonists as potential therapeutic agents for obesity and type 2 diabetes mellitus. *Prog Med Chem.* 2003;41:167–94.
96. **Hesselink MKC, Mensink M, Schrauwen P.** Human uncoupling protein-3 and obesity: an update. *Obes Res.* 2003; 11:1429–43.
97. **Grover GJ, Mellstrom K, Ye L, et al.** Selective thyroid hormone receptor-beta activation: a strategy for reduction of weight, cholesterol, and lipoprotein (a) with reduced cardiovascular liability. *Proc Natl Acad Sci U.S.A.* 2003;100:1006–72.
98. **Wolf G.** Adiponectin: a regulator of energy homeostasis. *Nutr Rev.* 2003;61:290–2.
99. **Collins CA, Kym PR.** Prospects for obesity treatment: MCH receptor antagonists. *Curr Opin Invest Drugs.* 2003;4:386–94.
100. **Lukic T, Pritchard H, Wasan KM.** Disodium ascorbyl phytostanyl phosphates, FM-VP4, decreases blood lipids and body weight without observed toxicity. International Symposium on Triglycerides, Metabolic Disorders, and Cardiovascular Disease, New York, NY, July 11, 2003.

101. **St-Onge MP, Lamarche B, Mauger JF, Jones PJ.** Consumption of functional oil rich in phytosterols and medium chain triglyceride oil improves plasma lipid profiles. *J Nutr.* 2003;133:1815–20.
102. **Bourque C, St-Onge MP, Papamandjaris AA, et al.** Consumption of an oil composed of medium chain triacylglycerols, phytosterols, and N-3 fatty acids improves cardiovascular risk profile in overweight women. *Metabolism.* 2003;52:771–7.
103. **Han J, Hamilton JA, Kirkland JL, Corkey BE, Guo W.** Medium-chain oil reduces fat mass and down-regulates expression of adipogenic genes in rats. *Obes Res.* 2003;11:734–44.
104. **St-Oge MP, Ross R, Parsons WD, Jones PJH.** Medium-chain triglycerides increase energy expenditure and decrease adiposity in overweight men. *Obes Res.* 2003;11:395–402.
105. **Lei T, Xie W, Han J, Corkey BE, Hamilton JA, Guo W.** Medium-chain fatty acids attenuate agonist-stimulated lipolysis, mimicking the effects of starvation. *Obes Res.* 2004;12:599–611.
106. **Habeck M.** A succulent cure to end obesity. *Drug Discov Today.* 2002;7:280–1.
107. **Lankisch M, Layer P, Rizza RA, DiMango EP.** Acute postprandial gastrointestinal and metabolic effects of wheat amylase inhibit (WAI) in normal, obese, and diabetic humans. *Pancreas.* 1998;17:176–81.
108. **Baek JS, Kim HY, Abbott TP, et al.** Acarviosine-simmondsin, a novel compound obtained from acarviosine-glucose and simmondsin by *Thermus maltogenicus* amylase and its in vivo effect on food intake and hyperglycemia. *Biosci Biotechnol Biochem.* 2003;67:532–9.
109. **Myers SE, Carrel AL, Whitman BY, Allen DB.** Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome. *J Pediatr.* 2000;137:43–9.
110. **Shadid S, Jensen MD.** Effects of growth hormone administration on human obesity. *Obes Res.* 2003;11:170–5.
111. **Heffernan MA, Jiang WJ, Thorburn AW, Ng FM.** Effects of oral administration of synthetic fragment of human growth hormone on lipid metabolism. *Am J Physiol Endocrinol Metab.* 2000;2779:E501–7.
112. **Heffernan MA, Thornburn AW, Fam B, et al.** Increase of fat oxidation and weight loss in obese mice caused by chronic treatment with human growth hormone or a modified C-terminal fragment. *Int J Obes Relat Metab Disord.* 2001;25:1442–9.
113. **Berdainier CD, Parente JA Jr, McIntosh MK.** Is dehydroepiandrosterone an antiobesity agent? *FASEB J.* 1993;7:414–9.
114. **Wellman M, Shane-McWhorter L, Orlando PL, Jennings P.** The role of dehydroepiandrosterone in diabetes mellitus. *Pharmacotherapy.* 1999;19:582–91.
115. **Engeli S, Bohnke J, Feldpausch M, et al.** Regulation of 11 beta-HSD genes in human adipose tissue: influence of central obesity and weight loss. *Obes. Res.* 2004;12:9–17.
116. **Walker BR.** 11 beta-hydroxysteroid dehydrogenase type 1 in obesity. *Obes Res.* 2004;12:1–3.
117. **Smith SR, Jonge DL, Pellymounter M, et al.** Peripheral administration of human corticotropin-releasing hormone: a novel method to increase energy expenditure and fat oxidation in man. *J Clin Endocrinol Metab.* 2001;86:1991–8.
118. **Hirsch J, Leibel RL.** The genetics of obesity. *Hosp Pract.* 1998;33:55–70.
119. **Polla MO, Tottie L, Norden C, et al.** Design and synthesis of potent, orally active, inhibitors of carboxypeptidase U (TAFIa). *Bioorg Med Chem.* 2004;12:1151–75.
120. **Makimura H, Mizuno TM, Yang XJ, Silverstein J, Beasley J, Mobbs CV.** Cerulenin mimics effects of leptin on metabolic rate, food intake, and body weight independent of the melanocortin system, but unlike leptin, cerulenin fails to block neuroendocrine effects of fasting. *Diabetes.* 2001;50:733–9.
121. **Thupari JN, Landree LE, Ronnett GV, Kuhajda FP.** C75 increases peripheral energy utilization and fatty acid oxidation in diet-induced obesity. *Proc Natl Acad Sci U.S.A.* 2002;99:9096–7.
122. **Current Patents Gazette.** Aventis claims anorexiants indanones and indanols, and their use in controlling obesity: two unidentified candidates with this indication are in clinical trials. <http://www.current-patents.com/news/2003/0311/11.asp> (accessed March 2004).
123. **Ganaera.** Development—other programs. <http://www.ganaera.com/otherprograms.html> (accessed March 2004).
124. **Phoenix Pharmaceutical Inc.** Obesity related peptide list. Available at: <http://www.phoenixpeptide.com/allobesity/index.html> (accessed July 2004).
125. **Thearle M, Aronne LJ.** Obesity and pharmacologic therapy. *Endocrinol Metab Clin.* 2003;32:1005–24.