Most of the drugs that have entered the market for treating obesity were originally developed to treat psychiatric diseases. During the past decade, understanding of the neural circuits that underlie food intake has increased considerably. Different aspects of ingestive behavior such as meal termination, meal initiation and overconsumption of highly rewarding and palatable foods are modulated by different neuroanatomical structures. Integration of the action of many signaling molecules (e.g., hormones, neurotransmitters and neuropeptides) in these structures results in a response that, ultimately, modulates food intake. Thus, the type of drug required by an obese patient might depend on the individual cause of obesity. In this article, we summarize the neural circuits that regulate food intake and we provide a framework for understanding how obesity drugs function. Several potential drug targets are expressed in different neural circuits, implying that current and future obesity drugs act on partially overlapping systems that control food intake.

Introduction

Obesity is a risk factor for the development of diseases such as type II diabetes, stroke, cardiovascular disease and certain forms of cancer. We believe that being lean is a physical state to which many overweight individuals aspire. Dieting and exercising to lose weight require effort, willpower and persistence, making weight-reducing drugs an extremely attractive option (Table 1). The obesity epidemic has boosted the interest of the pharmaceutical industry in the development of anti-obesity drugs.

The discovery of drugs that have entered the market for the treatment of obesity is characterized by serendipity. Fenfluramine and sibutramine were discovered during the search for new antidepressants, and rimonabant was developed for smoking cessation, among other indications. When it was discovered that these drugs reduce food intake and induce weight loss, focus was turned towards the treatment of obesity [1–3].

Obesity is caused by energy intake (by ingestion) exceeding energy expenditure (by basal metabolic rate, diet-induced thermogenesis and exercise), with surplus energy stored in the form of fat. Over the past six decades, research has unraveled neural circuits that are implicated in the regulation of feeding. The entry of food into the stomach and intestines and the delivery of nutrients to the liver generate neural signals to the brainstem, via the vagal nerve, that have a role in the termination of a meal. The destruction of these neural inputs by vagal nerve cutting results in greater food intake (by increased meal size and frequency) [4]. Rats with knife-cut lesions between the brainstem and the midbrain (caudal–hypothalamus) do not increase meal size when food is restricted, as hungry rats normally do [5]. These data implicate the involvement of neural circuits in the brainstem during satiation (the process that limits meal size) but not during hunger, for which more-rostral neural circuits are required.

Electrical lesioning and stimulation studies in the hypothalamus have identified several nuclei that are important in the regulation of feeding behavior. Electrolytic destruction of the ventromedial hypothalamus increases feeding behavior (by causing meals to be eaten more frequently) and induces obesity [6–8]. In addition, lesions of the hypothalamic paraventricular nucleus (PVN) and the arcuate nucleus (ARC), which are highly interconnected nuclei, also result in hyperphagia and obesity [9,10]. Moreover, electrical stimulation studies of the lateral hypothalamus (LH) activated a motor program that elicits feeding and hoarding even when sated [11], emphasizing the role of this nucleus in meal initiation and hunger signaling. Overall, these data implicate the hypothalamus in the initiation of feeding behavior.

In addition to the homeostatic control of feeding, which involves the brainstem and the hypothalamus, animals – including humans – also eat because palatable food is rewarding. It is hypothesized that this is because of the hedonic value of food [12]. Food reward and the anticipation of meals implicate the nucleus accumbens (NAcc) – a brain structure that is important in reward processing – in the control of food intake [13,14]. The NAcc is connected to both cortical and limbic brain regions such as the amygdala and orbitofrontal cortex (OFC), the LH and ventral tegmental area (VTA) [15], and is implicated in motivation to eat [16].

In this article, we describe how peripheral signals that affect energy balance modulate neural circuits. We then delineate the functional role of these circuits and describe how they are targets for anti-obesity drugs. Although anti-obesity drugs also have peripheral modes of action, we focus on the central mechanisms by which they affect food intake.
Peripheral hormones involved in satiation

Gastrointestinal and pancreatic hormones such as cholecystokinin (CCK), amylase, insulin and glucagon are released during, or in anticipation of, meals and act to limit meal size (reviewed in Refs [17–19]). Other hormones that affect meal size are peptide YY (PYY), glucagon-like peptide (GLP)-1 and oxyntomodulin, which are released during, or in anticipation of, meals and act to limit meal size (reviewed in Refs [17–19]). Another peripheral hormone that affects energy balance is the adipocytokine leptin, which is hypothesized to signal adiposity rather than short-term fluctuations in energy stores [28]. Plasma leptin levels do not fluctuate with the ingestion of meals [29]. Low levels of leptin strongly trigger food intake and activate the hypothalamus [30]. Although leptin receptors have been detected in the brainstem [31], leptin might also reduce meal size through the activation of arcuate pro-opiomelanocortin (POMC) neurons, which project to the NTS–dorsal motor nucleus of the vagus (DMV) to modulate initiation and acts at the level of the vagus and in the hypothalamus [32]. In this way, hormones that signal adiposity (a longer-term energy balance signal) could affect satiety signaling.

Thus far, ghrelin is the only known peripheral hormone that increases food intake. This hormone, which is released from the stomach, is associated with hunger and meal initiation and acts at the level of the vagus and in the hypothalamus [33]. It has been shown that the ARC neuropeptides Agouti-related protein (AgRP) and neuropeptide Y (NPY) mediate the effects of ghrelin on food intake [34]. In the brainstem, ghrelin increases meal size and number [35].

**The ARC**

Two distinct neuronal populations in the ARC have been identified that are responsive to gastrointestinal and pancreatic hormones: POMC and NPY–AgRP neurons (reviewed in Ref. [26]) (Figure 2). The activity of these ARC neurons is also modulated by metabolites such as ghrelin, which increases meal size and number [36].

plasma levels of these hormones are highest after meal termination, they physiologically affect satiety (postponing initiation of the next meal) rather than satiation (ending a meal). Indeed, PYY3–36 postpones meal initiation, in addition to its effect on meal size [27]. Another peripheral hormone that affects energy balance is the adipocytokine leptin, which is hypothesized to signal adiposity rather than short-term fluctuations in energy stores [28]. Plasma leptin levels do not fluctuate with the ingestion of meals [29]. Low levels of leptin strongly trigger food intake and activate the hypothalamus [30]. Although leptin receptors have been detected in the brainstem [31], leptin might also reduce meal size through the activation of arcuate pro-opiomelanocortin (POMC) neurons, which project to the NTS–dorsal motor nucleus of the vagus (DMV) to modulate the response to CCK [32]. In this way, hormones that signal adiposity (a longer-term energy balance signal) could affect satiety signaling.

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Figure 1. Regulation of meal size. (a) Different patterns of gastrointestinal and pancreatic hormone release in plasma in relation to an ingested meal. Hunger refers to a feeling of appetite, whereas satiety refers to post-meal events that limit the chance of meal initiation. Satiation refers to the processes that limit meal size. (b) Brainstem review.
glucose and fatty acids [36,37]. Thus, the ARC is a key center for the integration of energy balance signals, propagating them further into the brain.

Following stimulation by leptin, POMC neurons release melanocortins and β-endorphin, which subsequently activate melanocortin (MC)3 and 4 receptors, and opioid receptors. The activation of MC receptors results in a decrease in feeding and an increase in energy expenditure [38]. Mutations in the leptin–melanocortin axis, such as those in leptin, leptin receptors, POMC or the MC4 receptor, are associated with the development of obesity (reviewed in Ref. [39]). Interestingly, another population of neurons in the ARC co-expresses AgRP and NPY. These orexigenic neurons are activated by ghrelin and low plasma levels of leptin [34], with higher levels of leptin inhibiting their activity. AgRP acts as an inverse agonist at MC receptors and, thus, MC receptor activity is tightly regulated by two neuropeptides – melanocortin and AgRP – with opposing activity [38].

A central role for the MC4 receptor in human energy balance is supported by the fact that heterozygote mutations in this receptor cause the most frequent monogenic form of child-onset severe obesity [40]. Thus, the MC4 receptor provides an interesting drug target for obesity treatment; MC receptor agonists are in the early phases of drug development for treating obesity and associated disorders [41].

Even before the discovery of leptin, NPY was known to stimulate food intake and decrease energy expenditure [42]. Recently, the NPY Y5 receptor antagonist MK0557 was shown to induce clinically insignificant weight-loss in humans [43]. In addition, the Y2–Y4 agonist TM30338 was shown to decrease food intake in obese human subjects [44]. ARC NPY–AgRP and POMC neurons project to several brain regions, including brain nuclei implicated in feeding such as the PVN, LH and NAcc. Here, so-called secondary leptin-responsive neurons propagate the metabolic signal further into the brain. The neuropeptides expressed in these neurons [e.g. melanin-concentrating hormone (MCH)] are targets for the treatment of obesity [45], and MCH receptor antagonists are in preclinical phases of development [46].

Peripheral hormones also engage hedonic neural feeding circuits

Highly palatable foods frequently overrule satiation and increase meal size [47]. Individuals who are susceptible to weight gain on palatable diets have a strong hedonic attraction to palatable foods and to eating [48]. Thus, feeding is strongly influenced by environmental factors, including stress, that engage higher brain areas in the control of food intake [49].

Recently, imaging studies have revealed roles for gastrointestinal hormones in the recruitment of hypothalamic and reward circuits. Leptin-deficient individuals showed neural activation of NAcc and associated neural circuits involved in reward processing after the visual presentation of food items; such activation was decreased when these individuals were treated with leptin [50]. In another study, the activation of brain areas was mapped in humans after PYY3–36 infusion. At high plasma concentrations of PYY3–36, which mimic the fed state, changes in neural activity within the OFC predicted feeding. By contrast, at low levels of PYY3–36, hypothalamic activation predicted food intake. Thus, the presence of a postprandial satiety factor switched the regulation of food intake from a homeostatic to a hedonic limbic cortical circuit [51]. It remains to be determined whether leptin and PYY3–36 directly modulate these limbic corticostriatal areas or whether the action of these hormones in other brain areas influences the limbic corticostriatal response. Regardless, these recent studies highlight the importance of limbic corticostriatal neural circuits for ingestive behavior in humans.

An interaction between homeostatic and hedonic regulation of food intake has also been demonstrated in rats [52]. In a rat model of diet-induced (saturated fat and sugar) obesity, the effort that an animal is willing to exert for sucrose is increased [52]. In addition to this increased motivation, we also observed that the willingness to work for sucrose predicted the response to a palatable-choice diet. Thus, being motivated to work for sucrose predicts obesity, which, in turn, increases food-motivated behavior – resulting in a loop of food motivation and obesity.

The NAcc

The NAcc has a key role in integrating four aspects of food intake: homeostatic, motivational, hedonic and cognitive [16] (Figure 3). The mesolimbic dopamine projection, which originates in the VTA and projects to the Nacc, mediates the motivational properties of food (i.e. the amount of time and effort that an animal is willing to invest to obtain food) [16,53,54]. Non-dopamine signals within the NAcc mediate the rewarding properties of food; thus, the stimulation of μ-opioid receptors or CB1 cannabinoid receptors enhances food reward [16,54–56], with the opioid and cannabinoid signals probably originating locally. Interestingly, opioid-mediated increases in the intake of high-fat food are insensitive to the blockade of NAcc dopamine receptors, indicating that the rewarding properties of food can override, or are mediated downstream from, motivational control over behavior [57].

In view of the role of CB1 cannabinoid receptors and μ-opioid receptors in food reward [16,54–56], it is not surprising that drugs such as rimonabant, naloxone and naltrexone function by reducing the palatability of food – an effect mediated within the NAcc. Interestingly, opioid and cannabinoid neurotransmission has been shown to be involved in the modulation of food intake [58,59], presumably by altering the rewarding and motivational properties of food: opioids and cannabinoids not only mediate food reward through their actions in the Nacc but also affect food motivation by stimulating dopamine-containing
neurons in the VTA [60,61]. In addition, cannabinoids seem to modulate food intake at other levels – including through the hypothalamus but also by acting peripherally in the gastrointestinal tract, adipose tissue and muscle tissue [62]. It has been proposed that endocannabinoids in the hypothalamus tonically activate CB1 receptors to maintain food intake and form part of the neural circuitry regulated by leptin [63]. The stimulation of CB1 receptors expressed on the vagal nerve reduces the effects of satiety signals in decreasing food intake [64,65]. However, recent behavioral analyses caution that the effects of rimonabant on food intake might be nonspecific [66].

**Inputs to the NAcc**

The VTA also sends dopamine projections to the basolateral amygdala (BLA), prefrontal cortex (PFC), OFC and ventral pallidum (VP). The OFC has been implicated in decision making on the basis of emotional information [67,68] and, in the context of feeding, was found to be activated in humans during choice of preferred items from a restaurant menu [69]. There are only sparse direct projections from the OFC to the NAcc, but the former indirectly innervates the latter through the BLA. OFC–BLA interactions have complementary roles in behavior: the BLA assigns value to environmental stimuli and the OFC subsequently uses this information to assist decision making [67,68]. Furthermore, the NAcc also receives viscerosensory and gustatory input from the PFC, the NTS and, indirectly, the PBN. In addition, the LH sends orexin- and MCH-containing projections to the NAcc (for review, see Ref. [16]).

**NAcc output systems**

Three main output pathways of the NAcc can modulate feeding. Two types of GABA-containing output neurons constitute the so-called direct and indirect pathways,
named on the basis of their direct and indirect projections to the ventral midbrain (including the VTA). There is little evidence to support a role for the direct pathway in feeding, whereas the indirect pathway has a major role. The cells of the indirect pathway contain dopamine D2 receptors, express enkephalin and project to the VP. The local release of enkephalin from these neurons probably mediates food reward [16]. Interestingly, the stimulation of μ-opioid receptors in the VP also enhances food reward, and opioid systems in the NAcc and VP interact in mediating these effects [56]. The third output source that modulates feeding is a projection to the LH from the shell subregion of the NAcc. Inhibition of these Nacc–LH neurons with GABA receptor agonists or AMPA receptor antagonists disinhibits LH feeding circuits [16]. According to current hypotheses, NAcc output neurons target the vicinity of LH neurons containing feeding-related peptides such as orexin and MCH [70,71].

From the LH, projections containing MCH and orexin run back to the NAcc, where infusions of these peptides enhance feeding [72,73]. Furthermore, LH orexin cells innervating the VTA also contribute to feeding [70]. Thus, the NAcc sends output signals to brain regions that mediate the motivational, in addition to the homeostatic and motor, aspects of feeding, making the NAcc a central area in the limbic circuitry that modulates feeding.

**Targeting obesity**

The discovery of leptin and other hormones involved in energy balance led to new opportunities for developing drugs to treat obesity (Table 2). Drugs that mimic the action of CCK, GLP-1, amylin and PYY3–36 could increase feelings of satiation and satiety, and antagonists of ghrelin receptors could decrease feelings of hunger (reviewed in Ref. [23]). Thus, these drugs would decrease appetite and caloric intake. CCK has an established role in satiation and satiety, but despite treatment with this hormone and its analogs limiting meal size, this is compensated for by an increase in meal frequency [74], which limits its therapeutic efficacy.

The neural circuits in the brainstem, hypothalamus and limbic corticostriatal system that are modulated by leptin...
also use several neurotransmitters; for example, GABA is used by NPY–AgRP neurons in the ARC and by MCH neurons in the LH [75]. Although POMC neurons have been reported to use GABA, they and LH orexin neurons also use glutamate and acetylcholine [76], which transmit signaling in corticostriatal systems. Thus, drugs such as topiramate and zonisamide, which are prescribed for epilepsy patients and shift the balance from glutamate to GABA signaling, also have efficacy in terms of decreasing body weight – potentially by affecting the regulation of energy balance at several levels in the brain, although peripheral modes of action of these drugs have also been proposed [77]. In contrast to GABA and glutamate, which function as neurotransmitters throughout the brain, the effects of monoamines (which are often targeted by current anti-obesity drugs) are anatomically more restricted.

5-Hydroxytryptamine
Neurons in the ARC are also modulated, at least in part, by 5-hydroxytryptamine (5-HT). Drugs affecting 5-HT that lower body weight and decrease food intake do so through a direct action on ARC neurons. For instance, the 5-HT-reuptake inhibitor and 5-HT-releasing agent fenfluramine stimulates POMC neuron firing [78]. 5-HT2C receptors on POMC neurons and 5-HT1B receptors on NPY–AgRP neurons have been implicated in mediating the effect of drugs such as fenfluramine and mCPP (chlorophenylpiperazine), which is a 5-HT2C-receptor-specific agonist, on energy balance [79]. Furthermore, blocking the output of POMC neurons by inhibiting MC receptor activity (e.g. by MC4 knockout and by co-treatment with the MC receptor antagonist SHU9119) limits the efficacy of fenfluramine at reducing food intake and body weight [80]. The ARC might not be the only site at which 5-HT drugs act because 5-HT neurons innervate the DMV and PBN, which have been implicated in the anorectic effect of mCPP and dexfenfluramine [79]. Moreover, 5-HT is one of the main transmitters in the gastrointestinal nervous system [81]. Thus, 5-HT drugs could directly affect digestion and energy uptake, or indirectly modulate the release of gastrointestinal hormones. In addition, 5-HT modulates, through various 5-HT receptors in a complex manner, the activity of the mesoaccumbens dopamine system [82]. For example, stimulation of 5-HT1B receptors on GABA interneurons in the VTA disinhibits dopamine neurons [83], whereas 5-HT2C receptors in the VTA exert a tonic inhibitory influence on dopamine activity [84].

The success of the fenfluramine–phentermine cocktail, before its withdrawal from the market, in terms of reducing body weight demonstrated the effectiveness of enhancing 5-HT and noradrenaline transmission to treat obesity. Sibutramine acts as a 5-HT- and noradrenaline-reuptake inhibitor, and drugs are currently in development that stimulate 5-HT transmission, particularly those that target the 5-HT2C receptor (e.g. APD356 and WAY-163909) [85,86].

Noradrenaline
Drugs such as sibutramine and amphetamine also stimulate noradrenaline neurotransmission [87]. Noradrenaline-containing fiber tracts from the brainstem project to the hypothalamus [88]. Activation of α1-, β2- and β3-adrenoceptors decreases food intake, whereas stimulation of the α2-adrenoceptor increases food intake. In PVN cells, the activation of α1-adrenoceptors by noradrenaline induces excitatory effects, which might inhibit food intake, whereas the activation of α2-adrenoceptors can induce inhibitory postsynaptic potentials in certain PVN cells; these potentials disinhibit descending satiety cells, thus stimulating food intake [89,90].

In addition, there is interplay between different catecholamine systems. For example, adrenaline receptors can modulate the firing rate of dopamine cells, but additive effects of dopamine- and noradrenaline-reuptake inhibitors have also been observed [91]. Interestingly, dopamine D1 and D2 receptors have been shown to exert opposing effects on noradrenaline release in the NAcc [92]. Amphetamine, which is a dopamine–noradrenaline-reuptake inhibitor and -releasing agent, has weight-reducing effects, which are probably mediated by increased noradrenaline signaling in the hypothalamus. A role for increased dopamine signaling caused by amphetamine in the NAcc is unlikely because enhanced NAcc dopamine activity is associated with an increase, rather than a decrease, in the motivation for feeding [16,53,54].

Histamine
The histamine system is also an attractive drug target for treating obesity [93]. Histamine neurons in the tuberomammillary nucleus project to hypothalamic nuclei such as the PVN and the VMN. Histamine H1 receptor antagonists increase food intake and body weight [94]. The H2 receptor is a presynaptic autoreceptor that inhibits histamine release but also acts as a heteroreceptor that regulates the release of other neurotransmitters. H3 receptor antagonists are being developed to reduce weight gain [95].

Concluding remarks
Research in recent years has further elucidated neural circuits that regulate food intake, providing a framework for understanding how drugs that suppress food intake function. Although these neural circuits do not act independently, from a drug discovery point of view, there are at least three levels at which ingestive behavior can be targeted: brainstem, hypothalamus and limbic corticostriatal system. These neural circuits use partially different signaling molecules. Anti-obesity drugs probably affect one or several of the systems that control food intake and energy expenditure. It is, therefore, unlikely that a single drug will be effective for treating all forms of obesity. This is reflected by the (combinations of) drugs that are in development for the treatment of obesity, which target multiple systems simultaneously – such as phentermine and topiramate (as in the drug Qnexa), bupropion and naltrexone (as in the drug Contrave), and zonisamide and buproprion [96].

The different neural circuits also indicate that the over-consumption of nutrients might have different causes. This was recently supported by genetic evidence; human genetic variance in the gene encoding CCK was shown to affect meal size, but not number of meals, in obese subjects,
whereas genetic variance in leptin and the leptin receptor explained, in part, the variation reported in meal frequency [97]. Better insights into the different causes of individual obesity could help to determine which (pharma-
co)therapy should be chosen. This also has implications for clinical phases of drug testing: the selection of obesity
patients for clinical trials should be based on better classi-
fication of the causes of obesity.
Side effects have been a drawback of anti-obesity drugs.
If the side effects are mediated by a different target than
that which results in weight loss, there is hope for the
development of drugs that act more specifically. The side
effect of the drug might also be inherently associated with
the anti-obesity effect of its target. Drugs acting through
the limbic corticostriatal circuit that are intended to inter-
fere with food reward might also decrease the pleasure
obtained from other rewards, which could explain why CB1
receptor antagonists are associated with depressive symp-
toms.
Obesity drug targets in the AP, the ARC and the vagus
nerve are of particular interest because they are in close
proximity to the bloodstream, and accessing these targets
might not require passage through the blood–brain bar-
rier. Thus, there are good prospects for the treatment of
obesity; there is a wealth of new drug targets, with candi-
date drugs in all stages of drug development.

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