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# Pharmacological Approaches for the Treatment of Obesity

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## Abstract

The high incidence of obesity, its multifactorial nature, the complexity and lack of knowledge of the bodyweight control system, and the scarcity of adequate therapeutics have fuelled anti-obesity drug development during a considerable number of years. Irrespective of the efforts invested by researchers and compa-

nies, few products have reached a minimum level of effectiveness, and even fewer are available in medical practice. As a consequence of anti-obesity research, our knowledge of the bodyweight control system increased but, despite this, the pharmacological approaches to the treatment of obesity have not resulted yet in effective drugs.

This review provides a panoramic of the multiple different approaches developed to obtain workable drugs. These approaches, however, rely in only four main lines of action: i) control of energy intake, mainly through modification of appetite; ii) control of energy expenditure, essentially through the increase of thermogenesis; iii) control of the availability of substrates to cells and tissues through hormonal and other metabolic factors controlling the fate of the available energy substrates; and iv) control of fat reserves through modulation of lipogenesis and lipolysis in white adipose tissue. A large proportion of current research is centred on neuropeptidic control of appetite, followed by the development of drugs controlling thermogenic mechanisms and analysis of the factors controlling adipocyte growth and fat storage. The adipocyte is also a fundamental source of metabolic signals, signals that can be intercepted, modulated and used to force the brain to adjust the mass of fat with the physiological means available.

The large variety of different approaches used in the search for effective anti-obesity drugs show both the deep involvement of researchers on this field and the large amount of resources devoted to this problem by pharmaceutical companies. Future trends in anti-obesity drug research follow closely the approaches outlined; however, the increasing mass of information on the molecular basis of bodyweight control and obesity will in the end prevail in our search for effective and harmless anti-obesity drugs.

## 1. Introduction

### 1.1 Obesity, Aetiology and Treatment

Obesity is one of the most common metabolic pathologies in contemporary society. The incidence and severity of overweight and obesity is rising both in developing and developed countries. Obesity has often been considered a consequence of excessive food availability and its high energy content,[1,2] but other factors are currently accepted as significant causal agents, such as sedentary behaviour[3,4] and stress.[5,6] Other factors cited to explain the growing epidemic of obesity are the presence of growth factors in food,[7] nutrient imbalance,[8] and the excessive consumption of energy,[9] saturated fat,[10] sugars,[11,12] animal products[13] and, simply, fats.[14,15] In spite of extensive campaigns to limit the consumption of some of these foods and nutrients, and a general drive to diminish the energy content of meals and increase variety and consumption of vegetables and fibre,[16,17] both the incidence and severity of obesity are still increasing.[18]

The standard treatment of obesity is still the use of different hypocaloric diets,[19,20] often supplemented with exercise,[21] food education and changes in eating habits.[22] At present, the only option available to the severely obese is bariatric surgery,[23,24] since relapses are extremely common with all treatments,[25] and in the morbidly obese most treatments do not achieve even a significant weight loss paralleled by improvement in the overall condition of the patient.[26] In spite of its considerable danger and drawbacks, bariatric surgery is currently used as a last-resort therapy for life-threatening obesity.

In recent years, considerable research has focussed on analysing the genetic basis of human

obesity; a drive spurred by important findings on the genetics of rodent obesity [27] and the discovery of leptin.[28] The results so far have shown that, in humans, obesity is seldom caused by failure in a single gene as in many rodent models,[29] but due more to the interaction of a genetic proclivity to obesity [30] and environmental, including developmental, factors.[31] Most obesity is essentially a metabolic alteration in which resistance to insulin is a key element both in the pathophysiology and outward manifestations of the disease. The relationship with insulin resistance is magnified in the metabolic or X syndrome,[32] and in the close relationship between obesity and type 2 (non-insulin–dependent) diabetes mellitus.

### 1.2 Control of Bodyweight and Obesity

Several homeostatic models have been proposed to explain the complexity of the mechanisms of bodyweight regulation such as the glucostatic[33,34] or lipostatic[35] schemes. In the latter, also known as the ponderostat model, the mass of fat reserves is maintained constant by the counteracting forces of synthesis and degradation, controlled by the brain, which in turn responds to a blood-borne ponderostat signal synthesised in adipose tissue. The search for this 'signal' has been underway for many years because of its potential in the treatment of obesity.[36,37]

However, the prevailing idea that obesity is the result of 'excessive' energy intake is deeply rooted, and the development of drugs for the treatment of this pathology have mostly relied on the reduction of energy availability, both using physical systems, such as bariatric surgery, and hypocaloric diets or anorectic agents. This is one of the research areas which is showing the greatest progress, and the constant unravelling of peptide and neurotransmitter interactions in the hypothalamus and near areas of the brain is producing many research communications.[38,39]

Other alternatives for the early treatment of obesity have included the disruption of metabolism and hormonal equilibrium, using metabolic poisons[40] and thyroid hormones;[41] however, these approaches have met with limited success and undesirable side effects. The discovery of adaptive thermogenesis in rodents as a key mechanism for shedding excess energy[42] and the special role of brown adipose tissue (BAT) in this process[43] has presented modulation of thermogenesis as a viable way to combat obesity. Thus, a second line of research into obesity was initiated.

### 1.3 Pharmacological Treatment of Obesity

Many of the drugs used today for the treatment of obesity were unexpected spin-offs from other areas of research, especially the development of antidepressants, as is the case of fluoxetine and other serotonergic drugs.[44] The potential market for anti-obesity drugs is huge,[45] and research effort to obtain effective slimming agents is considerable. Nevertheless, the limited number of drugs marketed is surprisingly small and the treatments available to fight this disease are extremely limited.

Although we tend to consider the bodyweight regulation as a simple process, it is one of the most complex and well-regulated systems of our bodies. Body mass (i.e. the amount of reserves stored) is critical for survival: an excess of reserves limits movement and thus the ability to flee from predators, but insufficient reserves limit survival during periods of low-food availability.[46] Modern humans do not have predators and most are also protected from famine; thus, we tend to minimise the impact of several aeons of evolution honing the control of bodyweight to a high degree of effectiveness. Redundant and compensatory mechanisms hinder its external manipulation through diet, but lack of selective pressure has allowed the unchallenged expression of gene-encrypted metabolic efficiency in an environment with ample high-energy and palatable nutrients.

In the obese, the bodyweight control system has probably been unbalanced, raising the fat mass reference level because of altered ponderostat settings; other maladjustment in the balance of leptin, insulin, glucocorticoids (corticosteroids) and other hormones may further complicate the condition.

However, the built-in compensatory mechanisms keep working and prevent changes in the fat mass of the obese when the system is externally challenged by decreased energy intake or by drug-induced increases in thermogenesis. This increase, and the overriding counter-regulative action of corticosteroids – the guardians of fat stores – account for the scant success in most therapeutic actions against obesity, as well as for most of the hopes put on drug development.

This review presents a panorama of the drugs developed or simply assayed for use against obesity but is limited to only the drugs that have been described or used in published papers. The high number of unpublished failed studies and those that appear only in other types of documents (i.e. patents, books) have not been included in the list. However, current trends in obesity research have been included because they are based on solid and partly understood principles, in spite of the limited amount of published material; we assume that the information from these studies will be available in due course.

Our review does not pretend to be exhaustive but intends to give an insight into the diverse strategies used in the treatment of obesity. For each compound, strategy or type of drug, a single reference is given; this reference is often the only citation we have been able to find. Alternatively, in the case of several available references we selected that which describes the effects of the drug or which makes the first report of the molecule. Other compounds show several references because they are complementary in definition, or show aspects that significantly alter the data given in earlier references. In general, we have tried to present the data for humans but in most cases only data from animal experimentation are available. However, the selection of references for each entry has been, in most cases, the result of availability of material and personal choice, since we tried to mainly present the spectrum of anti-obesity drugs and not to describe each of the products and their effects.

## 2. The Bodyweight Control System: Avenues for Anti-Obesity Drug Development

### 2.1 Main Systems Controlling Bodyweight

Bodyweight is controlled by the brain and most of the relevant centres are located in the hypothalamus. The system consists of a series of afferent information signals and pathways, which inform the centre of key circulating metabolite status and the state of replenishment of the alimentary canal and its contents, as well as the status of body reserves of nutrients. This information is complemented by cortical signals and inputs from the senses. The integration of these inputs, as well as the built-in genetic and developmental plans, are all programmed to generate several efferent signals: (i) appetite signals that control food intake; (ii) sympathetic signals that control lipolysis and thermogenesis, the main pilfering and reserve-decreasing activities; and (iii) hormonal and parasympathetic signals that prevent the loss of energy and favour its accumulation. Figure 1 shows a general outline of this process.

The key points and mechanisms through which fat mass can be regulated are essentially: (i) the control of energy availability, by acting on either the hypothalamic control of appetite or by limiting food absorption; (ii) the control of thermogenesis and lipolysis, either through direct effects on adipose tissues [BAT and white adipose tissue (WAT)] or through modulation of sympathetic nervous system responses; (iii) direct actions on fat deposition (i.e. insulin) or WAT mass; and (iv) modulation of the whole system through changes in ponderostat signals. The amount of research – and published results – is predominantly devoted to the first, which is followed by thermogenesis research and by the other two fields in a distant third place.

Thermogenic drugs act mainly by stimulating the activity of BAT, by specific activation of adrenergic pathways, either by means of stimulation[47] or more specifically through $\beta_3$-adrenergic recep-

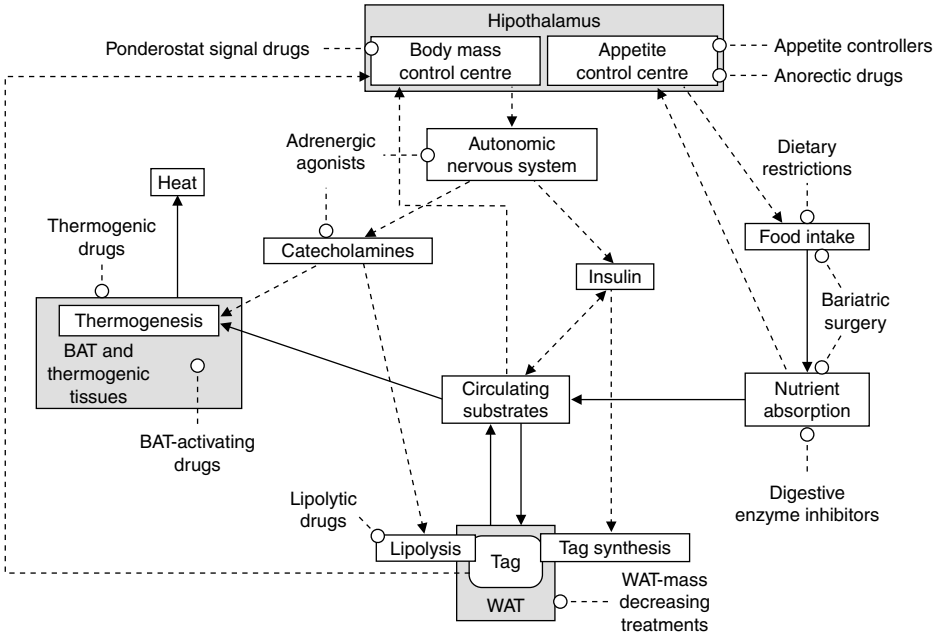


**Fig. 1.** Main pathways for energy metabolism, and key elements for control of the energy budget and bodyweight in the mammal. Solid arrows indicate substrate pathways and dashed arrows show control relationships. The sites where different anti-obesity therapeutic actions and drugs act are marked with lines ending in a circle. **BAT** = brown adipose tissue; **Tag** = triacylglycerols; **WAT** = white adipose tissue.

tors.[48] In addition to these effects, sympathetic stimulation also increases lipolysis[49] in WAT.

### 2.2 Control of Food Energy Availability

Because of the concentration of research on the control of energy availability, the number of strategies developed in this field is also considerable. In addition to appetite control, the amount of food ingested can be diminished either by hypocaloric diets or by the consumption of acaloric foods, such as food substitutes. The dilatation of the stomach walls results in the emission of satiety signals to the brain.[50] For some time stomach balloons have been used to reduce food intake and hunger signals,[51] thus by delaying the emptying of the stomach the satiating effects of stomach wall stretching are maintained for longer. The retardation of gastric emptying, together with inhibition of nutrient absorption and modification of intestinal transit, has been used to reduce the availability of nutrients for absorption in the intestine. In addition to the beneficial effects of fibre on colonic mucosa,[52] it also regulates intestinal peristalsis, dilutes waste and toxic components,[53] and retards the absorption of nutrients, especially starch-derived glucose.[54] The positive effect of some fibre types may be both a consequence of their bulk effects and their role in regulating glucose absorption,[55] which minimises the response to insulin.

The inhibition of enzymes that act on starch and other slowly digesting complex carbohydrates (α-amylases)[56] and lipases that act on dietary triacylglycerols[57] constitute a fairly simple method to limit nutrient availability, since these substrates cannot be properly digested (and their energy content absorbed) and only a limited part of their energy content is assimilated after partial metabolisation by intestinal flora.

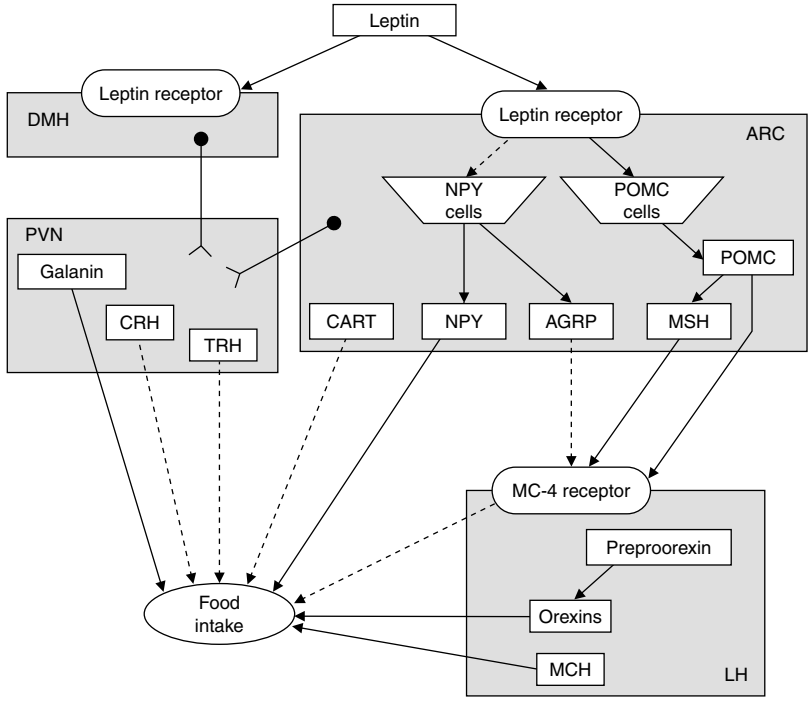


**Fig. 2.** Main peptides and inter-nuclear relationships in the hypothalamus related to the control of appetite. Solid lines represent production and activation effects; dashed arrows indicate inhibitory effects. **AGRP** = agouti-related protein; **ARC** = arcuate nucleus; **CART** = cocaine and amphetamine-related trascript; **CRH** = corticotropin-releasing hormone; **DMH** = dorso-medial hypothalamus; **LH** = lateral hypothalamus; **MC** = melanocortin; **MCH** = melanin-concentrating hormone; **MSH** = melanocyte-stimulating hormone; **NPY** = neuropeptide Y; **POMC** = proopiomelanocortin; **PVN** = para-ventricular nucleus; **TRH** = thyrotropin-releasing hormone.

Most of the research into drugs to treat obesity, however, are centred on the control of appetite, and specifically on the unravelling of the extremely complex pathways that regulate food ingestion in the hypothalamus and neighbouring brain nuclei.[39] In this respect, there are two main strategies being developed simultaneously: (i) classic pharmacological studies, mainly centred on drug modification of adrenergic, serotonergic and other neurotransmitter responses; and (ii) molecular and cellular biology studies in which the spatial relationships between hypothalamic nuclei and the peptides that act on specific receptors and groups of cells are identified. Figure 2 shows a partial scheme of the main relationships between the key hypothalamic nuclei involved in the control of appetite.

### 2.3 Role of Glucocorticoids

The role of glucocorticoids (corticosteroids) in the control of bodyweight has been recognised for some time.[58] Exaggerated responses to stress have been observed in the obese,[59,60] and the role of these corticosteroids in the development of resistance to insulin[61] and leptin[62] – which are the root causes of most metabolic complications of obesity, if not obesity itself – has been widely accepted. Corticosteroids blunt the response to $\beta_3$-adrenoceptor agonists,[63] and are needed for the development of obesity in several animal models.[64] In most obesities, the hypothalamus-pituitary-adrenal axis is deeply altered,[65,66] and cortisol availability is modified because of changes in levels and activity of corticosteroid-binding globu-

lin.[67] Corticosteroids are the main counter-regulatory element that prevents the loss of body fat, and their activity is enhanced by almost any of the pharmacological actions directed to the diminution of fat mass through increased energy expenditure and/or limited energy availability.

The counter-regulatory role of corticosteroids is often not considered but it is probably responsible for the rapid loss of effect of some of the most promising anti-obesity drugs. The control of corticosteroid effects may allow the success of many of the experimental drugs available; however, the current single-drug strategies have limited effectiveness because the compensatory nature of the mechanisms that control body fat rapidly counteract any manipulation of the system unless these mechanisms – often triggered by corticosteroids – are defused simultaneously. The development of combined strategies to tackle obesity will probably be much more successful than the prevailing single-drug studies; the companies involved in the development of anti-obesity drugs have barely explored synergistic combinations of drugs, as those used in the treatment of some infectious diseases, such as tuberculosis or AIDS.

## 3. Drugs Modifying the Availability and Absorption of Nutrients

### 3.1 Hypocaloric Food Substitutes

Table I shows the main types of drugs and food substitutes used to limit the availability of nutrients. One of the most common strategies used to limit the energy ingested is by substituting some high-energy nutrients with acaloric or hypocaloric substitutes. Because of their energy content and palatability, the main nutrients substituted have been sugar (and sweets) by acaloric sweeteners and fats by oil substitutes. The use of sugar substitutes is extremely widespread; the lack of a satiating response, coupled to their increased ingestion of food often results in exaggerated intakes,[68] and

**Table I.** Drugs that control digestion

| Mechanism and compounds | Effect and comments |
|---|---|
| **Hypocaloric and acaloric food substitutes** | |
| Acaloric sweeteners: aspartame,[71] saccharin,[72] sucralose[73] | Decrease FI (short-term) and sugar intake |
| Bulk acaloric sweeteners: tagatose[74] | Non-metabolisable |
| Acaloric lipid, oil substitutes: methyl-glucoside fatty acid esters (MGP),[75] olestra,[76] simplesse[77] | Substitute fat; altered intestinal function; liquid waste; hampered lipophilic vitamin absorption |
| **Nutrient absorption modifiers** | |
| Gastric emptying delayers: chlorocitrate,[78] trans-epoxy-aconitate,[79] pluronic L-101,[80] pramlintide[81] | Decrease FI and BW gain; inhibit lipid absorption |
| Nutrient absorption delayers: poliglusam (chitosan);[82,83] PFB (perfluoro-octyl-bromide)[84] | Decrease fat absorption; bulk effect; lipid sequestering effect; cover absorptive surfaces hampering absorption; lower BW in association with hypocaloric diets |
| Glucose absorption inhibitors: AO-124[85] | Anorectic; delay gastric emptying |
| Fibre, bulk effect: colextran (DEAE-dextran),[86,87] glucomannan,[88] guar gum,[89] methyl-cellulose,[89] pectin,[90] polysiloxane[91] | Increase peristaltism; induce satiety; retard nutrient absorption |
| **Digestive enzyme inhibitors** | |
| Inhibitors of intestinal disaccharidases (sucrase-isomaltase): voglibose (AO-128)[92] | Decrease postprandial rise of glucose; adjunct to dietary management of obesity and diabetes mellitus |
| α-Amylase inhibitors: acarbose (BAY-G-5421),[93,94] BAY-D-7791,[95] BAY-E-4609,[95] miglitol (BAY-M-1099),[95] phaseolamin,[96] voglibose[97] | Decrease glucose assimilation from starch; colonic fermentation and discomfort, no effect on BW |
| α-Amylase inhibitors and lipase inhibitors: BAY-N-2920[95] | Decrease starch and fat hydrolysis |
| Lipase inhibitors: BAY-1442,[95] BAY-N-4605,[95] CT-II,[98] chondroitin-sulfate,[99] orlistat (tetrahydrolipstatin, RO-18-0647),[100-104] tea saponins[105] | Decrease fat intestinal hydrolysis and absorption; limited loss of BW; dietary lipid-related intestinal discomfort |

**BW** = bodyweight; **FI** = food intake.

may elicit other effects, such as the anti-diabetic effects of saccharin[69] or the damaging interaction of aspartame-derived formaldehyde with cell components.[70]

Fat substitutes are usually polyesters of carbohydrates, large molecules that cannot be hydrolysed by lipases, which result in a sustained permanence in the environment because they are practically unaltered by intestinal flora.[106] In addition to intestinal discomfort, continued use of these substitutes leads to altered absorption of lipophilic vitamins and other nutrients.

### 3.2 Nutrient Absorption Modifiers

Gastric emptying delayers act either on the stomach wall, or simply cover it with a layer of surfactant that hampers digestion and thus voiding.[80] Other compounds delay nutrient absorption by repeating the wall-covering strategy on the intestine,[84] thereby limiting the absorption of fats and other nutrients by diluting them within their bulk[53] or by adsorbing nutrient lipophilic molecules on the indigestible fibre strands.[107]

The agents decreasing glucose absorption have been widely studied, especially in connection with the treatment of type 2 diabetes, closely related to obesity. Some of the drugs initially developed for diabetes reduce glucose absorption and have been postulated to improve the conditions of the obese,[108] despite their limited overall effect on bodyweight.

Digestive enzyme inhibitors have recently received considerable attention. In spite of existing disaccharidase inhibitors, research in this field has been centred mainly on amylase and lipase inhibitors, because starches and fats are probably the largest contributors to our food-derived energy budget. The early success of orlistat and its availability in the market has spurred additional research in the field. Nevertheless, despite their proven effectiveness in the treatment of overweight and mild obesity,[109] the effects of these therapeutic treatments can only be complementary in the treatment of obesity, since, at most, treatment with digestive enzyme inhibitors can limit energy intake but at the expense of enhancing colonic fermentation, and the body easily adapts to lower intake in the long run; therefore, the effects on fat stores are limited.[110]

## 4. Drugs Modifying Appetite

Research in appetite suppression has been carried out essentially along four lines: (i) hypothalamic neuropeptides; (ii) satiety-inducing (mainly intestinal) peptide systems (iii) monoamine transmitters such as serotonin and noradrenaline; and (iv) leptin and related hormonal pathways.[111]

### 4.1 Hypothalamic Peptides

Table II shows the main lines along which peptidic control of appetite translates into drug-discovery research strategies. The main body of hypothalamic peptide research corresponds to neuropeptide Y (NPY), one of the main orectic neurotransmitters,[112,113] which is greatly affected by leptin.[114] The search for NPY antagonists is widespread and some success has already been obtained in the laboratory. However, the problem of administration and targeting into hypothalamic nuclei seriously hampers future development in this direction, since the half-life of peptides in the bloodstream is extremely short and crossing the blood-brain barrier poses additional logistical problems to most peptide-based drugs.

The anorectic effects of corticotropin-releasing hormone (CRH) have been known for some time;[119] however, the role of CRH in the control of the synthesis of adrenocorticotrophic hormone (ACTH) and therefore that of corticosteroids makes it an inadequate target for appetite control. Enhancement of CRH production may affect appetite, but it also increases corticosteroid synthesis, which can counteract the lower intake with higher protection of fat reserves.

Recent advance in the understanding of the role of proopiomelanocortin in the control of appetite[205] has led to considerable research on melanocortins, such as α-melanocyte–stimulating hormone (αMSH), and specially on melanocortin receptors, since their agonists have profound ano-

**Table II.** Drugs controlling appetite: peptides

| Mechanism and compounds | Effect and comments |
|---|---|
| **Hypothalamic peptides** | |
| Agouti-related protein (AGRP) antagonists[115,116] | |
| Cocaine and amphetamine related transcript (CART) agonists[117,118] | Decrease appetite and FI; mediate the response to stress |
| CRH agonists: corticorelin (CRH),[119-121] urocortin[122] | Inhibit appetite; increase EE; increase glucocorticoids |
| Fibroblast growth factor 1 (FGF-1)[123] | Decrease FI; satiety factor |
| Galanin antagonists: [124,125] C7,[126] M-40[126,127] | Inhibit galanin stimulation of FI |
| MC4 and MC3 receptor agonists: [128,129] MTII,[130] RO-274680,[131] TRG-2405252[132] | Decrease appetite and FI |
| MCH antagonists[133] | Decrease appetite and FI |
| Nerve growth factor antagonists[134] | Decrease appetite and FI |
| Neuromedin U[135] | Decrease FI |
| Neurotensin agonists: neurotensin,[136] NT-69L,[137] xenin [138] | Decrease FI |
| NPY antagonists:[139-143] 1229U91,[143] BIBO-3304,[144] BIBP-3226,[142]GI-264879A,[145] J-104870,[146] J-11584,[147] LY-377897,[148] PD-160170,[149] SR-120562A,[146] SR-120819A,[150] CCP-71683A,[151] JCF-104[146] | Decrease appetite and FI |
| Anti-orexin compounds: hypocretin (orexin) antagonists,[152]anti-orexin antibodies[153] | Decrease appetite and FI; antagonists inhibit orexin release; antibodies inactivate orexin |
| Protirelin (thryotropin-releasing hormone; TRH)[154] | Decrease FI and BW |
| **Intestinal peptides** | |
| Apolipoprotein-A IV[155] | Decrease FI |
| Bombesin: bombesin,[156] neuromedin B[157] | Anorectic |
| CCK protease inactivators: butabindide[158] | Potentiate CCK action; satiety factor |
| CCK agonists: A-71375,[159] A-71623,[160,161] ARL-14294 (FPL-14294),[162] ARL-15849)[163,164] | Satiety factor, decrease FI |
| CCK peptides: CCK,[165-169] CCK-4,[170] CCK-6,[170] CCK-7,[170,171] CCK-8,[172] U-67827E[173] | Limited effects on time, destroyed by proteases |
| CCK release inducers: phenylalanine[174] | Decrease FI |
| Enterostatin agonists: cyclo Asp-Pro,[175] enterostatin (VPDPR)[176-178] | Satiety factor; decrease FI, decrease fat intake |
| Gastrin-releasing peptide[179] | Decrease FI |
| Glucagon-like agonists: exendin-4,[180] glucagon,[181] glucagon-like peptide-1 (GLP-1)[182-184] | Satiety signal; decrease FI and BW |
| **Calcitonin**[185,186] | Anorectic, decrease FI |
| **Cytokines** | |
| Interleukins: interleukin (IL)-1β,[187-189] IL-6[190] | Anorectic; pyretic |
| Tumour-necrosis-factor (TNF): TNFα,[190-192] TNFβ[193] | Anorectic; decrease BW; wasting effects, increase insulin resistance |
| Leptin agonists: CNF (ciliary neurothrophic factor),[194] leptin,[195,196] OB3 (LEP-116-130),[197] R-128Q[198] | Possible ponderostat signal; decrease FI, mildly increase EE; leptin induces puberal development |
| **Human chorionic gonadotrophin (HCG)**[199,200] | Anorectic, decrease FI |
| **Oxytocin**[201] | Decrease FI |
| **Somatostatin**[202] | Anorectic, decrease FI |
| **Satietin**[203] | Anorectic; decrease FI |
| **Vasopressin**[204] | Decrease FI; inhibits gastric emptying |

**BW** = bodyweight; **CCK** = cholecystokinin; **CRH** = corticotropin-releasing hormone; **EE** = energy expenditure; **FI** = food intake; **MC** = melanocortin; **NPY** = neuropeptide Y.

rectic effects.[206] The advantage of working on receptors whose structure and location is well known[206,207] is the possibility to test large numbers of molecules without the drawbacks inherent to peptides. Other avenues open for hypothalamic control of appetite which are currently under development are cocaine and amphetamine-related transcript (CART), orexins, agouti-related protein (AGRP) and melanin-concentrating hormone (MCH).

### 4.2 Intestinal Peptides

A large group of molecules tested as appetite suppressants or satiety signals is derived from the intestine. This approach is based on mimicking the chemical signals sent by the gut to the brain which indicate its replenishment and the type of foodstuffs contained. Many signals have been tested but the main line of research has focussed on cholecystokinin (CCK), a key satiety factor.[165] CCK research has produced many synthetic and semisynthetic agonists that induce satiety, thus decreasing food intake without the lability of the natural peptide to protease inactivation. The limitations of the development of intestinal peptides as anorectic drugs are similar to those already indicated for hypothalamic peptides; however, the higher stability and concentration of intestinal peptides in the blood may be counteracted by their lower overall potency on hypothalamic systems.

### 4.3 Cytokines and Other Peptides

Other peptides have been found to influence bodyweight. Cytokines have been the subject of considerable research, especially on tumour necrosis factor α (TNF-α) because of it induces the loss of fat (and protein) during cancer-induced cachexia.[208] However, the direct involvement of this cytokine in the development and maintenance of insulin resistance[209] and its dangerousness have all but precluded its development as an anti-obesity agent; these same drawbacks can easily be extended to most cytokines.

The discovery of leptin carried considerable hope that it would constitute a true ponderostat signal[28] and thus become a perfect anti-obesity treatment, since its action on the ponderostat model would induce the activation of natural homeostatic mechanisms to readapt body mass to the desired level. Unfortunately, leptin levels in the obese were in almost all cases higher than expected,[210] thus practically ruling out its direct application as an anti-obesity drug. In spite of this early drawback, leptin is the subject of thousands of publications which explore almost all conceivable aspects of its function and regulation.[211,212] Furthermore, the development of drugs based on leptin is currently very intense.[212] Nevertheless, the publication of human trials using leptin or leptin agonists is extremely scarce.[195] It must be noted, however, that studies spurred by leptin have opened the field of the genetics of obesity[213] to the development of new strategies, and have helped to put on track neurochemical studies such as those centred on hypothalamic peptides.

### 4.4 Adrenergic Agents

The more classical pharmacological approach to appetite control can be shown by the early use of adrenergic and serotonergic agonists as anorectic drugs (table III). Amphetamines were initially used to increase alertness and to fight fatigue.[214] The loss of appetite was observed later and was fully exploited against excess eating and overweight. Other adrenergic agonists were studied and often discarded because of the marked adrenergic adverse effects, e.g. nervousness, insomnia, anxiety, high heart rate, hypertension and altered intestinal peristalsis, and last, but not least, the rapid development of addiction[214] and equally rapid loss of anorectic effects. In spite of their dangerous side effects and lack of anti-obesity effects, amphetamines are still used for the treatment of obesity. This clearly reflects the scarcity of effective pharmacological products for the treatment of obesity.

A significant development in the use of adrenergic agents as appetite suppressants is drugs that inhibit the re-uptake of noradrenaline; this inhibition maintains the action of the neurochemical on

**Table III.** Drugs controlling appetite: adrenergic and serotenergic agents investigated for use in obesity

| Mechanism and compounds | Effect and comments |
|---|---|
| **Adrenergic agents** | |
| Global adrenergic (mainly β) agonists: amphetamine,[215-218] clortermine,[219] metamphetamine,[220] phendimetrazine,[221] phenmetrazine (AN-448)[219,222] | Anorectic; decrease FI and BW; some of them addictive, rapid loss of efficacy |
| $\alpha_1$-Adrenergic agonists: cathine,[223] cirazoline,[224] flutiorex,[225] metaraminol,[226] phenylephrine,[226] phenylpropanolamine (PPA, racemic norephedrine)[227-230] | Decrease FI |
| $\beta_1$-Adrenergic agonists: benzphetamine,[231] isoprenaline (isoproterenol)[231] | Anorectic, decrease FI |
| $\beta_2$-Adrenergic agonists: clenbuterol,[232] salbutamol,[233] terbutaline[234] | Increase protein deposition; anorectic, decrease FI |
| NA release enhancers and NA reuptake inhibitors: chlorphentermine,[235] phentermine[222,236] | Decrease FI, increase EE |
| NA reuptake inhibitors: LY-368975 (r-thionisoxetine),[237] mazindol[238,239] | Anorectic, decrease FI; increase EE |
| **Serotonergic agents** | |
| Serotonin precursors: 5-hydroxy-tryptophan,[240] tryptophan[241-243] | Decrease FI; increase thermogenesis |
| Serotonin agonists: serotonin (5HT, 5-hydroxy-tryptamine),[244] 8-hydroxy-DPAT [8-hydroxy-2-(di-N-propyl-amino)-tetralin],[245] CM-57493,[246] CP-94,253,[247] DOI,[248] indorenate (TR-3369),[249] chlorophenyl-piperazine (mCPP),[247,250,251] MK-212,[247] quipazine,[252] RO-600175 (ORG-35030),[251,253] RO-600332 (ORG-35035),[253] RU-24969,[247,254] TFMPP (trifluoro-methyl-phenylpiperazine)[255] | Decrease FI; increase thermogenesis |
| Serotonin reuptake inhibitors: CGS-10686B,[256] citalopram,[257] femoxetine,[258,259] fluoxetine,[44,260-262] fluvoxamine,[263] indalpine,[264] LM-5008,[265] ORG-6582,[266] paroxetine,[264] sertraline,[267-269] litoxetine (SL-810385),[270] zimeldine[270] | Anorectic, decrease FI |
| Serotonin release enhancers and serotonin reuptake inhibitors: benfluorex,[271] CM-57227,[272] CM-57373,[246,272] dexfenfluramine (d-fenfluramine),[273-277] fenfluramine,[278] norfenfluramine[244] | Anorectic, decrease FI; fenfluramine and dexfenfluramine may induce aortic valvulopathy; pulmonary hypertension |
| **Adrenergic and serotonergic agents** | |
| NA and serotonin release enhancers: amfepramone (diethylpropion),[279,280] clobenzorex,[281] cyclo His-Pro,[282] fenproporex,[281] fen-phen (fenfluramine + phentermine)[283-287] | Anorectic, decrease FI; adrenergic adverse effects; pulmonary hypertension, aortic valvulopathy |
| NA and serotonin reuptake inhibitors: sibutramine (BTS-54254)[288-290] | Decrease FI; decrease BW; limited loss of weight; variable effectiveness; need for high compliance |

**BW** = bodyweight; **EE** = energy expenditure; **FI** = food intake; **NA** = noradrenaline (norepinephrine)

the post-synaptic membranes for longer periods, thus enhancing adrenergic stimulation. These drugs were found during research into antidepressants, and the good results obtained with inhibition of serotonin recaptation. Mazindol is probably the best known of these drugs: it induces typical adrenergic stimulation (including adverse effects) but is not addictive. Some widely known drugs, such as phentermine and amfepramone (diethylpropion), combine the inhibition of noradrenaline reuptake with increased release of catecholamine, thus significantly improving the overall adrenergic effect. The main drawback of most of these adrenergic appetite suppressants is that their effects wear off because of the down-regulation of adrenoceptors.[291]

### 4.5 Serotonergic Agents

The development of serotonergic drugs as appetite suppressants is similar to that of adrenergic drugs. The main difference is that serotonergic drugs have achieved a higher level of development and have been marketed as specific anti-obesity drugs. Serotonin levels in key areas of the brain greatly affect behaviour, especially the thymic state;[292] this is why considerable research has been devoted to the study and pharmacological maintenance of these levels as a way to treat de-

pression. Fluoxetine, a selective serotonin reuptake inhibitor, gave some of the best results of serotonergic drug development. The massive use of this drug and its adverse effects of appetite suppression and concurrent losses of bodyweight indicated its use for the treatment of obesity,[44] since in this way not only was appetite reduced, but the depressive states that often accompany obesity were also treated. However, the effects of fluoxetine on appetite and bodyweight were limited in extent and time.[260]

Fenfluramine and dexfenfluramine have probably been the most widely marketed anti-obesity drugs. The former was initially developed as an antidepressant but its marked anorectic effects soon changed the course of its development; it is a racemic mixture of which the d-isomer, dexfenfluramine, is the active drug. Fenfluramine was widely used for the treatment of overweight and obesity until some dangerous side effects were observed (valvulopathy, pulmonary hypertension)[293,294] in patients combining this drug with adrenergic appetite suppressants (phentermine-fenfluramine), a cocktail which was widespread despite the lack of studies on its risks. The consequences were dramatic, and both fenfluramine and dexfenfluramine were withdrawn because of their poor safety profiles and in spite of the merits of synergistic combination of drugs with complementary mechanisms of action[295]

Other serotonergic drugs have been developed as anorectic agents using other approaches: they act on post-synaptic serotonin receptors, by increasing serotonin release, and supplying the indole nucleus for serotonin synthesis (tryptophan). Many of these lines are still being probed for drug or nutraceutical development.

A new family of drugs combines serotonergic and adrenergic effects not through the binary combination of drugs (fen-phen), but by using a single drug to induce effects on both systems. This is a complex approach that also has the advantage of dividing the counteractive response by affecting different lines of neurons. Amfepramone is one such drug in which both serotonin and noradrenaline release are enhanced, but probably the most refined example of this line of research has been the development of sibutramine, an inhibitor of both noradrenaline and serotonin reuptake.[288] Sibutramine is already on the market and has proven efficacy in inducing moderate losses in overweight patients.[289] It seems ready to occupy the slot left by fenfluramine and dexfenfluramine, and perhaps going somewhat further.

### 4.6 Other Anorectic Agents

Other anorectic drugs (table IV) have been studied as prospective anti-obesity drugs; these include neurotransmitter function-modifying agents, such as dopaminergic and gabaergic drugs, together with opioids and other compounds. In most cases, anorectic effects were found accidentally during the development of other drugs or studies, as is the case of naloxone and naltrexone. Cannabinoids induce food intake[296] and their antagonists are anorectic.[297] The finding that the inhibition of nitrogen oxide synthase has anorectic effects[298] clearly suggests the implication of nitrogen oxide pathways in the control of appetite.

The control of energy metabolism largely relies on the levels of key metabolic substrates and intermediate products of their metabolism. Glucose is probably the best known,[350] thus glucose analogues have been tested as possible anorectics in spite of their toxicity. Other metabolic signals that may partially induce anorexia are 3C and 4C compounds derived from lipid and carbohydrate metabolism, as well as the interesting family of endogenous sugar-acid derivatives that control hunger, appetite and satiety.[344] A number of peptides have also been isolated from excreta and have been found to inhibit appetite, probably because of their structural relationship with other active peptides.[314,315]

A number of plant-derived compounds, with different structures (lectins, glucosides, polyphenols, etc.) have been found to affect appetite and usually explain the effects of the crude plant preparations from which they are derived.

**Table IV.** Other anorectic agents investigated for use in obesity

| Mechanism and compounds | Effect and comments |
|---|---|
| Benzodiazepine inverse agonists: CGS-8216;[299] FG-7142[299] | Decrease FI |
| Cannabinoid antagonists: rimonabant (SR-141716)[297] | Decrease FI |
| Cholinergic antagonists: atropine methyl nitrate[300] | Decrease FI |
| Diazepam-binding inhibitors (DBI): ODN (octadecaneuropeptide DBI 35-50)[301] | Anorectic; decrease FI |
| Histamine antagonists: cimetidine,[302] thioperamide[303] | Decrease FI or BW |
| Nitric oxide synthase inhibitors: nitro-l-arginine[298] | Anorectic |
| Opioid antagonists: DALCE [d-Ala2,Leu5,Cys6]-enkephalin],[304,305] funaltrexamine (BFNA),[304,305] NTII (naltrindole isothiocyanate),[304,305] NBNI (n*or*-binaltorphamine),[304,305] naloxonazine,[304,305] diprenorphine,[299] nalmefene,[306,307] naloxone,[308-310] naltrexone[311,312] | Decrease FI and BW |
| Nociceptin antagonists: nocistatin[313] | Decrease FI |
| Excreted peptides: faecal anorexigenic substance,[314] pyro-Glu-His-Gly-OH[315] | Anorectic, decrease FI |
| **Dopamine agents** | |
| Dopaminergic agonists:[316]apomorphine,[317] bromocriptine [ergoset],[318] lisuride,[319] quinpirole (LY-171555),[247] N-docosahexanoyl-3-hydroxytyramine,[320] N-0923 (N-0437),[321] pergolide,[322] piribedil,[323] SKF-38393,[247,324,325] SKF-77434,[325] SKF-82958[325] | Anorectic; decrease FI and BW |
| Dopamine uptake inhibitors: cocaine,[326-328] nomifensine[328] | Anorectic; decrease FI |
| **GABA agents** | |
| GABA receptor desensibilisers: pregnelonone sulfate[329] | Decrease FI |
| GABA agonists: gaboxadol (THIP;4,5,6,7-tetrahydro-isoxazolo [4,5-c]-pyridin-3-ol)[330] | Decrease FI |
| GABA transaminase inhibitors: BW-357U,[331] EOS (ethanolamine-O-sulphate),[332] vigabatrin (γ-vinyl GABA)[333] | Decrease FI and BW; increase EE |
| **Melatonin**[334] | Decrease BW and visceral fat; independent of FI |
| **Metabolites** | |
| Glucose analogues: 1-deoxy-glucosamine,[335] 1,5-anhydro-glucitol[336] | Anorectic |
| Carbohydrate catabolism-derived metabolites: lactate,[337] pyruvate[338] | Decrease FI (limited effects) |
| Lipid catabolism-derived metabolites: glycerol,[337,339] 3,4-dihydroxybutyrate,[340] 3-hydroxybutyrate[341,342] | Decrease FI and BW; limited effects |
| Spermidine-coupled cholesterol metabolites: MSI-1436[343] | Anorectic, decreases BW and FI; antidiabetic |
| Sugar-acid derivatives: 2-deoxytetronic acid (2-DTA),[344] 2-buten-4-olide (2-B-4-O)[345] | satiety agents; decrease FI |
| **Plant secondary metabolism compounds** | |
| Lectins: POL (*Pleurotus aureatus* lectin)[346] | Decrease FI; haemaglutinin |
| Polyphenols: gallic acid,[347] propyl gallate[347] | Decrease FI |
| Cyanoglucosides: simmondsin[348,349] | Decrease FI; from jujuba meal |

**BW** = bodyweight; **EE** = energy expenditure; **FI** = food intake; **GABA** = γ-amino-butyrate.

## 5. Thermogenic Drugs

### 5.1 Adrenergic Drugs

The use of drugs that elicit increases in energy expenditure, essentially through increased thermogenesis, constitutes a widely explored field in the search of novel anti-obesity drugs (table V). Most of the agents studied are adrenergic and act at different levels but always mimic the normal stimulation of the sympathetic nervous system that controls lipolysis and thermogenesis. The $\beta_3$-adrenergic receptor agonists probably constitute the group of anti-obesity drugs that is studied by most companies in parallel, with most of these compounds sharing their mechanism of action. Many adrenergic drugs previously described as anorectics can be equally described as inducers of energy-expenditure or thermogenic drugs. The pharmacological distinction is limited, thus we arbitrarily have

**Table V.** Thermogenic agents investigated for use in obesity

| Mechanism and compounds | Effect and comments |
|---|---|
| **Adrenergic agents** | |
| Global adrenergic (mainly β) agonists: capsaicin,[351,352] cathinone,[353] cimaterol,[354] cyanopindolol,[355] ephedrine,[356-358] isothiocyanate,[352] methoxyphenamine,[359] nicotine,[360,361] norpseudoephedrine,[359] pseudoephedrine[362] | Increase EE; increase lipolysis; increase BAT thermogenesis; unwanted adrenergic adverse effects [high heart rate, etc.] |
| $\beta_3$-Adrenergic agonists:[363] AJ-9677,[364] BMS-187413,[365] BMS-187257,[366] BRL-26830A,[367-369] BRL-28410,[370] BRL-35135,[371] BRL-37344,[372] carazolol,[373] CGP-12177,[355,374] CL-316243 (BTA-243),[375,376] CP-114271 (UL-TG-307),[377] CP-331679,[365] FR-149175,[378] FR-165914,[379] L-739574,[380] L-742791,[379] L-749372,[381] L-750355,[381] L-755507,[377] LY-79771,[382,383] RO-168714,[384] RO-402148,[385] SB-206606,[386] SB-226552,[379] SM-11044,[387] SR-58611A,[388] SR-59062A,[389] trecadrine,[390,391] UL-TG-307,[392] ZD-2079,[377] ZD-7114 (ICI-D7114)[393-395] | Increase EE; increase lipolysis; increase BAT thermogenesis; some of them have been tested and are active in humans, most are effective only on rodents |
| α-Adrenergic antagonists: MPV-1743AIII,[396] yohimbine[397,398] | Increase BAT thermogenesis and UCP-1 activity, decrease BW gain |
| α/β-Adrenergic receptor antagonists: arotinolol[399] | Increase BAT thermogenesis, decrease BW |
| Adrenergic agonist + phosphodiesterase inhibitor associations: ephedrine + caffeine,[400,401] ephedrine + caffeine + aspirin[402,403] | Increase EE; increase lipolysis; [prolonged action]; unwanted adrenergic adverse effects (high heart rate, etc.) |
| Phosphodiesterase inhibitors: aminophylline,[404] amrinone,[405] caffeine[406] | Increase lipolysis and thermogenesis through higher cAMP levels; inhibit phosphodiesterase III |
| Agents increasing NA levels: alliin (garlic)[407] | Increase thermogenesis |
| BAT NA reuptake inhibitors: ciclazindol[408] | Increase BAT thermogenesis |
| **Uncouplers** | |
| Respiratory chain / ATP synthesis uncouplers: benzoxazolin-2-one,[409] dinitrophenol,[40] PM-170[410] | Inhibit/ arrest electron transfer in respiratory chain and ATP synthesis; low therapeutic margin |
| UCP activators: adrenergic agonists,[411] carotenoids,[412] liothyronine (triiodothyronine)[413] | Increase EE through increased thermogenesis; induce UCP-1 expression |
| UCP poisons: hexadecane,[414] TCDD [2,3,7,8-tetrachloro-dibenzo-p-dioxin][415] | Increase EE through BAT thermogenesis; anorectic; induce wasting |
| Calcium antagonists: benidipine[416] | Increase NA levels and thus increase BAT thermogenesis |
| GABA agonists: baclofen[417-419] | Increase BAT thermogenesis |
| Opioid agonists: dihydrocodeine[420] | Increase thermogenesis by sympathetic activation of BAT; increase BAT blood flow |
| Polyphenols: green tea extracts,[421] mate extracts,[422] tea catechin polyphenols[423] | Increase thermogenesis and EE |

**ATP** = adenosine triphosphate; **BAT** = brown adipose tissue; **BW** = bodyweight; **cAMP** = cyclic adenosine monophosphate; **EE** = energy expenditure; **GABA** = γ-amino-butyrate; **NA** = noradrenaline; **UCP** = uncoupling protein.

grouped the known agents as either anorectic or thermogenic drugs based on their main described effects.

The main enhancers of thermogenesis are the adrenergic agents. These predominantly act through β-adrenoceptors; ephedrine is probably the most widely used drug and is often combined with methyl-xanthines (e.g. caffeine) for their phosphodiesterase-inhibiting effects that prolong the effects of cyclic adenosine monophosphate (cAMP) derived from adrenergic pathways. Probably the most widely – and often unsuspected – used adrenergic drug in this group is nicotine. Tobacco addicts are subjected to constant exposure to the drug and tend to increase weight when smoking is discontinued.[424]

The group of $\beta_3$-adrenergic receptor agonists is fairly homogeneous in effects but, chemically, several families of compounds can be found.[365,379,380] Most of the compounds ever synthesised and studied are not generally known, and curiously, most retain their internal identification given by the de-

veloping company. This means that very few have reached the level of effectiveness and absence of adverse effects at which a drug can be fully developed, and even fewer have appeared in scientific manuscripts. The lack of overall success in this line of drug development cannot be attributed to the soundness of the principle of specifically activating the adrenergic receptors responsible for most of the thermogenic effects without inducing adverse effects such as those described above. The reasons why they have not been marketed is 2-fold. On the one hand there is the down-regulation of $\beta_3$-adrenoreceptors which results from the continued pharmacological exposure to agonists, a process enhanced by corticosteroids.[63,425] However, on the other, probably the main factor responsible for the lack of success of $\beta_3$-adrenoceptor agonists is the marked differences of rodent and human $\beta_3$-adrenoreceptors in structure and responsiveness to drugs.[426,427] The development of cultured cells and transgenic mice carrying the human receptor has sped up the selection of adequate drugs,[428] but the different importance of BAT in rodents and humans and the down-regulation of receptor expression have so far impeded the use of $\beta_3$-adrenoreceptor agonists for the treatment of obesity.

### 5.2 Uncoupling Agents and Other Thermogenic Drugs

Table V also shows other thermogenic agents that, like adrenergic drugs, share effects on food intake and energy expenditure with other drugs that act on the brain, such as gabaergic and opioid agonists, as well as other compounds.

A special reference must be made to uncoupling agents. Uncoupling protein (UCP-1) is the key component of the thermogenic activity of BAT,[429] thus agents that act on its expression,[411,413] activation pathway or that prevent its reversibility to the inactive state (i.e. hexadecane) may be considered possible targets for thermogenic drug development. The discovery of other possible uncoupling proteins from their DNA sequences (UCP-2, UCP-3, etc.)[430] has opened up further possibilities, especially because of their wider tissue distribution than UCP-1. However, little is known of their physiological function,[431] and thus their possible involvement in the development of other thermogenic drugs is, at present, speculation.

Several relatively unknown and ill-defined secondary-metabolism–derived plant products have shown some effects on bodyweight, usually in combination with other active compounds such as caffeine. However the overall effects of these products are much less significant than the commercially available 'natural herbal' preparations used for the treatment of obesity.[422]

## 6. Other Pharmacological Approaches

### 6.1 Thyroid Hormones

Since the availability of metabolic energy is controlled mainly by metabolite levels and hormones, those compounds have always been a logical subject of study for the development of anti-obesity drugs (table VI). Probably the oldest and most persistent references to hormonal treatment of obesity are thyroid hormones and other thyroid receptor agonists, despite their long-term inutility and adverse effects, since they may induce thyrotoxicosis and other hyperthyroid-derived complications. Thyroid hormones increase energy expenditure and lipolysis, and have been postulated for the treatment of obesity at low concentrations,[41] however, they may easily alter the hypothalamic-pituitary-thyroid axis. Nevertheless, many untested and often illegal anti-obesity formulations contain heavy doses of thyroid extracts[432] and are responsible for an undetermined number of toxic complications.

### 6.2 Insulin Activity Modifiers

The modulation of insulin function is an obvious target for the development of anti-obesity drugs because of the direct relationship between most obesities and insulin resistance and type 2 diabetes. This resistance, which can be induced by resistin[501] may be countered in part by adiponectin,[433] which may represent a starting point for

**Table VI.** Other agents investigated for use in obesity

| Mechanism and compounds | Effect and comments |
|---|---|
| **Hormones controlling energy metabolism** | |
| Antidiabetic agents: adiponectin (Acrp30, Adipo Q, apM1, GBP28),[433,434] amylin,[435-437] diazoxide,[438] metformin,[108,439-441] phenformin[442] | Lower glucose; decrease FI and BW |
| Insulin function enhancers: chromium salts (picolinate)[443-447] | Increase lean body mas; decrease body fat; decrease cholesterol |
| Phosphotyrosyne phosphatase (PTP) inhibitors:[448,449] vanadate[450] | Decrease FI and BW gain; decrease insulin resistance |
| Retinoid X receptor agonists: LG-100268,[451] LG-100324,[451] LG-100641[452] | Decrease FI and BW gain; decrease insulin resistance |
| GHRH agonists: ibutamoren (MK-677)[453,454] | Increase GH, IGF-1 and IGF-binding protein |
| Growth hormone: somatropin (growth hormone),[455-459] AOD,[460] AOD-9401[461] | Increase lipid oxidation, and protein accrual; increase EE; decrease lipogenesis |
| Thyroid hormones: thyroxine [$T_4$],[41,462] liothyronine (triiodothyronine; $T_3$),[458,463] tiratricol (TRIAC; 3,3',5-triiodothyroacetic acid)[464] | Increase EE, increase lipolysis; may induce hyperthyroidism; refractory obesity |
| Adrenal antiglucocorticoids: prasterone (DHEA; dehydroepiandrosterone)[465-468] | Decrease fat mass, increase protein accrual; inhibit pentose-phosphate pathway; very high doses needed; mildly estrogenic; mildly hepatotoxic |
| Other antiglucocorticoids: metyrapone,[469] mifepristone (RU-486)[470-472] | Block glucocorticoid synthesis; increase thermogenesis and lipolysis |
| Estrogens: estradiol[473,474] | Decrease BW |
| Acylated steroid hormones: oleoyl-estrone[475-478] | Possible ponderostat signal; decrease FI and maintain EE; decrease insulin resistance |
| Androgens: testosterone[479] | Increase protein synthesis, alter WAT distribution; inhibit testicular function; hepatotoxic [oral]; androgenic effects |
| **Lipid metabolism controllers** | |
| Fatty acid synthesis inhibitors: cerulenin (C75),[480,481] RO-220645,[482] β-hydroxycitrate [*Garcinia cambogia*][483,484] | Decrease FI and BW gain |
| Lipolytic agents: conjugated linoleic acid[485-487] | Increase EE, decrease BW and body fat; increase adipocyte apoptosis |
| Lipoprotein lipase activators: NO-1886[488] | Decrease BW; increase fat oxidation |
| Mitochondrial fatty acid transport enhancers: carnitine[489] | Theoretically enhance lipid oxidation; poor results |
| **Adipose tissue growth and differentiation controllers** | |
| Adipose tissue differentiation agents: ADRP (adipose differentiation-related protein) antagonists,[490] fenofibrate,[491] HIV protease inhibitors[492] | Decrease BW and blood lipids; activate PPARα; decrease WAT mass; may induce lipodystrophia, hyperlipidemia and insulin resistance |
| Adipocyte antibodies[493-495] | Cytotoxic; help destroying adipocytes; specificity and control are key issues |
| Perilipin antagonists[496,497] | Increase lipolysis; control of access to lipids in cell vacuoles |
| **Compounds acting through unknown or unspecified mechanisms** | |
| Bee royal jelly[498] | Decrease BW, blood triacylglycerols and cholesterol |
| Herbal preparations: *Galega officinalis;*[499] slimax[500] | Decrease BW and/or FI |

**BW** = bodyweight; **EE** = energy expenditure; **FI** = food intake; **GH** = growth hormone; **GHRH** = growth hormone-releasing hormone; **IGF** = insulin-like growth factor; **PPAR** = peroxisome proliferator-activated receptor; **WAT** = white adipose tissue.

the development of new anti-obesity and anti-diabetic drugs.

Chromium salts are known to improve insulin response[443,444] through glucose tolerance factor;[445] chromium picolinate is often taken by the obese and diabetic alike, and it has been found to help regulate both insulinaemia and glycaemia.[446] Vanadate, another inorganic drug, has been widely tested for the treatment of diabetes; its effect on phosphotyrosine phosphatase helps decrease insu-

lin resistance and thus, in addition to limiting bodyweight gain, improves the metabolic condition of the obese.

### 6.3 Steroid Hormones

Estrogens decrease body fat to a limited extent;[473] in general steroid hormones greatly affect body fat[502] but because of their main function as sexual hormones or, in the case of corticosteroids, as inducers of fat deposition. A special case is the anti-corticosteroid agents, principally prasterone (dehydroepiandrosterone; DHEA). In addition to its anti-corticosteroid properties,[503] prasterone is also a mild androgen and plays a number of other metabolic control functions.[465] When given in very large doses, prasterone slims rats without other appreciable effects;[466] however, at lower doses these effects were not observed in humans.[504]

Oleoyl-estrone (merlin-2) is a natural hormone synthesised by WAT that provokes the massive loss of fat, but spares protein, when administered to experimental animals.[475] Since it affects both appetite and energy expenditure and also improves insulin resistance,[476] it has been postulated as a putative ponderostat signal.[505] Androgens decrease body fat and significantly increase skeletal muscle mass.[506,507]

### 6.4 Agents Acting on Adipose Tissue and Lipid Metabolism

The objective of the pharmacological treatment with lipid metabolism controllers is to prevent the synthesis of fatty acids or their incorporation into triacylglycerols. A promising example is that of inhibitors of fatty acid synthesis. Carnitine is widely used as a 'fat-eating molecule' because it may enhance cytoplasm-mitochondrial transport of fatty acids, easing their oxidation. However, carnitine does not seem to be a limiting factor for this process,[508] and in addition, when in excess, it can easily be removed or disposed of.

Another anti-obesity strategy is that of preventing the growth of WAT by limiting its ability to differentiate or its removal using anti-adipocyte antibodies. The latter is a dangerous strategy that has not yet been commercialised because of its inherent risks.

### 6.5 Other Anti-Obesity Treatments

Finally, we include a small example of abundant unproven and untested drugs for the treatment of obesity, such as bees royal jelly and herbal treatments that are often unspecified. Some of the materials, generally plant-derived products or concoctions, that are commonly sold to treat ailments contain effective principles that can also be isolated, tested, checked and finally used to treat specific problems. However, there is considerable mystification surrounding the use of 'traditional' and undisclosed 'herbal' treatments, especially in the case of obesity, in which the lack of viable orthodox therapeutics leaves the door open to faith healers and snake-fat sellers. Many herbal treatments are simply mild diuretics, which lead to rapid losses of weight that are later recovered with similar ease. Diuretics have not been included in the list of drugs used to treat obesity, since they may provoke transient weight losses but in no way do they help shed fat, which is precisely what obesity treatment does.

## 7. Conclusion

Pharmacological treatment of overweight and obesity is currently based on a small group of drugs, the most widely used being sibutramine and orlistat. However, a major effort is being made to obtain more effective and tolerable drugs. The main open avenues for development are based on appetite control through hypothalamic peptidergic pathway modulation and thermogenic agents. Nevertheless, and because of the compensating nature of the bodyweight control mechanisms, the success attained from such studies alone has so far been limited. The development of drugs affecting the core of the bodyweight regulatory system (i.e. lipostat setting) or the development of combined strategies of appetite suppressants and thermogenic agents are probably better options for the successful pharmacological treatment of obesity.

The development of the anti-obesity drugs presented here not only shows the enormous investment in research time and imagination, but also the decided resolve of researchers and drug companies to develop viable and functional strategies that will put an end to this scourge of modern humankind.

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