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REVIEW

Turning the clock forward: New pharmacological and non pharmacological targets for the treatment of obesity

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Abstract *Aims:* Obesity and its main metabolic complication, type 2 diabetes, have attained the status of a global pandemic; there is need for novel strategies aimed at treating obesity and preventing the development of diabetes. A healthy diet and exercise are basic for treatment of obesity but often not enough. Pharmacotherapy can be helpful in maintaining compliance, ameliorating obesity-related health risks, and improving quality of life. In the last two decades, the knowledge of central and peripheral mechanisms underlying homeostatic and hedonic aspects of food intake has significantly increased. Dysregulation of one or more of these components could lead to obesity.
Data synthesis: In order to better understand how potential innovative treatment options can affect obesity, homeostatic and reward mechanisms that regulate energy balance has been firstly illustrated. Then, an overview of potential therapeutic targets for obesity, distinguished according to the level of regulation of feeding behavior, has been provided.

Moreover, several non-drug therapies have been recently tested in obesity, such as non-invasive neurostimulation: Transcranial Magnetic Stimulation or Transcranial Direct Current Stimulation. All of them are promising for obesity treatment and are almost devoid of side effects, constituting a potential resource for the prevention of metabolic diseases.
Conclusions: The plethora of current anti-obesity therapies creates the unique challenge for physicians to customize the intervention, according to the specific obesity characteristics and the intervention side effect profiles; moreover, it allows multimodal approaches addressed to treat obesity and metabolic adaptation with complementary mechanisms.

Abbreviations: Amyg, Amygdala; Arc, Arcuate Nucleus; BAT, Brown Adipose Tissue; Caud/Put, Caudate/Putamen; CB1, Cannabinoid-1; DA, Dopamine; DMH, Dorsomedial Hypothalamus; GABA, gamma-Aminobutyric acid; GIP, Glucose-dependent Insulinotropic Polypeptide; GLP-1, Glucagon-Like Peptide-1; Hipp, Hippocampus; LCFA-CoA, Long-chain fatty acyl-CoA; LH, Lateral Hypothalamus; MCH, Melanin-Concentrating Hormone; NAcc, Nucleus Accumbens; NPY, Neuropeptide Y; NPY/AgRP, Neuropeptide Y/Agouti-Related Peptide; PFC, Prefrontal Cortex; POMC/CART, Pro-Opiomelanocortin/Cocaine- and Amphetamine-Regulated Transcript; PPARs-γ, Peroxisome Proliferator-Activated Receptors-γ; PVN, Paraventricular Nucleus; PYY, Peptide YY; SoN, Solitary Nucleus; tDCS, transcranial Direct Current Stimulation; TMS, Transcranial Magnetic Stimulation; VMH, Ventromedial Hypothalamus; VN, Vagus Nerve; VTA/SN, Ventral Tegmental Area/Substantia Nigra; WAT, White Adipose Tissue; 5-HT, 5-hydroxytryptamine or Serotonin.

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1. Introduction

According to the WHO, the global prevalence of obesity has nearly tripled since 1975 [1]. Currently, the obesity prevalence in U.S.A. stands at 42.4%, the first time the national rate has passed the 40 percent mark, supporting the evidence of the country's obesity crisis [2]. Across the European countries, the average prevalence of obesity reaches 24% [3], and it is becoming alarming also in developing countries [4], especially due to the risk of developing metabolic complications such as type 2 diabetes (T2D). Counteracting this issue is urgent and requires not only strong and comprehensive medical interventions on individuals with obesity, but also health-care task forces, policy makers, and the implementation of clear and organised cross-sector strategies [5].

A long-term energy imbalance between too many calories consumed and too few calories expended has been commonly identified as the fundamental cause of obesity. Notwithstanding, the main strategies for the treatment of obesity aimed at reducing energy intake and increasing exercise are frequently not successful, suggesting a more complex aetiology underlying obesity [6]. In fact, numerous other factors could affect the chronic positive energy balance in obesity: age, sex, genetics, neuroendocrine factors, gut microbiota, concomitant medications, socio-cultural level, lack of knowledge, homeostatic hunger, uncontrolled eating, and emotional eating [6,7].

Wideworld increasing rates of obesity and life-threatening comorbidities and complications, especially T2D, require as soon as possible effective strategies to treat this complex medical condition. Objectives of the management and treatment of obesity are focused not only on the weight loss, but also on complication risk reduction and health improvement [8]. A modest weight loss (i.e. 5-10% of the initial body weight), associated with lifestyle modifications (diet variations and modest increase in physical activity), is considered sufficient to achieve a clinical improvement. However, other non-negligible aims should be contemplated in the obesity management: maintenance of body weight loss, prevention of weight regain, improvement in body composition, prevention and management of comorbidities and complications, improvement of quality of life and well-being, evaluation of psychological status [8].

Although a change in lifestyle habits is unavoidable for the treatment of obesity, it is often not enough. Bariatric surgery is the most effective weight-lowering treatment available to date. However, 20–40% of patients exhibit insufficient weight loss after surgery [9]. For example, individuals with higher preoperative BMI, older age, male sex and obesity-associated comorbidities such as T2D, arterial hypertension and sleep apnoea syndrome exhibit more frequently insufficient weight loss [9]. Furthermore, pre-surgery disordered eating behaviours, increased hedonic hunger and psychopathological issues emerged as negative predictors of weight loss after surgery [10,11].

In these situations, pharmacotherapeutic approach to treat obesity represents an important option. Pharmacotherapy can be helpful in maintaining compliance, ameliorating obesity-related health risks and improving quality of life [8]. According to the current guidelines, pharmacological treatment should be considered as part of a comprehensive strategy of the disease management for patients with a BMI $\geq$30 or $\geq$27 kg/m^2 with at least one obesity-related co-morbidity (T2D, hypertension, dyslipidemia, and sleep apnea). The efficacy of pharmacotherapy should be assessed after the first 3 months of treatment [12]. Since the mid-1990s, the U.S. Food and Drug Administration (FDA) has established stringent criteria for a drug to be approved for the treatment of obesity. The new drug, compared to placebo, must induce a weight loss of >5% at 1 year or >35% of patients should achieve >5% weight loss. Furthermore, the FDA requires that the anti-obesity drug should be able to improve cardio-metabolic biomarkers, including blood pressure, lipid levels and glycaemic control [13,14].

To date, U.S. FDA approved the following anti-obesity medications: phentermine, orlistat, phentermine/topiramate extended release (ER), naltrexone sustained release (SR)/bupropion SR, liraglutide and semaglutide. A sixth approved drug, setmelanotide, is limited to individuals who have been diagnosed with one of three specific rare genetic disorders, which must be confirmed by genetic testing. In the early 2020, FDA recommended the withdrawal from the market of the previous approved drug for obesity, lorcaserin, due to severe adverse events.

Among these drugs, phentermine, orlistat, naltrexone SR/bupropion SR, and liraglutide have also been approved by the European Medicines Agency (EMA). The effectiveness of the approved drugs in inducing weight loss is estimated to range between 3 and 7% [14].

In consideration of their safety profile, all the listed above drugs have been considered for long-term use. At the same time, both FDA and EMA approved a group of four agents (diethylpropion, phendimetrazine, benzphetamine, and phentermine) for short-term (8–12 weeks) treatment of obesity. Any of these drugs may be used in patients with an initial BMI of 30 kg/m^2 or higher who have not responded to an appropriate weight-reducing regimen. Their use has been temporally restricted due to potential long-term side effects, especially on the cardiovascular system.

With the exception of orlistat, most of current drugs for obesity act on the Central Nervous System (CNS) by modulating some neuro-endocrine systems involved in the complex regulation of hunger/satiety balance. In the last decades, several other both pharmacological and not pharmacological interventions are under investigation and revealed promising in promoting body weight loss.

In view of the increased knowledge of the central and peripheral mechanisms underlying homeostatic and non-homeostatic hunger, the aim of the present review is to summarize recent research, which attempts to identify

new future neuropharmacological targets for the treatment of obesity.

2. Mechanisms of hunger/satiety regulation

In order to better understand how potential innovative treatment options can affect obesity, a brief overview of homeostatic and reward mechanisms that regulate energy balance has been herein provided. The appetite/satiety balance is regulated by a complex neurocircuitry which involves key receptors, hormones, neuropeptides, metabolic and exogenous signals, as well as intracellular mechanisms (see Fig. 1).

The caudal brainstem plays a crucial role in integrating direct inputs from vagally-mediated gastrointestinal satiation signals, alterations in glucose and other circulating metabolites/petides, and descending neural, neuroendocrine, and neuropeptidergic (such as ghrelin and leptin) signals from the midbrain and forebrain. These energy status informations are, in turn, transmitted to other ascending neural regions to control behavior, autonomic, and endocrine responses [15].

While the caudal brainstem receives input mainly from the blood glucose levels via specific glucoreceptors, the nucleus tractus solitarius (NTS) receives direct information about the nutritive, osmotic and volumetric properties of food from the vagus nerve [15]. In turn, the NTS neurons project to forebrain regions, involved in appetite and feeding behavior regulation, and to the paraventricular nucleus (PVH) of the hypothalamus, implicated in the neuroendocrine response [15]. Other projections of the NTS are addressed to the dorsal motor nucleus of the vagus for the modulation of the autonomic (parasympathetic) gastrointestinal response, especially insulin secretion and gastric emptying [16].

2.1. Homeostatic regulation of feeding behavior

The arcuate nucleus (ARC), within the hypothalamus, plays a key role in integrating endocrine and exogenous signals, by essentially involving two different populations of cells: the agouti-related peptide (AgRP)/neuropetide Y(NPY)-coexpressing neurons and the pro-opiomelanocortin (POMC)-expressing neurons [17].

AgRP neurons are activated by food deprivation via glutamatergic afferents and release NPY, increasing appetite and feeding; however, in few seconds, AgRP neurons are inhibited by even just the sensory perception of food

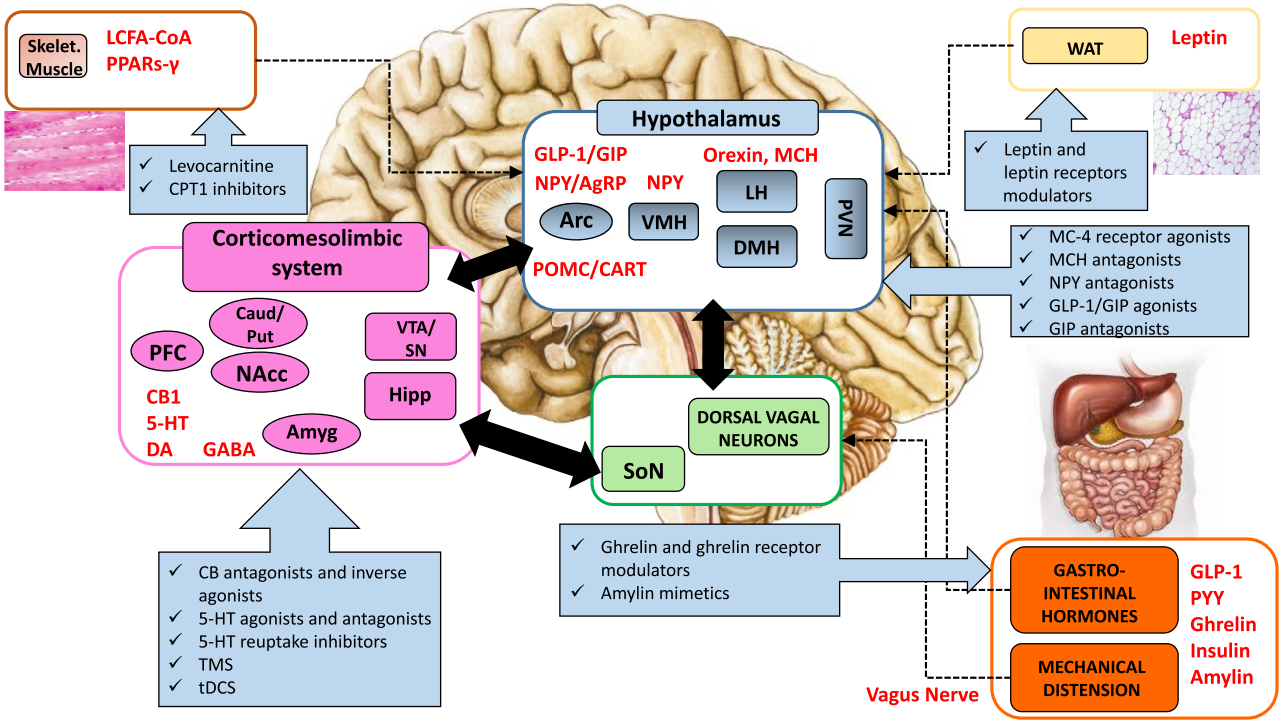

Figure 1 Schematic representation of the interaction between homeostatic hypothalamic and brainstem structures and non-homeostatic (hedonic) brain areas involved in the control of food intake. The meso-cortico-limbic system includes the ventral tegmental area, nucleus accumbens, prefrontal cortex, hippocampus, amygdala, and regulates mainly the hedonic aspects of food intake. Hormones from peripheral compartments like white and brown adipose tissues, and gastrointestinal tract reach these areas, directly or indirectly to activate pathways controlling both energy balance and other aspects associated with eating (hunger level, palatability of the food, past experiences, mood and level of stress). This picture illustrates the complex interplay between peripheral compartments and the hypothalamus and meso-cortico-limbic system involved in feeding behavior, highlighting for each sector the potential new targets on which new pharmacological and non-pharmacological treatments can act (in red), and related new interventions that have been tested for the treatment of obesity (in blue). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

via inhibitory inputs from the PVH. Excitatory and inhibitory signals are integrated by the AgRP neurons, which drive feeding behavior via efferent projections to the PHV, lateral hypothalamic area (LHA), and the periventricular thalamus, engaging neurotransmitter pathways, e.g. γ-aminobutyric acid (GABA), NPY and the same AgRP [18].

In turn, these second order neurons project to the NTS in the brainstem and the dorsomotor nucleus of the vagus, whose role has been previously described.

Another neuron hypothalamic population involved in the regulation of food intake expresses both the POMC, from which the α-melanocyte-stimulating hormone (α-MSH) derives, and the cocaine and amphetamine regulated transcript (CART). Alpha-MSH binds and activates melanocortin receptors (MCRs), especially MC4R, inhibiting food intake and increasing energy expenditure [18].

AgRP as well as POMC neurons express receptors for and are modulated by peripheral hormonal signals including insulin, leptin, peptide YY, and ghrelin.

2.2. Hedonic regulation of feeding behavior

In addiction to homeostatic control on feeding behavior, brain "reward system" plays a major role in regulating non-homeostatic feeding. Conditioned food cues associated with consumption of highly palatable and fat-rich foods can override homeostatic signals, and can trigger food intake in absence of energy or metabolic requirements [15]. Hedonic regulation can be exercised at different levels.

Cortical regulation of feeding behavior involves the Prefrontal Cortex (PFC) that plays a role in regulating impulse control, self-monitoring, and goal-directed behaviors, that are all involved in the regulation of eating behavior. Specifically, the medial orbitofrontal cortex (mOFC), integrates sensory modalities such as taste, smell, and vision, and, through its dense reciprocal projections into thalamic, midbrain, and striatal regions, it acts as a critical hub for decision-making on highly motivating stimuli [19]. There is much evidence for possible disruption of neurobiology and operations of the OFC in the obesity condition [19]. For example, individuals with obesity and binge eating disorders exhibit a decreased baseline activity in the PFC [20], resulting in a reduced inhibitory control over eating behavior. Recently, an altered connectivity seeding from the OFC regions and a loss of prefrontal-orbitofrontal connectivity, correlated with BMI, have been shown in elderly females with obesity, therefore proving a decreased connectivity in crucial control/decision-making circuits [21].

Another level of regulation of hedonic hunger is the mesolimbic dopamine (DA) pathway (“reward system”). Within this system, the Ventral Tegmental Aerea (VTA) plays a crucial role in encoding the rewarding properties of food, through its dopaminergic efferent projections to the nucleus accumbens [15]. Exposure to palatable food as well as to drug self-administration activates mesolimbic DA pathways [22] with DA release in the nucleus accumbens and dorsal striatum, mediating primary reward, motivation and habit formation [11].

Along with the dopaminergic system, other neurotransmitter systems are involved in regulation of non-homeostatic eating behavior: the opioidergic system, which modulates some aspects of food reward, as the hedonic experience of eating preferred foods [23]; the endocannabinoid signaling; the serotonin system, which is implicated both in the homeostatic and in hedonic circuits of food intake regulation; the endogenous catecholamines, which, by binding to different adrenoceptors in the PVN, might activate (α2-adrenoceptors) or inhibit (α1-adrenoceptors) eating.

Given the complexity of the feeding behavior regulation system, it is conceivable that numerous other targets for the development of antiobesity drugs exist within and outside the CNS.

3. New pharmacological targets for the homeostatic regulation of hunger

3.1. Melanocortin MC-4 receptor agonists

The α-MSH, a POMC-derived peptide, binds and activates MCRs, especially MC4R, inhibiting food intake and increasing energy expenditure [18]. A decreased activity of the melanocortin system is involved in the initiation of feeding and hunger. Moreover, mutations in the MC4R are the most common cause of monogenic obesity. The central role of MC4R in the regulation of feeding behavior makes MC4R an interesting target for studies on development of new anti-obesity drugs.

Numerous molecules have been tested as MC4R agonists: melanotan II (MTII), tetrapeptides, MK-0489, MK-0493, urea-based piperazine, Ro27-3225, cyclophanes, ACTH-derivates, compound 1, pyrrolidine diastereoisomer, BIMs (BIM-22493 and BIM-22511) and β-MSH analogues [24].

Most studies on these compounds analysed most frequently acute effects in animals. Furthermore, the main issues related to these studies concern the aim of generating compounds with increased specificity for MC4R in determining metabolic effects (avoiding side effects) and the crossing the blood–brain barrier (BBB) which is necessary to reach the MC4R [24].

Among these molecules, the MC4R agonist setmelanotide (also known as RM-493 or BIM-22493), a cyclic peptide able to cross the BBB, has been proven to be effective in promoting weight loss in patients with diverse MC4R pathway deficits, both in preclinical [25] and clinical studies [26,27]. A randomized, double-blind, placebo-controlled study investigated the effects of continous s.c. infusion of RM-493 (1 mg/24 h) on resting energy expenditure in healthy obese adults compared to placebo. RM-493 resulted in a 6.4% increase in resting energy expenditure and in increase of plasma GLP-1 and PYY

levels. Otherwise, an impairment of insulin sensitivity emerged in association with the RM-493 treatment [26].

More recently, the effectiveness of setmelanotide was assessed in 21 patients, by highlighting a body weight loss $\geq$10% in patients with POMC or proprotein subtilisin/kexin type 1 (PCSK1) deficiency and in 46% of patients with leptin receptor (LEPR) [28] deficiency.

Recently, the drug received its first approval from the U.S. FDA for promoting weight loss in patients 6 years and older with obesity caused by POMC, PCSK1 and LEPR deficiency and has been granted PRIority MEdicines (PRIME) designation by the EMA for the treatment of obesity and the control of hunger associated with deficiency disorders of the MC4 receptor pathway [28].

3.2. Melanin concentrating hormone antagonists

Within the hypothalamus, the LHA is especially involved in the regulation of feeding behavior, body weight and metabolism; it contains neurons expressing melanin-concentrating hormone (MCH), an orexigenic neuropeptide, which acts as an important mediator of energy homeostasis. Intra cerebro-ventricular injection of MCH in rats stimulates food intake and increases body weight [29], via activation of MCH_1 receptors, accompanied by a sustained increase in hepatic steatosis, glucose, insulin, and leptin levels [29]. Therefore, MCH antagonism has been identified as an attractive new target for obesity treatment.

Several peptide and non-peptide compounds were tested and found active as MCH_1 receptor antagonists [30–32] in preclinical studies. They have been administered by intracerebroventricular injection, or intraperitoneal injection, or less frequently, orally. Among the various MCH_1 receptor antagonist molecules, S38151 was the most frequently used for its higher stability, compared to its purely peptide counterpart. Daily intraperitoneal injection of S38151 (10 and 30 mg/Kg) revealed effective in reducing body weight gain into genetically obese ob/ob mice or diet-induced obese mice [32].

Recently, GPS18169, a pseudopeptide antagonist at the MCH-R1 receptor, given at 5 and 10 mg/Kg intraperitoneally once daily for 12 weeks, showed a decreased accumulation of adipose tissue and, collaterally, a normalization of the insulin level in high-fat diet-induced obese mice, while no change in food or water consumption was observed [33].

Although antagonism to the MCH_1 receptors is certainly validated in rodent models as a target for obesity treatment, few compounds have been progressed into clinical trials [34], especially for the propensity to develop significant cardiovascular side-effects (e.g. drug-induced QTc prolongation).

Apart from some previous clinical pharmacokinetic studies on MCH_1 receptor antagonists, a Phase I study on Alb-127,158 provided promising results, by showing its effectiveness in slightly reducing sensations of motivation to eat, “hunger” and “desire to eat” (at high dose of 300 mg/die orally administered), compared to placebo [35]. Alb-127,158 revealed to be safe and well tolerated. Another MCH_1 antagonist, NGD-4715, used three times per day (but not twice per day) for 14 days, was efficacious in inducing liver enzyme CYP 3A4 and lowering lipid levels in healthy individuals with obesity exposed to high caloric diet [36]. Some clinical data are also available for the MCH1 receptor antagonist BMS-830216: although it showed a good safety profile, its effects on food intake and body weight were negligible [34]. Rather than potential side effects, probably the main limitation in the clinical use of this class drug is the difficulty in reaching a therapeutic concentration in the CNS, except by increasing the dosage and thus, exposing you to a greater risk of adverse events.

3.3. Neuropeptide Y antagonists

Neuropeptide Y (NPY) exerts several effects on the CNS through Y1, Y2, Y4 and Y5 receptors, which are expressed throughout the forebrain and brainstem [37]. Y1 and Y2 receptors are widely abundant in the CNS; Y4 and Y5 receptors are mainly located in the hypothalamus, thalamus and amygdala. NPY acts as an orexigenic agent: in fact, the administration of NPY induces marked stimulation of feeding and energy expenditure through an activation of NPY_1 and NPY_5 receptors within the hypothalamus [38].

Therefore, NPY receptors have been proposed as important drug target for the treatment of obesity.

Among the NPY antagonists, for the first time, the Y5 antagonist MK0557 was tested in a multi-center, randomized, double-blind, placebo-controlled trial involving 1661 patients with overweight and obese; the results were not particularly meaningful, with an additional annual weight loss of just 1.1 kg compared with placebo, after 52 weeks of treatment [39]. More recently, a phase IIa clinical trial, involving 342 individuals with obesity tested another Y5 receptor antagonist, the velneperit (S-2367). An average weight loss of 5.3 Kg (5.6%) over 16 weeks has been reported in the high-dose group of velneperit, compared to placebo group (2.5 Kg or 2.7%); a dose-dependent response has been also shown between 400 mg/day and 1600 nmg/day [44]. Subsequent studies on velneperit, aimed at confirming previous findings (phase IIb) and at assessing the efficacy of the combination NPY inhibitor/orlistat, revealed disappointing and were discontinued [40].

In a recent preclinical study, antagonism of Y2-receptors with the new compound BIIE0246 exhibited beneficial effects on fat deposition and the metabolic status, but only when energy-rich environment was combined with NPY excess [41].

The poor understanding of receptor–ligand interactions could explain these conflicting and mildly significant findings; accordingly, drugs targeting NPY receptors are not currently available [42].

Rather, agonists and antagonists of NPY receptors have shown potential therapeutic effects in other conditions, as mood disorders and drug addiction [42].

3.4. Ghrelin receptor targeting

As the orexigenic neuropeptide Y, also ghrelin receptor targeting is considered a potential therapeutic objective

for the treatment of obesity. Agents counteracting ghrelin activity can act at various levels [43]. Two compounds: the polyethylene glycolmodified l-RNA oligonucleotide RNA Spiegelmer (NOX-B11) and a growth hormone secretagogue receptor (GHS-R) 1a-fusion construct of GHSR/Fc are able to bind ghrelin and consequently to prevent ghrelin's effect.

Specifically, NOX-B11, in the 3 different compounds (l-NOX-B11, NOX-B11-2, NOX-B11-3), was able to suppress the ghrelin-induced c-Fos expression in the arcuate nucleus [44], to inhibit ghrelin-induced food intake both acutely and chronically [45], and to induce weight loss via a reduction of fat mass [45–47] in mice.

Promising results have been obtained also by a mammalian expression plasmid vector encoding the ligand-binding domain of the GHS-R1a, fused with a human IgG constant region (Fc) to form GHSR/Fc. Intramuscular injection of GHSR/Fc reduces circulating levels of acylated ghrelin and decreases weight gain and intraperitoneal fat content, in mice fed a high-fat diet [48]. Simultaneously, glucose metabolism and insulin sensitivity improved in vivo [48].

Another counteraction level of ghrelin activity is the blocking of the catalyzing enzyme, the ghrelin-O-acyl transferase (GOAT), which is involved in generating the active form of ghrelin (acyl-ghrelin). In the last decade, several GOAT inhibitors have been identified: the octanoylated ghrelin pentapeptide [49]; the GO-CoA-Tat, which successfully inhibits ghrelin-induced food intake and weight gain in animals [50,51], and other GOAT inhibitors tested only in vitro or in rodents [43].

Several ghrelin receptor antagonists (GHRP-6, JMV2810, JMV2844, JMV2959, JMV3002, and JMV3021) have been also observed as potential agents able to reduce food intake and body weight, but only in preclinical studies [43].

The liver-expressed antimicrobial peptide 2 (LEAP-2), an endogenous full antagonist of the ghrelin receptor, is effective in suppressing ghrelin-induced food intake [52]. Neverthless, the use of ghrelin receptor antagonists and vaccines have shown promise with reduced food intake and body weight mainly in pre-clinical studies, rather than in human studies. Currently, ghrelin receptor inverse agonists displayed more successful results than antagonists in humans. Recently, several highly potent and selective inverse agonists of GHSR based on the 1,2,4-triazole scaffold have been developed [53].

3.5. Leptin and leptin receptor modulators

Leptin is an anorexigenic hormone, signaling satiety at the hypothalamic level; higher levels of leptin typically reduce appetite and food intake [54]. Therefore, it was assumed that treating obese people with exogenous leptin would be an effective antiobesity therapy, but these hypotheses have not been supported by robust scientific evidence [55]. In fact, recombinant leptin failed to induce significant weight loss in most people with overweight and obesity, who are typically leptin-resistant [56].

Several studies identified numerous leptin-related peptide analogs capable of binding and activating leptin receptors (OBR) likewise the natural hormone. A synthesized fragment of leptin, the OBGRP 22–56, intracerebrally administered has been found to reduce food intake in rats [57]. More recently, the permeability through the BBB of new leptin agonists has been improved, for example, by conjugating leptin fragments with polyethylene glycol (PEG), and those peptides revealed capable to decrease body weight in mice [58]. Other synthetic leptin peptides, as the OB-3, not acting directly through OBR, were able to efficiently cross the BBB and mimic leptin action, reducing body weight and food intake in db/db mice deficient in OBR [58]. The pharmacokinetic profile of OB-3 was better for the nasal and oral formulations than for the intraperitoneal administration [59,60]. However, PEG-modified leptin is able to pass BBB and induces body weight loss in humans [61].

Another way to restore leptin sensitivity in individuals with obesity is decreasing the activity of cytokine signaling 3 (SOCS3) and phosphor-tyrosine protein phosphatase (PTP1B), which are involved in the mechanisms of leptin resistance, by inhibiting the leptin-induced phosphorylation of the receptor (SOCS3) and the downstream leptin signaling (PTP1B) [62]. Thiazolidinedione derivates or trodusquemine seem to act through this mechanism in rats [63,64]. However, several concerns have risen for these inhibitors in the human application, due to their low specificity for neuronal circuits and possible teratogenic effect [61].

In absence of interaction with leptin, the OBR is characterized by high degree of constitutive internalization, in fact only 5–25% of OBR are expressed on the plasma membrane [55,61]. It has been hypothesized that therapies aimed at mobilizing OBR from intracellular pools and at increasing OBR on the cell surface (e.g., ubiquitin ligase RNF41 and LRP2) might represent a new approach to improve leptin-sensitivity in individuals with obesity [55,61].

Other promising therapeutic targets against leptin resistance and obesity are chemical chaperons decreasing the Endoplasmic Reticulum (ER) stress, which is implicated in several diseases including obesity and T2D. 4-phenylbutyrate (4-PBA) and tauroursodeoxycholic acid (TUDCA) can stabilize the folding of proteins, decrease abnormal protein aggregation and reduce hypothalamic ER stress, with consequent increased leptin sensitivity, reduced food intake and body weight in mice [65]. In humans, 4-PBA and TUDCA have proved capable to improve insulin signaling and glucose homeostasis in individuals with insulin-resistance, and to improve insulin-sensitivity in individuals with obesity [66,67].

As for other neuropeptides, intranasal administration of leptin can easily reach the CNS and hence, exert its anorexigenic and induce weight loss in rats with diet-induced obesity effect, likewise in non-obese rats [68]. Its use in humans could be limited by the high doses of peptidic hormone, the variability of nasal absorption, and the high price [61].

Finally, another potential therapeutic approach to leptin-resistant obesity could be the reduction of circulating leptin levels using polyclonal anti-leptin antibodies; they have been found to reduce leptin levels, food intake and body weight (about 5%) in rats with diet-induced obesity [69].

3.6. Amylin mimetics

Another potential target of anti-obesity drug therapy is the agonism of amylin receptors. Amylin is a pancreatic hormone co-secreted with insulin, involved in glucose metabolism regulation, delay of gastric emptying and suppression of postprandial glucagon release [70].

Furthermore, amylin has been shown to reduce energy intake and regulate appetite/satiation via an action on hypothalamus, VTA, and laterodorsal tegmental nucleus. In the past, several amylin analogues, as the pramlintide and davalintide were tested as anti-obesity drugs. Pramlintide displayed a weak efficacy in inducing weight loss in humans over 24 weeks in monotherapy, rather than in co-administration with either the sympathomimetic sibutramine or phentermine [71]. About davalintide, results were disappointing, with weight loss comparable to pramlintide and inferior compared with pramlintide/metreleptin, also resulting in its discontinuation of its development [72].

Recently, more promising results in body weight loss in humans were obtained by testing an amylin mimetic, the cagrilintide. Results of a phase 2 trial, published in 2020, found dose-dependent reductions in body weight of up to 10.8% in participants with overweight and obesity after treatment with once-weekly subcutaneous cagrilintide at doses of 0.30–4.5 mg [73]. Its efficacy has been confirmed also in association with semaglutide 2.4 mg, displaying an acceptable safety profile [74].

3.7. Glucose-dependent Insulinotropic Polypeptide (GIP) receptor agonists and antagonists

Glucagon-Like Peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Polypeptide (GIP) are gut hormones responsible for the amplification of insulin secretion after oral nutrient intake. Infusion studies have shown that only GLP-1, but not GIP, is capable of stimulating insulin secretion in patients with T2D [75]. Furthermore, GLP-1 is able to inhibit appetite and food intake, promoting weight loss upon chronic administration, whereas GIP generally is thought to have no effects on food intake [75]. The numerous evidences of efficacy of GLP-1 receptor agonists in promoting weight loss have led to establish that the agonism to the GLP-1 receptor, especially in the form of semaglutide, currently represents the best pharmacological target for the treatment of obesity, along with phentermine-topiramate [76]. In recent years, a role of the GIP as a potential target for the treatment of obesity has also emerged. Specifically, GIP analogs, modified to play activity also on other receptors including the GLP-1 receptor, have been developed with the aim of improving body weight and glycemic balance [75]. Favorable results were recently disclosed about the tirzepatide, a long-acting GIP-GLP-1 co-agonist, which revealed effective in near-normalizing glycated hemoglobin and reaching a weight loss of about 5–10% [77] within 6 months, in overweight patients with T2D. At the same time, preclinical data highlighted that also a GIP receptor antagonist, both alone and in combination with GLP-1, is effective in reducing body weight in non-human primates with obesity [78]. It has been hypothesized that antagonizing endogenous GIP action would result in increased GIP receptor expression in the tissues, which is downregulated by extended exposure to GIP, whereby the sensitivity of the system is restored [75]. Differences in the agonist-induced internalization of the GLP-1 and GIP receptors and modifications of the ligand structures seem to be implicated in this joint effect of both agonist ang antagonist of the GIP receptor on body weight loss.

3.8. Activin receptor signaling

Activins are expressed in various tissues and have a role in the regulation of gonadal function, hormonal homeostasis, growth and differentiation of musculoskeletal tissues, regulation of growth and metastasis of cancer cells, proliferation and differentiation of embryonic stem cells, and even higher brain functions [79]. Effects of activins are mediated by Type I and II transmembrane serine/threonine kinase receptors, which are modulated also by multiple transforming growth factor-β (TGF-β) ligands such as myostatin, growth and differentiation factor-11 and nodal [79].

The inhibition of the activin receptor type IIB (ActRIIB) by the novel ActRIIB-Fc (a soluble ActRIIB protein comprised of a form of the extracellular domain of ActRIIB fused to a human Fc) suppresses diet-induced obesity and metabolic dysfunctions in mice fed a high-fat diet, by increasing skeletal muscle mass [80]. Furthermore, ActRIIB blockade by myostatin can enhance the amount and function of brown adipose tissue (BAT), increasing mitochondrial function, uncoupled respiration, and thus, energy expenditure in mice [81]. One of the main clinical trials on the application of ActRIIB (bimagrumab) in humans with obesity and T2D for 48 weeks demonstrated its safety and efficacy not only in increasing lean mass, but also in decreasing fat mass and improving glycemic control [82]. A recent metanalysis including 244 participants highlighted that the myostatin inhibitor, BYM338, may contribute to body weight loss also by increasing the walking performance [83].

These preliminary findings make ActRIIB attractive as a therapeutic option for sarcopenic obesity or obesity associated with impaired glucose homeostasis.

3.9. Hypothalamic effects of levocarnitine

Levocarnitine is an amino-acid derivative; it is synthesized in the liver and in the kidney, or is obtained from certain foods. Levocarnitine facilitates long-chain fatty acid (LCFA)

entry into mitochondria, delivering substrate for oxidation and subsequent energy production. Several mechanisms seem to be involved in the role of levocarnitine in decreasing body weight: for example, the central inhibition of carnitine palmitoyltransferase-1 (CPT1) leads to increased LCFA-CoA in selective hypothalamic neurons, signaling 'nutrient abundance', and activating a chain of neuronal events aimed to promote a switch in fuel sources from carbohydrates to lipids, and to limit the further entry of exogenous and endogenous nutrients into the circulation [84]. Furthermore, it has been shown that levocarnitine could induce the expression at both the mRNA and protein levels of the transcription factor, the proliferator-activated receptors (PPARs)-γ, which are associated with adipocyte differentiation through the storage of long chain fatty acids as triacylglycerols deposition in the subcutaneous adipose tissue, instead of in the visceral fat, and utilization of adiponectin in adipocytes in order to maintain relevant metabolic activity and insulin sensitivity [85].

Although several preclinical studies highlighted the efficacy of levocarnitine in weight management, findings obtained by clinical studies were conflicting. A recent metanalysis including 43 Randomized Clinical Trials (RCTs) demonstrated the efficacy of levocarnitine supplementation in reducing body weight, BMI, fat mass (but not body fat percent) and waist circumference. Some of these effects are dependent on the participants BMI and on dose of levocarnitine, and seem to be more significant in significant in individuals with a BMI below 25 kg/m^2 [86].

However, the reducing effect of levocarnitine on body weight (about 1.08 kg in studies with follow-up period of $\leq$12 weeks and 1.48 kg in studies with follow-up period of $>$12 weeks) [85], BMI and fat mass is still considered modest and need to be confirmed by larger studies.

4. New pharmacological targets for the hedonic regulation of hunger

4.1. Cannabinoid antagonists and inverse agonists

The endocannabinoid system (ECS), formed by specific receptors [cannabinoid type 1 and type 2 (CB1 and CB2)], their endogenous ligands (endocannabinoids), and enzymes involved in their synthesis and degradation, is also implicated in the control of appetite and body weight [87]. Specifically, the ECS within the nucleus accumbens regulates food intake by acting on hedonic impact of palatable foods. Endocannabinoids indirectly modulate DA function: on the one hand, activation of CB1 receptors on GABAergic terminals in VTA induces disinhibition of the DA neurons, with resulting increased VTA firing, on the other side, the binding of endocannabinoids to CB1 receptors decreases excitatory glutamatergic input to VTA and nucleus accumbens, affecting activity of neurons projecting from the PFC [18].

CB1Rs are widespread both in the central and peripheral nervous systems, i.e., in the cerebral cortex, with a high accumulation in the cingulate cortex, and the frontal and motor cortex, as well as in the hippocampus, amygdala, striatum, deep cerebellar nuclei, brain stem. In the hypothalamus, its accumulation is relatively low. CB2Rs, although more spread peripherally, have also been found in the striatum, hypothalamus, cerebral cortex, hippocampus, amygdala, and substantia nigra [87]. Endocannabinoids have been found to stimulate food hunger and food intake, and to promote mechanisms aimed to energy storage, by acting on adipocytes, hepatocytes, islet cells, the gastrointestinal tract, and skeletal muscles [87].

Blocking CB1R signaling has been assumed to be a potential mechanism to induce hypophagia. The CB receptor blocker rimonabant was the first successful anti-obesity drug in this class [88]. After several studies demonstrating its efficacy in reducing weight loss in preclinical models of obese animals [89], rimonabant demonstrated its efficacy in promoting weight loss in humans ($\geq$10% of baseline body weight) both at the dosage of 5 mg and 20 mg, in a large randomized, double-blind, placebo-controlled, multicentre study [90]. Furthermore, rimonanbant showed its effectiveness in improving cardio-metabolic risk factors [91], reducing liver fat content [92], and improving glycemic control [93]. Nevertheless, due to its ability of blocking reward pathways, rimonabant was responsible for the occurrence of severe psychiatric side effects (mood disorders and depression) [88]. For this reason, in 2008, use of rimonabant has been suspended in European nations.

Another compound similar to rimonabant, the taranabant, has been developed as novel CB1 inhibitor and inverse agonist. Two randomized, placebo-controlled clinical trials assessed its safety and efficacy in individuals with overweight/obesity [94,95]. All analyzed doses led to a clinically meaningful, yet relatively modest, weight loss. Same as for the rimonabant, the main concern was linked to a dose-related increase in the occurrence of psychiatric adverse events, such as depression, anxiety, anger, aggression, mood change and irritability. Therefore, its clinical use has been discontinued.

Another compound structurally like rimonabant, the AM 251, has been tested as inverse agonist of CB1R in preclinical studies. It was shown to decrease feeding and promote weight loss in animals [96], thereby improving glucose and lipid metabolism, alleviating the steatosis present in the metabolic syndrome [97], and alleviating adipose tissue inflammation [98]. To date there are no studies that have investigated the effects of AM 251 in humans. To contain the known severe cerebral side effects, new CB1R inverse agonists with lower CNS penetrance have been developed: e.g., TM38837 which has been tested in humans [99]; AJ5012 which seems to induce weight loss by increasing energy expenditure [100]; JD5037 which also ameliorates glycemic control and increases energy expenditure [101]; SM-11 that reduces hedonic aspect of food intake through a dopamine-dependent mechanism [102], and numerous other compounds [89].

Promising results in suppressing hunger and promoting weight loss have been obtained by some CB1 inverse agonists, as the WIN 55, 212-2 [103], especially, in association with the GLP-1 agonist, the exendin-4 [104].

Although it is well established that the primary psychoactive component of cannabis, the Tetrahydrocannabinol (THC), promotes food intake by acting as a CB1 partial agonist, one of its non-psychoactive metabolites, the tetrahydrocannabivarin (THCV) induces hypophagia and weight reduction at low doses in mice [105] and ameliorates insulin sensitivity in two mouse models of obesity [106]. In a randomized, double-blind, placebo-controlled study involving 62 individuals with T2D, THCV significantly decreased fasting plasma glucose and improved pancreatic β-cell function, showing a good safety profile [107].

THCV has been found to modulate resting state functional connectivity (measured by fMRI) in key networks, crucial for control over food intake, such as the default mode network and the cognitive control network, in healthy volunteers, suggesting a possible therapeutic role of THCV in obesity [108,109].

4.2. Serotonin agonists and antagonists

Serotonin (5HT) exerts its biological actions mainly in peripheral tissue as a vasoactive amine, but in the CNS plays a role as a modulator of behavior (including feeding behavior) and mood. Moreover, 5HT signaling plays a role both in the homeostatic and in hedonic circuits of food intake regulation: at the hypothalamic level, serotonin interacts with endogenous orexigenic (Neuropeptide Y/Agouti related protein) and anorexigenic (α-MSH) peptides [110]; whilst, in the nucleus of the solitary tract, 5HT integrates peripheral satiety signals [110]. In the main, it has been observed that reduction in 5HT levels causes hyperphagia.

5-HT receptors are widespread in the central and peripheral nervous systems and can be divided into 7 families (5-$HT_{1\text{-}7}$). For a while now, it is known that stimulation of 5-HT_{2C} receptors, for example by fenfluramine, decreases food intake and body weight [37]; in this connection, a significant role of 5-HT_{2C} receptors located on POMC has been hypothesized [37]. In the past, several 5-HT agonists (e.g., fenfluramine, dexfenfluramine …) have been investigated as potential treatment for obesity, but the occurrence of severe side effects like hallucination, valvulopathy and pulmonary hypertension has counteract their spread [111]. Lorcaserin, a selective 5-HT_{2C} agonist, proved to be better tolerated and effective in inducing weight [37], although in the early 2020 the FDA requested that the manufacturer of lorcaserin voluntarily withdraw the drug from the market, because of a signal of increased cancer risk [112].

For several years, the effects of serotonin re-uptake inhibitors (especially fluoxetine) as anti-obesity drugs have been extensively studied in numerous studies, never having received approval as a conventional treatment despite. A recent Cochrane systematic review analyzed 19 published trials (15 parallel trials, and four with a cross-over design), including a total of 2216 individuals with overweight or obesity, and without depression, mental illness or abnormal eating patterns, who were followed up for between three weeks and one year [113]. The results of the systematic review highlighted that 60 mg/d fluoxetine compared with placebo was able to decrease body weight by 2.5 Kg; however the 95% prediction interval ranged between a 6.4 Kg weight loss and a 1.4 Kg weight increase. The systematic review concluded that off-label fluoxetine could decrease body weight compared with placebo, but with low-certainty evidence [113].

More recently, the blockade of 5-HT_6 receptors has attracted the attention as a potential target for the treatment of obesity. The 5-HT_6 antagonist, Ro 04–6790, administered for 3 days, attenuated body weight gain in growing rats [114] and reduced food intake [115].

Moreover, idalopirdine, a potent and selective 5-HT_6 receptor antagonist, increases cortical levels of dopamine and noradrenaline and is used as an adjunctive therapy for the treatment of cognitive deficits, showing anorexic effects in obese animals [116], and a reduction of caloric intake with prevention of obesity in the animal model of excessive eating [117]. The underlying mechanism seem to be a block of the serotonin-dependent activation of GABA neurons, which results in a reduction of inhibitory effects of GABA on POMC neurons in the arcuate nucleus, with subsequent inhibition of hunger signal induction.

5. Non-pharmacological targets for the treatment of obesity

5.1. Neurostimulation and corticomesolimbic dopaminergic system

As we have previously detailed, underlying mechanisms of hedonic hunger mainly involve the dopaminergic mesocorticolimbic pathway (“reward system”), which principally consists of the VTA, the nucleus accumbens, and dorso-lateral-PFC (DLPFC). In individuals with obesity, repeated and prolonged exposure to high-fat diet and/or obesity induces dysfunctions in DA homeostasis, specifically reduces DA activation and induces habituation, as this blunted activation can trigger compensatory overeating [118]. Furthermore, a decreased striatal DA D2 receptor density has been reported in comparison to non-obese individuals, probably as a compensatory effect for a decreased activation of the reward circuit [119]. Decreased striatal D2 receptors lead to overeating via modulation of striatal prefrontal pathways, and resulting in impaired inhibitory control and salience attribution [120].

Pharmacological intervention affecting the dopaminergic signaling displayed a therapeutic potential to treat obesity. For example, the combined DA and norepinephrine reuptake inhibition (as with bupropion) exhibits an anti-obesity effect, through a significant impact on energy homeostasis and hyperphagia [121].

Building on promising evidences in neuro-psychiatric indications such as depression and addiction [122,123], in the last decades, brain stimulation has been explored for the treatment of eating disorders and obesity, by targeting the PFC which is implicated in higher-order reward processing, as part of its involvement in the “reward system”.

Neurostimulation could be delivered by electrodes implanted in the brain parenchyma [Deep Brain Stimulation (DBS)] or more frequently, in the shape of non-invasive brain stimulation (NIBS) which, in turn, includes transcranial magnetic stimulation (TMS), transcranial and direct current stimulation (tDCS). TMS acts by generating an electro-magnetic field via a specify coil able to reversibly modulate neuronal excitability in underlying brain structures; a variant of TMS is the deep TMS (dTMS), equipped with a special coil (H-shaped or double-cone coil) able to stimulate deeper brain regions as the insula; tDCS generates a weak direct current through cortical tissue via scalp electrodes, affecting the spontaneous firing activity.

Starting from the early 2000s, NIBS' effects on food craving and eating behavior have been investigated in healthy individuals, in those reporting frequent food cravings, and in patients with bulimia nervosa (BM) and anorexia nervosa (AN) [124]. In most of these studies, high-frequency (excitatory) repetitive TMS addressed to the left PFC has been employed, and showed promising results in controlling food craving and reducing binge eating episodes [124], with a reassuring safety profile.

Nevertheless, surprisingly, no studies have investigated NIBS potential in binge eating or obesity for several years. Recently, Ferrulli et al. demonstrated the safety and efficacy of dTMS, targeted to the PFC and insula bilaterally, in controlling food craving and reducing body weight up to 1 year period (body weight −7.83 Kg; BMI -2.83 kg/m^2), in individuals with obesity and without eating disorders [125,126]. An enhancing inhibitory capacity of PFC, specifically of the mOFC [127], and of the fronto-parietal network [128] on overeating behavior has been considered the main mechanism underlying this effect. Other potential involved mechanisms may be a TMS-induced increase in activity energy expenditure [due to augmented metabolic equivalent of tasks (METs), steps, and travelled kilometres] [125]; reduction of impulsivity [129]; reversal of obesity-associated gut microbiota variations [130]; improvement of neuropeptides implicated in the regulation of appetite/satiety balance [eg. cholecystokinin (CCK), brain-derived neurotrophic factor (BDNF), β-endorphins] [131,132].

The potential for NIBS to become an effective and safe strategy for the management of obesity has been confirmed by other following randomized clinical trials [133,134]. A recent meta-analysis, evaluating the efficacy of NIBS in 8 randomized clinical trials on weight reduction, highlighted that high-frequency dTMS over bilateral DLPFC and the insula is associated with the largest decrease in BMI, whilst high-frequency TMS addressed to the left DLPFC is associated with the largest decrease in totally energy intake and craving severity [135].

Several studies in the field of food craving, eating behavior, and obesity, assessed also the effects of tDCS applied over the DLPFC, showing a prevalent efficacy in reducing food craving and appetite, and less promising results in decreasing food intake and body weight, probably due to high interindividual variability [136,137]. Larger clinical trials will be needed to confirm the null or active tDCS effect in promoting weight loss. Evidence of efficacy of tDCS, targeted to the motor cortex, in improving exercise performance revealed more solid, suggesting that a manageable tDCS device could be a valuable resource for individuals needing to weight loss and seeking to improve physical fitness in their daily life [138].

Most of the NIBS techniques applied to obesity revealed well tolerated and with a good safety profile as evidenced by the low drop-out rate. However, future RCTs aimed at defining the optimal neurostimulation protocol for treating obesity are recommended.

6. Conclusions

In view of the alarming growth rate of obesity worldwide, scientific community, policy makers, and pharmaceutical industries have increasingly recognized the need for safe and effective pharmacotherapy to counteract obesity. Several anti-obesity medications, in combination with lifestyle modification, are currently in various stages of development. This review article focused on the interventions aimed to control food intake (via modulation of homeostatic and hedonic regulation of feeding) in the CNS. However, some of the described treatment options have been shown to affect not only energy intake, but also energy expenditure. Each of the above-mentioned pharmacological categories displayed advantages and disadvantages, and no intervention is currently considered ideal for the treatment of obesity.

Brain neurostimulation, specifically repetitive TMS and tDCS, revealed an effective and non-invasive modality with a low profile of adverse effects, but as for other pharmacological interventions, its efficacy needs to be confirmed in larger and long-term studies.

As obesity is a multifactorial disorder, a single treatment may not be enough for patients to achieve the therapeutic goals: to loss body weight and to maintain the lost weight at long-term.

The plethora of currently available anti-obesity medications creates the unique challenge for physicians to customize the intervention, according to the specific obesity characteristics, contraindications, and medication side effect profiles; moreover, it allows multimodal approaches addressed to treat obesity and metabolic adaptation with complementary mechanisms.

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Author contribution

AF and LL conceptualized the paper; AF, LL, IT, PS, MS and DC drafted the first version of the manuscript. AF and LL revised it and contributed significantly with intellectual

content. All the authors read and revised the manuscript and approved the final version.

Data availability statement

Not applicable.

Declaration of competing interest

The authors declare that they have no competing interests.

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