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Obesity: Current and Potential Pharmacotherapeutics and Targets

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Abstract

Obesity is a global epidemic that contributes to a number of health complications including cardiovascular disease, type 2 diabetes, cancer and neuropsychiatric disorders. Pharmacotherapeutic strategies to treat obesity are urgently needed. Research over the past two decades has increased substantially our knowledge of central and peripheral mechanisms underlying homeostatic energy balance. Homeostatic mechanisms involve multiple components including neuronal circuits, some originating in hypothalamus and brain stem, as well as peripherally-derived satiety, hunger and adiposity signals that modulate neural activity and regulate eating behavior. Dysregulation of one or more of these homeostatic components results in obesity. Coincident with obesity, reward mechanisms that regulate hedonic aspects of food intake override the homeostatic regulation of eating. In addition to functional interactions between homeostatic and reward systems in the regulation of food intake, homeostatic signals have the ability to alter vulnerability to drug abuse. Regarding the treatment of obesity, pharmacological monotherapies primarily focus on a single protein target. FDA-approved monotherapy options include phentermine (Adipex-P®), orlistat (Xenical®), lorcaserin (Belviq®) and liraglutide (Saxenda®). However, monotherapies have limited efficacy, in part due to the recruitment of alternate and counter-regulatory pathways. Consequently, a multi-target approach may provide greater benefit. Recently, two combination products have been approved by the FDA to treat obesity, including phentermine/topiramate (Qsymia®) and naltrexone/bupropion (Contrave®). The current review provides an overview of homeostatic and reward mechanisms that regulate energy balance, potential therapeutic targets for obesity and current treatment options, including some candidate therapeutics in clinical development. Finally, challenges in anti-obesity drug development are discussed.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

Keywords

homeostasis; obesity; pharmacotherapy; reward

1. Introduction

Obesity is a complex medical condition characterized by excessive, abnormal fat accumulation as a result of increased intake of energy-dense foods and decreased physical activity (WHO, 2015). The dramatic rise in obesity is attributed to genetic susceptibility, environmental factors such as availability of energy dense foods and sedentary life style lacking adequate physical activity. The prevalence of obesity in the Unites States during 2009-2010 was about 36% among adult men, 36% among adult women, and 17% among children and adolescents (National Health and Examination Survey, 2010). Projections based on current trends suggest an increase in obesity prevalence by 2050 to 60% in adult men, 40% in adult women and 25% in children (CDC Report, 2014). The rise in global obesity rates over the last three decades has been substantial, presenting a major public health epidemic in both developed and developing countries (Ng et al., 2014). A systematic analysis in 2013 of the global burden of disease revealed that more than 50% of the world's 671 million obese individuals live in 10 countries (ranked from most to least): United States, China, India, Russia, Brazil, Mexico, Egypt, Germany, Pakistan and Indonesia (Ng et al., 2014). Once considered a problem predominantly in western countries, obesity has become a global epidemic.

Obesity is a major contributor to the metabolic syndrome, a constellation of metabolic abnormalities including increased blood pressure, high blood sugar, excess body fat around the waist, high serum triglycerides, and low levels of high-density lipoproteins (Mokdad et al., 2001; Bloomgarden, 2002; Montani et al., 2002; Eckel et al., 2005; Grundy et al., 2005). The metabolic syndrome increases the risk for severe health problems including cardiovascular disease, type 2 diabetes and stroke (Eckel et al., 2005). Compared to non-obese women, obese women exhibit 60-fold greater probability of type 2 diabetes (Colditz et al., 1990). Overweight and obese men exhibit increased risk for ischemic and hemorrhagic stroke (Kurth et al., 2002).

In addition to the metabolic syndrome, obesity also increases risk for certain types of cancer. As examples, the contribution of obesity to cancer is as high as 40% for endometrial and esophageal adenocarcinoma (NCI, 2012). Current trends indicate that by 2030, there will be an additional 500,000 cases of cancer associated with obesity in the United States. Furthermore, the prevalence of neuropsychiatric disorders, particularly, dementia, depression and anxiety, is increased in obesity (Petry et al., 2008). Escalating rates of obesity and concomitant life-threatening disorders underscore the need for safe and effective strategies to treat this complex medical condition.

Multiple approaches and strategies are used for the treatment of obesity including lifestyle modifications (making healthy dietary choices and increasing exercise), bariatric surgery and pharmacotherapy (Polonsky and Klein, 2008). A healthy diet and increase in exercise are beneficial for both the prevention and treatment of obesity. Nonetheless, lifestyle

modifications require self-discipline and persistence to ensure and maintain the necessary beneficial weight loss. Moreover, effective lifestyle management of obesity results from a partnership between a highly motivated patient and a committed team of health professionals that may include a physician, a psychologist, psychiatrist, physical and exercise therapists, dietitians and other sub-specialists, depending on the patient's comorbidities (Polonsky and Klein, 2008).

Importantly, lifestyle management is just one component of a comprehensive approach to treat obesity and associated metabolic abnormalities (Smith et al., 2011). Surgical approaches, such as bariatric surgery, produce significant weight loss and ameliorate associated cardiovascular complications and type 2 diabetes in morbidly obese patients (Abdeen and le Roux, 2015). However, surgical procedures are invasive, expensive and have their own inherent risks and side-effects, including increased alcohol use, which suggests that these procedures facilitate an addiction transfer or exchange of palatable food reinforcers for an alternate reinforcer such as alcohol (Lent et al., 2013; Polston et al., 2013). Durability of diabetes remission and incident relapse following bariatric surgery was assessed from 1995 to 2008 in a large, population-based study of three integrated health care delivery systems in the United States (Arterburn et al., 2013). Although bariatric surgery resulted in complete diabetes remission within five years in 68% of severely obese adults, one-third of the individuals undergoing surgery relapsed within five years of initial remission (Arterburn et al., 2013). Further investigation is needed to understand the mechanisms underlying the cardio-metabolic effects of bariatric surgery and the long-term efficacy and safety of these procedures.

Given the limitations of lifestyle interventions and bariatric surgery, pharmacotherapeutic approaches for the treatment of obesity are important options. During the past 20 years, several anti-obesity drugs have been discovered, marketed and subsequently withdrawn from the market. Despite showing efficacy during initial stages of treatment, therapeutics for obesity have been accompanied by adverse side-effects following long-term use. Nevertheless, robust escalations in obesity and associated health complications constitute major driving forces for the discovery of novel targets and for the development of safe and effective weight loss therapeutics. The current review discusses potential therapeutic targets for obesity and provides an overview of current FDA-approved anti-obesity drugs, as well as several therapeutic candidates under clinical investigation. With respect to the discovery of novel therapeutic targets, employment of powerful molecular and genetic tools has increased our knowledge of central and peripheral mechanisms underlying homeostatic energy balance. The current review discusses interactions between homeostatic and nonhomeostatic hedonic mechanisms underlying excessive food intake. Centrally and perimpherally derived factors that regulate homeostatic and non-homeostatic hedonic mechanisms underlying food intake are summarized in Figure 1.

2. Homeostatic regulation of energy balance

Obesity results from a long-term positive energy balance, that is, increased food intake and decreased energy expenditure (Spiegelman and Flier, 2001). Homeostasis is the maintenance of equilibrium of energy balance through adjustments in physiological processes. Both

central and peripheral mechanisms are involved in the maintenance of body weight set point. Set point is a descriptor of long-term weight maintenance that involves coordinated adjustments in both intake and expenditure of energy that serve to stabilize an individual's weight at a specified level and to resist displacement from this level (Keesey and Hirvonen, 1997). Distinct neuronal circuits and signaling molecules within the hypothalamus and brain stem regulate energy balance. Peripherally-derived satiety, hunger and adiposity signals are integrated within hypothalamic and brainstem circuits to regulate feeding and metabolism. Satiety is a state of feeling full after eating such that eating behavior is inhibited subsequently (Blundell, 1991). The desire to eat in response to sensory stimulation is generally considered to represent appetite (Blundell, 1991). Biological stimuli leading to feeding are considered to represent hunger, which is triggered by *i)* a contracting empty stomach, *ii)* an empty small intestine, *iii)* the hormone ghrelin produced between meals and *iv)* other signals that affect the brain (Read, 1992; Sanger et al., 2010). Hunger initiates the motivation to seek and consume food (Harrold et al., 2012). Adiposity signals include feedback signals that are generated in response to food intake and accumulation of fat mass. Importantly, the majority of these central and peripheral mechanisms serve as potential therapeutic targets for obesity.

2.1. Central mechanisms

Hypothalamic neuronal circuits are implicated as the primary regulators of energy homeostasis and include the arcuate nucleus, which is located ventrally around the third ventricle of the brain (Wynne et al., 2005; Morrison and Berthoud, 2007). Arcuate nucleus neurons are called 'first order' neurons since peripheral adiposity factors act directly on these neurons (Hillebrand et al., 2002). Circulating adiposity signals such as leptin and insulin are transported actively across the blood brain barrier and bind to respective receptors on arcuate cell bodies. While the cell bodies of hypothalamic secretory neurons are localized in areas protected by the blood-brain barrier, their axon terminals are localized in the median eminence, which lacks a blood-brain barrier, thereby allowing central nervous system neurons to secrete hormones into the blood stream (Peruzzo et al., 2000). Activation of distinct neuronal populations within the arcuate nucleus either stimulates or inhibits food intake. From the arcuate nucleus, neurons project to 'second order' neurons in the paraventricular nucleus, lateral hypothalamus, perifornical area and dorsomedial hypothalamus (Schwartz et al., 2000). Second order neurons project to the nucleus tractus solitarius (NTS) in the brainstem and the dorsomotor nucleus of the vagus (Hillerband et al., 2002). NTS and area postrema integrate afferent signals and relay them to other regulatory brain centers, including the arcuate nucleus (Berthoud, 2002; Harrold et al., 2012). NTS lesion results in elevated consumption of palatable foods (Hyde and Miselis, 1983). Thus, hypothalamus and brain stem contain distinct neuronal circuits, signaling molecules and reciprocal connections regulating energy homeostasis. Previous reviews have provided comprehensive details regarding central mechanisms implicated in the regulation of energy homeostasis (Parker and Bloom, 2012; Williams and Elmquist, 2012; Sohn, 2015). The current section briefly introduces these mechanisms and provides insight regarding potential therapeutic targets for the treatment of obesity.

2.1.1. Arcuate nucleus: Orexigenic and anorexigenic systems—Within the arcuate nucleus, one subpopulation of neurons expresses orexigenic peptides including neuropeptide Y (NPY) and agouti-related protein (AgRP). NPY is co-expressed with AgRP in the arcuate nucleus, and these neurons project to second order neurons in paraventricular nucleus, ventral medial hypothalamus, dorsomedial hypothalamus and lateral hypothalamus (Elias et al., 1998; Hahn et al., 1998; Kalra et al., 1999). Repeated bilateral injection of NPY (235 pmol; 3 times/day for 10 days) into the paraventricular nucleus of rats resulted in increased food intake, body weight gain and body fat accumulation (Stanley et al., 1986). Orexigenic effects of NPY are mediated predominantly by G-protein coupled receptors (GPCRs), Y1 and Y5 within the paraventricular nucleus (Sohn et al., 2013). Also, γ-aminobutyric acid (GABA) is colocalized with NPY and AgRP in the arcuate nucleus (Broberger, et al., 1998; Cowley, et al., 2001). AgRP neurons express receptors for peripheral hormonal signals including insulin, leptin and ghrelin (Elmquist, et al., 1998; Willesen et al., 1999). Acute intracerebroventricular (ICV) injection of AgRP (1.5–15.0 μg/10μl) increased in a dose-dependent manner cumulative food intake and body weight in rats (Ebihara et al., 1999). Also, leptin (2 μg, ICV) inhibition of food intake and body weight was reversed dose-dependently by co-injection of AgRP (0.15-1.5 μg, ICV).

Another subpopulation of arcuate nucleus neurons expresses anorexigenic peptides including α-melanocyte stimulating hormone (α-MSH) and cocaine and amphetamine regulated transcript (CART) (Mains and Eipper, 1980; Elias et al., 1998). The anorexigenic role of CART is emphasized by the demonstration that CART-deficient mice fed a high-fat diet showed increased food consumption, body weight and fat mass relative to wild-type littermates (Asnicar et al., 2001). Once cleaved from precursor hormone pro-opiomelanocortin (POMC), α-MSH binds to melanocortin-4 receptors (MC4Rs) (Eipper and Mains, 1980). Acutely, α-MSH (1 nmol/10 μl, ICV) decreases food intake in rats (Rossi et al., 1998). Mutations in MC4R are associated with morbid obesity in humans (Krude et al., 1998; Yeo et al., 1998), consistent with findings that MC4R deficient mice exhibit an obesity phenotype (Huszar et al., 1997). MC4R signaling is necessary for Roux-en-Y gastric bypass surgery-induced weight loss, decreases in food intake and food preference, and increases in energy expenditure (Hatoum et al., 2012). Compared to wild-type mice, MC4R knockout mice exhibited decreased weight loss after Roux-en-Y gastric bypass surgery (Hatoum et al., 2012). Chronic treatment with a highly-selective, novel, MC4R peptide agonist, RM-493 (Ac-Arg-Cys(1)-D-Ala-His-D-Phe-Arg-Trp-Cys(1)-NH2; 0.5 mg/kg/day for 8 wk, subcutaneous (SC)), transiently decreased (35%) food intake, resulted in weight loss (13.5%), decreased adiposity, and improved glucose tolerance in a non-human primate model of diet-induced obesity (DIO) (Kievit et al., 2013). Currently, RM-493 is in Phase II clinical trials to evaluate its safety and efficacy in obese human subjects. Taken together, arcuate nucleus dysfunction, including increased activity of NPY/AgRP versus POMC neurons, at least in part, underlies some forms of obesity, and moreover, NPY, AgRP, MC4R and CART may serve as viable targets for obesity therapeutics.

2.1.2. *Lateral hypothalamus: Orexigenic systems*—Within the lateral hypothalamus/perifornical area, second-order neurons express orexigenic neuropeptides, orexin (hypocretin) and melanin-concentrating hormone (MCH) (Qu et al., 1996; de Lecea

et al., 1998; Sakurai et al., 1998). Prepro-orexin, a 130 amino acid precursor peptide, is processed to orexin A and orexin B, which are 33 and 28 amino acid peptides, respectively (Sakurai et al., 1998). Administration of orexin A and B (3 and 30 nmol/5 µl, ICV) promotes hyperphagia in rats (Sakurai et al., 1998). Orexins activate two GPCR subtypes, the orexin-1 receptor that is highly expressed in the ventral medial hypothalamus and the orexin-2 receptor that is expressed predominantly in the paraventricular nucleus (Trivedi et al., 1998). Orexin A binds with high affinity to both orexin-1 and -2 receptors, whereas orexin B selectively binds to orexin-2 receptors (Sakurai et al., 1998). Prepro-orexin knockout mice and orexin-neuron ablated transgenic mice exhibit a hypophagic phenotype (Hara et al., 2001; Willie et al., 2001). Repeated intraperitoneal (IP) administration of the orexin-1 receptor antagonist, SB334867-A (1-(2-methyl-1,3-benzoxazol-6-yl)-3-(1,5-naphthyridin-4-yl) urea hydrochloride; 30 mg/kg for 2 wk, IP) to genetically obese ob/ob (leptin-deficient) mice decreased cumulative food intake, body weight, fat mass gain, fasting blood glucose and plasma insulin levels, compared to vehicle-treated ob/ob mice (Haynes et al., 2002). Also, acute treatment with SB334867-A increased energy expenditure in ob/ob mice, determined by indirect calorimetry.

Similar to orexins, central administration of MCH (5 or 30 µg, ICV) increased food intake in rats (Qu et al., 1996). MCH acts through two GPCRs, MCH1 and MCH2 receptors (Pissios et al., 2006). In mammals, MCH1 and MCH2 receptors are expressed in frontal cortex, amygdala, nucleus accumbens, arcuate nucleus and ventral medial hypothalamus (Hervieu et al., 2000). However, non-primate animal models lack MCH2 receptors, limiting their usefulness in understanding the physiological role of MCH2 (Tan et al., 2002). MCH1 receptor knockout mice are lean, resistant to DIO, exhibit hyperactivity and exhibit hypermetabolism compared to wild-type controls (Chen et al., 2002; Marsh et al., 2002; Pissios, 2009). Taken together, orexin-1 receptor antagonists and MCH1 receptor antagonists appear to have therapeutic potential for the treatment of obesity.

2.1.3. Paraventricular nucleus: Anorexigenic systems—In contrast to lateral hypothalamus, paraventricular nucleus neurons express anorexigenic peptides including the peptide hormones, thyrotropin-releasing hormone and corticotrophin-releasing hormone, as well as brain derived neurotrophic factor (BDNF; Fekete et al., 2000; Kernie et al., 2000; Sarkar and Lechan, 2003). Central administration of corticotrophin-releasing hormone in rats (3 mg/rat, ICV) reduced food intake, compared to vehicle-treated rats (Vergoni et al., 1999). Also, thyrotropin-releasing hormone (4, 16 and 64 mg/kg twice/day, SC) dose-dependently decreased food intake in rats (Choi et al., 2002). The effect of BDNF was assessed on NPY-induced feeding in rats (Wang et al., 2007). The paraventricular nucleus is an integral site for the anorectic effects of BDNF. NPY (100 pmol/0.5 µl) was infused directly into the rat paraventricular nucleus 4 h after infusion of BDNF (0.1-0.5 µg/0.5 µl). NPY increased food intake, and BDNF (0.3 and 0.5 µg) decreased NPY-induced feeding by 56% and 82%, respectively, compared to the NPY-infused controls.

In a study using agouti lethal yellow mutant mice (A^y), ectopic expression of the agouti protein (a homologue of AgRP) produced hyperphagia and obesity (Miller et al., 1993). Importantly, the phenotype of the MC4R null mutant mice is identical to that of the A^y mutant mice (Miller et al., 1993). Moreover, agouti protein is reported to be an antagonist of

MC4R, but not of the melanocortin-3 receptor (Lu et al., 1994; Huszar et al., 1997; Chen et al., 2000). In A^y mutant mice fed a high-fat diet, which have disrupted MC4R signaling, BDNF (200 ng/µl for 14 days, ICV) suppressed daily food intake and body weight gain, compared to the vehicle-treated control mice (Xu et al., 2003). These results suggest that BDNF may regulate energy homeostasis downstream of MC4R. Additional animal and human studies exploring these systems may provide novel targets for obesity drug discovery.

2.1.4. *Hindbrain mechanisms*—Hindbrain neurons integrate behavioral, autonomic and endocrine responses to regulate energy balance (Grill and Hayes, 2012). Within the brainstem, the dorsal vagal complex plays an important role in relaying peripheral signals via vagal afferent fibers from the gut to the hypothalamus (Bailey, 2008). The dorsal vagal complex consists of the dorsal motor nucleus of vagus, area postrema and NTS (Stanley et al., 2005). The NTS is considered an integral part of the brain stem that receives inputs and processes peripherally-derived energy-status signals such as leptin, ghrelin, and glucose as well as signals from hypothalamic neurons (paraventricular nucleus, lateral hypothalamus and arcuate nucleus) (Grill and Hayes, 2012). Additionally, NTS neurons in caudal regions project to vagal efferent neurons in the dorsal motor nucleus of vagus that regulates parasympathetic gastrointestinal responses, including insulin secretion and gastric emptying, and project to other subregions of the hypothalamus that regulate neuroendocrine responses (Grill and Hayes, 2012).

Monoamine neurotransmitters, norepinephrine (NE) and serotonin (5-HT), are synthesized in brain stem and regulate food intake (Schwartz et al., 2000). NE is synthesized by discrete neuronal populations in brain stem, including the dorsal vagal complex and the locus coeruleus (Foote et al., 1983; Palkovits, 1999). Neuronal fibers from these areas project to the hypothalamus, thalamus, cortex and spinal cord (Foote et al., 1983; Palkovits, 1999). Genetically obese ob/ob mice exhibit increased NE levels in paraventricular nucleus and lateral hypothalamus, compared to lean littermate controls, suggesting a role for hypothalamic NE in obesity (Oltmans, 1983). Repeated NE injection (20 nmoles, 4 times/ day) into the paraventricular nucleus promotes hyperphagia and body weight gain in rats (Leibowitz et al., 1984). NE is an agonist at α1- and α2-adrenoceptors (Wellman, 2000). Radioligand binding studies reveal the presence of both α1- and α2-adrenoceptors within the paraventricular nucleus, and the stimulatory effect of NE on eating is linked to activation of α2-adrenoceptors (Leibowitz et al., 1982). Intra-paraventricular nucleus injection of either NE (40 nmol) or the α2-adrenoceptor agonist, clonidine (20 nmol), increased feeding in rats, compared to controls (Goldman et al., 1985). Further, hyperphagia induced by NE (40 nmol) was inhibited dose-dependently by pretreatment with a α2-adrenoceptor antagonist, yohimbine (12.5-200 nmol), supporting an orexigenic role of paraventricular nucleus α2-adrenoceptors. Expression of α2-adrenoceptors in paraventricular nucleus is under circadian control, with increased expression at dark phase onset, when feeding behavior in rodents is increased (Wellman, 2000). In contrast to the hyperphagic effect of α2-adrenoceptor stimulation, injection of α1-adrenoceptor agonist, cirazoline (3-24 nmol) into paraventricular nucleus suppressed food intake in rats, compared to control (Davies and Wellman, 1992). Taken together, these results suggest that the relative balance of α1- and

α2-adrenoceptors within the paraventricular nucleus modulates the impact of various adrenergic agonists on feeding.

With respect to the 5-HT system, raphe nucleus cell bodies in caudal brainstem project widely throughout brain, and activation of 5-HT receptors suppresses food intake (Leibowitz et al., 1988). Seven families of 5-HT receptors ($5\text{-}HT_{1\text{-}7}$) comprised of at least 14 distinct subtypes have been described; $5\text{-}HT_{1B}$, $5\text{-}HT_{2C}$ and $5\text{-}HT_6$ are the primary subtypes implicated in energy balance (Garfield and Heisler, 2009). Fenfluramine, an indirect 5-HT agonist that releases 5-HT from vesicular stores and reverses 5-HT transporter function, was approved in combination with phentermine, a NE transporter inhibitor, for the treatment of obesity (Ioannides-Demos et al., 2011). This drug combination was withdrawn from the market due to adverse cardiovascular side-effects. Sibutramine, a dual 5-HT and NE uptake inhibitor, was found to be effective in the treatment of obesity (Ioannides-Demos et al., 2011). Sibutramine was withdrawn from the market also due to cardiovascular side-effects including increased systolic and diastolic blood pressure and heart rate (Scheen, 2011).

Genetic studies reveal the role of specific 5-HT receptor subtypes in the development of obesity. In contrast to $5\text{-}HT_{2C}$ receptors, $5\text{-}HT_6$ receptor activation promotes obesity, since $5\text{-}HT_6$ receptor knockout mice exhibit decreased food intake and body weight gain upon exposure to a high-fat diet for 11 wk (Frassetto et al., 2008). In DIO rats, the $5\text{-}HT_6$ receptor antagonist, PRX-07034 (*N*-[1-(5-chloro-2,3-dimethoxyphenyl)ethyl]-2-methylsulfonyl-5-piperazin-1-ylaniline; 10 mg/kg,2 times/day for 6 wk; IP), reduced food intake throughout treatment and decreased (12.7%) body weight (Gannon et al., 2006). Body composition analysis revealed that the PRX-07034-induced reduction in body weight was the result of a selective reduction in fat mass with minimal effects on either body water or protein content. Consistent with a marked decrease in white adipocyte fat mass, plasma leptin was decreased by more than 75% in the PRX-07034-treated rats compared to the vehicle control. In a randomized, double-blind, placebo-controlled Phase Ib clinical trial, PRX-07034 (600 mg, twice/day) produced significant weight loss in healthy obese patients (Heal et al., 2012). Phase II and III clinical trials will provide further information regarding its safety and efficacy as a treatment of obesity. Thus, pharmacotherapies targeting specific monoamine receptor subtypes may be beneficial for the treatment of obesity.

2.2. Endocannabinoids: Central and peripheral regulation of energy balance

Endocannabinoids are implicated in the central and peripheral regulation of energy balance. Anandamide and 2-arachidonylglycerol (2-AG) are the primary endocannabinoids in brain (Freund et al., 2003). Upon release by postsynaptic neurons, these molecules act as retrograde messengers activating presynaptic cannabinoid-1 (CB1) receptors to inhibit synaptic transmission by either excitatory glutamatergic or inhibitory GABAergic neurons (Freund et al., 2003). In contrast to CB1 receptors, cannabinoid-2 (CB2) receptors are highest in immune cells (Maresz et al., 2007). The role of endocannabinoids in the regulation of homeostatic energy balance is evident from CB1-positive axonal innervation of the arcuate nucleus, paraventricular nucleus, dorsomedial hypothalamus and ventral medial hypothalamus (Wittmann et al., 2007). Importantly, corticotrophin releasing hormone mRNA is increased in paraventricular nucleus of CB1 knockout mice (Cota et al., 2007).

Mice deficient in fatty acid amide hydrolase, the enzyme responsible for anandamide metabolism, exhibit decreased levels of CART-immunoreactivity in the arcuate nucleus, dorsomedial hypothalamus and paraventricular nucleus, compared to wild-type control (Osei-Hyiaman et al., 2005a). Moreover, treatment of fatty acid amide hydrolase deficient mice with CB1 inverse agonist, rimonabant (3 mg/kg/day for 7 days, IP) increased CART in these brain regions compared to wild-type controls (Osei-Hyiaman et al., 2005a).

Endocannabinoid stimulation of central CB1 receptors results in orexigenic effects. Anandamide (50 ng/0.5μl) infused into the ventral medial hypothalamus of pre-satiated rats produced hyperphagia that was attenuated by pretreatment with rimonabant (30 μg/0.5μl) (Jamshidi and Taylor, 2001). Selective CB1 receptor deletion in mouse forebrain results in DIO resistance (Quarta et al., 2010). Consistent with these results, transgenic mice that overexpress monoacylglycerol lipase, the enzyme that deactivates 2-AG, in forebrain are DIO resistant and express high levels of thermogenic proteins in brown adipose tissue, compared to wild-type control (Jung et al., 2012). These mutant mice are hypersensitive to β3-adrenergic-stimulated thermogenesis that is normalized by a single dose of JZL184 (4-nitrophenyl-4-[bis(1,3-benzodioxol-5-yl)(hydroxy)methyl]piperidine-1-carboxylate; 16 mg/kg, IP), an irreversible monoacylglycerol lipase inhibitor. JZL184 normalization of β3-adrenergic-stimulated thermogenesis was reversed by rimonabant (10 mg/kg, IP), indicating that impaired forebrain 2-AG signaling at CB1 receptors underlies enhanced thermogenesis in these mutant mice.

Alterations in energy status modulate the balance between hypothalamic excitatory and inhibitory synaptic transmission and synaptic plasticity to facilitate homeostatic adaptation (Cristino et al., 2013). In obesity, CB1-expressing excitatory vs. inhibitory inputs to orexin-A containing neurons in lateral hypothalamus are altered. In lean mice, these inputs are mostly excitatory, whereas in ob/ob and DIO mice, orexinergic neurons receive predominantly inhibitory CB1-expressing inputs (Cristino et al., 2013). To determine if the altered synaptology of orexigenic neurons was due to leptin deficiency, glutamatergic and GABAergic inputs to orexigenic neurons were analyzed in ob/ob and wild-type mice following leptin (5 mg/kg, IP). Increased vesicular glutamate transporter-2 and decreased vesicular GABA transporter were found in lateral hypothalamus of ob/ob mice after leptin, resembling vehicle-injected wild-type mice (Cristino et al., 2013). Effects of leptin were abolished by a leptin receptor antagonist, indicating that leptin reverses remodeling of orexigenic neurons in ob/ob mice. Thus, in obesity, endocannabinoid neuromodulatory control is altered as a result of leptin-dependent reorganization of glutamatergic and GABAergic synapses in hypothalamus.

In Europe, rimonabant was used as an adjunct to diet and exercise for the treatment of obesity (Christensen et al., 2007). However, rimonabant (20 mg/day, oral) increased the risk of psychiatric events including depressed mood disorders, anxiety and suicidal ideation, resulting in its withdrawal from the European market (European Medicines Agency, 2008). While lacking the deleterious psychiatric effects of rimonabant, NESS0327 (8-chloro-1-(2,4-dichlorophenyl)-N-piperidin-1-yl-5,6-dihydro-4H-benzo[2,3]cyclohepta[2,4-b]pyrazole-3-carboxamide, 0.03-0.3 mg/kg, IP), a neutral CB1 antagonist, decreased food intake and body weight in rats (Meye et al., 2013). In contrast to rimonabant, NESS0327 did not alter

GABAergic and glutamatergic postsynaptic currents in ventral tegmental area (VTA) neurons or in basolateral amygdala. NESS0327 (0.1 mg/kg, IP) was not anxiogenic and blocked the anxiogenic response as well as decreases in motivation for sucrose produced by rimonabant (1 mg/kg, IP; Meye et al., 2013). Results suggest that alternate mechanisms may underlie hypophagic effects of NESS0327.

Interestingly, co-administration of rimonabant (0.3 mg/kg, IP) and an MCH1 receptor antagonist, SNAP-94847(N-(3-[1-([4-(3,4-difluorophenoxy)phenyl]methyl)(4-piperidyl)]-4-methylphenyl)-2-methylpropanamide, 10 mg/kg for 21 days, IP) to DIO mice resulted in a transient reduction in food intake, adipocyte size and fat mass (Verty et al., 2013). SNAP-94847 decreased immobility time (depressive-like effect) in the Porsolt's forced swim test and normalized immobility time produced by rimonabant. Thus, MCH1 receptors may have a role in rescuing adverse behavioral effects of rimonabant. A combination pharmacotherapy targeting both CB1 and MCH1 receptors may be beneficial for the treatment of obesity. Pharmacological agents that inhibit CB1 receptors or that increase monoacylglycerol lipase and fatty acid amide hydrolase activity (2-AG and anandamide degrading enzyme, respectively) may treat obesity.

Despite similar caloric intake upon exposure to a high-fat diet, CB1 knockout mice are resistant to DIO, suggesting a role for endocannabinoid signaling in the regulation of peripheral energy metabolism (Ravinet Trillou et al., 2004). The role of endocannabinoids in mediating hepatic lipogenesis is indicated by a marked increase in hepatic and hypothalamic mRNA levels of the lipogenic transcription factor, SREBP-1c, and fatty acid synthase following administration of CB1 agonist, HU210 ((6aR,10aR)-9-(hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrobenzo[c]-chromen-1-ol; 20 μg/kg, IP) to mice (Osei-Hyiaman et al., 2005b). Pretreatment with rimonabant (3 mg/kg, IP) blocked these HU210-induced effects.

Endocannabinoid mediation of hepatic lipogenesis is supported also by increased basal rates of de novo fatty acid synthesis in wild-type mice fed a high-fat diet for 3 wk, compared to lean controls fed a regular diet (Shimano et al., 1996; Osei-Hyiaman et al., 2005b). Rimonabant (3 mg/kg, IP) decreased de novo fatty acid synthesis rate in mice fed high-fat diet, compared to control mice fed high-fat diet. Consistent with these findings, CB1 knockout mice fed a high-fat diet did not exhibit a change in basal rate of fatty acid synthesis, compared to chow-fed controls. Thus, CB1 stimulation increases de novo fatty acid synthesis, contributing to development of DIO. This interpretation is supported by an increase in hepatic levels of anandamide as well as CB1-mediated fatty acid synthesis in mice fed high-fat diet (Osei-Hyiaman et al., 2005b). Thus, the fatty acid biosynthetic pathway represents a common molecular target for central appetitive and peripheral metabolic effects of endocannabinoids.

Obesity is associated with fatty liver, insulin and leptin resistance, and changes in plasma lipid profile. The role of hepatic CB1 receptors in the metabolic consequences of a high-fat diet was studied using liver-specific CB1 knockout mice fed high-fat diet for 14 wk (Osei-Hyiaman et al., 2008). Compared to wild-type mice, liver-specific CB1 knockout mice fed high-fat diet exhibited decreased steatosis, hyperglycemia, dyslipidemia, and insulin and

leptin resistance. CB1 agonist (HU210, 20 μg/kg, IP)-induced increase de novo hepatic lipogenesis, decrease in carnitine palmitoyl transferase-1 activity and decrease in total energy expenditure were found in CB1 global knockout mice and liver-specific CB1 knockout mice (Osei-Hyiaman et al., 2008). Thus, endocannabinoid activation of hepatic CB1 receptors contributes to steatosis and hormonal and metabolic changes occuring with high-fat diets. However, since liver specific CB1 knockout mice exhibited increases in body weight upon long-term exposure to high-fat diet (Osei-Hyiaman et al., 2008), endocannabinoid activation of hepatic CB1 receptors does not contribute to the increase in adiposity with high-fat diet. Thus, endocannabinoids act at central CB1 receptors to indirectly influence peripheral energy metabolism, or endocannabinoids produce effects via CB1 receptors at extrahepatic sites (e.g., adipose tissue) (Tedesco et al., 2008). Peripheral CB1 receptors could be targeted selectively for the treatment of fatty liver, impaired glucose homeostasis and dyslipidemia to minimize neuropsychiatric side-effects of central CB1 receptor antagonism.

Orosensory positive feedback plays a key role in promoting excessive intake of foods rich in dietary fat (Greenberg and Smith, 1996). In addition to regulation centrally, endocannabinoids localized to gut are implicated in positive feedback control of fat preference and intake (DiPatrizio et al., 2011, 2013; DiPatrizio and Piomelli, 2015). To isolate effects of orosensory signals from post-ingestive influences, a sham-feeding paradigm in rats was employed, such that ingested liquid diets are removed from the stomach via a chronically implanted gastric cannula (Schwartz et al., 2008). Sham-feeding of a high-fat liquid meal resulted in accumulation of 2-AG and anandamide in the jejunal small intestine, but not in other peripheral tissues or brain (DiPatrizio et al., 2011). Sham feeding of meals containing either carbohydrate or protein failed to exert this effect, indicating that orosensory properties of fat alone mobilize small intestine endocannabinoids. Vagus nerve transection blocked effects of fat sham feeding on endocannabinoid mobilization, indicating that gustatory signals are transmitted from brainstem to intestine through the vagus nerve. Duodenal infusion of rimonabant (0.3 and 1 mg/kg), and systemic administration of peripherally restricted CB1 receptor antagonist, URB447 ([4-amino-1-[(4-chlorophenyl)methyl]-2-methyl-5-phenyl-1H-pyrrol-3-yl]phenyl-methanone, 20 mg/kg, IP), reduced sham fat feeding, indicating that gut endocannabinoids may be critical for positive orosensory feedback mechanism driving fat intake (DiPatrizio et al., 2011).

Dietary fats are comprised of complex lipids, such as triglycerides and phospholipids. Gut endocannabinoid signaling may be mediated by textural properties or fatty acid composition of complex lipids. Mineral oil has a texture similar to nutritive oils, but contains no fatty acids (Mindell et al., 1990). Rats were allowed to sham feed either a corn oil emulsion or a liquid diet containingd only mineral oil (DiPatrizio et al., 2013). In contrast to corn-oil emulsion, sham intake of mineral oil did not modify jejunal 2-AG levels, suggesting that dietary fat texture alone is not sufficient to trigger jejunal 2-AG mobilization. Sham-feeding emulsions containing monoenoic or dienoic fatty acids resulted in a 2-fold accumulation of jejunal endocannabinoids, whereas emulsions containing stearic acid or linoleic acid had no effect. Given that peripheral blockade of CB1 receptors reduces intake of corn oil (DiPatrizio et al., 2011), preference for linoleic acid, the most abundant fatty acid constituent of corn oil (Moreau, 2011), over mineral oil was assessed in a 2-bottle choice test in sham

feeding rats (DiPatrizio et al., 2013). Vehicle-treated rats preferred linoleic acid over mineral oil; this preference was blocked by URB447 (20 mg/kg, IP). Thus, small-intestinal endocannabinoids mediate orexigenic responses produced by tasting fat-containing foods, and gustatory signals elicited by dietary fat-containing selective long chain unsaturated fatty acids are transmitted from brainstem to intestine through the vagus nerve (DiPatrizio et al., 2011, 2013).

Fasting increases anandamide and 2-AG levels in rat duodenum, suggesting that endocannabinoid signaling in small intestine promotes food intake (Gomez et al., 2002; Izzo et al., 2009). Food deprivation (12 and 24 h) increases 2-AG and its lipid precursor 1, 2-diacylglycerol in rat jejunum mucosa, and re-feeding normalizes this response (DiPatrizio et al., 2015). These findings suggest that gut 2-AG may serve as a hunger signal. Feeding-dependent regulation of 2-AG was absent in other peripheral tissues. Increases in jejunal 2-AG levels induced by food-deprivation were abrogated by vagus nerve surgical resection or pharmacological blockade of muscarinic M3 receptors using DAU5884 ((8-methyl-8-azabicyclo-[3.2.1]octan-3-yl) 2-oxo-1,4-dihydroquinazoline-3-carboxylate, 300 nmol) in small intestine, but not by inhibition of muscarinic M1 receptors (pirenzepine, 300 nmol) (DiPatrizio et al., 2015). These results suggest that food deprivation stimulates 2-AG-dependent CB1 receptor activation through a mechanism that requires efferent vagal activation of jejunum muscarinic M3 receptors, which promotes feeding after a fast (DiPatrizio et al., 2015). Thus, endocannabinoid overactivity in proximal small intestine may contribute to obesity. Targeted inhibition of endocannabinoid signaling in intestine may control excessive fat intake and reduce obesity. Taken together, both central and peripheral CB1 receptors serve as potential therapeutic targets for the treatment of obesity.

2.3. Peripherally-derived satiety, hunger and adiposity signals

Peripherally-derived satiety, hunger and adiposity signals are integrated within the hypothalamic and brainstem circuits to regulate feeding and metabolism. These peripheral signals include short-term, meal-related afferent satiety and hunger signals from gut and long-term afferent signals from adipocytes and pancreatic β-cells. Peripheral signals that regulate satiety include cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY), amylin and oleoylethanolamide (OEA). In contrast to satiety signals that promote meal termination, ghrelin, a peptide hormone released by the stomach, promotes meal initiation. Lastly, adiposity signals, including leptin and adiponectin released from white adipocytes and insulin released from pancreatic β-cells, are involved in body weight regulation. Previous reviews have described peripheral mechanisms that regulate energy homeostasis (Sam et al., 2012; Camilleri, 2015). The current section provides a brief overview of these mechanisms and identifies potential therapeutic targets for obesity.

2.3.1. *CCK*—The peptide hormone, CCK is released from I-cells of the proximal intestine following absorption of fat or protein (Liddle et al., 1985). Molecular forms of CCK range from 4 to 83 amino acids as a result of post-translational processing of products from the pro-CCK gene (Rehfeld et al., 2001). In the human intestine and circulation, predominant CCK forms include CCK-8, CCK-22, CCK-33 and CCK-58. CCK-induced satiety signaling is mediated via CCK receptors, which are members of the GPCR family (Ballinger et al.,

1995; Blevins et al., 2000; Degen et al., 2001). Two CCK receptor subtypes include CCK-A receptors that are expressed in the pancreas, on vagal afferent enteric neurons, NTS, area postrema and dorsomedial hypothalamus and CCK-B receptors that are expressed in stomach, afferent vagus nerve and throughout brain (Dufresne et al., 2006). Inhibition of CCK-A, but not CCK-B receptors, attenuates CCK-induced satiety (Moran et al., 1992). CCK (100 μg/kg, IP)-induced inhibition of glucose consumption in rats was decreased in a dose-dependent manner by CCK-A antagonist, devazepide (L-364718: N-(1-methyl-2-oxo-5-phenyl-3H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,10-100 μg/kg, IP). On the other hand, the CCK-B antagonist, L-365260 (1-(1-methyl-2-oxo-5-phenyl-3H-1,4-benzodiazepin-3-yl)-3-(3-methylphenyl)urea,10-1000 μg/kg, IP) failed to attenuate the inhibitory effect of CCK on gucose consumption. In agreement with these findings, Otsuka Long Evans Tokushima Fatty (OLETF) rats that lack CCK-A receptors are hyperphagic, obese and diabetic (Bi and Moran, 2002). Evaluation of patterns of hypothalamic gene expression in OLETF rats reveals upregulation of NPY in the dorsomedial hypothalamus, which also may underlie the hyperphagia and development of obesity (Bi et al., 2001).

Investigation of the effects of a stable CCK-8 analog, (pGlu-Gln)-CCK-8, on metabolic control and hypothalamic gene expression in mice fed a high-fat diet for 20 wk provides additional evidence that CCK regulates food intake (Montgomery et al., 2013). (pGlu-Gln)-CCK-8 (25 nmol/kg twice daily for 16 days, IP) decreased energy intake, circulating glucose, insulin levels and body weight in mice fed a high-fat diet, compared to lean control mice. However, the CCK analog elevated hypothalamic mRNA levels of NPY and decreased POMC mRNA levels. While these effects suggest an orexigenic effect, it is possible that the reported alterations in mRNA levels represent a counter-regulatory physiological response induced by CCK-8 analog-induced decreases in feeding. Further elucidation of hypothalamic mechanisms underlying the anorexigenic effects of the CCK-8 analog is needed. Overall, CCK agonists appear to have a role in the regulation of energy balance.

2.3.2. _GLP-1_—The peptide hormone GLP-1 is synthesized by L-cells of the distal small intestine and is released in response to carbohydrate and fat digestion (Lavin et al., 1998; Thomsen et al., 1999). Two forms of GLP-1 are in blood including the predominant variants GLP-1(7–36) amide and GLP-1(7–37) amide (Marks et al., 1991). GLP-1 mediates appetite control via insulin release, glucagon inhibition as well as absorption and metabolism of macronutrients (Naslund et al., 1999; Flint et al., 2001). GLP-1 receptors are members of the GPCR family and are expressed widely in pancreatic islets, kidney, lung, heart, and numerous regions of the peripheral and central nervous systems (Bullock et al., 1996; Gutzwiller et al., 2004; Drucker, 2006). Within the islets, GLP-1 receptors are localized predominantly to β-cells (Drucker, 2006).

GLP-1(7-36) or GLP-1 receptor agonists (e.g., exendin-4 or liraglutide) given systemically reduce food intake in a dose-dependent manner in rodents and non-human primates. GLP-1 (0.5-170 pmol/kg/min for 3h, IV) at dark onset dose-dependently inhibited food intake in rats (Chelikani et al., 2005). In adult male rhesus macaques trained to lever press for food pellets, a long-lasting GLP-1 receptor agonist (exendin-4, 0.1-3.0 μg/kg, IM) dose-dependently suppressed food intake specifically through a reduction in meal size, compared to vehicle-control (Scott and Moran, 2007). In rats, the GLP-1 receptor antagonist, exendin-

(9–39) (100 μg/2 μl, ICV), attenuated the decrease in food intake induced by GLP-1 agonists, exendin-4 (3 μg/kg, IP) and liraglutide (10 μg/kg, IP) (Kanoski et al., 2011). Further, to assess the contribution of GLP-1 receptors expressed on subdiaphragmatic vagal afferents to the anorectic effects of exendin-4 and liraglutide, food intake in rats with complete subdiaphragmatic vagal deafferentation was compared to surgical controls. Both exendin-4 (1 or 3 μg/kg, IP) and liraglutide (10, 25 or 50 μg/kg, IP) decreased food intake in controls. However, in rats that underwent subdiaphragmatic vagal deafferentation, only the higher doses of the GLP-1 receptor agonists decreased food intake. These findings suggest that exendin-4 and liraglutide reductions in food intake are mediated by a combined action on vagal afferents and central GLP-1 receptors. Overall, GLP-1 receptor agonists appear to be a promising target for the treatment of obesity.

2.3.3. PYY—The 36-amino acid peptide hormone, PYY, is released from L-cells of the distal small intestine in response to fatty acids, dietary fibers and bile (Onaga et al., 2002). In human plasma, $PYY_{1–36}$ predominates over $PYY_{3–36}$ under fasting conditions; whereas after a meal, $PYY_{3–36}$ is the major circulating peptide (Grandt et al., 1994a, b). PYY receptors are widely expressed in the central nervous system. $PYY_{1–36}$ activates at least three receptor subtypes including, Y1, Y2, and Y5; $PYY_{3–36}$ is more selective for the Y2 subtype (Dumont et al., 1995). Direct injection of $PYY_{3–36}$ into arcuate nucleus as well as peripheral administration of $PYY_{3–36}$ to rodents increased arcuate c-fos immunoreactivity and decreased food intake (Batterham and Bloom, 2003). While peripheral administration of $PYY_{3–36}$ inhibited food intake in wild-type control mice, $PYY_{3–36}$ did not alter food intake in mice with an arcuate-specific deletion of Y2 receptors (Sainsbury et al., 2002; Batterham and Bloom, 2003). These results indicate that the anorectic effects of $PYY_{3–36}$ are mediated via Y2 receptors.

Expression of a genetic variant of the PYY gene, PYY Q62P, correlated with body weight in obese compared to lean men, suggesting that sequence variants within the PYY gene may influence susceptibility to obesity (Ahituv et al., 2006). Compared to control, obese humans exhibited decreased plasma PYY levels as well as an attenuated PYY response to meals across a range of caloric content (le Roux et al., 2006). Importantly, in obese humans, high caloric content was required to increase plasma PYY relative to normal-weight humans (le Roux et al., 2006). Co-administration of PYY with GLP-1 produced a synergistic effect by decreasing energy intake and promoting satiety in healthy subjects, suggesting benefit of a combination therapy (Steinert et al., 2010). Thus, reduced plasma PYY appears to underlie decreased satiety and increased food intake in obesity.

2.3.4. Amylin—Amylin, a 37-amino acid peptide hormone released with insulin from pancreatic β-cells in response to high glucose levels in blood, reduces both food intake and body weight though actions in brain stem (Rushing et al., 2001). Amylin (0.1-1 μg/kg, IP) dose-dependently reduced food intake in rats (Lutz et al., 1994). Anorectic effects of amylin are mediated by amylin receptor complexes in brain stem composed of calcitonin receptors coupled to receptor activity-modifying proteins (Chen et al., 1997; Christopoulos et al., 1999). A synthetic analog of amylin, pramlintide, is available for the treatment of both type 1- and type 2-diabetes (Whitehouse et al., 2002; Hollander et al., 2003). Diabetic patients

treated with pramlintide for a year exhibited weight loss relative to placebo-treated controls (Hollander et al., 2003). Leptin is an adipose-derived hormone that decreases food intake and increases lipolysis (Halaas et al., 1995; Campfield et al., 1996). Concurrent peripheral administration of amylin and leptin resulted in synergistic weight loss in leptin-resistant DIO rats, and amylin pre-treatment restored leptin signaling, suggesting that amylin restores leptin sensitivity in the DIO model (Roth et al., 2008). A pharmacologically optimized amylin analog, davalintide, has undergone Phase II clinical trials for the treatment of obesity (Colon-Gonzalez et al., 2013). Further clinical development of davalintide has not been reported. Overall, amylin analogs as well as a combination of amylin and leptin exhibit therapeutic potential for the treatment of obesity.

2.3.5. OEA—Food intake stimulates small-intestinal mucosal cells to produce the lipid messenger, OEA, which serves as a satiety signal (Rodriguez de Fonseca et al., 2001; Fu et al., 2007; Piomelli, 2013). Investigation of the nutrients involved in OEA generation revealed that intraduodenal infusion of fat stimulates intestinal OEA production in rats, whereas, infusion of proteins and carbohydrate did not produce this effect (Schwartz et al., 2008). Thus, dietary fat is necessary and sufficient to trigger the production of OEA by small intestinal enterocytes. Both peripheral (5-20 mg/kg, IP) and oral (50-200 mg/kg) administration of OEA decreases in a dose-dependent manner food intake in rodents (Gaetani et al., 2003; Oveisi et al., 2004). Moreover, sub-chronic administration of OEA (5 mg/kg once/day for 2 wk, IP) reduces food intake, lowers body weight and decreases serum cholesterol and triglyceride levels in obese Zucker rats, compared to vehicle-treated control (Fu et al., 2005). These results suggest that in addition to satiety, OEA regulates lipid metabolism.

OEA elicits satiety primarily by prolonging the post-meal interval and reducing meal frequency (Gaetani et al., 2003; Oveisi et al., 2004). OEA-induced anorexic response involves *i)* local activation of the peroxisome proliferator-activated receptor-α, which is implicated in regulating absorption, storage and utilization of dietary fat; *ii)* stimulation of afferent vagus nerve fibers; and *iii)* recruitment of appetite-controlling paraventricular nucleus and NTS circuits (Rodriguez de Fonseca et al., 2001; Fu et al., 2003; Evans et al., 2004; Bookout et al., 2006; Lefebvre et al., 2006; Gaetani et al., 2010; Azari et al., 2014; Provensi et al., 2014). Hypophagic effects of exogenous OEA are abolished by genetic deletion of peroxisome proliferator-activated receptor-α and are mimicked closely by administration of synthetic peroxisome proliferator-activated receptor-α agonists (Astarita et al., 2006; Fu et al., 2003). Anorexic effects of OEA were absent in rats treated with capsaicin to remove the peripheral sensory fibers, supporting a role for afferent vagus fibers in mediating hypophagic effects of OEA (Rodriguez de Fonseca et al., 2001). In contrast, subdiaphragmatic vagotomy in rats did not block OEA-induced hypophagia, necessitating further investigation of the role of vagal afferents in OEA-mediated satiety signaling (Azari et al., 2014; DiPatrizio and Piomelli, 2015). Food deprivation decreased OEA mobilization in jejunum of lean rats, while feeding restores jejunal OEA levels (Rodriguez et al., 2001; Fu et al., 2007). Feeding-dependent OEA production is disrupted in gut of DIO rodents, suggesting that high-fat DIO is accompanied by alterations in post-digestive machinery responsible for OEA biosynthesis, which may contribute to reduced satiety and hyperphagia

(Igarashi et al., 2015). Mechanistic understanding of intestinal OEA signaling in obesity will assist in the development of pharmacological strategies to control appetite in obesity.

2.3.6. *Ghrelin*—Ghrelin, a 28-amino acid appetite-stimulating peptide, is found in highest concentrations in gut (Korbonits and Grossman, 2004). In addition to peripheral localization, ghrelin is synthesized in the arcuate (Mondal et al., 2005). Ghrelin crosses the blood brain barrier and binds to ghrelin receptors, a growth hormone secretagogue receptor 1A (GHSR1A), expressed in hypothalamus (Cummings, 2006; Harrold et al., 2008). Ghrelin levels are dependent on nutritional status such that peak levels occur prior to meal initiation, followed by a decrease in levels upon food consumption (Cummings et al., 2001; Callahan et al., 2004). Compared to lean controls, obese individuals are more sensitive to appetite-stimulating effects of ghrelin (Druce et al., 2005).

Ghrelin regulates adipocyte metabolism through a central mechanism. Compared to vehicle control, ghrelin (2.5 nmol/day for 6 days, ICV) decreased expression of thermogenesis-related mitochondrial uncoupling proteins 1 and 3 in brown adipocytes; while in white adipocytes, gherlin increased mRNA expression of fat storage-promoting enzymes (lipoprotein lipase, acetyl-CoA carboxylase α, fatty acid synthase and stearoyl-CoA desaturase-1) and decreased mRNA of carnitine palmitoyl transferase-1α, the rate-limiting enzyme in fat oxidation (Theander-Carillo et al., 2006). Expression of these fat storage enzymes was decreased in ghrelin-deficient mice, compared to wild-type control (Theander-Carillo et al., 2006). When exposed to a high-fat diet, both GHSR1A knockout mice and ghrelin-deficient mice exhibit resistance to DIO, compared to respective wild-type controls (Cummings, 2006). Vaccination against ghrelin decreases body weight gain in adult male Wistar rats (Zorrilla et al., 2006). These findings suggest that ghrelin receptor antagonists have therapeutic potential. Further investigation of ghrelin antagonists in animal models of obesity and in obese humans is needed.

2.3.7. *Leptin*—Leptin, a leptin gene (Lep(ob)) product, is produced and secreted by white adipocytes in proportion to fat mass (Zhang et al., 1994; Maffei et al., 1995; Porte et al., 2002). Leptin decreases food intake and body weight by activating leptin receptors in the arcuate (Fei et al., 1997; Elmquist et al., 1998; Myers et al., 2008). Both leptin deficiency (ob/ob mice) and leptin resistance (db/db mice; defective leptin receptors) result in hyperphagia and decreased energy expenditure (Tartaglia et al., 1995; Lee et al., 1996). Importantly, correction of the leptin deficiency in ob/ob mice results in a reduction in food intake and body weight (Halaas et al., 1995; Campfield et al., 1996). Leptin production increases proportionally with adiposity, such that leptin levels are increased in rodent and human models of DIO (Halaas et al., 1995; Heymsfield et al., 1999; Levin and Dunn-Meynell, 2002). However, increased leptin levels in obesity leads to decreased central leptin sensitivity and increased leptin receptor resistance, and as a result, obese individuals fail to respond to leptin treatment (Levin and Dunn-Meynell, 2002). Nevertheless, administration of both leptin and amylin result in a synergistic decrease in food intake and body weight in rats (Roth et al., 2008). Importantly, amylin restored hypothalamic leptin receptor signaling in obesity (Roth et al., 2008). Also, CCK potentiates leptin effects to decrease food intake

and body weight (Matson and Ritter, 1999; Colon Gonzalez et al., 2013), suggesting the potential combination of CCK and leptin for the treatment of obesity.

2.3.8. *Insulin*—Insulin is a metabolic polypeptide hormone synthesized in the pancreas by the β-cells of the islets of Langerhans (Woods et al., 1974; Brange and Langkjoer, 1993). Similar to leptin, plasma insulin levels correlate positively with adiposity (Woods et al., 1974). Insulin-induced decreases in food intake and body weight are mediated via stimulation of hypothalamic insulin receptors (Menendez and Atrens, 1991). Central administration of an antisense oligodeoxynucleotide designed to blunt the expression of hypothalamic insulin receptors resulted in hyperphagia and increased fat mass in rats (Obici et al., 2002). Compared to control non-diabetic rats, streptozotocin-treated diabetic rats exhibited increased NPY expression in the paraventricular nucleus, ventral medial hypothalamus and lateral hypothalamus; and, insulin replacement normalized NPY levels in these diabetic rats (Williams et al., 1989). With respect to interactions between insulin and melanocortin systems in hypothalamus (Benoit et al., 2002), immunohistochemical analysis revealed insulin receptor expression on arcuate POMC neurons. Also, administration of insulin (4 mU/μl, ICV) to fasted rats increased POMC mRNA expression. Further, the anorectic actions of insulin were blocked by non-selective melanocortin antagonist, SHU-9119 (Ac-Nle-c[Asp-His-dNal(2′)-Arg-Trp-Lys]-NH$_2$, 0.1 nmol/μl, ICV). These results suggest a role for the hypothalamic melanocortin system in mediating the anorexic effects of central insulin. Thus, both melanocortin and NPY systems appear to be important downstream mediators of the anorectic effects of insulin.

2.3.9. *Adiponectin*—Adiponectin, a 244-amino acid polypeptide, is another adipocyte-derived protein that decreases body weight and plasma lipid levels, and enhances the ability of insulin to suppress hepatic glucose production (Berg et al., 2001; Qi et al., 2004; Kadowaki and Yamauchi, 2005). Plasma adiponectin levels increase following food restriction in rodents and following weight loss induced by a calorie-restricted diet or gastric partition surgery in obese humans (Hotta et al., 2000; Berg et al., 2001;Yang et al., 2001). Peripheral administration of adiponectin to rodents attenuates body weight gain without altering food intake (Berg et al., 2001; Fruebis et al., 2001). Adiponectin effects on energy expenditure in rats appear to be mediated within the hypothalamus, as indicated by increased c-fos expression in the paraventricular nucleus (Qi et al., 2004). In contrast to carbohydrate-rich foods, diets including soy protein, fish oils and linoleic acid increase plasma adiponectin levels (Pischon et al., 2005). Two distinct adiponectin receptors, adipoR1 and adipoR2, are expressed highly in skeletal muscle and liver, respectively, and in hypothalamus (Yamauchi et al., 2003; Qi et al., 2004). Expression of adipoR1 and adipoR2 are decreased in muscle and adipose tissue of ob/ob mice, suggesting decreased adiponectin sensitivity (Tsuchida et al., 2004). In obese humans, an inverse correlation between plasma adiponectin and insulin resistance was found (Arita et al., 1999; Matsuzawa, 2010). Therapeutic strategies that increase adiponectin signaling may be beneficial to ameliorate obesity and insulin resistance.

In summary, regulation of appetite and body weight involves a complex and interacting network of neural systems and peripherally-derived signals. Importantly, these central and

peripheral mechanisms present numerous viable targets for pharmacotherapeutic intervention.

3. Non-homeostatic hedonic regulation of food intake

Brain reward systems play a major role in feeding behavior (Saper et al., 2002; Lutter and Nestler, 2009). Hedonic properties of food can stimulate non-homeostatic feeding, despite that energy requirements have been met, contributing to weight gain and obesity (Berthoud, 2011). Palatable sugar- and fat-rich foods are salient, motivating, natural rewards that can override homeostatic signals (Berthoud, 2011). Palatable food consumption is associated with reward processing of food-related sensory cues regulating preference and hedonic value (Rolls, 2011). Orosensory properties (taste, texture and smell), and post-ingestive effects of palatable foods drive preference and promote excessive food consumption, relative to less palatable foods (Warwick and Weingarten, 1995; Sclafani et al., 1998; Macht and Mueller, 2007).

Hedonic properties of palatable foods and addictive drugs are regulated in brain by a common reward circuitry, such that excessive consumption of palatable foods and drugs produces similar neuroadaptation (Volkow et al., 2008, 2012; Kenny, 2011). Both non-homeostatic food consumption and drug self-administration activate mesolimbic dopamine (DA) pathways (Koob and Volkow, 2010). While drugs typically activate the reward circuitry via direct effects, food activates this circuitry through cephalic or post-ingestive mechanisms that indirectly activate mesolimbic DA systems. Obesity and substance use disorders are defined by *i)* abnormal enhancement of reinforcer saliency, *ii)* excessive consumption habits that strengthen with behavioral repetition, and *iii)* difficult to control behaviors, despite potential untoward consequences (Berridge and Robinson, 1998; Volkow et al., 2012). Neurobiological mechanisms of drug abuse provide a framework for understanding non-homeostatic hedonic mechanisms and motivational processes underlying palatable food consumption in obesity.

Functional magnetic resonance imaging (fMRI) evaluating blood-oxygen level dependent (BOLD) activity in brain reveals that hedonic food consumption and food-related sensory cues activate mesocorticolimbic reward circuits including orbitofrontal cortex, insula, striatum, amygdala, lateral hypothalamus, VTA and substantia nigra (Pelchat et al., 2004; Simmons et al., 2005; Schur et al., 2009; Bragulat et al., 2010). Immediate early gene-expression (c-fos) in rats exposed to palatable foods shows increased activation of of striatum, nucleus accumbens, amygdala and other limbic structures (Angeles-Castellanos et al., 2007). Lateral habenula deep brain stimulation decreased non-homeostatic and hedonic sucrose self-administration in rats (Friedman et al., 2011). Lesion of lateral habenula delayed extinction responding and increased sucrose-seeking behavior. Results such as these suggest that non-homeostatic, hedonic feeding behavior is regulated by brain regions implicated in reward processing and motivation.

Regarding response to food-related sensory cues, exposure of healthy non-obese women to visual cues (palatable food photographs) resulted in greater BOLD signals and activation in dorsolateral prefrontal cortex, lateral orbitofrontal cortex, insular cortex, dorsal striatum,

accumbens, amygdala, hypothalamus and brainstem, compared with non-food object photos (Schur et al., 2009). Compared with non-appetitive odors, palatable food-related odors elicited greater BOLD signals in medial prefrontal cortex, accumbens and VTA, when response was collapsed across obese and control; obese women exhibited greater BOLD activation in hippocampus, compared to lean women (Bragulat et al., 2010). Upon tasting palatable foods, both obese men and women exhibited enhanced somatosensory cortex activity, and greater activation of insula and midbrain, compared to lean individuals (Wang et al., 2002). Thus, brain reward relevant regions are activated in response to palatable food-related visual, olfactory and taste cues, and obesity may be associated with increased sensitivity to these sensory cues.

In obese humans, striatal DA D2 receptor density is decreased in comparison to non-obese individuals (Wang et al., 2001; Stice et al., 2008). Decreased D2 density may be compensatory for reduced reward circuit activation. Striatal D2 receptor availability in obese humans was decreased relative to control and was positively correlated with glucose metabolism in dorsolateral prefrontal, medial orbitofrontal, anterior cingulate gyrus and somatosensory cortices (Volkow et al., 2009), suggesting that decreased striatal D2 receptors contribute to overeating via modulation of striatal prefrontal pathways, which participate in inhibitory control and salience attribution. Whether decreases in striatal D2 receptor density precede development of obesity or are a consequence of obesity remains unclear. Increases in extracellular DA in dorsal striatum, but not ventral striatum, were found in response to nonhedonic food stimulation (food display without consumption) in food-deprived, normal weight men and women (Volkow et al., 2002). DA was correlated with increased hunger and food desire. Thus, striatal DA signaling plays a distinct role in food motivation, different from nucleus accumbens DA in regulating food reward.

An obesity model posits that non-homeostatic hedonic food intake reflects an imbalance between circuits that motivate behavior (due to involvement in reward and conditioning) and circuits that control and inhibit pre-potent responses (Volkow et al., 2008). This model identifies circuits for *i)* reward-saliency, *ii)* motivation-drive, *iii)* learning-conditioning and *iv)* inhibitory control-emotional regulation-executive function. In vulnerable individuals, consumption of large quantities of palatable food disrupts the balance, resulting in enhanced sensitivity of the reward circuitry to conditioned stimuli associated with palatable foods and impaired function of executive control circuitry weakening inhibitory control over appetitive behaviors. DA-, opioid- and endocannabinoid mediated regulation of reward circuits in the context of nonhomeostatic hedonic food intake and the development of obesity is discussed herein.

3.1. DA

DA regulates appetitive and food-motivated behavior and facilitates conditioning to food cues (Mark et al., 1994; Martel and Fantino, 1996; Wang et al., 2002). Palatable foods ingestion results in accumbal and dorsal striatal DA release, mediating primary reward, motivation and habit formation (Martel and Fantino, 1996; Small et al., 2003; Kelley, 2004; Yin et al., 2004). Neural systems regulating reward and motivation underlie behaviors associated with compulsive food intake (Volkow and Wise, 2005; Johnson and Kenny,

2010). Compulsive, non-homeostatic consumption of large quantities of highly palatable food in a short time period characterizes binge eating in humans (American Psychiatric Association, 2013).

Dysregulated striatal DA function is a potential mechanism underlying excessive food intake in obesity. Consistent with human studies, striatal D2 receptors are downregulated in rodents fed a palatable high-fat diet for an extended time (Colantuoni et al., 2001; Johnson and Kenny, 2010; Narayanaswami et al., 2013). Striatal D2 receptor knockdown, using a lentiviral vector delivering a short hairpin interfering RNA (lenti-D2Rsh), increases brain reward threshold and accelerates reward dysfunction and compulsive eating upon extended access to a palatable high-fat diet, compared to lenti-control lean rodents (Johnson and Kenny, 2010). In contrast, reward thresholds are not altered in lenti-D2Rsh and lenti-control rats with extended chow access. Thus, extended access to palatable foods elevates brain reward thresholds, compared to both chow access and restricted access to palatable foods. Lenti-D2Rsh rats with extended access to palatable foods showed increased resistance to disruption of food consumption by aversive conditioned stimuli, relative to lenti-control lean rats. Compulsive-like feeding behavior is measured as palatable food consumption that is resistant to disruption by an aversive conditioned stimulus. These results suggest that deficits in neural reward responses and maladaptive behavioral responses in obesity arise from high-fat diet-induced deficits in striatal D2 receptor signaling. Excessive consumption of palatable energy-dense food over stimulates brain reward systems and decreases reward system sensitivity leading to compulsive-like food seeking behavior. Decreases in striatal D2 receptors likely precede the development of obesity and the increased vulnerability to maladaptive behavioral responses upon palatable food exposure, which compensates for a reward deficit. Over consumption of palatable foods triggers neuroadaptive reward circuit responses leading to compulsive food-seeking, and deficits in striatal D2 receptor signaling supports this addictive process.

Evidence reveals dysregulation of DA homeostasis in response to prolonged exposure to high-fat diet and/or obesity. Accumbens DA turnover was decreased in obese rats with free-access and non-obese rats with restricted access to high-fat diet for 12 wk, when compared to free-access to standard chow (Davis et al., 2008). DA release from accumbens shell, striatal and medial prefrontal cortex was decreased in inbred obese rats compared to those inbred for obesity resistance, both maintained on standard chow (Geiger et al., 2008). In cultured VTA neurons from these inbred obesity-prone rats, tyrosine hydroxylase mRNA expression, DA transporters (DAT) and D2 receptors were decreased. Collectively, deficient DA homeostasis contributes to decreased food-associated primary reward and to the obesity phenotype.

DA is regulated primarily by DAT, which translocates DA across the plasmalemma from the extracellular space into the cytosol of DA neurons (Sulzer et al., 2005). As revealed by genetic-linkage analysis, binge eating is associated with DAT gene polymorphisms (greater frequency of short alleles; 7 or 9 repeats) and reduced DAT expression (Heinz et al., 2000; Fuke et al., 2001; Shinohara et al., 2004). DAT-deficient mice have increased extracellular DA and exhibit greater food intake relative to wild-type mice (Pecina et al., 2003). Kinetic analysis and no-net flux microdialysis reveal that striatal DAT function is decreased and

extracellular DA increased in a DIO model of obesity-prone outbred rats fed high-fat diet for 8 wk, compared to obesity-resistant rats fed the same diet (Narayanaswami et al., 2013). Decreased DAT function and DA dysregulation did not precede DIO development, but were consequences of obesity (Narayanaswami et al., 2013). Decreased DAT function in obesity may be explained by decreased D2 autoreceptor function, given that D2 autoreceptor activation increases DAT function (Cass and Gerhardt, 1994). Quinpirole (3-100 nmol/L) stimulation of D2 receptors attenuated the inhibition of VTA DA neurons in obese mice, compared with lean mice (Koyama et al., 2014). Investigation of D2 agonist-induced facilitation of DAT function in obesity may provide insight about the ability D2 agonists to normalize DA homeostasis and ameliorate maladaptive eating behaviors.

The D2 receptor agonist, bromocriptine, reduced body fat, increased lean muscle mass, increased glucose tolerance and insulin function, and reduced triglycerides and free fatty acids, compared to control (Cincotta and Meier, 1996; Pijl et al., 2000). Bromocriptine has been evaluated in leptin receptor-deficient obese Zucker rats and in polygenetic DIO rat models (Davis et al., 2009). Bromocriptine (10 mg/kg daily for 4 wk, IP) increased D2 receptor expression in obese Zucker rats, and increased DAT expression in DIO rats. In obese Zucker rats, D2 receptor density correlated inversely with food intake, and directly with locomotor activity. In DIO rats, DAT expression correlated inversely with food intake, body fat composition and directly with locomotor activity. These results underscore bromocriptine's potential in ameliorating behavioral and pathophysiological components of obesity and suggest that pre- or postsynaptic D2 receptors and/or DAT may serve as targets for the treatment of obesity.

3.2. Opioids: Role of μ-opioid receptors

Opioids modulate caloric intake, macronutrient preference and motivational aspects of feeding behavior. Endogenous opioid peptides (endorphins, enkephalins, dynorphins and endomorphins) act at μ-, δ- or κ-opioid receptors, members of the GPCR family (Mansour et al., 1994; Nogueiras et al., 2012). μ-Opioid receptor signaling has a role in the regulation of non-homeostatic hedonic food intake, however, a limited understanding of the role of δ- or κ-opioid receptors exists. Rats treated with μ-opioid receptor agonist, morphine (10-30 mg/kg, IP), exhibit increased fat intake and decreased carbohydrate intake compared to control (Marks-Kaufman and Kanarek, 1980). Naloxone (0.1-10 mg/kg, IP), a non-selective opioid antagonist, decreased fat intake (Marks-Kaufman and Kanarek, 1981). Opioid signaling in accumbens shell modulates food palatability and non-homeostatic hedonic feeding (Peciña and Berridge, 2005). In satiated rats, intra-accumbens infusion of μ-opioid receptor agonist, DAla^2,N,Me-Phe^4,Gly-ol^{5}enkephalin (0.025-2.5 μg/0.5 μl), increased palatable food consumption and preference for high-fat diet vs. high-carbohydrate diet (Zhang et al., 1998). Irreversible μ-opioid receptor antagonist, β-funaltrexamine (8 nmol/0.8 μl), into accumbens shell selectively decreased palatable food consumption, underscoring the role of μ-opioid receptors in hedonic eating (Ward et al., 2006). Competitive μ-opioid receptor antagonist, 6-(4-{[(3-methylbutyl)amino]methyl}phenoxy)-nicotinamide (10 or 50 mg/kg and 1, 3 or 10 mg/kg, PO), given to DIO mice and rats, respectively, dose-dependently decreased acute food intake and weight gain (Zhang et al., 2006). Compared to wild-type mice, μ-opioid receptor deficient mice are resistant to DIO, attributed to increased

skeletal muscle expression of carnitine palmitoyl transferase-1 and increased fatty acid oxidation (Tabarin et al., 2005). Thus, results support the therapeutic potential of μ-opioid receptor antagonists for obesity.

μ-Opioid signaling in food-motivated behavior has been assessed using a progressive ratio (PR) schedule of reinforcement (Cleary et al., 1996; Zhang et al., 2003; Papaleo et al., 2007). Animals press a lever to obtain food reinforcement, and number of active lever responses required to obtain a reinforcer is increased progressively within a session, i.e., each successive reinforcer requires increased effort (Richardson and Roberts, 1996). Escalation of response requirements continues until responding ceases (breakpoint), indicating the motivation level (Richardson and Roberts, 1996; Shippenberg and Koob, 2002). Naloxone (0.3-10 mg/kg, IP) dose-dependently decreased the breakpoint to obtain a sucrose reinforcer in rats (Cleary et al., 1996). Infusion of D-Ala^2,N,Me-Phe^4,Gly-ol^5-enkephalin (0.25 μg/0.5μl) into accumbens core increased breakpoint for sucrose (Zhang et al., 2003). Using knockout mice, the specific role of μ-opioid receptors in motivational properties of food intake was assessed (Papaleo et al., 2007). During a fixed ratio-1 schedule (1 response provides 1 reinforcer), nose-poke responding was not different between μ-opioid receptor knockout and wild-type mice, suggesting that cognitive and learning processes were not altered. Compared to wild-type, responding for chow or sucrose pellets was decreased in μ-opioid receptor knockout mice during fixed ratio-3 responding (3 responses provide 1 reinforcer). Under PR, μ-opioid receptor knockout mice had lower breakpoints for chow or sucrose pellets compared to wild-type, supporting a role of μ-opioid receptors in mediating food-motivated behavior. μ-Opioid receptor knockouts had higher breakpoints for sucrose pellets than for chow pellets; thus, genetic inactivation of μ-opioid receptors did not eliminate sucrose-directed behavior. Decreased motivation to eat despite preserved hedonic processing of sucrose pellets in μ-opioid receptor knockout mice support the role of μ-opioid receptors in motivational properties of ingestive behavior, which may be independent of hedonic properties of food intake. Together, these findings indicate μ-opioid receptors are potential targets for decreasing food motivated behavior.

Inhibition of μ-opioid receptors prevents both food seeking and binge-like eating in rats, as demonstrated using a second-order schedule of chocolate pellet reinforcement, measuring both motivation for palatable food and impact of ingested food on subsequent food seeking (Everitt et al., 1987; Giuliano et al., 2012). In this complex schedule, every 10 lever presses results in a brief (1 s) cue light signaling a fixed interval 15 min schedule. After the 15 min, 10 lever presses results in delivery of chocolate pellets and cue light for 20 s. Number of chocolate pellets delivered at the end of the fixed interval increased progressively from 2 to 20. GSK1521498 ((N-[[2, 6-difluoro-4-[3-(1H-1, 2, 4-triazol-5-yl)phenyl]phenyl]methyl]-2, 3-dihydro-1H-inden-2-amine; 0.1-3 mg/kg, IP) or naltrexone (0.1-3 mg/kg, SC) were given 30 and 10 min, respectively, before the session. GSK1521498 has a 14-fold greater selectivity for μ-opioid over δ- and κ-receptors (Ignar et al., 2011; Kelly et al., 2015). In the first interval, GSK1521498 (1 and 3 mg/kg) decreased responding compared to control; however, there was no effect in naltrexone-treated rats. In the post-ingestive second interval, both GSK1521498 (1 and 3 mg/kg) and naltrexone (1 and 3 mg/kg) decreased responding. Thus, both GSK1521498 and naltrexone reduced palatable food seeking post ingestion, indicating a reduction in hedonic value. However, only GSK1521498 reduced seeking before

ingestion, indicating a role of μ-opioid receptors in incentive motivation for palatable food seeking behavior.

Binge eating is characterized by consumption of an unusually large amount of high calorie food (fat and/or sugar) during a discrete time period (American Psychiatric Association, 2013). Binge eating and increased response to food-associated stimuli are associated frequently with obesity. μ-Opioid receptor availability in reward brain areas increases in response to binge eating of palatable foods (Colantuoni et al., 2001). Rats were provided with access to chow with or without 25% glucose solution for 12 h, followed by a 12-h period of food deprivation each day. After 10 days, exposure to glucose resulted in doubled glucose intake and excessive chow intake in the first h of daily access. After 30 days, μ-opioid receptor expression was increased in cingulate cortex, hippocampus, locus coeruleus and accumbens shell in the glucose binge group, compared to chow-only controls (Colantuoni et al., 2001).

Binge-like eating of a highly palatable chocolate diet was determined after GSK1521498 (0.1-3 mg/kg, IP) and naltrexone (0.1-3 mg/kg, SC) in rats (Cottone et al., 2008; Giuliano et al., 2012). Brief access (10 min) to chocolate diet promoted rapid consumption of large amounts of chocolate and self-restriction of chow intake in anticipation of palatable food access. Both GSK1521498 and naltrexone dose-dependently reduced binge-like palatable food hyperphagia, indicating that inhibition of μ-opioid receptors reduces motivational properties of stimuli eliciting binge eating and regulates hedonic mechanisms of binge-like eating. Thus, μ-opioid receptor antagonists may assist with treatment of maladaptive eating, common with obesity.

A randomized, double-blind, placebo-controlled, single dose, 2-way crossover design evaluated GSK1521498 (25 mg, PO) effects on hedonic taste preference (pleasantness) and taste perception using 20 samples of sweetened commercial dairy products, with varying sucrose and fat content, and a standard 9-point hedonic preference scale that ranged from dislike extremely to like extremely (Nathan et al., 2012). Compared with placebo, GSK1521498 reduced hedonic ratings for the highest levels of fat and sucrose. GSK1521498 selectively reduced caloric intake of snack foods in the high-fat/high-sugar category, while having no effects on low-fat/low-sugar, lowfat/high-sugar and high-fat/low-sugar categories. These results support the role of μ-opioid receptors in non-homeostatic hedonic aspects of palatable food consumption and identify μ-opioid receptors as potential therapeutic targets for the treatment of maladaptive eating behavior associated with obesity.

3.3. Endocannabinoids

In addition to contributing to homeostatic energy balance, endocannabinoids regulate hedonic aspects of food intake. Although pharmacological and genetic studies suggest a role of CB2 receptors in drug addiction (Navarette et al., 2013), this is not as well defined in food reward. CB2 receptors expression in striatum, hippocampus and thalamus (Wotherspoon et al., 2005; Gong et al., 2006; Onaivi et al., 2006) with overlap in reward circuits underlying obesity and addiction (Volkow et al., 2008; Kenny, 2011) suggest CB2 participation in non-homeostatic, hedonic food intake. Diacylglycerol lipase-α, endocannabinoids, 2-AG, anandamide and CB1 receptors localized to accumbens shell and VTA play a role in

motivation and reward mechanisms underlying food intake (Di Marzo et al., 2009). Acquisition of conditioned place preference (CPP) associated with sucrose pellet consumption was decreased dose-dependently by pretreatment with rimonabant (0.03-3 mg/kg, IP; Chaperon et al., 1998). Motivation for palatable food was assessed using PR schedules in CB1 knockout and wild-type mice (Sanchis-Segura et al., 2004). CB1 knockouts exhibited decreased PR breakpoints for sucrose reinforcement, indicating reduced motivation for palatable food. Thus, CB1 receptors are important targets mediating reinforcing and motivational properties of palatable foods.

Activation of CB1 receptors on GABAergic terminals in VTA disinhibits DA neurons, leading to increased VTA firing (Riegel and Lupica, 2004). Activation of CB1 receptors decreases excitatory glutamatergic input to VTA and nucleus accumbens, thereby regulating activity of neurons projecting from prefrontal cortex (Melis et al., 2004). Endocannabinoids do not directly depolarize DA neurons, but indirectly act via pre- and postsynaptic inhibition of interneurons and as retrograde messengers at CB1 receptors, modulating glutamatergic and GABAergic synaptic inputs in VTA and accumbens (Fride, 2002; Szabo et al., 2002; Piomelli, 2005). Thus, endocannabinoid modulation of DA function depends on GABAergic inhibitory and glutamatergic excitatory balance in VTA (Maldonado et al., 2006).

Endocannabinoid signaling within accumbens shell is implicated in food intake and hedonic impact of palatable foods. 2-AG (0.5 μg/0.5 μl) or anandamide (25 ng/0.5 μl) into rat accumbens shell increased food intake (Kirkham et al., 2002; Mahler et al., 2007), which was inhibited by rimonabant (0.5 mg/kg; SC; Kirkham et al., 2002). Anandamide enhanced hedonic 'liking' reactions (orofacial expressions) elicited by sucrose taste (Berridge, 2000; Mahler et al., 2007). Compared with chow, highly palatable food (candied cherry) consumption increased DA in rat accumbens shell; rimonabant (0.3 and 1 mg/kg, IP) decreased DA and highly palatable food consumption (Melis et al., 2007). Inhibitory effects of rimonabant on DA were prevented by pretreatment with a CB1 agonist, WIN 55,212-2 ((*R*)-(+)-[2,3-dihydro-5-methyl-3[(4-morpholinyl)-methyl]pyrrolo-[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)-methanone; 0.3 mg/kg, IP). Thus, rimonabant attenuates palatable food-induced increases in accumbal DA, confirming mesolimbic DA involvement in mediating endocannabinoid effects on palatable food intake.

Compared to standard chow, rats fed a palatable, high-fat diet for 8 wk exhibited decreased CB1 receptor expression in cortex, entopeduncular nucleus, accumbens and hippocampus, which was interpreted as adaptive to elevated endocannabinoids following long term exposure to palatable food (Harrold et al., 2002). Exposure to food with high incentive salience may stimulate endocannabinoid tone to release DA in mesolimbic areas, which feedbacks negatively on endocannabinoid levels (Di Marzo et al., 2009). However, after prolonged high-fat diet consumption and the development of obesity, this negative feedback may be impaired leading to chronically elevated endocannabinoid tone in accumbens shell. Consequently, DA stimulation may lead to both increased motivation to consume palatable foods and heightened reward after consumption.

Taken together, reward mechanisms implicated in the regulation of non-homeostatic food intake serve as potential central targets for the treatment of obesity.

4. Interactions between homeostatic and non-homeostatic hedonic mechanisms

Anatomical and functional interactions exist between homeostatic and nonhomeostatic reward circuits that regulate food intake. Medial hypothalamic nuclei, part of the homeostatic circuit involved in the regulation of energy balance, are connected extensively with brain regions mediating reward and motivation (Berthoud, 2002). The arcuate nucleus of the hypothalamus directly projects to lateral hypothalamus, which is reciprocally connected to the limbic reward circuit (De Olmos and Heimer, 1999; Everitt and Robins, 2005). The central nucleus of the amygdala projects to lateral hypothalamus, and amygdala and lateral hypothalamus receive direct taste inputs from NTS (Berthoud, 2002). Other connections include projections from nucleus accumbens to VTA and lateral hypothalamus (Berthoud, 2002; Kelley and Berridge, 2002). Reciprocal connections between hypothalamic, brain stem and limbic reward circuits establish an anatomical framework for interactions and crosstalk between homeostatic and reward mechanisms in obesity.

4.1. Adiposity signals: Leptin and insulin

Peripherally-derived hormones, leptin and insulin, modulate feeding behavior, independent of actions in hypothalamus (Palmiter, 2007). In addition to widespread expression in hypothalamus, leptin and insulin receptors are co-localized on catecholaminergic neurons containing tyrosine hydroxylase, the rate limiting enzyme in DA and NE synthesis (Figlewicz et al., 2003), providing direct connections between peripheral adiposity signals and mesolimbic brain circuits that regulate motivational and hedonic elements of ingestive behavior.

Behavioral studies provide evidence of a role for leptin and insulin in food reward. Compared to control rats, CPP associated with a high-fat diet was blocked by leptin (0.2 μg, ICV) or insulin (5 mU, ICV) (Figlewicz et al., 2004). Also, ICV infusion of leptin or insulin decreased PR breakpoints for sucrose self-administration in rats, compared to vehicle control (Figlewicz et al., 2006). Leptin and insulin reductions in motivation for food were absent in rats on a high-fat diet for 5 wk; such that, despite ICV leptin or insulin, rats fed a high-fat diet exhibited increased PR breakpoints for sucrose self-administration, compared to chow-fed controls (Figlewicz et al., 2006). Thus, these adiposity signaling molecules modulate activity of neural circuits mediating reward and food-motivated behavior. Further, deficits in leptin and insulin signaling in reward circuits may underlie non-homeostatic hedonic food intake in obesity.

Behavioral paradigms also implicate DA as playing a major role in reward and motivation (Agmo et al., 1995; Figlewicz et al., 2001). Leptin receptor signaling in VTA modulates DA activity and food intake (Hommel et al., 2006). Leptin (3 mg/kg, IP) increases pSTAT3 expression, a marker of leptin signaling in VTA. pSTAT3 expression in VTA was robust following leptin infusion (1 μg) directly into VTA, indicating that this was not likely the result of a primary effect in hypothalamus. Moreover, pSTAT3 was expressed in tyrosine hydroxylase-positive neurons, indicating that primarily DA neurons in VTA are responding

to leptin. In anesthetized rats, leptin (2 mg/kg, IV) reduces VTA DA neuronal firing, compared to control.

Evidence that VTA is important in leptin regulation of food reward and palatable food intake derives from viral-mediated RNA interference studies, generating rats with conditional gene knockdown of leptin receptors specifically in VTA (Hommel et al., 2006). Using two-bottle choice, leptin receptor knockdown rats consumed 50% more of a 0.2% sucrose solution compared to water, thus showing increased sensitivity to sucrose reward. In contrast, sucrose preference was absent in control rats. Also, leptin receptor knockdown increased palatable high-fat food intake, while high-fat food intake was not altered in controls. Leptin receptor knockdown selectively in midbrain augmented PR responding for sucrose, also supporting a role for midbrain leptin signaling in food-motivated behavior (Davis et al., 2011). Compared to control, leptin (15 ng/side, bilateral) injected into VTA elevated brain reward thresholds during intracranial self-stimulation (Bruijnzeel et al., 2011). Thus, leptin independently signals within reward circuits to decrease food reward and consumption of palatable foods.

Leptin regulation of DA reward pathway is evident in leptin deficient ob/ob mice (Fulton et al., 2006). In contrast to leptin's ability to suppress mesolimbic DA signaling (Hommel et al., 2006), leptin-deficient ob/ob mice show decreases in mesolmbic DA signaling. Compared to wild-type mice, ob/ob mice exhibit decreased tyrosine hydroxylase and phosphorylated tyrosine hydroxylase-ser40 expression, an indicator of tyrosine hydroxylase activity, in VTA and accumbens. Consistent with these findings, ob/ob mice exhibit decreased electrically-evoked accumbal DA release, compared to wild-type mice. In the presence of, nomifensine (3 μM; DAT inhibitor), a reduction in electrically-evoked DA signal was maintained, suggesting that DAT is not responsible for DA release deficits in ob/ob mice. In ob/ob mice, leptin (500 ng/h; 12 μg/day, SC) corrected the decrease in tyrosine hydroxylase expression in VTA and accumbens and phosphorylated tyrosine hydroxylase-ser40 in accumbens. However, leptin's ability to correct defects in accumbens DA release in ob/ob mice was not determined. Discrepancies found in ob/ob mice may be attributed to compensatory changes resulting from a long-term leptin deficiency (Opland et al., 2010). Thus, mesolimbic system hypoactivity may underlie compensatory overeating in leptin deficient ob/ob, enhancing a deficient DA system. Overall, these results suggest that reward deficits found in obesity (Geiger et al., 2008), may be attributed to deficient leptin signaling in reward circuits.

Given synaptic connections between lateral hypothalamus and the mesolimbic DA system including VTA and nucleus accumbens, the role of lateral hypothalamus leptin receptors in regulating mesolimbic DA function also was evaluated in ob/ob mice (Leinninger et al., 2009). Leptin (250 pg) injection into lateral hypothalamus decreased feeding, increased VTA tyrosine hydroxylase expression and increased accumbens DA content in ob/ob mice, compared to vehicle control ob/ob mice. These results suggest that leptin acts via lateral hypothalamus neurons expressing leptin receptors to modulate mesolimbic DA function.

Leptin resistance predisposes rodents to high-fat DIO. Rats with pre-existing leptin resistance due to leptin overexpression or age-related leptin resistance, have exacerbated excessive food consumption and weight gain upon subsequent exposure to a high-fat diet,

compared with leptin responsive rats (Scarpace et al., 2005; Judge et al., 2008; Scarpace and Zhang, 2009). Given the role of VTA leptin receptors in decreasing food reward and motivation for palatable food, disruption in leptin function in VTA suggests an increased vulnerability to palatable foods and high-fat diet-induced weight gain (Hommel et al., 2006). Leptin resistance in VTA of DIO rats was determined by pSTAT3 expression (Matheny et al., 2011). Relative to chow-fed controls, increased leptin resistance in VTA and arcuate of DIO rats (evidenced by decreased pSTAT3 expression), provides a potential mechanism for increased susceptibility of DIO rats to palatable food consumption and the development of obesity (Matheny et al., 2011).

A role for DA in modulating leptin in humans comes from a single-blind crossover study conducted in obese women assigned to either bromocriptine (5 mg; oral) or placebo treatment for 8 days (Kok et al., 2006). Compared to placebo, bromocriptine decreased circulating leptin levels, suggesting that DA is involved in control of leptin release in humans. The ability of bromocriptine to modulate palatable food consumption and restore leptin function in hypothalamic and reward circuits will increase our understanding of reciprocal interactions between leptin and D2 receptor signaling.

DAT is a potential cellular target for insulin modulation of reward circuits (Jaber et al., 1997). Central administration of insulin in rats increases DAT mRNA expression in VTA/ substantia nigra compacta, compared with DAT in vehicle controls (Figlewicz et al., 1994, 2003). A functional consequence of increased DAT expression is decreased DA signaling that further decreases palatable food reward. To elucidate contributions of insulin signaling on VTA DA, insulin's effect on electrically-evoked DA release in VTA was determined using fast-scan cyclic voltammetry in mice (Mebel et al., 2012). In a concentration-dependent manner, insulin (10-1000 nM; bath-applied) attenuated electrically-evoked DA release from VTA slices. Insulin receptor activation triggers a variety of signal transduction cascades involving activation of phosphatidylinositol-3 kinase pathway, that triggers activation of the mammalian target of rapamycin (Taha and Klip, 1999). Activation of phosphatidylinositol-3 kinase increases DAT trafficking (Simon et al., 1997; Carvelli et al., 2002; Garcia et al., 2005). Insulin (500 nM) failed to attenuate electrically-evoked DA release when VTA slices were pre-incubated with either a phosphatidylinositol-3 kinase inhibitor, wortmannin (100 nM), or an inhibitor of the mammalian target of rapamycin (50 nM) (Mebel et al., 2012), suggesting that phosphatidylinositol-3 kinase and rapamycin signaling are necessary for insulin suppression of DA release in VTA. Insulin (500 nM) suppression of DA release was abolished by GBR 12909 (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)-piperazine; 500 nM; DAT inhibitor) and in mice lacking DAT (Mebel et al., 2012). However, insulin's effect in mice lacking the NE transporter was not different from wild-type mice, suggesting that DAT plays a role in the underlying mechanism responsible for the insulin-mediated decrease in DA release in VTA.

Insulin effects in VTA, specifically on palatable food consumption, was evaluated in sated mice (Mebel et al., 2012). Insulin (0.3 μg/0.2 μl) or vehicle was administered intra-VTA after mice consumed regular chow during 4-h access, and prior to a 1-h exposure to palatable sweetened high-fat food. Control mice consumed a similar quantity of sweetened high-fat food as during the first hour of regular chow access, indicating that mice consume

palatable food even when sated. In contrast, insulin reduced the amount of sweetened high-fat food consumed during the 1-h exposure. Thus, insulin acting in VTA inhibits sated consumption of palatable food (Mebel et al., 2012). The insulin-mediated decrease in DA release in VTA may be the mechanism underlying the reduction in palatable food salience once satiety is attained. Insulin signaling in VTA producing a decrease reward is supported by an elevated brain reward threshold (intracranial self-stimulation) following intra-VTA insulin (0.005 mU/side) (Bruijnzeel et al., 2011). Thus, disrupted insulin function in VTA may promote hedonic intake of palatable foods, and serve as a mechanism underlying reward and contributing to obesity. Overall, leptin and insulin not only modulate satiety and metabolism, but also decrease food reward. This ability to influence homeostatic and non-homeostatic hedonic mechanisms underlying obesity makes central leptin and insulin receptors attractive targets for intervention.

4.2. Hunger signal: Ghrelin

Ghrelin produces a potent orexigenic effect when food is available (Wren et al., 2000). In addition to homeostatic regulation of energy balance, ghrelin modulates DA reward circuitry and influences motivational and reinforcing aspects of palatable foods, promoting hedonic food consumption (Jerlhag et al., 2007; Skibicka et al., 2011, 2012a). Ghrelin influences the responsiveness of brain regions involved in processing food cues in humans. Using fMRI, cerebral response to food and non-food (scenery) images was determined following single-blinded ghrelin infusion (1 μg/kg) in healthy humans (Malik et al., 2008). BOLD response to visual food cues was increased in amygdala, orbitofrontal cortex, anterior insula and striatum. Also, self-reports of hunger were increased in ghrelin vs. control conditions, and were correlated positively with ghrelin-induced increases in amygdala, orbitofrontal cortex and pulvinar activity. These regions encode salience, hedonic and incentive value of visual cues. Thus, ghrelin enhances palatable food consumption by increasing the hedonic response to food-related cues.

Similar to leptin and insulin, ghrelin modulates VTA DA activity and alters behaviors associated with mesolimbic reward circuitry. Ghrelin (30 μg; IP) produces synaptic remodeling in VTA DA cells in mice in a GHSR-dependent manner (Abizaid et al., 2006). Compared to saline control mice, ghrelin increased frequency of miniature excitatory postsynaptic currents and decreased the frequency of miniature inhibitory postsynaptic currents in VTA DA neurons. These ghrelin effects were absent in GHSR-deficient mice. Using another approach, infusion of ghrelin (0.5 μg/0.5 μl) directly into VTA in awake rats increased food intake for 2 h (Abizaid et al., 2006). Ghrelin (5 μg, IP) induced feeding responses in rats that were attenuated by intra-VTA infusions of GHSR antagonist, BIM28163 (4-[[(2S)-2-[[(2R)-2-[[(2R)-3-(1-benzothiophene-3-yl)-2-(piperidine-3-carbonylamino)propanoyl]amino]-3-(1H-indol-3-yl)propanoyl]amino]-3-phenylpropanoyl]amino]piperidine-4-carboxamide; 0.5 μg/0.5 μl) given 1 h prior to ghrelin (Abizaid et al., 2006). Thus, circulating ghrelin reaches VTA in physiologically relevant amounts to elicit a feeding response via activation of mesolimbic DA circuitry.

Ghrelin (1 μg/1 μl) infusion into VTA increases DA release from accumbens core in freely moving mice (Jerlhag et al., 2007). Infusion of ghrelin (0.33 and 1μg/0.5 μl) into VTA

increases motivation for sucrose reward assessed using the PR schedule of reinforcement (Skibicka et al., 2011, 2013). However, increases in motivation for sucrose reward were absent in rats receiving ghrelin in accumbens core, suggesting that VTA is the target for ghrelin's action on food motivation. Pretreatment with D1 receptor antagonist, SCH-23390 or D2 receptor antagonist, eticlopride (1 μg/0.5 μl; intra-accumbens shell) attenuated ghrelin-induced increases in motivation to seek sucrose, but not chow consumption. Therefore, VTA-accumbens DA signaling mediates ghrelin's effect on effort-based food reward seeking, but not food intake.

A cholinergic-DA link is implicated in ghrelin-induced increase in motivation for food reward (Dickson et al., 2010). Ghrelin (1 μg/μl, ICV)-induced food intake in mice was suppressed by mecamylamine (2 mg/kg, IP), a non-selective nicotinic receptor antagonist, but not by hexamethonium (2 mg/kg, IP), a peripheral nicotinic receptor antagonist (Dickson et al., 2010), indicating central effects of mecamylamine on ghrelin-induced food intake. Mecamylamine (2 mg/kg, IP) blocked food intake induced by ghrelin infusion (1 μg/0.5 μl) into VTA and blocked palatable food-induced CPP in rats. However, ability of ghrelin to rescue CPP for palatable food was not assessed. These results suggest that ghrelin-induced food intake is mediated via nicotinic receptors and nicotinic receptor antagonists decrease rewarding properties of food.

NPY and opioid modulation of ghrelin's effects on food motivated behavior has been investigated (Skibicka et al., 2012b). Inhibitory effects of a selective NPY Y1 receptor antagonist, LY 1229U91 (1-12 μg/2 μl), or opioid receptor antagonist, naltrexone (50 μg/2 μl), injected either ICV or intra-VTA on ghrelin (1 μg/2 μl, ICV)-induced increases in food motivated behavior were assessed using a PR reinforcement schedule. Ghrelin-induced increases in sucrose-motivated behavior were blocked by ICV pre-treatment with LY 1229U91 and naltrexone. However, ghrelin effects were blocked only by intra-VTA naltrexone, not by LY 1229U91 (Skibicka et al., 2012b). These findings suggest that opioid signaling in VTA mediates ghrelin effects on food reward. Thus, ghrelin, an important gut-brain signal, promotes food intake not only in response to energy deficit, but also to reward from palatable foods.

4.3. Satiety signal: GLP-1

GLP-1, an incretin hormone and peripherally-derived satiety signal, has been linked centrally to non-homeostatic and motivational processes associated with food reward (Alhadeff et al., 2012; Dickson et al., 2012; Skibicka, 2013). In addition to homeostatic centers, GLP-1 receptors are expressed in VTA and accumbens (Merchenthaler et al., 1999; Alhadeff et al., 2012). Peripheral administration of exendin-4, a synthetic GLP-1 analog, activates Fos in accumbens (Gu et al., 2013), suggesting that GLP-1 modulates hedonic feeding behavior. Compared to vehicle control, exendin-4 (0.03-3 μg/1 μl, ICV) dose-dependently decreased PR responding for sucrose reinforcement (Dickson et al., 2012). Pretreatment with exendin-3 (20 μg/μl, ICV; a selective GLP-1 receptor antagonist) reversed the exendin-4-induced (0.2 μg/μl, ICV) reduction in motivation to obtain sucrose reinforcement, further confirming a role of central GLP-1 receptors in food-motivated behavior. Both intra-VTA (0.03 and 0.1 μg/0.5 μl) and intra- accumbens (0.1 μg/0.5 μl)

infusion of exendin-4 decreased motivation for sucrose reinforcement, compared to vehicle control (Dickson et al., 2012). Thus, these findings are consistent with mesoaccumbens GLP-1 signaling playing a role in food reward.

GLP-1 receptor activation in NTS-induced suppression of food reward suggests that neurobiological targets underlying GLP-1-mediated food reward are not limited to the DA mesolimbic system. Exendin-4 (0.05 μg/ 0.3 μl) infusion into rat NTS resulted in selective reduction in palatable food intake, relative to chow (Richard et al., 2015). Compared to vehicle-control, exendin-4 (0.05 μg/0.3 μl) infusion into NTS resulted in less time in the sucrose-paired chamber in the CPP test, suggesting that NTS GLP-1 signaling decreases palatable food reward. GLP-1 (2.0 μg/0.3 μl) and exendin-4 (0.05 or 0.1 μg/0.3 μl) injected into NTS suppressed motivation to obtain sucrose reward assessed using a PR schedule of reinforcement. GLP-1 receptor stimulation with exendin-4 (0.05 μg/ 0.3 μl) infusion into NTS resulted in a 4-fold increase in tyrosine hydroxylase mRNA expression and 2-fold increase in D2 receptor mRNA expression in VTA. These findings suggest that NTS GLP-1 receptor activation decreases food reward and motivation for palatable food by modulating mesolimbic DA activity (Richard et al., 2015). Further understanding of interactions between NTS GLP-1 and mesolimbic DA in the regulation of non-homeostatic hedonic food intake is needed.

GLP-1 receptor agonist effects were evaluated recently in a randomized crossover study in obese humans with type-2 diabetes treated for 10 days with either the GLP-1 receptor agonist, liraglutide (1.8 mg, SC), or insulin glargine (100 units/ml, IM), and brain response to pictures of food were assessed using fMRI (Ten Kulve et al., 2015). Under a fasted state, liraglutide decreased BOLD responses in insula and putamen upon viewing food pictures, compared with those treated with insulin glargine. Insula is involved in processing and evaluation of food cues and in craving for food (Small et al., 2001; Pelchat et al., 2004). These results suggest that liraglutide-induced decreases in food reward and perhaps craving contribute to reduction of palatable food consumption. Thus, central GLP-1 receptors are potential therapeutic targets for obesity that modulates reward mechanisms underlying palatable food consumption.

4.4. Orexins and MCH

In addition to homeostatic processes, the lateral hypothalamic orexin system is involved in non-homeostatic reward-driven feeding behavior (Borgland et al., 2009; Cason et al., 2010; Cason and Aston-Jones, 2013; Williams, 2014). Orexin neurons project locally within hypothalamus and widely throughout brain, including projections to VTA and locus coeruleus (Peyron et al., 1998). Both orexin receptor subtypes, orexin-1 and orexin-2, are located in reward relevant brain regions including DA projections from VTA to accumbens, prefrontal cortex and amygdala (Sakurai et al., 1998; Marcus et al., 2001). Orexin-1 receptors are involved predominantly in reward and feeding behaviors (deLecea et al., 1998; Sakurai et al., 1998). Orexin-1 receptor antagonist, SB334867 (10 mg/kg, IP) decreased the PR breakpoint for high-fat chocolate flavored pellets, relative to vehicle control mice (Borgland et al., 2009), revealing a role for this receptor subtype in motivation for palatable food.

The role of orexin signaling in compulsive binge consumption of palatable food was assessed using a binge model in rats (Picolli et al., 2012). Binge eating of highly palatable food was evoked by 3 cycles of food restriction, stress elicited by exposure to palatable food for 15 min (rats see the food, but do not have access), and finally access to palatable food. Effects of a selective orexin-1 receptor antagonist, GSK1059865 ([(2S,5S)-2-[[(5-bromopyridin-2-yl)amino]methyl]-5-methylpiperidin-1-yl]-(3-fluoro-2-methoxyphenyl)-methanone; 10 and 30 mg/kg, PO), a selective orexin-2 receptor antagonist, JNJ-10397049 (1-(2,4-dibromophenyl)-3-[(4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]urea; 1 and 3 mg/kg, IP), and a dual orexin-1/orexin-2 receptor antagonist, SB649868 (*N*-[((2*S*)-1-{[5-(4-fluorophenyl)-2-methyl-1,3-thiazol-4-yl]carbonyl}-2-piperidinyl)methyl]-1-benzofuran-4-carboxamide; 1 and 3 mg/kg, PO) were determined. Compared to vehicle control, GSK1059865 and SB649868 decreased palatable food intake, however, JNJ-10397049 did not alter feeding behavior, suggesting that orexin-1 receptors, but not orexin-2 receptors, mediate binge eating. Given that binge eating contributes to obesity, orexin-1 receptors are a target for decreasing binge eating of palatable foods.

Immunohistochemistry studies show orexin-1 receptor expression and orexin neuron projections to the dorsal vagal complex, including NTS, area postrema and dorsal motor nucleus of the vagus (Peyron et al., 1998; Hervieu et al., 2001; Marcus et al., 2001; Zheng et al., 2005). The role of caudal brainstem orexin-1 receptors in food reward was evaluated in rats by determining effects of fourth cerebral ventricle infusion of orexin-A and a orexin-1 receptor antagonist, SB334867, on PR responding for sucrose pellets and on expression of high-fat diet induced CPP (Kay et al., 2014). Orexin-A (1 nmol/2 μl) robustly increased the breakpoint for sucrose reinforcement, compared to vehicle. SB334867 (20 nmol/2 μl) decreased the breakpoint to obtain sucrose reinforcement and inhibited CPP. These results suggest that hindbrain orexin-1 receptor activity modulates food-motivated behavior and plays a role in the response to environmental cues assocated with palatable food.

Excessive consumption of palatable foods contributes to obesity. While people attempt to control food intake through healthy choices including dieting, most relapse to unhealthy eating occurs after acute exposure to palatable foods, associated cues or stress (Peterson and Mitchell, 1999; Torres and Nowson, 2007). The reinstatement paradigm, which commonly is used to study relapse to seeking abused drugs, has been employed to study relapse to seeking palatable food (Self and Nestler, 1998; Shaham et al., 2003; Ghitza et al., 2006). In the reinstatement paradigm, food-restricted rats are trained using operant procedures to obtain palatable food reinforcement, typically employing a fixed ratio schedule (Calu et al., 2014). Following food pellet training and extinction of the food-reinforced responding, palatable food seeking behavior is reinstated by priming with palatable food pellets, food-associated cues, or stress, e.g., induced by yohimbine administration (Bremner et al., 1996). A role for orexin-1 receptor signaling in reinstatement of palatable food seeking behavior is supported by results showing that the orexin-1 receptor antagonist, SB334867 (5 and 10 mg/kg, IP), decreased yohimbine-induced reinstatement of sucrose seeking in food-sated rats trained to self-administer 5% sucrose solution (Richards et al., 2008). Pretreatment with SB334867 (30 mg/kg, IP) decreased cue (tone and light)-induced reinstatement of saccharin-seeking behavior, which had been extinguished, in both sated and food-restricted rats (Cason and Aston-Jones, 2013). These results suggest that orexin-1 signaling plays a role in motivation

to obtain palatable food and in the response to cues previously associated with palatable foods.

Orexin-1 signaling mediates cue-induced feeding in rats (Cole et al., 2015). Through repeated pairings of a neutral stimulus (a tone) with delivery of palatable food, rats learn that the cue predicts food availability. Ability of cue to stimulate overeating is assessed later in sated rats by presenting the tone and measuring food consumption. In the presence of cue, rats eat greater amounts of food. SB334867 (20 mg/kg, IP), an orexin-1 receptor antagonist, had no effect on baseline eating, but reduced cue-induced consumption in sated rats, while activating Fos in medial prefrontal cortex and paraventricular thalamus. Thus, orexin signaling through cortical and thalamic sites drives cue-induced eating in the absence of hunger. Orexin-1 receptor antagonists appear beneficial in decreasing motivation for palatable food reward and preventing relapse to palatable food seeking behavior and serve as targets for therapeutics.

Subsets of orexin neurons in lateral hypothalamus secrete the orexigenic neuropeptide MCH and have input to accumbens (Georgescu et al., 2005; Sears et al., 2010). The role of MCH-1 receptors in cue-potentiated feeding of palatable food is supported by findings that sated MCH-1 receptor knockout mice fail to overconsume sucrose in response to a conditioned stimulus, relative to sated wild-type mice (Sherwood et al., 2015). Thus, cue-potentiated feeding requires intact MCH-1 receptor signaling. MCH-1 receptor antagonists may be beneficial to reduce excessive drive to consume high salience food reinforcers. MCH-1 receptors also appear to be excellent pharmacologic targets for therapeutic discovery.

In summary, homeostatic circuits interact functionally with the reward circuitry in brain, underscoring that both systems are important in regulation of food intake. Understanding the functional interaction between homeostatic and reward systems will provide anti-obesity strategies that address food intake from energy balance and hedonic perspectives. Discoveries highlighting the impact of homeostatic signals (leptin, insulin and GLP-1) on the reward system extend the potential therapeutic range of these targets. For example, GLP-1 receptors mediate aspects of palatable food consumption including satiety, reward and motivation. Thus, preclinical and clinical evaluation of these targets should investigate therapeutic candidates for effects on energy balance (decreases in food intake and weight loss) and non-homeostatic hedonic mechanisms (motivation for palatable foods and relapse to food-seeking behavior). Such targets may offer long-term efficacy in the treatment of obesity.

5. Adiposity and hunger signals: Vulnerability to drug abuse

Adiposity signals modulate mesolimbic DA reward circuits and regulate nonhomeostatic hedonic food intake. Given overlapping neuronal circuits in obesity and substance use disorders (Volkow et al., 2008), these peripherally-derived signals also alter sensitivity to reward produced by drug reinforcers, including nicotine and alcohol. For example, smoking rates in adults with diabetes are greater than in the general population (Bishop et al., 2009). Furthermore, tobacco use is a risk factor that promotes negative health consequences of type-2 diabetes (Cho et al., 2009). Given epidemic increase in type-2 diabetes, a metabolic

sequela of obesity, diabetes-induced changes in reward pathways may increase susceptibility to tobacco use.

As a model of diabetes, streptozotocin treatment produces toxic effects on pancreatic-β cells and induces hypoinsulinemia and hyperglycemia. In streptozotocin-treated rats, IV self-administration using a fixed ratio-1 schedule of reinforcement and extended access (23 h) to increasing nicotine doses (0.03-0.09 mg/kg/0.1 ml infusion) revealed increased nicotine intake, compared to vehicle control rats (O'Dell and Koob, 2007; O'Dell et al., 2014). High-fat diet models of obesity resemble the etiology of type-2 diabetes, as animals develop insulin resistance and hyperglycemia (Woods et al., 2003). Using another diabetes model, the magnitude of nicotine CPP was greater in insulin-resistant rats fed a high-fat diet for 5 wk compared to regular diet (Richardson et al., 2014). Further, nicotine CPP was absent in rats fed regular diet and in non-insulin-resistant rats fed high-fat diet. Nicotine reward was exacerbated in rats that received the high-fat diet and displayed insulin resistance, suggesting an enhancement of nicotine reward via disruption of insulin signaling. Thus, individuals with diabetes may experience greater nicotine reward, augmenting the risk for tobacco addiction.

Peripherally-derived adiposity and hunger signals alter the sensitivity to nicotine and alcohol reward. Human studies reveal a positive correlation between circulating leptin levels and tobacco craving in smokers after 24 h of abstinence (Von der Goltz et al., 2010; al'Absi et al., 2011), suggesting that leptin modulates DA reward circuits during nicotine withdrawal to facilitate nicotine seeking. Further investigation of links between appetite regulation, obesity and nicotine dependence is warranted.

Similarly, central ghrelin signaling is implicated in alcohol reward (Jerlhag et al., 2009). Ghrelin (2 μg, ICV, intra-VTA or laterodorsal tegmental area) increased alcohol (10% alcohol in water) consumption in a 2-bottle choice limited access paradigm in mice (Jerlhag et al., 2009). Alcohol intake was suppressed by GHSR1A antagonists, BIM28163 (5 μg, ICV) or JMV2959 (2-amino-N-[(1R)-2-(1H-indol-3-yl)-1-[4-[(4-methoxyphenyl)methyl]-5-(2-phenylethyl)-1,2,4-triazol-3-yl]ethyl]acetamide, 6 mg/kg; IP). Alcohol produced CPP in wild-type mice and GHSR1A antagonists blocked alcohol-induced CPP. Alcohol-induced CPP was not found in GHSR1A knockout mice. Thus, central ghrelin signaling via GHSR1A mediates alcohol reward.

Recent human studies emphasize ghrelin's role in alcohol abuse. In a 12-wk study conducted in alcohol-dependent humans, plasma ghrelin was correlated positively to alcohol intake and craving (Leggio et al., 2013). These results support a role for ghrelin in alcohol-seeking behavior. Effects of ghrelin (1, 3 μg/kg, IV) or placebo on alcohol craving (assessed using a visual analog scale) in alcohol-dependent, non-treatment-seeking, heavy-drinkings humans were determined in a double-blind, placebo-controlled cue-reactivity study (Leggio et al., 2014). A positive correlation between cue-induced alcohol craving and blood ghrelin was found, suggesting that ghrelin plays a role in facilitating alcohol-seeking behavior. Further, ghrelin (3 μg/kg, IV) decreased serum leptin levels in non-treatment-seeking, alcohol-dependent, heavy drinkers, compared with vehicle control (Haass-Koffler et al., 2015). Moreover, ghrelin-induced decreases in leptin levels correlated negatively with increased

alcohol craving in heavy drinkers, suggesting that leptin and ghrelin exert opposite effects on alcohol seeking behavior. Thus, ghrelin and leptin interact to influence alcohol craving and are potential therapeutic targets for alcohol addiction.

In summary, the role of adiposity and hunger signals extends beyond homeostatic and non-homeostatic regulation of food intake, such that these signals are involved in mediating reward sensitivity to drug reinforcers. Further studies are needed to establish the links between obesity and drug abuse vulnerability.

6. Pharmacotherapies for obesity

A healthy diet and exercise are beneficial for both prevention and treatment of obesity. However, lifestyle modification alone has failed to ameliorate the obesity epidemic, necessitating the development and implementation of effective pharmacotherapeutic strategies. Based on FDA guidelines, an anti-obesity medication is deemed effective if the drug produces >5% reduction in body weight compared to placebo, or if at least 35% of study participants lose >5% of their baseline body weight (FDA draft guidance, 2007). A 5-10% weight loss reduces the incidence of both type 2 diabetes and cardiovascular complications (Avenell et al., 2004). Current pharmacotherapeutics and candidates under clinical development for obesity are categorized herein as follows: 1) medications that act peripherally to impair dietary fat absorption; 2) medications that act centrally to decrease food intake; and 3) medications that facilitate energy expenditure. Despite compliance with weight loss guidelines, the majority of drugs launched for the treatment of obesity over the last two decades have been withdrawn due to safety issues associated with increased risk of cardiovascular and psychiatric complications. The failure of these medications is attributed to the multifactorial pathogenesis and the complex neuro-hormonal regulation of energy balance. Although some efficacy has been found with monotherapies that target a single protein or pathway involved in obesity, physiological counter-regulation mechanisms involving alternate pathways pose major limitations (Rodgers et al., 2012). Consequently, a disease with multiple etiologies, requires a multi-target approach. In this context, two most recently approved combination therapies for obesity include Qsymia®, a combination of phentermine and topiramate, and Contrave®, a combination of naltrexone and bupropion. Importantly, combination therapies are postulated to have increased efficacy through a synergistic action that counteracts compensatory mechanisms, decreases adverse effects and increases tolerability with low dose combinations (Gadde and Allison, 2009). This section discusses FDA approved anti-obesity medications (Table 1), therapeutic candidates undergoing clinical development (Table 2), and compounds that have potential as therapeutic candidates based on findings from preclinical and preliminary human studies (Table 3).

6.1 . Approved anti-obesity drugs

6.1.1. *Phentermine (Adipex-P®)*—Phentermine (2-methyl-1-phenylpropan-2-amine) is a sympathomimetic amine approved by the FDA in 1959 for short-term (12 wk) weight management as an adjunct to caloric restriction and lifestyle modifications for obese and overweight individuals with weight-related comorbidities (Sweeting et al., 2014). Phentermine is the most commonly prescribed anti-obesity medication in the United States

(Hampp et al., 2013). In a randomized, double-blind, placebo-controlled 12-wk trial, the safety and efficacy of phentermine (30 mg) in a diffused-controlled release formulation was assessed in obese participants with controlled diabetes, hypertension or dyslipidemia (Kang et al., 2010). Compared to placebo, participants given phentermine exhibited significant body weight reductions (8 vs. 2 kg). Total cholesterol and low-density lipoprotein cholesterol levels also were improved with phentermine. No between-group differences in systolic and diastolic blood pressure were found.

Frequently, phentermine is prescribed off-label for longer than the FDA approved period (Hampp et al., 2013). Physicians typically prescribe the generic 37.5 mg tablet and advise patients to administer a half tablet (18.75 mg) mid-morning, once daily (Adipex-P prescribing information, 2012). Despite a long history of use, limited information is available with respect to controlled trials demonstrating efficacy of phentermine monotherapy for a year or more or regarding risk for cardiovascular disease. The longest (36 wk) placebo-controlled trial evaluating 108 obese women treated with phentermine 30 mg per day administered either continuously or intermittently (alternating months) reported a mean weight loss of 12.2 and 13.0 kg, respectively, compared with 4.8 kg given placebo (Munro et al., 1968). However, only 59% of participants completed the trial, underscoring the need for controlled long-term studies to demonstrate safety and efficacy. The most common adverse events include dry mouth and insomnia (Yanovski and Yanovski, 2014). Serious complications include palpitations, tachycardia and hypertension (Sweeting et al., 2014). Long-term, dose-ranging clinical trials are needed to confirm the safety and efficacy of phentermine as an anti-obesity therapeutic.

6.1.2. *Orlistat (Xenical®)*—Orlistat ((S)-((S)-1-((2S, 3S)-3-hexyl-4-oxooxetan-2-yl)tridecan-2-yl) 2-formamido-4-methylpentanoate) is the first gastrointestinal lipase inhibitor approved by the FDA in 1999 for the treatment of obesity (McNeely and Benfield, 1998; Heal et al., 2012). Dietary fat is metabolized by gastric and pancreatic lipases into absorbable free fatty acids and monoglycerides, facilitating intestinal absorption. Orlistat inactivates gastrointestinal lipase, reducing the absorption of dietary fat (Hogan et al., 1987). Obese individuals treated with orlistat (360 mg/day, in 3 divided doses) for 12 wk and maintained on a hypocaloric diet had greater body weight loss compared with placebo (5% vs. 3.5%; McNeely and Benfield, 1998). In several randomized controlled trials, orlistat exhibited long-term (2-4 years) efficacy for body weight reduction (Hauptman et al., 2000; Heymsfield et al., 2000; Torgerson et al., 2004). Importantly, orlistat improved blood pressure, insulin resistance and serum lipid levels (Torgerson et al., 2004; Siebenhofer et al., 2009).

Commonly experienced gastrointestinal side-effects of orlistat include diarrhea, flatulence, bloating, abdominal pain and dyspepsia (Siebenhofer et al., 2009). Often, daily multivitamins are co-prescribed to prevent fat-soluble vitamin deficiencies (Padwal and Majumdar, 2007). Following oral administration, orlistat is excreted almost entirely in the feces within 3-5 days, undergoes minimal systemic absorption and exhibits no accumulation (Zhi et al., 1996; Sjostrom et al., 1998). Several cases report acute kidney injury in orlistat users predisposed to metabolic conditions such as diabetes (Courtney et al., 2007; Karamadoukis et al., 2009). Upon renal biopsy, increased urinary oxalate and oxalate crystal

deposition were found (Ferraz et al., 2004; Sarica et al., 2008). Oxalate crystal deposition has been attributed to unabsorbed dietary fat binding to calcium in the gut lumen, which competitively inhibits calcium binding of oxalate, which is absorbed and deposited in renal parenchyma (Karamadoukis et al., 2009). In 2012, a safety label warning for orlistat was approved, which indicates that some patients may develop increased urinary oxalate levels and that renal function should be monitored in those at risk for renal insufficiency. From 1999 to 2008, the FDA received 32 reports of serious liver injury in patients using orlistat, including 6 cases of liver failure (FDA drug safety communication, 2010). In May 2010, a warning of severe liver injury was included. Nevertheless, orlistat provides an overall reasonable benefit to risk ratio for the treatment of obesity. Given the established safety profile of orlistat, a 60-mg over-the-counter dose was approved as a weight loss aid for overweight adults along with a reduced-calorie, low-fat diet and exercise program (FDA, 2007). The 60-mg dose is tolerated better than the 120-mg dose as gastrointestinal side-effects are minimal when individuals consume less than 30% of their energy from fat (Anderson, 2007).

6.1.3. _Lorcaserin (Belviq®)_—5-HT has a role in the short-term regulation of food intake and its actions are implicated in satiety (Blundell, 1977). Dexfenfluramine, an inhibitor of the 5-HT transporter, was approved initially as an appetite suppressant for obesity, but subsequently withdrawn due to serious adverse side-effects including hallucinations induced by 5-HT$_{2A}$ receptor activation, heart valve disease (cardiac valvulopathy), and pulmonary artery hypertension induced by 5-HT$_{2B}$ receptor activation (Weissman et al., 1998; Launay et al., 2002). In 2012, the FDA approved lorcaserin, ((1R)-8-chloro-1-methyl-2, 3, 4, 5-tetrahydro-1H-3-benzazepine), a selective 5-HT$_{2C}$ agonist, and a milestone therapeutic for the treatment of obesity. About 13 years after the approval of orlistat, lorcaserin was launched as the second anti-obesity drug. Importantly, lorcaserin exhibits high selectivity for 5-HT$_{2C}$ receptors and is devoid of adverse effects associated with 5-HT$_{2A}$ and 5-HT$_{2B}$ receptor activation (Martin et al., 2011). Anti-obesity effects of lorcaserin are regulated by 5-HT$_{2C}$ receptors that are expressed on POMC neurons of arcuate nucleus and their activation results in increased satiety (Lam et al., 2008). Mice lacking melanocortin MC4R are not responsive to 5-HT$_{2C}$ agonist-induced hypophagia, suggesting that 5-HT$_{2C}$ receptor agonists, such as lorcaserin, promote hypophagia by downstream activation of the melanocortin pathway.

The FDA approved lorcaserin at a dose of 10 mg twice daily when supplemented by a reduced calorie diet and increased physical activity for patients with a body mass index of 30, or 27 kg/m^2, with at least one weight-related comorbidity, such as hypertension, type 2 diabetes or dyslipidemia (FDA, 2012a). The approved labeling indicates that at wk 12, if body weight is not decreased by 5% or more, lorcaserin treatment should be discontinued (Taylor et al., 2013). Safety and efficacy of lorcaserin for weight loss in obese and overweight patients with type 2 diabetes in conjunction with a lifestyle modification program were evaluated in a 1-year, randomized, double-blind, placebo-controlled trial (O'Neil et al., 2012). In this study, 38% of participants treated with lorcaserin (10 mg, twice daily) exhibited at least a 5% reduction in body weight (O'Neil et al., 2012). The weight reduction was evident at 2 wk, and remained greater in the lorcaserin group than in the

placebo group throughout the study. At wk 52, participants treated with lorcaserin exhibited greater body weight loss compared to those treated with placebo (4.5% vs. 1.5%; O'Neil et al., 2012). Weight loss was accompanied by improvements in glycemic control; however, symptomatic hypoglycemia occurred in 7.4% of lorcaserin-treated participants. As such, regular monitoring of glucose levels before and during treatment as well as appropriate anti-diabetic regimen modifications are recommended. Most common adverse reactions (>5%) in non-diabetic participants were headache, dizziness, fatigue, nausea, dry mouth, and constipation; in diabetic participants, adverse reactions included hypoglycemia, headache, back pain, cough and fatigue (O'Neil et al., 2012). In contrast to fenfluramine, no increase in rate of cardiac valvulopathy was found after a 2-year lorcaserin treatment (Smith et al., 2010).

Abuse liability was evaluated in a randomized, double-blind placebo-controlled study of recreational polydrug users given acute doses of lorcaserin (20, 40 and 60 mg), zolpidem (15 and 30 mg), ketamine (100 mg) and placebo (Shram et al., 2011). Abuse liability was evaluated using a visual analog scale for drug liking, which directly correlates with abuse potential (FDA, draft guidance, 2009). While subjective effects of 20 mg lorcaserin were similar to placebo, supratherapeutic lorcaserin doses (40 and 60 mg) were associated with "dislike" compared with placebo. In contrast to effects produced by lorcaserin, ketamine and zolpidem produced greater "liking" than placebo (Shram et al., 2011). These findings suggest that lorcaserin is well tolerated and lacks abuse liability at therapeutic doses.

Of note, increased serotonin transmission can lead to the serotonin syndrome, which is potentially life-threatening and characterized as a combination of mental status changes, autonomic instability, and neuromuscular hyperactivity (Sternbach, 1991; Brown et al., 1996). Since lorcaserin stimulates the serotonergic system, drug interactions may occur, suggesting that studies are needed which assess the development of the serotonin syndrome in patients using lorcaserin when in combination with other serotonergic agents (Gustafson et al., 2013).

6.1.4. *Phentermine and Topiramate (Qsymia®)*—In 2012, the FDA approved phentermine and topiramate as a combination therapy for use with a reduced-calorie diet and increased exercise to achieve effective weight loss in obesity (FDA, 2012b). Qsymia® is a fixed dose, controlled-release, combination product containing immediate-release phentermine hydrochloride and extended-release topiramate. Appetite suppressant effect of phentermine, a potent inhibitor of the NE transporter, is thought to be mediated by activation of POMC arcuate nucleus neurons (Fleming et al., 2013). Topiramate (2, 3, 4, 5-bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate), a GABA agonist, was approved for the treatment of epilepsy (Lee et al., 2003). Patients treated with topiramate exhibited decreased calorie intake and weight loss (Ben-Menachem et al., 2003). Topiramate-induced appetite suppression may be due to modulation of voltage-gated ion channels, increased activity at GABA-A receptors and/or inhibition of AMPA/kainite glutamate receptors (Richard et al., 2000; Bray et al., 2003). Clinical studies demonstrate topiramate's ability to inhibit compulsive food cravings and addictive behavior. Patients with a binge eating disorder receiving topiramate (starting dose of 25 mg/day, titrated over 8-wks to 400 mg/day) experienced reductions in binge eating days and episode frequency, body weight and

compulsive features of binge eating disorder, compared to placebo (McElroy et al., 2007). Ability of Qsymia® to modulate compulsive food-seeking behavior at a clinically relevant dose combination has not been determined. Nevertheless, Qsymia® is the first combination therapy approved for the treatment of obesity that targets both homeostatic (phentermine) and non-homeostatic (topiramate) mechanisms.

The recommended daily dose of Qsymia® contains 7.5 mg of phentermine and 46 mg of topiramate extended-release, although it is available also at a higher dose (15 mg of phentermine and 92 mg of topiramate extended-release) for selected patients (FDA, 2012b). After one year of treatment with the recommended and highest daily dose of Qsymia®, obese patients had a weight loss of 7.8% and 9.8%, respectively, compared to 1.2% with placebo (Gadde et al., 2011). Treatment with Qsymia® ameliorated obesity-associated cardio-metabolic conditions, with reductions in high blood pressure, improved total cholesterol and high-density lipoprotein ratios, and decreased glycated hemoglobin levels in overweight and obese participants with type 2 diabetes (Allison et al., 2012; Colman et al., 2012).

Adverse reactions occurring at a rate of 5% and at least 1.5 times greater than placebo include paresthesia, dizziness, dysgeusia, insomnia, constipation and dry mouth (Garvey et al., 2012). Qsymia® increases heart rate, thereby requiring regular monitoring, especially when initiating or increasing the dose (FDA, 2012b). Prior to treatment, patients should be assessed for depression and suicide ideation since topiramate increases risk of suicidal thoughts (Colman et al., 2012). Qsymia® is contraindicated during pregnancy since topiramate exposure in the first trimester of pregnancy increases risk of cleft lip with or without cleft palate (Margulis et al., 2012). Therefore, Qsymia® is classified as a pregnancy category X drug, due to teratogenic risk (Margulis et al., 2012).

Given structural similarities between phentermine and amphetamine, Qsymia® is a Schedule IV drug under the FDA Controlled Substances Act (Lonneman et al., 2013). Evaluation of phentermine's addictive potential revealed no abuse liability in overweight, obese and weight loss maintenance patients (Hendricks et al., 2014). Amphetamine-like withdrawal was absent upon abrupt treatment cessation at doses much higher than commonly recommended and after treatment durations of up to 21 years (Hendricks et al., 2014).

6.1.5. *Naltrexone and Bupropion (Contrave®)*—Naltrexone ((4R,4aS,7aR,12bS)-3-(cyclopropylmethyl)-4a,9-dihydroxy-2,4,5,6,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline-7-one) is a non-selective opioid receptor antagonist used to treat opioid and alcohol dependence (Heal et al., 2012). Buproprion ((±)-2-(tert-butylamino)-1-(3-chlorophenyly)propan-1-one) is an inhibitor of DA and NE transporters and is approved to treat depression and nicotine addiction (Dwoskin et al., 2006). In 2014, Contrave®, an extended release oral formulation of naltrexone and bupropion, was approved by the FDA as a combination product for adults with a body mass index of 30 and above or with a body mass index of at least 27 with obesity-related comorbidities (FDA, 2014a). Contrave®treatment is initiated with once daily tablet of 8 mg naltrexone and 90 mg bupropion for wk 1, and escalated to a maintenance 2 tablets twice daily for a total daily dose of 32 mg naltrexone and 360 mg bupropion (FDA, 2014a).

In a double-blind, placebo-controlled randomized study, obese or overweight participants with dyslipidemia and/or hypertension that received Contrave® (naltrexone 32 mg/day; burpoion 360 mg/day) for 56 wk exhibited greater weight loss (6.4%) compared to placebo (1.2%) (Apovian et al., 2013). Participants treated with Contrave® exhibited greater improvement in various cardiometabolic risk markers, participant-reported weight-related quality of life, and control of eating compared to placebo (Apovian et al., 2013). The most common adverse reactions reported in ≥5% participants included nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth and diarrhea. This combination therapy carries a black box warning of increased risk of suicidal behavior and ideation, and neuropsychiatric symptomology (FDA, 2014a). Post-marketing evaluations were required for Contrave® with respect to cardiovascular risks, clinical efficacy and safety in pediatric patients, dosing in patients with renal or hepatic impairment and interactions with other drugs, as well as a juvenile animal toxicity study to evaluate effects on growth, development, and learning and memory (FDA, 2014a).

The precise mechanism of action of Contrave® as an anti-obesity agent is poorly understood. Modulation of both homeostatic (hypothalamic melanocortin system) and non-homeostatic systems (mesolimbic DA reward system) has been suggested based on evidence that naltrexone (1 μmol/L), bupropion (10 μmol/L) and their combination increase firing frequency of POMC neurons in hypothalamic slices (Cowley et al., 1999; Greenway et al., 2009). The postulated mechanism is that bupropion stimulates hypothalamic POMC neurons releasing α-MSH, which binds to MC4Rs, leading to a decrease in food intake and an increase in energy expenditure. Under physiological conditions, when α-MSH is released, POMC neurons simultaneously release β-endorphin, a μ-opioid receptor agonist, which inhibits further release of α-MSH, thus activating a negative feedback loop (Kelly et al., 1990; Cowley et al., 2001; Ibrahim et al., 2003). Naltrexone blocks μ-opioid receptors, preventing the β-endorphin-mediated negative feedback, and the subsequent increase in POMC activity may underlie the weight loss effects of Contrave® (Billes et al., 2014).

Involvement of the DA reward system in mediating anti-obesity effects of Contrave® is suggested by studies measuring food intake in fasted mice following intra-VTA injection of naltrexone (1 μg), bupropion (1 μg) or the combination (Sinnayah et al., 2007; Billes et al., 2014). The drug combination produced a greater reduction in food intake compared to either drug alone, revealing a synergistic effect on food intake likely involving food reward mechanisms. Contrave® (naltrexone 32 mg/day; bupropion 360 mg/day for 4 wk) effects on reactivity to food cues was evaluated in an fMRI study conducted in obese humans under a food-deprived condition (Wang et al., 2014). Contrave® attenuated activation in hypothalamus and enhanced activation in regions involved in inhibitory control (anterior cingulate), internal awareness (superior frontal, insula, superior parietal) and memory (hippocampal) in response to food cues. These findings suggest that, in addition to hypothalamic mechanisms, Contrave®-induced weight loss also may be due to favorable alterations in cortical reactivity to food cues, memory and self-control. Thus, Contrave® impacts brain regions influencing both homeostatic and non-homeostatic food intake.

6.1.6. _Liraglutide (Saxenda®)_—Liraglutide is a long-acting GLP-1 analog approved for the treatment of type 2 diabetes (Victoza®, [produced by recombinant DNA technology

(rDNA origin)], 1.8 mg; SC; FDA, 2010). In 2014, the FDA approved Saxenda® ([rDNA origin], 3 mg; SC), for chronic weight management in obese and overweight adults with at least one weight-related comorbidity, such as hypertension, diabetes or dyslipidemia (FDA, 2014b). Saxenda® is not used in combination with any other drug belonging to the GLP-1 analog class, including Victoza® (FDA, 2014b). In a 56-wk, randomized, placebo-controlled study, safety and efficacy of Saxenda® (3 mg; SC) for chronic weight management was evaluated in overweight and obese adults without diabetes (Pi-Sunyer et al., 2015). Participants treated with Saxenda® (8.1%) exhibited greater body weight loss compared to placebo (2.7%). Saxenda® also reduced cardio-metabolic risk factors, improved fasting and postprandial glycemic variables, β-cell function and insulin sensitivity, and resulted in a delayed onset of type 2 diabetes. Safety and efficacy of Saxenda® for the treatment of diabetes have not been established.

Adverse reactions reported in 5% of patients included nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain and increased lipase activity. Serious adverse events included acute pancreatitis, chest pain and bronchitis. Saxenda® can raise heart rate and should be discontinued in those with a sustained increase in resting heart rate. Saxenda® has a boxed warning stating that thyroid gland tumors (thyroid C-cell tumors) have been observed in rodent studies (FDA, 2014b). Although this effect has not been found in humans, Saxenda® should not be used in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 (a disease which predisposes patients to medullary thyroid carcinoma) (FDA, 2014b). The FDA has required post-marketing evaluations for Saxenda® including case registry of medullary thyroid carcinoma for at least 15 years to identify any increase in incidence, and an evaluation of the potential risk of breast cancer. Also required are clinical trials to evaluate dosing, safety and efficacy in paediatric patients, assessment of potential effects on growth, sexual maturation and central nervous system development and function in immature rats, (FDA, 2014b).

6.2 . Anti-obesity drugs in clinical development

6.2.1. *Tesofensine*—Tesofensine ((1R, 2R, 3S, 5S)-3-(3, 4-dichlorophenyl)-2-(ethoxymethyl)-8-methyl-8-azabicyclo[3.2.1]octane)) is a novel potent, non-selective uptake inhibitor of NE, DA and 5-HT (Astrup et al., 2008b). Tesofensine was developed for the treatment of Alzheimer's and Parkinson's disease, but lacked efficacy (Astrup et al., 2008b). Meta-analysis revealed that tesofensine (0.125-1.0 mg, once daily; oral) produced dose-dependent weight loss, and 32% of obese patients had 5% weight loss following 14 wk of treatment. Weight loss was accompanied by hypophagia, suggesting an appetite suppressant action. In a 24-wk randomized, double-blind, placebo-controlled Phase II trial conducted in obese participants, tesofensine (0.25 mg, 0.5 mg and 1 mg) resulted in weight loss of 5%, 9%, and 11%, respectively, compared to placebo (2%) (Astrup et al., 2008a). After 24 wk, heart rate was increased by tesofensine (0.5 mg and 1 mg). An increased incidence (6%) of depressed mood was reported. Comprehensive assessment of neuropsychiatric adverse events following tesofensine treatment in obese patients is warranted.

The mechanism underlying the anti-obesity effects of tesofensine was evaluated in a DIO rat model (Axel et al., 2010). Treatment with tesofensine (2 mg/kg, SC) for 16 days suppressed daily food intake (49%) and produced weight loss (14%), compared to vehicle. Acute tesofensine (0.5-3 mg/kg; SC) dose-dependently decreased food intake, with an ED_{50} of 1.3 mg/kg. Tesofensine-induced hypophagia was inhibited by co-administration of prazosin ($a1$ adrenoceptor antagonist, 1 mg/kg, SC) and SCH23390 (D1 receptor antagonist, 0.03 mg/kg, SC), and not inhibited by RX821002 ($a2$ adrenoceptor antagonist, 0.3 mg/kg, SC), haloperidol (D2 receptor antagonist, 0.03 mg/kg, SC), NGB2904 (D3 receptor antagonist, 0.1 mg/kg, SC), or ritanserin (5-HT$_{2A/C}$ receptor antagonist, 0.03 mg/kg, SC). Thus, $a1$ and D1 receptors appear to be involved in the anti-obesity effects of tesofensine.

6.2.2. *Bupropion and Zonisamide (Empatic)*—Weight-loss is a common side-effect of the anti-convulsant drug, zonisamide, and this prompted its evaluation as a treatment for obesity (Gadde et al., 2003). Zonisamide (1, 2-benzoxazol-3-ylmethanesulfonamide) is a potent inhibitor of carbonic anhydrase, which is proposed to contribute to weight-loss (De Simone et al., 2008). Detrimental effects of zonisamide, such as depression and sedation, may be overcome by its combination with bupropion (Ioannides-Demos et al., 2011). A 24-wk Phase II clinical trial of the sustained release formulation of bupropion (360 mg)-zonisamide (360 mg) combination produced greater weight loss (9.2%) than bupropion (6.6%) or zonisamide (3.6%) alone or compared to placebo (0.4%) (Ioannides-Demos et al., 2011). The most common adverse events reported were headache, nausea and insomnia. Phase III clinical trials with the fixed dose combination are underway (George et al., 2014).

6.2.3. *Exenatide*—A study conducted in overweight women with insulin resistance and polycystic ovary syndrome showed the anti-obesity effects of exenatide, a GLP-1 agonist regulating glucose metabolism and insulin secretion (Kolterman et al., 2003; Elkind-Hirsch et al., 2008). Participants were randomized into three treatment groups: exenatide (10 μg twice a day, SC); metformin, an oral anti-diabetic drug (2000 mg/day); or the combination of metformin (2000 mg) and exenatide (20 μg) (Elkind-Hirsch et al., 2008). After 24 wk of treatment, the combination therapy resulted in a mean weight loss of 6 kg, whereas each therapeutic alone produced a 2-3 kg weight loss. Obese subjects treated with exenatide (10 μg twice daily, SC) for 24 wk also showed greater loss (5 kg) from baseline relative to placebo (2 kg) (Rosenstock et al., 2010). Moreover, a greater percentage of exenatide-treated subjects experienced 5% body weight reduction at 24 wk compared with placebo (32 vs. 17%, respectively). A once/wk administration of a long-acting formulation of exenatide (0.8 or 2 mg, SC, for 15 wk) was evaluated in a randomized, placebo-controlled Phase II study in participants with type 2 diabetes (Kim et al., 2007). Participants receiving 2 mg exenatide exhibited body weight reductions (3.8 kg), whereas body weight was not changed in participants treated with either 0.8 mg exenatide or placebo. Thus, higher exenatide doses were required for body weight loss. Fasting plasma glucose and A1C levels were decreased significantly in participants treated with either doses of exenatide, compared to placebo. Exenatide (Byetta®) was approved by the FDA to improve glycemic control in patients with type 2 diabetes. Further clinical studies investigating the long-term efficacy of exenatide for the treatment of obesity are needed (Dushay et al., 2012).

6.2.4. Cetilistat—Cetilistat (2-hexadecoxy-6-methyl-3,1-benzoxazin-4-one) is a gastric- and pancreatic-lipase inhibitor that is currently undergoing Phase III clinical trials for the treatment of obesity (Charmot, 2012; Jackson et al., 2014). Although the mechanism of action and efficacy of cetilistat is similar to that of orlistat, Phase II clinical trials reveal a superior safety profile for cetilistat (Kopelman et al., 2010). A randomized, placebo-controlled, double-blind study conducted in obese participants with type 2 diabetes revealed that cetilistat (80 and 120 mg; three/day) or orlistat (120 mg; three time/day) for 12 wk, combined with a hypocaloric, moderate fat diet, produced significant reductions in body weight compared to placebo (Kopelman et al., 2010). Increased body weight loss was found in participants receiving cetilistat 80 or 120 mg (3.9 kg and 4.3 kg, respectively) or orlistat 120 mg (3.8 kg) compared to placebo (2.9 kg). Weight loss was accompanied by significant reduction in waist circumference, a risk factor for cardiovascular disease, as well as improved glycemic control in participants treated with both doses of cetilistat and orlistat. The percentage of reported severe gastrointestinal adverse events in cetilistat-treated participants (9-14% for 40-120 mg) was lower than for orlistat-treated participants (22%). Also, the proportion of participants with gastrointestinal adverse events leading to discontinuation was lower in the cetilistat groups (2.5-5%) compared to orlistat (11.6%). The difference in severity of adverse events between these drugs could be attributed to structural differences between the molecules which may influence the manner in which these they interact with fat micelles in the intestine (Kopelman et al., 2010). Overall, cetilistat appears to be better tolerated than orlistat and associated with greater compliance as a treatment.

6.2.5. Beloranib—Beloranib ([(3R,4S,5S,6R)-5-methoxy-4-[(2R,3R)-2-methyl-3-(3-methylbut-2-enyl)oxiran-2-yl]-1-oxaspiro[2.5]octan-6-yl] (E)-3-[4-[2-(dimethylamino)ethoxy]phenyl]prop-2-enoate;oxalic acid), a methionine aminopetidase 2 (MetAP2) inhibitor, is an investigational drug candidate for the treatment of obesity. MetAP2, a member of the dimetallohydrolase family, is encoded by the *METAP2* gene in humans, and increased expression of this gene is associated with various cancers (Selvakumar et al., 2002). Inhibitors of MetAP2 were developed originally as anti-angiogenic agents (Yeh et al., 2006). Interestingly, MetAP2 inhibition also reduces fat biosynthesis and stimulates fat oxidation and lipolysis, suggesting anti-obesity potential.

Beloranib, a synthetic analog of fumagillin, is a potent and selective MetAP2 inhibitor (Sin et al., 1997). Peripheral administration of beloranib for 7 days reduced cumulative food intake and body weight in obese rodent models including, OLETF rats (1 mg/kg per day, SC) and mice with lesions in the arcuate nucleus (1mg/kg per day; SC), compared vehicle control (Kim et al., 2007). Adipocyte, epididymal and mesenteric fat pad size were decreased in beloranib-treated rats. Beloranib is suggested to act in adipose tissue to inhibit formation of new blood vessels and stimulate apoptosis of endothelial cells, thereby inhibiting adipose tissue expansion. Conditioned taste aversion was assessed in beloranib-treated OLETF rats as a potential mechanism underlying decreases in food intake (Kim et al., 2007). Compared to vehicle control, single peripheral injection of the positive control, lithium chloride (0.15 M; vol was 2% body weight) and beloranib (1 or 10 mg/kg) produced conditioned taste aversion (decreased saccharin solution intake) in OLETF rats. The

anorexigenic effect of beloranib can be explained partly by the induction of taste aversion. Further studies are needed to elucidate the mechanistic effects of beloranib on appetite.

A proof of concept clinical trial was conducted in obese women to evaluate the safety, weight loss and cardio-metabolic risk factors of beloranib in the absence of dietary intervention or exercise (Hughes et al., 2013). In a double-blind, placebo-controlled study, obese women were randomized to intravenous beloranib (0.1, 0.3, or 0.9 mg/m2) or placebo twice/wk for 4 wk. Beloranib (0.3 and 0.9 mg/m2) resulted in median body weight loss of 3.5% at the end of 4 wk, compared to 0.6% following placebo. Beloranib (0.9 mg/m^2) also produced a significant reduction in triglycerides and low-density lipoprotein cholesterol, C-reactive protein (marker of inflammation) and hunger, evaluated using a visual analog scale. The most frequent adverse effects of mild or moderate intensity included headache, infusion site injury, nausea and diarrhea; however, no serious adverse events were found.

A follow up, Phase II double-blind, randomized, placebo-controlled study investigated the efficacy, safety and tolerability of a beloranib suspension (0.6, 1.2 and 2.4 mg, SC) in obese women for 12 wk (Kim et al., 2015). At wk 12, beloranib resulted in dose-dependent weight loss of 5-10% compared to 0.3% with placebo. Beloranib-induced weight loss was accompanied by reductions in waist circumference and body fat mass. Reduced caloric intake likely contributed to weight loss, as the beloranib-treated participants reported a marked reduction in hunger. The highest dose of beloranib resulted in significant improvements in mean total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol, triglyceride levels and systolic blood pressure, compared with placebo. No serious adverse events were reported. The most common side-effects included sleep disturbance and gastrointestinal disorders, which were generally mild to moderate in the high dose group. Long-term studies are needed in a larger and diverse patient population, which includes participants with obesity-related comorbidities, to confirm the safety, efficacy and tolerability of beloranib for weight loss and improvements in cardio-metabolic risk factors.

6.2.6. _RM-493_—RM-493 is a selective, novel, MC4R peptide agonist, which has been evaluated in a non-human primate model of DIO (Kievit et al., 2013). Chronic SC infusion of RM-493 for 8 wk in obese rhesus macaques decreased food intake, increased energy expenditure, reduced body weight, and improved glucose tolerance without causing adverse cardiovascular effects. A recent randomized, double-blind, placebo-controlled, crossover study examined the effects of RM-493 on resting energy expenditure in healthy obese adults (Chen et al., 2015). RM-493 (1 mg/24 h) or placebo was given by continuous SC infusion over 72 hr. Participants received a weight-maintenance diet (50% carbohydrate, 30% fat and 20% protein) and performed 30 min of standardized exercise daily. Compared to placebo, RM-493 resulted in a 6.4% increase in resting energy expenditure and increased plasma GLP-1 and PYY levels. No adverse effect on heart rate or blood pressure was found. Surprisingly, RM-493 treatment was associated with increased plasma glucose, insulin and C-protein levels. Long-term clinical studies are needed to elucidate the effects of RM-493 on insulin sensitivity. RM-493 is undergoing evaluation in a parallel mechanistic Phase Ib study in obese participants to determine whether RM-493-induced weight loss is caused by decreased appetite, increased metabolism or both (Jackson et al., 2014). Long-term studies

in a diverse and larger population are needed to obtain a better understanding of the safety, efficacy and tolerability of RM-493 for the treatment of obesity.

6.2.7. KD026—KD026 (1-[[3-methoxy-2-[4-(trifluoromethyl)phenyl]benzoyl]amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid) is a novel, nonsystemically available intestinal microsomal transfer protein inhibitor under clinical investigation for the treatment of obesity (Kim et al., 2011; Jackson et al., 2014). Microsomal transfer protein is a heteromeric protein involved in the synthesis of chylomicrons and apolipoprotein B-containing lipoproteins, impacting the transport of lipids and cholesterol from the intestine and liver to tissues (Cuchel et al., 2013). First-generation microsomal transfer protein inhibitors were designed to inhibit hepatic proteins and provide a novel treatment for dyslipidemia (Roevens et al., 1999). While potent inhibitors of hepatic microsomal transfer protein were efficacious in reducing low-density lipoprotein-cholesterol, these inhibitors resulted in elevation of liver enzymes and hepatic steatosis in animals and humans (Roevens et al., 1999; Gruetzmann et al., 2000).

Microsomal transfer protein is highly expressed in the enterocytes lining the lumen of the jejunum and is critical to the production of chylomicrons assembled from lipid or cholesterol, and their transfer into the systemic circulation (Gordon and Jamil, 2000; Hussain and Bakillah, 2008). KD026 was designed to selectively inhibit microsomal transfer protein (IC_{50} =~8 nM) in the intestinal lining without exerting an impact on the liver (Kim et al., 2011). KD026 (30 mg/kg; oral) reduced postprandial lipids by >50% with an ED_{50} value of ~7 mg/kg in rats (Kim et al., 2011). Chronic effects of KD026 were evaluated in apolipoprotein-E deficient mice, a dyslipidemic animal model, in which the severity of hyperlipidemia is exacerbated by high-fat diet. Apolipoprotein-E deficient mice maintained on a high-fat diet and KD026 (19 mg/kg/day or 67 mg/kg/day; oral) for 10 wk exhibited decreased levels of plasma triglycerides, total cholesterol and low-density lipoprotein cholesterol and increased levels of high-density lipoprotein cholesterol, compared to vehicle and high-fat diet (Kim et al., 2011). Moreover, KD026 (19 or 67 mg/kg/day) decreased body weight gain in apolipoprotein-E deficient mice over the course of treatment and reduced visceral fat and liver weight. Enterocytic selectivity of KD026 was supported by lack of elevation of liver transaminases even at the highest dose tested. Sub-chronic studies revealed that KD026 was devoid of any toxic effects when administered to rats for 90 days at a dose of 1000 mg/kg per day (Kim et al., 2011). Overall, inhibition of enterocytic microsomal transfer protein appears to be a promising peripheral target for the treatment of obesity.

6.2.8. Remogliflozin etabonate—The bulk of the filtrated glucose in kidney tubules is reabsorbed mainly by the low-affinity sodium-glucose cotransporter 2 (Kanai et al., 1994). Sodium-glucose cotransporter 2 inhibitors block the re-absorption of glucose by the kidney, thereby enhancing glucose excretion through the urine and resulting in a reduction in fasting plasma glucose levels and haemoglobin A1c levels. Remogliflozin etabonate (ethyl [(2R,3S, 4S,5R,6S)-3,4,5-trihydroxy-6-[5-methyl-1-propan-2-yl-4-[(4-propan-2-yloxyphenyl)methyl]pyrazol-3-yl]oxyoxan-2-yl]methyl carbonate) is a prodrug of remogliflozin, a selective inhibitor of the sodium-glucose cotransporter 2 (Fujimori et al., 2008). In both mice and rats, remogliflozin etabonate (3-30 and 1-10 mg/kg, respectively,

oral) increased urinary glucose excretion in a dose-dependent manner (Fujimori et al., 2008). In normal rats, remogliflozin etabonate (1-10 mg/kg) inhibited increases in plasma glucose after glucose loading without stimulating insulin secretion (Fujimori et al., 2008). In agreement, a single dose of remogliflozin etabonate (150 mg or 500 mg) was shown to increase urine glucose excretion and lower plasma glucose in human participants with type 2 diabetes mellitus (Kapur et al., 2013). Remogliflozin etabonate is being evaluated currently in obese patients as a potential weight loss therapy (Jackson et al., 2014).

In a 12-wk Phase 2b clinical trial, canagliflozin ((2S,3R,4R,5S,6R)-2-[3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl]-6-(hydroxymethyl)oxane-3,4,5-triol; 50, 100 and 300 mg), another sodium-glucose cotransporter 2 inhibitor, decreased body weight and increased urinary glucose excretion in a dose-dependent manner in overweight and obese participants without diabetes mellitus compared with placebo (Bays et al., 2014). A limitation of this trial was the 25% participant discontinuation rate. Canagliflozin was associated with higher rates of genital mycotic infections in women. Long-term safety and efficacy studies of are needed in obese individuals with metabolic abnormalities.

6.3. Potential anti-obesity candidates and targets based on preclinical and preliminary human studies

6.3.1 *RM-493 and Liraglutide*—Efficacy of adjunctive RM-493 and liraglutide treatment was evaluated in an animal model of DIO (Clemmensen et al., 2015). DIO mice were treated with RM-493 (3.6 μmol/kg/day), liraglutide (10 nmol/kg/day), the combination of liraglutide and RM-493 or vehicle for 5 consecutive days. Treatment with either monotherapy decreased body weight relative to vehicle. While no differences in weight reduction were found between mice treated with liraglutide and RM-493 alone, co-treatment resulted in greater weight loss relative to either monotherapy. Moreover, the combination therapy decreased caloric intake, improved glycemic control and cholesterol metabolism beyond that achieved with either monotherapy. Acute (48 h) treatment with liraglutide decreased (83%) hypothalamic GLP-1 receptor mRNA levels, compared to vehicle. The liraglutide-mediated down-regulation of GLP-1 receptor mRNA was prevented when RM-493 was co-administered with liraglutide, suggesting the possible role for RM-493 in maintaining GLP-1 receptor expression. Future studies to define the molecular mechanisms underlying the combinatorial benefits of MC4R and GLP-1 receptor agonism in energy metabolism are warranted. These findings suggest therapeutic potential of RM-493 and liraglutide combination for the treatment of obesity and diabetes.

6.3.2. *Pramlintide and Metreleptin*—Leptin plays a pivotal role in the physiological regulation of body weight. However, as a result of leptin resistance in obesity, development of recombinant leptin as a stand-alone obesity treatment has proven unsuccessful. The ability of amylin to restore leptin responsiveness in DIO rats suggests the therapeutic potential of a leptin and amylin combination for the treatment of obesity (Roth et al., 2008). Concurrent peripheral administration of amylin (100 μg/kg/day for 14 days, SC) and leptin (500 μg/kg/day for 14 days, SC) produces synergistic, fat-specific weight loss in leptin-resistant, DIO rats compared to vehicle control (Roth et al., 2008). In a 24-wk randomized, double-blind, proof-of-concept study in overweight/obese individuals, co-administration of

the amylin analog, pramlintide (180 μg twice daily for 2 wk and 360 μg twice daily thereafter, SC) and recombinant human leptin, metreleptin (5 mg, twice daily, SC) resulted in a 12.7% mean weight loss, which was significantly more than with either treatment alone (8.4% for pramlintide and 8.2% for metreleptin) (Ravussin et al., 2009). The most common adverse events reported in the combined treatment group were reactions at the injection site (58.9%) and nausea (12.5%). In most patients, nausea subsided after 5 wk of treatment. Together, these findings provide both preclinical and clinical evidence that integrated neurohormonal approaches may result in greater weight loss. Further clinical evaluation of the safety and efficacy of pramlintide-metreleptin for the treatment of obesity are needed.

6.3.3. *Glucagon and GLP-1 receptor agonism*—Glucagon and GLP-1 are pancreatic and intestinal hormones, respectively, derived from the same proglucagon peptide, but with divergent roles in metabolism (Tan et al., 2013). Glucagon is a 29 amino acid peptide hormone that is derived from pancreatic islet α cells as well as brainstem (Drucker and Asa, 1988; Sadry and Drucker, 2013). Under conditions of hypoglycemia, glucagon elevates blood glucose by promoting glycogenolysis and gluconeogenesis, as well as hepatic fatty acid β-oxidation and ketogenesis (MacDonald et al., 2007; Cryer, 2012). Peripheral administration of glucagon decreases food intake in rats and humans (Penick and Hinkle, 1961; Martin and Novin, 1977). Moreover, glucagon infusion increases oxygen consumption in rats and increases resting energy expenditure in humans (Davidson et al., 1957; Nair, 1987). GLP-1 is an incretin hormone released postprandially that enhances β-cell insulin response, inhibits gastric emptying, and suppresses appetite (Drucker, 2007). The role of glucagon and GLP-1 receptor activation in the regulation of satiety and metabolism suggests that co-agonists exhibiting optimal ratios of GLP-1 and glucagon agonism might produce additive or synergistic effects on weight loss (Sadry and Drucker, 2013). While activation of glucagon receptors increases glucose production posing a hyperglycemic risk, simultaneous activation of GLP-1 receptors counteracts this effect (Pocai, 2014).

Oxyntomodulin, a 37-amino acid peptide hormone secreted from gut along with GLP-1 following nutrient ingestion, is produced in brainstem and transported distally to hypothalamus (Blache et al., 1988; Drucker and Asa, 1988; Kieffer and Habener, 1999). Oxyntomodulin serves as an agonist at both GLP-1 and glucagon receptors; however, with 10- to 100-fold reduced potency compared with the cognate agonists GLP-1 and glucagon, respectively (Gros et al., 1993; Mayo et al., 2003; Baggio et., 2004). A randomized, controlled, double-blind, crossover study investigated the effect of oxyntomodulin on body weight in obese, non-diabetic participants (Wynne et al., 2005). Subcutaneous self-administration of pre-prandial oxyntomodulin (400 nmol; 3 times/day for 4 wk) decreased body weight and plasma leptin levels and increased plasma adiponectin levels, compared to control. Moreover, pre-prandial oxyntomodulin (400 nmol; 3 times/day for 4 days) increased energy expenditure and decreased energy intake compared to control. Further mechanistic understanding and long-term studies of oxyntomodulin in individuals with diabetes are needed.

The anti-obesity effects of a long-acting, protease-resistant, dual GLP-1/glucagon receptor agonist was compared to that of a long-acting GLP-1 receptor selective agonist in a mouse DIO model (Pocai et al., 2009). Repeated treatment with the dual agonist (1.9 μmol/kg every

other day for 2 wk; SC) resulted in greater weight loss and lipid lowering in DIO mice, compared to mice treated with the GLP-1 receptor selective agonist (1.9 μmol/kg every other day for 2 wk; SC). Moreover, compared to vehicle-treated DIO mice, plasma glucose levels were normalized and glucose tolerance was improved upon treatment with either the dual agonist or selective GLP-1 receptor agonist. Improvements in plasma metabolic parameters including insulin, leptin, and adiponectin, increased fatty acid oxidation and reduced hepatic steatosis were more pronounced upon treatment with the dual agonist than with the selective GLP-1 receptor agonist alone in DIO mice. Weight loss was observed with dual agonist treatment in both GLP-1 receptor knockout and glucagon receptor knockout mice; however, efficacy was reduced compared with body weight effects in weight-matched wild-type mice (Pocai et al., 2009). These results suggest that the anti-obesity effects of the dual agonist requires activation of both GLP-1 and glucagon receptors.

In a randomized, double-blinded crossover study, overweight or obese participants without diabetes were given GLP-1 (0.8 pmol/kg/min, IV), glucagon (50 ng/kg/min, IV) or a combination of both GLP-1 and glucagon (Tan et al., 2013). Compared to control, resting energy expenditure was increased upon treatment with glucagon alone and the combination of glucagon and GLP-1, but was not altered by GLP-1 infusion. Although glucagon infusion was accompanied by a rise in plasma glucose levels, addition of GLP-1 ameliorated this effect. Together, drugs with glucagon and GLP-1 agonist activity may be beneficial for the treatment of obesity and type 2 diabetes.

6.3.4. *Growth hormone*—Growth hormone, or somatotropin, is best known for its action on linear growth such that deficiency leads to dwarfism and excess leads to gigantism (Berryman et al., 2013). In addition to normal growth, growth hormone stimulates the production of insulin-like growth factor-1 in most tissues, which collectively regulate fat, protein and glucose metabolism. Clinical features of adults with severe growth hormone deficiency as a result of hypothalamic-pituitary disease include increased total body adipose tissue mass, abdominal obesity, atherogenic lipid profile, premature atherosclerosis, reduced exercise capacity and insulin resistance (Johannsson, 2007). In obesity, both spontaneous and stimulated growth hormone secretion are blunted (Williams et al., 1984; Veldhuis et al., 1991). An inverse association exists between growth hormone secretion and the amount of ectopic fat deposition in the muscle and liver (Clasey et al 2001; Bredella et al., 2009). Moreover, the metabolic clearance rate of growth hormone is accelerated in individuals with obesity (Veldhuis et al., 1991). Overall, there appears to be dysregulated growth hormone function associated with obesity.

Growth hormone treatment (0.5 and 5 μg/g/day for 6 wk; SC) results in fat mass reduction and increase in lean mass in DIO mice, despite free access to a high-fat diet during the treatment period, compared to vehicle-control mice maintained on a low-fat diet (List et al., 2009). Also, growth hormone reduced liver triacylglycerol and fasting blood glucose and improved glucose tolerance in DIO mice to levels in low-fat fed controls. Liver, skeletal muscle and adipose tissue develop insulin resistance in response to acute growth hormone administration in humans (Jessen et al., 2005; Nielsen et al., 2008). Mechanisms responsible for growth hormone-induced insulin resistance remain unclear. Insulin resistance may be secondary to stimulation of lipolysis and subsequent free fatty acid release, which results in

competition between glucose and free fatty acid as a substrate for energy production (Møller, N. & Jørgensen, 2009).

A 12-wk, placebo-controlled trial of growth hormone treatment combined with caloric restriction was conducted in obese participants with type 2 diabetes (Nam et al., 2001). Growth hormone treatment (0.15 IU/kg for 12 wk) reduced visceral adipose tissue mass and levels of low density lipoprotein cholesterol and improved insulin sensitivity measured by euglycaemic hyperinsulinaemic clamp. In a double-blind, placebo-controlled crossover design, growth hormone administration (0.03 mg/kg for 5 wk) in obese women resulted in increased resting energy expenditure, decreased respiratory exchange ratio and increased rate of lipid oxidation (Jørgensen et al., 1994). Alterations in body composition and an increase in energy expenditure might counteract the direct effects of growth hormone on insulin resistance (Berryman et al., 2013). Overall, both animal and human studies demonstrate the therapeutic potential of growth hormone in the treatment of obesity.

6.3.5. Bile acid sensors: farnesoid X receptor (FXR) and membrane bound bile acid receptor (GPR131)—Bile acids are synthesized in the liver from cholesterol where they are conjugated to glycine (human) or taurine (mouse), and metabolized to secondary bile acids in the gut by the microbiota (Midtvedt, 1974; Sayin et al., 2013). Bile acids serve as signaling molecules that act through the nuclear receptor, FXR, and membrane-bound GPCR, GPR131 or TGR5, to regulate lipoprotein and glucose metabolism (Makishima et al., 1999; Sinal et al., 2000; Maruyama et al., 2002; Kawamata et al., 2003). In addition to their role in lipid emulsification and absorption of fat-soluble vitamins, emerging evidence demonstrates the role of bile acids and their receptors in the regulation of energy balance (Maruyama et al., 2006; Penney et al., 2015).

FXR is a ligand-activated transcriptional factor expressed in diverse peripheral tissues including the adrenal gland, kidney, stomach, duodenum, jejunum, ileum, colon, gall bladder, liver and macrophages, as well as in white and brown adipose (Forman et al., 1995). The complex role of FXR in metabolic homeostasis is evident from studies conducted in whole body and liver-specific FXR null mice. During maintenance on a standard chow diet, FXR null mice exhibit elevated levels of serum bile acid, cholesterol, and triglycerides, increased hepatic cholesterol and triglycerides, a proatherogenic serum lipoprotein profile, and reduced fecal bile acid excretion, compared to wild-type mice (Sinal et al., 2000). This suggests that FXR is critical for bile acid and lipid homeostasis. In order to investigate the role of FXR in the adaptation to obesity and its metabolic complications, the impact of FXR deficiency was studied in rodent models of obesity (Prawitt et al., 2011). FXR deficiency attenuated body weight gain in ob/ob mice and mice maintained on a high-fat diet for 20 wk by reducing adipose tissue mass, compared to wild-type controls. FXR deficiency improved glucose homeostasis in both rodent models of obesity as a result of enhanced glucose clearance and adipose tissue insulin sensitivity. These metabolic improvements were not mediated by hepatic FXR, since liver-specific FXR deficient mice were not protected from DIO and insulin resistance. Overall, in contrast with lean mice, FXR deficiency in obesity improves energy and glucose homeostasis.

In response to a meal, bile acids are secreted into intestine from the gall bladder and acutely activate intestinal FXR (Fang et al., 2015). In order to study the specific role of intestinal FXR activity in the regulation of energy metabolism, DIO mice were orally administered a synthetic FXR agonist, fexaramine (methyl (E)-3-[3-[cyclohexanecarbonyl-[[4-[4-(dimethylamino)phenyl]phenyl]methyl]amino]phenyl] prop-2-enoate; 100 mg/kg daily for 5 wk), (Fang et al., 2015). Compared to vehicle control, fexaramine resulted in a significant reduction in body weight gain that was attributed to reduced overall fat mass including subcutaneous and visceral adipose depots. Consistent with reduced adiposity, fexaramine-treated mice showed significant metabolic improvements including reduced glucose, insulin, leptin, cholesterol and resistin levels. Furthermore, fexaramine resulted in improvements in glucose tolerance, insulin sensitivity, reduced adipose tissue inflammation and enhanced thermogenesis and browning of white adipose tissue. These results suggest that FXR agonism is a potential approach to the treatment of obesity and insulin resistance.

Previous studies support the beneficial effects of whole body FXR deficiency in rodent models of obesity (Prawitt et al., 2011). Mice with intestine-specific FXR deletion are resistant to DIO (Li et al., 2013). FXR signaling is activated in distal ileum biopsies from obese humans compared to lean humans, as evidenced by increase in mRNAs encoded by FXR and FXR target genes (Jiang et al, 2015). Based on these results, glycine-β-muricholic acid, an orally available, intestine-specific FXR inhibitor, was used to examine whether selective inhibition of intestinal FXR ameliorates obesity and associated metabolic abnormalities (Jiang et al., 2015). Compared to vehicle control, glycine-β-muricholic acid (10 mg/kg daily for 5-6 wk) increased energy expenditure, decreased body weight, fat mass, fat/lean mass ratio, insulin resistance and hepatic steaosis when orally administered to leptin-receptor deficient mice and DIO mice. Inhibition of FXR resulted in decreased expression of ceramide synthesis-related genes suggesting that decreases in intestinal-derived ceramides likely mediate the resolution of DIO and hepatic steatosis. These results demonstrate that specific inhibition of intestinal FXR may be a therapeutic strategy for the treatment of obesity and metabolic disorders. However, these findings are in contrast to prior evidence suggesting a role of gut-restricted FXR agonism in ameliorating DIO and associated metabolic dysfunction (Fang et al., 2015). Studies are needed regarding the mechanistic role of FXR in the pathophysiology of obesity.

The gut microbial community (microbiota) is considered an environmental factor that modulates host metabolism and contributes to the development of obesity and metabolic diseases. Gut microbiota is essential for processing dietary polysaccharides (Backhed et al., 2004). Conventionalization of adult germ-free mice with normal microbiota harvested from the distal intestine (cecum) of conventionally raised animals produced a 60% increase in body fat content, de novo hepatic lipogenesis and insulin resistance within 14 days (Backhed et al., 2004). Also, faecal microbiota transplants from lean glucose-sensitive human donors were shown to improve insulin sensitivity in humans with the metabolic syndrome (Vrieze et al., 2012). These results identify altered gut microbiota as a contributing factor to the pathophysiology of obesity.

Recent evidence suggests that microbiota-mediated changes in bile acid profiles and signaling through FXR contribute to impaired host metabolism (Parseus et al., 2016). Germ-

free and conventionally raised wild-type and FXR deficient mice were fed a high-fat diet for 10 wk. Gut microbiota promoted weight gain, adipose tissue inflammation, beta-cell mass and hepatic steatosis in an FXR-dependent manner. Bile acid profiles and composition of faecal microbiota differed between FXR deficient and wild-type mice suggesting that gut microbiota promotes DIO through effects on the bile acid profile and altered FXR signaling. Further understanding of gut microbiota-mediated modulation of bile acids and signaling through FXR may provide novel therapeutic targets for obesity and metabolic diseases.

Another bile acid receptor that is expressed in diverse tissues and is suggested to regulate energy homeostasis is TGR5 (Hodge and Nunez, 2016). In enteroendocrine cells, TGR5 stimulates the release of both GLP-1 and PYY thereby maintaining glucose homeostasis and decreasing food intake (Thomas et al., 2009; Bala et al., 2014). In muscle and brown adipose tissue, TGR5 regulates energy expenditure through activation of thyroid hormone-activating enzyme, type 2 iodothyronine deiodinase (Eggink et al., 2014). TGR5 is also located in neurons of the enteric nervous system, where they influence gut motility (Poole et al., 2010), and in neurons and astrocytes in the central nervous system, where its function is unknown. Further animal studies are needed to investigate the therapeutic potential of TGR5 for the treatment of obesity and type 2 diabetes.

7. Challenges for anti-obesity drug development

Considering the numerous withdrawals of anti-obesity drugs from the market due to untoward effects, benchmarks for safety and efficacy for anti-obesity drugs are heavily scrutinized. With respect to safety, the FDA requires that anti-obesity drugs should not adversely affect cardiovascular function. Cardiac valvulopathy is highlighted as a serious adverse effect in the Unites States as a result of past experience with both dexfenfluramine and the fenfluramine/phentermine (fen/phen) combination (Heal et al., 2009). The majority of currently approved anti-obesity drugs and those in clinical development have effects mediated by central mechanisms (homeostatic and/or reward systems). For centrally-acting drug candidates, psychiatric adverse events, abuse liability, and side-effects including dependence and withdrawal are potential safety issues that require careful investigation. Preclinical research that offers predictive validity with respect to the assessment of abuse potential and other neuropsychiatric complications are beneficial particulary in early stages of drug development.

FDA criteria for weight reduction after 1 year of treatment with an anti-obesity drug is defined as 5% body weight compared to placebo control (FDA draft guidance, 2007; Heal et al., 2009). The FDA also states that in order to ensure that drug-induced weight loss is due to primarily a reduction in fat content, not lean-body mass, a representative sample of subjects should be assessed for body composition by dual energy x-ray absorptiometry or using a suitable alternative at baseline and follow-up (FDA draft guidance, 2007). In addition to weight reduction, FDA regulations stipulate that an effective weight-management product should provide improvements in blood pressure, lipids, glycemia or other metabolic complications. Thus, clinical trials of candidate anti-obesity medications need to include assessments of efficacy for common weight-related comorbidities.

Tolerance develops to the anti-obesity effects of pharmacological monotherapies as a result of counter-regulation. As such, drug discovery has shifted to a multi-target approach with an overall objective of enhancing therapeutic outcome. An additional layer of complexity in clinical assessment arises regarding the safety and efficacy of fixed-dose combination products. With respect to efficacy, therapeutic effects of the combination product must be superior to placebo and to the relevant doses of the individual drugs in the combination product (Nathan et al., 2011). While a combination strategy may facilitate therapeutic efficacy, the incidence of adverse effects may increase. Nevertheless, if adverse events are not severe and if a synergistic effect is found with the combination product, then doses of the individual drugs may be reduced to overcome safety issue.

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders list the diagnostic criteria for behavioral disorders including depression, substance abuse and other personality disorders. A striking similarity is noted between behaviors that are considered criteria for a diagnosis of substance abuse and for obesity, including a persistent desire for food and maintenance of overeating despite knowledge of adverse physical and psychological consequences caused by excessive food consumption (Volkow and O'Brien, 2007). Obesity may be considered a "food addiction", although further examination of this concept is needed. The Yale Food Addiction Scale was developed to operationalize the concept of "food addiction" (Gearhardt et al., 2009). This scale allows application of substance dependence diagnostic criteria to eating behavior and provides two scoring options; one that measures food addiction "symptoms" and another option that provides a food addiction "diagnosis" based upon the substance dependence diagnosis (Gearhardt et al., 2012). Using the Yale Food Addiction Scale, the nature of "food addiction" was examined in treatment-seeking obese participants with binge-eating disorder (Gearhardt et al., 2012). Classification of "food addiction" was met by 57% of participants with binge eating disorder. However, it should be noted that the proportion of binge eaters in the obese population is a small minority. In another study, addictive-like eating patterns in children, as measured by the Yale Food Addiction Scale, were related to elevated BMI and a greater tendency to overeat in response to emotional stimuli (Gearhardt et al., 2013). Overall, the issue of "food addiction" as a cause of or result of obesity remains controversial and requires further investigation.

Common brain substrates regulate the hedonic properties of palatable food and addictive drugs, suggesting that excessive consumption of food or drugs of abuse produces similar neuroadaptive responses in brain reward circuitries (Kenny, 2011). As such, behavioral paradigms that have been employed extensively to assess motivational aspects of drug addiction and relapse may be beneficial in the assessment of anti-obesity drugs. For example, 5-HT neurotransmission via 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors have been implicated in mediating cocaine abuse as well as impulsive behaviors that contribute to the development of cocaine addiction and relapse in humans (Howell and Cunningham, 2015). However, a gap in our knowledge exists with respect to the ability of centrally-acting weight loss drugs to inhibit relapse of palatable food-seeking behavior. Clinical trials have not determined whether monoamine-based anti-obesity medications that lack abuse liability have efficacy in reducing craving and preventing relapse of palatable food consumption. Thus, in addition to the evaluation of cardio-metabolic improvements, assessment of relapse to palatable food

consumption and of abuse potential for alternate reinforcers (e.g., abused drugs) would enhance evaluations of anti-obesity treatment.

8. Conclusions

Research over the past two decades has advanced substantially our knowledge of central and peripheral mechanisms underlying energy balance, making these mechanisms attractive targets for anti-obesity therapeutics. In addition to homeostatic systems, targeting non-homeostatic mechanisms may prove beneficial in the amelioration of maladaptive reward-driven palatable food consumption. Given that multiple central and peripheral mechanisms underlie the development and maintenance of obesity, combination therapies may exert greater and longer-term weight loss compared to monotherapies. Currently two combination products have been approved by the FDA for the treatment of obesity. There are several potential combination therapy approaches that appear beneficial. However, additional long-term studies are needed, especially for centrally acting anti-obesity drugs, to evaluate potential neuropsychiatric adverse effects and the benefit to risk ratio. Future studies focusing on not only central, but also peripheral targets governing energy expenditure, may offer novel treatment strategies.

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ABBREVIATIONS

AgRP	agouti-related protein
α-MSH	alpha-melanocyte stimulating hormone
2-AG	2-arachidonoylglycerol
BDNF	brain derived neurotrophic factor
BOLD	blood-oxygen level dependent
CB1	cannabinoid-1
CB2	cannabinoid-2
CART	cocaine and amphetamine regulated transcript
CCK	cholecystokinin
CPP	conditioned place preference
DIO	diet-induced obesity
DA	dopamine
DAT	dopamine transporter

FXR	farnesoid X receptor
fMRI	functional magnetic resonance imaging
GLP-1	glucagon-like peptide-1
GHSR1A	growth hormone secretagogue receptor 1A
GABA	γ-aminobutyric acid
GPCRs	G-protein coupled receptors
ICV	intracerebroventricular
IP	intraperitoneal
MCH	melanin-concentrating hormone
MC4R	melanocortin-4 receptor
MetAP2	methionine aminopetidase 2
NE	norepinephrine
NPY	neuropeptide Y
NTS	nucleus tractus solitarius
OEA	oleoylethanolamide
OLETF	Otsuka Long Evans Tokushima Fatty
POMC	pro-opiomelanocortin
PR	progressive ratio
pSTAT3	phosphorylated signal transducer and activator of transcription 3
PYY	peptide YY
5-HT	serotonin
SC	subcutaneous
VTA	ventral tegmental area

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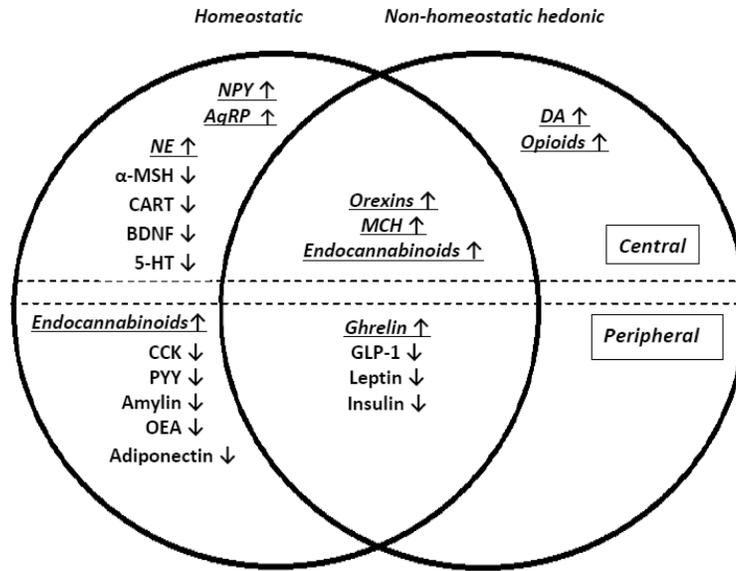
Figure 1.
Homeostatic and non-homeostatic hedonic factors that regulate food intake. Central and peripheral signals are provided above and below, respectively, the double line. "↑" indicates increases in food intake induced by orexigenic factors (also represented by the underline). "↓" indicates decreases in food intake induced by anorexigenic factors. Increased orexigenic signaling facilitates the development of obesity and increased anorexigenic signaling inhibits the development of obesity.

Table 1

Approved Anti-obesity Drugs

Drug	Mechanism of Action
Phentermine (Adipex-P®)	NE transporter inhibitor; Appetite suppression mediated by activation of POMC neurons in the arcuate nucleus
Orlistat (Xenical®)	Gastric- and pancreatic-lipase inhibitor; Reduces absorption of dietary fat
Lorcaserin (Belviq ®)	Selective 5-HT$_{2C}$ agonist; Promotes satiety
Phentermine and Topiramate (Qsymia ®)	Phentermine: NE transporter inhibitor; Appetite suppression mediated by activation of POMC neurons in the arcuate nucleus Topiramate: GABA agonist; Appetite suppression may be due to modulation of voltage-gated ion channels, increased activity at GABA-A receptors and/or inhibition of AMPA/kainite glutamate receptors
Naltrexone and Bupropion (Contrave ®)	Naltrexone: Opioid receptor antagonist; Prevents β-endorphin-mediated negative feedback on α-MSH release Bupropion: DA and NE transporter inhibitor; Stimulates hypothalamic POMC neurons that release α-MSH resulting in decreased food intake and increased energy expenditure
Liraglutide (Saxenda ®)	GLP-1 agonist; Decreases appetite

Table 2

Anti-obesity Therapeutics in Clinical Development

Drug	Mechanism of Action	Clinical Phase
Tesofensine	5-HT, DA and NE transporter inhibitor	Phase III
Bupropion and Zonisamide (Empatic ®)	Bupropion: DA and NE transporter inhibitor; Stimulates hypothalamic POMC neurons releasing α-MSH that leads to decreased food intake and increased energy expenditure Zonisamide: Carbonic anhydrase inhibitor; Reduces lipogenesis	Phase III
Exenatide	GLP-1 agonist; Decreases appetite	Phase III
Cetilistat	Gastric- and pancreatic-lipase inhibitor; Reduces absorption of dietary fat	Phase III
Beloranib	MetAP2 inhibitor; Reduces fat biosynthesis, stimulates fat oxidation and lipolysis	Phase II
RM-493	Selective MC4R agonist; Decreases appetite and increases metabolism	Phase II
KD026	Selective intestinal microsomal transfer protein inhibitor; Reduces fat absorption	Phase II
Remogliflozin etabonate	Selective inhibitor of sodium-glucose cotransporter 2	Phase II

Table 3

Anti-obesity Therapeutic Candidates and Targets

Drug/Target	Mechanism of Action
PRX-07034	5-HT$_6$ antagonist
Rimonabant and SNAP-94847	Rimonabant: CB1 antagonist SNAP-94847: MCH1 antagonist
GSK1521498	Selective μ-opioid receptor antagonist; Decreases binge eating of palatable foods
RM-493 and Liraglutide	RM-493: MC4R agonist Liraglutide: GLP-1 agonist
Pramlintide and Metreleptin	Pramlintide: Amylin analog; Restores leptin sensitivity Metreleptin: Recombinant human leptin; Decreases food intake and increases energy expenditure
Glucagon and GLP-1 receptor co-agonism	Decreases appetite and increases energy expenditure
Growth hormone	Increases energy expenditure
Bile acid receptors: FXR and TGR5	Intestinal FXR: Regulates energy expenditure TGR5: Decreases appetite and increases energy expenditure