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Pharmaceutical approaches to the treatment of obesity

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The recent increase in pharmaceutical companies' efforts toward the treatment of obesity reflects recognition of the related health risks, the growth of knowledge about mechanisms that control energy balance, and the potential market for new compounds. The current patent literature gives a picture of the targets that are available for pharmaceutical intervention; these include signals of satiety and signals related to fat storage that act in the hypothalamus. The regulation of energy use and storage in adipocytes and the reduction of intestinal absorption of energy are also pharmaceutical focus areas. The multiplicity of targets illustrates not only the many potential approaches to the treatment of obesity but also the complexity and redundancy of the processes that regulate energy storage in the body.

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▼ Pharmacotherapy is defined as the treatment of undesirable or unhealthy symptoms through the use of drugs. Implicit in a review of the pharmacotherapy of obesity is the recognition of the condition of obesity as being undesirable and/or unhealthy. The last decade has seen not only a change in the prevalence of obesity [1–3], but also has highlighted the fact that obesity is a highly risky pathological condition. Health risks associated with obesity are now recognized to exceed those associated with smoking [4,5]. Morbid obesity, which is linked to many chronic health conditions, has increased much faster than obesity in general in the USA [3,6]. A common definition of obesity, based upon the body mass index (BMI), has been adopted by the World Health Organization and the National Institutes of Health. BMI is defined as body weight (in kg) divided by height (in m^2). A BMI between 20 and 25 is considered normal; a BMI between 25 and 30 is considered overweight; and a BMI over 30 is considered obese. Morbid obesity is defined as a BMI over 40 and has the greatest associated health risks.

Besides increased awareness of the associated health risks of obesity, there has been a rapid increase in the understanding of biochemical events thought to be causative factors. A strong impetus underlying much of this research was the discovery of leptin and its receptors and their relationship to energy balance [7–10]. The subsequent discovery of the importance of specific anabolic and catabolic circuits in the brain that control energy homeostasis [11–18] also helped focus research for obesity treatments on specific molecular targets.

Novel perceptions of the risks and causes of obesity have consequently been a stimulus for the development of pharmaceutical approaches to the reduction of body adipose tissue and to the prevention of its gain. We discuss current strategies that are being employed by the pharmaceutical industry and that are designed to influence the biochemistry that controls eating behavior and energy utilization. More specifically, after a brief overview of what is known of the control system over energy homeostasis and storage, we review the approaches that are being taken by pharmaceutical companies based on US patents issued from 2001 to spring of 2004. We take this approach to complement several excellent reviews of the potential theoretical approaches to intervene in ingestive behavior and energy expenditure [16,19–25].

Energy homeostasis

The energy equation holds that if body weight is to remain stable, food intake (i.e. energy intake) must equal energy expenditure (i.e. metabolism plus the effects of exercise) over long intervals. If the energy equation is not in balance, body weight will drift upwards or downwards over time. In practical terms, if an individual is going to lose weight (or not gain it in the first place), dieting and/or increased exercise should be the first line of defense. For those individuals for whom these are not feasible in a compliance sense, a pharmaceutical approach targeting energy intake or energy expenditure, or else the energy storage system, might be the best second option.

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The hypothalamus is generally considered to be an integrator of signals that influence energy intake and energy expenditure ([11–18]; see Figure 1). These signals can be partitioned into one of three general categories:

(1) Signals arising during meals that indicate caloric quantity and quality to the brain. These are collectively called satiety signals because when they are administered before meals less food is eaten. As a generality, these signals are gastrointestinal peptides that help coordinate digestion. Many of them also act on receptors on sensory neurons innervating the gut such that their message is conveyed neuronally to the hindbrain and subsequently relayed anteriorly to the hypothalamus [26–28].

(2) Signals related to the amount of fat stored throughout the body. These adiposity signals, as they are called, are hormonal, circulating in the blood in proportion to body fat. These signals interact with receptors on neurons directly in the hypothalamus (see Figure 1). The best known adiposity signals are insulin and leptin, and when they are administered directly into the brain, animals eat less food and expend more energy [11–18]; a third such signal might be the newly described adipose tissue hormone, adiponectin [29–31].

(3) The third category includes the myriad neural transmitters and modulators synthesized and secreted within the brain itself. Although some generalities can be made, such as a rough subdivision into signals that elicit net catabolic activity versus other signals that elicit net anabolic activity, this is a broad category that includes much of the brain in addition to the hypothalamus.

There are many other points for possible pharmaceutical intervention. For example, compounds that interfere with digestion or absorption of ingested nutrients are obvious possibilities, as are compounds that act locally on energy storage depots (adipose tissue or possibly glycogen stores) to reduce the efficiency of storage and/or increase the efficiency of shedding stored energy.

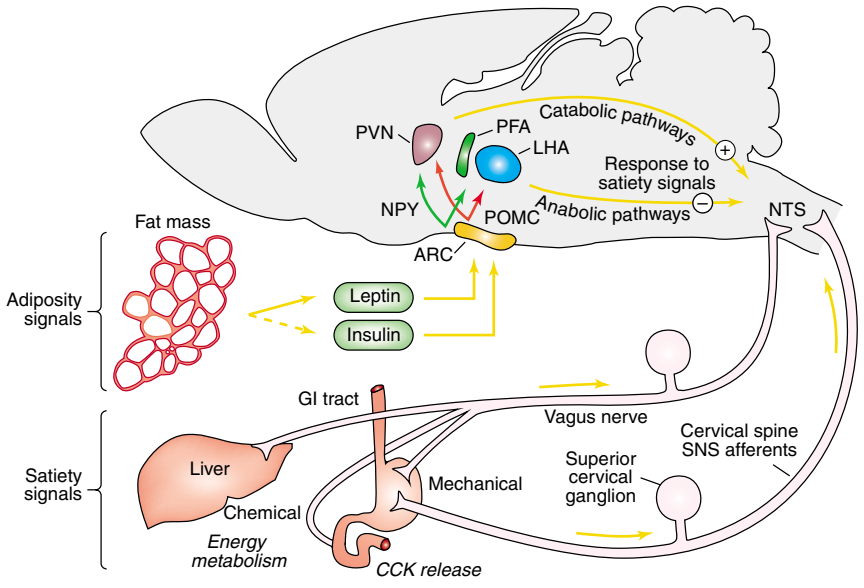

Figure 1. Model summarizing different levels of control over energy homeostasis. During meals, signals such as CCK (cholecystokinin) or distension of the stomach that arise from the gut (stomach and intestine) trigger nerve impulses in sensory nerves traveling to the hindbrain. These satiety signals synapse with neurons in the nucleus of the solitary tract (NTS) where they influence meal size. Signals related to body fat content such as leptin and insulin, collectively called adiposity signals, circulate in the blood to the brain. They pass through the blood–brain barrier in the region of the arcuate nucleus (ARC) and interact with neurons that synthesize proopiomelanocorticotropin (POMC) or NPY and AgRP (NPY). These neurons in turn project to other hypothalamic areas including the paraventricular nuclei (PVN) and the lateral hypothalamic area (LHA). The net output of the PVN is catabolic and enhances the potency of satiety signals in the hindbrain. The net output of the LHA, by contrast, is anabolic, suppressing the activity of the satiety signals. In this way, body fat content tends to remain relatively constant over long intervals by means of changes of meal size. Figure reproduced, with permission, from Reference [17]. Abbreviations: GI, gastrointestinal; NPY, neuropeptide Y; PFA, perifornical area; SNS, sympathetic nervous system.

Adipose tissue

Given the evolutionary pressure to preserve ingested energy in preparation for periods without reliable sources of food, the body has an efficient system for storing calories not immediately needed for work or heat production [32,33]. Adipocytes take up and store fatty acids as triacylglycerol, an efficient molecule providing 9 kcal g^{-1} of energy. The balance between anabolism (lipogenesis) and catabolism (lipolysis) in the adipocyte parallels that of the entire organism. After a fatty meal, fat circulates in large lipoprotein particles [chylomicrons and/or very low density lipoproteins (VLDLs)], and fatty acids are delivered to many tissues, including adipocytes, through the action of locally produced lipoprotein lipase (LPL). During fasting, the enzyme hormone sensitive lipase causes adipocytes to release fatty acids, a process that is of use in achieving weight loss only if the released fatty acids are used for work or energy. Cachexia is a syndrome characterized by chronically increased lipolysis and loss of body fat as well as loss of lean body mass [34].

Adipose tissue lipolysis is stimulated by catecholamines acting at β-adrenergic receptors stimulating cyclic AMP production and thereby phosphorylating hormone sensitive lipase. Insulin stimulates LPL, favoring storage over utilization of fatty acids. Perilipin, a protein in the adipocyte, reduces the activity of hormone sensitive lipase, and mice that cannot produce perilipin have reduced body fat [35]. Strategies that target LPL or hormone sensitive lipase could prove therapeutically useful.

Brown adipose tissue and uncoupling proteins

When most tissues oxidize glucose or fatty acids, ATP is produced and made available for work. By contrast, brown adipose tissue (BAT), a tissue characteristic of rodents and newborn infants, synthesizes the uncoupling protein, UCP-1, which reduces the proton gradient across the inner mitochondrial membrane and thereby reduces the production of ATP and generates heat instead of usable energy. The discovery of other uncoupling proteins (UCP-2 and UCP-3) in other tissues suggests that stimulating their activity might be a useful approach [36,37], although the relevance of these UCPs to human metabolism is controversial.

The gut and absorption

As a general rule, all of the calories in ingested food are absorbed and made available for use as a source of energy. For example, the capacity of the enzymatic and transport systems involved in fat absorption is greatly in excess of those needed during normal absorption. Kasper reported that the ingestion of more than 600 g day^{-1} of fat, more than six times normal consumption, is well tolerated [38]. Dietary fat must be hydrolyzed before it can be absorbed into the enterocytes. Fat that is not hydrolyzed is not absorbed and is therefore excreted. Excreted fat normally accounts for 1–10% of ingested fat. Interference with either fat hydrolysis or fat absorption obviously results in reduced utilization of ingested energy, although the appearance of relatively large quantities of undigested fat and/or carbohydrate in the colon can result in untoward events.

Current therapies

Currently, only two pharmaceuticals are approved for the long-term treatment of obesity in the USA (i.e. that can be prescribed for a year or more). One is designed to reduce food intake and the other the utilization of ingested energy.

Sibutramine, marketed as Meridia® and Reductil®, is a serotonin, norepinephrine and dopamine reuptake inhibitor. It reduces food intake and, in published trials using approved doses in the USA, reduces body weight modestly (~5%) for up to a year with small increases of blood pressure and heart rate in some patients [25,39].

Orlistat, marketed as Xenical®, reduces the efficiency of absorption of fat in the small intestine. Orlistat inactivates pancreatic lipase by covalent bonding, thereby inhibiting hydrolysis and absorption of dietary triacyglycerol. This approach has achieved modest long-term reductions in body weight; however, the appearance of high levels of fatty acids in the large intestine can lead to gastrointestinal side effects that limit compliance with the regimen. As discussed below, the inactivation of pancreatic lipase continues to be considered a viable approach in the development of future drugs, and there are methods being developed to ameliorate the side effects associated with lipase inhibitors.

There are also drugs that are currently approved for the short-term (i.e. up to 6 months) reduction of appetite, including phentermine and fenfluramine.

Current pharmaceutical research: patent literature 2001–2004

A review of recent patents directed toward the treatment of obesity by major pharmaceutical companies provides one type of assessment of the emphases on various systems and targets. Table 1 summarizes the areas and activity of research and discovery related to these areas. The data in Table 1 were obtained by searching US patents issued from January 2001 to March 2004, for any that included the word 'obesity' in the abstract. As can be seen, there is a wide range of targets, with several of the targets having numerous related patents. Among the targets with the highest number of new patents are serotonin receptor ligands (24 patents), NPY receptor ligands (20 patents) and adrenergic receptor ligands (20 patents). Each of these three categories in turn covers a broad spectrum of approaches because of the diversity and distribution of the receptor types. As an example, included in the NPY receptor ligand category are compounds based upon receptors for $PYY_{3–36}$ as well; $PYY_{3–36}$ is a peptide that reportedly reduces food intake in animals and humans when administered systemically [40,41] although its efficacy is controversial [42]. PYY is a member of the NPY family of peptides.

As another example, there are at least 15 distinct serotonin receptors divided into 7 major families [43]. Serotonin receptors influence most behaviors, and different serotonin receptors often have opposing actions on the same behavior. As a generality, excess serotonin tone is thought to decrease food intake and elicit weight loss [44]. Because many antipsychotic drugs target the serotonin system, it is not surprising that some of these drugs have as a side effect the ability to influence appetite and body weight. Dexfenfluramine, a drug widely prescribed a decade ago to treat obesity when combined with phentermine (Fen-Phen) was in this category before being withdrawn from the

Table 1. US patents issued between January 2001 and March 2004 with 'obesity' in the abstract

Target/Treatment	Number issued	Assignees
Adrenomedullin receptor polypeptide	1	SmithKline Beecham
Blocking $\alpha_2$adrenergic receptor	2	Allergan
$\beta_3$adrenergic receptor agonists	18	Bristol-Myers Squibb, Lilly, Merck, Pfizer, Warner-Lambert, Wyeth
Ciliary neurotrophic factor	3	Regeneron, Insitituto di Richerche di Biologia Molecolare P. Angeletti
Corticotropin releasing factor (CRFP) ligands	1	Neurogen
Dipeptidyl peptidase IV (DPP-IV) inhibitors	4	Bristol-Myers Squibb, Novartis, Pfizer
Estrogen agonists/antagonists	2	Pfizer
Fat binding polymers	2	GelTex
Fatty acid synthase	1	Bayer
Galanin receptor (GALR2)	5	Merck
Glucagon-1 like peptide crystals	2	Lilly
Glucagon antagonists/inverse agonists	4	Novo
Glucocorticoid receptor	4	Abbott, Pfizer
Glycogen synthase kinase 3	2	Chiron
GPR10 target	1	Millenium
Growth hormone secretogues	18	Bristol-Myers Squibb, Pfizer
Leptin/Ob receptor	8	Millenium, SmithKline Beecham
Lipase inhibitors	7	Alizyme, GelTex, Laboratoire Laphal
MCH antagonists	1	Schering Corporation
Melanocortin receptor agonists	7	Merck, Procter & Gamble
Motilin antagonists	1	Ortho McNeil
Neurokinin receptor ligands	1	Neurogen
Neurotensin receptor ligand	1	Pfizer
NPY, NPY1, NPY5 antagonists, modulators	20	Amgen, Bayer, Hoffman-La Roche, Lilly, Merck, Neurogen, Pfizer, Schering Plough
Orexin antagonists	1	SmithKline Beecham
PPAR (α,δ,γ) modulators	9	Bristol-Myers Squibb, Merck, Ortho McNeil
PTPase (PTP1B) inhibitors	10	Merck Frosst, Novo
Serotonin ($5HT_{5, 1A, 2C}$), agonists, antagonists, reuptake inhibitors	24	Abbott, American Home Products, Bristol-Myers Squibb, Hoffman-La Roche, Pfizer, Wyeth
Thyromimetics, thyroid receptor ligands	8	Bristol-Myers Squibb, Novartis, Pfizer
Tubby polypeptides	1	SmithKline Beecham
Uncoupling proteins	3	Amylin, Novartis, SmithKline Beecham

market due to adverse side effects [45]. An important point is that the control of mood and the control of energy homeostasis often use overlapping brain circuits [46]. Hence, many mood-altering drugs cause changes of body weight. Some atypical antipsychotics, for example, increase body weight and thereby compromise compliance; these agents include clozapine, olanzapine, risperidone and ziprasidone [47]. Several other antipsychotic or antiepileptic drugs are being used off-label to treat excess body weight, including topiramate [48,49] and prozac [50].

It should be clear that our approach provides only a single, narrow window into research activity aimed at pursuing new therapeutic targets for obesity. It necessarily misses very recently awarded patents and research directions. For example, oleoylethanolamide (OEA), a fatty acid structurally related to endogenous cannabinoids, has been found to reduce food intake and body weight [51,52] and is currently under active investigation.

Analogously, we do not report on approaches or agents that are currently active but for which patents were filed before our starting date cutoff. As an example, an antagonist of the CB_1 endocannibinoid receptor (Rimonabant®; Sanofi-Synthelabo, http://www.sanofi-synthelabo.com) is currently in Phase III clinical trials because it significantly reduces food intake and body weight in humans [53,54]. Likewise, ciliary neurotrophic factor (CNTF) is also well along in the evaluation pipeline for consideration as a weight-loss agent [55].

New strategies under consideration

Many of the targets in Table 1 are obvious, being based upon well-known catabolic or anabolic actions of neurotransmitters or hormones. This is true for adrenergic and serotonin receptors, corticotropin releasing factor, CNTF, estrogen, galanin, growth hormone, glucagon, glucagon-like peptide-1 (GLP-1), corticosteroids, leptin, melanocortins, melanin concentrating stimulating hormone (MCH), neurokinin, neurotensin, neuropeptide Y (including $PYY_{3–36}$), orexin and thyroid hormone. Others are based on enzyme systems for synthesizing or oxidizing fat. In the subsequent sections, we briefly discuss a few of the less obvious targets.

Adrenomedullin

Adrenomedullin is a peptide found in many tissues. In pancreatic islets, it is co-localized with pancreatic polypeptide in F cells [56], and its binding protein is expressed in insulin-secreting B cells [57]. Adrenomedullin reduces insulin secretion [58], making it and its receptor potentially important targets.

PPARs

Peroxisome proliferator-activated receptors (PPARs) comprise a family of nuclear receptors that are directly linked to DNA. PPARs are sensitive to fatty acids and cause transcriptional changes that alter the utilization of fatty acids and glucose for energy [59]. The activity of specific PPARs has been implicated in the regulation of insulin sensitivity and symptoms of obesity [60,61] as well as the control of food intake [62,63]. Activators of PPARγ, including the thiazolidinediones, increase insulin sensitivity but are associated with weight gain through induction of adipogenesis. Activation of PPARα, however, results in increased lipolysis and oxidation of fatty acids [64]. PPARδ (also called PPARβ) is implicated in the development of diet-induced obesity [65]. The development of compounds that alter one or another PPAR is a particularly active area.

Lipase inhibitors and reduced fat absorption

Inhibiting pancreatic lipase deprives the body of ingested calories because unhydrolyzed triacylglycerols are not absorbed from the intestine. Experience with the currently marketed drug, Xenical®, has demonstrated that up to 25% of ingested fat can be diverted from absorption, and a consequent loss of body weight has been demonstrated in clinical trials. Lipase inhibiting compounds other than Xenical® have been developed, and polymers that bind fat to prevent its absorption have also been reported. As discussed previously, unwanted gastrointestinal side effects can result from inhibition of pancreatic lipase, and approaches directed toward amelioration of these side effects are included in the patent literature for lipase inhibitors.

An alternative approach to reduce absorption of ingested fat has been the development of fat that cannot be hydrolyzed. Olestra, a sucrose molecule esterified with six to eight long-chain fatty acids, has the physical properties of dietary fats but is not hydrolyzed in the intestine [66]. This approach minimizes gastrointestinal side effects so long as the unabsorbed fat contains appropriate high-melting fatty acids [67]. The resistance to lipase also prevents hydrolysis catalyzed by bacterial lipases in the colon so that irritant fatty acids are not produced. Adding olestra to a reduced energy diet results in improved weight loss, presumably reflecting improved adherence to the diet [68].

Uncoupling proteins

As discussed above, uncoupling proteins generate heat without producing ATP, such that diversion of fat to uncoupled heat production remains an option for reducing body fat. UCP-1 is mainly expressed in brown adipocytes, and UCP-2 is expressed in many tissues. UCP-3, which is preferentially expressed in skeletal muscle in humans, is the primary target for pharma-ceuticals [69]. One recent patent describes the discovery of UCP-4, which is expressed in brain, heart, pancreas and muscle [70].

β_3 adrenergic receptors and agonists

Because β_3 adrenergic receptors stimulate lipolysis of triacylglycerols in adipose tissue, discovering agonists that are selective for β_3 receptors while avoiding the side effects of β_1 and β_2 receptor activation (e.g. increased heart rate, smooth muscle relaxation) is a logical strategy.

DPP-IV inhibitors

Dipeptidyl peptidase-IV (DPP-IV) is a proteolytic enzyme that acts in the circulation to degrade several hormones including glucagon-like peptide-1 (GLP-1) and gastric inhibitory compound (GIP) [71]. Reducing the activity of DPP-IV and thereby prolonging the half-life and circulating levels of GLP-1 and GIP is a viable strategy for treating obesity and improving insulin insensitivity. DPP-IV

inhibitors are also claimed to prevent degradation of NPY and PYY [72].

Protein tyrosine phosphatase (PTPase) inhibitors

PTPases influence many intracellular signaling pathways. PTP-1B-sensitive pathways are implicated in insulin resistance, and their inhibition has been suggested to be useful in the treatment of diabetes [73]. Kennedy reported that the absence of PTP-1B in mice resulted in a resistance to obesity [74].

Motilin

Motilin, a 22-amino acid peptide produced in the gut, induces gastric smooth muscle contraction. Motilin agonists induce stomach emptying, and it has been suggested that motilin antagonists would be useful in reducing gastrointestinal motility and treating eating disorders associated with obesity. Changing gut motility is a strategy being applied to many functional bowel disorders [75].

GPR10

GPR10, the prolactin-releasing peptide receptor, is a G protein-coupled receptor that has been presented as a target for obesity [76]. GPR-10 has been identified as the receptor for prolactin-releasing peptide in the mouse hypothalamus. GPR10 knockout mice were reported to become hyperphagic and obese relative to wild type animals [77].

Fat-binding polymers

An approach to the reduction of energy intake that differs from the inhibition of pancreatic lipase is that of reducing the absorption of dietary fat by binding the intestinal triacylglycerol or its hydrolysis products to non-absorbable polymers. This binding would reduce their bioavailability and thus their utilizable energy.

Tubby proteins

The 'tubby' mouse, which is obese and insulin resistant [78], lacks tub protein that is normally expressed in areas of the hypothalamus that control energy homeostasis [79]. Although the mechanism by which tub protein prevents the development of obesity in the brain is not clear, it does not seem to act through the same pathways as insulin [80].

Summary

This assessment of recent awards of patents that relate to the treatment and prevention of obesity is meant to give an indication of the research effort that is being supported. This approach is not a complete view of all possible pharmaceutical targets, but rather a kind of snapshot of the effort that is being applied to specific areas. We do not suggest that the number of patents in an area is a quantitative indicator of the amount of research activity. We do, however, believe that this view of obesity research shows which of the myriad steps in energy balance regulation are deemed to provide the best chance for development of effective treatment and prevention of obesity.

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