The availability of nutrients (energy) to fuel biological reactions is fundamental for life, but continuous overnutrition leads to the accumulation of fat and ultimately to obesity. In modern societies, it is highly unlikely that a period of starvation sufficient to deplete these fat stores would occur, and cheap and abundant food supplies may contribute to a growing obesity epidemic. The economic and social burdens that this poses are considerable, particularly as obesity is a high-risk factor for other chronic diseases, for example, cardiovascular disorders, diabetes and cancer.

So far, effective and safe pharmacological options for the prevention and treatment of obesity remain elusive, and despite the growing amount of resources being applied to research in the field the development of anti-obesity drugs has been plagued by failures. One of the reasons for these failures might be that our understanding of the pathogenesis of obesity is incomplete. Alternatively, the molecular underpinning of biological processes that underlie the emergence of obesity may not lend themselves to selective manipulations that successfully reduce adipose tissue stores without impairing long-term health and survival.

Indeed, many of the putative novel drugs for obesity have not achieved the level of clinical effectiveness that is required by regulatory authorities such as the US Food and Drug Administration (FDA), while the few that are sufficiently effective are associated with adverse side effects that preclude their long-term use in patients. The number and diversity of these side effects indicate that the pathways targeted so far are ubiquitously important in several tissues, and not just in those directly implicated in the regulation of energy balance and obesity. Most, if not all, pharmacotherapies for obesity attempt to reduce food intake by either curbing appetite or suppressing food cravings. Thus, the basic principle behind the development of these drugs has been to target pathways that promote satiety.

This Review evaluates the evidence indicating that anti-obesity drugs targeting satiety pathways may be destined to fail owing to adverse side effects. Therefore, we propose that such treatments should be used for short periods of time in combination with intense behavioural interventions. In addition, we discuss how targeting hunger, or the molecular pathways involved in hunger (such as during calorie restriction), may be a successful alternative approach to improving health in patients with chronic metabolic disorders such as obesity.

**Hunger drives mnemonic functions**

Hunger, or appetite, is the adaptive response by an organism to the need for higher energy levels for cellular metabolism. Hunger has been a driving force for creativity and for the development of civilization in general, and there is a large body of evidence supporting the idea that hunger was a primary driver of higher brain
function during human evolution. Experimental neuroscience has also widely utilized approaches of positive reinforcement that hinge upon hunger or appetite as the motivational force to learn new tasks. Although there are many other methods for the study of mnemonic functions, the profound role that hunger plays in promoting complex brain functions is evident from these studies. More recently, the humoral, neuronal and molecular mechanisms that are involved in the regulation of hunger and satiety (Fig. 1) have emerged and implicate a fundamental role of the hypothalamus and peripheral tissues in coordinating these processes. Because hunger has such notable effects on cognitive functions, we propose that interventions designed to interfere with hunger might ultimately also interfere with cognition.

**Food restriction drives longevity**

Late-onset chronic diseases, including obesity, dementias, diabetes, cardiovascular disorders and cancer, are leading causes of mortality and morbidity in industrialized/developed countries, creating a huge emotional and financial burden on society. Guided by the idea that late-onset chronic diseases are a consequence of prolonged overworking of various tissues that have certain vulnerabilities (for example, genetic or epigenetic), it is possible that the cellular energy metabolism of different tissues will determine health and longevity. Supporting this idea is the finding of a positive effect of calorie restriction on lifespan in a broad range of animal models, including the worm, fruitfly, rodents and non-human primates. To date, this is the only

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**Table 1 | Anti-obesity drugs**

<table>
<thead>
<tr>
<th>Drug (company*)</th>
<th>Mechanism of action</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine†‡</td>
<td>An amphetamine that increases the release of noradrenaline, dopamine and serotonin</td>
<td>• Cardiovascular: elevation in blood pressure, tachycardia &lt;br&gt; • CNS: insomnia, restless sleep, alters sexual behaviour, hormonal secretion and mood</td>
<td>• Approved by the FDA in 1959 &lt;br&gt; • Recommended for short-term use (less than 3 months)</td>
</tr>
<tr>
<td>Orlstat (Roche)‡</td>
<td>Pancreatic lipase inhibitor</td>
<td>• Steatorrhoea, fecal incontinence, flatulence, and malabsorption of fat-soluble vitamins &lt;br&gt; • Rare cases of severe liver injury &lt;br&gt; • Potential risk of kidney injury</td>
<td>• Approved by the FDA in 1999</td>
</tr>
<tr>
<td>Lorcaserin (Arena Pharmaceuticals)¶§</td>
<td>5-hydroxytryptamine receptor agonist that is more specific than previous compounds on the market, for example, fenfluramine</td>
<td>• Headache, dizziness, nausea, valvulopathy &lt;br&gt; • Possible carcinogenic effects in rodents</td>
<td>• Approved by the FDA in June 2012 &lt;br&gt; • Under evaluation by the EMA &lt;br&gt; • Post-marketing, long-term cardiovascular outcomes trial required</td>
</tr>
<tr>
<td>Phentermine + topiramate (Orexia; formerly Qnexa; Vivus)¶§</td>
<td>Phentermine: mechanism of action as above &lt;br&gt; Topiramate: anticonvulsant, precise mechanism of action unknown</td>
<td>• Possible teratogenic effects with topiramate &lt;br&gt; • Can increase heart rate</td>
<td>• Approved by the FDA in July 2012 &lt;br&gt; • Post-marketing, long-term cardiovascular outcomes trial required</td>
</tr>
<tr>
<td><strong>Withdrawn</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenfluramine†‡</td>
<td>Increases the release of serotonin &lt;br&gt; Serotonin re-uptake inhibitor</td>
<td>• Hallucinations, valvulopathy, pulmonary hypertension</td>
<td>• Approved by the FDA in 1973 &lt;br&gt; • Withdrawn in 1997</td>
</tr>
<tr>
<td>Sibutramine†‡</td>
<td>Noradrenalin and serotonin re-uptake inhibitor</td>
<td>• Increased risk of heart attack and stroke in patients with high risk of cardiovascular disorders</td>
<td>• Approved by the FDA in 1997 &lt;br&gt; • Withdrawn in 2010</td>
</tr>
<tr>
<td>Rimonabant†‡</td>
<td>Cannabinoid 1 receptor antagonist</td>
<td>• Risk of suicide</td>
<td>• Approved by the EMA in 2006 &lt;br&gt; • Withdrawn in 2009</td>
</tr>
<tr>
<td><strong>Awaiting decision</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion + naltrexone (Contrave; Orexigen)**</td>
<td>Bupropion: inhibitor of dopamine and noradrenaline uptake &lt;br&gt; Naltrexone: µ-opioid receptor antagonist</td>
<td>• Nausea, constipation, vomiting, dry mouth &lt;br&gt; • Potential cardiovascular risk</td>
<td>• FDA will not approve Contrave without cardiovascular assessment &lt;br&gt; • Orexigen will run a cardiovascular outcome trial</td>
</tr>
</tbody>
</table>

CNS, central nervous system; EMA, European Medicines Agency; FDA, US Food and Drug Administration; NDA, new drug application; PDUFA, prescription drug user fee act. †If applicable. §Never approved by the FDA owing to concerns related to adverse psychiatric side effects.

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**Food cravings**

Intense desires to ingest specific types of food. These desires are not necessarily linked to hunger.

**Satiety**

A state in which the individual is fed and/or gratified with the amount of energy ingested.

**Mnemonic functions**

Cognitive functions of the brain that are involved in memory processes.

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physiological intervention known to have a consistent and predictable effect on maintaining health and prolonging life in all species studied.

The robust effects of calorie restriction, a form of protracted negative energy balance, on chronic diseases lends support to the argument that late-onset disorders are the consequence of sustained high levels of substrate oxidation by various tissues. A negative energy balance is thought to promote the activity of specific populations of neurons in the hypothalamus that drive hunger. Thus, hunger, and the promotion of activity of these specific populations of neurons (see below), may promote a healthier and longer life. By contrast, satiety may have the opposite effect in that it promotes metabolic overload in tissues, thereby leading to chronic diseases. These observations have implications for the development of anti-obesity drugs, because compounds that target satiety pathways will ultimately promote the homeostatic mechanisms that are related to metabolic overload and therefore chronic disorders.

**Hypothalamic principles of obesity**

Leptin is a hormone produced by adipocytes, and leptin is lacking in the naturally occurring obese mouse model (ob/ob mice)\(^{39,40}\). Furthermore, leptin and leptin receptor deficiencies lead to obesity in both mice and humans\(^{39,41-46}\). Therefore, it was hoped that this hormone could have applications in the treatment of obesity. However, leptin replacement therapy exerts a beneficial effect on only a small subset of obese subjects: those that carry a leptin gene deficiency\(^ {47,48}\). Surprisingly, it has been found that leptin levels are actually high in obese individuals (both in rodents and in humans)\(^ {39,50}\) and its administration has little effect in reducing body weight\(^ {41,52}\). This scenario has been described as leptin resistance, and the mechanisms that lead to such a situation in obese subjects are still largely unknown. FIGURE 2 shows mutations found in humans that lead to obesity, which involve leptin signalling and the melanocortin system.

It is thought that leptin mainly mediates its effects on energy metabolism regulation by targeting the melanocortin circuitry in the brain\(^ {39,53}\), which is a key regulator of energy balance\(^ {41,54}\). Thus, it has been proposed that leptin resistance occurs primarily in the hypothalamus. For example, it was shown that an increase in endoplasmic reticulum (ER) stress and activation of the unfolded protein response (which is activated in response to an accumulation of unfolded or misfolded proteins in the lumen of the ER) occur in the hypothalamus of obese subjects, and lead to inhibition of local leptin receptor signaling\(^ {55}\). In mice, treatments with various chemical chaperones that decrease ER stress increase sensitivity to leptin, thereby suggesting that this is an anti-obesity strategy that could be translated to humans\(^ {55}\). Interestingly, ER stress seems to be a common trait in chronic metabolic disorders\(^ {56}\), such as obesity and type 2 diabetes, and chemicals that decrease ER stress have shown beneficial effects in both of these conditions\(^ {56,57}\).
Appetite
Satiety

MC<sub>4</sub> receptor

NPY/AgRP/GABA neuron

POMC/CART neuron

α-MSH

Figure 1 | **Humoral and nutritional crosstalk between peripheral tissues and the brain.** To adapt to daily variations in energy balance, our bodies sense and integrate information about energy availability that is conveyed to the brain by peripheral hormones (for example, pancreatic polypeptide (PP), cholecystokinin (CCK) and peptide YY (YY)) and nutrients (for example, glucose, free fatty acids (FFA) and amino acids (AA)). These molecules regulate feeding behaviour by acting on neurons in the hypothalamus and the brainstem. During periods of satiety, the body works towards storage of the acquired nutrients. Satiety is associated with increased sympathetic activity, which promotes both insulin release by the pancreas (and thus stimulates glucose storage in the liver and muscle) and fat deposition (which leads to a rise in leptin levels). Food ingestion results in a release of incretins by the gut. These include glucagon-like peptide 1 (GLP1), which stimulates the pancreas to secrete insulin; both GLP1 and insulin are thought to reduce food intake by acting directly on the brain. In pancreatic β-cells, the hormone amylin is released together with insulin in response to a meal. Amylin is a potent satiety signal, which inhibits digestive secretion and slows gastric emptying. The precise brain targets of amylin are not known, but include the area postrema in the brainstem and the lateral hypothalamus. Conversely, during periods of hunger, the hypothalamus regulates the activity of the autonomic nervous system to promote fat release from white adipose tissue and trigger gluconeogenesis in the liver. These changes in peripheral nutrient levels lead to a decrease in the levels of thyroid hormones, insulin and leptin, and to an increase in the level of ghrelin and corticosteroids, which increase food-seeking behaviour through their effect on the brain. The hormones and peptides mentioned above are only a few among many molecules that are thought to be involved in the regulation of energy balance. In the brain, the hypothalamus (small boxed area in mid-sagittal view of the brain) contains two critical subsets of neurons (enlarged in boxed area): the neuropeptide Y/agouti-related protein/γ-aminobutyric acid (NPY/AgRP/GABA) neurons, which, when activated owing to decreasing glucose and leptin levels and increasing ghrelin levels, promote hunger and appetite, in part by suppressing the activity of neighbouring pro-opiomelanocortin (POMC) neurons, and antagonizing melanocortin 4 (MC<sub>4</sub>) receptors in target areas. Increasing glucose and leptin levels with subsiding ghrelin availability inhibit NPY/AgRP neurons and activate POMC cells, which in turn lead to satiety. The POMC neurons also co-express the cocaine- and amphetamine-regulated transcript (CART), and when activated they release α-melanocyte-stimulating hormone (α-MSH) in target regions, which functions as an endogenous agonist of MC<sub>4</sub> receptors and promotes satiety. Research into this complex system continues to identify new candidates that could be pharmacologically targeted to regulate energy balance.© 2012 Macmillan Publishers Limited. All rights reserved
The central melanocortin system resides in the arcuate nucleus (ARC) region of the medial-basal hypothalamus, where neurons that produce both neuropeptide Y (NPY) and agouti-related protein (AgRP) and neurons that produce pro-opiomelanocortin (POMC) are located. The POMC neurons produce a series of different peptides that are encoded by the POMC gene, including a-melanocyte-stimulating hormone (a-MSH). Melanocortin peptides are endogenous agonists of melanocortin (MC) receptors, a family of G protein-coupled receptors comprising at least five members (MC₁-MC₅). In the brain, MC₄ and MC₅ receptors are the most abundant receptors for melanocortins, and they mediate the effects of a-MSH. POMC-expressing neurons are not exclusively found in the ARC, but also reside in the nucleus of the solitary tract (NTS) in the brainstem.

The second population of neurons that form the central melanocortin system is the NPY/AgRP neurons, which also produce GABA (γ-amino butyric acid)²². AgRP acts as a strong endogenous antagonist of MC₄ and MC₅ receptors²³, and is thought to regulate the signalling of these receptors by blocking the activity of a-MSH. Indeed, most of the areas of projection of the POMC neurons and AgRP neurons overlap, emphasizing the crosstalk between these two populations of cells.

Genetic mutations in the melanocortin system lead to obesity, in both mice²⁴⁻²²⁷ and humans²²⁸⁻²³⁵. In addition to effects on obesity and food intake, the central melanocortin system has also been implicated in several different homeostatic functions, including the control of insulin levels²³⁶, cholesterol levels²³⁷, thyroid function²³⁸ and blood pressure²³⁹⁻²⁴².

One of the unique properties of the ARC melanocortin system is that NPY/AgRP neurons send inhibitory projections to the neighbouring POMC neurons²⁴³. This unidirectional synaptic organization of the circuitry allows NPY/AgRP neurons to coordinate feeding by directly inhibiting target areas (such as the paraventricular nucleus) and/or by inhibiting POMC neurons, thereby releasing the target areas of the excitatory inputs from the POMC cells. Accordingly, selective knockdown of GABA release in AgRP neurons leads to weight gain and an increased POMC tone in mice²⁴⁴. However, the melanocortin signalling does not seem to be essential to sustain feeding in AgRP-null mice²⁴⁵,²⁴⁶, whereas GABA signalling is required for feeding in adult mice²⁴⁷⁻²⁴⁹.

A more recent report²⁵⁰ further dissected the circuitry involved in long-term regulation of food consumption, and identified the parabrachial nucleus (PBN) as a key hub that integrates information from different brain areas to regulate energy balance. Excitatory neurons in the PBN receive strong inhibitory inputs from the NPY/AgRP/GABA neurons from the hypothalamus²⁵¹. This inhibitory tone is important for maintenance of long-term orexigenic responses. The PBN also receives glutamatergic and serotoninergic inputs from the NTS and raphe nuclei, respectively. These projections are important in increasing the excitatory tone of the PBN and decreasing appetite, integrating vagal and sensory inputs in the network that are responsible for governing energy balance²⁵². However, this circuitry seems to be important for long-term control of feeding but not acute promotion of appetite²⁵³. The NPY/AgRP/GABA neurons acutely stimulate food intake through projections to the paraventricular nucleus within the hypothalamus, in a circuitry that is independent of projections to the PBN²⁵⁴.

The metabolic overload that occurs during obesity, leading to ER stress in the hypothalamus²⁵⁵, correlates with increased peroxisome proliferation in POMC neurons²⁵⁶, which is consistent with the idea that peroxisomes are formed from the ER²⁵⁶⁻²⁶⁰. This increased peroxisome proliferation during diet-induced obesity is regulated by peroxisome proliferator-activated receptor-γ (PPARγ), and is an adaptive response to control the levels of reactive oxygen species (ROS) in POMC cells²⁵⁸. ROS are crucial regulators of hypothalamic neuronal activity²⁵⁸⁻²⁶³, and in lean mice their levels within the hypothalamus correlate with circulating leptin levels²⁶⁴. The sustained increase in ROS production that occurs during a positive energy balance scenario (for example, in obesity), and the concomitant increase in peroxisome proliferation to control ROS levels, is probably another important mechanism underlying leptin resistance in the hypothalamus. Additionally, this sustained increase in ROS is consistent with the occurrence of increased degenerative processes (for example, hypothalamic injury and reactive gliosis) in conditions of overnutrition²⁶⁵⁻²⁶⁷. A chronic positive energy balance promotes the metabolic intracellular state that is related to satiety and an increased ROS production that may contribute to the development of chronic disorders such as type 2 diabetes. Thus, when pharmacological therapies are considered for obesity with the aim of promoting satiety (resulting in states of increased ROS), the potential for degenerative side effects (such as cellular damage due to excess ROS) must be considered.

Mechanism of action of obesity therapeutics

Obesity therapies currently on the market. Although the development of obesity drugs has been plagued by failure, there are drugs currently on the market, the oldest example of which is the amphetamine phentermine, which was approved by the US FDA in 1939. At that time, clinical trials and rigorous safety tests were not required by the FDA, and thus phentermine has not been subjected to the type of scrutiny that new drugs now undergo. However, it is known from the long-term use of this drug that it causes numerous adverse side effects, which are all characteristic of the amphetamines, but thought to be milder than other compounds of the same family. In 2001, phentermine was withdrawn from the European market following litigation. Another amphetamine approved by the FDA at about the same time as phentermine was diethylpropion (also known as amfepramone), and it is still on the market today.

Both phentermine and diethylpropion act by increasing the release of serotonin, dopamine and noradrenaline, having the greatest effect on noradrenaline. At least two other drugs are available with mechanisms of action similar to phentermine and diethylpropion: benzphetamine (approved in 1960) and phenmetrazine (approved in 1982). All of these compounds are approved for short-term use only (less than 3 months) and all act to promote satiety through the release of serotonin and catecholamines in the brain. The action of these compounds is not selective and it is thought that their anorexic effect is due to increased levels of monoamines in several brain nuclei, including hypothalamic areas. Because of the mechanism of action of these compounds, they are considered sympathomimetic (that is, their action is similar to stimulation of the sympathetic nervous system). The increase in noradrenaline concentration in the synaptic cleft stimulates β-adrenergic receptors, resulting in appetite inhibition. The precise mechanism and site of action of these compounds is not known, and many other functions that are controlled by the brain may be altered by this class of drugs, such as sexual behaviour, hormonal secretion, mood, cognition and sleep²⁶⁸⁻²⁶⁹. Therefore, although they remain on the market, these drugs are of limited utility.

Several agents were developed on the basis of the anorexigenic effect of amphetamines. These drugs aimed to specifically promote serotonin signalling in the brain (instead of dopamine and noradrenaline), which
The promotion of these changes in the ARC melanocortin tors in NPY/AgRP neurons 2C (thalamic melanocortin system. Later, it was established the levels of the activity of these cells) while activating 5
will consequently the thereby unrelated confirm motivated feeding (resulting also these energy suppression (NPY) shown Signals More More

Intriguingly, besides the acute electrophysiological neuronal effects of ghrelin, peripheral ghrelin administration also rapidly re-organized the synaptic inputs on POMC neurons35, thereby further promoting the suppression of these arcuate cells, which is consistent with an overall orexigenic influence of ghrelin.

More recently, ghrelin has been shown to regulate NPY/AgRP neuronal activity by modulating presynaptic excitatory inputs into these cells254,255, in a mechanism similar to what has been described in other neuronal populations158,255. The possibility that ghrelin modulates feeding by both direct252,256 and indirect effects254 raises the possibility that there are other important factors that are involved in appetite regulation255.

Ghrelin also controls higher brain functions and may represent a molecular link between learning capabilities and energy metabolism. For example, circulating ghrelin enters the hippocampal formation and midbrain where it binds to neurons and promotes the formation of synapses197,198. Ghrelin-regulated synapse formation and long-term potentiation of synapses in the hippocampus positively correlates with spatial memory and learning157. Beyond the alteration of these mnemonic functions, hippocampal administration of ghrelin also promotes feeding251. The interference of ghrelin signalling in the midbrain also suppresses feeding that is triggered by peripheral ghrelin administration, therefore arguing for a role of the midbrain reward circuitry in feeding regulation. However, the dopamine system within this area also projects to the prefrontal cortex, which suggests that there are direct roles for ghrelin in motivated behaviour (resulting from cortical modulation) and in working memory.

The ventral tegmental area is in the immediate vicinity of the substantia nigra, where dopamine neurons play a critical role in the regulation of motor functions. The loss of this dopamine system is the underlying cause of Parkinson’s disease, and ghrelin was recently found to promote and protect the activity of the dorso-striatal dopamine system251. In addition to the well-known effect of this dorso–striatal dopamine system in the regulation of movement, it also directly affects feeding behaviour252–255.

Like ghrelin, the adipose hormone leptin also affects these structures and associated brain functions, such as motivated behaviour, learning and memory256. Functional magnetic resonance imaging studies of the human brain confirm that these effects of the peripheral metabolic hormones target the same brain regions that were unmasked in experimental animal models213,201,202.

More recently, the NPY/AgRP neurons have been shown to influence the development of the dopaminergic system in the midbrain with consequent implications for behavioural responses in adulthood245. Motivational behaviours unrelated to feeding and responses to cocaine were altered by selective manipulation of the NPY/AgRP neurons245, thereby adding the complexity of the brain circuitries that govern appetite and other complex behaviours.

Together these findings emphasize that the function of all aspects of the central nervous system (CNS) is under the control of the metabolic needs of the body, and that peripheral tissues exert their requirements by shifting the activity of various brain regions, in part, by humoral signals. The hypothalamus senses hormonal signals and metabolites from the periphery and also integrates inputs from other brain areas. Hypothalamic neurons command hormonal axes by projecting to the pituitary, and also influence the sympathetic neural output from the brainstem to peripheral organs.

Both hormonal and neural outputs from the brain are important to regulate peripheral tissues function, and consequently the feedback release of hormones, nutrients and metabolites in the circulation. All these, in turn, become important regulators of brain function, and different metabolic states will lead to concomitant changes in brain activity and plasticity. Thus, it is plausible that modulations of hormonal or nutrient signals important for these metabolic shifts will affect higher-level brain functions and, consequently, generate psychiatric and neurological responses with probable implications in the aetiology of related disorders.

is thought to promote an anorectic response24. Indeed, earlier studies identified an inverse correlation between serotonin levels in the brain and appetite66,70. The administration of serotoninergic compounds to rodents increased the levels of POMC and decreased NPY mRNA in the hypothalamus12, thereby indicating that the promotion of serotonin signalling inhibits appetite through the hypothalamic melanocortin system. Later, it was established that serotonin agonists activate the 5-hydroxytryptamine 2C (5-HT₃) receptors in POMC neurons2–4 (to promote the activity of these cells) while activating 5-HT₃ receptors in NPY/AgRP neurons12 (to inhibit their activity). The promotion of these changes in the ARC melanocortin system was dependent upon downstream melanocortin signalling73,74 to bring about weight loss. However, some of the compounds that act more specifically in serotonin signalling have recently been withdrawn from the market, mainly owing to concerns about their cardiovascular side effects, and these drugs are discussed below.

The only drug currently available for the long-term treatment of obesity is orlistat, a lipase inhibitor that promotes a reduction in fat absorption in the gastrointestinal tract75. Because orlistat inhibits fat absorption, it causes major gastrointestinal side effects (for example, flatulence and fatty stools (steatorrhoea), and is better tolerated in combination with a low-fat diet75–78. A new compound called cetilistat79,80 (TABLE 1) is under development and is thought to have less severe gastrointestinal side effects

Box 2 | CNS function during metabolic shifts: implications for brain disorders

Signals from the periphery, in the form of hormones and nutrients, initiate a brain response to declining energy availability. Among the various hormones involved, only the gut-derived acylated polypeptide ghrelin19,20 has been shown to trigger feeding behaviour, which is mediated by the activation of neurons that produce both neuropeptide Y (NPY) and agouti-related protein (AgRP), which are located in the arcuate nucleus19,20,21. However, ghrelin also exerts actions at extra-hypothalamic sites202,203.

Ghrelin is secreted from the stomach when the stomach is empty. In hypothalamic slice preparations, AgRP neurons were activated by ghrelin directly, whereas it indirectly inhibited the anorexigenic pro-opiomelanocortin (POMC) neurons62,235. Intriguingly, besides the acute electrophysiological neuronal effects of ghrelin, peripheral ghrelin administration also rapidly re-organized the synaptic inputs on POMC neurons35, thereby further promoting the suppression of these arcuate cells, which is consistent with an overall orexigenic influence of ghrelin.

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compared with orlistat\textsuperscript{79–83}. When compared with all other agents in the anti-obesity pharmacopoeia, orlistat may be the only compound that is not aimed at promoting satiety, but instead promotes malabsorption with a theoretical promotion of appetite owing to impaired absorption of nutrients. Paradoxically, the modest effect of orlistat in reducing body weight may be due to its adverse side effects that motivate the patient to maintain a low-fat diet. Because the severity of the side effects increases if the diet deviates from the goal of being low fat, the patients may sense the gastrointestinal distress as punishment and this in turn may help them to maintain a healthier diet and therefore result in an effective treatment. It is noteworthy that on a low-fat diet, patients receiving orlistat may have no side effects, but still have modest decreases in body weight, therefore highlighting that food aversion is not the only factor resulting in weight loss. In agreement with the fact that orlistat does not promote satiety, it has other potential benefits besides weight loss, such as improving diabetes and cardiovascular outcomes\textsuperscript{84–88}.

**Obesity therapies recently withdrawn from the market.**

The first compounds approved by the US FDA as appetite suppressants, fenfluramine (approved in 1973) and dexfenfluramine (1996), promote serotonin signalling in the brain and significantly decrease body weight when taken alone or in combination with phentermine\textsuperscript{89,90}. However, in 1997, the FDA withdrew these drugs from the market owing to an increased incidence of valvular heart disease and primary pulmonary hypertension in individuals taking these drugs\textsuperscript{91–96}. These side effects were thought to be due to widespread effects of serotonin on 5-HT receptors, other than those located in the ARC and important for metabolic regulation. During the same time period, the FDA approved sibutramine, another serotoninergic drug that aimed to reduce body weight in obese individuals.

Sibutramine is a serotonin and noradrenaline reuptake inhibitor that has minor effects on dopamine uptake and neurotransmitter release. Besides this mechanism of action, sibutramine is also thought to decrease body weight and appetite through its action on central \(\alpha_{2}\)-adrenergic and \(\beta_{1}\)-adrenergic receptors, and peripheral \(\beta_{2}\)-adrenergic receptors. For a period of time, sibutramine was the standard in anti-obesity therapies to which newly developed drugs would be compared, and it effectively reduced body weight in patients with various underlying pathological conditions\textsuperscript{97–106}. However, in 2010, the FDA withdrew sibutramine from the market owing to concerns over the increased risk of cardiovascular events (heart attack and stroke) in individuals taking this drug. One of the limitations of using serotoninergic compounds to effectively treat obesity is that serotonin receptors are not, in principle, area-specific and any drug that is developed to act in one region of the body will probably have an effect somewhere else in the body, with possible detrimental results.

The cannabinoid system plays an important role in brain function by modulating synaptic transmission. Endogenous cannabinoid neurotransmitters, like anandamide, activate G protein-coupled cannabinoid 1 (CB\(_{1}\)) receptors, which are located throughout the brain and the peripheral nervous system. Administration of inverse agonists of CB\(_{1}\) receptors in both humans and animals inhibits food intake and increases energy expenditure, thereby leading to a more negative energy balance. Treatment with a CB\(_{1}\) receptor inverse agonist was therefore thought to be beneficial in the treatment of obesity and related disorders\textsuperscript{107,108}. In 2006, rimonabant\textsuperscript{109,110}, a pioneering CB\(_{1}\) receptor inverse agonist, was granted marketing approval in Europe to treat obesity based on results of four large Phase III trials\textsuperscript{111–115} (whereas the FDA issued an approvable letter requesting further information). Rimonabant was viewed as a promising drug for treating obesity, as it not only decreased food intake, but also increased energy expenditure and promoted other beneficial outcomes, such as improved glycaemic control and lipid profile\textsuperscript{111–113}. However, meta-analyses and systematic reviews later showed that rimonabant increased the likelihood that patients would develop severe side effects, specifically related to brain function\textsuperscript{114,116}, in particular, an increased risk for anxiety and depression, including a high risk of suicide. These major psychiatric side effects led to the withdrawal of rimonabant from the European market in late 2008, and the permanent suspension of all clinical studies that were testing rimonabant in obesity.

Taranabant\textsuperscript{108,117,118}, another CB\(_{1}\) receptor inverse agonist, was also under investigation to treat obesity, but failed to pass Phase III trials\textsuperscript{119–122} and was discontinued\textsuperscript{123}. CP-945598 was recently discovered to be a potent CB\(_{1}\) receptor antagonist\textsuperscript{124,125} but, despite decreasing body weight\textsuperscript{126}, was also discontinued. The ubiquitous expression of CB\(_{1}\) receptors in the brain led to the hypothesis that antagonists (or inverse agonists) that act solely on the periphery might promote weight loss without the psychiatric side effects. Research on this subject is underway and is showing some promise\textsuperscript{107,127,128}. Among the peripheral tissues that express the CB\(_{1}\) receptor, the white adipose tissue is the most studied. Blockade of this receptor in white adipocytes induces lipolysis, which increases the availability of free fatty acids in circulation that could ultimately lead to an increase in energy expenditure\textsuperscript{129}.

**Obesity therapies recently reviewed by the US FDA.**

Experimental evidence has revealed that the 5-HT\(_{2c}\) serotonin receptor subtype in the brain may be an effective and safe target for promoting satiety\textsuperscript{130}. Lorcaserin (developed by Arena Pharmaceuticals) is a selective 5-HT\(_{2c}\) agonist\textsuperscript{131,132}, with a 15-fold to 100-fold selectivity for this receptor over 5-HT\(_{2a}\) and 5-HT\(_{2b}\) receptors, respectively\textsuperscript{132}. The selectivity of lorcaserin and the observed lack of effect on the release of serotonin and other monoamines in *in vitro* assays\textsuperscript{132} represented an important difference from previous drugs that promote serotonin signalling such as dexfenfluramine.

Three large-scale clinical trials with lorcaserin demonstrated an effective weight loss when compared to placebo: BLOOM\textsuperscript{133}, BLOOM-DM\textsuperscript{134} and BLOOM-DM\textsuperscript{135}. In 2009, after completing two Phase III trials (BLOOM and BLOOM-DM), a new drug application was submitted to the FDA. In October 2010, the FDA issued a complete
response letter stating that lorcaserin could not be approved for clinical use, citing concerns about the possibility of increased malignancy in rats treated with lorcaserin, along with its modest effects in reducing body weight, thus giving lorcaserin a poor benefit–risk profile.

Arena Pharmaceuticals resubmitted a new drug application in December 2011. The FDA Endocrinologic and Metabolic Drugs Advisory Committee met on 10 May 2012 to evaluate lorcaserin and voted 18 to 4 that the benefits of long-term treatment with this drug outweigh the risks in overweight and obese patients. Concomitantly, the European Medicines Agency has accepted the filing of a marketing authorization application for lorcaserin, which also starts the evaluation process of lorcaserin in Europe. A report of the BLOOM-DM trial early this year showed that the use of lorcaserin for up to 1 year in obese and overweight patients with type 2 diabetes who were also receiving metformin and/or sulphonylurea improved weight loss, with concomitant improvements in glycaemic control\textsuperscript{136}. In June 2012, the FDA approved the use of lorcaserin to treat select populations of obese individuals. Arena Pharmaceuticals has agreed to run post-marketing studies to further evaluate cardiovascular risks. Lorcaserin is thought to reduce body weight by acting as an agonist of 5-HT\textsubscript{2C} receptors in POMC neurons; however, it is noteworthy that 5-HT\textsubscript{2C} receptors are expressed in other areas of the brain, such as the cerebral cortex, substantia nigra and cerebellum\textsuperscript{137-140}. Thus, despite the promising effects of lorcaserin to reduce body weight, it may take longer than the time periods studied so far to prove that it is a safe, specific and effective drug in the treatment of obesity. In addition, the Endocrinologic and Metabolic Drugs Advisory Committee recently voted 17 to 6 in favour of additional clinical trials to evaluate the cardiovascular risk of any anti-obesity drug filed for approval. Whether or not this decision will affect the evaluation of the current obesity drugs under scrutiny by the FDA remains to be seen\textsuperscript{141,142}.

In addition to monotherapies to treat obesity, it has been proposed that combination therapies could provide additional benefits in terms of weight reduction and improved co-morbidities, with a decrease in the incidence of undesirable side effects, thereby leading to a more acceptable benefit–risk profile. Two examples of combined therapies that are in advanced stages of development are Contrave (bupropion plus naltrexone) and Qsymia, formerly Qnexa, (phentermine plus topiramate).

The two drugs that constitute Contrave (developed by Orexigen Therapeutics) have been approved by the FDA to treat disorders other than obesity over long periods of time. Bupropion is an atypical antidepressant that is thought to act by inhibiting both noradrenaline and dopamine reuptake at the synapse. It also reduces body weight\textsuperscript{143,144} by a mechanism proposed to be dependent upon dopaminergic and noradrenergic signalling in POMC neurons\textsuperscript{45}. However, the evidence supporting this mechanism of action is weak. Indeed, the effects of noradrenaline on feeding are complex (see above), and it can elicit feeding behaviour by acting on other hypothalamic areas, mainly the paraventricular nucleus\textsuperscript{46}. The role of dopamine on the regulation of food intake is also evolving, and it is certainly not restricted to the regulation of POMC neuronal activity\textsuperscript{147-149}.

Naltrexone, as well as its metabolites, is a long-acting opioid receptor antagonist (mainly \(\mu\)- and \(\kappa\)-receptors), which has been used for many years in clinics to treat alcohol and opioid dependences. It is thought to act synergistically with bupropion to release POMC neurons from the inhibitory feedback mechanism that limits their activity\textsuperscript{140}. Despite the nonspecific mechanism of action, the bupropion–naltrexone combination has shown efficacy in reducing body weight in Phase III clinical trials without presenting with major side effects\textsuperscript{150-152}. The FDA has recommended Contrave for approval, subject to favourable results from a reasonable and feasible cardiovascular outcomes trial\textsuperscript{153,154}. Orexigen Therapeutics started to recruit volunteers for such a trial in the first half of 2012, and it estimates potential approval in 2014.
Qsymia (developed by Vivus) is a pharmacological combination of controlled-release phentermine (see above) plus topiramate. Although phentermine was approved by the FDA in 1959 for the short-term treatment of obesity, it has not been studied in long-term clinical trials as a monotherapy. At the doses usually used to manage obesity, phentermine is thought to act mainly by modulating noradrenaline signalling in the brain. Topiramate has several mechanisms of action, and little is known about where and how it works. The FDA approved topiramate for the treatment of epilepsy in 1996 and for the prevention of migraine in 2004. Clinical trials showed that topiramate as a monotherapy induced weight loss in obese subjects with concomitant benefits in other metabolic markers (such as, improvements in blood pressure, glucose and insulin levels). However, topiramate has considerable side effects, which are mainly related to brain function; for example, difficulty with concentration, memory and attention, depression, nervousness, and psychomotor impairment. Additionally, topiramate also inhibits carbonic anhydrase, which can account for the paresthesias, taste alteration, decreased serum concentrations of bicarbonate and potassium, and increased risk of nephrolithiasis experienced in patients taking it. Topiramate also has a serious teratogenic potential, which has raised concerns over its use as an anti-obesity treatment.

Qsymia aims to utilize lower doses of these two drugs compared to the doses used in a monotherapy setting to maximize weight loss and minimize side effects. Three large randomized clinical trials have been completed using different doses of Qsymia against placebo (EQUATE, EQUIP and CONQUER). Qsymia was highly effective in reducing body weight and surpassed the FDA’s criteria for an anti-obesity pharmacotherapy. However, an FDA expert panel voted against approval of Qsymia owing to potential side effects. Of particular note, the FDA panel raised concerns regarding the possible occurrence of psychiatric events, cognitive dysfunction, increased heart rate and teratogenic effects, despite the fact that lower doses of Qsymia have a much safer profile. However, in February 2012 the Endocrinologic and Metabolic Drugs Advisory Committee reversed its position and recommended marketing approval of Qsymia by the FDA for the treatment of obesity. The committee voted 20 to 2 based on the favourable benefit–risk profile of Qsymia for the treatment of obesity. In July 2012, the FDA approved Qsymia with a risk evaluation and mitigation strategy. Of course, the long-term benefits and risks cannot be deciphered from an ad hoc panel’s decision. Rather it will arise from the exposure of subjects to the compounds for a prolonged period of time and unbiased assessment of clinical outcome. The FDA required Vivus to perform long-term cardiovascular outcome trials to further evaluate the effects of Qsymia.

The risk of anti-obesity drugs

There is an inherent catch-22 in the promotion of satiety as a means to treat obesity. The activation of POMC neurons in the hypothalamus is among the crucial mechanisms involved in the promotion of satiety, which leads to suppression of feeding and increased energy expenditure. The fundamental and long-term problem of such a strategy is that it relies on glucose metabolism within the hypothalamus and it promotes glucose utilization in the periphery (see below: “The ROS Paradox”). At first glance, this may seem to be a positive approach to follow (for example, lowering circulating glucose), but when the cellular consequences of these processes are considered, it becomes evident that maintaining satiety in the long run can be detrimental for tissue integrity and survival, as discussed below.

The ROS paradox. POMC neurons utilize glucose as the main fuel to generate action potentials. Whether the fuel for neuronal firing is glucose (POMC neurons) or fatty acids (NPY/AgRP neurons), the by-products of substrate oxidation are free radicals. However, recent data argue that ROS generation is not a simple by-product of substrate oxidation, but rather plays a critical role in the promotion of POMC neuronal firing. For example, when NPY/AgRP neurons are activated during a negative energy balance scenario and they utilize long-chain fatty acids, ROS levels are not increased in these cells despite increased firing and substrate utilization. However, if ROS generation is uncontrolled in NPY/AgRP neurons, neuronal firing of these cells is impaired. By contrast, during a positive energy balance scenario, when glucose-utilizing POMC neurons are firing at high levels, ROS is accumulating in these cells. Thus, sustained ROS levels in POMC neurons appear to favour satiety. We recently reported that glucose-induced ROS generation in POMC neurons is actually fundamental to the promotion of satiety.

The involvement of ROS in support of POMC neuronal function has implications for the long-term consequences of satiety promotion. The fact that satiety relies on continuous ROS production in the hypothalamus and an associated glucose-triggered ROS production in the periphery, suggests that sustained satiety, by default, will result in ROS-induced damage in central and peripheral tissues. One of the peripheral tissues that is more vulnerable to increased glucose load is the heart. The preferred fuel for cardiomyocytes is fatty acids, and when the fuel source shifts from fatty acids to glucose in cardiomyocytes, their ability to function properly in the long-term is impaired. Indeed, the reason for the most recent withdrawal of the obesity drug sibutramine was due to cardiovascular side effects. The preferred fuel for cardiomyocytes is fatty acids, and when the fuel source shifts from fatty acids to glucose in cardiomyocytes, their ability to function properly in the long-term is impaired. Indeed, the reason for the most recent withdrawal of the obesity drug sibutramine was due to cardiovascular side effects.

Strategies for future obesity therapies

Promoting pathways involved in negative energy balance scenarios. We believe that by promoting satiety, the majority of the current proposed anti-obesity drugs shift metabolic and behavioural adaptations to a homeostatic state that can lead to an increased risk for the development of other chronic diseases. That is, despite ameliorating obesity, these interventions may lead to other undesirable consequences such as cardiovascular disorders and cancer. This notion is supported by data showing that promotion of pathways involved with
hunger, rather than those that promote satiety, lead to more successful outcomes on long-term health. Hunger and related metabolic and physiological adaptations are default and mandatory elements in chronic calorie restriction. In this process, there is a shift from glucose metabolism to increased reliance on lipid oxidation for ATP generation, which together result in hypoinsulinaemia. In these conditions, cellular and tissue growth (anabolism) is suppressed, and all processes that depend on growth (including neoplasms) become compromised. Indeed, a negative energy balance, whether it be due to acute or chronic calorie restriction, seems to suppress cancer development in animals and humans.\textsuperscript{15,170–174}

As discussed above, calorie restriction extends lifespan in various organisms\textsuperscript{15}; although it has also been shown to have the opposite effect\textsuperscript{175}. In humans, even though it is difficult to analyse lifespan in a large cohort of calorie-restricted volunteers, there is increasing evidence...
to show that calorie restriction delays ageing and the development of chronic diseases. For example, calorie restriction decreased circulating levels of growth factors and hormones that are usually linked to increased cancer risk. Additionally, calorie restriction improved insulin resistance, reduced most of the coronary heart disease risk factors and improved diastolic function. Regular exercise also promoted similar benefits in humans. In contrast to regular exercise, although long-term calorie restriction in humans has been linked to substantial decreases in bone mineral density, subsequent studies have not found differences in bone quality between calorie-restricted volunteers and age-matched controls.

Overall, calorie restriction seems to promote substantial benefits on human health, many of which are shared with the effect of regular exercise.

Another important aspect of calorie restriction is its impact on reducing inflammation and downregulating immune responses. These can have a direct impact on brain areas that are important for the regulation of energy homeostasis (see above). Hypothalamic inflammation can occur in response to overnutrition in both rodents and humans, and so decreases in hypothalamic inflammation during calorie restriction could account for some of the beneficial effects of this regimen. For example, treatment of obese or overweight subjects with salsalate, which decreases inflammation, improved diastolic function and improved diastolic function.

Therefore, we propose that an alternative strategy to accomplish improvements in health in obese subjects is to promote the pathways that are involved in chronic positive energy balance. Together with the optimal diet and exercise programme, pharmacological treatments may help to improve health without severe side effects and also without promoting increases in energy intake and fat deposition. As is the case for type 2 diabetes, we believe that pharmacological treatment of obesity alone will not solve this epidemic, and it will have to be combined with strong behavioural interventions.

One compound has emerged as a potential lead for the development of future pharmacotherapies to treat obesity. Resveratrol, a natural phenol found in several plants, can improve the health profile of murine models and such effects resemble those of calorie restriction. More recently, in a small study with 11 obese subjects, 30 days of treatment with resveratrol indicated that this compound may act as a calorie restriction mimetic and enhance health indexes, despite not ameliorating obesity. However, the precise molecular mechanisms by which resveratrol promotes such beneficial health effects is unknown, because resveratrol is a ubiquitous activator of several intracellular pathways. It is important to consider that when a cellular pathway that is associated with calorie restriction is targeted, the true beneficial effect may arise only when it is promoted during the physiological window of a negative energy balance. For example, ghrelin administration is protective of the nigrostriatal dopamine system in models of Parkinson’s disease; however, this effect only occurs if ghrelin is administered in the absence of food. This concept is important to bear in mind when developing calorie restriction mimetics to treat metabolic disorders.

It is intuitive to think that calorie restriction increases hunger, and, therefore, the use of a calorie restriction mimetic would have a similar effect in obese patients, potentially leading to an even greater vulnerability to accentuated weight gain. However, if used only during periods when food is not available and in limited doses, temporary and minor alterations in the cellular and physiological mechanisms involved in metabolic disorders to pathways resembling calorie restriction could possibly soften the consequences of obesity without a major impact on appetite.

Promoting pathways involved in exercise. Another strategy that can be followed for the development of more effective anti-obesity agents is to pharmacologically promote the molecular pathways involved in the effects of regular exercise. For example, it was recently shown that exercise induces autophagy in muscle, and this mechanism is important for the beneficial effects of exercise during high-fat feeding in mice. Therefore, it is not surprising...
that developing an exercise mimetic could promote health in obese subjects (as well as in other chronic metabolic disorders). One example of such a compound is metformin, a well-known and broadly used diabetes therapy. Its mechanism of action has been linked to the induction of AMP-activated protein kinase (AMPK) signalling, as seen during exercise\textsuperscript{195,196}.

FIGURE 5 illustrates what we consider should be the approach in searching for effective treatments for obesity.

**Targeting central versus peripheral tissues.** Together, the data so far indicate that it is virtually impossible to alter behavioural aspects of feeding or energy expenditure by targeting the central nervous system without also having a major impact on many other brain regions associated with higher brain functions. When specific neurotransmitter systems are affected, such as the serotonin or noradrenaline circuits, the intervention, by default, will affect higher brain functions such as emotional states and sleep–wake cycles. Even if highly specific circuits in the hypothalamus that govern feeding (such as the NPY/AgRP neurons or POMC neurons) could be selectively manipulated, similar effects could be expected: the promotion of satiety would lead to a metabolic state of increased levels of circulating glucose, insulin and leptin with a concomitant decrease in the levels of circulating ghrelin and glucocorticoid. In turn, each of these metabolic signals generated from the periphery could have major direct effects on multiple sites of the central nervous system\textsuperscript{193,197–203}.

In accordance with this theory is the observation that melanocortin agonists, which act on melanocortin receptors to decrease food intake, have limited use owing to the promotion of hypertension\textsuperscript{204,205}. Similarly, selective manipulation of the peripheral nervous system by various means to promote weight loss will result in an altered constellation of circulating metabolic signals, which will consequently affect the central nervous system. Thus, from the perspective of long-term intervention, it is reasonable to conclude that either central or peripheral interventions will affect both the brain and peripheral tissues.

The targeted ablation of adipose tissue can reverse obesity in mice\textsuperscript{216} and non-human primates\textsuperscript{217}. Several obesity therapies that target peripheral tissues, such as the adipose tissue, as a means to avoid undesirable side effects on the central nervous system are under development. One such family of compounds that shows promise is the methionine aminopeptidase 2 (MetAP2) inhibitors. MetAP2 inhibitors are thought to inhibit angiogenesis in the adipose tissue that occurs during the course of obesity, resulting in decreased fat accumulation. Fumagillin is one of these compounds, and it has shown beneficial effects in murine models of obesity\textsuperscript{218}, although there is controversy surrounding its mechanism of action\textsuperscript{219}. In humans, Phase Ib studies have been completed, which have demonstrated the promising effects of MetAP2 inhibitors, and Phase II studies are scheduled to start in 2012. However, although this new class of compounds shows promising effects in reducing adiposity, these results are still preliminary. The finding that such compounds reduce food intake\textsuperscript{216} indicates that they may also cause changes in the brain. Peripherally acting cannabinoids are also in the pipeline of drug development (see above), but data are still premature.

More recently, brown adipose tissue (BAT) has emerged as a potential target for developing obesity therapeutics. The BAT is a specialized tissue that generates heat\textsuperscript{211} by uncoupling the proton flux through the mitochondrial membranes, via uncoupling protein 1 (UCP1)\textsuperscript{212}. Intriguingly, mutations in UCP1 have been identified in the long-lived naked mole rat, which is unable to self-regulate body temperature, and this lack of body temperature regulation may contribute to the extended longevity of these rodents\textsuperscript{213}. BAT has been identified in humans\textsuperscript{214}, and is associated with non-shivering thermogenesis\textsuperscript{215}. Cold-induced BAT oxidative metabolism is associated with an increase in glucose and free fatty acid uptake in BAT, but not in adjoining muscle and white adipose tissue, and leads to increases in whole body energy expenditure\textsuperscript{215}.

In humans, intracellular triglycerides are the main source of fuel for BAT activation\textsuperscript{216}; in mice, however, BAT is also able to take up extracellular triglycerides and regulate their clearance from the circulation\textsuperscript{216}. Promotion of the mechanisms that are involved in increasing energy expenditure by the BAT may be a future approach to combating obesity, as may behavioural interventions such as exposure to cold temperatures. Brown fat or brown-fat-like cells can also be found intermingled within white adipose tissue. A recent report\textsuperscript{217} described a new hormone produced by the muscle, called irisin, which is released into the circulation in response to exercise. Irisin acts in white adipose tissue to stimulate the expression of UCP1 and brown-fat development. This newly identified hormone was able to increase energy expenditure and has emerged as a novel target for exercise mimetics in BAT or brown adipose-like tissues.

**Benefit–risk profile for new therapies**

As the obesity epidemic continues to grow and the development of associated chronic disorders increases concomitantly, the need for alternative treatments of obesity has become more evident. The lack of pharmacological options and the persistent failure of anti-obesity drugs to promote weight loss without significant side effects raise questions about what should be viewed as an acceptable benefit–risk profile. Currently, the FDA’s criteria for the effectiveness of an anti-obesity drug are twofold: the treatment leads to a mean reduction in body weight of 5% (compared to placebo) and/or at least 35% of the subjects receiving the treatment (compared to placebo) maintain at least a 5% reduction in body weight compared with the baseline weight.

These factors highlight the emphasis that the FDA places on weight reduction in the search for drugs to treat obesity. One possible problem in applying such a paradigm to assess anti-obesity drugs is that it narrows the clinical evaluation of compounds to just those that promote weight loss. However, weight gain in individuals that go on to become clinically obese usually occurs over a long period of time, which also leads to complex metabolic adaptations. Most of the investigational
studies evaluate the acute or short-term effects of drugs on reducing appetite or food intake or promoting weight loss. However, it is possible that the metabolic and behavioural changes that will lead to a sustained reduction in body weight may take longer to occur, thus leading to a biased investigational approach. Additionally, the criteria proposed by the FDA do not take into account the improvements in morbidity and mortality, which may be even more important than weight reduction per se. It is possible that some treatments might help to treat and/or delay co-morbidities related to obesity, but not obesity itself. Thus, it seems imperative that the FDA considers additional and/or alternative factors (besides weight loss) in their approval process of new treatments for obesity.

Obesity levels in the United States and elsewhere continue to increase, with the expectation that not only a larger proportion of the population will become clinically obese, but that obese subjects will become even heavier. This, in turn, would lead to an increased risk of co-morbidities, and a consequent stratification of risk of obese patients to develop other chronic diseases based on the level of obesity. Thus, it is also anticipated that the FDA might evaluate the benefit–risk profile of distinct anti-obesity treatments on the basis of the degree of obesity of the patients, and eventually vote in favour of compounds with a higher risk of developing adverse side effects, but which can be beneficial to extremely obese individuals.

It is also noteworthy that a proportion of obese subjects do not exhibit clear co-morbidities, a condition sometimes classified as healthy obesity. However, recent reports have refuted this notion and indicate that obese patients without other metabolic disorders are at risk of developing such co-morbidities. We propose that pharmacological therapy for this subpopulation of patients should be discouraged. Instead, strong behavioural interventions (see below) and very close monitoring of their health conditions should be implemented.

Finally, two recent reports highlight the fact that behavioural interventions (such as increased exercise and decreased calorie intake) may be highly effective in reducing body weight in a subpopulation of obese individuals, and may be as effective as the best pharmacological interventions available on the market. Thus, there is still plenty of room to address new ways to pursue behavioural changes in obese patients with the aim of increasing physical activity and decreasing calorie intake.

We believe that intensive long-term behavioural interventions in a multidisciplinary team will be the most effective strategy to achieve sustained health in
Conclusions

As obesity is a major contributor to the development of chronic diseases, the need for more effective treatments is clear. However, when the biological mechanisms of behavioural and metabolic correlates of obesity are analysed closely, it becomes less apparent which paths should be taken by the pharmaceutical industry to develop therapeutics without the risk of adverse side effects.

Weight loss can be accomplished by many different ways using individual or a combination of compounds. Whether chemically it will ever be possible to shift energy balance by decreasing appetite, without negatively affecting long-term tissue function and survival is a question that will continue to tax both the pharmaceutical industry and the public. However, it is possible to envision alternatives, such as targeting the pathways involved in the beneficial effects of exercise and calorie restriction.

lipase inhibitor: a 12
lipid profiles in rats. 

Effects of tryptamine and 5-


REVIEWS

126 Aronne, L. J. et al. Efficacy and safety of CP-94,559, a selective 5,7-dihydroxytryptamine-1-methyl-
benzazepine (lorcaserin), a selective serotonin 5-HT
target receptor antagonist for the treatment of obesity.

127 Thomasen, W. J. et al. Lorcaserin, a novel selective
human 5-hydroxytryptamine2C agonist, in vitro and in vivo pharmacological characterization.


129 Fidel, C. M. et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight

130 Arena Pharmaceuticals. Lorcaserin Phase 3 Clinical
Trial in Patients with Type 2 Diabetes Shows Statistically Significant Weight Loss. Arena


132 Clemett, D. A., Punhani, T., Duxon, M. S., Blackburn, T. P. & Fone, K. C. Immunohistochemical


137 Bard, G. A. et al. Controlled-release phentermine/
topiramate in severely obese adults: a randomized
controlled trial (EQUIP). Obesity 20, 530–542
(2011).

138 Katz, A. Modulation of glucose transport in skeletal

139 Ritchie, R. H. & Delbridge, L. M. Cardiac hypertrophy,
metabolism and heart dysfunction.

140 Greenway, F. L. et al. Randomized controlled trial of bupropion SR-enhanced weight loss and maintenance.

141 Pessin, J. E. & Ingber, D. E. Energy balance regulation by FoxO1 and HNF

142 Bupropion SR enhances weight
loss and maintenance.

143 C2C12 myotubes by activating AMP-
kinase activity in neurons.

144 Augustris, A. S. et al. Loss of lipoprotein lipase-derived fatty acids leads to increased cardiac glucose metabolism and heart dysfunction.

145 Fiddell, A. Panel recommends more testing for obesity drugs.
nytimes.com/2012/05/30/health/panel-recommends-
mORE-testing-for-obesity-drugs.html (2012).

146 Ledford, H. Heart studies needed for obesity drugs.
FDA advisers say. Nature [online]. http://blogs.nature.com/2012/05/heart-studies-needed-for-obesity-


148 Anderson, J. W. et al. Bupropion SR enhances weight loss:


150 Pollack, A. Panel recommends more testing for obesity
nytimes.com/2012/05/30/health/panel-recommends-
mORE-testing-for-obesity-drugs.html (2012).

151 Ledford, H. Heart studies needed for obesity drugs.
FDA advisers say. Nature [online]. http://blogs.nature.com/2012/05/heart-studies-needed-for-obesity-

152 Gaddis, K. M. et al. Bupropion for weight loss:

153 Anderson, J. W. et al. Bupropion SR enhances weight loss:


155 Pollack, A. Panel recommends more testing for obesity
nytimes.com/2012/05/30/health/panel-recommends-
mORE-testing-for-obesity-drugs.html (2012).

156 Ledford, H. Heart studies needed for obesity drugs.
FDA advisers say. Nature [online]. http://blogs.nature.com/2012/05/heart-studies-needed-for-obesity-

157 Alzheimer’s disease and cognition in obesity.

Brochu, M. & Karelis, A. D. Acute cold exposure in humans.


Pavlova, B., Stala, L. & Scheel-Kruger, J. Evidence that GABA in the nucleus dorsalis raphe induces stimulation and eating.


Kohno, D., Sone, H., Minokoshi, Y. & Vadas, T. Ghrelin releases acetylcholine from a hypothalamic neurosecretory neuron.


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FURTHER INFORMATION

IUPHAR Database of Receptors and Ion Channels:

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