REVIEW

Melanocortin Pathways: Suppressed and Stimulated Melanocortin-4 Receptor (*MC4R*)

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Summary

Leptin-melanocortin pathway plays an essential role in the body weight regulation. Enhanced melanocortin signaling in the hypothalamus results in both decreased food intake and increased energy expenditure. The discovery of monogenic obesities with dysfunction of melanocortin-4 receptor (MC4R) greatly contributed to understanding of energy balance regulation. This review presents phenotypical characterization and prevalence of the MC4R gene mutations. Genome-wide association studies revealed that MC4R gene is significantly related not only to monogenic obesities but also to common obesity. An interaction of variants in the MC4R gene with fat mass and obesity associated (FTO) gene significantly increases the risk for obesity, particularly in adolescence. On the other hand, about 15 % of the MC4R gene variants result in a gain of function that protects against obesity and is associated with favorable metabolic profile. Long-term attempts to activate the MC4R have recently been finalized by a discovery of setmelanotide, a novel specific MC4R agonist that is devoid of untoward cardiovascular side-effects. The employment of specific MC4R agonists may open new horizons not only in the treatment of rare monogenic obesities but also in some common obesities where stimulation of MC4R could be achieved.

Key words

Melanocortin-4 receptor (MC4R) function • Monogenic obesity • Common obesity • Gene polymorphisms • MC4R agonists

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Introduction

Both melanocortin peptides derived from pro-opiomelanocortin, α-melanocyte stimulating hormone (α-MSH) and adrenocorticotrophic hormone were originally related to regulation of pigmentation and adrenocortical hormones secretion (Anderson *et al.* 2016). However, the cloning of genes that encode melanocortin receptors in 1992 contributed to reveal an additional role of melanocortin system in the regulation of energy homeostasis (Mountjoy *et al.* 1992). Several hormones affect energy balance through the melanocortin pathways. The effect of leptin, cholecystokinin, fatty acids, ghrelin and serotonin on energy balance is dependent on melanocortin system while the effect of peptide YY, pituitary adenylate cyclase-activating peptide and glutamate on energy balance is independent on melanocortin system (Shen *et al.* 2017). Adipose tissue derived hormone leptin induces negative energy balance by stimulating α-MSH and melanocortin-4 receptor (*MC4R*) (Friedman 1997, Kask *et al.* 1998). Increased melanocortin signaling in hypotalamus leads not only to decreased food intake but also increases sympathetic nervous system outflow to skeletal muscle, energy expenditure and physical activity (Gavini *et al.* 2016). A recently published review emphasized the role of the brain *MC4R* for activation of sympathetic nervous system in hypertension (Da Silva *et al.* 2019). On the other hand, a reduced brain-

melanocortin activity increases fat mass in experimental animals through signals conveyed by vagus nerve (Holland *et al*. 2019). In experimental animals agouti-related peptide (AGRP) suppresses *MC4R* activity. An ectopic expression of AGRP in mouse leads to obesity and inhibition of eumelanin pigment synthesis (Fan *et al*. 1997) as AGRP acts as an antagonist of both *MC4R* and *MC1R*. A quantitative mass spectrometry for human melanocortin peptides *in vitro* and *in vivo* also suggested an important role of β-MSH and desacetyl α-MSH in regulation of energy homeostasis (Kirwan *et al.* 2018). These authors characterized sequences of more than 20 hypothalamic peptides, most of them being involved in regulation of energy balance. This finding supported previous clinical studies which had demonstrated that children with early onset obesity carrying the Tyr221Cys variant of β-MSH were hyperphagic and showed increased linear growth, similarly as children with *MC4R* mutations (Lee *et al.* 2006).

Suppressed *MC4R* activity in monogenic obesities

Mutations in genes involved in leptin-melanocortin pathway result in usually early-onset fat accumulation. Cases of severe obesity involve mutations in leptin (*LEP*), leptin receptor (*LEPR*), proopiomelanocortin (*POMC*), β-MSH, prohormone convertase (*PCSK*) and *MC4R* genes. Mutations of *MC4R* are most common forms of monogenic obesities and include mostly missense mutations with different losses of function (Farooqi *et al*. 2003). Farooqi *et al*. (2003) defined MC4R syndrome characterized by early-onset obesity, increased linear growth, increased bone mineral density, hyperphagia and hyperinsulinemia. In our Czech cohort, as in several others, *MC4R* mutations were not associated with hyperinsulinemia and increased bone mineral density (Hainerová *et al*. 2007, Dubern *et al*. 2001, Lubrano-Berthelier *et al*. 2004, Mergen *et al*. 2001). Our study (Hainerová *et al*. 2007) as well as that of Hebebrand *et al.* (2004) did not find binge eating as a characteristic phenotype of *MC4R* gene mutations (Branson *et al.* 2003). The prevalence of *MC4R* mutations greatly varies in different populations, from 0.5 to 5.8 %. Until 2013, 166 different obesity-associated mutations of *MC4R* have been reported (Hinney *et al.* 2013). Among Czech children with early-onset obesity the prevalence of *MC4R* mutations was 2.4 % (Hainerová *et al*. 2007) whereas that in obese Slovak children was 0.7 %, one of the lowest frequencies in Europe (Stanikova *et al.* 2015).

Similarly to *MC4R* mutations in humans, disruption of the *MC4R* in mice resulted in hyperphagia, obesity and increased linear growth (Huszar *et al.* 1997). Gavini *et al.* (2019) has recently described a new trafficking C2-domain protein (C2CD5) located in the paraventricular hypothalamus that involves in *MC4R* endocytosis and energy balance regulation. The loss of functional C2CD5 protein in knockout mice increased the number of non-functional *MC4R* at the cell surface and resulted in increased food intake in comparison with wild-type mice. In addition, mice lacking C2CD5 exhibited a lower reduction of food intake in response to treatment with *MC4R* agonist. Diet-induced obesity in mice was shown to be associated with blunted expression of C2CD5 in the hypothalamus.

MC4R genes polymorphisms leading to weight gain

Genome-wide association studies revealed fat mass and obesity associated (*FTO*) and *MC4R* genes as the first genes related to common obesity (Frayling *et al.* 2007, Loos *et al.* 2008). Obesity risk associated with *MC4R* polymorphisms largely differs between studies carried out in different populations. The risk of severe obesity associated with rs17782313 variant was particularly expressed in childhood (Loos *et al.* 2008). The risk ratio in 10,583 children from three studies reached 1.30 (1.22-1.41). *MC4R* variants rs17782313 and rs12970134 showed strong association with adiposity measures in Indian population (Dwivedi *et al.* 2013). On the other hand, *MC4R* variant rs12970134 was associated with adiposity measures in Czech women with polycystic ovary syndrome, but not in normoglycemic women and those with type 2 or gestational diabetes (Bradnová *et al.* 2015). A stronger association of *MC4R* polymorphisms with adiposity was confirmed in children. A meta-analysis of 61 studies that included 80,957 subjects with rs17782313 variant of *MC4R* and 220,223 controls (Xi *et al.* 2012a) showed a clear association with obesity risk (risk ratio = 1.18, $p<0.001$). The association of the *MC4R* rs17782313 C allele with obesity and fat mass deposition was more expressed in males than in females (Cauchi *et al.* 2009). The interaction of *MC4R* rs17782313 and *FTO* rs1421085 risk alleles was demonstrated in cohorts of Finnish adolescents (n=4,762) and French adults

(n=3,167) (Cauchi *et al.* 2009). Subjects carrying *FTO* and *MC4R* risk alleles (7-10 % of studied populations) had a 3-fold increased risk of developing obesity during adolescence. However, such risk declined to 1.8-fold in adulthood. The presence of three or more high-risk alleles of *FTO* and *MC4R* genes resulted in 4-fold increase in the risk for obesity in Greek children and adolescents (Lazopoulu *et al.* 2015). A recent Chinese study confirmed combined effect of *FTO* and *MC4R* gene polymorphisms in children and adolescents (Yang *et al.* 2019). Subjects carrying genotypes of *FTO* rs9939609, *MC4R* rs17782313 and *MC4R* rs12970134 had 2.45-fold risk for developing obesity compared to subjects without such polymorphisms.

Reduced function of *MC4R* and metabolic syndrome

Loss of function in subjects carrying mutations or variants of the *MC4R* is associated with obesity. Such subjects may therefore be predisposed to develop metabolic syndrome. Adipose tissue hormone adiponectin possesses antiatherogenic and antiinflammatory properties and increases insulin sensitivity (Nedvídková *et al.* 2005) and hypoadiponectinemia in *MC4R* deficiency may contribute to development of metabolic syndrome. Trevaskis *et al.* (2007) demonstrated that *MC4R* deficiency in *MC4R* knock-out mice is associated with low levels of adiponectin, insulin resistance and inflammation of adipose tissue. However, an association of the *MC4R* function with metabolic syndrome is not unequivocal because of the decreased sympathetic nervous activity and lower blood pressure accompanying loss of the receptor function. In order to investigate an association of the *MC4R* rs12970134 and rs17782313 variants with metabolic syndrome we studied a cohort of 1,443 adolescents aged 13.0-17.9 years (Dušátková *et al.* 2013). Our cohort included subjects in different weight categories: underweight (n=60), normal weight (n=713), overweight (n=194) and obese (n=476). The prevalence of metabolic syndrome in this cohort was 7.7 %. *MC4R* rs 17782313 variant was significantly associated with metabolic syndrome (OR=1.51, p=0.009). The association of the *MC4R* rs12970134 variant with metabolic syndrome was weaker (OR=1.40, p=0.035). Increased risk of metabolic syndrome in the studied *MC4R* variants is probably mediated by their effects on abdominal obesity. It was demonstrated, however only in boys, that both *MC4R* variants were related to abdominal circumference (Dušátková *et al.* 2013). Liu *et al.* (2010) studied a cohort of 1,890 European and African-American youth and observed a significant association of the rs17782313 variant with waist circumference in both genders.

Several studies investigated a relationship between the function of the MC4R and individual components of metabolic syndrome. MC4R activation increases sympathetic nervous activity with subsequent increase in blood pressure and pulse rate (DaSilva *et al.* 2019). On the other hand, mutations characterized by the *MC4R* deficiency in humans are associated with lower blood pressure, less frequent hypertension, lower heart rate and decreased diurnal urinary excretion of catecholamines (Greenfield *et al.* 2011).

Both variants of the *MC4R*, rs17782313 and rs17700633, were associated with lower high-density lipoprotein cholesterol (Kring *et al.* 2010) whereas only polymorphism of rs17782313 was related to higher serum triglyceride levels (Katsuura-Kamano *et al.* 2015, Fernandes *et al.* 2015).

Studies on association of *MC4R* with type 2 diabetes yielded conflicting results. However, a meta-analysis of 19 studies which included 123,373 individuals (comprising 34,195 cases and 89,178 controls) revealed that the rs17782313 *MC4R* polymorphism was significantly associated with the risk of type 2 diabetes in this large cohort (Xi *et al.* 2012b).

MC4R gene polymorphisms protecting against obesity

Several polymorphisms of *MC4R* have been found to be related to favorable metabolic profile. Initially the V103I polymorphism of *MC4R* was associated with decreased risk for developing obesity (Geller *et al.* 2004, Heid *et al.* 2005, Young *et al.* 2007). Later on, large meta-analyses demonstrated that V103I and I251L *MC4R* variants reduce the risk of obesity by 21 % in 103I-allele carriers and by 50 % in 251L-allele carriers (Loos 2011). Meta-analysis of 37 studies conducted by Wang *et al.* (2010) included 55,195 subjects of different ethnic groups with 19,822 obese cases and 35,373 nonobese controls. In this large cohort subjects with *MC4R* V103I polymorphism had 21 % lower risk for obesity. The prevalence of V103I polymorphism was rather low ranging from 2 % to 5 % in different populations. It should be pointed out that Val103Ile polymorphism of *MC4R* was characterized by

increased metabolic rate and high rates of glucose oxidation with low fasting serum levels of free fatty acids (Rutanen *et al.* 2004). The common single nucleotide polymorphism (SNP) of the *MC4R* gene rs1350341 was associated with lower visceral fat accumulation and higher postprandial carbohydrate accumulation (Adamska-Patruno *et al.* 2019). The joint effect of *MC4R* and *LEP* polymorphisms on reduced body weight was demonstrated in females (Hart Sailors *et al.* 2007). Moreover, subjects carrying both *MC4R* 103I and *LEP* A19 alleles exhibited lower BMI over the 9 years of follow-up.

A recently published paper by Lotta *et al.* (2019) described 61 variants of *MC4R* in half million people in the United Kingdom. These variants greatly differed with regard to function of the *MC4R*; 77 % resulted in a loss of function and 15 % in a gain of function. The gain of function in *MC4R* variants was associated with protection against obesity and exhibited signaling bias for the recruitment of G protein-independent β-arrestin pathways rather than for the recruitment of canonical G protein-dependent cyclic adenosine monophosphate (cAMP) production. About 6 % of the studied population carried BMI-lowering genetic variants. Carriers of two alleles promoting gain of function due to β-arrestin signaling exhibited 50 % lower risk for developing obesity, type 2 diabetes, and coronary artery disease. On the other hand, the gain of *MC4R* function mediated by cAMP did not affect the risk of obesity and cardiometabolic diseases and was associated with an increase in systolic blood pressure.

MC4R and weight loss

Hereditary factors play an important role in weight loss and weight loss maintenance (Hainer *et al.* 2000, Hainer *et al.* 2008). Similar weight loss in response to a short-term weight management was observed in *MC4R* mutation carriers and non-carriers (Hainerová *et al.* 2007). Reinehr *et al.* (2009) confirmed ability to lose weight in response to a lifestyle intervention in children with *MC4R* mutations with reduced receptor function. However, these children were unable to maintain the weight loss. In a 20-year-old male homozygous *MC4R* mutation carrier a stable body weight was achieved over one year when the patient was treated with anti-obesity drug sibutramine (Aldhoon Hainerová *et al.* 2011). In the study of Kochkapoor *et al.* (2016), surprisingly, children carrying *MC4R* risk alleles achieved greater weight loss in response to a short-term lifestyle intervention compared to non-carriers, however their ability to maintain weight loss was limited in the long-term.

Huvenne *et al.* (2016) reviewed studies on bariatric surgery in patients with heterozygous *MC4R* mutations. The weight loss in 18 mutation carriers was similar as that in noncarriers. On the other hand, a 18-year-old patient with complete *MC4R* deficiency due to homozygous mutation regained his preoperative body weight after initial weight loss and gained additional 6.5 kg (+7 %) at 12 months after laparoscopic adjustable gastric banding combined with truncal vagotomy (Aslan *et al.* 2011). Valette *et al*. (2012) evaluated weight loss 3, 6 and 12 months after bariatric surgery in patients with functional *MC4R* mutations and in *MC4R* SNPs. Both *MC4R* mutations and SNPs did not affect weight loss and body composition over the studied period. Recently, the effect of *MC4R* polymorphism on body weight and weight loss after bariatric surgery has been studied in 141 women with extreme obesity (Resende *et al.* 2018). Women with the rs17782313 *MC4R* polymorphism (n=65) exhibited higher pre-surgical body weight and BMI than non-carriers (n=76). Twenty four months after bariatric surgery the BMI<30 kg/m^2 was achieved in 17 % of the risk allele carriers and in 37 % in non-carriers. Significantly more risk allele carriers than non-carriers maintained BMI>35 kg/m^2 (51 % vs. 32 %) after surgery as a marker of the treatment failure.

Anti-inflammatory and neuroprotective effects of *MC4R* in multiple sclerosis

MC4R activity in multiple sclerosis was broadly studied by Kamermans *et al*. (2019). *MC4R* are expressed in astrocytes, cells which reflect disease progression. *MC4R* immunoreactivity was significantly increased in active lesions of multiple sclerosis compared to controls. An activation of *MC4R* in astrocytes exhibited significant antiinflammatory and neuroprotective effects *in vitro*. The treatment with *MC4R* agonist setmelanotide significantly reduced expression of reactive astrocyte markers induced by the proinflammatory cytokines tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). On the other hand, setmelanotide increased production of antiinflammatory interleukin-6 and interleukin-11. Neuroprotective effects of *MC4Rs* were also studied by Benjamins *et al.* (2018) who revealed that *MC4Rs* located on brain oligodendroglia and oligodendroglial precursor

cells are engaged in activation of pathways that protect against damage of these cells in multiple sclerosis.

MC4R agonists

During past decades there have been several attempts to develop specific *MC4R* agonist in order to treat obese patients with disrupted function of *MC4R*. Both experimental and clinical studies demonstrated reduction in food intake and body weight, however, with simultaneous activation of sympathetic nervous system with subsequent increase in blood pressure and heart rate and activation of sexual arousal (Sharma *et al.* 2019). Five MC4R agonists have so far been investigated in humans (Sharma *et al.* 2019).

Eight-week treatment with a novel *MC4R* agonist setmelanotide (RM 493) reduced food intake by 35 %, induced weight loss by 13.5 % and reduced insulin resistance in diet-induced obese macaques without concomittant increase in blood pressure and heart rate (Kievit *et al.* 2013). No increase in blood pressure and pulse rate was observed in obese subjects who received subcutaneous infusion of setmelanotide over 72 h (Chen *et al.* 2015). Moreover, in this trial setmelanotide compared to placebo significantly increased resting energy expenditure and fat oxidation. Later setmelanotide was evaluated on mutant *MC4Rs* in cells as well as in experimental studies and clinical trials (Collet *et al.* 2017). Setmelanotide was about 10 to 20-fold more efficient ligand than endogenous α-MSH at wild type *MC4R*. Mice with diet-induced obesity were treated with setmelanotide. Wild type (*MC4R*+/+) and heterozygous (*MC4R*+/-) mice on high fat diet lost weight, while homozygous null (*MC4R*-/-) mice failed to lose weight in response to setmelanotide treatment. Similar results were obtained in a clinical trial. Patients with heterozygous *MC4R* deficiency and obese controls were treated either with setmelanotide or placebo infusions for 28 days. *MC4R* deficient subjects lost 3.48 kg after setmelanotide vs. 0.85 kg after placebo. Obese controls treated with setmelanotide lost 3.07 kg, while obese subjects obtaining placebo gained 0.90 kg. Setmelanotide treatment should be indicated in patients with loss of function mutations within the *MC4R* pathway as *leptin, leptin receptor, proopiomelanocortin, prohormone convertase 1* and *MC4R* genes (Ayers *et al.* 2018). Successful treatments of severely obese patients with both proopiomelanocortin deficiency and leptin receptor deficiency by setmelanotide were reported by Kuhnen *et al.* (2016) and Clément *et al.* (2018). Trials investigating an employment of setmelanotide in the treatment of syndromic obesity, e.g. Prader-Willi syndrome, have also been suggested. Moreover, some individuals with common obesity may be sensitive to setmelanotide treatment due to reduced *POMC*-ergic tone (Muller *et al.* 2016). However, a minor non-specific stimulation of the *MC1R* by setmelanotide should be seriously considered concerning stimulation of melanocytes. Addition of setmelanotide to GLP-1 receptor agonist liraglutide in the treatment of diet-induced obesity in mice amplified beneficial effect of monotherapy on weight loss, glycemic control and cholesterol profile (Clemmensen *et al.* 2015). The potential use of this novel combinatorial approaches may open new horizons in the treatment of obesity (Muller *et al.* 2016).

Conflict of Interest

There is no conflict of interest.

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