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Methods in the treatment of obesity

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Abstract

Obesity is a widespread crippling and life-shortening disease that can be defined as a pathologic accumulation of fat reserves. In spite of its epidemic distribution, no fully effective treatments are available. The strategies used for the treatment of obesity have relied mainly on the limitation of energy intake or/and increasing energy expenditure. The most widely used method to limit energy intake has been the use of hypocaloric diets. Their effectivity is limited and fade away rapidly with time. Nevertheless, the sound use of hypocaloric diets is yet the mainstay of the fight against overweight. Inhibition of the absorption of nutrients through specific digestive enzyme inhibitors has been also used. Bariatric surgery is now practically the only fairly effective way to treat the morbidly obese. Conductist conditioning has been used to maintain the obese as far as possible from food, but the results are often poor. However, adequate instruction of the obese on basic nutritional knowledge, and nutritional reeducation are a tool not to be neglected. Exercise is the easiest way to increase energy expenditure. but this increase is only transient; in any case it potentiates the slimming effects of dietary restriction. There are a growing number of drugs used for the treatment of obesity, and more are just being under study and development. The main target of these drugs is to diminish the cravings of appetite as a way to help the obese to limit ingestion, but other drugs tend to increase thermogenesis, easing the consumption of fat reserves; often both effects add up. The most widely studied drugs are serotonergic drugs acting on the brain and adrenergic agents acting both on appetite and heat production. Several hormones, metabolites and even poisons have been postulated as antiobesity agents, but now the most promising areas of study rely on hypothalamic control of appetite, thermogenesis and regulatory control of the mass of fat, the latter achieved through signalling molecules produced by the adipose tissue. Many avenues have been

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Resum

L'obesitat és una malaltia molt estesa que limita l'activitat i escurça la vida, i que es pot definir com un emmagatzemament patològic de reserves de greix. Malgrat la difusió epidèmica, no hi ha cap sistema plenament efectiu disponible per tractar-la. Les estratègies emprades per al tractament de l'obesitat s'han basat principalment en la limitació de la ingesta i/o l'increment de la despesa energètica. El mètode més emprat per limitar la ingesta energètica ha estat la utilització de dietes hipocalòriques, però l'efectivitat és limitada i es perd ràpidament amb el temps. Malgrat això, la utilització adequada de dietes hipocalòriques constitueix encara el principal procediment en la lluita contra el sobrepès. També s'ha emprat el bloqueig de l'absorció de nutrients mitjançant la inhibició específica d'enzims digestius. La cirurgia bariàtrica és ara pràcticament l'únic mètode prou efectiu per tractar els obesos mòrbids. S'ha utilitzat el condicionament conductista per mantenir els obesos allunyats del menjar, però els resultats són sovint poc satisfactoris. No obstant això, la informació adequada que reben els obesos sobre els principis elementals de la nutrició, així com la reeducació nutricional són una eina que no s'ha de deixar de costat. L'exercici és la forma més senzilla d'augmentar la despesa energètica i, tot i que aquest increment és sols transitori, potencia els efectes aprimadors de la restricció dietètica. Hi ha un nombre considerable de fàrmacs que han estat emprats per al tractament de l'obesitat i encara n'hi ha més que estan essent estudiats i desenvolupats. El principal objectiu d'aquests fàrmacs és disminuir la gana a fi d'ajudar l'obès a reduir la quantitat de menjar, però altres drogues tendeixen a incrementar la termogènesi, tot facilitant la utilització de les reserves grasses; sovint ambdós efectes tenen lloc a l'hora. les drogues més àmpliament estudiades són les serotoninèrgiques, que actuen sobre el cervell, i els agents adrenèrgics que actuen sobre la gana i la producció de calor. Diverses hormones, metabòlits i fins i tot verins han estat postulats pee al tractament de l'obesitat, però ara per ara les àrees d'estudi amb més possibilitats de futur són les basades en el control hipotalàmic de la gana, la termogènesi i el control regulador de la massa de greix mitjançant molècules senyal produïdes pel propi teixit adipós. S'han investigat moltes vies per trobar formes efectives per tractar l'obesitat, però la major part dels esforços encara es-

probed to try to find an effective way to treat obesity. However, most of the efforts are yet focussed on the development of partial solutions to the complex problem of obesity. Coordinated effort of basic research, and the development of effective drugs together with adequate information of the patients and actualization of the knowledge of the health personnel working in the field are needed to face the threat of dangerous and uncontrollably spreading obesity

tan orientats a trobar solucions parcials al complex problema de l'obesitat.

L'esforç coordinat en recerca bàsica i el desenvolupament de fàrmacs efectius, junt amb una adequada informació als pacients i l'actualització dels coneixements del personal sanitari que treballa en aquest camp, són les condicions essencials per poder fer front a aquesta malaltia perillosa que s'estén d'una manera incontrolada: l'obesitat.

Keywords: Obesity treatment, obesity, diet, appetite, thermogenesis

Obesity is one of the main health hazards afflicting our contemporary society. Its widespread occurrence and increasing severity would undoubtedly qualify it as an epidemic [1], if only its origins could be traced to a transmissible agent. Obesity has for too long now been considered simply as a case of an unbalanced energy budget, the emphasis being placed on the intake [2]; the association between excessive food intake and obesity having been established at a time beyond historical memory and frequently in conjunction with sinfulness, lack of control and a delight in earthly pleasures [3, 4]. Unfortunately, most of these time-worn beliefs remain alive and deeply ingrained in the minds of a large section of our society, even in those of a sizeable part of the medical establishment [5]. An awareness of the perils of obesity and being overweight has been awakened by major medical advances in the treatment of many of the other scourges facing humankind in the last century. However, the efforts devoted to the treatment of obesity have not kept pace with our knowledge of other diseases; furthermore, the assumption that obesity is more a consequence of moral flaws or feeding incontinence has given rise to an often complacent indifference in the fruitless struggle of the obese to shed their *sinful* blubber.

Attempts at the global treatment or prevention of obesity have led to marked alterations in the diet of whole countries - restricting the intake of carbohydrates, energy, fats, and other dietary components [6-8]. These large scale experiments failed to achieve their goals and instead led to higher incidences of obesity, disrupted dietary habits, and increases in the pathologic fears of being overweight resulting in anorexia and bulimia [9].

However, the ever-growing numbers of people afflicted with weight problems and obesity [10, 11], the increasing numbers of people fearful of becoming obese [12], the limited effects of anti-obesity therapy, and a better scientific knowledge of the disease, mean that these beliefs are now being called into question. Obesity is a disease [13] -a crippling and life-shortening disease - that probably has no single metabolic origin [14]. Our understanding of certain obesity syndromes in rodents has persuaded a number of researchers to look upon genetics as the source of human obesity [15].

Obesity as a disease

Obesity can be defined as a pathologic accumulation of fat reserves; the extent of lipid storage far outstrips what the body would be able to use in an emergency, and so this storage just adds weight, thereby limiting movement, overloading the respiratory and cardiovascular systems and destabilising the homeostatic equilibrium of the body [16]. The medical definition of obesity, however, is somewhat more difficult, since a considerable grey area extends between what is considered normal and being overweight and also between this mild situation and a fully developed obesity. In addition, the actual mass of fat is not as critical as is its specific location in terms of the pathological effects of this fat and its impact on the hormonal and metabolic environment. In fact, there are a number of grossly obese patients that show much less marked metabolic abnormalities than others in whom fat accumulation is not severe but who present concurrent pathologic traits. These include hypertension, hypercholestrolemia, hypertriacylglycerolemia and type 2 diabetes mellitus: the metabolic or X syndrome [17]. It is still unclear as to whether hormonal alterations (i.e. in insulin and glucocorticoids) are an early consequence of excessive fat accumulation, or whether the latter is a consequence of the former. Given the wide diversity of obesities, there are probably many explanations of the etiology of obesity. There is a considerable body of evidence, however, linking obesity and type 2 diabetes mellitus, which suggests that alterations in insulin functionality and responses play a key role in the development and maintenance of obesity; the almost universal existence of insulin resistance in the obese points to this single metabolic alteration as the most critical element in the etiopathogenics of obesity [18, 19].

Figure 1 shows a simplified diagram of the system that controls body weight. The hypothalamic control of food intake is modulated by signals from the intestine, the levels of metabolites in the blood and by signals from other brain nuclei; these also control efferent signals through the sympathetic nervous system that regulates fat mobilisation and thermogenesis. Two other major elements complete the picture: insulin, the main endocrine agent enhancing the build-

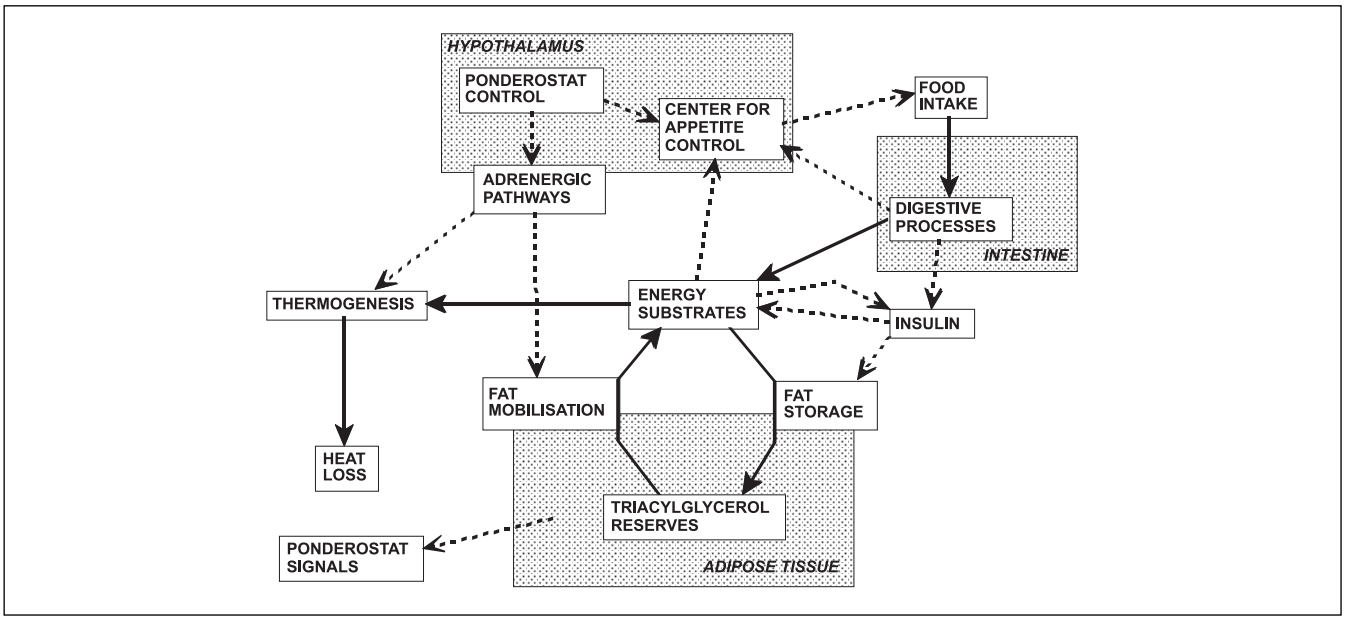

Figure 1. Main mechanisms controlling the mass of body fat reserves.

up of reserves, and ponderostat signals emanating from the adipose tissue and informing the brain about the mass of fat stores.

Since obesity is in itself evidence that the energy budget has been altered, most efforts at treating it have been aimed at its external manipulation: i.e. increasing energy expenditure and decreasing energy availability. However, the manifold system that controls the body energy budget is able to maintain its homoeostatic integrity by withstanding external manipulation and diminishing the impact of the therapeutic measures used to diminish the mass of fat. The body reacts in a similar way to starvation in times of famine and limited food availability because of the use of therapeutic hypocaloric diets: in both cases the mass of fat reserves is protected by limiting energy expenditure [20], mainly thermogenesis [21, 22], and by improving the overall efficiency of the system. This alone may explain why it is so difficult to shed fat simply by dieting and the rapid recovery of weight once the energy intake limitations are lifted [23].

Dietary treatment

Table 1 summarises the procedures available for the treatment of obesity, and Tables 2-5 present in more detail the pharmacological strategies developed to achieve this goal. The energy balance can be shifted to reduce the mass of stored energy either by diminishing energy intake, increasing energy expenditure or by altering the overall settings of energy homeostasis by adequately modulating metabolic signals. The main avenue taken for obesity treatment has been the limitation of energy intake. This could be achieved by decreasing the amount of food eaten - either by decreasing the availability of the nutrients contained in the food or by decreasing appetite, i.e. the drive to get that food. The main problem with decreasing food availability is the reactive enhancement of appetite pangs, which cause deep and constant discomfort, regardless of the method adopted to prevent access to food. Thus, the control of appetite seems a safer way to limit food intake, thus preventing this food from fuelling the overall energy budget.

The most widely used method to limit energy intake has been the use of hypocaloric diets [24]. Their effectiveness is limited and fades rapidly with time, but it may be sufficient to correct a problem of excess weight if properly applied [24]. The earlier use of therapeutic fasting or zero-energy diets [25] proved to be fairly ineffective in the long run, and potentially harmful for the patients; in any case, the ordeal of nil energy intake and the dangers this represented for the nitrogen balance did not justify the slow and limited loss of fat, which, moreover, were often matched by similar losses of lean body mass [26]. This problem was partially corrected with very low calorie diets (VLCDs), which supplied only limited energy (1-3 MJ/day) but provided enough protein to counter the obligatory nitrogen losses [27, 28]. In any case, a significant part of the protein is simply used as a source of energy, which in the end results in negative nitrogen balances. This may limit the prolonged application of VLCDs, and thus hamper their success on morbid obesity. After overcoming a number of problems related to the quality of the protein used [29, 30], VLCDs remained a widely used tool for the management of the obese, probably because of the scarcity of other proven therapeutic tools [31].

Hyperproteic diets have been used to shed fat and to build up muscle masses, often in combination with anabolic steroids and extensive exercise, especially by bodybuilders [32]. Diets exclusively composed of protein are not adequate for humans, because of the heavy overload of ni-

Table 1. Systems for the treatment of obesity

diminishing energy intake	decreasing energy intake	restrictive hypocaloric diets	
		low calorie or acaloric foods	
		mechanical barriers to intake	jaw wiring
			gastric balloon
			gastroplastia
	decreasing nutrient availability	decreasing food absorption	surgical bypasses
			drugs decreasing nutrient availability
		dietary manipulation	dissociated and ketogenic diets
			hyperproteic diets
	decreasing appetite	psychologycal methods	conductist conditioning
			suggestion, autocontrol and magic
		anorectic drugs	
increasing energy expenditure	exercise		
	increasing thermogenesis	exposure to cold	
		thermogenic drugs	
modulating energy homeostasis	diminishing adipose tissue mass	inhibition of adipocyte differentiation	
		surgical removal	lipectomy
			liposuction
		localized adipose tissue lysis	
		immunological targeting of adipose tissue	
	homones / drugs modulating energy homeostasis		

trogen waste, the relatively low amount of energy derived from it and other, as yet, unascertainable reasons that make them highly dangerous. People using them for a long time tend to lose weight, but no hard data are available as to why they are invariably discontinued. The use of amino acid mixtures as supplements has been postulated as a way to diminish body fat [33], but the mechanism has not been explored and the results are poor.

The use of hypocaloric diets, often without medical supervision, is widespread. This repeated use favoured the appearance of a number of fad diets, some of them extremely dangerous [34]. Also, the half-hearted repetitive exposure to hypocaloric diets often results in an adaptation to them. Refractary obesity is virtually impossible to treat with dietary measures, since the body adapts to periodic low-energy availability exposure and effectively protects fat stores [35]. Nevertheless, the sound use of hypocaloric diets, complete with enough carbohydrate protecting protein oxidation and a variety of appetising meals, remains the mainstay of the fight against excess weight [24]. The use of dissociated and ketogenic diets do not result in greater fat loss than those produced by most of the hypocaloric diets [36]. However, the former are dangerous because of acidosis and the threat to lean body mass [37], and they represent a constant overload on the hepatic function. Moreover, the ketone bodies further lower thermogenesis [38], thus making it even more difficult to imbalance the energy equilibrium to drain the fat reserves.

The availability of acaloric foods or low-calorie food substitutes (Table 2), combined with the so-called «light» products, in which the energetic density is lower than in similar foods, has brought upon us a culture of non-energy foods fuelled by considerable commercial interests. The main targets for these substitutes have been sugars, with the widespread availability of artificial sweeteners [39] such as saccharin, cyclamate, aspartame, acesulfame-K, etc. [40], but also fat substitutes, such as olestra [41].

Another way to diminish the availability of nutrients is to use nutrient absorption modifiers. These disturb or retard the absorption of certain nutrients [42]. The use of high-fibre foods or fibre preparations helps prolong the absorption of glucose and other nutrients, thus limiting the insulin response, but it also helps to limit cholesterol and the reabsorption of bile salts [43]. The use of these modifiers in the

Table 2. Drugs used –and drug-developing trends– for the treatment of obesity: I - Drugs decreasing nutrient availability

action, types		*examples*	*references*
hypocaloric and acaloric food substitutes	acaloric sweeteners	aspartame	[128]
	acaloric or low-calorie fat substitutes	olestra	[129]
nutrient absorption modifiers	gastric emptying delayers	chlorocitrate	[130]
	nutrient absorption delayers	chitosan	[43]
	bulk effect	glucomannan	[131]
digestive enzyme inhibitors	intestinal disaccharidase inhibitors	—	[132]
	α-amylase inhibitors	acarbose	[133]
	lipase inhibitors	orlistat	[134]

treatment of obesity is fairly irrelevant, but they may be useful in the improvement of diabetes and hypercholesterolemia so often associated with obesity.

Complex carbohydrate and fats constitute the bulk of energy intake for most humans. To be absorbed and further metabolized or incorporated in our body systems, they need to be digested by specific hydrolases in our intestine. The inhibition of these processes, then, would prevent the assimilation of their energy. This is the reason why digestive enzyme inhibitors have been developed to help limit the extraction of energy from the foods. Inhibitors of disaccharidases, amylases and lipases have been developed and tested [44], but only one example of a lipase inhibitor, orlistat, is currently available for the treatment of overweight conditions and mild obesity [45]. The chronic use of inhibitors, however, should be considered essentially as a complementary measure accompanying hypocaloric dieting, since they cannot act alone [46]. Dieting is necessary also because the undigested substrates (essentially starches) can be easily used by the colonic flora, which may produce discomfort and generate a number of short-chain fatty acids that are assimilated and contribute to our energy budget. The presence of undigested lipid in stool may also induce intestinal discomfort and incontinence, a reason why the administration of this drug should be made in parallel to a diet with limited fat content [47].

Surgical treatment

Jaw-wiring has been used to a limited extent to prevent patients from eating [48]; in addition to the obvious inconveniences of such a drastic procedure, the unlimited intake of often highly hypercaloric fluids may easily circumvent the effectiveness of the device. The need for these heroic methods is inversely proportional to the commitment of the patient to limit food intake - no barrier could overcome the ingenuity of a starving human being. The active and enthusiastic collaboration of the patient is essential for any restrictive measure to be effective.

The stretching of the stomach using inflatable balloons also prevents food ingestion, but also quells the appetite to some extent [49]. However, the contraptions are cumbersome to install and to inflate and they cannot resist the highly acidic gastric juice for a long time; these complications and the danger of rupture practically rule out their use.

The surgical removal of part of the stomach effectively limits the amount of food that can be eaten, but it is irreversible. The introduction of reversible gastroplastic manipulations [50], a relatively simple procedure, is now practically the only fairly effective way to treat the morbidly obese [51]. However, these surgical procedures often need to be complemented by intestinal by-passes [50] and vagotomy. [52], thus adding malabsorption to the restriction effects. Bariatric surgery is, thus, a major procedure, which in addition to the avatars of any surgical operation, offer no absolute guarantee of success, since it may result in massive and continued losses of weight or in just a limited amount of fat being shed [53]. Bariatric surgery also calls for a considerable psychological preparation on the part of the patient and a fairly long period of adaptation to life with small stomach capacity and malabsorptive intestines [54, 55]. In spite of these obvious drawbacks, however, extensive bariatric surgery remains for many morbid obese the only option to some degree of improvement in their condition [51].

Psychological treatment

The corollary of the assumption that obesity is a direct consequence of excessive food intake is that the obese remain as such because they lack enough stamina and willpower to distance themselves from food, but also that they need much less food to maintain their heavy bulk. In any case if they are obese it is because they ingest more energy than needed and the rest becomes fat [2]. Psychological methods, especially conductist conditioning, have been used to maintain the obese as far as possible from food [56]. The results are often poor. However, adequate instruction of the obese concerning basic nutritional knowledge, and nutritional re-education are tools that should not be neglected, especially in the aftermath of a significant reduction in body weight, since adequate food habits are needed to maintain the low weight attained [57, 58]. Stress is a significant con-

Table 3. Drugs used –and drug-developing trends– for the treatment of obesity: II - Anorectic agents

action, types			*examples*	*references*
adrenergic agents	α_1-adrenergic agonists		phenylpropanolamine	[135]
	β-adrenergic agonists		amphetamine	[61]
	NA release enhancers		phentermine	[62]
	NA reuptake inhibitors		mazindol	[63]
serotonergic agents	5HT precursors		tryptophan	[136]
	agents decreasing 5HT turnover		buspirone	[137]
	5HT post-synaptic agonists		serotonin	[138]
	5HT release enhancers and reuptake inhibitors		dexfenfluramine	[66]
	NA and 5HT release enhancers and reuptake inhibitors		sibutramine	[71]
intestinal peptides	bombesin agonists		bombesin	[139]
	CCK	CCK protease inactivators	butabindide	[140]
		CCK agonists	CCK-8	[141]
	glucagon-like agonists		GLP-1	[76]
	galanin antagonists		—	[75]
	enterostatin agonists		enterostatin	[142]
dopaminergic agonists			bromocriptine	[143]
GABA-ergic agents	GABA agonists		—	[144]
	GABA transaminase inhibitors		ethanolamine-sulphate	[48]
histamine antagonists			cimetidine	[145]
opioid antagonists			naloxone	[146]
melatonin agonists			malatonin	[147]
cannabinoid antagonists			—	[148]
NO synthase inhibitors			nitro-arginine	[149]
cytokines			TNFα	[150]
metabolites			glycerol	[151]
hypothalamic peptides	CRH agonists		CRH	[152]
	TRH agonists		TRH	[153]
	CART agonists		—	[154]
	MCH agonists		—	[155]
	MC3 and MC4 receptor agonists		—	[156]
	AGRP antagonists		—	[157]
	nerve growth factor antagonists		—	[158]
	NPY antagonists		—	[159]
	anti-orexin compounds		—	[160

NA = noradrenaline; 5HT = serotonin; CCK = cholecystokinin; GABA = y-aminobutyrate; NO = nitrogen oxide; CRH = corticotropin rereasing hormone; TRH = thyrotropin releasing hormone; CART = cocaine and amphetamine-related transcript; MCH = melanin-concentrating hormone; MC = melanocortin; AGRP = Agouti-related peptide; NPY = neuropeptide Y; TNFα = tumour necrosis factor α; GLP-1 = glucagon-like peptide 1.

tributor to the development and maintenance of obesity [59], and changes in daily habits, removal of stressful influences, especially the morbid fear of becoming obese, may contribute to check – albeit not to reduce – obesity.

Some of the bizarre treatments used for the treatment of the obese are effective on a limited number of individuals because of unknown mechanisms. However, where some see magic we must interpret them as powerful cortical influences which we would very much like to understand and extend.

Appetite control: anorectic drugs

The obvious way to control food intake is to diminish the cravings for food as a way to help the obese to limit ingestion, ensuring that the process is as painless as possible. In the absence of hunger pangs not even the obese feel the urge to eat. The control of the appetite has thus been a key objective in drug development and today concentrates most of the efforts for the development of anti-obesity drugs [60]. Table 3 shows a list of the types of drugs available and the trends now being followed for the pharmacological control of appetite.

The earlier drugs used for appetite control were amphetamines [61], but soon their massive secondary (adrenergic) effects, dependence and waning anorectic effect demonstrated their scant efficiency as antiobesity drugs. Other adrenergic agents have been developed and used [62, 63], but in general their effects are limited and they are not adequate for the treatment of obesity; common practice relegates them to the treatment of limited overweight conditions and then in combination with other therapeutic measures.

Serotonergic agents were initially developed as antidepressants; in some cases, as in the well known fluoxetine [64], loss of appetite and diminution of body weight were a common occurrence, which prompted first the use of fluoxetine [65] and later the development of a series of compounds that helped control moderate obesity and overweight conditions, often in combination with hypocaloric diets. Fenfluramine and its active component, dexfenfluramine, were widely used for several years [66]. The combination of fenfluramine and phentermine [67], an adrenergic drug [62], resulted in significant weight losses, but also produced dangerous side-effects that resulted in the removal of fenfluramine and dexfenfluramine from the market [68]. Sibutramine is the only serotonergic drug available for the treatment of moderate obesity [69, 70]. Its effects have been thoroughly tested, inducing moderate weight losses in susceptible patients when taken in combination with hypocaloric diets [71]. Long-term treatment results in a significant improvement in obese patients [72]. This, and the limited availability of other more powerful drugs makes sibutramine the choice drug for combined diet-exercise and the pharmacological approach to the treatment of moderate obesity [73].

The complex signalling pathways between the intestine and the brain constitute another important research area for the development of antiobesity drugs. Cholecystokinin (CCK) has been the main target for these studies [74], but other intestinal peptides, such as bombesin, galanin and glucagon are currently being studied – essentially using animal models – in order to develop anorectic drugs [75, 76].

However, most of the efforts devoted to the development of anorectic drugs are centred on the hypothalamus, where the control over the appetite resides [77]. Both adrenergic and serotonergic anorectic drugs act on the hypothalamus; the ample variety of neurotransmitters involved in the control of appetite is indicative of the extreme complexity of the mechanisms involved [78]. The number of peptides known to act on appetite control grows constantly, and with it the expectations of new pathways for which drugs can be developed also keep widening [60]. Nevertheless, the sheer complexity of the pathways involved, the size of the target, the labile nature of peptides and the blood-brain barrier pose huge obstacles to such developments. Furthermore, the compensating nature of the systems controlling the mass of body fat suggest that in any case anorectics may play only a partial role in treating obesity, since simply by acting on complementary systems (i.e. appetite *and* thermogenesis) uncompensated fat losses may occur in the long run.

Treatment through increased energy expenditure

Exercise is the easiest way to increase energy expenditure, but the increase is only transient - limited to the duration of exercise. In addition, during exercise, thermogenesis is inhibited in order to prevent excessive use of the energy available and to facilitate the elimination of the heat evolved during muscular action [79]. Thus, the effectiveness of exercise as a tool in the treatment of obesity is a direct consequence of its duration, and this is related to its intensity and the onset of fatigue. Most obese show fatigue soon after beginning even mild exercise, which further limits the eventual energy expending effects of exercise. Moreover, the increase in respiratory and cardiovascular activity caused by exercise among the obese are more marked than in individuals with normal weight, which enhances the risk [80]. The use of moderate exercise practised in a constant manner, however, in combination with hypocaloric diets helps prevent the decrease in basal energy expenditure elicited by low energy intake [21]. The combination of physical activity and low energy intake, thus, is the method of choice for the treatment of moderate obesity and overweight conditions when this exercise is feasible and well tolerated [81].

Other systems to increase energy expenditure include exposure to the cold, since low temperatures are counteracted by parallel increases in thermogenesis [82]. However, this is an impractical procedure that is most uncomfortable and prone to develop complications, such as respiratory ailments. These drawbacks prevent the actual use of cold exposure for treatment of obesity. But thermogenesis has a clear appeal for the pharmacological treatment of obesity: any drug eliciting thermogenesis may help unbalance the energy budget drawing reserves that end up simply as heat. This has spurred considerable research (Table 4), based especially on the uniqueness of brown adipose tissue as a key thermogenic organ in rodents [83], and the finding of un-

Table 4. Drugs used –and drug-developing trends– for the treatment of obesity: III - Thermogenic drugs

action, types		*examples*	*references*
adrenergic agonists	α_1-adrenergic antagonists	—	[161]
	α/β-adrenergic receptor blockers	arotinolol	[162]
	β-adrenergic agonists	ephedrine	[163]
	β_3-adrenergic agonists	—	[164]
	phosphodiesterase inhibitors	amrinone	[165]
	BAT NA reuptake inhibitors and NA level enhancers	ciclazandol	[166]
calcium antagonists		benidipine	[167]
GABA agonists		GABA	[168]
respiratory chain / ATP synthesis uncouplers		—	[169]

coupling protein (UCP-1) and its mechanism of action [84, 85]. The presence of atypical β-adrenergic receptors in this tissue (β_3-adrenoceptors) [86] prompted the active search for specific agonists [87], which were expected to promote thermogenesis without unwanted general adrenergic stimulation [88]. Unfortunately, some species-specific differences between murine and human receptors [89], and the counteracting effects of glucocorticoids [90] limited the effectiveness of these drugs. In spite of magnificent perspectives and a major effort by many pharmaceutical companies, none of the β_3 have yet been commercialised.

Direct elimination of adipose tissue

The direct action on adipose tissue is a fairly expedient way to dispose of the problem – at least for a time. Several strategies have been developed to achieve this goal, the most obvious is the surgical removal of tissue, a huge task because of the wide distribution of adipose tissue masses below the skin and the location of visceral fat around and between key splanchnic organs, muscles, vases and nerves. Extirpation of a sizeable amount of fat through surgical means may require extensive and complex surgical procedures whose risks are not justified. However, the excision of masses of readily accessible fat –lipotomy– is used sometimes to ease the burden of the obese, though more often for aesthetic reasons; in any case it may significantly affect the body in other ways [91]. Liposuction also removes fat, but its applications are also more common in plastic surgery than in the treatment of obesity [92], since the mass of adipose tissue removed is usually small. Massive liposuctions [93], eliminating significant amounts of fat have seldom been used because of the painful and complicated recovery process.

Local treatment of adipose tissue masses with the injection of hormones and other lipolytic agents, as well as other localised manipulations of subcutaneous fat depots are extensively used to shape the body for cosmetic purposes, but their overall effect on adipose tissue mass is negligible. In fact, the extensive use of thyroid hormone analogues in local applications may unbalance the hormonal equilibrium and induce reactive obesity [94], a reason why these localised hormonal treatments should be ruled out.

The drastic elimination of adipose tissue using the immunological system is a possibility that has been explored repeatedly by researchers [95], using anti-adipocyte antibodies to wipe out adipose tissue [96]. These procedures, however, entail considerable risks derived from the specificity of the antibodies and also because if successful, the total elimination of adipose tissue would seriously hamper the regulation of the energy budget, since the adipocyte is not a mere store of fat reserves [97] but a source of hormones: leptin, estrone and other regulatory components [98].

Modification of energy control

The external modification of energy-transfer and utilization mechanisms might also increase overall inefficiency, disrupting the energy equilibrium and drawing energy from the fat stores (Table 5). The most effective uncouplers are metabolic poisons, in which therapeutic levels are extremely close to those that produce dangerous side-effects [99]. These uncouplers are generally unsafe and not-discriminating, and their use may be seriously detrimental to the patient's health, even resulting in death. More specific targeting, however, such as the inhibition of fatty acid synthesis may constitute a viable mechanism to help prevent fat accumulation [100]. Carnitine is extensively used as a food supplement because it is often thought – without any hard data though to support this belief – that a high availability of this compound may help oxidize fats [101]. Other compounds that tend to «enhance metabolism», such as amino acid mixtures, have been suggested as alternatives for achieving these goals, though here again, often without any sound experimental data to support their use.

Manipulation of energy control by either controlling intake or increasing expenditure needs to take into account both the counteracting modulation of the opposite mechanism and the overall hampering effect of glucocorticoids [102-105]. The best way to overcome these drawbacks is pre-

Table 5. Drugs used –and drug-developing trends– for the treatment of obesity: IV - Hormones and drugs modulating energy homeostasis action, types

action, types			*examples*	*references*
hormones	insulin action modulators	antidiabetic agents	amylin	[107]
		insulin function enhancers	chromium picolinate	[170]
		phosphotyrosine phosphatase inhibitors	—	[106]
	growth hormone agonists		growth hormone	[111]
	thyroid hormone agonists		thyroxin	[108]
	antiglucocorticoids		DHEA	[116]
	androgen agonists		testosterone	[113]
	estrogen agonists		β-estradiol	[118]
	oleoyl-estrone agonists		oleoyl-estrone	[125]
	leptin agonists		leptin	[171]
metabolic controllers	respiratory chain blockers		dinitrophenol	[99]
	fatty acid synthesis inhibitors		—	[100]
	mitochondrial fatty acid transport enhancer		carnitine	[101]

DHEA = dehydroepiandrosterone

cisely to target the center that modulates both legs of the system, by affecting the ponderostat setting, and by allowing those mechanisms that we have been trying to rein in to work without external interference and in the required lipolytic direction. Since in obesity insulin resistance is perhaps the main metabolic trait [18, 19], any improvement in this condition by means of antidiabetic drugs may help restore an adequate insulin homeostasis [106, 107].

Other hormones have been used to treat obesity: thyroid hormones have been extensively used in the past [108], and remain a significant component in unproven concoctions prescribed by charlatans to their unsuspecting patients [109]. Thyroid hormones do induce significant losses of body weight [110] but may induce alterations in thyroid operation. The availability of recombinant growth hormone led to its being used in the treatment of obesity [111], and in spite of limited success, research continues to develop GH-related compounds that might be useful in the treatment of obesity [112].

Androgens are not useful as anti-obesity drugs, but they do reshape the distribution of fat and increase muscle mass [113]. Massive doses of dehydroepiandrosterone (DHEA), a mild androgen, induce slimming in rats with no ill-effects [114], however, lower-dose applications to humans had no significant effects on body weight [115]. Nevertheless, DHEA tends to diminish the fat mass and to increase body protein [116], and is extensively used as a food supplement. Probably the main beneficial effect of DHEA is derived from its antiglucocorticoid function [117], thus limiting the fat-promoting actions of cortisol. Estrogens also tend to decrease body weight by enhancing thermogenesis [118], but the effects are limited and overshadowed by their estrogenic action.

Leptin is produced by the adipocyte [119], as is oleoyl-estrone, in proportion to its mass [120, 121]. Leptin has been postulated as a ponderostat signal [119], but hyperleptinemia of obese humans [120] precludes its use as an anti-obesity drug, since the problem does not seem to lie in the availability of the protein but rather in how its signal reaches the hypothalamic nuclei [122]. Oleoyl-estrone has also been postulated as a ponderostat signal [123]; its administration to rats reduces the mass of fat without affecting body protein [124, 125]. In spite of the considerable amount of research conducted to date on these putative ponderostat signals [126, 127], further research has to be undertaken before this promise can be turned into effective antiobesity drugs.

This overview of the treatment of obesity shows that many avenues have been explored in an effort to find an effective means of treatment. However, time-honoured concepts and ideas endure and most of these efforts still focus on the development of partial solutions to the complex problem of obesity. More basic research and greater insights into obesity are needed, if we are going to be able to tackle this ever increasing problem in the next few years. A coordinated effort in the development of powerful, yet harmless, drugs is needed together with the gathering of adequate information about patients, while at the same time ensuring that the health personnel working in this field are kept up to date in their understanding of obesity; but most importantly, the real threat of obesity as a dangerous illness that is spreading without control must be clearly accepted and resoundingly denounced.

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About the authors

The authors belong to the CCN-IEC (Catalan Center of Nutrition from the Institute for Catalan Studies), an organism created recently in order to facilitate contact and collaboration between the different Catalan-speaking research groups studying Nutrition from different points of view and strategies. This review is one of the first fruits of this collaboration, since Drs. Remesar, Fernández-López and Alemany are from the Nitrogen-Obesity Research Group of the University of Barcelona, and Dr. Foz is from the Unit of Food Disorders at the Germans Trias i Pujol University Hospital, and both groups participate in the tasks of the CCN-IEC.

The Nitrogen-Obesity Research Group has published steadily front-line research papers on obesity in the last 15 years. The main subjects of the study have been: thermoregulatory responses to cold and feeding; thermogenesis; brown adipose tissue metabolism and energy substrates; muscle heat transfer and substrate utilization under cold exposure; insulin turnover and breakdown in obesity; steroid hormone status during obesity; metabolic and hormonal characterization of the obese; and, specially, the discovery and development of a new line of research on oleoyl-estrone, an adipostat signal that is being developed as a possible antiobesity drug. The study of oleoyl-estrone is being developed over a wide range of aspects covering both the pharmacokinetics, mechanism of action, and interaction with other hormones and physiological situations. A very significant part of the research carried out by the Nitrogen-Obesity group has been done under contracts from the Pharmaceutical Industry and a significant share of the investigation has been done in collaboration with other research groups such as the Unit of Eating Disorders of the Hospital Germans Trias i Pujol.

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The Unit of Eating Disorders at the Trias i Pujol University Hospital was the first medical and research Unit in Spain integrat-

ing medical, surgical and psychiatric attention in a single therapeutic approach. The unit treats the morbidly obese in addition to anorectic and bulimic patients. The Unit has a remarkable research production, with new developments in bariatric surgery and endocrine and metabolic studies carried out mainly on morbidly obese subjects.

Màrius Foz is doctor in Medicine, and specialist in Internal Medicine and Endocrinology and Nutrition. He is emeritus professor of Medicine at the Autonomous University of Barcelona and, until his jubilee last year, Head of the Department of Internal Medicine at the Trias i Pujol University Hospital, where he has developed most of his research, teaching and medical career, and where he founded the Unit of Eating Disorders. He has been President of the Academy of Medical Sciences of Catalonia, and is life-member of the Biological Section of the IEC. He has been founder and current Director of the CCN-IEC. He is also President of the Spanish Society for the Study of Obesity (SEEDO). His research interests have been focussed on endocrinological aspects of diabetes, obesity, corticoid metabolism and other endocrine disorders.