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Mendelian obesity, molecular pathways and pharmacological therapies: a review

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Abstract. – OBJECTIVE: In this qualitative review we analyze the major pathways and mechanisms involved in the onset of genetically-determined obesity (Mendelian obesity), identifying possible pharmacological treatments and trials.

MATERIALS AND METHODS: We searched PubMed with the keywords (obesity[Title/Abstract]) AND mutation[Title/Abstract], and OMIM with the keyword "obesity". In both cases, we selected non-syndromic Mendelian obesity. We then searched ClinicalTrials.gov with the following criteria: "recruitment status: active, not recruiting and completed"; "study type: interventional (clinical trial)"; "study results: with results"; type of intervention: "drug or dietary supplement".

RESULTS: From the PubMed and OMIM searches we obtained a total of 15 genes associated with monogenic Mendelian obesity. From ClinicalTrials.gov we retrieved 46 completed or active trials of pharmacological treatments.

CONCLUSIONS: We summarized the molecular bases of Mendelian obesity and searched for any clinical trials completed or underway for the treatment of severe forms of obesity. Most Mendelian obesities are linked to dysfunctions in the leptin/melanocortin signaling pathway, and most of the possible drugs target this pathway in order to improve energy expenditure and reduce food intake.

Key Words:
Mendelian obesity, Leptin/melanocortin pathway, Adipogenesis, Clinical trials.

Introduction

Adipocytes are the major constituents of white adipose tissue. They control energy balance by storing and mobilizing triacylglycerol, and they play roles in endocrine and paracrine regulation. Adipose tissue controls glucose metabolism, appetite, immunological and inflammatory responses, angiogenesis, blood pressure, and reproductive function through many specific factors. When adipocytes accumulate, they form adipose tissue. The amount of adipose tissue in the body is mainly regulated by leptin, a hormone produced by adipocytes themselves. Adipose tissue expands when the number and size of adipocytes increases[1]. An excessive amount or size of adipocytes can generate a morbid condition called obesity. Obesity is highly heritable and arises from the interplay of many genes and environmental factors. It is defined as resulting from a prolonged imbalance between calorie intake and energy utilization. An understanding of how these variations influence susceptibility to become or remain obese will hopefully provide insights into how obesity occurs and how to prevent and treat it[2]. It is important to note that about 5% of cases of obesity are monogenic[3]. Most mutant genes in Mendelian obesity are also involved in a predisposition for common obesity through the action of common single nucleotide polymorphisms (SNPs) (minor allele fre-

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quency >1%). In this qualitative review, we clarify and analyze the major pathways and mechanisms involved in the onset of genetically-determined obesity (Mendelian obesity). We also review drugs that may be or are already used to treat obesity.

Materials and Methods

To identify genes involved in isolated monogenic obesity we searched articles published in English up to October 2018 in PubMed with the following combination of terms: (obesity[Title/Abstract]) AND mutation[Title/Abstract], whereas in OMIM we searched using the word: "obesity". From the records retrieved, we only selected publications dealing with Mendelian non-syndromic obesity. We only considered disorders for which the pathogenicity of the mutations was supported by segregation studies in more than one multigenerational family and/or by functional studies. To find drugs useful to treat obesity we searched ClinicalTrials.gov with the following criteria: "recruitment status: active, not recruiting, and completed"; "study type: interventional (clinical trial)"; "study results: with results"; type of intervention "drug or dietary supplement". From the list obtained, we selected drugs that were used to treat obesity, excluding drugs used only to treat obesity-related complications.

Results

From the PubMed and OMIM searches, we obtained 1878 and 655 entries, respectively, from which we extracted a total of 15 genes associated with monogenic Mendelian non-syndromic obesity. From ClinicalTrials.gov we retrieved a total of 433 entries and as described in "Methods", we selected 46 completed or active trials of pharmacological treatments.

Mendelian Monogenic Obesity

Most genes known to be associated with monogenic obesity are related to the leptin/melanocortin pathway (Figure 1) and are expressed in the hypothalamus. They code for proteins involved in food intake/energy expenditure balance. Another pathway associated with obesity leads to the formation of mature white adipose tissue and involves several growth and transcription factors.

The Leptin/Melanocortin Pathway

Leptin (LEP) is secreted by adipose tissue and binds to leptin receptors (LEPR) in the hypothalamus, where it controls food intake through the melanocortin pathway. Leptin acts in the arcuate nucleus where it activates neurons that express the anorexigenic peptides pro-opiomelanocortin (POMC), as well as cocaine- and amphetamine-related transcript preprotein (CARTPT) derivatives that control food intake. Leptin also has inhibitory effects on the neurons that express the orexigenic peptides neuropeptide Y (NPY) and Agouti-related protein (AGRP), which increase food intake. Both POMC/CARTPT and NPY/AGRP subsets of neurons have many connections with other hypothalamic nuclei. The binding of leptin to its receptor initiates a cascade of signal transduction pathways, deficits of which may cause leptin resistance. With the help of Src homology 2B adapter protein 1 (SH2B1), LEPR recruits JAK2, which in turn phosphorylates the intracellular domain of LEPR. The phosphorylated intracellular domain of LEPR binds and activates STAT3, which with the aid of Tubby bipartite transcription factor (TUB), translocates to the nucleus and acts as a transcription factor, mediating the anorexigenic effects of leptin[4]. Besides the JAK/STAT pathway, another important intracellular pathway for energy homeostasis is the PI3K pathway. Indeed, LEPR stimulation mediates tyrosine phosphorylation of IRS proteins by JAK2. IRS in turn activates PI3K that generates phosphatidylinositol-3,4,5-trisphosphate (PIP_3) from phosphatidylinositol-4,5-bisphosphate (PIP_2). The importance of this pathway in the regulation of energy balance is highlighted by the fact that administration of myo-inositol (the core constituent of PIP) may improve endocrine and metabolic parameters, and reduce BMI in overweight patients with polycystic ovary syndrome[5]. PIP_3 induces activation of PDK1 that triggers a cascade including Akt and members of the PKC family. Akt activates mTOR and inhibits the transcription factor FOXO1[6]. Note the close interaction between STAT3 and FOXO1, both of which bind AGRP and POMC promoters. While STAT3 inhibits expression of AGRP and activates expression of POMC, FOXO1 has the opposite effect[6].

After its synthesis, POMC is cleaved by prohormone convertase 1 and 2 (PC1/2) and by carboxypeptidase E (CPE), which are expressed in the feeding centers of the ARC, to yield melanocortins α-, β- and γ-MSH. The actions of melanocortins are mediated by two G-protein cou-

pled receptors known as melanocortin 3 and 4 receptors (MC3R, MC4R) that play a central role in the control of body weight, decreasing food intake and favoring weight loss[6]. Melanocortin 2 receptor accessory protein 2 (MRAP2) can reduce the responsiveness of MC3R and MC4R to α- and β-MSH. On the other hand, single-minded 1 (SIM1) acts as a facilitator of MC4R activity. MC4R activity also stimulates the release of brain-derived neurotrophic factor (BDNF), which binds to the neurotrophin receptor (NTRK2) and influences food intake and energy expenditure[7].

Adipogenesis

Mesenchymal stem cells (MSCs) are the precursors of adipocytes. They can differentiate into adipocytes, chondrocytes, myocytes or osteocytes. Differentiation towards the adipocyte lineage is induced by chronic excessive energy intake and elevated glucose uptake. Lineage determination is regulated by a network of extracellular signaling factors[8]. Although many molecular details of adipogenesis are still unknown, numerous factors involved in this process have been identified. Some stimulators include peroxisome proliferator-activated receptor γ (PPARG), enhancer binding proteins α, β and δ (CEBPA, CEBPB, CEBPD), single transducers and activators of transcription (STATs), the transcriptional factor sterol-regulatory-element-binding protein-1 (SRBP1), insulin-like growth factor I (IGF1), macrophage colony stimulating factor, fatty acids, prostaglandins, glucocorticoids, Kruppel-like factors (KLFs), wingless and INT-1 proteins (WNTs), various cell cycle proteins, clock proteins (BMAL1, NR1D1), interferon regulatory factors (IRF3, IRF4), B-cell factor 1 (EBF1), GATA-binding proteins 2 and 3, bone morphogenetic proteins (BMPs), transforming growth factor β (TGF-β), fibroblast growth factors (FGFs), insulin-like growth factor (IGF), Notch-mediated signaling and pro-inflammatory cytokines. Inhibitors include glycoproteins, TGF-β, inflammatory cytokines and growth hormone[1]. In particular, PPARG is necessary and sufficient for adipocyte differentiation, and is therefore a master regulator of adipogenesis. It is not surprising that mutations in this gene cause a form of Mendelian obesity[9].

Obesity Due to mutations in the Leptin Gene, LEP, and its Receptor, LEPR

LEP encodes a protein that is secreted into circulation by white adipocytes and plays a major role in the regulation of energy homeostasis. Circulating leptin (LEP) binds to the leptin receptor (LEPR) in the hypothalamus, which activates downstream signaling pathways that inhibit feeding and promote energy expenditure. Consistently, loss of function mutations in this gene leads to the onset of obesity. Obesity linked to mutations in *LEP* has a prevalence of < 1/1,000,000 and autosomal recessive inheritance. *LEP* was first linked to human Mendelian obesity in 1997 by Montague and collaborators studying an inbred Pakistani family. They found a homozygous deletion of a G in *LEP* in codon 133 in two individuals (c.398delG). The mutation disrupted the reading frame, leading to a premature stop codon[10]. In 2002, a third child from an inbred Pakistani family with the same single-base deletion was reported[11]. A fourth case with severe hyperphagia and obesity, reported by Gibson et al[12] in 2004, had the recurrent homozygous deletion[12]. In three obese individuals with very low serum concentrations of leptin, Strobel et al[13] (1998) found the first pathogenic missense mutation in *LEP* (c.313C > T; p.Arg105Trp). All three affected individuals were hyperphagic and one was hyperglycemic[13].

Obesity due to mutations in *LEPR* has autosomal recessive inheritance and unknown prevalence. Clement et al[14] (1998) were the first to report a mutation in the human leptin receptor gene, a G > A transition at the donor splice site in intron 16 (c.2598 + 1G > A) that causes obesity and pituitary dysfunction[14]. The mutation was homozygous in an inbred family of Algerian origin in which 3 out of 9 siblings had morbid obesity with onset in early childhood. In addition to obesity, the affected sibs had no pubertal development and reduced secretion of growth hormone and thyrotropin[14]. To determine the prevalence of pathogenic *LEPR* mutations in severely obese patients, Farooqi et al[15] (2007) sequenced *LEPR* in 300 patients with hyperphagia and severe early-onset obesity, finding nonsense or missense *LEPR* mutations in 2.7% of them. All missense mutations resulted in impaired receptor signaling. Affected individuals were characterized by hyperphagia, severe obesity, alterations in immune function and hypogonadotropic hypogonadism. Their clinical features were less severe than those of patients with congenital leptin deficiency[15]. In general, the clinical phenotypes associated with leptin and LEPR deficiencies are broadly similar[10,15]. Patients have normal birth weight but show rapid weight gain in the first few months of life. They often accumulate subcutaneous fat over the trunk and limbs. The most notable feature is intense hyperphagia.

Children with leptin deficiency also have striking abnormalities in T cell number and function[11]. Leptin and LEPR deficiency are generally associated with hypothalamic hypothyroidism and hypogonadotropic hypogonadism[11,13].

Obesity Due to Mutations in TUB

Tubby bipartite transcription factor (TUB) is a member of the tubby-like proteins. It is a membrane-bound transcription regulator that translocates to the nucleus in response to phosphoinositide hydrolysis[16]. TUB is a substrate for insulin and leptin receptors in the hypothalamus. It is translocated to the nucleus after binding to LEPR via JAK2. Inhibition of TUB expression in the hypothalamus results in increased food intake, fasting glucose levels and hepatic glucose output, and in reduced oxygen consumption and POMC sensitivity to leptin[17]. Only a single mutation in TUB has so far been reported. The subject was a boy with deteriorating vision, obesity and normal glucose/cholesterol/triglycerides levels from an inbred Caucasian family[18]. The mutation was a homozygous frameshift variant in *TUB* (c.1194_1195delAG, p.Arg398Serfs*9) that results in a truncated form of TUB.

Obesity Due to Mutations in Melanocortin Receptor MC4R

MC4R is a G-protein-coupled receptor mainly expressed in the brain and involved in energy intake and expenditure[19]. *MC4R* mutations are the most common cause of human monogenic obesity, having a frequency of 1.5%[4] and a prevalence of 1-5/10,000 in the general population. Besides obesity, MC4R-deficient children also display hyperinsulinemia and increased linear growth[20]. Interestingly, patients experience an increase in adiposity as well as lean mass[21]. The first mutations in *MC4R*, c.631_634delGAGA and c.732insCATT, were discovered in humans in 1998. They are heterozygous frameshifts and were found in a severely obese child and an adult, respectively. Neither had evidence of impaired adrenal function, and sexual development and fertility were normal[22,23]. Several other cases were subsequently reported in extremely obese individuals whose BMIs all exceeded the 99th percentile[4,24]. Farooqi et al[21] (2003) defined the clinical spectrum, mode of inheritance and genotype-phenotype correlations. They found patients with heterozygous and homozygous loss-of-function mutations: heterozygous carriers had severe obesity, increased lean mass, increased linear growth, hyperphagia, and severe hyperinsulinemia, whereas homozygotes were more severely affected than heterozygotes. *MC4R* mutations are therefore inherited in a co-dominant manner[21].

Obesity Due to Mutations in POMC

POMC encodes a preproprotein that undergoes extensive post-translational processing via cleavage by prohormone convertases. There are eight cleavage sites in the preproprotein and processing may yield as many as ten biologically active peptides, involved in various cell functions. Peptides with roles in energy homeostasis, such as alpha-melanocyte-stimulating hormone (α-MSH), which has anorexigenic effects, are generated in the hypothalamus[25]. Obesity associated with POMC mutations has autosomal recessive inheritance and a prevalence of < 1/1,000,000 in the general population. The first pathogenic mutations in *POMC* were discovered in 1998. One patient had biallelic loss-of-function mutations in exon 3 of *POMC* (c.7013G > T; p.Glu79* and c.7133delC) that interfered with the appropriate synthesis of adrenocorticotropic hormone (ACTH) and α-MSH. The other patient was homozygous for a mutation (c.-11C > A) in exon 2 that abolished POMC translation. The *POMC* gene was chosen for investigation because studies in animal models elucidated a central role of α-MSH in the regulation of food intake by activation of brain MC4R[26]. In addition to obesity, patients with *POMC* mutations displayed hypocortisolism, hair and skin hypopigmentation, neonatal hypoglycemia, seizures, cholestasis, and voracious appetite[26]. Although most research has been focused on α-MSH, a missense loss-of-function mutation in β-MSH (c.14G > A; p.Cys5Tyr) has also been associated with childhood obesity. The lack of function of β-MSH reduces the amount of MSH peptide in the POMC/MC4R pathway, resulting in obesity[27].

Obesity Due to Mutations in PCSK1

Another gene involved in the onset of Mendelian obesity is *PCSK1* that translates for pro-protein convertase subtilisin/kexin type 1. Obesity linked to *PCSK1* mutations has a prevalence of < 1/1,000,000 in the general population and autosomal recessive inheritance. Complete prohormone convertase 1 deficiency was reported for the first time in a patient with a compound heterozygous mutation in *PCSK1* (c.1447G > A; p.Gly483Arg, c.285 + 4A > C) characterized by severe early-onset obesity, hyperphagia, hypoglycemia, hypo-

gonadotropic hypogonadism, hypocortisolism, elevated plasma proinsulin and elevated POMC but low insulin concentrations[28]. Partial loss-of-function heterozygous mutations in *PCSK1* seem associated with a non-fully penetrant intermediate obesity phenotype[29].

Obesity Due to Mutations in SH2B1

The protein translated by *SH2B1* is an adapter protein for several members of the tyrosine kinase receptor family involved in multiple signaling pathways mediated by JAK and receptor tyrosine kinases, such as the receptor of insulin or the receptor of brain-derived neurotrophic factor (BDNF). In leptin signaling, SH2B1 is a key regulator of leptin sensitivity, binding to and potentiating activation of JAK2 by globally enhancing downstream pathways. SH2B1 binds simultaneously to JAK2 and IRS1 or IRS2, thus mediating formation of a JAK2, SH2B1 and IRS1 or IRS2 complex. The result of this interaction is the activation of the PI3K pathway[30]. Obesity associated with mutations in this gene has autosomal dominant inheritance with a prevalence of < 1/1,000,000 in the general population. In humans, loss-of-function mutations in *SH2B1* result in severe early-onset obesity. Eight different mutations have been reported: seven missense and one frameshift variant[31,32]. All patients exhibit hyperphagia, early onset obesity, insulin resistance, and short stature[31]. Note that recurrent deletions of the *SH2B1*-containing region on the short arm of chromosome 16 have been associated with behavioral disorders and obesity[33].

Obesity Due to Mutations in the Receptor NTRK2 and its Ligand BDNF

Neurotrophic receptor tyrosine kinase 2 (NTRK2) is a member of the neurotrophin family, known to be involved in the development and in maintenance and function of peripheral and central neurons; it is thought to play a role in mediating neuronal plasticity in the hypothalamus[34]. NTRK2 and its ligand BDNF are also known to be involved in the regulation of food intake and body weight[35]. A *de novo* heterozygous missense mutation (c.2165A > G; p.Tyr722Cys) in the neurotrophic tyrosine kinase receptor type 2 (NTRK2) gene was found in a boy with early onset obesity, hyperphagia, developmental delay, impaired short-term memory, and impaired nociception. Further analysis showed an impairment in BDNF-stimulated protein kinase phosphorylation[36].

A girl with loss of one functional copy of *BDNF*, due to a *de novo* chromosomal inversion (inv(11)(p13p15.3)), presented with hyperphagia, severe obesity, cognitive impairment, and hyperactivity[35]. Since cases associated with mutations in *NTRK2* and *BDNF* are rare, their prevalence in the general population is unknown.

Obesity Due to Mutations in SIM1

Single-minded homolog 1 (SIM1) is a member of the helix-loop-helix PAS family of nuclear transcription factors. It is expressed in kidneys and the central nervous system and plays an essential role in the formation of the paraventricular nucleus (PVN) of the hypothalamus[37,38]. This could be a mechanism in which SIM1 plays a role in energy homeostasis, as PVN neurons express MC4R which inhibits food intake[5]. Severe early-onset obesity was observed in a girl with haploinsufficiency of *SIM1*. The proband had early-onset obesity and a *de novo* balanced translocation between chromosomes 1p22.1 and 6q16.2. Her weight gain was due to excessive food intake[39]. Further support for the involvement of *SIM1* in obesity came from studies in which patients displayed Prader-Willi-like phenotype due to heterozygous mutations in *SIM1*. In particular, three mutations showed strong loss-of-function effects (p.Thr46Arg, p.His323Tyr, and p.Thr714Ala) and were associated with high intra-family risk for obesity[40]. In another study, at least six severely damaging heterozygous variants in *SIM1* (p.Ser71Arg, p.Arg171His, p.Leu238Arg, p.Pro497Arg, p.Arg550His, p.Thr712Ile) were associated with severe obesity and neurobehavioral phenotype. It is noteworthy that *SIM1*-mutant patients share many features with melanocortin-deficient patients, but they do not share the accelerated linear growth and increased final height seen in MC4R deficiency[41].

Obesity Due to Mutations in KSR2

Kinase suppressor of Ras 2 (KSR2) is a molecular scaffold that facilitates and regulates the intensity and duration of Raf/MEK/ERK signaling[42]. KSR2 also promotes activation, by direct interaction, of the primary regulator of cell energy homeostasis, 5′-adenosine monophosphate-activated protein kinase (AMPK)[43,44]. The interaction between KSR2 and AMPK is suggested to be involved in obesity, high insulin levels and impaired glucose tolerance observed in Ksr2 KO mice[45]. Under conditions of nutrient deprivation and cell stress, intracellular ATP levels fall and

levels of AMP rise, promoting AMPK activation that in turn promotes catabolic processes and inhibits anabolic pathways[46]. Many of the variants studied impaired signaling through the Raf-MEK-ERK pathway, while some reduced the interaction between KSR2 and AMPK, compared to wild-type KSR2[47]. In 2013, Pearce et al[47] sequenced the coding exons of *KSR2* in 1770 Europeans with severe, early-onset obesity (age of onset < 10 years) to clarify whether genetic variants in *KSR2* contribute to obesity. They also retrospectively analyzed data from whole-exome sequencing of a further 331 unrelated individuals belonging to a cohort patients with severe, early-onset obesity. They identified 27 different rare variants in 45 of the 2101 unrelated severely obese individuals screened. Most variants were found in heterozygous form, although one severely obese subject was homozygous for two variants (p.Arg253Trp and p.Asp323Glu). Twenty-three variants were only identified in severely obese individuals; many were predicted to be functionally deleterious and altered highly conserved residues[47]. Nine of them were truncating variants.

Obesity Due to Mutations in ADCY3

ADCY3 encodes adenylyl cyclase 3 which is a membrane-associated enzyme that catalyzes the formation of the secondary messenger cyclic adenosine monophosphate (cAMP). This protein is widely expressed in various human tissues, showing high levels in subcutaneous and visceral fat cells. The cAMP is an essential second messenger in intracellular signaling of key metabolic factors such as glucagon-like peptide 1, ghrelin and α-melanocyte stimulating hormone. cAMP signaling has been linked to control of adipose tissue development and function, as well as insulin secretion in beta cells. Leptin resistance may possibly occur through disrupted cAMP signaling in primary cilia in the hypothalamus, affecting downstream signaling and neuron morphology[46]. Two papers published in 2018 link homozygous loss-of-function mutations to onset of obesity and type 2 diabetes[46,47]. The studies were performed in a small inbred population (Greenlandic) and in an inbred Pakistani family, respectively[46,47].

Obesity Due to Mutations in NR0B2

NR0B2 belongs to the nuclear hormone receptor family and contains a putative ligand-binding domain, while lacking a conventional DNA-binding domain. The protein has been shown to interact with retinoid, thyroid hormone, and estrogen receptors. Furthermore, NR0B2 has the ability to modulate the transcriptional activity of the nuclear receptor 4-alpha (HNF4A) involved in maturity onset diabetes of the young (MODY). In 2001, *NR0B2* was screened in 173 Japanese patients diagnosed with MODY. The authors reported that seven heterozygous mutations (p.Arg57Trp, p.Gly189Glu, p.His53Alafs, p.Leu98_Ala101delinsPro, p.Arg34*, p.Ala195Ser, p.Arg213Cys), found in 12 subjects who were mildly or moderately obese at the onset of diabetes, were associated with obesity rather than with diabetes. All were truncating or loss-of-function mutations[48]. Although 7% of Japanese obese and diabetic patients showed *NR0B2* mutations, this association seems absent in the UK and very rare in Danish subjects[49,50]. Studies in mice suggest that NR0B2 may also be linked to the hypothalamic-pituitary axis, important in the regulation of appetite and energy expenditure[51].

Obesity Due to Mutations in PPARG

PPARG encodes a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors. PPARs form heterodimers with retinoid X receptors (RXRs). Three subtypes of PPARs are known: PPAR-alpha, PPAR-delta, and PPAR-gamma. The protein encoded by this gene is PPAR-gamma, a regulator of adipocyte differentiation. PPAR-gamma has been implicated in the pathology of diseases such as obesity and diabetes.

In 1998, Ristow et al[53] studied 121 obese subjects and identified the p.Pro115Gln mutation in exon 6 of *PPARG* in four of them. The four German patients with the mutant allele had severe obesity, their body mass indexes ranging from 37.9 to 47.3[52]. Significantly, the mutation was in the codon immediately adjacent a Ser114 phosphorylation site that down-regulates the transcriptional activity of the protein[53]. Over-expression of the mutant gene in murine fibroblasts led to the production of a protein with defective phosphorylation of Ser114, accelerated differentiation into adipocytes and greater cell accumulation of triglycerides than for the wild-type[53].

Obesity Due to Mutations in DYRK1B

DYRK1B encodes a member of a family of nuclear-localized protein kinases and participates in cell cycle regulation. *DYRK1B* inhibits the SHH and WNT1 pathways, thereby enhancing adipogenesis. In affected members of three Iranian families with metabolic syndrome and early-onset

coronary artery disease, Keramati et al[54] identified a heterozygous missense mutation in *DYRK1B* (p.Arg102Cys) that segregated with disease in all three families. Functional characterization showed that the p.Arg102Cys allele has a gain-of-function effect. To further confirm the involvement of *DYRK1B* in obesity, analysis of the gene in 300 morbidly obese Caucasian individuals with coronary artery disease and multiple metabolic phenotypes identified another heterozygous missense mutation (p.His90Pro) in five unrelated patients[54,55].

Discussion

Obesity is generally a multifactor disorder associated with the Western lifestyle and linked to genetic and environmental factors. However, in a small percentage of cases (~5%)[3], obesity is clearly associated with specific mutations in specific genes. 5% might seem a rather small percentage but if one considers that million people are obese, the absolute number might be quite high. These forms of obesity are defined as Mendelian obesity or monogenic obesity. Many studies have already elucidated the pathways deregulated in patients with monogenic obesity. In most cases, it is the leptin/melanocortin hypothalamic pathway that regulates food intake and energy expenditure. Pathways that lead to adipocyte differentiation have also recently been found deregulated in Mendelian obesity. Considering the role played by genetics in obesity, we developed genetic tests for the diagnosis of Mendelian obesity and for the identification of genes encoding elements of these pathways. We also analyze genes involved in candidate pathways, studied in mice, or for which mutations have been identified in single cases without additional information about pathogenicity[56,57]. As the understanding of the genetic, behavioral and biochemical basis of obesity increases, more and more drugs are being tested to treat this disorder. We summarized the molecular bases of Mendelian obesity and searched for clinical trials, completed or underway, of drugs to treat severe forms of obesity. Some of these drugs, such as liraglutide and topiramate activate the thermogenic activity of beige adipocytes, inducing the catabolism of the stored fat; others reduce fat absorption such as the lipase inhibitor orlistat; other drugs target hypothalamic neurons in order to reduce food consumption or increase energy expenditure. Some of these drugs will be extensively discussed in the following sub-section, whereas other drugs will only be enlisted in Table I.

Liraglutide is a glucagon-like peptide 1 (GLP1) agonist. It modulates AMPK, a protein expressed in the ventromedial hypothalamus and involved in activation of thermogenic activity in beige adipocytes. While liraglutide increases AMPK phosphorylation in various tissues (endothelium, heart, liver, muscle and white fat), it reduces AMPK phosphorylation in pancreatic beta cells and the hypothalamus (Figure 1). The main effect of liraglutide is a decrease in inflammation, improvement of insulin sensitivity, induction of β-cell proliferation and an increase in beige adipocyte thermogenic capacity[58]. Since 2009, liraglutide has been used to treat type 2 diabetes, and subsequently obesity. Its mechanism of action is based on glucose-dependent stimulation of insulin secretion by pancreatic β-cells, inhibition of glucagon secretion by α-cells under normoglycemic conditions, slowing of gastric emptying, and appetite suppression. Liraglutide results in weight loss in more than 5% of patients with obesity. In obese non-diabetics, the therapeutic effects are significant compared to placebo (5.9% weight reduction in obese diabetics and 8.0% in obese and overweight non-diabetics compared to about 2% in placebo-treated patients). Liraglutide also reduces the probability of developing type 2 diabetes and has a positive effect on blood pressure and lipid profile when used in the treatment of obesity (Table I)[59].

Orlistat is a gastric and pancreatic lipase inhibitor that reduces dietary fat absorption from the gastrointestinal tract by around 30%[60]. Approved by the FDA in 1999, it is indicated for obesity management, including weight loss and weight maintenance when used in conjunction with a low-calorie diet, and to reduce the risk of weight regain after weight loss. Patients on orlistat are prescribed a balanced, low-calorie diet with approximately 30% of calories from fat. They should also take a multivitamin dietary supplement during orlistat therapy, as the drug may decrease absorption of fat-soluble vitamins (A, D, E, K). In a double-blind prospective study that randomized 3305 patients with a BMI $\geq$ 30 kg/m^2 with orlistat or placebo, mean weight loss was significantly greater with orlistat (5.8 kg) than with placebo (3 kg) after 4 years; 53% of the patients assigned orlistat lost $\geq$ 5%, and 26.2% lost $\geq$10% of their initial body weight. Besides promoting weight loss, orlistat lowers serum levels of glucose and improves insulin sensitivity. However,

orlistat is not commonly used for obesity management because of side effects such as oily stool and fecal incontinence (Table I)[61].

Lorcaserin is a 5-hydroxytryptamine (5-HT; serotonin) 2C receptor agonist. Its precise mechanism of action is not known but it is believed to reduce food consumption and promote satiety by selectively activating 5-HT2C receptors located on anorexigenic pro-opiomelanocortin neurons in the hypothalamus. Available data suggests it does not alter energy expenditure. The 5-hydroxytryptamine (serotonin) system is a fundamental component of brain control of energy homeostasis. The neurotransmitter serotonin has a well-defined role in eating behavior and is associated with decreased food intake, increased satiety, and appetite suppression. Pharmacological agents that selectively target the 5-HT2C receptor subtypes that mediate the anorectic effects of 5-HT offer a novel approach to improving weight-loss intervention programs. 5-HT2C receptors are located in the choroid plexus, limbic structures, extrapyramidal pathways, thalamus, and hypothalamus. The key mechanism of 5HT2C modulation of body weight occurs in the brain melanocortin circuit. About 40% of hypothalamic pro-opiomelanocortin neurons (POMC) express 5HT2C receptors. POMC activation leads to the release of α-MSH, which binds to melanocortin 4 receptors leading to a reduction in appetite and increased energy expenditure (Figure 1). In addition, pharmacological activation of 5-HT2C receptors improves glycemic control, whereas their inactivation leads to weight gain and insulin resistance. Lorcaserin is indicated as an adjunct to diet and exercise for chronic weight management, including weight loss and maintenance, in patients with obesity [BMI $\geq$ 30 kg/m^2], or in patients with overweight (BMI $\geq$ 27 kg/m^2) and at least one weight-related comorbid condition (hypertension, dyslipidemia or type 2 diabetes). The safety and tolerability profile of lorcaserin has been documented in three Phase III studies (NCT00603902, NCT00395135, NCT00603291) (Table I)[62,63].

Phentermine, initially approved for obesity treatment in 1959, is a derivative of amphetamine but has less abuse potential than the latter. It is estimated that phentermine can lead to an average weight loss of 3.6 kg in obese patients[64]. Its antiobesity effect could be due to its ability to release norepinephrine in the brain. Phentermine is currently approved as a short-term adjunct in a regimen of weight reduction based on exercise, behavioral modification, and calorie restriction in the management of obesity for patients with an initial body mass index of $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 and other risk factors (hypertension, diabetes, hyperlipidemia). It generally appears to be relatively well-tolerated[65]. The exact mechanism of phentermine is not known but it is known to stimulate neurons to release or maintain high levels of catecholamines, such as dopamine and norepinephrine. High levels of these catecholamines tend to suppress hunger signals and appetite. The drug seems to inhibit reuptake of noradrenaline, dopamine, and serotonin through inhibition of reuptake transporters, and to inhibit monoamine oxidase enzymes leaving more neurotransmitter available at synapses. Through catecholamine elevation, phentermine may also indirectly raise leptin levels in the brain (Figure 1). Increased levels of catecholamines are theoretically responsible for halting neuropeptide Y, that initiates eating, decreases energy expenditure, and increases fat storage[66].

Topiramate was approved for seizure treatment in 1996 and migraine prophylaxis in 2004. Its weight-loss properties were initially reported in patients with seizure, mood, binge eating, and borderline personality disorders. Topiramate treatment leads to an average weight loss of 5.3 kg[67]. It blocks voltage-gated sodium channels, reduces L-type calcium currents, increases potassium conductance, antagonizes α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor/kainate glutamate receptors and enhances γ-aminobutyric-acid-mediated chloride channels[68]. Studies in mice have provided insights into its mechanisms of action in the hypothalamus. The administration of topiramate to mice fed a high-fat diet reduced food intake and increased energy expenditure, leading to diminished adiposity and increased insulin and leptin signaling in the hypothalamus. The signaling of insulin and leptin in the hypothalamus is a key to inducing anorexia and weight loss. Treatment with topiramate also reduces hypothalamic levels of negative modulators of insulin signaling, such as the phosphatases LAR, PTP1B, and PHLPP1, suggesting that their reduction may have a role in improving the action of insulin. Topiramate-treated obese mice also showed activation of the leptin-induced JAK2/STAT3 pathway, important for food intake reduction and weight loss (Figure 1). This pathway is necessary to enhance the downstream melanocortin pathway, which contributes to hypophagia and increased energy expenditure. The MAPK/ERK pathway is regulated by leptin

and insulin in the hypothalamus. Activation of the SHP2/ERK pathway, induced by leptin, mediates thermogenesis and energy expenditure: topiramate may interfere with energy use efficiency, enhancing thermogenesis. Topiramate treatment also increases UCP-1 and PGC-1α levels in brown adipocytes of obese mice. In addition, it can lead to increased phosphorylation of AMPK in skeletal muscle, heart, adipose tissue and liver, causing enhanced glucose uptake and fatty acid oxidation[69].

Although phentermine and topiramate, taken singly, have body weight reduction effects, their combination is more effective. Comparison of the effects of single and combined use is the subject of a study that showed that combined phentermine/topiramate led to a ~11% reduction in baseline weight, compared with ~2% for placebo, ~5% for phentermine and ~6% for topiramate. Patients who received high doses of phentermine/topiramate achieved an average weight loss of ~9%, compared with ~1.5% with placebo, ~6% with phentermine, ~6% with topiramate. This demonstrates additive weight loss when the two drugs are combined (Table I)[70,71].

Naltrexone is an opioid antagonist with high affinity for the μ-opioid receptor, implicated in eating behavior. Its activity may influence food intake and body weight via the hypothalamic melanocortin and reward systems containing opioid neurons. Indeed, studies in animals indicate that acute naltrexone administration influences the activity of the reward system and eating behavior. Systemic naltrexone prevents the increase in dopamine in the nucleus accumbens caused by food ingestion and reduces food intake, food seeking, binge-like eating and preference for high-calorie foods. Human studies demonstrate that naltrexone reduces the subjective pleasantness of palatable foods, in line with the role of opioids in the rewarding aspects of eating. Despite the indications of these preliminary studies, naltrexone monotherapy-mediated blockade of opioid neurotransmission is insufficient to produce reliable decreases in food intake in humans[72].

Bupropion is an antidepressant that inhibits reuptake of catecholamines, such as dopamine and norepinephrine. In mice, acute treatment with bupropion produces changes in extracellular dopamine and norepinephrine concentrations in the brain and alters the activity of dopamine- and norepinephrine-releasing neurons. The activity of the melanocortin system is influenced by both dopamine and norepinephrine, and reduced dopaminergic tone in the hypothalamus is associated with obesity. The hypothalamic melanocortin system is, therefore, a potential site of action of bupropion. Indeed, bupropion stimulates the activity of POMC cells *in vitro* and increases α-MSH secretion. It reduces short-term food intake and increases energy expenditure by increasing heat production, although the overall effect of bupropion on body weight in mice is modest. In humans, weight loss is a common side effect of bupropion use for the treatment of depression. In overweight and obese adults, bupropion treatment leads to limited weight loss[72].

Combining naltrexone and bupropion was proposed on the basis of *in vitro* studies in the mouse hypothalamus, and was linked to melanocortin and reward pathways. The effect of bupropion in increasing POMC activity is limited by μ-opioid receptors, which mediate autoinhibition of POMC cells by β-endorphin, resulting in the modest weight loss and reduction of calorie intake of bupropion monotherapy. On the other hand, blockade of the μ-opioid receptor with naltrexone alone gradually increases POMC activity. The simultaneous administration of bupropion and naltrexone produces a large increase in POMC activity (Figure 1): the combination stimulates POMC cells (bupropion) and removes β-endorphin inhibition on POMC cells (naltrexone). At the same time, injection of bupropion or naltrexone alone directly into the reward system is sufficient to reduce food intake in hungry mice, while direct injection of naltrexone and bupropion produces a synergistic reduction in food intake. Initial Phase 2 clinical studies comparing the naltrexone/bupropion (NB) combination with naltrexone or bupropion monotherapy for weight loss in obese subjects demonstrated that NB produces synergistic weight loss. In Phase 3 studies, NB-treated subjects showed more than twice the weight loss of those in the bupropion monotherapy group and NB therapy was associated with corresponding reductions in visceral and total body fat (Table I)[72].

Exenatide is a GLP-1 agonist and was approved for the treatment of type 2 diabetes mellitus (T2DM) in 2005. It is a synthetic exendin-4 (a hormone found in the saliva of the lizard *Heloderma suspectum*) that is resistant to peptidase degradation, but has a short half-life due to rapid clearance by glomerular filtration. The short-acting compounds suppress postprandial glucose elevation by inhibiting gastric emptying[73]. In studies of patients with T2DM, exenatide treatment was usually associated with reductions in

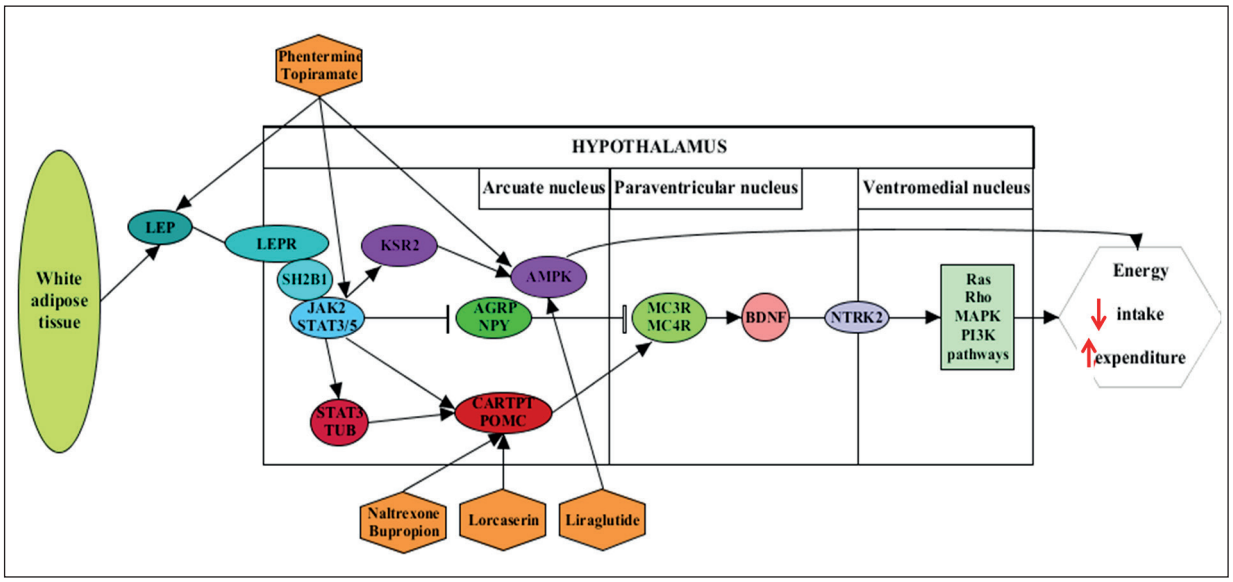

Figure 1. Graphical representation of the leptin/melanocortin pathway in the hypothalamus, with the main molecular members of this signaling pathway. Drugs that may be beneficial for the treatment of obesity are indicated.

body weight of about 2-3 kg. This was also seen in obese non-diabetics with normal or impaired glucose tolerance or impaired fasting glucose and BMI 39.6 ± 7 kg/m^2, who showed a progressive reduction in body weight over 24 weeks and improved glucose tolerance. In a small, double-blind, placebo-controlled crossover study, 41 obese (BMI 33.1 ± 4.1 kg/m^2) female non-diabetics, treated with exenatide for 16 weeks, showed a significant weight loss of 2.49 ± 0.66 kg. Other clinical trials are testing the effect of exenatide on obese patients[74]. Exenatide was also tested in patients with type 1 diabetes: a crossover study with high doses of exenatide was performed for 6 months in 13 adults who showed a significant average weight loss of 4.2 kg (Table I)[73].

Gymnema sylvestre (GS) is a tropical plant of the Asclepiadaceae family. It is well known for its antihypercholesterolemic, anti-inflammatory, antimicrobial, antidiabetic and anti-obesity effects. The leaves are known to contain gymnemic acids, stigmasterol, quercitol and amino acid derivatives of betaine, ethylamine, and choline. Major active compounds are gymnemic acids found in all parts of the plant[75]. Gymnemic acids are molecules similar to that of glucose that bind the taste buds receptors of the tongue, temporarily destroying the taste of sweetness[76]. They also suppress absorption of glucose from the intestine into the blood by binding Na^+-glucose symporters in the intestine[77]. Furthermore, 3T3-L1 adipocytes (a cell line derived from murine 3T3 cells that is used in research on adipose tissue) treated with gymnemic acids conjugated with gold nanoparticles (GA-AuNPs) showed enhancement in glucose uptake efficiency by translocating GLUT4 glucose transport vesicles from the cytosol to the plasma membrane. These findings suggest that GA-AuNPs may act as suppressors of mitochondrial ATP synthase in the presence of insulin or an inducer of AMPK (an activator of fatty acid oxidation) in the absence of insulin[78,79]. Although clinical approval and scientific validation are necessary before they can be approved for the treatment of diabetes, several studies have reported anti-diabetic effects, sugar inactivation properties and anti-obesity action of gymnemic acids in pre-clinical studies (cell and animal models) and clinical studies[75,77,80-85]. A recent interventional, randomized, double-blind clinical study (NCT02370121) reported a statistically significant reduction in body weight, reduced BMI and lower values for very-low-density lipoprotein (VLDL) (Table I)[86], thereby justifying the interest of the scientific community in this promising molecule.

Conclusions

We found that most Mendelian forms of obesity are linked to dysfunctions in the leptin/mela-

Table I. List of active (not recruiting) and completed interventional clinical trials using drugs or dietary supplements for the treatment of obesity (retrieved from ClinicalTrials.gov).

Drug (target pathway/ metabolism)	NCT ID (phase)	Condition (age of treated patients in years)	Number of participants	Aim	Results	Sponsor/Collaborators
Acipimox (lipase activity)	NCT01488409 (2)	Abdominal obesity with insulin resistance and hypertriglyceridemia (18-55)	20 (drug); 19 (placebo)	To examine whether acipimox can improve mitochondria in order to reduce free fatty acids	Significant reduction in low density lipoprotein (LDL) cholesterol	Massachusetts General Hospital, American Diabetes Association
Actiponin, dietary supplement (AMPK pathway)	NCT01667224 (2)	Obesity (19-65)	40 (drug); 40 (placebo)	To test the efficacy and safety of actiponin in obese Korean subjects	Significant reduction in body fat mass, total visceral fat, body weight, body mass index	Chonbuk National University Hospital
Barley β-glucan, dietary supplement	NCT01402128 (2 and 3)	Overweight and hyperlipidemia (19-70)	40 (drug); 40 (placebo)	To investigate whether barley β-glucan supplements reduce visceral fat, serum LDL and total cholesterol in mildly hypercholesterolemic subjects	No significant results	Chonbuk National University Hospital
Bupropion (melanocortin pathway)	NCT00414167 (2 and 3)	Binge eating disorder and obesity (18-65)	31 (drug); 30 (placebo)	To test the efficacy of bupropion on overweight women with binge eating disorder	No significant results	Yale University
Canagliflozin (re-absorption of glucose from renal tubule lumen)	NCT00650806 (2)	Obesity (18-65)	98 (canagliflozin 50 mg), 93 (canagliflozin 100 mg), 96 (canagliflozin 300 mg), 89 (placebo)	To assess the safety and effectiveness of canagliflozin (JNJ-28431754) in promoting weight loss in overweight and obese non-diabetics	Significant reduction in body weight and body mass index. Both reductions are positively correlated with dose of the drug	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Canagliflozin + Phentermine (re-absorption of glucose from tubule lumen and dopamine/leptin pathway)	NCT02243202 (2)	Obesity (18-65)	82 (placebo), 85 (phentermine 15 mg), 84 (canagliflozin 300 mg), 84 (canagliflozin 300 mg/ phentermine 15 mg)	To test the effects of co-administration of canagliflozin and phentermine with placebo in the treatment of overweight and obese non-diabetics	Significant reduction in body weight with phentermine and phentermine plus canagliflozin	Janssen Research & Development, LLC
Linoleic acid, conjugated (fat oxidation)	NCT00204932 (2)	Obesity (18-44)	24 (drug); 24 (placebo)	To determine whether consumption of a purified form of conjugated linoleic acid (CLA) results in loss of body fat compared to control; to determine whether CLA consumption increases oxidation of total fat	Significant reduction in fat mass	University of Wisconsin, Madison

Table continued

Table I *(Continued)*. List of active (not recruiting) and completed interventional clinical trials using drugs or dietary supplements for the treatment of obesity (retrieved from ClinicalTrials.gov).

Drug (target pathway/ metabolism)	NCT ID (phase)	Condition (age of treated patients in years)	Number of participants	Aim	Results	Sponsor/Collaborators
Exenatide (glucose metabolism)	NCT00856609 (3)	Obesity (18-55)	41 (drug); 39 (placebo)	To evaluate whether exenatide treatment leads to weight loss in obese non-diabetics	Significant decrease in energy intake, body weight, and increase in energy expenditure	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Health, Clinical Center (CC)
	NCT00886626 (2)	Obesity (8-19)	11 (drug); 11 (placebo)	To test the effect of a GLP-1 agonist (exenatide) on glucose disposal, glucose tolerance, weight loss	Decrease in BMI but sample size too small	University of Minnesota - Clinical and Translational Science Institute
	NCT01237197 (2)	Obesity (12-19)	13 (drug); 13 (placebo)	To test the effect of exenatide in pediatric extreme obesity	Decrease in BMI but sample size too small	University of Minnesota - Clinical and Translational Science Institute, Children's Hospitals and Clinics of Minnesota
	NCT02160990 (4)	Obesity (18-70)	10 (drug); 10 (placebo)	To evaluate the effect of exenatide vs placebo on gastric emptying, satiety, satiation and weight loss in obese participants	Reduction in gastric emptying time but sample size too small	Mayo Clinic, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
	NCT00500370 (2)	Obesity (> 18)	80 (drug); 83 (placebo)	To test the effect of exenatide on body weight in obese non-diabetics	Significant decrease in body weight, BMI	AstraZeneca, Eli Lilly and Company
Glycin max (L.) Merr. peel extract, dietary supplement	NCT02108691 (2 and 3)	Obesity (19-65)	40 (drug); 40 (placebo)	To evaluate the efficacy and safety of Glycin max (L.) Merr. peel extract on decrement of body fat	No significant results	Hanyang University
Growth hormone releasing hormone (growth hormone pathway)	NCT00675506 (2)	Abdominal obesity and growth hormone deficiency (18-55)	31 (drug); 29 (placebo)	To evaluate the effect of synthetic GHRH in decreasing abdominal fat and improving cardiovascular function in obesity	Reduction in visceral fatty tissue, triglycerides and increase in glucose tolerance; no statistical analysis provided	Massachusetts General Hospital, National Heart, Lung, and Blood Institute (NHLBI)
Gymnema sylvestre (glucose metabolism, insulin pathway)	NCT02370121 (2)	Metabolic syndrome (30-60)	12 (drug); 12 (placebo)	To evaluate the effect of Gymnema sylvestre on metabolic syndrome and insulin resistance	No significant results	University of Guadalajara

Table continued

Table I *(Continued).* List of active (not recruiting) and completed interventional clinical trials using drugs or dietary supplements for the treatment of obesity (retrieved from ClinicalTrials.gov).

Drug (target pathway/ metabolism)	NCT ID (phase)	Condition (age of treated patients in years)	Number of participants	Aim	Results	Sponsor/Collaborators
IQP-VV-102, dietary supplement	NCT01681069 (3)	Obesity or overweight (18-60)	60 (drug); 60 (placebo)	To evaluate the safety and efficacy of IQP-VV-102 in reducing body weight in overweight and obese subjects	Reduction in body weight, body fat, waist circumference, but no statistical analysis provided	In Qpharm Group
Liraglutide (AMPK pathway)	NCT01272219 (3)	Obesity (> 18)	959 (liraglutide 3 mg, no pre-diabetes); 487 (placebo); 1528 (liraglutide 3 mg, pre-diabetes); 757 (placebo)	To test the effect of liraglutide on body weight in obese/overweight non-diabetics with co-morbidities	Significant reduction in body weight and number of patients with type 2 diabetes	Novo Nordisk A/S
	NCT01272232 (3)	Obesity (> 18)	423 (liraglutide 3 mg), 211 (liraglutide 1.8 mg), 212 (placebo)	To test the effect of liraglutide on body weight in overweight/ obese subjects with type 2 diabetes	Significant reduction in body weight, glycosylated hemoglobin, waist circumference	Novo Nordisk A/S
	NCT02647944 (2)	Obesity (18-65)	19 (drug); 21 (placebo)	To test the effect of liraglutide on weight loss and gastric unctions in obesity emptying time but without statistical analysis	Significant reduction in body weight and increase in gastric Diseases (NIDDK), Novo Nordisk A/S	Mayo Clinic, National Institute of Diabetes and Digestive and Kidney
Liraglutide and orlistat (AMPK pathway and lipase activity)	NCT00422058 (2)	Obesity (18-65)	98 (placebo/liraglutide 2.4 mg/liraglutide 3 mg), 95 (liraglutide 1.2 mg/liraglutide 3 mg), 90 (liraglutide 1.8 mg/ liraglutide 3 mg), 93 (liraglutide 2.4 mg/ liraglutide 3 mg), 93 (liraglutide 3 mg), 95 (orlistat)	To test the effect of liraglutide on body weight in obese subjects without diabetes no statistical analysis	Decrease in body weight only with highest dose of liraglutide;	Novo Nordisk A/S

Table continued

Table I *(Continued)*. List of active (not recruiting) and completed interventional clinical trials using drugs or dietary supplements for the treatment of obesity (retrieved from ClinicalTrials.gov).

Drug (target pathway/ metabolism)	NCT ID (phase)	Condition (age of treated patients in years)	Number of participants	Aim	Results	Sponsor/Collaborators
L-leucine, dietary supplement	NCT00683826 (NA)	Overweight or obesity (18-65)	8 (drug); 8 (control)	To determine whether oral leucine supplementation in overweight/obese individuals increases basal metabolic rate, reduces body weight, improves glucose tolerance and/or insulin sensitivity, and/or reduces circulating LDL-cholesterol levels	No significant results	Columbia University
Lorcaserin (serotonin/ melanocortin pathway)	NCT00603902 (3)	Obesity (18-65)	802 (lorcaserin 10 mg); 1603 (lorcaserin 10 mg); 1603 (placebo)	To test the effects of lorcaserin hydrochloride on overweight or obese volunteers	Significant reduction in body weight	Arena Pharmaceuticals
	NCT00395135 (3)	Obesity (18-65)	1595 (year 1, lorcaserin 10 mg); 1587 (year 1, placebo); 573 (year 2, lorcaserin 10 mg (year 1)/lorcaserin 10 mg (year 2) 283 (year 2, lorcaserin 10 m (year 1)/placebo (year 2); 697 (year 2, placebo)	To assess the safety and efficacy of lorcaserin hydrochloride in obese patients	Significant reduction in body weight	Arena Pharmaceuticals
	NCT00603291 (3)	Obesity (18-65)	95 (lorcaserin 10 mg, once a day); 256 (lorcaserin 10 mg, twice a day); 253 (placebo)	To assess the weight loss effect of lorcaserin in overweight and obese patients with Type II diabetes mellitus treated with metformin, sulfonylurea or both with other oral hypoglycemic agents.	Significant reduction in body weight	Arena Pharmaceuticals
Metformin (AMPK pathway)	NCT02274948 (4)	Obesity (8-16)	166 (drug); 173 (control)	To evaluate the effect of metformin on changes in insulin resistance, fatty liver status, body fat content, BMI and other metabolic markers	Reduction in body weight, BMI, insulin resistance; no statistical analysis provided	University of Colombo

Table continued

Table I *(Continued)*. List of active (not recruiting) and completed interventional clinical trials using drugs or dietary supplements for the treatment of obesity (retrieved from ClinicalTrials.gov).

Drug (target pathway/ metabolism)	NCT ID (phase)	Condition (age of treated patients in years)	Number of participants	Aim	Results	Sponsor/Collaborators
Naltrexone + Bupropion (opioid and melanocortin pathway)	NCT00532779 (3)	Obesity or overweight (18-65)	578 (naltrexone 16 mg/ bupropion 360 mg /day); 583 (naltrexone 32 mg/ bupropion 360 mg /day); 581 (placebo)	To test the safety and efficacy of the combination of naltrexone SR and bupropion SR compared to placebo in obese subjects and in overweight/obese subjects with hypertension and/or dyslipidemia	Significant decrease in body weight, waist circumference, triglycerides and fasting glucose, increase in HDL	Orexigen Therapeutics Inc.
	NCT00711477 (2)	Obesity (18-45)	23 (drug); 23 (placebo)	To assess the effects of naltrexone SR / bupropion SR on overweight or obese subjects	No significant results	Orexigen Therapeutics Inc.
	NCT00567255 (3)	Obesity or overweight (18-65)	1001 (drug); 495 (placebo)	To test the safety and efficacy of the combination of naltrexone SR and bupropion SR compared to placebo in obese subjects and in overweight/obese subjects with hypertension and/or dyslipidemia	Significant decrease in body weight, waist circumference and triglycerides, increase in HDL	Orexigen Therapeutics Inc.
	NCT02317744 (NA)	Binge-eating disorder (21-65) (18-60)	12 (drug); 10 (placebo)	To test the effect of the combination of naltrexone and bupropion relative to placebo on binge eating in persons with obesity and binge eating disorder	No significant results	Yale University
	NCT01764386 (3)	Obesity or overweight	153 (drug); 89 (control)	To assess the effects of combination therapy with naltrexone SR/bupropion SR (NB) and comprehensive lifestyle intervention (CLI) on body weight and cardiovascular risk factors compared to the effects of usual care in overweight or obese dyslipidemic subjects with or without controlled hypertension	Significant reduction in body weight, waist circumference, triglycerides, glucose, fasting insulin, insulin resistance and binge eating, increase in HDL	Orexigen Therapeutics Inc.
Orlistat (lipase activity)	NCT00752726 (4) (18-60)	Obesity or overweight	65 (drug); 66 (placebo)	To determine if weight loss with orlistat affects visceral adipose tissue compared to placebo	Significant reduction in visceral fat mass, body weight, total fat mass	GlaxoSmithKline

Table continued

Table I *(Continued)*. List of active (not recruiting) and completed interventional clinical trials using drugs or dietary supplements for the treatment of obesity (retrieved from ClinicalTrials.gov).

Drug (target pathway/ metabolism)	NCT ID (phase)	Condition (age of treated patients in years)	Number of participants	Aim	Results	Sponsor/Collaborators
Phentermine Psychiatric (dopamine/leptin pathway)	NCT01886937 (4)	Obesity (18-60)	7 (drug); 6 (placebo)	To determine whether phentermine changes food intake compared to placebo administration	No significant results	New York State Institute, AstraZeneca
Phentermine+ Topiramate (dopamine/leptin, insulin/leptin signaling)	NCT00554216 (3)	Obesity (18-70)	241 (phentermine + topiramate, low dose); 512 (phentermine+ topiramate, high dose); 514 (placebo)	To evaluate the efficacy and safety of VI-0521 compared to placebo in the treatment of obesity (BMI ≥35)	Significant reduction in body weight	VIVUS Inc., Medpace Inc
	NCT00553787 (3)	Obesity and type 2 diabetes (18-70)	154 (phentermine + topiramate, low dose); 295 (phentermine + topiramate, high dose); 227 (placebo)	To evaluate the long-term safety and efficacy of VI-0521 compared to placebo in the treatment of adult overweight and obesity	Significant reduction in body weight	. VIVUS Inc., Medpace Inc.
	NCT00796367 (3)	Obesity (18-70)	154 (phentermine + topiramate, low dose); 295 (phentermine + topiramate, high dose); 227 (placebo)	To evaluate the safety and efficacy of VI-0521 compared to placebo in the treatment of overweight and obese adults	Significant reduction in body weight	VIVUS Inc., Medpace Inc.
	NCT00563368 (3)	Obesity (18-70)	108 (7.5 mg phentermine); 107 (46 mg topiramate); 108 (7.5 mg/46 mg phentermine/topiramate); 107 (15 mg phentermine); 108 (92 mg topiramate 15 mg/92 mg phentermine/ topiramate); 109 (placebo)	To compare the effect of VI-0521 (topiramate+phetermine) or topiramate or phentermine alone with placebo treatment of obesity in adults	Significant reduction in body weight	VIVUS Inc., Medpace Inc.
	NCT01834404 (4)	Obesity (18-70)	12 (phentermine+ topiramate); 12 (placebo)	To determine the effect of phentermine and topiramate ER on gastric emptying, gastric accommodation, satiety and satiation in obesity	No significant results due to the low number of participants	Mayo Clinic, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Table continued

Table I *(Continued)*. List of active (not recruiting) and completed interventional clinical trials using drugs or dietary supplements for the treatment of obesity (retrieved from ClinicalTrials.gov).

Drug (target pathway/ metabolism)	NCT ID (phase)	Condition (age of treated patients in years)	Number of participants	Aim	Results	Sponsor/Collaborators
Pramlintide and metreleptin (calcitonin receptor pathway and leptin/ melanocortin pathway)	NCT00673387 (2)	Overweight or obesity	77 (pramlintide 360 mcg); 72 (metreleptin 5 mg); 75 (pramlintide 180 mcg + metreleptin 2.5 mg); 78 (pramlintide 180 mcg + metreleptin 5 mg); 78 (pramlintide 360 mcg + metreleptin 1.25 mg); 78 (pramlintide 360 mcg + metreleptin 2.5 mg); 75 (pramlintide 360 mcg + metreleptin 5 mg); 75 (placebo)	To examine the safety, tolerability and effect on body weight of metreleptin and pramlintide in obese and overweight subjects	Significant reduction in body weight	AstraZeneca
	NCT00819234 (2)	Obesity (18-65)	242 (drug); 31 (placebo)	To examine the long-term safety, tolerability and effect on body weight of pramlintide administered in combination with metreleptin	Significant reduction in body weight	AstraZeneca
Recombinant human growth hormone (growth hormone pathway)	NCT01169103 (2)	Obesity (13-21)	11 (drug); 11 (placebo)	To test the effect of recombinant human growth hormone (rhGH) on reduction of abdominal fat and cardiovascular risk in obese girls	No significant results due to the low number of participants	Massachusetts General Hospital, Genentech Inc.
Rosuvastatin (lipid synthesis)	NCT01068626 (3)	Abdominal obesity (40-65)	30 (drug); 29 (placebo)	To investigate whether treatment with rosuvastatin reduces visceral fat in obese men	No statistical significance provided	Göteborg University, Sahlgrenska University Hospital, Sweden
SCH 497079 (Histamine H3 receptor pathway)	NCT00642993 (2)	Obesity or overweight (>18)	267 (drug); 134 (placebo)	To evaluate the effect of SCH 497079 on weight in obese and overweight participants	No significant results	Merck Sharp & Dohme Corp.
Topiramate (insulin/ leptin signaling)	NCT01859013 (2)	Obesity (12-17)	16 (drug); 14 (placebo)	To evaluate the safety and efficacy of topiramate therapy with meal replacement therapy in adolescents with severe obesity	No statistical significance provided	University of Minnesota, Clinical and Translational Science Institute

Table continued

Table I *(Continued)*. List of active (not recruiting) and completed interventional clinical trials using drugs or dietary supplements for the treatment of obesity (retrieved from ClinicalTrials.gov).

Drug (target pathway/ metabolism)	NCT ID (phase)	Condition (age of treated patients in years)	Number of participants	Aim	Results	Sponsor/Collaborators
Vitamin D, dietary supplement	NCT00493012 (NA)	Overweight or obesity (18-70)	100 (drug); 100 (placebo)	To investigate the influence of vitamin D supplement on weight loss and body composition in overweight patients	No statistical significance provided	Heart and Diabetes Center North-Rhine Westfalia
Zonisamide (GABAergic synaptic activity)	NCT00275834 (NA)	Obesity (18-65)	76 (zonisamide 200 mg; 75	To test the effect of zonisamide on weight reduction in obese adults	No statistical significance provided	Duke University, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
β3-adrenergic receptor agonist (β-adrenergic pathway)	NCT01783470 (2)	Obesity (18-65)	12 (drug); 12 (placebo)	To test the hypothesis that human brown adipose tissue can be activated using a β3-adrenergic receptor agonist. The efficacy of β3-AR agonist will be compared with cold exposure and a placebo control	Significant increase in BAT activity	Aaron Cypess, National Institutes of Health (NIH), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Beth Israel Deaconess Medical Center

nocortin hypothalamic signaling pathway. Most of the drugs being evaluated target this pathway with the aim of improving energy expenditure and/or reducing food intake. The results of these trials are promising in many cases, though in others the sample has been too small to obtain significant results. Of course, the possibility of severe side effects should be weighed by clinicians when prescribing these medications.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Contributorship Statement

MB conceived the study; SP, TD, DV and MB collected information; SP wrote the manuscript; SP, AB, LS, FCC, TD, JK, DV, TB, VU, MB reviewed and edited the text; MB supervised the work.

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