The metabolic syndrome (MetS) encompasses medical conditions such as obesity, hyperglycemia, high blood pressure, and dyslipidemia that are major drivers for the ever-increasing prevalence of type 2 diabetes, cardiovascular diseases, and certain types of cancer. At the core of clinical strategies against the MetS is weight loss, induced by bariatric surgery, lifestyle changes based on calorie reduction and exercise, or pharmacology. This Review summarizes the past, current, and future efforts of targeting the MetS by pharmacological agents. Major emphasis is given to drugs that target the CNS as a key denominator for obesity and its comorbid sequelae.
CNS-targeting pharmacological interventions for the metabolic syndrome

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The metabolic syndrome (MetS) encompasses medical conditions such as obesity, hyperglycemia, high blood pressure, and dyslipidemia that are major drivers for the ever-increasing prevalence of type 2 diabetes, cardiovascular diseases, and certain types of cancer. At the core of clinical strategies against the MetS is weight loss, induced by bariatric surgery, lifestyle changes based on calorie reduction and exercise, or pharmacology. This Review summarizes the past, current, and future efforts of targeting the MetS by pharmacological agents. Major emphasis is given to drugs that target the CNS as a key denominator for obesity and its comorbid sequelae.

Introduction

The metabolic syndrome (MetS) encompasses a cluster of pernicious metabolic diseases that include visceral obesity, dyslipidemia, hyperglycemia, and hypertension (1). It is considered to be a silent killer owing to increases in the risk of heart attacks and related cardiovascular maladies (2). Additional evidence suggests a role for the MetS in the etiology of certain types of cancer (3) and cognitive impairments, particularly Alzheimer’s disease (4). Reducing body weight by 5%-10% substantially lowers all MetS components, and thereby the risk of fatal concomitant diseases (5). However, in most obese individuals, dieting and exercise fail to achieve persistent weight loss (6). These obese individuals could benefit from pharmacological interventions that decrease energy intake by enhancing satiety and reducing hunger and food cravings or increase energy expenditure and improve glycemic control (7).

Homeostatic and hedonic mechanisms underlying CNS-regulated metabolism

The CNS plays a pivotal role in regulating food intake and energy balance by adjusting daily energy requirements and sustaining bodily functions (8). The CNS receives satiation signals about energy input and availability from the gastrointestinal (GI) tract, as well as adiposity signals about energy storage from the white adipose tissue (WAT). These inputs are integrated in multiple centers within the CNS and incorporated into humoral and neuronal outputs to peripheral effector organs to tightly balance energy, glucose, and lipid metabolism (ref. 9 and Figure 1).

Homeostatic control centers in the hypothalamus and the brainstem are of particular importance for metabolic control.

Both of these brain areas are in close proximity to circumventricular organs (e.g., the median eminence or area postrema) that contain “leaky,” fenestrated capillaries to allow access of peripheral nutrients, metabolites, and hormones. The brainstem integrates short-term satiation signals from the GI tract either directly via the blood, or via input from vagal afferents that innervate the esophagus, stomach, and small intestine. The nerve endings respond to mechanical stimuli such as gastric dilatation, as well as to chemical satiety signals including the postprandially secreted GI hormones cholecystokinin (CCK) (10), glucagon-like peptide-1 (GLP-1) (11, 12), peptide YY (PYY) (13), and apolipoprotein A-IV (ApoAIV) (14). After binding to specific receptors on the vagal afferents, all of these signals converge in the nucleus of the solitary tract in the brainstem and are subsequently relayed to other brain areas to be finally incorporated into output signals to induce satiety.

The hypothalamus, particularly the arcuate nucleus (ARC), provides the pivotal sensing region for adiposity signals including leptin (15) and insulin (16), as well as for glucose. It also receives input from many other parts of the CNS, including the hindbrain. In the ARC, glucoregulatory and glucose-sensing neurons exist alongside two distinct and functionally antagonistic populations of neurons, each characterized by the expression of specific neuropeptides: the anorexigenic proopiomelanocortin-expressing (POMC-expressing) neurons, which are active during a positive energy balance, and orexigenic neurons, which coexpress agouti-related peptide (AgRP) and neuropeptide Y (NPY) and are active during a negative energy balance (17, 18). Neurons within the ventromedial, dorsomedial, and lateral hypothalamus and the paraventricular nucleus play an equally important role in controlling energy and glucose homeostasis. Together, they form a hypothalamic network that integrates with multiple neurocircuits outside of the hypothalamus in order to govern food intake, energy expenditure, glucose metabolism, and insulin sensitivity (18).

Homeostatic signals can be overpowered by nonhomeostatic cues of high hedonic valence (19). For instance, food enriched with fat and sugar can serve as potent reward stimulus. Consequently, highly rewarding food can initiate eating even in the absence of an...
energetic requirement. Several brain regions and neurotransmitter systems, including dopamine, serotonin, endocannabinoids, and opioids, are involved in the rewarding effect of food (20–23). Also, homeostatic signals such as leptin (24), insulin (25), and ghrelin (26) affect the brain reward system.

Reward in the context of ingestive behavior is built upon two separable functional components: first, the hedonic “liking” of food, which is related to pleasure and palatability and primarily involves the opioid and cannabimimetic systems in the nucleus accumbens, ventral pallidum, parabrachial nucleus, and nucleus of the solitary tract; and second, the “wanting” of food, which is related to appetite and the incentive motivation to eat and which is mainly related to the mesolimbic dopaminergic system with its projections from the ventral tegmental area to the nucleus accumbens and neural circuits involving the prefrontal cortex, amygdala, and hypothalamus (27–29).

Small-molecule CNS stimulants have been shown to tackle both components of the food reward system to ultimately suppress appetite. They have thus long been recognized as potential anti-obesity drugs, and were the first drugs in use, as outlined below.

**Principles and strategies in targeting the CNS-regulated metabolism**

In the 1920s, at a time before it was recognized that obesity accounts for a growing prevalence of harmful chronic diseases (30), attitudes concerning body weight began to shift in favor of a slimmer and athletic appearance. The perceptual change boosted the search for pharmacological strategies to facilitate weight loss. The first weight-lowering drugs were identified at a time when the mechanisms for food intake and weight control were largely unknown. Today we know that these appetite suppressants were mainly targeting monoamine neurotransmitter systems, which comprise a network of neurons within homeostatic and hedonic circuits of the brain that use monoamine neurotransmitters including the catecholamines dopamine and norepinephrine and the indolamine serotonin.

**Amphetamines, the first monoamine-targeting weight loss drugs.**

The first monoamine neurotransmitter-based weight loss drug was introduced in the 1930s, when Smith, Kline & French Laboratories synthesized and commercialized the two optical enantiomers of amphetamine: dextroamphetamine and levoamphetamine. Benzedrine contained the racemic mixture of both isomers, while Dexedrine only included the more potent dextroamphetamine. Originally advertised as a treatment for narcolepsy or postencephalitic parkinsonism, the cognitive-enhancing properties of amphetamine were long recognized (31). The observation of its potent appetite-suppressing side effect caused an erratic increase in the use of amphetamines as weight loss therapy (31, 32). Therapies arose that combined amphetamine with barbiturates to counter adverse side effects, such as insomnia, restlessness, and increased blood pressure (Dexamyel). Clorkotabs added thermogenic thyroid hormone to enhance weight loss, along with phenobarbital, aloin, and atropine sulfate to reduce undesirable adverse effects. Furthermore, N-methyl-substituted amphet-
action on the lateral hypothalamus was inhibited by local administration of dopaminergic and β-adrenergic antagonists, and by inhibitors of catecholamine synthesis (36). Amphetamine-induced anorexia was linked to a decreased hypothalamic expression of orexigenic NPY (37, 38). Amphetamine therapy was further shown to increase the expression of cocaine- and amphetamine-regulated transcript (CART) (39), a neuropeptide secreted by anorexigenic POMC neurons that decreases food intake (40).

Over time, the widespread consumption of amphetamines displayed a dark side. Multiple users experienced addictive behavior.
iors that went beyond a mere habituation to the effects of amphet-
amines. This addictive behavior was later assigned to the compet-
titive binding of amphetamine to the norepinephrine transporter
(NET) and the dopamine transporter (DAT) (41), which inhibited
the reuptake of endogenous norepinephrine and dopamine into
the presynaptic neurons. Amphetamines were further shown to
promote the reverse transport (efflux) of both monoamines, and to
slow catecholamine catabolism by inhibiting monoamine oxidase
(ref. 42 and Figure 2). In consequence, amphetamines induced an
amplification of the mesolimbic dopaminergic signal transmis-
sion in the striatum that profoundly escalated their rewarding and
addicting properties (43).

Past failures and evolution of monoaminergic drugs. The abusive
potential of amphetamines prompted the pharmaceutical indus-
try to develop structural derivatives with the goal of decreasing
the dopaminergic effect and the risk of habituation (31). Several
amphetamine congeners were developed and put into clinical
use, some of them with catastrophic results. Aminorex, phenyl-
propanolamine, and phenmetrazine — are approved for the treat-
mant naltrexone (ref. 44, Table 2, and Figure 3). Phase III clinical
trials are currently investigating the weight-lowering effects of
bupropion in combination with the anticonvulsant zonisamide
(ref. 45 and Table 2).

To overcome some of the challenges associated with amphet-
amines mainly acting on dopaminergic and noradrenergic circuit-
ry, novel classes of monoaminergic drugs were developed with a
preference for targeting the serotonin system. Serotonin (5-HT)
acts as a hormone and a neurotransmitter that regulates a variety
of physiological processes in the CNS and in peripheral organs.
Serotonin cannot cross the blood-brain barrier, which explains why
the peripheral and the central serotonergic systems are function-
ally separated. In the CNS, serotonin is synthesized and released
by serotonergic neurons, which are organized into nine nuclei (B1–
B9) and located in the midbrain and hindbrain areas. The most
substantial portion of total brain serotonin is synthesized in the
dorsal raphe (B7) of the brain stem, which has projections to hypo-
thalamic nuclei and other feeding-related forebrain areas (46).
Serotonin acts as a key anorexigenic signal mainly via two distinct
types of serotonin receptor–expressing neurons. First, the activa-
tion of serotonin 2C receptors (5-HT2CRs) on POMC neurons (47,
48) leads to an increased release of -melanocyte-stimulating hor-
mone (α-MSH) and subsequent stimulation of the melanocortin-3
and -4 receptor system (MC3/4Rs) (49). Second, the stimulation
of 5-HT3Rs on NPY and AgRP orexigenic neurons blocks the release
of NPY and AgRP and abolishes the inhibitory effect of GABA on
POMC neurons (50). In addition, 5-HT3 antagonists can potently
reduce food intake and body weight gain in rodents, but the under-
lying mechanisms remain to be determined (51). Overall, the sero-

<table>
<thead>
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<th>Reason for suspension</th>
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<tr>
<td>Case reports of intracranial hemorrhage and stroke in young women due to an unresolved mechanism (164)</td>
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<td>Psychoactive effects including euphoria, delusions, and paranoia (166)</td>
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<tr>
<td>Pulmonary hypertension and related death cases (168)</td>
</tr>
<tr>
<td>Valvular heart disease and pulmonary hypertension (52), likely as a result of 5-HT2B receptor activation, expressed on cardiac valvular interstitial cells (170)</td>
</tr>
<tr>
<td>Valvular heart disease and pulmonary hypertension (52)</td>
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<tr>
<td>See fenfluramine above</td>
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<tr>
<td>Excess of nonfatal cardiovascular events in the SCOUT trial (53)</td>
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<tr>
<td>Drug, first approval, DEA schedule</td>
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<td>-----------------------------------</td>
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<tr>
<td>Phendimetrazine (Bontril and generics), 1959, III</td>
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<tr>
<td>Diethylpropion (Tenuate and generics), 1959, IV</td>
</tr>
<tr>
<td>Phentermine hydrochloride (Adipex-P and generic), 1959, IV</td>
</tr>
<tr>
<td>Benzphetamine (Regimex, Didrex), 1960, III</td>
</tr>
<tr>
<td>Phentermine / topiramate ER (Qsymia), 2012, IV</td>
</tr>
<tr>
<td>Lorcaserin (Belviq), 2012, IV</td>
</tr>
<tr>
<td>Naltrexone/bupropion (Contrave), 2017, not scheduled</td>
</tr>
<tr>
<td>Tesofensine (NS2330), in phase III trials, not scheduled</td>
</tr>
<tr>
<td>Bupropion/zonisamide (Empatic) ER, in phase III trials, not scheduled</td>
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The Journal of Clinical Investigation

REVIEW SERIES: MECHANISMS UNDERLYING THE METABOLIC SYNDROME

The serotonin system continues to be a viable target for weight control and has led to the development of three classes of serotonergic drugs: serotonin-releasing agents, serotonin reuptake inhibitors, and selective 5-HT2CR agonists (Figure 2).

In the 1990s, fenfluramine, a first-generation serotonin-releasing agent, was combined with the sympathomimetic drug phentermine to create the weight-lowering drug Fen-Phen. This combination drug gained great popularity until an increasing number of valvular heart disease and pulmonary hypertension cases were associated with its use (52), ultimately causing the suspension of the combination drug as well as fenfluramine and its derivative dexfenfluramine (Table 1). Similarly, sibutramine, a selective reuptake inhibitor for serotonin and norepinephrine, was withdrawn owing to severe cardiovascular side effects (53) (Table 1). In 1995, the finding that 5-HT2CR agonists as well as cannabinoid receptor type 1. Endogenous opioids such as enkephalins, endorphins, or dynorphins are important in our response to and moderation of pain and pleasure, and influence both homeostatic and hedonic aspects of eating behavior. Similar actions on food intake are reported for endocannabinoids such as anandamide or 2-arachidonoylglycerol. Accordingly, both systems have been at the focus of the development of antiobesity drugs based on receptor antagonists. To date, only the 5-HT2CR agonist lorcaserin and the type 1 cannabinoid receptor (CB1R) antagonist rimonabant have gained market access as weight loss drugs, but psychiatric liabilities led to withdrawal of rimonabant. On presynaptic neurons, both drugs act via inhibition of presynaptic intracellular calcium influx and/or potassium efflux, which ultimately blocks calcium-dependent neurotransmitter vesicle release. Postsynaptically, the antagonist naltrexone inhibits μ- and to a lesser extent κ-opioid signaling to decrease neuronal activity. Rimonabant and naltrexone may further activate astrocyte cannabinoid and opioid signaling to modulate both presynaptic and postsynaptic neuronal processes.

Drugs targeting the opioid and cannabinoid system. Multiple homeostatic and hedonic control centers of food intake express δ-, κ-, and/or μ-opioid receptors as well as cannabinoid receptor type 1. Endogenous opioids such as enkephalins, endorphins, or dynorphins are important in our response to and moderation of pain and pleasure, and influence both homeostatic and hedonic aspects of eating behavior. Similar actions on food intake are reported for endocannabinoids such as anandamide or 2-arachidonoylglycerol. Accordingly, both systems have been at the focus of the development of antiobesity drugs based on receptor antagonists. To date, only the 5-HT2CR agonist lorcaserin and the type 1 cannabinoid receptor (CB1R) antagonist rimonabant have gained market access as weight loss drugs, but psychiatric liabilities led to withdrawal of rimonabant. On presynaptic neurons, both drugs act via inhibition of presynaptic intracellular calcium influx and/or potassium efflux, which ultimately blocks calcium-dependent neurotransmitter vesicle release. Postsynaptically, the antagonist naltrexone inhibits μ- and to a lesser extent κ-opioid signaling to decrease neuronal activity. Rimonabant and naltrexone may further activate astrocyte cannabinoid and opioid signaling to modulate both presynaptic and postsynaptic neuronal processes.

Drugs targeting the endocannabinoid system. In the late 1980s, the discovery of type 1 and type 2 cannabinoid receptors (CB1R and CB2R) and their endogenous ligands, the endocannabinoids, prompted the development of synthetic receptor agonists and antagonists in order to study the physiological function of the endocannabinoid system (ECS). Major attention has been paid to CB1R, which is the more abundant CBR in the CNS, particularly the hippocampus, basal ganglia, and hypothalamus (57). CB1R has also been identified in the GI tract, adipose tissue, skeletal mus-
cule, and cardiovascular system. One of the first described CB₁R inverse agonists (functional antagonist) was SR141716A (rimonabant) (ref. 58 and Figure 3). Chemically, rimonabant is a pyrazole and piperidine derivative, which upon daily i.p. (intraperitoneal) injection caused a profound reduction in body weight and food intake in lean rats (59). This finding was in line with the hypophagic and lean phenotype of mice lacking CB₁R (60). The weight-lowering effect of chronic rimonabant administration was further confirmed in diet-induced obese (DIO) mice (61) and in hypophagic Lep⁻/⁻ mice (62). Peripheral CB₁R antagonism was shown to contribute to the weight-lowering effect by enhancing lipolysis in adipocytes (63). The finding of reduced drug-seeking behavior in rimonabant-treated rats (64), and of an attenuated reward behavior in the CB₁R-KO mouse (65), provided strong evidence for the involvement of the ECS in motivation and hedonic behaviors.

Clinical trials confirmed the weight loss efficacy of rimonabant (20 mg) by showing a placebo-subtracted weight loss of 2.6 to 6.3 kg (66, 67). In addition, rimonabant caused a significant improvement in cardiovascular risk factors associated with the MetS (66, 67). In 2009, only three years after rimonabant was introduced to the European market, it was withdrawn based on novel data that linked it with depression and an increased risk for suicide (68). Accumulating evidence suggests that the mood-changing effects were caused by rimonabant’s inverse agonism, which rendered CB₁R in the amygdala and the ventral tegmental area constitutively active (69).

Recently, neutral CB₁R antagonists were developed. They lack the inverse agonist properties of rimonabant and the mood-changing effects, but continue to reduce weight gain and food intake (69). Whether such neutral CB₁R antagonists can represent a novel and safer alternative for the treatment of the MetS remains to be determined. Currently, a novel neutral peripheral cannabinoid antagonist (AM6545) with limited CNS penetration is under investigation (70).

Weight loss drugs that mimic WAT adiposity signals. The increasing understanding of the physiology of food intake and energy balance, and the pathophysiology of its dysregulation, resulted in the development of drugs that interfere with neuropeptide hormone signaling pathways, such as leptin-melanocortin signaling. The adipokine leptin is secreted in direct proportion to fat mass. As an adiposity signal it targets hypothalamic leptin receptors (LeprRs) and their downstream JAK2/STAT3, MAPK, and PI3K signaling to decrease food intake and increase energy expenditure in lean individuals. Its main action is driven by Lepr-positive AgRP (71, 72) and POMC (73, 74) neurons in the ARC. These first-order neurons sense leptin levels and numerous other hormonal and nutritional cues, and orchestrate the activation of melanocortin-3 and -4 receptor-positive (MC3/4R-positive) neurons in the paraventricular nucleus via direct synaptic innervation or via the concomitant release of the neuropeptide MC3/4R agonist AgRP or the MC3/4R antagonist α-MSH, a cleavage product of POMC (75). The fine-tuning of melanocortin tone by competing neuropeptides ultimately governs ingestive behaviors and behaviors beyond feeding (76–78) as well as non-CNS processes such as thermogenesis and WAT browning (79) or bone metabolism (80).

Subjects with loss-of-function mutations in leptin, Lepr, or downstream signaling components such as POMC or MC4R suffer from severe forms of morbid obesity and comorbid sequelae (81). Treatment with recombinant leptin can fully normalize body weight in leptin-deficient patients, but has no beneficial effects in patients with mutations in Lepr or its downstream signaling. Currently, only one recombinant leptin analog, metreleptin (Myalepta), is approved for patients with leptin deficiency. The search for downstream mediators of leptin deficiency resulted in the discovery of the orexigenic hypothalamic peptide melanin-concentrating hormone (MCH) (82). Pharmacological blockade of MCH receptor 1 (MCHR1) emerged as promising drug target for the treatment of obesity. However, years of efforts failed to validate the MCHR1 antagonist concept in phase I clinical trials (83).

While monogenic forms of obesity may often involve mutations in leptin melanocortin signaling, they remain rare and insignificant for the overall majority of obese individuals. These individuals have high leptin levels but exhibit leptin resistance, i.e., a relative inability of endogenous leptin or exogenous recombinant leptin to decrease food intake and body weight. Molecular underpinnings for the insensitivity toward leptin action are not entirely understood and need further investigation. Impaired leptin transport, Lepr trafficking, and leptin feedback signaling have been discussed (84), but more recent reports found little evidence for perturbed transport or signaling (85) and suggest fully intact CNS leptin action even in a state of diet-induced obesity (86).

Although leptin resistance remains an enigma, recent results have nonetheless encouraged reconsideration of therapeutic obesity strategies built on leptin sensitization. Increasing evidence has demonstrated that leptin sensitivity can be restored by pharmacologically induced weight loss (87–90). Notably, caloric restriction alone was not sufficient to restore leptin sensitivity (89). Pramlintide (Symlin), a synthetic analog of pancreatic amylin, sensitizes mice to the effects of leptin (90). Currently, pramlintide is clinically approved as adjunct therapy to mealtime insulin for the control of blood sugar. The combination of pramlintide with metreleptin resulted in a mean weight loss of 12.7% (90), and future weight loss therapies based on amylinomimetics or combinatorial therapies (e.g., with leptin) appear plausible. In addition, inhibition of the protein tyrosine phosphatase PTP1B, a negative regulator of the leptin and insulin signaling pathway, by trodusquemine (MSI-1436) and related analogs was shown to elic- it weight loss and leptin resensitization (91, 92).

Screenings for novel leptin-sensitizing molecules using the bio-informatical Connectivity Map (CMAP) tool led to the identification of the plant constituents celastrol and withaferin A, which increase leptin sensitivity and reduce body weight of obese mice (93, 94). The leptin-sensitizing properties of celastrol were later confirmed (95) and attributed to the hypothalamic inhibition of the protein tyrosine phosphatases PTP1B and TCPTP (96) and to an upregulation of the hypothalamic interleukin-1 receptor 1 (IL1R1) (97).

Restoring leptin sensitivity constitutes a challenge in the field of obesity and offers the unprecedented opportunity to develop an efficient weight loss and weight maintenance therapy. However, clinical data on these novel small-molecule sensitizing drugs are not yet available. They may further be complemented by additional drugs that elicit weight-lowering actions via the leptin-melanocortin system. These drugs include a new generation of small-molecule MC4R agonists such as setmelanotide (RM-493), which has
recently been successfully used to treat patients with Lepr deficiency (98) or with mutations in POMC (98, 99). Earlier small-molecule MC4R agonists had shown limited weight-lowering efficacy and/or severe cardiovascular liabilities, i.e., increases in blood pressure or heart rate (100, 101). Nonetheless, efforts continue to search for safe yet efficacious MC4R agonists, but their full potential as antiobesity drugs in obese patients remains underexplored.

**Weight loss drugs that mimic GI satiety signals.** Bariatric surgery is an effective albeit highly invasive option for obese subjects to achieve and sustain long-term weight loss and reductions in all MetS-related symptoms. The finding that bariatric surgery leads to profound changes in the secretion of gut hormones that have effects on food intake and glycemic control provided guidance to the search for new drugs that harness the CNS response to multiple satiety signals from the GI tract.

CCK mainly targets type 1 CCK receptors (CCK1Rs) on vagal afferent neurons to regulate satiety by terminating meals (102). Accordingly, CCK1R agonists were considered as promising antiobesity drugs. However, to date, their therapeutic utility has been limited by compensatory increases in meal frequency (103), by the development of drug tolerance in response to prolonged drug application (104), and by limited weight loss efficacy in phase II clinical trials (105). Additional efforts have been directed toward exploring antiobesity effects of gut-derived PYY3-36. However, discrepant results in rodents (106, 107) and high levels of nausea in humans (108) impeded further clinical developments. PYY3-36 has high affinity for the NPY receptor Y2, which is one of several NPY receptors that play important roles in the regulation of food intake. Major ongoing efforts have been directed toward finding centrally acting agonists or antagonists against Y1, Y2, Y4, or Y5 receptors, but progress to date has been limited (109).

Extensive efforts were directed toward the generation of drugs that mimic the actions of the incretin GLP-1 (Table 3). In the periphery, GLP-1 receptor (GLP-1R) agonists exhibit properties ranging from glucose-dependent stimulation of insulin secretion (110, 111), suppression of glucagon secretion (112), and preservation of β cell mass (113), to the reduction of hepatic glucose output (114), which together leads to improvements in glycemic control. GLP-1R signaling in the brain is crucially involved in the anorectic and weight-lowering effects of GLP-1 (115), which are in part mediated via direct activation of hypothalamic POMC/CART neurons in the ARC (116) or GLP-1R-positive neurons in the nucleus of the solitary tract of the hindbrain (117). Moreover, there is evidence that the inhibitory effect of GLP-1R agonists on food

### Table 3. Incretin mimetics for the treatment of obesity and type 2 diabetes

<table>
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<tr>
<th>Drug</th>
<th>First approval</th>
<th>Chemical specifications</th>
<th>Dosage</th>
<th>Major efficacy results in phase III clinical trials</th>
</tr>
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<tbody>
<tr>
<td>Exenatide (Byetta)</td>
<td>2005</td>
<td>Synthetic analog of exendin-4 with 53% homology to native GLP-1; increased half-life of 2.4 hours due to resistance to DPP-4–mediated degradation and an enhanced stability of the secondary structure (188)</td>
<td>s.c. (twice daily), 5 μg or 10 μg</td>
<td>DURATION-1 (30-week trial in inadequately controlled T2D patients, 10 μg twice daily) (189); HbA1c reduction from baseline: –1.5%; patients achieving HbA1C &gt; 7.0: 61%; mean weight loss from baseline: –3.6%</td>
</tr>
<tr>
<td>Lixisenatide (Adlyxin)</td>
<td>2013 (EU)</td>
<td>Synthetic analog of exendin-4 with a C-terminal deletion of a proline residue and the addition of 6 lysine residues, leading to a half-life of 3 hours (190)</td>
<td>s.c. (once daily), 10 μg or 20 μg</td>
<td>GetGoal-X (24-week trial in inadequately controlled T2D patients, 20 μg once daily) (191); HbA1c reduction from baseline: –0.8%; patients achieving HbA1C &gt; 7.0: 48.5%; mean weight loss from baseline: –2.8%</td>
</tr>
<tr>
<td>Exenatide ER (Bydureon)</td>
<td>2012</td>
<td>Exenatide (formulation in microsphere permits a prolonged absorption of exenatide from the subcutaneous depot allowing once-weekly dosing) (192)</td>
<td>s.c. (once weekly), 2.0 mg</td>
<td>DURATION-1 (30-week trial in inadequately controlled T2D patients, 2 mg once weekly) (193); HbA1c reduction from baseline: –1.9%; patients achieving HbA1C &gt; 7.0: 77%; weight loss from baseline: –3.7%</td>
</tr>
<tr>
<td>Albiglutide (Tanzem)</td>
<td>2014–2018 (discontinued for economic reasons)</td>
<td>Genetic fusion of a DPP-4–resistant GLP-1 dimer to human albumin, leading to a reduced renal clearance and an increased half-life of 5–8 days (193)</td>
<td>s.c. (once weekly), 30 mg or 50 mg</td>
<td>HARMONY-7 (32-week trial in inadequately controlled T2D patients, 50 mg once weekly) (194); HbA1c reduction from baseline: –0.78%; mean weight loss from baseline: –0.64 kg</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity)</td>
<td>2014</td>
<td>Fusion of a DPP-4-resistant GLP-1 dimer to a human IgG4-Fc heavy chain by a small peptide linker, leading to a reduced renal clearance and an increased half-life of 4 days (195)</td>
<td>s.c. (once weekly), 0.75 mg or 1.5 mg</td>
<td>AWARD-6 (26-week trial in inadequately controlled T2D patients, 1.5 mg once weekly) (196); HbA1c reduction from baseline: –1.42%; patients achieving HbA1C &gt; 7.0: 68%; weight loss from baseline: –2.9 kg</td>
</tr>
<tr>
<td>Liraglutide (Victoza or Saxenda)</td>
<td>2009</td>
<td>GLP-1 analog with 97% sequence homology to human GLP-1 with only 2 amino acid changes and the addition of a palmitic acid through a γ-glutamyl spacer; this lipid anchor causes strong albumin binding leading to a reduced renal clearance and a prolongation of the half-life to 13 hours (197)</td>
<td>s.c. (once daily), 0.6 mg, 1.2 mg, 1.8 mg, and 3.0 mg</td>
<td>LEAD-6 (26-week trial in inadequately controlled T2D patients, 1.8 mg once daily) (198); HbA1c reduction from baseline: –1.12%; patients achieving HbA1C &gt; 7.0: 54%; weight loss from baseline: –3.24 kg</td>
</tr>
<tr>
<td>Semaglutide (Ozempic)</td>
<td>2016</td>
<td>GLP-1 analog with 94% sequence homology to human GLP-1; it resembles liraglutide with an additional Aib8 to prevent DPP-4–mediated cleavage and a C18-based fatty acid chain connected to Lys26 through a miniPEG spacer leading to a half-life of 160 hours (199)</td>
<td>s.c. (once weekly), escalating dose up to 1.0 mg</td>
<td>SUSTAIN-7 (40-week trial in inadequately controlled T2D patients, 1 mg once weekly) (200); HbA1c reduction from baseline: –1.8%; patients achieving HbA1C &gt; 7.0: 79%; weight loss from baseline: –6.5 kg</td>
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</table>
intake goes beyond satiation and includes effects on food reward and motivation (118).

Native GLP-1 has a half-life of 2–3 minutes due to rapid degradation by dipeptidyl peptidase-4 (DPP-4), and several GLP-1R agonists have been developed to provide prolonged bioavailability. Depending on their half-life, they can be categorized either as short- or long-acting compounds (Table 3). The short-acting compounds include a synthetic version of exendin-4, exenatide (Byetta), and lixisenatide (Adlyxin). The long-acting compounds include albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide long-acting release (Bydureon), liraglutide (1.8 mg Victoza or 3.0 mg Saxenda), and semaglutide (Ozempic). Differences in the bioavailability of these compounds lead to important differences in their biological actions. Short-acting GLP-1R agonists are applied before a meal and cause a profound deceleration of gastric emptying and a reduction in postprandial glycemia (119, 120). In contrast, long-acting GLP-1R agonists exert stronger effects on fasting glucose levels by causing prolonged stimulation of insulin secretion, but the effects on gastric emptying are subject to rapid tachyphylaxis (121). Consequently, short-acting GLP-1R agonists could be more suitable for the treatment of patients suffering primarily from postprandial hyperglycemia, whereas long-acting GLP-1R agonists would be more suitable for patients with predominant fasting hyperglycemia (122).

Head-to-head comparisons of incretin mimetics so far rendered liraglutide as the most effective antglycemic GLP-1R agonist (123). The weight-lowering effect of GLP-1R agonists are dose-dependent and are most pronounced for high-dose liraglutide (3 mg) or semaglutide treatment. The latter caused a placebo-subtracted body weight loss of up to 16% in obese patients after 52 weeks of treatment (124), which for the first time comes close to the weight loss achieved by bariatric surgery. Remarkably, an alternative formulation of semaglutide is currently being evaluated as a precedent-setting peptide-based antiobesity/antidiabetes drug that is given by oral administration (125).

The most common adverse effects seen with all GLP-1 therapies include nausea, vomiting, and injection-site reactions. Importantly, GLP-1R agonists do not seem to negatively affect cardiovascular risk in type 2 diabetes (T2D) patients. Novel findings even suggest a cardioprotective action of GLP-1R agonists (126, 127), which may render them as the treatment of choice for MetS patients with cardiovascular symptoms.

A new generation of combinatorial peptide drugs. Structural similarity between GLP-1, glucagon, and the incretin glucose-dependent insulinotropic polypeptide (GIP) and their low-potency cross-reactivity at their respective receptors facilitated integration of each activity into sequence-intermixed unimolecular hybrids. GLP-1 has now been successfully combined with glucagon (128, 129) or GIP into unimolecular dual or tri-agonists (130, 131) in order to achieve synergistic reductions of adiposity and hyperglycemia. The first GLP-1-based multi-agonist was GLP-1 combined with glucagon action. Apart from its hyperglycemic effect, glucagon is a potent anorectic hormone. It mediates its weight-lowering effect mainly by acting on the CNS as a satiety signal to reduce food intake and by increasing energy expenditure and thermogenesis (132). Accordingly, it was hypothesized that glucagon would increase the weight-lowering effect of GLP-1, while the insulinotropic actions of GLP-1 would counter the hyperglycemic liability of glucagon. A large variety of GLP-1/glucagon receptor agonists have been developed and advanced to clinical evaluation (133). Two of them, SAR425899 and MEDI0382, were recently shown to induce clinically meaningful reductions in blood glucose and body weight in obese T2D patients (134, 135).

Like GLP-1, the incretin GIP is secreted from the gut in response to nutrient ingestion and promotes insulin secretion in a glucose-dependent manner. While insulinotropic effects of GIP are well defined, controversy exists regarding its weight-lowering potential. Surprisingly, the pharmacological targeting of the GIP receptor (GIPR) by agonists (130, 136–138) as well as by antagonists (139, 140) led to body weight loss in obese rodents. Notably, a recent study aimed at disentangling these contradictory observations by comparing the in vivo potency of several structurally diverse GIPR agonists with a potent long-acting antagonist (138). This study confirmed weight loss in DIO mice only for selective GIPR agonists, but not for the GIPR antagonist. A combination of GLP-1R and GIPR agonism may thus have superior effects on glucose tolerance and body weight loss. Indeed, several studies on GLP-1R/GIPR dual agonists favor beneficial effects of GIP activation in glycemic control in preclinical (130) and clinical trials (141, 142). Tirzepatide (LY3298176), a once-weekly GLP-1/GIP coagonist, was recently shown to be superior to the GLP-1R agonist dulaglutide in terms of body weight loss and improved glycated hemoglobin (HbA1c) in obese human subjects with T2D (142). Whether GIP-based coagonists can provide greater maximal clinical efficacy and fewer side effects compared with the current best-in-class GLP-1R mono-agonist, semaglutide, will require the development of additional coagonist variants and a thorough clinical evaluation.

Based on the promising clinical trials using GLP-1/GIP and GLP-1/glucagon dual agonists, it was predicted that tri-agonist molecules with agonism at all three receptors would provide superior metabolic improvements. Indeed, in DIO mice and obese monkeys, the reduction of body weight by a GLP-1/GIP/glucagon tri-agonist was greater than that by the same dose of a GLP-1/GIP dual agonist (131). The potential benefits of GLP-1/GIP/glucagon tri-agonism for the management of obese individuals with T2D are currently being investigated in clinical trials (133).

The above-described hybrid GLP-1–based multi-agonists are limited to structurally similar molecules. In addition to this approach, fusion peptides have been generated in which structurally diverse hormones or oligonucleotides can be connected to GLP-1 via a chemical linker. GLP-1 fusion molecules with other peptide hormones including gastrin, amylin, and CCK have been generated and shown to achieve enhanced metabolic efficacy (143–145). Finally, there are recently reported successes in developing hybrid drugs that use GLP-1 as a hormonally active peptide for the cell type–specific delivery of chemically conjugated nuclear receptor agonists (146, 147) and antisense oligonucleotides (148). For instance, GLP-1 targeting has been leveraged to deliver estrogen to metabolically relevant tissues, where it enhanced the body weight–lowering, insulinotropic, and islet-preserving effects of estrogen through complementary pharmacology. Importantly, endocrine toxicities in non–GLP-1R–expressing organs were absent, which highlights the cell type–specific delivery (146, 149). In preclinical mouse models, the combination of GLP-1 with the glucocorticoid receptor agonist
dexamethasone synergistically drove weight loss, likely mediated by a concomitant decrease in hypothalamic inflammation and GLP-1R-dependent activation of anorexigenic neurons (147). Currently, hybrid drugs are still in preclinical testing, and their clinical safety and efficacy remain to be determined.

Outlook and perspective

Weight reduction plays a fundamental role in managing the MetS. With emerging knowledge about neuronal pathways and peripheral feedback mechanisms controlling hunger and appetite, CNS-targeted weight loss pharmacology continues to evolve toward safer and more efficacious strategies. Currently, targeting strategies are mostly directed toward neuronal networks involved in the regulation of systemic metabolism. Built on the recent observation that systemic metabolism is also functionally controlled by non-neuronal cells in the CNS, including astrocytes, microglia, and tanyctyes (150), future targeting strategies may require a wider focus and extraordinary approaches. However, at present it remains largely elusive whether and how disrupted non-neuronal glial networks are functionally involved in the development of the MetS.

Novel therapies may be built on the hormonal signals and CNS pathways discussed above, but they may also use entirely different concepts and strategies. For instance, the past decades saw the discovery of multiple new, hitherto unknown peripheral factors such as meteorin (151), meteorin-like (152), adipsin (153), irisin (154), or GDF15 (155), which have all been linked to energy and glucose homeostasis. These novel factors may hold great promise as backbone for future therapies against the MetS. GDF15 appears to be at center stage in this competitive search for new antiobesity drugs, and has recently been reported as a potent anorexigen that exerts its weight-lowering action via the receptor GDNF family receptor a-like (GFRAL) (156–158). The large family of fibroblast growth factors (FGFs) has gained similar attention in the search for anti-obesity and antidiabetes drugs. Secreted by multiple tissues, FGF21 has been shown to exert weight loss and other multisystemic metabolic benefits in rodent models, and several FGF21 mimetics and receptor antagonists have hence entered the clinical testing phase (159). A single dose of FGF1 injected into the hypothalamus was further shown to induce a sustained and full remission of diabetic hyperglycemia in rodents (160, 161), which highlights the potential of FGF-based drugs in the fight against the MetS.

Overall, it is becoming increasingly clear that the complex and individual manifestation of the MetS requires pursuit of tailored therapies that ensure improved efficacy and safety in specific patient cohorts. Such novel therapies further require pioneering new pharmacological concepts and drugs that help close the current therapeutic gap and the relative lack of CNS-driven antiobesity drugs. Lastly, novel therapeutic concepts will greatly benefit from the increasing availability of large data sets and the development of advanced algorithms that facilitate an earlier and individualized patient diagnosis to enrich the prediction of individual risks for the development of comorbidities.

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