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Pharmacotherapy in Childhood Obesity

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Abstract
Background: The increasing number of obese children and adolescence is a major problem in health-care systems. Currently, the gold standard for the treatment of these patients with obesity is a multicomponent lifestyle intervention. Unfortunately, this strategy is not leading to a substantial and long-lasting weight loss in the majority of patients. This is the reason why there is an urgent need to establish new treatment strategies for children and adolescents with obesity to reduce the risk for the development of any comorbidities like cardiovascular diseases or diabetes mellitus type 2. ***Summary:*** In this review, we outline available pharmacological therapeutic options for children and compare the available study data with the outcome of conservative treatment approaches. ***Key Messages:*** We discussed, in detail, how knowledge about underlying molecular mechanisms might support the identification of effective antiobesity drugs in the future and in which way this might modulate current treatment strategies to support children and adolescence with obesity to lose body weight.

Introduction

The increasing number of patients with obesity worldwide is a major challenge for health care systems in industrial and in low- and middle-income countries. It has been estimated that worldwide approximately 13% of adults (WHO 2018) and 9.3% of European children suffer from obesity [1]. Rapid weight gain in early childhood results in high risk for obesity in adolescence [2]. The latter is even more dramatic because about 80% of adolescents with obesity will remain affected from obesity as adults. This underlines the importance of obesity as a lifelong chronic, progressive disease [3]. Furthermore, obesity is accompanied by an increased individual risk for the development of diabetes mellitus type 2 and cardiovascular diseases [4, 5], as well as by a decrease in health-related quality of life [6]. It has been estimated that OECD countries will spend 8.4% of total health expenses each year for the treatment of overweight/obesity and related diseases [1]. For this reason, to "halt the rise of diabetes and obesity" has been included as a target in the global

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WHO agenda on prevention and control of noncommunicable diseases [7, 8].

Until now, no country in the world has been able to reduce the number of individuals with obesity, which clearly points toward the necessity to establish new treatment strategies. The gold standard for the treatment of overweight/obesity remains a multimodal conservative treatment regime including different experts (physicians, nutritionists, and psychologists) to improve physical activity and reduce caloric intake. Unfortunately, the impact on body weight is overall modest and the majority of patients regain weight within 5 years [9, 10].

In the last decade, bariatric surgery has become another therapeutic option for adults and adolescents with obesity. Gastric bypass operation is leading to a reduction of approximately −26% of body weight in operated adolescents and approximately −29% in adults [11]. However, weight loss response differs dramatically between individuals, and for this reason, a comprehensive stratification of patients who might benefit from surgery is of importance.

Hence, there are major limitations of currently performed conservative and surgical treatment strategies. Against the background of the still remaining medical need to reduce the number of patients with obesity, this review will discuss pharmacological treatment options and its potential value for future approaches with a specific focus on the use of available molecular knowledge to develop pathway-specific drugs with reduced side effects.

Current Status: FDA/EMA-Approved Antiobesity Drugs

There are only a few FDA/EMA-approved antiobesity drugs available at the moment for the treatment of adult patients and each one with its own limitations. Recently, several reviews provide comprehensive overviews about available antiobesity drugs [12, 13]; hence, we delineate a brief summary about currently approved medications for adult patients:

Orlistat (Xenical®; Alli®) has been approved by FDA (year: 1999) and EMA (1998). It inhibits a lipase function in the mucous membranes of the intestinal endothelium. Thereby, hydrolysis of triglycerides and fatty acids absorption is reduced. After 1 year, orlistat treatment led to a reduction of −10.6 kg (placebo control group: −6.2 kg) and, after 4 years, to a reduction of −5.8 kg (placebo control group: −3.0 kg) (XENDOS study) [14]. In total, this is a placebo-subtracted weight loss of −3 kg within 208 weeks [12]. Based on the mechanism, steatorrhea, flatus, constipation, fecal incontinence, and occasionally deficit of fat-soluble vitamins are main side effects, observed during orlistat treatment. Because these side effects could potentially have a disturbing influence on daily life, orlistat is uncommon in usual care.

Phentermine/Topiramate (Qsymia®) has been approved in 2012 by FDA and has not been approved by EMA. This is a combination of norepinephrine activation, GABA agonist and glutamate antagonist, which is leading to a reduction of hunger feeling – although the exact mechanism for this effect remains elusive. In clinical trials, treatment led to a reduction of body weight for −10.9% after 1 year (placebo group: −1.6%) (EQUIP) and −7.8% (dosage: 7.5/46 mg) and −9.8% (dosage: 15/92 mg) after 1 year (placebo group: −1.2%) (CONQUER). In the 2-year extension trial (SEQUEL), a decrease of body weight persists (−9.3% [dosage: 7.5/46 mg] and −10.5% [dosage: 15/92 mg]) [15, 16]. Side effects consist of hypokalemia, metabolic acidosis, nephrolithiasis, myopia, glaucoma, anhidrosis, paresthesia, dry mouth, anxiety, depression, and increased heart rate [13]. These side effects limit the prescription especially in older people with obesity.

Naltrexone/Bupropion (Contrave®; Mysimba®) has been approved in 2014 by FDA and 2015 by EMA. This is a combination of an opioid antagonist (especially μ-opioid receptor) and an inhibitor of dopamine and norepinephrine reuptake. It has been postulated that the reduction of hunger feeling is mediated via an activation of *POMC*-expressing hypothalamic neurons [17, 18]. In the clinical trial, Naltrexone/Bupropion led to a placebo-subtracted weight loss of −4.7 kg after 56 weeks (COR-I) [19], −4.9 kg after 56 weeks (COR-II) [20], −4.1 kg after 56 weeks (COR-BMOD) [21], −3.4 kg after 56 weeks (COR-Diabetes) [22], and −2.7 kg after 121 weeks (LIGHT) [12]. The side effect spectrum includes nausea, seizures, insomnia, constipation, vomiting, dry mouth, and headache.

Liraglutide (Victoza®, Saxenda®) is a GLP-1R (glucagon-like peptide 1 receptor) agonist and has been approved as an antiobesity drug in 2014 by FDA and in 2015 by EMA. It acts centrally by activating hypothalamic, limbic, and cortical centers of body weight regulation [23, 24]. Moreover, in the periphery GLP-1R activation is leading to inhibition of glucagon and stimulation of insulin secretion and delayed gastric emptying [25]. Within randomized clinical trials (RCTs), liraglutide led to a placebo-subtracted weight loss of −4.9 kg after 32 weeks (SCALE-Sleep Apnea study), −4 kg after 56 weeks (SCALE-Diabetes study), −5.6 kg after 56 weeks (SCALE-

Obesity and prediabetes study [26]), −5.9 kg after 56 weeks (SCALE Maintenance study), and −4.6 kg after 160 weeks (SCALE Obesity and Prediabetes 2-year extension study) [12, 27–29]. Major side effects include gastrointestinal symptoms such as nausea, vomiting, and diarrhea.

Semaglutide is another GLP-1R agonist with different pharmacokinetics allowing once-weekly injection. A clinical trial program, including 4 studies, showed −10.6% mean change in body weight with semaglutide 2.4 mg and −7% with semaglutide 1.0 mg [124, 125]. Transient and mild-to-moderate gastrointestinal symptoms (e.g., nausea and diarrhea) were the most frequently observed side effects. Semaglutide (injectable once-weekly) was approved by the FDA for obesity in adults in June 2021. Semaglutide in an oral formulation was tested only in type 2 diabetes so far.

In summary, a wide spectrum of pharmacological substances were studied with regard to their impacts on weight course in humans with obesity. Moderate success in long-term weight reduction on one hand and relevant side effects on the other hand limited the frequent use of antiobesity drugs up to date.

Use of Antiobesity Drugs in Children and Adolescents: The Past and the Future

The situation for children and adolescents differs with regard to available treatment options. For some children and adolescents with obesity, multicomponent lifestyle intervention can be effective. However, for the majority, long-term weight loss and maintenance are not possible to reach, even if pediatric obesity experts fulfill the most versatile challenges by exploiting their expertise in different age-groups.

As for preschool children, aged 0–6 years with overweight or obesity, multicomponent lifestyle interventions appear to be an effective treatment option, but the current Cochrane review is only based on 7 RCTs with a total of 923 participants. A reduction in body mass index (BMI) *z* score was significantly higher in the intervention groups than the standard care (6–12 months' follow-up: mean difference (MD) −0.3 units (95% confidence interval [CI] −0.4 to −0.2); $p < 0.00001$); 12–18 months: MD −0.4 units (95% CI −0.6 to −0.2); $p = 0.0001$). In this age-group, the role of dietary interventions is more equivocal [30].

The intervention review for school children with overweight or obesity, aged 6–11 years, included 70 RCTs with a total of 8,461 participants. Behavior-changing interventions (with various components) compared to standard care significantly reduced BMI and BMI *z* score. MD in BMI was −0.53 kg/m^2 (95% CI −0.82 to −0.24); $p < 0.00001$; 24 trials; 2,785 participants. MD in BMI *z* score was −0.06 units (95% CI −0.10 to −0.02); $p = 0.001$; 37 trials; 4,019 participants. In general, the evidence quality was low; for example, because only few trials reported adverse event, health-related quality of life or behavior change outcomes [31].

Interestingly, parent-only interventions for childhood overweight or obesity in children aged 5–11 years (intervention review: 20 RCTs, including 3,057 participants) are an effective treatment tool compared to waiting list controls and had similar effects compared to parent-child interventions [32]. This indicates that there is a need to include the situation in the family of children with obesity into consideration before the start of interventions.

A particular challenge is the successful treatment of adolescents with obesity or even extreme obesity. The effect of diet, physical activity, and behavioral interventions for treatment in adolescents aged 12–17 years was summarized in an intervention review including 44 completed RCTs (4,781 participants) and 50 ongoing studies. In general, behavior-changing interventions were able to significantly reduce BMI, BMI *z* score, and body weight to a limited extent (BMI −1.18 kg/m^2 (95% CI −1.67 to −0.69); 2,774 participants; 28 trials; low-quality evidence; BMI *z* score −0.13 units (95% CI −0.21 to −0.05); 2,399 participants; 20 trials; low-quality evidence; body weight −3.67 kg (95% CI −5.21 to −2.13); 1,993 participants; 20 trials; moderate-quality evidence) [31].

Multidisciplinary lifestyle interventions including a combination of diet, physical activity, and behavioral components slightly reduce childhood and adolescents' obesity and moderately improve health-related quality of life, particularly in comparison to no treatment. The effect is relatively low in age-groups with a high prevalence of overweight and obesity – mainly school children and adolescents [33]. Nevertheless, lifestyle modification therapy is the cornerstone of obesity treatment during childhood and adolescence. Despite the overall low success rate of weight reduction and maintenance, lifestyle intervention is effective in improving obesity-related comorbidities (e.g., insulin resistance, hypertension, hyperlipidemia, fatty liver disease, and exercise capacity), even in the absence of sustained weight loss [34–36]. The limitations of multicomponent behavioral modification programs are grounded in the biological mechanisms of energy homeostasis. The leptin-melanocortin pathway and the incretin system are deeply involved in a complex regulation including peripheral signals, for example, from

adipose tissue, muscle or gastrointestinal tract, and central signals, for example, from the hypothalamus [37, 38]. There is evidence that this system assists a positive energy balance [39]. In addition to lifestyle modification, antiobesity drugs (and bariatric metabolic surgery) have the potential to discourage these mechanisms. Several medications have been investigated for the treatment of obesity in adults over the last decades [40]. However, total weight loss in 12 months for the 3 monotherapies (orlistat, lorcaserin, and liraglutide) ranged from −5.8 to −8.8 kg (5.8–8.8% of initial body weight). Placebo-subtracted weight loss, determined from a meta-analysis, ranged from −2.6 to −5.3 kg [41].

In the following section, we will summarize FDA- and EMA-approved and commonly prescribed antiobesity medications in the pediatric population (for efficacy and side effects in adults, see above):

Orlistat (Xenical®) is the only FDA (not EMA)-approved drug for the long-term treatment of adolescents with obesity older than 12 years. A large RCT (N = 352) analyzed orlistat versus placebo in combination with a multimodal lifestyle intervention, showing a significant weight loss after 12 months' treatment (−2.61 kg placebo-subtracted weight loss; $p < 0.001$). This trial was also included into a recent pediatric meta-analysis (N = 779; average BMI 37.4 kg/m^2). There were only small BMI differences between orlistat and placebo [42]. The side effects are comparable to those in adults. Long-term use might potentially cause vitamin and mineral deficiency with a negative impact on growth or pubertal development. However, none of these effects were reported, perhaps due to reduced use of orlistat in adolescents with obesity.

The sympathomimetic amine Phentermine (Adipex®, Suprenza®) was FDA approved already in 1959. There have been very few studies in the 1960s examining phentermine for obesity treatment in the pediatric population with marginal reports about safety and efficacy reported. Since the substance is an amphetamine analog, it acts to increase catecholamines and serotonin in the central nervous system, resulting in appetite suppression. Common side effects may include increased heart rate and blood pressure. Phentermine is FDA (not EMA) approved for short-term treatment (<12 weeks) in adolescents (>16 years) with obesity because of a lack of long-term observations and frequent side effects. Recent retrospective data in a small adolescent cohort (N = 25) suggested a modest effect on BMI % at 1 month (−1.6%; 95% CI: −2.6, −0.6%; $p = 0.001$), 3 months (−2.9%; 95% CI: −4.5, −1.4%; $p < 0.001$), and 6 months (−4.1%; 95% CI: −7.1, −1.0%; $p = 0.009$) compared with standard care [43].

The combination Phentermine/Topiramate (Qysmia®) is FDA approved for long-term treatment of obesity in adults (see above). In December 2020, the FDA approved liraglutide 3 mg (Saxenda®) for the treatment of obesity in adolescents aged 12–17 years with a body weight of at least 60 kg and an initial BMI corresponding to 30 kg/m^2 or greater for adults (https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-weight-management-drug-patients-aged-12-and-older). In June 2021, the Committee for Medicinal Products for Human Use (CHMP) from the European Medicines Agency (EMA) decided that the indication for liraglutide 3 mg (Saxenda®) is expanded for the treatment of obesity in adolescents aged 12–17 years (https://www.ema.europa.eu/en/documents/product-information/saxenda-epar-product-information_en.pdf). Liraglutide 3.0 mg (Saxenda®) is a once-daily GLP-1 analog with 97% similarity to natural human GLP-1, a hormone that is secreted in response to food intake.

Like human GLP-1, liraglutide works on glucose metabolism and body weight due to various mechanisms: (i) promoting insulin secretion from pancreatic β-cells; (ii) reducing glucagon secretion from pancreatic α-cells (resulting in hepatic gluconeogenesis); (iii) improving insulin sensitivity; (iv) reducing gastric emptying; and (v) improving central appetite regulation.

Common side effects include nausea, dizziness, abdominal pain, low blood sugar, and pain at the injection site. Other serious side effects may include medullary thyroid cancer (MTC), angioedema, pancreatitis, gallbladder disease, and kidney problems.

Liraglutide causes dose-dependent and treatment duration-dependent thyroid C-cell tumors, at exposures 8 times greater than those used in humans, in both genders of rodent models. Even if the relevance for humans of such tumors identified in rodents has not been determined, liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2; https://www.drugs.com/monograph/liraglutide.html). A small, short-term pediatric RCT studied the safety, tolerability, and pharmacokinetics of liraglutide in adolescents with obesity (5 weeks; N = 25; 12–17 years). Twelve hypoglycemic episodes occurred in 8 participants in the liraglutide group and 2 in the placebo group (no severe hypoglycemic episodes). The adult dosing regimen for weight reduction seemed to be appropriate for the use in adolescents as well [44]. Furthermore, the therapeutic effect of high-dose liraglutide (3.0 mg/days; Saxenda®) additional to lifestyle intervention on BMI in adolescents with obesity was addressed in a larger RCT (N = 251; 12–17 years; a 56-week

treatment period; a 26-week follow-up period). A liraglutide decrease in BMI-SDS in the liraglutide group was superior to placebo after 56 weeks (estimated difference, −0.22; 95% CI: −0.37 to −0.08; $p = 0.002$). BMI reduction of at least 5% was achieved more frequent with liraglutide than with placebo (43.3% vs. 18.7%). BMI-SDS regain in the follow-up period was higher in the liraglutide group (estimated difference, 0.15; 95% CI, 0.07–0.23). At 56 weeks, cardiometabolic parameters and weight-related quality of life did not differ between both groups [45]. Results and conclusions of this study were discussed intensively. Frequent gastrointestinal side effects could potentially induce weight reduction and could be associated with malabsorption [46]. Weight regain immediately after the end of medication as well as the potential risk of severe long-term adverse events as MTC requires a critical discussion of benefits and risks for the use of liraglutide in adolescents with obesity [47]. Even with some promising evidence for the efficacy and safety of liraglutide in treatment of adolescents with obesity, liraglutide should only be used as an adjunct to intensive lifestyle intervention [48].

In children and adolescents with type 2 diabetes and obesity, liraglutide (1.8 mg/day; additional to metformin and/or insulin) improved glycemic control in relation to placebo [126]. In a further pediatric RCT with exenatide (Byetta®; $N = 44$), a substance related to liraglutide and with similar effects on the GLP-1R, a 6-month weekly injection leads to the modest BMI-SDS reduction and a moderate improvement of glucose tolerance and serum-cholesterol in adolescents with obesity [49]. Exenatide (Byetta®) is FDA/EMA approved for type 2 diabetes mellitus in adults, but not for obesity or younger age-groups. Some other medications, primarily not FDA/EME approved for obesity in childhood, have been applied in clinical studies, recording also body weight as the second end point.

Metformin (an activator of the protein kinase pathway) is the first-line medication for type 2 diabetes mellitus in patients older than 10 years. In addition, for the polycystic ovary syndrome in females, especially in combination with obesity and insulin resistance, metformin is indicated. There are some reports about metformin modestly reducing body weight in adolescents with obesity, even with improving insulin sensitivity – but the evidence remained elusive [50–52]. Frequent gastrointestinal side effects like diarrhea or flatulence possibly cause reduced food intake. Lactic acidosis is a very rare but severe side effect mainly in older patients with renal insufficiency.

Topiramate (Topamax®, central acting via modulation of neurotransmitters) is indicated for the treatment of epilepsy for children older than 2 years and for migraine or cluster headache in adolescents older than 12 years. The combination with phentermine is approved for long-term treatment of obesity in adults (see above), but also in adult patients with binge-eating disorder and bulimia nervosa [53]. There is some evidence that topiramate could support weight reduction in addition to lifestyle intervention in adolescents with obesity [54], based on a small observational study ($N = 28$; mean age 15.2 ± 2.5 years, mean baseline BMI 46.2 ± 10.3 kg/m^2; 6-month change in BMI −4.9, 95% CI −7.1 to −2.8, $p < 0.001$) [55]. Severe potential side effects, such as kidney stones, metabolic acidosis, cognitive dysfunction, and teratogenicity (mandatory contraception for females), is limiting even the off-label use.

Central nervous stimulants are approved for children with attention-deficit hyperactivity disorder. A common side effect is decreased weight due to decreased appetite or diarrhea, with a long-term effect on growth and pubertal development. A negative impact on brain maturation was demonstrated in animal models [56, 57]. Hypothalamic obesity (following CNS insult, e.g., craniopharyngioma, meningitis) in children and adolescents is a challenge for patients, families, and treatment teams because alteration of the hypothalamus results in the combination of decreasing physical activity (lethargy) and increased hunger feeling. Central nervous stimulants were at least able to prevent further weight gain in small case studies up to 1 year of follow-up [58, 59]. The clinical experience provides evidence that the effect in children and adolescents with common obesity is often the very reverse: low food intake during school hours, followed by food craving in the afternoon and eating during the night (in combination with media consumption). It is therefore essential to critically evaluate the off-label use of central nervous stimulants on an individual level and to use central documentation of patient data (pseudonymized) to gain new insights.

In summary, the diversity of primary diseases in children and adolescents with obesity (common obesity, monogenic obesity, and syndromic obesity) results in a greater variety of pharmacological options [60]. But the effect is comparable with the results in adults with obesity. Additional lifestyle intervention is considered to be the fundament for all age-groups.

Proof of Concept: Pharmacological Treatment of Patients with Monogenic and Syndromic Obesity

In contrast to patients with common obesity, pharmacological treatment strategies for patients with monogenic or syndromic obesity differ substantially in some cases.

The knowledge about the molecular cause for the development of obesity in these particular patients led to the possibility to a mechanism-driven treatment approach.

Patients with Prader-Willi syndrome (or other obesity syndromes) suffer from hypothalamic obesity. The situation is even more difficult because of existing mental handicaps and reduced muscle mass. While feeding problems in floppy infants are the prominent clinical features early in life, food graving and hypothalamic obesity usually start at kindergarten age. Over the years, many substances were used in single or small case studies to prevent or treat this condition, but without enjoying any great success; for example, clinical studies on oxytocin (or oxytocin analogs) have resulted in conflicting outcomes about hyperphagia and repetitive behaviors in young children with PWS.

More recently, a methionine aminopeptidase 2 (MetAP2) inhibitor (Belorani), originally aproved as an angiogenesis inhibitor for the treatment of cancer and supposed to directly act on the adipose tissue, showed promising results in phase III study, with significant weight reduction and improved hyperphagia-related behavior in patients with PWS. Further development was stopped because of a severe side effect (2 deaths) [61]. Exenatide (Byetta®) reduced significantly appetite scores and HbA1c in 10 adolescents and young adults with PWS (13–25 years), but without effect on BMI [62].

Rimonabant (endocannabinoid receptor CB1 antagonist) was a promising candidate and tested 2006–2008 as antiobesity medication in patients with PWS. Because of psychotic reactions and depression, 50% of subjects on treatment withdrew and the study was terminated [63]. These examples illustrate the difficulties to treat hypothalamic obesity in patients with PWS successfully [64, 65].

The discovery of the leptin-melanocortin signaling cascade was a milestone for the understanding of central body weight regulation. The analysis of rodent models with defects in *leptin* or *leptin receptor* gene (*ob/ob* mice [66] or *db/db* mice [67, 68]) provides new insights into the hormonal regulation of satiety. Leptin activation of leptin receptors within the hypothalamus leads to the secretion of melanocyte-stimulating hormones (α- and β-MSH in humans) derived from *POMC* (pro-opiomelanocortin)-expressing neurons. MSH derivatives are ligands for the G-protein-coupled receptor (GPCR) MC4R (melanocortin 4 receptor) in the paraventricular nucleus. Gene mutations in one of the involved genes lead to impaired pathway function and severe hyperphagia and obesity in animal models and human variant carriers [69–74]. Hope and enthusiasm raised after successful leptin treatment of leptin deficient rodents and first leptin treatment of severely obese *LEP* gene mutation carriers [75, 76]. Here, leptin led to a substitution of the missing signal in these patients and restored function of the leptin-melanocortin signaling pathway. This led to normalization of the initially increased hunger feeling and reduction of body weight. Unfortunately, leptin treatment is not successful in patients with nongenetic obesity to decrease body weight [77]. Apart from leptin, studies had been performed to investigate the treatment with MC4R agonists. Former first-generation MC4R agonist led to a reduction of food intake in POMC-deficient rodents, but studies in humans were accompanied by the occurrence of severe side effects like increased blood pressure or were not successful to induce weight loss [78, 79] (see Drug Failure and Its Molecular Mechanisms: Scope for Improvement). However, recently, a new MC4R agonist setmelanotide (former name: RM-493, BIM-22493) has been studied initially in an investigator-initiated phase 2 proof-of-concept study (EudraCT No. 2014-002392-28) in patients with mutations in the genes *POMC* or *LEPR*. In 2 enrolled POMC deficient patients, this treatment led to a reduction of body weight for −51.0 kg after 42 weeks and −20.5 kg after 12 weeks of treatment. Furthermore, patients with *LEPR* mutation ($n = 3$) lost −25.1 kg (after 61 weeks), −13.9 kg (after 36 weeks), and −10 kg (after 13 weeks). These results were confirmed in phase 3 trials (ClinicalTrials.gov, NCT02896192 and NCT03287960) in which patients with POMC deficiency lost −25.6% and LEPR-deficient patients lost −12.5% of pretreatment body weight. Importantly, no cardiovascular adverse events have been detected. However, skin hyperpigmentation due to cross-activation of the melanocortin 1 receptor (MC1R) has been observed in the majority of treated patients. Setmelanotide has been approved for patients with POMC/PCSK1 and LEPR deficiency by the US Food and Drug Administration (FDA) in 2020. Of note, prior to the usage of setmelanotide as an treatment option, loss of function of identified mutations in candidate genes of the leptin-melanocortin pathway has to be tested in the state-of-the-art functional characterization. Ongoing studies investigate whether further groups of patients might benefit from the MC4R agonist treatment. Within a phase 2 study including patients with the ciliopathy Bardet-Biedl syndrome/Alström syndrome, setmelanotide led to a mean reduction of −16.3% of pretreatment body weight after 12 months of treatment ($n = 7$) [80].

Apart from leptin and MC4R agonists, recently the GLP-1R agonist liraglutide has been tested in patients with heterozygous and homozygous *MC4R* mutations [81, 82]. Over a maximum period of 16 weeks, liraglutide led to a reduction of −9.7 kg in the homozygous *MC4R* variant carrier and to a reduction of −6.8 kg ± 1.8 kg in heterozygous *MC4R* variant carriers. In 28 matched control participants, the treatment led to a decrease of body weight for −6.1 kg ± 1.2 kg after 16 weeks.

These examples indicate that there is growing evidence that there are now new pharmacological treatment options available, which might be beneficial for patients with certain monogenic obesity types. This is important because conservative treatment strategies (increased exercise and reduced caloric intake) and even in some cases with biallelic gene mutations bariatric surgery do not lead to a long-lasting reduction of body weight. However, in the majority of children and adolescents with obesity, a precise gene mutation is not explaining the development of obesity. It might be of interest whether heterozygous variant carriers (e.g., for the genes *POMC* and *LEPR*) would also benefit from such a pharmacological treatment. However, this question remains to be answered.

Drug Failure and Its Molecular Mechanisms: Scope for Improvement

All of the above-described pharmaceutical US FDA/EMA-approved treatment options were either only suboptimal effective in a few patients or cause adverse side effects but are not suitable for a generalized treatment of children with common obesity. The result of so far available studies might be that not a "simple and safe" obesity treatment is successful for most children with obesity and that there is a need to rethink the currently available multidisciplinary concept of obesity treatment. It is now time to combine the current concepts with genetic studies and available molecular biology information of those cells/neuros/tissues that are involved in energy homeostasis to achieve an obesity 2.0 treatment strategy.

Here, our intention is to highlight one of the molecular players that are involved in weight regulation and might serve as a potential treatment target: GPCRs.

General Aspects of Consideration If a GPCR Shall Be Used as Drug Target

GPCRs are involved in many if not in all physiological functions [83], which classified them as drug targets. Indeed, currently approximately 35% of approved drugs in the USA and Europe target a GPCR [83, 84]. For antiobesity treatment, a variety of such GPCRs were targeted such as the cannabinoid 1 receptor (CB1R), the serotonin 2C receptor (5HT2CR), the GLP-1R, or the MC4R. Unfortunately, many of former approved drugs were now withdrawn from the market because of severe side effects.

To understand why these side effects occur offers the chance to improve a drug design and to make the treatment more specific and effective. To achieve this, a general understanding about the receptors' function is necessary. Very simplified, GPCRs consist of 7 α-helical transmembrane-spanning domains that are connected by 3 extracellular and 3 intracellular loops with the N-terminal part at the extracellular space and the C-terminus intracellularly [85]. Based on structural aspects, GPCRs were separated in 5 different classes [86]. Class A is by far the largest class. In this class are mainly receptors with short N-terminal domains and a structural homology to adrenergic receptors or rhodopsin. Receptors with longer N-terminal domains belong to class B such as the GLP-1R, which is the target for GLP-1 analogs such as liraglutide.

When an endogenous ligand (a synonym for an agonist or a hormone stimulating signaling) binds to the receptor, it occupied the orthosteric binding site, which is for class A receptors mainly located within the transmembrane bundle. Receptors with a larger extracellular domain such as GLP-1R bind its endogenous ligand at the N-terminal domain. If the therapeutic ligands are designed, they will bind either to the orthosteric binding site and thereby competing with endogenous ligand binding, or they use another binding site also known as allosteric binding site, which differs from the orthosteric binding site.

Binding of a ligand, either the endogenous one or an artificial, results in a conformational change of the receptor, leading to the activation of signaling, which is, for example, G protein activation, and subsequently modifies second messenger concentrations (e.g., cyclic AMP).

However, the situation is much more complex because:

1. The GPCR of interest is activated by several endogenous ligands (e.g., the MC4R by α-MSH and β-MSH) [87].
2. In addition to endogenous ligands also an antagonist or an inverse agonist exists (e.g., AGRP at MC4R) (Fig. 1) [87].
3. A ligand can induce more than one signaling pathway (e.g., MC4R: Gs, Gi, Gq/11, ERK, and β-arrestin) [88, 89] (Fig. 2).

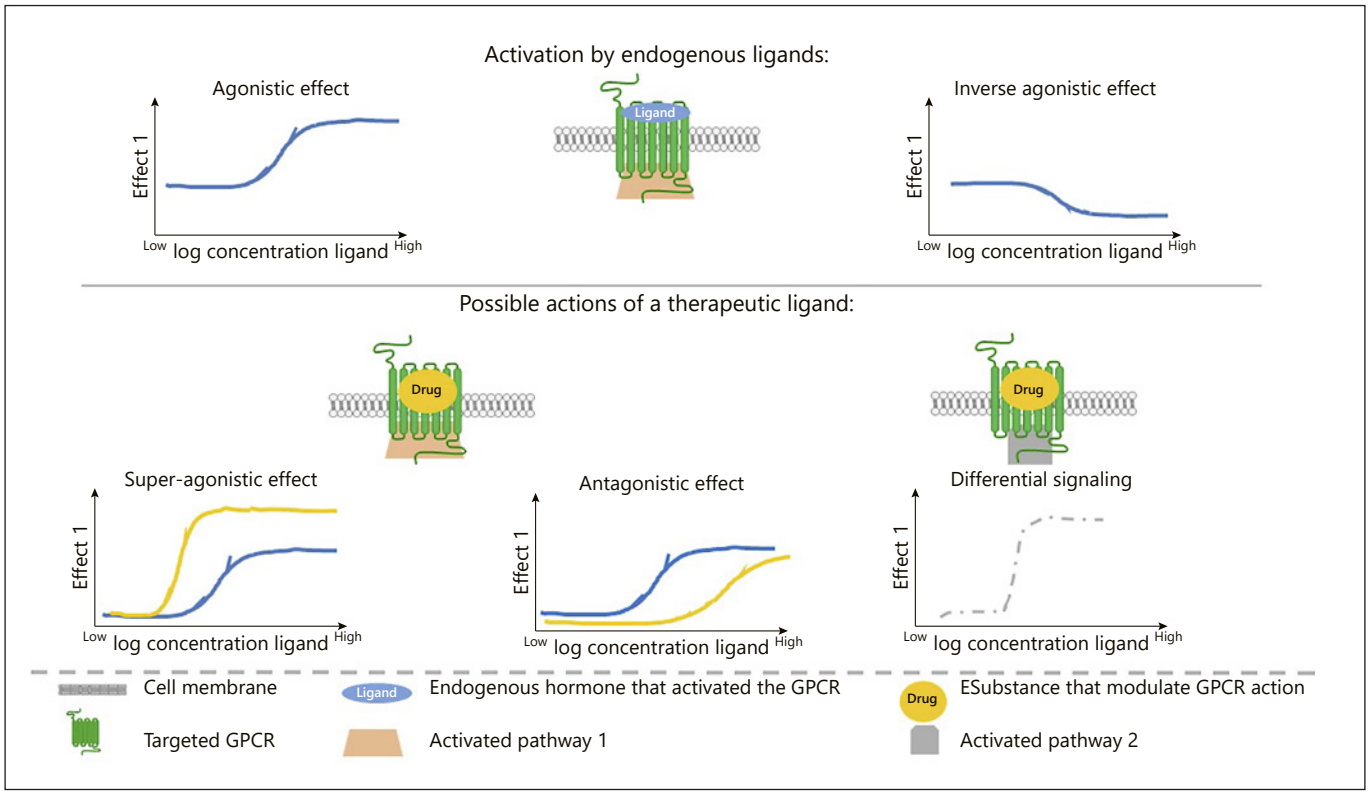

Fig. 1. Schematic illustration of GPCR activation by endogenous ligands and possible therapeutic drug effects at this GPCR. GPCRs are prominent targets for drug development, for example, to treat obesity. The upper part of the cartoon demonstrates 2 possible actions at a GPCR of interest that are exerted by the endogenous ligand (e.g., a hormone). On the left site, the action of the endogenous ligand at its GPCR to activate the major signaling pathways (effect 1) is depicted in a blue concentration-response curve. In case of GPCRs with high constitutive activity (activity in the absence of ligand), the endogenous ligand can act by reducing the constitutive activity of effect 1, known as an inverse agonistic effect, shown on the upper right site. On the lower part of the cartoon, some possible effects of a therapeutic substance, a drug (e.g., a peptide or a small molecule) at the GPCR, are shown. One action can be hyperstimulation of the GPCR by the drug to induce pathway 1 (effect 1) shown on the left side (higher activation by the drug in yellow compared to the endogenous ligand in blue). In the middle, another possibility is indicated where inactivation (in yellow) of the effect 1 of the endogenous ligand (in blue) by an antagonist is shown (shift of the concentration response curve to higher concentrations for activation). On the left side, a very attractive possibility is depicted where a drug can activate an additional pathway (effect 2) in comparison to the endogenous ligand. This so-called biased agonist can exert differential signaling. GPCR, G-protein-coupled receptor.

4. The GPCR of interest is expressed in different tissues: for example, obesity targets CB1R, 5HT2CR, and MC4R are centrally and peripherally expressed [90].
5. In different tissues, a GPCR may activate different signaling pathways [89, 91].
6. The GPCR of interest may function as a homodimer (one GPCR interacts with the same GPCR) or as a heterodimer (GPCR of interest interacts with another GPCR or another membrane protein). These interactions are dependent on the tissue of expression and may change the signaling properties [92] (Fig. 2c, d).
7. Intracellular proteins may interfere with GPCR function [91]. As the expression of these proteins is cell-type specific, they thereby also modify the signaling properties of the GPCR of interest (Fig. 2b).
8. It might matter where in a cell or a neuron a GPCR of interest is located. Compartmentalization might influence the signaling outcome of a targeted GPCR as it is the case for β-adrenergic receptors in cardiomyocytes. Here the Gs-coupled β2 adrenergic receptor (ADRB2) exerts cAMP signals in deep transverse tubules, whereas the ADRB1 is distributed all over the healthy cardiomyocyte. In the disease condition, this "healthy" distribution is destroyed and the ADRB2 is diffusely distributed, which might contribute to the disease phenotype [93]. In contrast to the previously expected

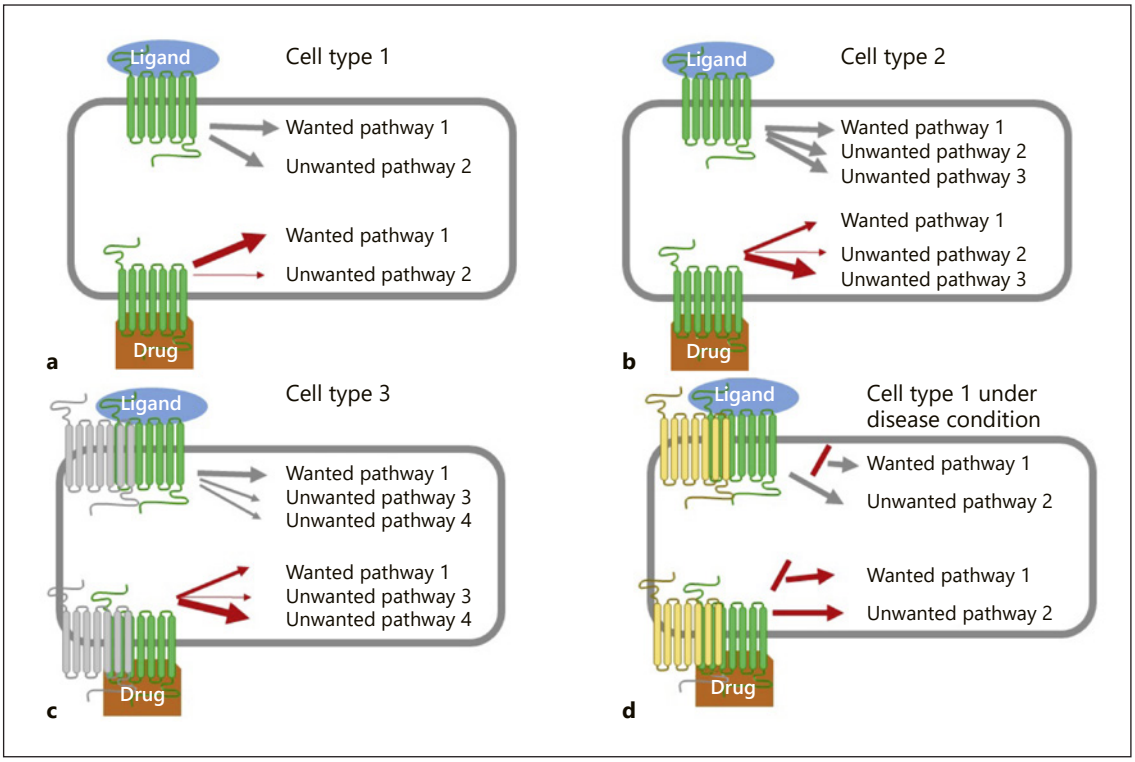

Fig. 2. Schematic illustration of wanted and unwanted effects if a drug target is a GPCR of interest. The GPCR of interest (in green) is activated by its endogenous ligand (in blue). Activated signaling pathways of the ligand are shown in gray, and the strength of the activation corresponds to the thickness of the arrows. The therapeutic ligand (drug in dark orange) activates signaling pathways indicated by red arrows, and the strength of the activation corresponds to their thickness. **a** Here the optimal situation is illustrated: The pathways of the GPCR of interest that should be targeted are known from signaling studies with the endogenous ligand. A drug is developed, which preferentially activates (red arrows) the pathway, which is of therapeutic interest (wanted pathway 1) but does not or only to a minor extend activate the side effect causing pathway 2. **b** GPCRs are often expressed in >1 type of cells or neurons. Here the case is depicted in which a cell type differs to the one in **a** activating more pathways, for example, due to other or different intracellular signaling proteins. In this case, in addition to the therapeutic important pathway 1, also pathways 2 and 3 are already activated by the endogenous ligand. If a drug targets the receptorof interest in this cell system, it might be that in addition to activation of the wanted pathway 1 (not as much activated compared to cell type 1 in **a**) unwanted pathways might be activated. **c** GPCRs often form homo- or heterodimers. Here as an example the heterodimeric state is shown by an additional GPCR (in gray). This constellation can modulate the signaling properties of the GPCR of interest, here shown as the activation of additional pathways after challenge with the endogenous ligand (pathways 3 and 4, both of them are unwanted in a therapeutic intervention). If a drug targets this heterodimer, it might be that in addition to the wanted effect (activation of pathway 1) also the unwanted pathways 3 and 4 are activated. **d** Under the disease condition, it might be that the content of interacting proteins of the GPCR of interest might change. This could be GPCRs, which are shown here in yellow, or other membrane proteins. This interaction can theoretically lead to uncoupling of the signaling pathway 1 that is needed for therapeutic intervention. In this case, the drug is ineffective, as due to uncoupling the therapeutic important pathway cannot be activated anymore. GPCR, G-protein-coupled receptor.

diffusion of cAMP through the cell, data now demonstrate that the cAMP signal is immobile in the basal state by binding to cAMP binding sites [94].

9. Disease progress of the metabolic status may influence the expression of the GPCR of interest. We have to expect that many GPCRs will be expressed on hypothalamic neurons that should be targeted for treatment. The expression of these GPCRs might be influenced due to hypothalamic inflammation, which is related to obesity. In this case, overexpression of so far non- or low-expressed GPCRs may occur as this is the case in bronchial asthma. Here, standard asthma treatment uses the bronchodilatation effect of activated β-adrenergic receptors; however in case of a respiratory infection, prostaglandin receptors are highly expressed and these receptors cause an uncoupling of adrenergic receptors from its signaling pathway [95, 96] (Fig. 2d).

Therefore, if a GPCR of interest should be targeted, a careful knowledge about the signaling pathway of the receptor is needed. This is of specific interest if the signaling properties may vary due to the expression of different cell types or the signaling outcome (the biological effect). In case of activation of the MC4R, which is expressed in the hypothalamus where it regulates feeding behavior as well as in the penile tissue, where it is involved in reproduction, overactivation of the receptor (Fig. 1) by artificial ligands might have multiple effects, which are not always wanted at a time [96–99].

To obtain specific knowledge about the receptor of interest is by far not trivial. Most knowledge was obtained by *in vitro* studies in nonhomologous cell systems. Since many GPCR involved in weight regulation are expressed in the brain [90], data from rodent studies may help in some cases; however, it has to be kept in mind that the expression profile of GPCRs in different areas of the mouse brain may be different to human brain, and differentially expressed GPCR might interact with GPCRs of interest [100]. For this reason, it might sometimes take many years since a complete signaling profile of a GPCR is evaluated [88].

Once the signaling pathway, which should be modulated, is identified, for example, the agonistic profile of the endogenous ligand or the inverse agonistic profile, a drug may enhance or reduce the endogenous ligands' signaling (overactivation or hyperstimulation vs. inactivation by antagonism) (Fig. 1). Over the last few years, it became more and more evident that an elegant way of drug development is so-called *biased ligands*, which have a signaling profile different to the endogenous ligand. A biased ligand is a ligand that is capable to activate signaling pathways different to the endogenous ligand; for example, if the endogenous ligand activates Gs signaling and β-arrestin recruitment and β-arrestin recruitment cause unwanted side effects, a biased ligand can, for example, only activate Gs signaling with no or only minor effect on β-arrestin recruitment. With these drugs, a specific pathway may be activated and by this activation an unwanted pathway can be reduced or excluded [89, 101, 102].

In addition, another aspect has to be taken under consideration: the binding mode of the endogenous ligand versus the drug. By definition the endogenous ligand binds to the orthosteric binding pocket. A designed drug that can attract this orthosteric pocket will thereby compete with the endogenous ligand or bind to another binding pocket, allosteric binding, and change by this the conformation of the reception, which may interfere with endogenous ligand binding [103].

Next, the mode of action matters: a drug can be a positive allosteric modulator, which by this alters the affinity or the efficacy of the endogenous ligand, and a negative allosteric modulator, which negatively alters the affinity or the efficacy of the endogenous ligand [104].

If a drug exerts the wanted effect (reduction of body fat) but also causes unwanted effects, the first enthusiasm due to their weight-lowering effects is dampened by recognition of side effects such as psychiatric side effects in case of CB1 antagonists (rimonabant; Acomplia®) [105]. MC4R agonists were either ineffective in reducing weight, for example, MK-0493 [79] or cause cardiovascular side effects such as LY2112688 [106]. For MC4R, however also a very effective drug exists, *setmelanotide*, which is highly effective in reducing hyperphagia and food intake in patients with a defect in the leptin-melanocortin pathway, such as POMC- or LEPR-deficient patients [107, 108]. 5-HT2CR ligand lorcaserin (Belviq®) is highly selective and reduces hunger and food intake; however, due to the induction of tumors and psychiatric side effects, it was withdrawn from the market [13]. In any case, either the targeted GPCR is activated in cells or tissues, where it should not be activated, or the signaling effect of the drug results in unexpected effects because the full spectrum of signaling events of the targeted GPCR is not fully unraveled.

Examples of Targeted GPCRs for Antiobesity Treatment

We will highlight 3 GPCRs that were targeted as obesity treatment over the last few years. These 3 GPCRs are accepted for a long time as potent obesity treatment targets of therapeutic substances – however, the efficacy and safety might be a matter of concern.

CB1R: The Location Matters

The CB1R is part of the endocannabinoid systems that is involved in many biological processes including appetite regulation and mood [109]. The CB1R is expressed centrally and in many peripheral tissues. Activation of CB1R stimulates feeding; thus, the design of inverse agonists at CB1R such as SR141716A (rimonabant) should counteract feeding as obesity treatment. Preclinical and clinical studies proved rimonabant as effective in reducing food intake, and it was approved as antiobesity therapeutic. Unfortunately, although rimonabant was effective in reducing weight, it causes severe psychiatric side effects such as depression anxiety and suicide [110],

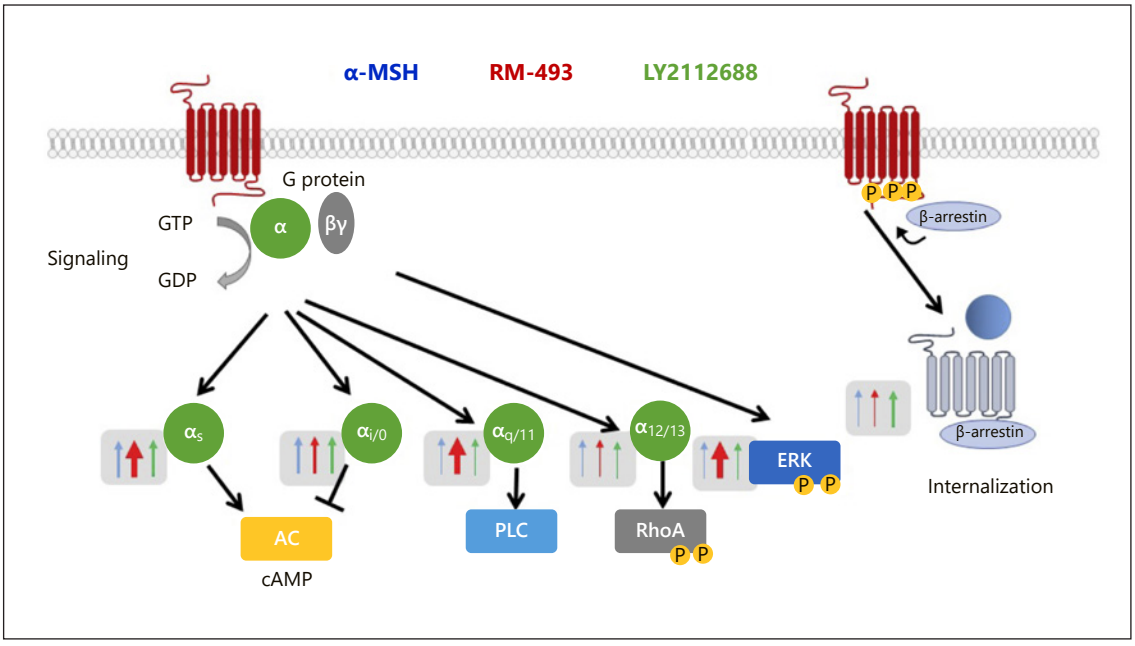

Fig. 3. Illustration of activated signaling pathways and β-arrestin recruitment after challenge with α-MSH, setmelanotide, and LY2112688 at MC4R. The MC4R can couple to all 4 G protein families, however, with different efficacies. The main signaling pathway is the activation of Gs, shown on the left side. The potency of activation with α-MSH (in blue), setmelanotide (in red), and LY2112688 (in green) is indicated by different thicknesses of arrows (own unpublished data). The effect of setmelanotide to activate Gq/11 and ERK signaling is superior to the other ligands and most likely the reason for the hyperphagia reducing effect. Activation of Gi/o and G12/13 and β-arrestin recruitment are comparable for all ligands. MSH, melanocyte-stimulating hormone.

which result in the withdrawn of rimonabant from the market.

Since CB1R is expressed not only in the brain but also in the peripheral tissue such as muscle and adipose tissue, efforts were undertaken to design a CB1R inverse agonist that acts only in the periphery. TM38837 can only target CB1R in the periphery because the penetrance in the central nervous system is reduced and acts as an inverse agonist comparable to rimonabant. Current studies suggest that the side-effect spectrum of this substance to induce psychiatric side effects was only seen at doses 100 times higher than used with rimonabant. More peripheral acting CB1R ligands are currently under investigation. A very comprehensive review [105] summarized all currently available CB1R ligands.

MC4R: The Signaling Pathway Matters

Already in the late 1980s of the last century, it became apparent that melanocortins are capable to reduce food intake [111]. The first melanocortins used were POMC-derived peptides in which the conserved binding motif at melanocortin receptor (HFRW, amino acid single letter code) exists. The design of the first potent melanocortin ligands was tested for their role in pigmentation by activating peripheral MC1R [112]. Since then, linear and cyclic peptidic MC4R ligands as well as small molecules acting specifically at melanocortin receptors were designed [106, 113]. In clinical studies, these ligands such as MK-0403 did not result in weight reduction, leading to the assumption that the MC4R is not an optimal target for obesity treatment [79], or cause severe side effects such as LY2112688 [106]. Nevertheless, more melanocortin agonists were created and recently one of them, RM-493 (setmelanotide), was highly effective in reducing of hyperphagia and body weight in POMC-deficient patients (see Proof of Concept: Pharmacological Treatment of Patients with Monogenic Obesity). After this first study, to explain why setmelanotide was more effective in weight reduction than other melanocortin receptor ligands, it was speculated that signaling pathway differences in the activation of Gs signaling, which is the primary MC4R pathway, might be involved [114]. Al-

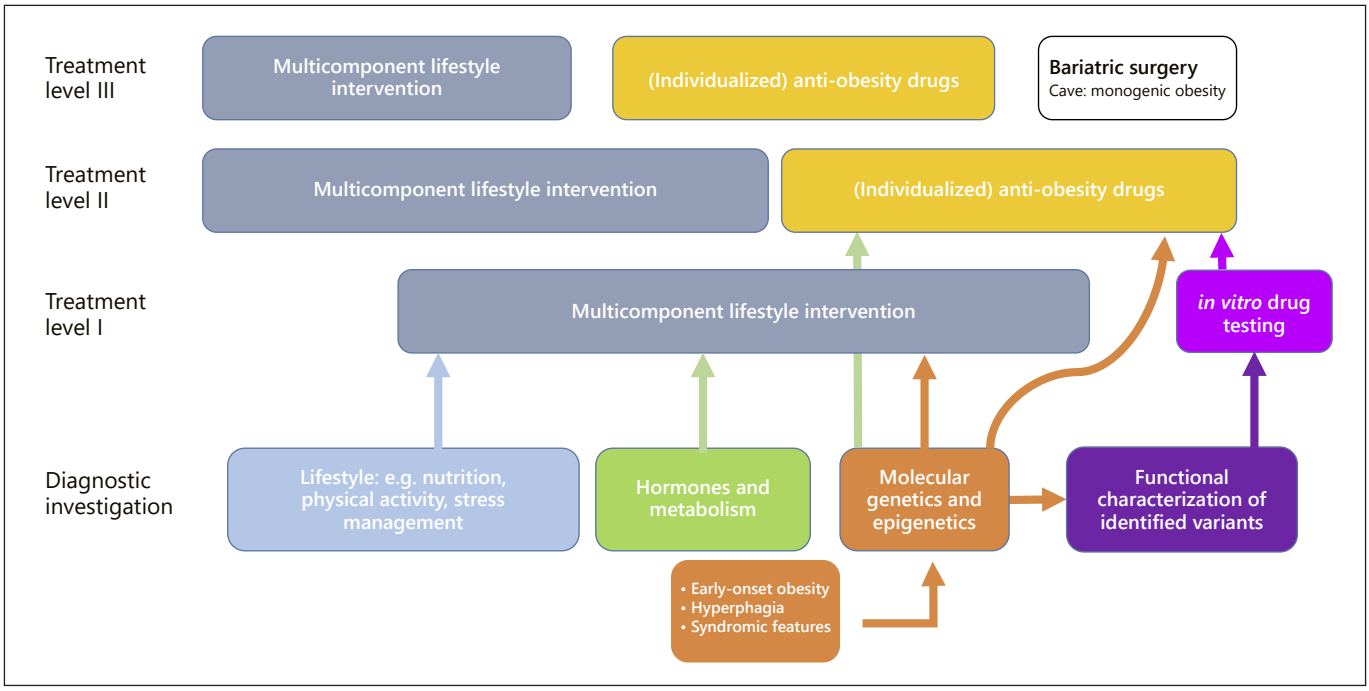

Fig. 4. To improve the treatment of nonadult patients with obesity, there is a need to adapt current strategies. We outline a multilevel diagnostic and treatment approach for children and adolescents with obesity considering the individual aspects of lifestyle, metabolism, and the genetic background. At the moment, bariatric surgery is only recommended for adolescent patients after completing growth development.

ready at this point, it has been speculated that Gq/11 signaling might play a role. This assumption was further strengthen by studies in mice, where either Gs or Gq/11 signaling in the hypothalamic paraventricular nucleus was abolished [115]. In the absence of Gq/11 signaling (active Gs signaling), activation of the MC4R causes an increase in the systolic blood pressure but not a reduction of food intake, whereas inactivated Gs signaling (active Gq/11) does not influence blood pressure but leads to a reduction of food intake [115]. These data confirm an older study where Gs signaling was disrupted by targeted deletion of CREB. In these mice, food intake was still activated by a potent MC4R ligand [116]. Characterization of the functional role of setmelanotide indeed points to a vital role of non-Gs signaling, which is most like activation of Gq/11 [108]. In-depth characterization of endogenous ligand α-MSH versus setmelanotide and LY2112688 points to profound differences in the signaling profile of the MC4R ligands, which may be the cause for the different level of efficacy at MC4R to reduce body weight in patients (Fig. 3).

GLP-1R: Peripheral and Central Action

The GLP-1R is expressed in the periphery mainly on pancreatic β-cells, in the stomach and gut [117]. In addition, GLP-1R is also expressed in various brain regions [13]. The beneficial role of GLP-1 analogs to reduce blood glucose levels in type 2 diabetic patients is known for a long time [118]. The stimulation of GLP-1R in β-cell promotes the insulin release. The central effect of insulin together with the anorectic effect of activated brain GLP-1R causes a reduction of body weight. This dual function of GLP-1R analogs such as liraglutide makes them a suitable therapeutic option in patients with common obesity and associated comorbidities [118].

Over the last years, several GLP-1R analogs were designed with the intention to enhance the half-life of GLP-1. In addition, single molecules have been created, which target more than one receptor. This includes the GIP receptor (GIPR) to take advantage of desired metabolic effects of glucose-dependent insulinotropic peptide GIP and/or the glucagon receptor to lower body weight [119] (for excellent overview, see Ref. [120]). Recent in-depth characterization of native GLP-1 compared to GLP-1 ag-

onists with potencies at GLP-1R and GIPR reveals that the superior effect of dual agonists is based on biased signaling compared to native GLP-1 with reduced rates of receptor internalization [121].

These single-molecule multiagonist ligands are a new and very promising class of antiobesity treatment options, which foster the superior effects of anorectic ligands and reduce potential side effects. In addition, a further very elegant concept of introduction of weight-regulating molecules into target cells is the so-called *Trojan-Horse* concept. Here a GPCR ligand, for example, glucagon or GLP-1, serves as a shuttle to transfer a molecule with weight-reducing capability, for example, triiodothyronine or estrogen [122, 123].

Summarizing Remarks and Outlook

It is clearly evident that a new treatment strategy is necessary to support children and adolescents with obesity to decrease especially the number of patients, in whom comorbidities like diabetes mellitus type 2 or cardiovascular diseases occur. Effective treatment regimens would be a milestone and would affect the health situation worldwide dramatically. The knowledge gathered in the last few years on different levels might allow a more sophisticated and individual approach. However, to achieve this, there is a need for a close cooperation and interaction between basic scientists and clinicians. In addition, it has to be pointed out that the treatment is only one side of the medal. New avenues of treatment will not be a breakthrough, if not in parallel prevention strategies are established.

Therefore, the overall intention is to develop an efficient and safe treatment option for children with obesity. Currently ongoing new achievements however point to a so far underestimated potential of a modular, personalized strategy that orchestrates: (i) an already established procedure such as the interdisciplinary involvement of pediatricians, psychiatrists, ecotrophologists, and many more with (ii) life-style intervention, in addition to (iii) available new basic science achievements ranging from genetic analysis (exome sequencing and single-cell RNA analysis) and pathway analysis.

As a result, a new case-sensitive strategy for each patient has to be designed (Fig. 4), which is able to react with changes in the patient's situations, for example, adaptation of treatment after initial weight loss to avoid weight regain and remain the improvement of glucose tolerance (Fig. 4). It is of importance to underline that the currently available antiobesity drugs are effective especially in patients with certain rare obesity forms. Hence, in the majority of patients, a pharmacological treatment could be an addendum to support and to stabilize the effect of a multimodal conservative treatment. The outlined strategic option should serve as a fundament for a discussion, which is essentially needed to turn the tide and establish a new and effective way to treat patients with obesity.

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Conflict of Interest Statement

The authors have no conflicting interests to declare.

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Author Contributions

Peter Kühnen, Heike Biebermann, and Susanna Wiegand wrote the manuscript and approved it.

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