

MC4R and MC3R Mutations

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Beatrice Dubern

Dr Beatrice Dubern, MD, PhD is assistant professor in the department of pediatric nutrition and gastroenterology at Trousseau hospital in Paris, France.

Introduction

The leptin/melanocortin pathway plays a key role in the hypothalamic control of food intake. It is activated following the systemic release of the adipokine leptin (LEP) and its subsequent interaction with the leptin receptor (LEPR) located on the surface of neurons of the arcuate nucleus region in the hypothalamus (figure 1).

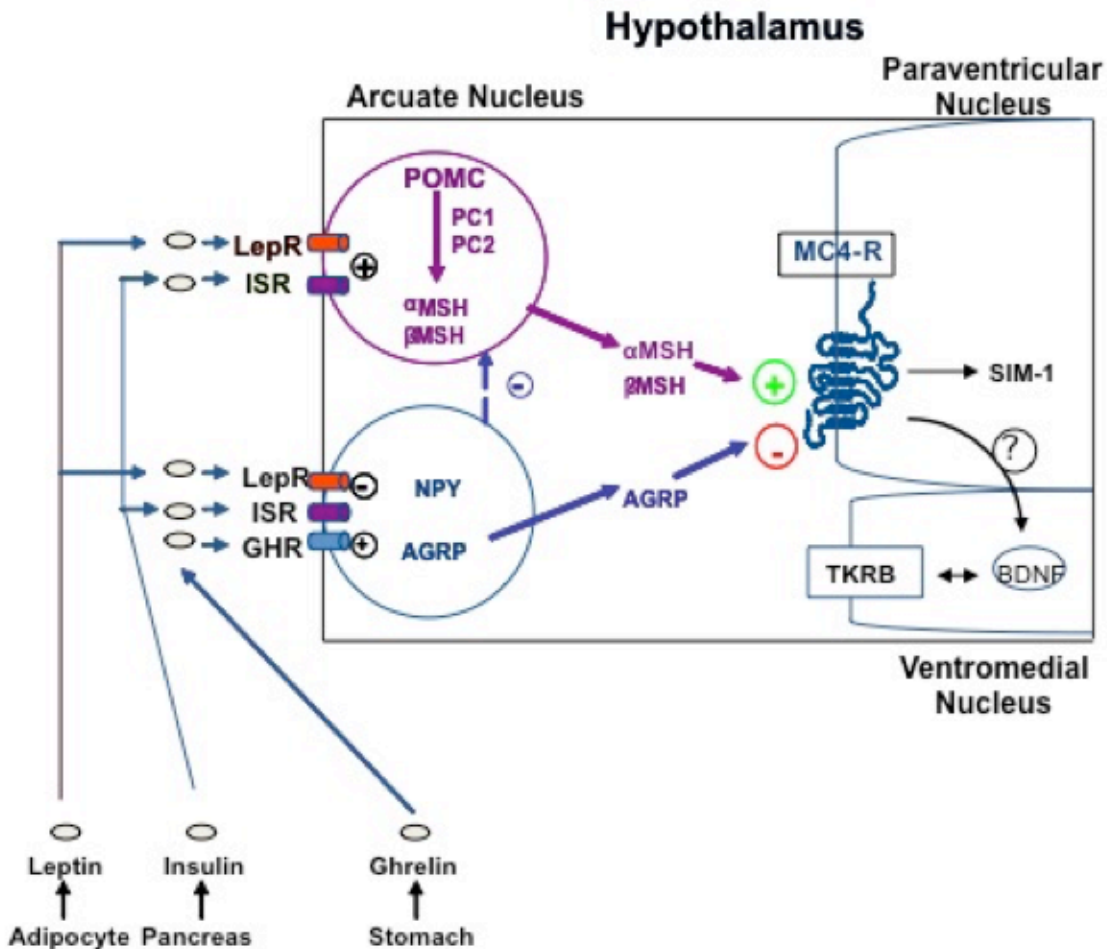


Figure 1: The leptin/melanocortin pathway

Neuronal populations propagate the signaling of various molecules (leptin, insulin, ghrelin) to control food intake and satiety. POMC-neurons in the arcuate nucleus are activated by leptin and insulin and produce the α -melanocyte stimulating hormone (α -MSH), which then activates the MC4R receptor in the paraventricular nucleus resulting in a satiety signal. The downstream roles of SIM1, BDNF and TKRB are currently being explored. A separate group of neurons expressing NPY and AGRP produce molecules that act as potent inhibitors of MC4R signaling. Several mutations of those genes involved in the leptin/melanocortin pathway are responsible for early-onset and severe obesity. POMC, proopiomelanocortin; LepR; leptin receptor; ISR, insulin receptor; GHR, ghrelin receptor; NPY,

neuropeptide Y; AGRP, agouti-related protein; SIM1, single-minded 1; BDNF, brain-derived neurotrophic factor; TRKB, tyrosine kinase receptor; PC1 and 2, proconvertase 1 and 2.

The downstream signals that regulate satiety and energy homeostasis are then propagated via proopiomelanocortin (POMC), cocaine-and-amphetamine-related transcript (CART), and the melanocortin system (1). While POMC / CART neurons synthesize the anorectic peptide α -melanocyte stimulating hormone (α -MSH), a separate group of neurons express the orexigenic neuropeptide Y (NPY) and the agouti-related protein (AGRP), which acts as a potent inhibitor of melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors.

Five melanocortin receptors are described (MC1R to MC5R). In periphery, POMC derived ACTH is a key factor of the adrenal axis via MC2R. In the skin, melanocortins have paracrine action via MC1R and play a key role in pigmentation. Melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors, mainly expressed in the hypothalamus, are involved in the control of food intake. MC4R is also expressed in others tissues such as erectile tissue and is implicated in the erectile function. Finally, MC5R may play a role in the secretion of exocrine glands (figure 2) (2).

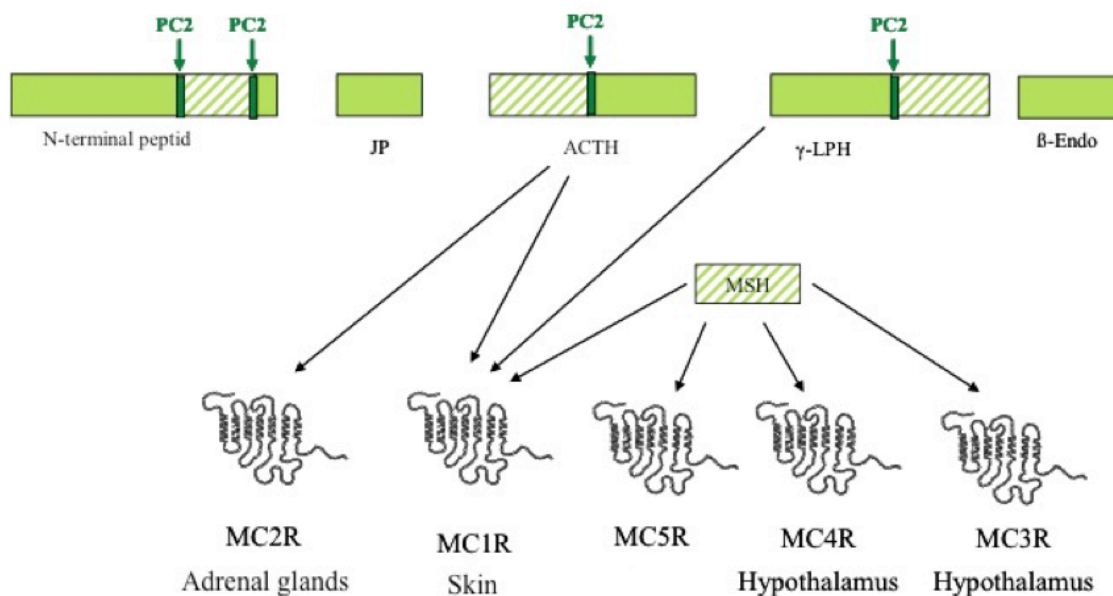


Figure 2: Role of the 5 melanocortin receptors activated by peptides derived from the cleavage of the pro-opiomelanocortin (POMC).

The adrenocorticotropic hormone (ACTH) acts on MC2R and plays a key role in the adrenal axis. ACTH, the γ LPH (γ -lipoprotein hormone) and α -MSH (α -melanocyte stimulating hormone) have a role in pigmentation via MC1R. The α -MSH and β -MSH probably (β – melanocyte stimulating hormone) act on the hypothalamus via MC3R and MC4R.

MC1-5R: melanocortin receptors-1 to 5; MSH melanocyte stimulating hormone; PC2: proconvertase 2; JP: Joint peptide; Endo- β : β -endorphins.

If mutations in human genes coding for proteins involved in leptin/melanocortin pathway (LEP, LEPR, POMC, etc) lead to severe early-onset obesity with a rapid and dramatic increase in weight soon after birth, the obesities linked to MC4R and MC3R mutations can be placed between these exceptional forms of monogenic obesity with complete penetrance and the polygenic forms of common obesity (3).

MC4R mutations

The MC4R is a 332 amino acid protein encoded by a single exon gene localized in chromosome 18q22 (4). It belongs to the family of seven transmembrane G-protein coupled receptors and transduces signal by coupling to the heterotrimeric Gs protein and activating adenylate cyclase. Predominantly expressed in hypothalamic nuclei involved in food intake regulation, it integrates a satiety signal provided by α -MSH and an antagonist (orexigenic) signal provided by AGRP. MC4R activation by natural or pharmacological agonists leads to a decrease in food intake. Its role in energy balance has been well demonstrated in mice (5). Mice lacking both alleles MC4R (MC4R $-/-$ mice) develop a severe obesity while heterozygous mice (MC4R $+/-$ mice) show an intermediate phenotype between MC4R $-/-$ and wild type mice.

a) Prevalence of MC4R mutations

Since 1998, systematic genetic evaluation of MC4R gene revealed that MC4R-linked obesity is the most prevalent form of oligogenic obesity identified to date. It represents approximately 2 to 3% of childhood and adult obesity with currently almost 200 different mutations described in different populations (European, North American and Asian) (3,6,7). They include frameshift, inframe deletion nonsense and missense mutations located throughout the MC4R gene. The frequency of heterozygous for these mutations in (extremely) obese individuals cumulates to approximately 2-5% (6). In addition, the frequency of such heterozygous carriers in non-obese controls or in the general population is about 10 fold lower than in the cohorts of obese patients (7,8).

In contrast with rare monogenic obesities, even a meticulous clinical analysis does not easily detect obesity stemming from MC4R mutations because of the lack of additional obvious phenotypes. In families with MC4R-linked obesity, obesity tends to have an autosomal dominant mode of transmission, but the penetrance of the disease can be incomplete and the clinical expression variable (moderate to severe obesity) underlying the role of the environment and other potentially modulating genetic factors (3,9,10).

Homozygous or compound heterozygous carriers of MC4R mutations are very rare (11-13). As expected from a dominant condition, obesity is developed earlier in life and is more severe than for heterozygous carriers, but it does not display any additional unrelated phenotypes. In heterozygous MC4R mutations carriers, the onset and severity of obesity vary and are related to the severity of the functional alteration caused by the mutation.

b) Phenotype associated to MC4R mutations

The phenotype of MC4R mutation carriers has been debated. Many authors agree on that MC4R

mutations facilitate early onset obesity. MC4R mutation carriers display increased linear growth, in particular in the first five years of life (14) but appear to be taller as adults only in rare cases (15,16). This trend is often observed in overweight and obese children. Assessment of body composition in these patients demonstrates increase in both fat and lean mass (14-16). One study performed in English children with MC4R mutations, has suggested that bone mineral density and size increase (14). This potential increase of bone density may be explained, at least in part, by a decrease in bone resorption, as illustrated by decreases in bone resorption markers in the serum of patients with MC4R homozygous and heterozygous mutations (17, 18).

Obese children carrying MC4R mutations have a marked hyperphagia that decreases with age, when compared to their siblings (14), while in both children and adults, no evidence has been found for a decreased metabolic rate in these patients. Meanwhile, the association between “binge eating” disorder and MC4R gene sequence changes (19) has not been confirmed (9,10,20).

Adult MC4R mutation carriers do not have an increased prevalence of diabetes or other obesity complications (8). In UK children, fasting insulinemia was found to be significantly elevated in MC4R mutation carriers, particularly before the age of 10 years when compared to age, sex and BMI matched control (14). This hyperinsulinemia has not consistently been observed in children (12, 13) and in adults (6,19). MC4R mutations were also associated to a reduced risk of hypertension (21).

Finally, with respect to endocrine function, hypothalamo-pituitary axis and reproductive axis (9,10, 14) as well as thyroid function are normal in MC4R mutation carriers.

c) In vitro functional consequences of MC4R mutations

The role of MC4R mutations in cases of human obesity relies on two main arguments based on the frequency of MC4R mutations in different populations and their in vitro functional consequences. Firstly, MC4R mutations are more abundant in obese populations. Indeed, functional mutations have also been reported in non-obese subjects but to a significantly lesser frequency (<1%) (8). Secondly, investigating the molecular mechanisms by which loss of function mutations in MC4R cause obesity have suggested a panel of functional anomalies: abnormal MC4R membrane expression, defect to the agonist response, and disruption in the intracellular transport of this protein. Normally, after ligand binding, MC4R activation stimulates Gs protein, leading to a subsequent increase in cAMP levels; however, the production of intracellular cAMP in response to aMSH peptides demonstrated a broad heterogeneity in the activation of the different MC4R mutants in response to aMSH, ranging from normal or partial activation to a total absence in activation (6, 7, 9, 10). The intracellular transport defect of the mutated receptor, by intracytoplasmic retention, has been described for the majority of MC4R mutations found in childhood obesity (22), but also in adults (6,7). This mechanism explains the impaired response to agonists. In addition, MC4R has a constitutive activity, meaning a basal activity not necessitating the presence of a ligand, for which agouti related peptide (AGRP) acts as an inverse agonist (23). In the absence of the ligand, MC4R has an inhibitory action on food intake. The systematic study of basal activity of some mutations has shown that an alteration in this activity may be the only functional anomaly found, in particular for mutations located in the N-terminal extra-cytoplasmic part of the receptor (24). A tonic satiety signal, provided by the constitutive activity of MC4R could be required in the long-term regulation

of energy balance.

It is accepted that MC4R mutations cause obesity by a haploinsufficiency mechanism rather than a dominant negative activity. While the roles of homo and hetero-dimerization in G protein synthesis and maturation are emphasized, some dominant negative effects of MC4R mutations might not be excluded.

d) Management of MC4R mutations carriers

Direct sequencing of the MC4R gene (1 exon) leads to the detection of MC4R mutations. To date, it is questionable to perform in routine systematic detection of MC4R mutations in obese subjects with a strong obesity familial history. Although knowing the biological reason (ie: altered melanocortin pathway) leading to an increased susceptibility to obesity might be of interest in some individuals, no specific therapeutic is still available and the severity of phenotype is highly variable within MC4R mutation carrier families. It may however become necessary in few years in case of development of specific drugs such as MC4R agonists in order to detect patients that may be eligible for such treatments (25).

To date, any specific management is necessary for MC4R mutation obese patients except for well-balanced diet and physical activity. However, interestingly, physical activity may have a specific role for modulating the obese phenotype in case of MC4R anomalies. In MC4R^{-/-} mice, regular physical activity is described to be more efficient for limiting the weight gain during life when compared to wild type (26). It suggests its specific role in the management of MC4R mutation related obesity and possibly the prevention of weight gain in relatives with MC4R mutation.

In addition, due to its important role in obesity, MC4R is becoming an attractive candidate drug target suggesting that identification and design of ligands or peptides may rescue the phenotype of the particular molecular mechanistic defect. Several synthetic ligands from the classical NDP-MSH peptides to the multiple tetrapeptides and small molecule MC4R agonists have been in vitro tested with variable results (27,28). But, they have to face normal concerns of targeting GPCRs and specific difficulties of possible side effects due to the widespread expression of MC4R in the brain and the already demonstrated role of MC4R in erectile function (27,28). At long term, this type of treatment should be evaluated in heterozygous patients for MC4R mutations with impaired aMSH activity, in specific clinical investigation protocols in order to provide effective anti-obesity treatment probably in combination with other approaches such as diet and physical activity. Actually, novel pharmacological MC4R agonists have been tested in vitro and can restore a normal activity in mutated receptor and preclinical trials are performed (25). So, treatment with a highly-selective novel MC4R agonist in obese non human primate model resulted in decreased food intake (35%), increased total energy expenditure (14%) and weight loss after 8 weeks of treatment (13.5%). No side effect, in particular in blood pressure or heart rate, was observed in this study (29).

Today, bariatric surgery is the only long-term efficient treatment for severe obesity (30) using several operative methods (laparoscopic gastric bypass, gastric banding or sleeve gastrectomy). The question of such treatment and its potential efficiency is crucial in patients with genetic abnormalities previously described in this chapter. Currently, data on bariatric surgery in patients with genetic obesity are limited

and controversial. In 4 patients with heterozygous MC4R mutations, weight loss after Roux-en-Y gastric bypass surgery was identical to controls without MC4R mutations suggesting that heterozygous MC4R mutation status should not influence the decision to perform surgery (31). Recent studies confirmed these findings in a group of obese adults (32, 33). In contrast, in a teenager with complete MC4R loss of function, laparoscopic adjustable gastric banding resulted in the absence of long-term weight loss (12 months postoperatively) suggesting that the full interruption of melanocortin pathway may not be counteracted by bariatric surgery (34). Other studies on the effect of bariatric surgery in MC4R mutated patients are needed.

MC3R mutations

MC3R, another receptor activated with POMC-derived peptides, has an important complementary role in the regulation of energy homeostasis next to MC4R. Indeed, MC3R deficient (MC3R^{-/-}) mice have increased fat mass, reduced lean mass and higher feed efficiency than wild-type littermates, despite being hypophagic and maintaining normal metabolic rates (35). In humans, strong evidence of a causative role for MC3R mutations is still lacking. Several rare mutations with functional alterations have been described to be associated with severe obesity in children (36,37). In adults, some MC3R mutations, leading to amino-acid changes in the receptor, have been also described in a group of 290 obese subjects (38) but the total prevalence of rare MC3R variants was not significantly different between cohorts of severely obese subjects and lean controls (39). No specific phenotype of MC3R mutations has been identified. As linkage studies are concordant with the presence of a susceptibility gene for human obesity at the MC3R locus (20q 13.2-13.3), further epidemiological and functional researches regarding the importance of MC3R mutations are necessary in order to confirm the importance of MC3R mutants and their potential combined effects with other genes in severe early-onset obesity (39, 40).

Concerning management of patients carrying MC3R mutations, few data are available. In a study, Santoro et al found that Thr6Lys and Val18Ile were associated with a differential weight loss in response to a negative energy balance in obese children (41). In adults, in a randomised trial of hypoenergetic high vs low-fat diet, the presence of MC3R mutations did not impact on weight evolution (42). To our knowledge, no data are available on the effect of bariatric surgery.

Conclusion

MC4R is recognized as the major candidate gene for human obesity due to MC4R pivotal role. The high frequency of MC4R mutation associated to obesity shows that they can be considered as the first cause of oligogenic obesity between the rare monogenic obesities (leptin deficiency,..) and polygenic obesities that the most common form. The implication of MC3R in obesity is still debated and need to be confirmed. Development of MC4R agonists in close future may be the first example of personalized treatment in obesity and may limit indications of bariatric surgery in young people.

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~ About the Authors ~

Beatrice Dubern



Dr Beatrice Dubern, MD, PhD is assistant professor in the department of pediatric nutrition and gastroenterology at Trousseau hospital in Paris, France. In clinics, she is taking care of children with severe early-onset obesity or syndromic obesity and others nutritional pathologies in childhood.

Her main research topic is the identification of genes implicated in early onset obesity and studied especially the role of the genes in the leptin/melanocortins pathway. She worked with Dr Christian Vaisse in San Francisco on MC4R and LEPR genes and is now part of Pr K Clement's team in the cardiometabolic institute ICAN, Paris

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