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MINIREVIEWS

Melanocortin 4 receptor mutation in obesity

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Abstract

Obesity is increasingly prevalent worldwide, with genetic factors contributing to its development. The hypothalamic leptin-melanocortin pathway is central to the regulation of appetite and weight; leptin activates the proopiomelanocortin neurons, leading to the production of melanocortin peptides; these in turn act on melanocortin 4 receptors (MC4R) which suppress appetite and increase energy expenditure. MC4R mutations are responsible for syndromic and non-syndromic obesity. These mutations are classified based on their impact on the receptor's life cycle: *i.e.* null mutations, intracellular retention, binding defects, signaling defects, and variants of unknown function. Clinical manifestations of MC4R mutations include early-onset obesity, hyperphagia, and metabolic abnormalities such as hyperinsulinemia and dyslipidemia. Management strategies for obesity due to MC4R mutations have evolved with the development of targeted therapies such as Setmelanotide, an MC4R agonist which can reduce weight and manage symptoms without adverse cardiovascular effects. Future research directions must include expansion of population studies to better understand the epidemiology of MC4R mutations, exploration of the molecular mechanisms underlying MC4R signaling, and development of new therapeutic agents. Understanding the interaction between MC4R and other genetic and environmental factors will be key to advancing both the prevention and treatment of obesity.

Key Words: Leptin-melanocortin pathway; Downstream; G protein; Cyclic AMP; Mutation; Obesity syndromes; Screening; Setmelanotide

Core Tip: The leptin-melanocortin pathway regulates energy balance and body weight. Melanocortin-4 receptor (MC4R) plays a key role in this pathway by reducing hunger, inducing satiety and increasing energy expenditure. Mutations of MC4R result in obesity and hyperphagia in childhood. Setmelanotide is an MC4R agonist approved for use in obesity caused by leptin-melanocortin pathway dysfunction.

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INTRODUCTION

Body weight is maintained by a balance between energy intake and expenditure through the central hypothalamic leptin-melanocortin pathway. Among the hormones involved, leptin acts by activating the release by proopiomelanocortin (POMC) which is further cleaved into melanocortin ligands a and b; the b- melanocyte-stimulating hormone (MSH) binds and activates the melanocortin-4 receptor (MC4R) which results in reduced hunger, induction of satiety and increased energy expenditure. Variants of MC4R are associated with rare forms of recalcitrant obesity, usually manifesting in infancy or early childhood. A number of other mutations by MC4R and its proximate and downstream signals have been identified to cause syndromic obesity. Less serious disruptions by the pathway are responsible for intermediate degrees of obesity.

While syndromic or genetic causes of obesity are rare, the prevalence of obesity has been rising. A 2021 global report from the World Health Organization reported that obesity nearly tripled since 1975. As of 2016, more than 1.9 billion adults were overweight[1]. Adverse outcomes of obesity are dependent on race and ethnicity[2], which are projected to peak between 2026 and 2054, first in the United States, followed by European nations[3]. Similar findings were reported from the United Kingdom[4], South East Asia[5] and Africa[6].

A trend towards increasing obesity and overweight rates is observed even in childhood[7]. A 2017 Lancet report[8] on worldwide trends in body-mass index (BMI) showed that the rate of excess body weight was increasing in Asia. The increase in overweight outpaced the lowered prevalence of underweight[9]. The obesity pandemic in children was observed even in regions where obesity rates had plateaued before the coronavirus disease 2019 pandemic[10].

Gao *et al*[11] published a comprehensive global analysis on spatial and temporal trends in childhood overweight and obesity from 191 countries. Although genetics and environmental factors have a role in the pathogenesis, the rapid increase suggests a greater contribution by environmental factors. Since childhood obesity is the precursor of obesity in adulthood, prevention is essential[11]. The first step is to recognize the underlying lifestyle factors, which can then be addressed.

One of the proposed theories for the burgeoning rates of obesity in low and middle-income countries is the 'modernization theory'. The 'dependency/world systems theory view' proposes that external structural factors were mainly responsible for the rising obesity trends (*viz*, flooding countries with obesogenic, nutrient-poor foods). Fox *et al*[12] compared the dependency theory and modernization theory and concluded that the latter better accounted for increasing obesity. Modernization theory views that countries with progressing economies pass through phases of nutrition transition. from lower calorie, chiefly plant-based diet to a meat and processed food diet resulting in weight gain. The 2023 study by Gao *et al*[11] showed that worldwide, boys tended to be more overweight and obese than girls. Curating data from multiple cross-sectional studies from 1975 and projecting to 2020, the prevalence was reported to increase in boys from 4.1% in 1975 to 19.3% in 2016. In girls it was projected to increase from 4.6% to 17.5%. Before 2000, when assessed by income levels, the occurrence and rate of increase of obesity in both boys and girls was greater in higher income countries; however after 2020, highest rates and faster growth rates were seen in lower and middle income countries[11]. There was a global association between the rate of urbanization and childhood overweight and obesity[12].

These trends were attributed to global economic development, and cultural differences as well as intergeneration effects by malnutrition in early life. Countries with the most rapid growth shared rapid economic development, social and cultural changes leading to consumption of unhealthy ultra-processed foods. Reversal or stabilization of trends occurred due to interventions by governments[13].

CENTRAL REGULATION OF APPETITE AND WEIGHT

Weight and appetite are principally regulated by the ventromedial nucleus in the hypothalamus. Other brain areas include the arcuate nucleus, paraventricular nucleus and lateral hypothalamic area, where MC4R regulates energy metabolism by suppressing food intake and increasing energy expenditure. Identification of monogenic or non-syndromic obesity disorders revealed a complex interplay among different hormones and neurotransmitters, among which MC4R plays a central role. Appetite suppressing hormones (anorexigenic) and appetite stimulating hormones (orexigenic) communicate between the peripheral tissues and the hypothalamus[14].

Leptin, a hormone secreted by the adipose tissue binds to its receptor expressed on POMC neurons located in the arcuate nucleus of the hypothalamus. This leads to the formation of propeptide POMC, which is then cleaved to melanocortin ligands and MSH. MSH in turn activates MC4R, expressed in the paraventricular nucleus, leading to its effects on metabolism[15] (Figure 1).

MELANOCORTIN SYSTEM

POMC is an ancient gene, having been in existence for over 700 million years[16,17]. The melanocortin system has three components: Pro-peptide POMC, the melanocortin peptides and endogenous antagonists by these receptors [agouti and agouti-related protein (AgRP)][18].

Among the many genes related to obesity, MC4R is by far the most significant. It is localized in chromosome 18q22 and codes a 332 amino acid transmembrane protein[19]. The gene does not contain introns and has the highest homology with melanocortin 3 receptor (MC3R), another member of the MCR family[20]. Evolutionary analysis by MC4R showed that it underwent purifying selection, resulting in low levels of silent polymorphisms in humans[21].

Melanocortin receptors

Five melanocortin receptors (MCRs) are responsible for diverse actions[22] (Table 1) which are named 1-5 based on the sequence by their cloning. MC1R receptor, expressed in the skin and hair follicles regulates skin pigmentation. MC2R in the adrenal cortex regulates adrenal steroidogenesis. MCR3 and MCR4 are referred to as neural MCRs as they are principally expressed in the central nervous system. MC5R has a wide tissue expression, particularly the exocrine glands.

Research studies of MCR4 showed it was chiefly expressed in brain regions such as thalamus, hypothalamus and hippocampus. mRNA of MCR4 was identified in dentate gyrus, cortex and amygdala and in astrocytes. MC4R mRNA was first expressed on embryonic day 14, followed by other tissues by day 19[22]. MC3R and MC4R are chiefly expressed in the brain and MC5R in the peripheral tissues[18].

MC4R signaling

Upon binding by α-MSH to MC4R, adenylate cyclase is activated *via* G protein (guanine nucleotide-binding protein). Cyclic AMP (cAMP) is increased intracellularly, followed by activation of protein kinase A, exchange protein, extracellular regulated kinases 1 and 2 and cAMP response element binding protein. In addition, there is increased transcription by the proto-oncogene c-FOS with a simultaneous reduction of 5' AMP-activated protein kinase (AMPK) [23].

In addition to this pathway, different ligands induce different signals on binding, which are not mutually exclusive. In case of MC4R, food intake is controlled *via* biased signaling controls involving the Kir7.1, the inward rectifier potassium channel[24].

The understanding of G-protein-coupled receptor (GPCR) signaling, of which MC4R is a member, has expanded in recent years. Initially, GPCR was believed to act as a lock which was opened by the ligand, functioning as a key[25]. As the complexity of GPCR was revealed, other models were proposed, such as ternary-complex model, in which signaling was initiated by three principal components: Ligand, receptor and transducer such as GPCRs[26]. The ternary-complex model was further expanded where the receptor exists in two equilibrated states: The inactive state that cannot signal and the active state that can recruit transducers to render them functional. Finally the cubic-ternary complex model was proposed in which G-proteins and ligands were considered to belong to a common pool accessible to each receptor[27]. Metzger *et al*[28] recently suggested downstream MC4R signaling *via* β-restin recruitment and activation by MAPK. MC4R signaling was also shown to occur through MC4R/Gq/11 pathway[28].

MC4R in metabolism and energy regulation

MC4R, through its regulatory role in body weight homeostasis may influence the course of metabolic syndrome and multiple sclerosis *via* its anti-inflammatory and neuroprotective effects[29]. It also plays a role the regulation of glucose homeostasis, erectile function and cardiovascular tone[30].

The melanocortin peptides act through central MC4R to regulate appetite, body weight and energy expenditure[30]. Despite early evidence that intracerebrovascular administration of α-MSH and adrenocorticotropic hormone reduced food intake in rats, the critical importance of MC4R in regulation of energy homeostasis was not fully recognized until the mid 1990s[22]. Hypothalamic melanocortinergic neurons exert a tonic inhibitory action on feeding. Disruption of this pathway led to changes in food intake, suggesting that MC4R which is highly expressed in PVC is the primary mediator of melanocortin regulation[31], playing a pivotal role in the complex neural regulation of appetite[32]. The role of MC4R in energy homeostasis has been identified from mice knock out models which showed a gene dosage effect[33]. Energy balance is a result of reduced food intake (responsible for 60% of the effect) while 40% is due to changes in the expenditure of energy. Thermogenesis is regulated *via* activation of sympathetic nervous system-BAT-uncoupling protein 1 axis and hypothalamic-pituitary-thyroid axis[34].

To summarize, in states of starvation, leptin levels are low, POMC neuronal activity is reduced and AgRP neuronal activity is increased resulting in reduced MC4R signaling. In the fed state, POMC neurons are activated along with inhibition of AgRP neurons and increased MC4R signaling; all these resulting in diminished food intake and increased expenditure of energy[22].

Table 1 Melanocortin receptors

Name	Tissue expression	Principal actions
MC1R	Skin, hair follicles	Regulates pigmentation
MC2R	Adrenal cortex	Regulates adrenal steroidogenesis
MC3R	Central nervous system	Regulates energy homeostasis
MC4R	Central nervous system	Regulates energy homeostasis
MC5R	Exocrine glands; wide expression	Regulates exocrine gland secretion

MCR: Melanocortin receptors.

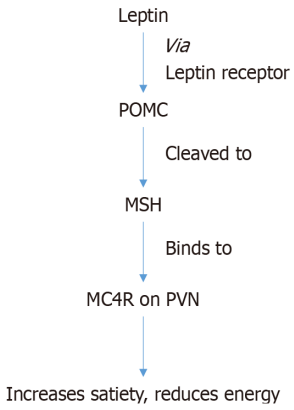

Figure 1 Overview of the leptin-melanocortin pathway. POMC: Proopiomelanocortin; MSH: Melanocyte-stimulating hormone; MC4R: Melanocortin 4 receptor; PVN: Paraventricular nucleus.

MC4R regulates energy homeostasis in other mammals and in lower vertebrates as well, including chickens and rainbow trout[22].

In a Chinese study, significant interactions were observed between variants near MC4R gene and obesity-related phenotypes (rs12970134), which was modified by physical activity[35-37].

MC4R MUTATIONS

Spontaneous and genetically induced variations of the melanocortin system showed the importance of this pathway in the regulation of body weight[38]. The first gene to be deleted in the mouse was the MC4R, which led to obesity. MC4R -/- phenotype was characterized by hyperphagia, adipocyte mass increase, increased growth and normal lean body mass [39]. The MC4R +/- model showed an intermediate phenotype in terms of body weight and food ingestion, supporting a gene dosage effect. Ste Marie *et al*[40] reported that inhibition of MC4R affected energy balance independent of food intake[40]. Therefore obesity in MC4R -/- mice was due to both increased food intake and diminished expenditure of energy[38]. Mutations of other genes in the melanocortin system such as MC3R and POMC also led to obesity.

Molecular classification by MC4R mutations

Identification of a variant MC4R in an obese individual does not necessarily imply that obesity is caused by the mutation [22]. Additional supporting information must be obtained such as familial co-segregation of the mutation and obesity; *in vitro* functional characterization by the mutant receptor confirms its causal role[41].

Classification of MC4R mutations is based on the receptor life cycle[22]: (1) Class I: Null mutations: impaired protein synthesis and/or enhanced protein degradation leads to low levels of protein (*e.g.* nonsense mutations); (2) Class II: Mutant receptors are produced in the cell but are misfolded and retained in the endoplasmic reticulum. This forms the largest group of mutations; (3) Class III: Binding defective mutants are expressed on the cellular surface but cannot bind with the ligands due to impaired binding capacity and/or affinity. Therefore signaling is impaired; (4) Class IV: Signaling-defective mutants properly reach the cell surface and bind the ligand, but transmit the signal with lower efficacy or not at all; and (5) Class V: Variants of unknown defect do not fit into any of the above.

More recently, Courbage *et al*[42] showed that MC4R variants can impact functions in three ways: (1) High: Nonsense, frameshift and splice variants, missense variants and rare variants with conclusive functional tests; (2) Moderate: Missense variants that are predicted as 'damaging' by at least four of the seven prediction tools; and (3) Low: Missense variants predicted as 'less likely damaging' by at least four of the seven prediction tools. The classification was used for

the analysis of 6467 subjects to assess the significance of heterozygous variants on the leptin-melanocortin system among the severely obese[42].

Feeding behavior in humans harboring MC4R mutants

To assess the prevalence and phenotypic effects of MC4R mutants, 20537 electronic medical records and genomics (eMERGE) participants with MC4R coding region sequencing data were studied; in addition 77454 independent persons with genome-wide genotyping data at this locus were also studied. The authors identified 125 coding variants (*n*: 1839 eMERGE participants), including 30 variants that were unreported earlier[43]. MC4R associated obesity was the most common form of monogenic obesity spectrum among 170 rare genetic variants associated with hyperphagia and early onset obesity[44,45].

CLINICAL PRESENTATION

The genotype-phenotype association of heterogeneous variants in leptin-melanocortin pathway was studied in 6467 subjects (6347 probands and 120 relatives)[42]. Specifically the MC4R gene was sequenced for 1165 subjects of the 1486 probands. To assess the combined effect of heterozygous variants on phenotype, subjects were chosen who were sequenced on the five genes, *viz LEP*, *LEPR*, *POMC*, *PCSK1* and *MC4R*. BMI of subjects with combined heterozygous variants was higher than in those with a single heterozygous variant (BMI65.2+/-13.2 kg/m^2 *vs* 49.0 +/-9.1 kg/m^2, $P < 0.01$)[42].

Body weight and growth

Aggregated data from 200 MC4R genetic mutations among nearly 1000 patients[46], (homozygous or compound heterozygous) showed early-onset severe obesity.

In heterozygous carriers, obesity was variable: Children carrying heterozygous mutation had similar BMI to wild-type children with obesity. In contrast, adults with heterozygous carriers had higher BMI compared to wild type patients with obesity. Gender differences were also observed; BMI was higher in middle aged women compared to middle aged men.

Where information on age of obesity was available (n = 104) mean age of onset of obesity was at 1.2 years old in homozygous carriers and 3.8 years old in those with heterozygous mutation. Children had an initial accelerated height, although the final height was lower than average.

Eating behavior

Hyperphagia was common in patients with MC4R mutations. When recorded (n = 175), hyperphagia was observed in 95% (100% in homozygous patients and 95.1% in heterozygous patients).

Other features

There was no specific change in the course of puberty and ultimate fertility in patients with MC4R mutations. Data on cognitive function was available in 30 cases; nine had mild disability: Speech delay, motor retardation, and mild mental retardation. Acanthosis nigricans was observed in 31%-41% of subjects.

Metabolic abnormalities

Hyperinsulinemia was observed more often in children (55%) than in adults (20%). Type 2 diabetes mellitus was reported in 16.9% of the cohort (n = 148). Dyslipidemia was present in 33% of mutation carriers (n = 20/60: 32% children and 34.8% adults). Advanced bone age and greater bone density were also reported.

In Qatar two subjects with MC4R mutation identified reduced expression of MC4R on the cell surface, intracellular retention by the MC4R protein, and failure to activate downstream signaling of the MC4R[47].

The obesity phenotype can be modified by the interaction of other genetic factors which may either be protective or deleterious, as well as by environmental factors[48].

SCREENING FOR MC4R MUTATIONS

Currently there are no established guidelines for newborn genetic screening. However with the availability of drugs to treat subjects with MC4R mutations (setmelanotide)[49,50], a case is made for childhood genetic screening in obesity. In childhood addition, genetic analysis by MC4R mutations could help predict responsiveness to drug treatment[51,52].

MANAGEMENT OF OBESITY DUE TO MC4R MUTATIONS

An understanding of the MC4R receptor, its expression and downstream signaling enabled the identification of agonists which mimic its physiological actions. Initially, analogues were hampered by MC4R activation of sympathetic nervous system, thereby affecting blood pressure and heart rate[53]; sexual arousal was another serious side effect. Development of a number of molecules was stalled early due to adverse effects including tachycardia, hypertension, sexual arousal and

skin pigmentation driven by MC1R activation[53]. These were largely due to the complex intracellular signaling by MC4R. It now seems likely that internalization of agonist induced MC4R could be the key element in the control of energy homeostasis.

Setmelanotide

Setmelanotide, an MC4R agonist has been approved for use in the treatment of obesity due to MC4R mutations. It showed no adverse effects on heart and blood pressure in humans, while having a substantial weight loss effect, with a favorable therapeutic index[53].

Animal studies published in 2016 showed that setmelanotide had the potential to be used as a replacement therapy for rare syndromic forms of obesity due to impaired POMC neuronal function[54]. Coulter *et al*[55] proposed that setmelanotide is a potential treatment for obesity caused by mutations of POMC system[55].

A number of case series showed that setmelanotide was effective in genetic and syndromic forms of obesity[49,50]. The Anti-Obesity Medications and Investigational Agents: An Obesity Medicine Association Clinical Practice Statement 2022 published guidelines for the use of setmelanotide along with other anti-obesity agents[56].

Setmelanotide is indicated for chronic weight management in adult and children aged 6 years or older when obesity is due to *POMC*, *PCSK1*, or *LEPR* deficiency. The diagnosis must be based on genetic testing which shows 'variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or by variant of uncertain significance'. The drug is discontinued if, after 12–16 weeks of treatment, there is no weight loss by 5% from baseline or 5% baseline BMI for children with continued growth potential.

Setmelanotide is started at a dose of 2 mg subcutaneously once daily for 2 weeks with monitoring for gastrointestinal (GI) adverse reactions. If this dose cannot be tolerated, it can be reduced to 1 mg once daily. If the lower dose is tolerated, uptitration to 2 mg can be attempted for additional weight reduction, with a further increase to 3 mg a day; however the lowest tolerable dose must be used for maintenance treatment.

In children between the ages of six and 12, the drug is begun at a dose of 1 mg injected subcutaneously once daily for 2 weeks, while monitoring for adverse GI events. If the dose is not tolerated, it must be reduced to 0.5 mg once daily. If it is tolerated and for additional weight reduction, the dose can be increased to 1 mg once daily. It can be further increased to 2 mg once daily. In case the higher dose is not tolerated, it can be reduced to 1 mg once daily. The highest dose that can be given is limited to 3 mg once daily.

Common side effects, seen in about 25% of subjects consist of injection site reactions, skin hyperpigmentation, nausea, headache, GI effects, depression, upper respiratory tract infection, and spontaneous penile erection.

Potential for newer agents

In addition to MC4R agonists and antagonists, inverse agonists are potential areas for investigation; these include AgRP and its mimics for MC4R[27] (Table 2).

Table 2 Drugs for use in genetic forms of obesity

Drug	Analogue
Setmelanotide	Analogue of α-melanocyte melanocyte-stimulating hormone
Metreleptin	Human leptin analogue
Liraglutide	Glucagon-like peptide-1 analogue
Semaglutide	Long-acting glucagon-like peptide-1 analogue
Others	

CONCLUSION

Identification of monogenic obesity syndromes due to dysfunction of MC4R clarified the role of leptin-melanocortin pathway in regulating energy balance[57]. Impaired activity of MC4R led to rare monogenic forms of obesity whereas gene polymorphisms were related to weight gain and metabolic syndrome. Other MC4R gene polymorphisms were protective against obesity. MC4R could also have anti-inflammatory and neuroprotective effects[57]. Understanding the expression and downstream effects of MC4R resulted in the development of agonists such as setmelanotide which is approved for treatment of obesity due to POMC disorders[56]. In addition to MC4R agonists and antagonists, inverse agonists could be developed such as AgRP and its mimics for MC4R[27]. Early identification of genetic forms of obesity helps in tailoring management from a young age, which can prevent progressive metabolic abnormalities and improve long term prognosis[52]. Future research on MC4R and its role in obesity should focus on studying larger and more diverse population groups. This enhances knowledge of the MC4R signaling pathways, and aids in the development of personalized and effective therapies. Finally, interdisciplinary collaboration combining genetics, endocrinology, and pharmacology is necessary for translation into clinical applications and better patient outcomes.

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