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Novel therapeutics in rare genetic obesities: A narrative review

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ABSTRACT

The better understanding of the molecular causes of rare genetic obesities and its associated phenotype involving the hypothalamus allows today to consider innovative therapeutics focused on hunger control. Several new pharmacological molecules benefit patients with monogenic or syndromic obesity. They are likely to be among the treatment options for these patients in the coming years, helping clinicians and patients prevent rapid weight progression and eventually limit bariatric surgery procedures, which is less effective in these patients. Their positioning in the management of such patients will be needed to be well defined to develop precision medicine in genetic forms of obesity.

1. Introduction

Childhood obesity is defined as an abnormal excess of body fat primarily due to impaired energy balance control; genetic factors play a predominant role [1]. Thanks to recent technological advances such as next generation sequencing (NGS), genome-wide association studies (GWAS) or whole exome sequencing (WES), hundreds of genes involved in the development of obesity have been discovered, revealing a continuum between common obesity due to polygenic inheritance and rare genetic obesity situations. These genetic forms are now considered to represent about 5–10% of severe childhood obesity [2] and constitute models for understanding its pathophysiology. Recent advances in new therapies in recent years now make possible innovative and effective solutions to control hyperphagia and weight progression in these very complex situations. These developments are currently helping clinicians to limit the stigma and burden of the disease but also open major perspectives for the treatment and even prevention of childhood obesity. In this narrative review, we describe the recent developments in therapeutics focusing on rare genetic obesities with early onset during childhood.

2. Better understanding of the pathophysiology of rare genetic obesities

The hypothalamus plays a central role in the regulation of body weight and interacts closely with several different organs that regulate eating behavior and metabolism, such as the brain's reward systems, cortical regions and peripheral organs [3]. Altered hypothalamic function, especially due to genetic defects, severely alters signaling in response to peripherally derived hormones such as leptin, insulin, ghrelin or peptide YY and several efferent signals such as stimulation of the autonomic nervous system or pituitary hormone pathways [4,5]. At the same time, decreased basal metabolic rate, central endocrine abnormalities (such as pituitary insufficiency with GH deficiency, hypogonadism) and metabolic abnormalities (such as hyperinsulinism) contribute to excessive fat mass development [2]. This hypothalamic impairment is responsible for a global neuroendocrine pathology also considered as hypothalamic obesity (HO). In case of associated neurodevelopmental disorder (NDD) (intellectual disability of variable intensity and/or other adaptive developmental disorders) and/or malformative syndrome, these obesities are part of the so-called syndromic obesities. Prader-Willi (PWS), X-fragile and Bardet-Biedl (BBS) syndromes are the most commonly described [2,6] (Table 1). HO due to pathogenic variants in genes involved in the hypothalamic leptin-melanocortin pathway are defined as monogenic obesities or

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Table 1
The main syndromic obesities.

Syndrome	Prevalence	Signs associated with obesity	Mode of transmission *Gene* Genomic region
Alström	1–9/1 000 000	Retinal dystrophy, sensorineural deafness, dilated cardiomyopathy, renal, pulmonary, and hepatic damage	Autosomal recessive *ALMS1* 2p13
Bardet-Biedl	1/13 500–1/175 000	Intellectual disability, retinal dystrophy or retinitis pigmentosa, polydactyly, hypogonadism, and renal anomalies	Autosomal recessive or multi-allelic transmission > 20 genes Most common *BBS1* (11q13) and *BBS10* (12q21)
CHOPS	< 1/1 000 000	Intellectual disability, thick features, cardiac anomalies, pulmonary anomalies, short stature, and skeletal dysplasia	Autosomal dominant *AFF4* 5q31
16p11.2 deletion	N.A.	Developmental delay, intellectual disability, autism spectrum disorders, macrocephaly, and epilepsy	Autosomal dominant 16p11.2 deletion
Microdeletion including *SH2B1 MYT1L*	< 1/1 000 000 N.A.	Intellectual disability and behavioural disorders	16p11.2 (28.7–28.9 Mb) Autosomal dominant *MYT1L* 2p25
MO1 syndrome (Morbid obesity 1)	< 1 / 1 000 000	Intellectual disability metabolic syndrome insulin resistance, spermatogenesis defect	Autosomal recessive *CEP19* *3q29*
Pseudo-hypoparathyroidism type Ia with Albright* osteodystrophy	1/10 000 à 1/30 000	Facial dysmorphia, brachymetacarpia and brachymetatarsia, variable developmental delay, hormonal resistance picture (hypocalcaemia, hypothyroidism, and pubertal delay	Autosomal dominant *GNAS1* 20q13
Prader-Willi[a]	N.A.	Neonatal hypotonia, intellectual disability, facial dysmorphia, stunting, hypogonadism, and hyperphagia	Anomaly in the 15q11-q13 region of paternal origin subject to imprinting
Schaaf-Yang	< 1/1 000 000	Prader-Willi-like (obesity, eating difficulties), hypotonia, intellectual disability, and autism spectrum disorders	Variants in the gene of paternal origin (imprinted region) *MAGEL2* 15q11
WAGR[a] **Syndrome**	N.A.	Wilms' tumour, aniridia, genitourinary malformations (hypospadias, cryptorchidism), and intellectual disability	Autosomal dominant *WT1, PAX6, BDNF* Deletion of 11p13-p14
X fragile[a]	1/5 000 (boys) 1/8 000 (girls)	Intellectual disability, hyperactivity, facial dysmorphia, and post-pubertal macro-orchidism	X-linked dominant *FMR1* Xq27

AFF4: AF4/FMR2 family member 4, ALMS1: Alström syndrome 1, BBS: Bardet-Biedl syndrome, CEP19: centrosomal protein 19, CHOPS: cognitive impairment, coarse face, heart defects, obesity, pulmonary involvement, short stature, skeletal dysplasia, CREBBP: FMR1: fragile X mental retardation 1, GNAS1: guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1, MAGEL2: MAGE family member L2, SH2B1: SH2B adaptor protein 1,WAGR: Wilms tumor, aniridia, genitourinary malformations, mental retardation, WT1: WT1 transcription factor

[a] PNDS (National Diagnostic and Care Protocol) available; N.A.: not applicable (reported cases, very rare)

non-syndromic obesities but even similarities can exist with all these conditions [6,7]. The leptin-melanocortin pathway is crucial for the regulation of energy balance (Fig. 1). Indeed, adipocyte-derived leptin activates its specific leptin receptors within the hypothalamus leading to the local production of melanocyte-stimulating hormones (α-MSH) derived from POMC (pro- opiomelanocortin). The α-MSH is the specific ligand for the G-protein-coupled receptor MC4R (melanocortin 4 receptor) expressed in the paraventricular nucleus inducing its activation and secondly decrease of food intake. The major genes involved in this pathway include leptin (*LEP*), leptin receptor (*LEPR*), proopiomelanocortin (*POMC*), prohormone subtilisin/kexin 1 convertase (*PCSK1*), melanocortin receptor type 3 and 4 (*MC3R and MC4R*) [6], MC4R regulatory protein, melanocortin receptor accessory protein 2 (*MRAP2*) [8] and adenylate cyclase 3 (*ADCY3*) [9]. Genetic variants in one or more of these genes result in altered function of the biological pathway and consequently severe hyperphagia and obesity occur [3,10,11]. Patients with compound heterozygous or homozygous variants for the *LEP, LEPR, POMC, PCSK1*, and *MC4R* genes develop severe obesity from the first 3 years of life accompanied by impaired hunger and satiety signals revealed by major hyperphagia and insatiable hunger. Along with severe obesity and uncontrolled eating, patients carrying a pathogenic homozygous variant of the *LEP* or *LEPR* genes present pubertal delay and/or a hypogonadotropic hypogonadism and sometimes thyrotropic insufficiency of central origin. Somatotropic insufficiency, leading to growth retardation, can also be observed in carriers of the pathogenic variant of *LEPR* [3,6]. Subjects with complete POMC deficiency (homozygous or compound heterozygous) thus show red hair, corticotropic insufficiency and sometimes other endocrine deficiencies as moderate thyrotropic insufficiency, somatotropic and gonadotropic insufficiency. Patients with rare pathogenic variants of the *PCSK1* gene that lead to complete PC1 deficiency (homozygosity or compound heterozygosity) show transient neonatal diarrhea, then severe early onset obesity, late postprandial hypoglycemia, and gonadotropic, thyrotropic, and corticotropic insufficiency. Finally, obesity linked to the presence of homozygous or heterozygous compound variants of MC4R is rare but severe, close to that of the other forms described for LEP and LEPR but without associated endocrine deficit (reproductive function and normal fertility, normal corticotropic function, no somatotropic deficit) [3,6] (Table 2). More recently, several other genes involved in or regulating this pathway have been also associated with early and severe obesity in case of pathogenic variants: steroid coreceptor activator-1 (*SRC-1*), semaphorin 3A-G (*SEMA3A-G*), plexinA1–4 (*PLXNA*1–4), neuropilin1–2 (*NRP*1–2), kinase suppressor of ras 2 (*KSR2*) [12] [13], and

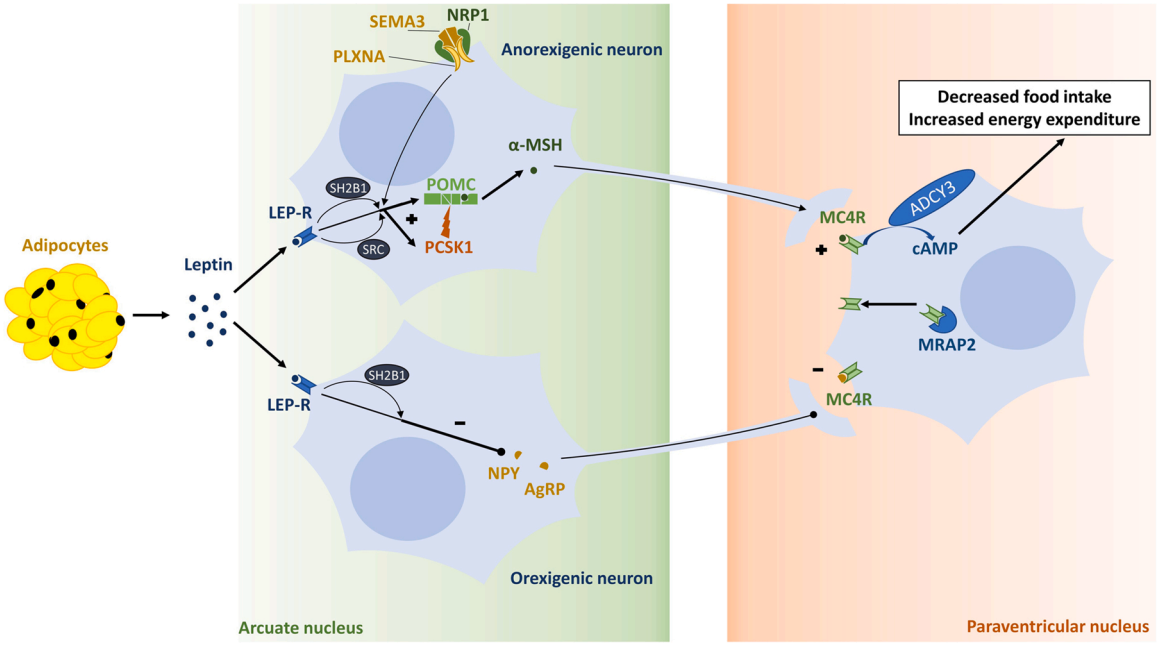

Fig. 1. The hypothalamic leptin-melanocortin pathway. Leptin acts at the level of the arcuate nucleus in the hypothalamus via its receptor LEP-R. It activates anorectic neurons expressing propiomelanocortin (POMC) and inhibits neurons expressing orectic peptides such as neuropeptide Y (NPY) and Agouti related-protein (AgRP). The POMC protein is cleaved by the enzyme prohormone convertase subtilisin/kexin 1 (PCSK1) leading to the production of melanocortins, in particular α-MSH (Melanocyte Stimulating Hormone) which activates the MC4R (Melanocortin Receptor Type 4). Its activation will lead to a reduction in food intake and increase energy expenditure. Other genes as *MRAP-2* (melanocortin receptor accessory protein 2), *SRC-1* (Steroid Receptor Co-activator 1) also named nuclear receptor co-activator-1 (*NCOA1*), *SH2B1* (Src homology 2 B adaptor protein 1) and *ADCY3* (adenylate cyclase 3) are involved in the regulation of the pathway.

Table 2
The main monogenic forms of obesity involving the leptin-melanocortin pathway.

Gene	Phenotype associated with obesity	Mode of transmission Genomic region
Adenylate cyclase 3 *(ADCY3)*	Olfaction disorders ± mild intellectual disability	Autosomal recessive 2p23
Brain Derived Neurotrophic Factor *(BDNF)*	Intellectual disability, hyperactivity, and hyperphagia	Autosomal dominant Deletion in 11p14
Leptin (*LEP*)	Gonadotropic and thyrotropic deficiencies and immune deficiency (variable)	Autosomal recessive 7q32
Leptin receptor (*LEPR*)	Gonadotropic, thyrotropic, and somatotropic deficiencies	Autosomal recessive 1p31
Melanocortin 4 receptor *(MC4R)*	Recessive: severe and early onset obesity	Autosomal recessive 18q21
Melanocortin Receptor Accessory Protein 2 *(MRAP2)*	High blood pressure, high blood sugar	Autosomal dominant 6q14
Neurotrophic tyrosine kinase receptor type 2 *(NTRK2)*	Developmental delay and behavioural problems	Autosomal dominant 9p21
Proprotein convertase subtilisin/kexin type 1 (*PCSK1*)	Corticotropic, gonadotropic, thyroid insufficiency, postprandial hypoglycaemic malaise, central diabetes insipidus, and neonatal diarrhoea	Autosomal recessive 5q15
Propiomelanocortin (*POMC*)	Corticotropic insufficiency, thyroid insufficiency ± red hair, and gonadal or somatotropic insufficiency	Autosomal recessive 2p23
SIM bHLH transcription factor1 *(SIM1)*	Behavioural disorders, autism spectrum disorders, and hyperphagia	Autosomal dominant 6q16

steroid-receptor co-activator 1 (*SRC-1*) [14]. These monogenic obesities are mainly due autosomal recessive variants in these specific genes. Subjects with heterozygous variants in some of these genes show a phenotype intermediate to that seen with homozygous variants, but the severity of the phenotype may depend on environmental and/or other genetic factors with potential cumulative effects, as recently described [7].

Importantly, the borderline between syndromic and non-syndromic monogenic obesity is not strict and an overlap of phenotypes is observed (Fig. 2). For example, some patients suffering from monogenic obesity present neurodevelopmental and/or psychiatric disorders close to those observed in so-called syndromic obesity and on the other hand, endocrine deficiencies such as corticotropic or gonadotropic deficiencies are observed in syndromic obesity such as PWS [6]. In addition, anomalies of the leptin-melanocortin pathway are described in some syndromic obesities. In PWS, proconvertase 1 (PC1) deficiency and alterations of the orexigenic Agouti-related protein (AgRP) hypothalamic neurons have been described [15] as the inactivation of *MAGEL2* with decreased density of MSH neurons in rodents [16]. In BBS, alteration of the LEPR transport and its localization at the ciliary membrane of POMC neurons is implicated in the development of hyperphagia and obesity [17,18]. In Smith Magenis syndrome linked to the 17p11.2 locus, encompassing the *RAI1* gene, haploinsufficiency of *RAI1* in murine models leads to a decrease expression of POMC and Brain Derived Neurotrophic Factor (BDNF), thus also involving the the leptin-melanocortin pathway explaining partly the excess weight gain [19].

Thus, these HOs share a common phenotype including severe early obesity and eating disorders associated with various endocrine and/or central neuropsychological abnormalities [2,3,20]. Obesity is characterized by its very early onset before the age of 6 years or even 3 years in the most severe cases, often associated with inexistent or earlier adiposity rebound (before the age of 3 years) and unusual feeding behavior (severe hyperphagia, lack of control, food impulsivity) [10, 21]. They represent complex medical situations lifelong with major

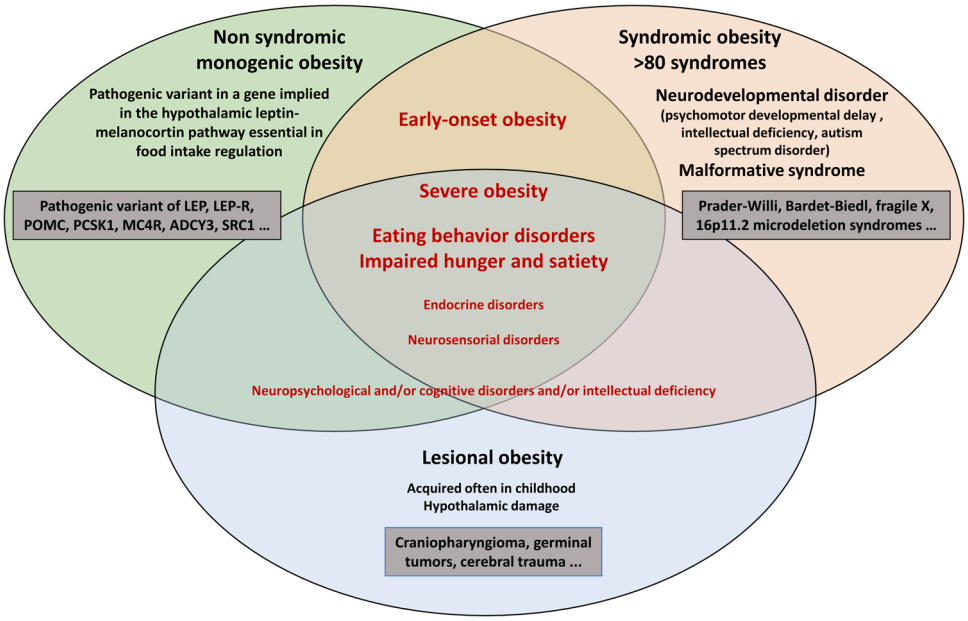

Fig. 2. Overlap between the different forms of hypothalamic obesities according to their etiology. LEP-R: leptin receptor; PCSK1: prohormone convertase subtilisin/kexin 1; POMC: proopiomelanocortin; MC4R: melanocortin 4 receptor; SRC-1: Steroid Receptor Co-activator 1 (also named nuclear receptor co-activator-1 (NCOA1)); ADCY3: Adenylate cyclase 3.

burden for caregivers and requirement for specialized and expert teams for their management [2]. Indeed, comprehensive, specialized, and multidisciplinary approaches is crucial. Control of eating behavior associated with adapted physical activity and combination of other approaches that may include psychomotor skills therapy, speech therapy, hormone replacement therapy, etc., is needed as early as possible during early childhood to improve the patients' condition [2].

3. Recent development of treatments targeting hyperphagia in rare genetic obesities

The better understanding of the molecular causes of rare genetic obesity and its associated phenotype allows today to consider a therapeutic approach focused on hunger control. Twenty-four years ago, leptin deficiency diagnosed in homozygous *LEP* gene mutation carriers with severe obesity was successfully treated by leptin administration [22]. Indeed, daily subcutaneous injection of leptin restores the satiety signal with a reduction of hyperphagia and body weight while inducing puberty, revealing the key role of leptin in the gonadotropic axis [23]. In 2016, a novel MC4R agonist named setmelanotide administrated to 2 patients with homozygous variants in *POMC* led to a drastic reduction of body weight (−51.0 kg after 42 weeks and −20.5 kg after 12 weeks of treatment respectively in the 2 subjects) confirming that this MC4R agonist can restore melanocortin signal [24]. These results were then confirmed in phase 3 trials in which the average weight loss was − 25.6% of pretreatment body weight in patients with POMC deficiency and − 12.5% in LEPR-deficient patients [25]. In parallel, rapid decrease of hunger score was observed with setmelanotide confirming the restoration of satiety signal. If no cardiovascular adverse events have been detected, skin hyperpigmentation due to the activation of melanocortin 1 receptor (MC1R) by setmelanotide is reported in more than 90% of the treated patients. A particular attention will be necessary given to the chronic stimulation of melanocytes even if its long-term administration seems to be safe [26]. Transient digestive manifestations are also reported as skin local reactions to injection as well as temporary increased sexual arousal. Recently, the evolution of the 2 first patients with POMC deficiency on setmelanotide for 7 years confirmed the persistent weight loss and reduced hunger without severe long term side effects except for hyperpigmentation [27]. In addition, the improved quality of life on treatment pleads for the early diagnosis of these rare genetic obesities in order to start early in life and limit weight evolution [28]. Since 2021, setmelanotide (IMCIVREE©) is approved for patients with POMC/PCSK1 or LEPR deficiency by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) with early access in several European countries.

Semelanotide has been tested in patients with other syndromic obesities, such as BBS and Alström syndromes, because of their described pathophysiology involving alterations of the leptin-melanocortin pathway [17]. Within a phase 2 study including 10 patients with BBS or Alström syndrome, setmelanotide led to a mean reduction of − 16.3% of pre-treatment body weight after 12 months of treatment and improvement of hyperphagia [29]. Recently, in a phase 3 trial, efficacy and safety of setmelanotide in BBS was confirmed in 38 patients with weight loss of at least 10% in 34% of patients after 52 weeks of treatment without additional adverse effects [29]. These results also led to the approval by regulatory agencies (e.g EMA, FDA) of setmelanotide for the treatment of obesity and binge eating disorder in BBS patients after 6 years in 2022 [30]. Its major beneficial effects on the quality of life of patients and their families should now encourage practitioners to use a medication targeted at binge eating disorder such as setmelanotide to support BBS patients and their families in weight control and stigma reduction [31].

As setmelanotide can restore satiety signal in case of impaired leptin melanocortin pathway, adults and children carrying pathogenic heterozygous variants are probably other potential candidates. Indeed, their phenotype can be closed to that described in case of homozygous variants including severe early-onset obesity and uncontrollable hyperphagia and may probably be improved with setmelanotide [7]. Questions remain whether other patients, such as those with lesional HOs or with heterozygous variants in *MC4R,* could benefit from this treatment. *In vitro*, setmelanotide was more efficient than the endogenous ligand in cells expressing various heterozygous pathogenic variants of *MC4R*. Moreover, it appeared that treatment with setmelanotide can induce weight loss in humans, with a varying response, depending on the type of *MC4R* pathogenic variant [32,33]. Currently, clinical trials with setmelanotide are underway in patients with heterozygous variants in 60 genes involved in the leptin melanocortin pathway, as well as in patients with heterozygous *MC4R* variants.

4. Innovative therapeutic approaches in others syndromic obesities

In recent years, additional innovative therapeutic approaches have been also developed, in others syndromic obesities, notably for PWS [34]. Molecules reported in NCT clinical trials for weight loss in these obesities are described in [35]. In PWS, the oxytocin system has been largely targeted since several clinical features, such as hyperphagia, obesity, and social interaction disorders, may be linked to alterations in oxytocin regulation. Thus, treatment with nasal oxytocin revealed to be beneficial, especially in neonates with PWS by improving sucking disorders [36] but also in adolescents and adults by improving emotions, autism spectrum disorders, or social interaction factors [37]. These promising results plead now for an early administration of nasal oxytocin in infants and young children to improve eating disorders, because the oxytocinergic system may be more plastic at earlier stages of development. Since 2021 in France, early access to nasal oxytocin is now possible for any newborn diagnosed with PWS. Carbetocin, an oxytocin receptor-selective compound, has also recently shown promising results with a rapid reduction in hyperphagia in young patients [38,39]. In addition to oxytocin, topiramate has been described to have a significant effect on hyperphagia in adults with PWS and might be indicated early in life in adolescents [40]. In adults with PWS, several other molecules are evaluated for their potential effect on hyperphagia as AZP-531 (livoletide), a non-acylated ghrelin analog, [41] (NCT03790865), GLWL-01, a ghrelin O-acyltransferase inhibitor (NCT03274856) or K+ -ATP channel agonists (diazoxide choline controlled released) [42,43]. The association of tesofensine and metoprolol showed also benefits on weight loss but with exacerbation of behavioral problems [44]. Finally, beloranib, a methionine aminopeptidase 2 inhibitor or rimonabant, a CB1 cannabinoid antagonist receptor, might be interesting but their side effects especially psychiatric limit their development currently.

Overall, these new molecules show promises in helping clinicians to control weight gain and binge eating in their patients, in addition to the necessary multidisciplinary management. These pharmaceutical tools could change the clinical management and prognosis, especially in the case of early diagnosis or during the transition period from pediatric care to adult medicine. However, they should not be separated from multidisciplinary management [45].

5. Current perspectives for Glucagon Like Peptid-1 receptor analogs (GLP-1R) in rare genetic obesities

Glucagon-like peptide 1 receptor (GLP-1R) agonists, such as liraglutide, exenatide and semaglutide are promising therapeutics in common obesity and need more investigations in rare genetic obesities [46,47]. The GLP-1R is mainly expressed in the pancreatic β-cells, the digestive tract but also in several brain regions [48]. Their analogs are now well known to improve insulin secretion and usually are indicated in the management of type 2 diabetes for several years. The synergy of the central effect of insulin with the anorectic effect of activated GLP-1R in brain has been shown to induce weight loss and increase satiety in treated patients. In addition, GLP-1R may regulate energy expenditure by acting through various hypothalamic sites [49]. This dual function of GLP-1R analogs makes them now as a potential therapeutic option in patients with obesity. The benefic effects of GLP-1R analogs and especially once weekly semaglutide are reported in adults and adolescents with common obesity with progressive weight-loss of at least 10% after 52 weeks of treatment and even more than 20% in a sub-group of patients [50,51]. The most frequent side-effects of these molecules targeting enterohormones are digestive manifestations with mainly nausea, diarrhea, abdominal pain. They can be responsible for their interruption by patients and be prevented by a dosage progressive increasing. In rare genetic obesities, GLP-1R analogs, especially liraglutide, have been administered in patients with *MC4R* variants or PWS. On 3 mg liraglutide/day for 16 weeks, weight loss of *MC4R* variant carriers was equivalent to that of non-carriers (approximately 6% weight loss), suggesting that this molecule can induce satiety despite dysfunction of MC4R [52]. Liraglutide led also to a reduction of − 9.7 kg in one homozygous *MC4R* variant carrier suggesting that GLP-1 R analogs can be partly restore satiety despite the genetic interruption of the melanocortin pathway.

Other molecules targeting more than one receptor are under development and are promising. They notably include the Glucose-dependent Insulinotropic Polypeptide receptor (GIP-R) due to its metabolic effects inducing weight loss. For example, tirzepatide a novel GIP and GLP1-R agonist has been reported to induce decrease of food intake and also to act on energy expenditure [53]. In a phase 3 clinical trial in patients with common obesity, tirzepatide induced weight loss from − 15% to - 21% with 5–15 mg weekly respectively while only weight loss of − 3% was observed with placebo [54,55]. Other novel molecules are still in development and tested in mouse. One other promising example is the triple agonists with concurrent activation of the GLP-1, GIP, and glucagon receptors combining the anorectic and insulinotropic activities of GLP-1 and GIP with the energy expenditure effect of glucagon [56]. Moreover, all these molecules have beneficial effects on some co-morbidities associated to obesity as type 2 diabetes and hepatic steatosis due to their metabolic effects [57].

6. Conclusions

There is now growing evidence that new pharmacological molecules targeting hunger control will benefit patients with monogenic or syndromic obesity. They are likely to be among the treatment options for these patients in the coming years, helping clinicians and patients prevent rapid weight progression and eventually limit bariatric surgery procedures, which is less effective in these patients. [58–60]. Moreover other potential innovative treatments are currently developed as targeting antibody-type melanocortin pathway activating receptors or restoration of their functionality or even alternative specific signaling of MC4R [33]. In addition, other innovative therapeutics as induced pluripotent stem cell (iPSC) technologies and CriSPr-mediated gene editing might benefit for patients with monogenic forms of obesity. For example, hypothalamic like neurons generated from iPSCs of patients with severe obesity were responsive to leptin and ghrelin and retained typical features [61]. Functional repair of defective gene variants by CRISPR-Cas9-mediated gene editing could be also considered [62]. Finally, the specific modulation of hypothalamic AMPK using a neuronal-targeted small extracellular vesicles (sEV)-based technology in obese mouse models showed food-independent weight loss associated with increased thermogenesis and browning of white adipose tissue [63,64]. The positioning of these different innovative options still needs to be well defined as the evaluation which pharmacological molecules for which patient in the future.

CRediT authorship contribution statement

B Dubern: preparation, creation, writing of the initial draft, preparation of the revised manuscripit. N Faccioli: writing of the initial draft, creation of figures. C Poitou, K Clement: preparation and writing the initial draft,

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dubern reports a relationship with rhythm Pharmaceuticals, Novo Nordisks that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement.

Data Availability

No data was used for the research described in the article.

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