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Review Series

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The Journal of Clinical Investigation

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

Conflict of interest: RDD is currently an employee of Novo Nordisk. RDD is a cofounder of Marcadia, a company that pioneered the discovery of glucagon mixed agonists. It was acquired by Roche and later Novo Nordisk. He is a coinventor on multiple patents owned by Indiana University. MHT is a scientific advisor for Erx Biotech.

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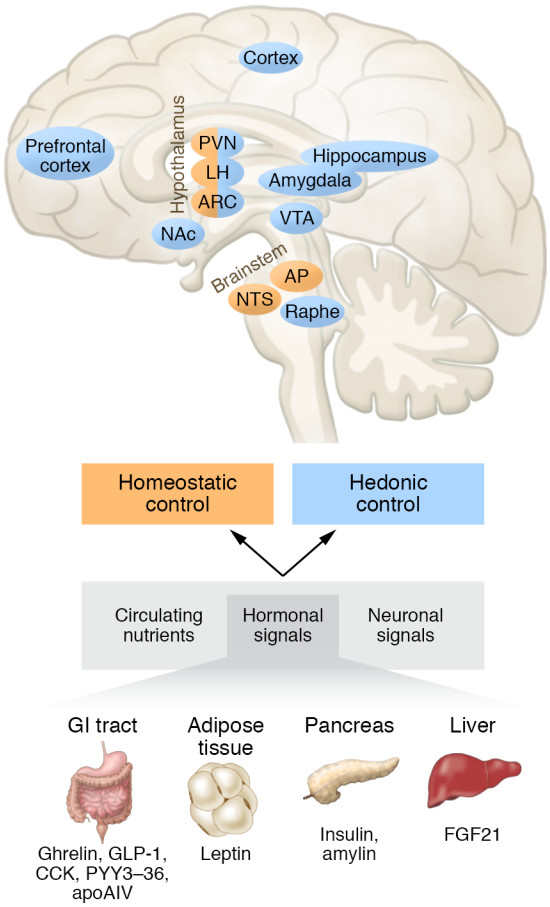

Figure 1. Homeostatic and hedonic control centers in the brain. Drugs targeting control of metabolism by the CNS act mainly via homeostatic and hedonic control centers that govern feeding behaviors, energy and glucose homeostasis, and body weight. The related brain areas are densely interconnected, and receive direct input from circulating nutrients such as glucose or fatty acids, peripheral neuronal networks, and hormonal satiation signals such as GLP-1 or amylin, or hormonal adiposity signals such as leptin. Within the homeostatic and hedonic control centers, the peripheral signals are integrated with sensory input, past experiences, and cues arising from the prevailing stress situation, emotional context, and mood. Ultimately, the signals converge in nuclei such as the hypothalamic paraventricular nucleus and lateral hypothalamus, and induce both adaptations to our ingestive behavior and brain stem–mediated changes to peripheral organ functions and our control of energy and glucose metabolism. AP, area postrema; ARC, arcuate nucleus; FGF21, fibroblast growth factor 21; GI tract, gastrointestinal tract; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; LH, lateral hypothalamus; NAc, nucleus accumbens; NTS, nucleus of the solitary tract; PVN, paraventricular nucleus; PYY3-36, peptide YY 3-36; VTA, ventral tegmental area.

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 cannabinoid 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 quickly 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 (Dexamyl). Clarkotabs 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-

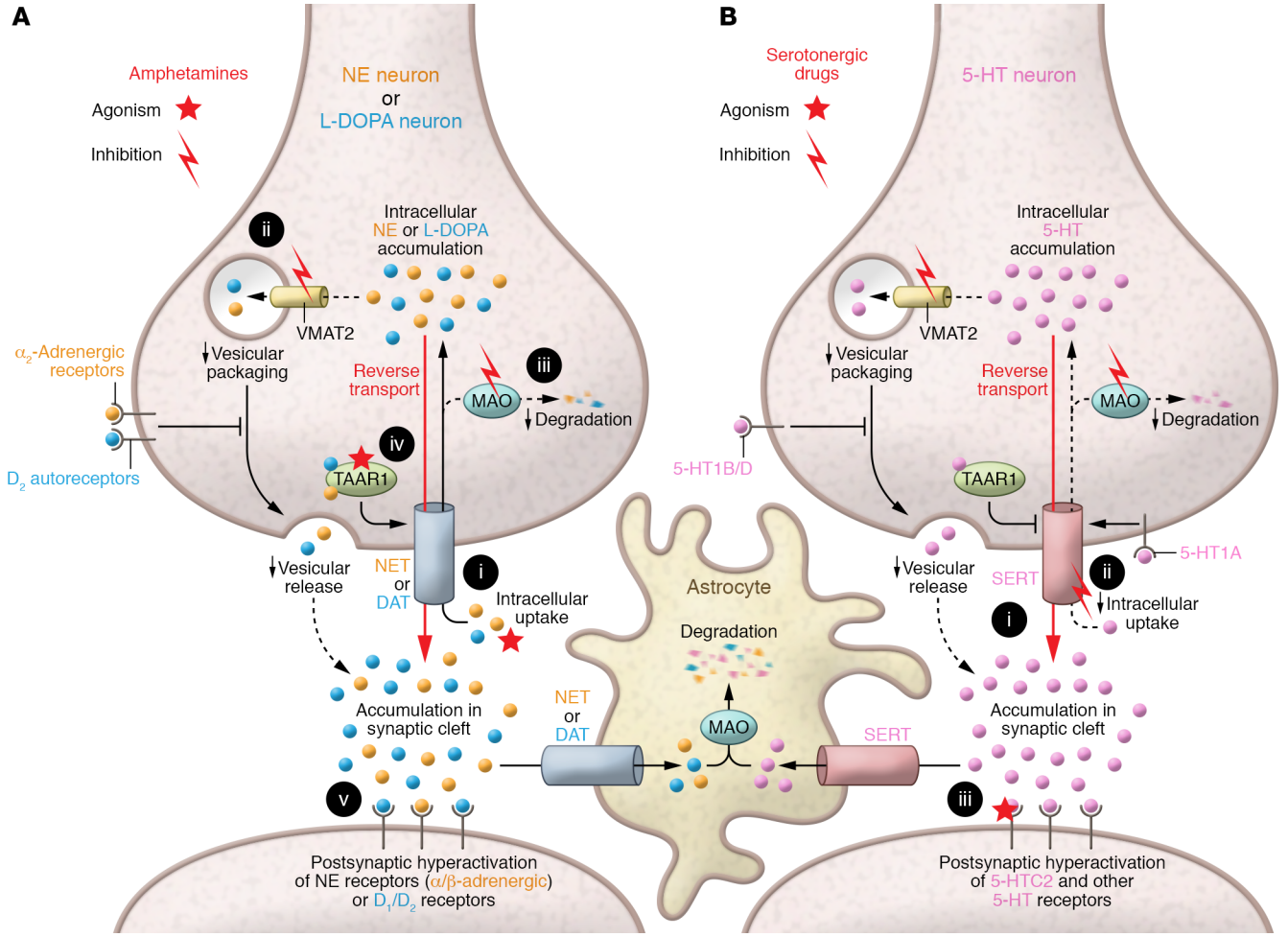

Figure 2. Central monoaminergic drug action. Pharmacological effects of amphetamines and their congeners are primarily mediated by increased synaptic release of monoamine neurotransmitters norepinephrine (NE), dopamine (DA), and, to a lesser extent, serotonin (5-HT). (**A**) (i) Amphetamines are competitive agonists for NET and DAT. (ii) Upon entering the presynaptic neuron, amphetamines bind to VMAT2, thereby inhibiting monoamine translocation from the cytosolic pool into storage vesicles. (iii) Amphetamines also weakly inhibit monoamine oxidase–mediated (MAO-mediated) monoamine breakdown, resulting in intracellular increase of monoamines. (iv) Amphetamines can further activate the intracellular trace amine-associated receptor 1 (TAAR1) to promote DA efflux. All processes contribute to reverse transport via NET or DAT, enhancing extracellular monoamine release. (v) Elevated monoamine release induces satiety and decreases feeding by activating postsynaptic α- and β-adrenergic (NE) and D1/D2 (DA) receptors. Increased DA signaling within the mesocorticolimbic system contributes to the addictive properties of amphetamines and their congeners. (**B**) Selective serotonergic drugs act either as (i) serotonin-releasing agents (SRAs), (ii) selective serotonin reuptake inhibitors (SSRIs), or (iii) selective 5-HT2C receptor agonists. SRAs (e.g., fenfluramine) increase synaptic 5-HT release, augmenting serotonergic function. Although SRAs' precise mechanisms remain unclear, they may be comparable to NE and DA releasers, i.e. reversing SERT- or VMAT2-mediated 5-HT transport. SSRIs (e.g., sibutramine) selectively bind SERT to inhibit 5-HT re-uptake. Postsynaptic 5-HT2C receptors appear to mediate the main effects of 5-HT on food intake and are the target of selective 5-HT2C receptor agonists such as lorcaserin. Presynaptic autoreceptor 5-HT1A and postsynaptic 5-HT1B, 5-HT2B, and 5-HT6 receptors may also contribute to the regulation of food intake by 5-HT. Monoaminergic drugs act at pre- and postsynaptic neurons, and they also interact with monoaminergic signaling on astrocytes. Astrocytic expression of NET, DAT, SERT, and metabolizing enzymes such as MAO can regulate monoamine levels in the synaptic cleft, neurotransmitter release from astrocytes and its transport into presynaptic neurons, and postsynaptic neuron activity.

amine (methamphetamine) derivatives, including Desoxyn and Methedrine, were hailed as weight loss drugs (33).

The weight-lowering effect of amphetamine was mainly assigned to a decrease in food intake. When humans were given amphetamine or placebo and required to maintain constant eating, the weight-lowering effect was eradicated (34). Later studies in rodents demonstrated that intraperitoneally injected amphetamine is less effective in suppressing appetite in rats with lateral hypothalamic lesions (35). Moreover, direct hypothalamic injections of amphetamine decreased food intake, and amphetamine 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 behav-

Table 1. Withdrawn monoaminergic antiobesity drugs

Drug	Mode of action	First approval	Withdrawn from market	Reason for suspension
Phenylproanolamine (Accutrim and generic)	Nonselective adrenergic receptor agonist and norepinephrine reuptake inhibitor (162, 163)	1910 as nasal anticongestive (US), 1976 as weight-lowering drug (US)	2000	Case reports of intracranial hemorrhage and stroke in young women due to an unresolved mechanism (164)
Phenmetrazine (Preludin)	Norepinephrine/dopamine-releasing agent (165)	1954 (EU)	1965	Psychoactive effects including euphoria, delusions, and paranoia (166)
Aminorex (Menocil)	Serotonin-releasing agent and uptake inhibitor (167)	1965 (EU)	1968	Pulmonary hypertension and related death cases (168)
Fenfluramine (Pondimin)	Serotonin-releasing agent by binding to the serotonin transporter (165, 169)	1964 (France), 1973 (US)	1997	Valvular heart disease and pulmonary hypertension (52), likely as a result of 5-HT_{2B} receptor activation, expressed on cardiac valvular interstitial cells (170)
Dexfenfluramine (Redux)	Serotonin-releasing agent and reuptake inhibitor (169)	1996	1997	Valvular heart disease and pulmonary hypertension (52)
Phentermine/Fenfluramine	Phentermine: releasing agent of norepinephrine and dopamine (171); fenfluramine: see above	1953 (phentermine), 1973 (fenfluramine), off-label combination	1997	See fenfluramine above
Sibutramine (Meridia)	Combined norepinephrine and serotonin reuptake inhibitor (172)	1997	2010	Excess of nonfatal cardiovascular events in the SCOUT trial (53)

iors that went beyond a mere habituation to the effects of amphetamines. This addictive behavior was later assigned to the competitive 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 transmission 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 industry 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, phenylpropanolamine, and phenmetrazine have been withdrawn from the market because of severe adverse effects (Table 1). At present, four amphetamine congeners — phendimetrazine, diethylpropion, phentermine, and benzphetamine — are approved for the treatment of obesity (Table 2). However, the safety concerns regarding their addictive potential were never fully reconciled. In 1977, all approved amphetamine-derived drugs were restricted to short-term use and were categorized as controlled substances by the US Drug Enforcement Administration (DEA), indicating their respective likelihood for physical addiction and mental dependence. In their capacity as CNS stimulants, their typical unwanted effects include, besides insomnia and nervousness, an increased heart rate. This particular side effect renders them counterindicated for patients with existing cardiovascular problems, including uncontrolled hypertension. Nevertheless, amphetamine congeners, and phentermine in particular, rank as some of the most prescribed antiobesity medications in the United States, either as monotherapy or as combination treatment with the anticonvulsant topiramate (Table 2). In 2017, bupropion, which chemically resembles the amphetamine derivative diethylpropion, was approved for weight loss in combination with the μ/κ-opioid receptor antagonist 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 amphetamines mainly acting on dopaminergic and noradrenergic circuitry, 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 functionally 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 hypothalamic 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 activation of serotonin 2C receptors (5-HT_{2C}Rs) on POMC neurons (47, 48) leads to an increased release of α-melanocyte-stimulating hormone (α-MSH) and subsequent stimulation of the melanocortin-3 and -4 receptor system (MC3/4Rs) (49). Second, the stimulation of 5-HT_{1B}Rs 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-HT_6R antagonists can potently reduce food intake and body weight gain in rodents, but the underlying mechanisms remain to be determined (51). Overall, the sero-

Table 2. Monoaminergic antiobesity drugs

Drug, first approval, DEA schedule	CNS-based mode of action	Dosage	Placebo-subtracted weight loss (PSWL)	Other effects
Phendimetrazine (Bontril and generics), 1959, III	Norepinephrine- and dopamine-releasing agent. After oral administration, ~30% of phendimetrazine is converted to the active metabolite phenmetrazine; based on its prodrug character and its slower release, phendimetrazine has a milder onset and likely less abusive potential than the *N*-demethylated metabolite phenmetrazine (165, 173)	p.o. 35 mg (2–3 times daily) or 105 mg (once daily); short-term treatment	7% weight loss relative to the baseline body weight after up to 32 wk of treatment (174)	CNS stimulant, which raises the heart rate and blood pressure; not recommended for MetS patients with a history of heart disease, pulmonary hypertension, or high blood pressure
Diethylpropion (Tenuate and generics), 1959, IV	Norepinephrine- and dopamine-releasing agent. The keto substitution at the β-carbon of the phenylamine backbone leads to a strong reduction of its dopaminergic action (165); an additional peripheral thermogenic effect that may contribute to weight loss was demonstrated in rats (175)	p.o. 25 mg (thrice daily) or 75 mg sustained release (once daily); short-term treatment	3.0 kg PSWL in studies ranging from 6 to 52 wk (176)	CNS stimulant, which raises the heart rate and blood pressure; not recommended for MetS patients with a history of heart disease, pulmonary hypertension, or high blood pressure
Phentermine hydrochloride (Adipex-P and generic), 1959, IV	Norepinephrine- and dopamine-releasing agent. As α-methylated amphetamine, it potently stimulates norepinephrine release (IC_{50} = 39.4 nM), with less effect on the release of dopamine (IC_{50} = 262 nM) (177)	p.o. (1–3 times daily), 15–37.5 mg; short-term treatment	Average PSWL of 3.5 kg in a 28-wk study (178) and in studies ranging from 2 to 24 wk (176)	CNS stimulant, which raises the heart rate and blood pressure; not recommended for MetS patients with a history of heart disease, pulmonary hypertension, or high blood pressure
Benzphetamine (Regimex, Didrex), 1960, III	Norepinephrine- and dopamine-releasing agent	p.o. (twice daily), 25–50 mg; short-term treatment	PSWL of 3.3 kg in studies with an average duration of 8.9 wk (176)	CNS stimulant, which raises the heart rate and blood pressure; not recommended for MetS patients with a history of heart disease, pulmonary hypertension, or high blood pressure
Phentermine/topiramate ER (Qsymia), 2012, IV	Synergistic action of the norepinephrine- and dopamine-releasing agent phentermine (see above) and the anticonvulsant topiramate. The weight-lowering and insulin-sensitizing mechanism of topiramate is uncertain; it may promote satiety and appetite suppression due to effects on neurotransmitters, neurotransmission, or inhibition of carbonic anhydrase (179, 180)	p.o. (once daily), 3.75 mg/23 mg, 7.5 mg/46 mg, 15 mg/92 mg; escalating dose regimen depending on individual response	EQUIP (52 wk, BMI ≥ 35): mean PSWL: 4.1 kg at 3.75 mg/23 mg, 10.7 kg at 15 mg/92 mg (181); CONQUER (56 wk, BMI ≥ 27 ± clinical comorbidity): mean PSWL: 6.7 kg at 7.5 mg/46 mg, 8.8 kg at 15 mg/92 mg (182)	Significant improvements in cardiometabolic risk factors and glycemic control (183)
Lorcaserin (Belviq), 2012, IV	Selective 5-HT_{2C} agonist that is thought to decrease food intake through the hypothalamic POMC-melanocortin axis without additional effects on energy expenditure (55)	p.o. (twice daily), 10 mg	BLOOM (52 wk, BMI ≥ 30 or BMI ≥ 27 ± clinical comorbidity); mean PSWL: 3.6 kg (184)	Improvement in multiple cardiovascular risk factors, including lipids, blood pressure, blood glucose, and renal function; decreases risk for incident diabetes, induces remission of hyperglycemia, and reduces the risk of microvascular complications (56)
Naltrexone/bupropion (Contrave), 2017, not scheduled	Synergistic action of the dopamine and norepinephrine reuptake inhibitor (bupropion) and the μ/κ-opioid receptor antagonist (naltrexone). By blocking the opioid receptor, naltrexone prevents autoinhibition of β-endorphin on POMC neuron activity	p.o. (twice daily), 8.0 mg/90 mg; long-term treatment	COR-I (52 wk, BMI ≥ 30 or BMI ≥ 27 ± clinical comorbidity); mean PSWL: 3.5 kg at 16 mg/360 mg ER, 4.7 kg at 32 mg/360 mg ER (44)	Weight loss associated with improvements in glycemic control and select cardiovascular risk factors in T2D patients (185)
Tesofensine (NS2330), in phase III trials, not scheduled	Serotonin-noradrenaline-dopamine reuptake inhibitor (186)	To be determined	Phase II (24 wk, BMI ≥ 30); mean PSWL: 4.5 kg at 0.25 mg, 9.1 kg at 0.5 mg, 10.6 kg at 1.0 mg (187)	Improvements in serum insulin, HbA1c, triglycerides, and cholesterol, but also an increase in blood pressure at the highest dose (187)
Bupropion/zonisamide (Empatic) ER, in phase III trials, not scheduled	Synergistic action of the norepinephrine- and dopamine-releasing agent bupropion with the anticonvulsant zonisamine. The weight-lowering effect of zonisamine is unknown and may include glutaminergic and GABAergic neurotransmission	To be determined	Phase II (24 wk, BMI ≥ 30 or BMI ≥ 27 ± clinical comorbidity); patients treated with a 360 mg/360 mg combination lost 9.9% of their baseline body weight (45)	Improvements in cardiometabolic risk factors such as serum triglycerides, fasting insulin, and blood pressure

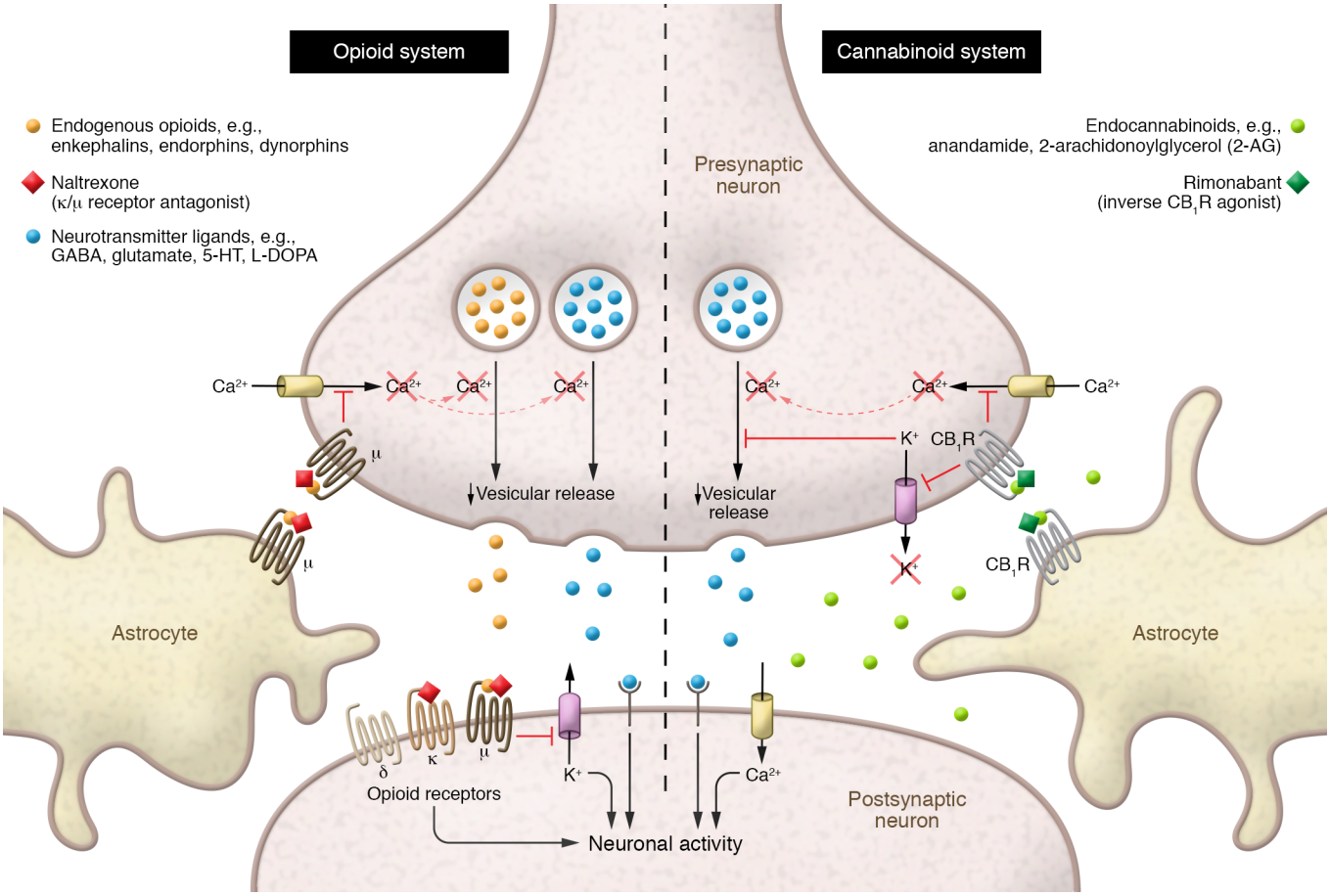

Figure 3. Drugs targeting the opioid and cannabinoid system. Multiple homeostatic and hedonic control centers of food intake express δ-, κ-, and/or μ-opioid receptors as well as cannabinoid receptor type 1. Endogenous opioids such as enkephalins, endorphins, or dynorphins are important in our response 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-arachidonoylglcerol. Accordingly, both systems have been at the focus of the development of antiobesity drugs based on receptor antagonists. To date, only the μ/κ-opioid receptor antagonist naltrexone and the type 1 cannabinoid receptor (CB_1R) 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.

tonin 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-HT_{2C}R 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-HT_{2C}Rs act as key regulators of satiety in rodents stirred the development of a third generation of serotonergic drugs (54). Lorcaserin is a selective 5-HT_{2C}R agonist that is thought to decrease food intake through the hypothalamic POMC-melanocortin axis (55) in the absence of serotonergic adverse events (Table 2). Importantly, lorcaserin treatment results in the reduction of multiple cardiovascular risk factors and leads to an improved glycemic control, which renders it applicable for the treatment of the MetS (56). The combined serotonin-noradrenaline-dopamine reuptake inhibitor tesofensine (NS2330) is currently being investigated in phase II clinical trials and may have weight-lowering properties beyond those of existing monoaminergic weight loss medications (Table 2).

Drugs targeting the endocannabinoid system. In the late 1980s, the discovery of type 1 and type 2 cannabinoid receptors (CB_1R and CB_2R) 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 CB_1R, which is the more abundant CBR in the CNS, particularly the hippocampus, basal ganglia, and hypothalamus (57). CB_1R has also been identified in the GI tract, adipose tissue, skeletal mus-

cle, and cardiovascular system. One of the first described CB_1R 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 CB_1R (60). The weight-lowering effect of chronic rimonabant administration was further confirmed in diet-induced obese (DIO) mice (61) and in hyperphagic Lep^{ob} mice (62). Peripheral CB_1R 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 CB_1R-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 CB_1R in the amygdala and the ventral tegmental area constitutively active (69).

Recently, neutral CB_1R 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 CB_1R 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 (LepRs) 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 monogenetic 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 antiobesity strategies built on leptin sensitization. Increasing evidence has demonstrated that leptin sensitivity can be restored by pharmacologically induced weight loss (87–90). Notably, calorie 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 elicit weight loss and leptin resensitization (91, 92).

Screenings for novel leptin-sensitizing molecules using the bioinformatical 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

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

Drug	First approval	Chemical specifications	Dosage	Major efficacy results in phase III clinical trials
Exenatide (Byetta)	2005	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)	s.c. (twice daily), 5 μg or 10 μg	DURATION-1 (30-week trial in inadequately controlled T2D patients, 10 μg twice daily) (189); HbA1c reduction from baseline: −1.5%; patients achieving HbA1C > 7.0: 61%; mean weight loss from baseline: −3.6%
Lixisenatide (Adlyxin)	2013 (EU)	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)	s.c. (once daily), 10 μg or 20 μg	GetGoal-X (24-week trial in inadequately controlled T2D patients, 20 μg once daily) (191); HbA1c reduction from baseline: −0.8%; patients achieving HbA1C > 7.0: 48.5%; mean weight loss from baseline: −2.8%
Exenatide ER (Bydureon)	2012	Exenatide (formulation in microsphere permits a prolonged absorption of exenatide from the subcutaneous depot allowing once-weekly dosing) (192)	s.c. (once weekly), 2.0 mg	DURATION-1 (30-week trial in inadequately controlled T2D patients, 2 mg once weekly) (189); HbA1c reduction from baseline: −1.9%; patients achieving HbA1C > 7.0: 77%; weight loss from baseline: −3.7%
Albiglutide (Tanzeum)	2014–2018 (discontinued for economic reasons)	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)	s.c. (once weekly), 30 mg or 50 mg	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
Dulaglutide (Trulicity)	2014	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)	s.c. (once weekly), 0.75 mg or 1.5 mg	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 > 7.0: 68%; weight loss from baseline: −2.9 kg
Liraglutide (Victoza or Saxenda)	2009	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)	s.c. (once daily), 0.6 mg, 1.2 mg, 1.8 mg, and 3.0 mg	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 > 7.0: 54%; weight loss from baseline: −3.24 kg
Semaglutide (Ozempic)	2016	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 space leading to a half-life of 160 hours (199)	s.c. (once weekly); escalating dose up to 1.0 mg	SUSTAIN-7 (40-week trial in inadequately controlled T2D patients, 1 mg once weekly) (200); HbA1c reduction from baseline: −1.8%; patients achieving HbA1C > 7.0: 79%; weight loss from baseline: −6.5 kg

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

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 antiglycemic 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 coagonists 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-1R 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 tanycytes (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 backbones 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 α–like (GFRAL) (156–158). The large family of fibroblast growth factors (FGFs) has gained similar attention in the search for antiobesity 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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