REVIEW

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Specific Functions of Melanocortin 3 Receptor (MC3R)

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Abstract

Melanocortin 3 receptor (MC3R) is a G-protein coupled receptor which has been defined mostly as a regulator of the appetite/hunger balance mechanisms to date. In addition to its function regarding the weight gain and appetite control mechanisms of MC3R, recent studies have shown that MC3R controls growth, puberty, and circadian rhythms as well. Despite the drastic effects of MC3R deficiency in humans and other mammals, its cellular mechanisms are still under investigation. In this review paper, we aimed to point out the importance of MC3R regulations in three main areas: 1) its impact on weight and appetite control, 2) its role in the control of growth, puberty, and the circadian rhythm, and, 3) its protein-protein interactions and cellular mechanisms.

Keywords: Childhood obesity, melanocortin 3 receptor, circadian rhythm, appetite control

Introduction

Excess amounts of fat consumption and overeating result in disruptions of the energy balance in the body and excess energy storage in adipose tissue. If this storing process continues for too long, due to increased adiposity and inflammations, obesity occurs (1). Along with obesity, there is an increase in the likelihood of diseases, such as cardiovascular diseases, type 2 diabetes, fatty liver, respiratory diseases and cancer, which all can reduce both health and quality of life and lead to early death (2). The cause of obesity is classified under three headings, namely monogenic, syndromic and common obesity (3). According to studies, obesity mutations belonging to the monogenic and syndromic obesity classes may be observed in 20 different genes which clearly cause inherited obesity (4,5). Single gene mutations causing obesity are known as monogenic or syndromic obesity. Monogenic (non-syndromic) obesity is a more severe and uncommon form of obesity in which people have mutations in a single gene which result in an obesity phenotype or inheritance in a Mendelian pattern (6,7). The leptin-melanocortin signaling pathway in the hypothalamus, which is crucial for maintaining energy homeostasis, contains the majority of these genes impacted by monogenic obesity (6). In addition, if mutations and/or chromosomal abnormalities are detected in more than one gene as the cause of obesity, the disease is also classified as syndromic obesity. Similar to other complex traits and disorders, the heritability of syndromic obesity follows a similar trend (7). In addition to the features seen in monogenic obesity patients, dysmorphic features are observed with various physical and mental developmental disorders in patients with syndromic obesity (3). Common obesity is a form of obesity which has an alarming prevalence and life-threatening implications. It is brought on by a combination of genetic and environmental factors, including a high-fat diet and a sedentary lifestyle (7). Differences in weight gain mechanisms observed in the common obesity class are about 40-70 % (8,9).

The creation of physiological activations and the metabolic balance of the organism are ensured by transmitting signals formed as a result of receiving environmental stimuli through the central nervous system (CNS) and evaluating them for metabolic response. In appetite control, glucose and fat metabolisms, the digestion and metabolic rates are regulated by physiological activations (10). The neurons, which are responsible for maintaining this order and balance throughout the life of the organism, maintain their

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plasticity and ensure that the living things have a healthy metabolism for their survival. Chronic over-nutrition may result in changes of the plasticity of neurons and the disruption of their organization in signal transmission (11). For this reason, the hypothalamic and especially the melanocortin pathway neurons within the CNS have been the focus of metabolic studies in recent years (12). As insulin and ghrelin, the hunger hormone leptin from the adipose tissue, are responsible for the control of the melanocortin pathway in the hypothalamus, they play a role in the regulation of the appetite, hunger, and energy mechanisms (13). Leptin modulates the melanocortin pathways, which are also controlled by four neuro-hormones which are synthesized and secreted in the arcuate nucleus (ARC) of the hypothalamus. These peptides for the eating and energy mechanisms are the neuropeptide Y (NPY), the agouti-related peptide (AgRP), proopiomelanocortin (POMC), and cocaine and amphetamine-related transcript (CART) (14). While leptin inhibits NPY and AgRP (which are associated with increasing eating/appetite and reducing energy expenditure), the opposite is true for POMC and CART (15). With the exception of CART (since its receptor has not yet been discovered), the other neuro-hormones carry out signal transmission via G protein-coupled receptors (GPCR) (16).

Among these hormones, POMC is synthesized as a precursor and transformed into eight biologically active hormones with different functions by passing through the regulated secretion pathways in POMC neurons and pituitary cells (17). Five melanocortin receptors have been identified to date, and signal transmission of POMC-derived hormones is provided via these receptors. MC3 and MC4 receptors belong to this family of receptors and interact with hormones involved in the eating and energy mechanisms in the brain (18). Melanocortin 3 receptor (MC3R) has a very high binding capacity for γ-melanocyte stimulating hormone (γ-MSH), while MC4R has a very high binding capacity for α and β-MSH. MC3R is a member of the GPCR family. It regulates pathways associated with nutrient partitioning, weight management, appetite, and hunger (Figure 1) (15,19).

Like most GPCR members, MC3R form dimers/oligomers among themselves and with different GPCR members which activate/deactivate and regulate secondary signaling pathways (20). In fact, 40% of the drugs in the pharmaceutical industry target the GPCR family (21).

Variations of MC3R result in both genetic obesity and delayed entry to sexual maturity in humans. Experimental studies have shown the importance of the MC3R role for the metabolism balance for nutrient partitioning, obesity, circadian rhythm and sexual maturity. Inspite of a broad range of physiological roles of the *MC3R* gene, unfortunately, there is still a lack of knowledge about its intracellular mechanisms in the literature.

MC3R Impact on Weight and Appetite Control

The most striking phenotype of MC3R loss of function variants and MC3R knock-out (KO) mice models is obesity.

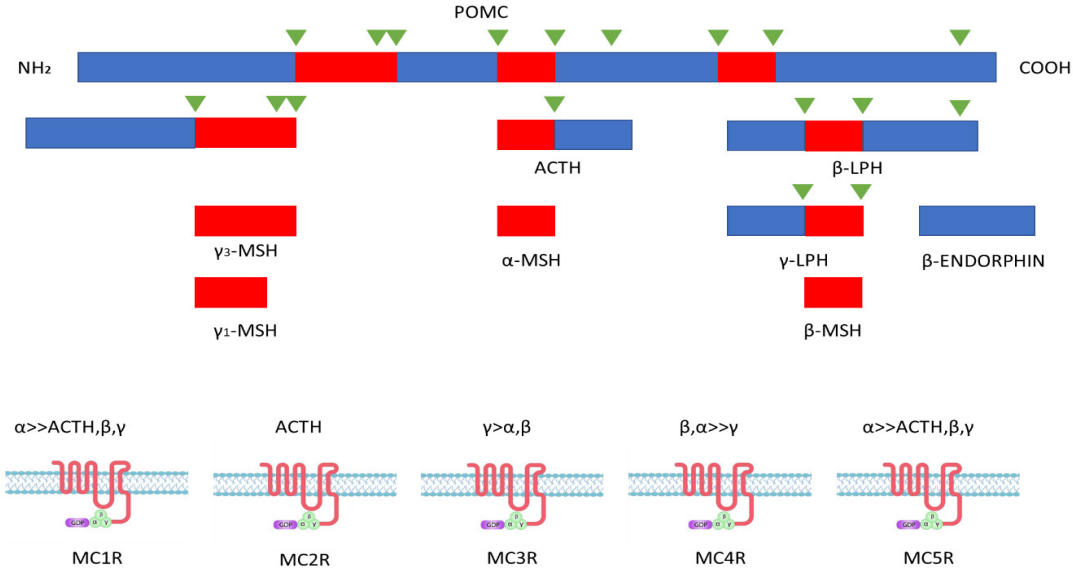

Figure 1. Eight separate active peptide hormones obtained from proopiomelanocortin (POMC) hormone after post-translation modifications in the regulated secretory pathway and melanocotin receptors with affinities to their ligands. Green arrows show where prohormone convertases (PCs) perform their proteolytic activity on POMC (19)

ACTH: Adrenocorticotropic hormone, β-LPH: Beta-lipotropin, γ and α-MSH: Gamma and alpha melanocorticotropin hormone

The obesity features of MC3R KO mice models were different from the MC4R KO mice obesity phenotype (22). First of all, the ratio of the fat mass over the lean mass was very high for the MC3R KO models. Secondly, MC3R KO mice models display decreased lean mass while increasing fat mass during a high fat diet (HFD), even though they had similar meal amounts vs. wild-type (WT) mice (23). Most interestingly, these mice models had trouble gaining weight after a restriction feeding period since they had trouble balancing their eating amount vs. their caloric requirement and so lost more weight during this period (24). The reason behind this increased fat mass during a regular chow diet causing the obesity phenotype could be a problem with the nutrient partitioning mechanisms. This possibility also helps to explain the mice losing more weight during restriction feeding and having trouble gaining weight afterwards.

The MC3R variants studied were mostly from Caucasian populations in humans. Mencarelli et al. (25) in 2011 investigated MC3R variants in French and Italian populations which revealed S17T, D158Y, V177I, and L249F novel variants which cause the obese phenotype, whereas the I87T and L285V novel variants did not show obese phenotype. In the French population, 1.81% of the obese group had the loss of function MC3R variant, while in the Italian obese patient group, the ratio was 1.16%. Interestingly, the number of point mutation caused variants without the obese phenotype was 7 out of 753 normal weight individuals in the French control group, while this number was only 1 out of 214 people in the Italian control group.

Ghamari-Langroudi et al. (26) in 2018 showed that MC3R signaling in presynaptic AgRP neurons modulates the activity of postsynaptic MC4R paraventricular nucleus neurons through regulation of GABA release. The results of their study revealed the importance of investigating the metabolic roles and intracellular mechanisms of MC3R in weight and appetite control and they emphasized the necessity of the clarification of their intracellular trafficking further, which is lacking in the literature. Unfortunately, the commercial MC3R antibodies used in experimental procedures have many specificities and binding capacities which give false conclusions for intracellular trafficking. To distinguish the intracellular trafficking of MC3R, more specific methodologies are necessary in order to obtain more reliable results.

Feng et al. (27) in 2005 discovered that 8.2% of 355 overweight children were pairwise homozygous for the MC3R Thr6Lys/Val81Ile variant. They transfected HEK293 cells with WT, Thr6Lys/Val81Ile variants together, Thr6Lys and Val81Ile variants of the *MC3R* gene were discovered from child populations of different countries. According to ligand saturation analysis, the Thr6Lys variant and Val81Ile variant of the *MC3R* gene have less ability to bind the ligand, however, the double mutant variant's ability to bind to the ligand decreased more dramatic compared to single mutant variants. The secondary messenger activation capacity of those MC3R variants was also compared using a β-galactosidase activity test in HEK293 cells. Based on their results, Thr6Lys/Val81Ile MC3R variant carrying subjects had the least ability to activate the cAMP dependent secondary messenger system. These results indicated that the combined inhibitory/loss of function mutations in the Thr6Lys/Val81Ile MC3R variant worked together and almost fully inhibited the function of MC3R (27).

Lee et al. (28) (2016) investigated C17A and G241A (Thr6Lys/Val81Ile) MC3R variant's effects on mice models for C57BL/6 mice as WT vs. human MC3R and Thr6Lys/Val81Ile MC3R variant mice. They showed that Thr6Lys/Val81Ile MC3R variant littermates had more body fat with reduced fat-free tissues, even when they were fed with normal rat chow. The mice groups were also compared for their leptin concentrations, their eating amounts and their energy expenditures in both fed and fasting states. The results indicated that Thr6Lys/Val81Ile MC3R variant littermates had higher serum leptin concentrations than the WT controls; however, there was no significant difference between meal amounts or energy expenditure between the two groups.

According to the studies above, the frequency of the Thr6Lys/Val81Ile MC3R variant in the obese population is dramatically high. Many studies have been performed in order to understand the effects of the Thr6Lys/Val81Ile MC3R variant; however, no study has been performed to understand the intracellular trafficking of the Thr6Lys/Val81Ile MC3R variant. The reason behind this situation could be the lack of specific antibodies or the unspecific binding capacity of commercial MC3R antibodies.

MC3R Has a Role in the Control of Growth, Puberty and the Circadian Rhythm

Over the years, scientific studies have investigated MC3R and its function focusing on the phenotype and metabolic responses. Many KO rat and mice models studies were performed on the "metabolic tuner" and "redundant" MC3R activities.

Numerous phenotypic observations were recorded about MC3R loss of function variants. One of the most interesting phenotype observations was that MC3R loss of function variants cause late growth and late onset of the puberty with irregular menstrual cycles for female patients.

Yung-Seng Lee et al. (29) (2002) performed genetic analyses on a 13-year-old obese Indian girl with irregular menstrual cycle with polycystic ovary syndrome and also on her obese father. They found that the Ile183Asn variant in their MC3R sequence was associated with these phenotypes. Their results clearly showed that MC3R function regulates menstruation cycles, as well as the circadian and ultradian rhythms.

Lam et al. (30) (2021) observed MC3R loss of function variants *in vitro* in a male patient carrying the G240W MC3R variant. The patient was obese with type 2 diabetes and the late onset of puberty phenotype. They investigated MC3R impacts on puberty onset and reproductively by studying MC3R KO mice models *in vitro*. Their findings showed that both male and female mice models delayed the onset of puberty and the female models had a shorter period of ovulation cycle than their WT littermates. The G240W MC3R variant resulted in obese and late onset of puberty phenotypical expressions on a male patient as a result of being a loss of function variant since the ability of the MC3R variant to activate the secondary messenger pathway was lost or significantly reduced. Moreover, the late onset of puberty phenotype with G240W MC3R variant carrier human patients demonstrated the same phenotype as the MC3R KO models. Consistent with the early findings in animal model phenotype investigations, the obese phenotype of the MC3R loss of function variant had a low lean mass with respect to the patient's body mass index with a high body fat. In addition, for female MC3R KO mice, the length of the estrous cycle was prolonged significantly. Thus, the dramatic MC3R effects on the ultradian cycle and neuroendocrinology were validated one more time.

The prolonged and irregular estrous cycles and late onset of puberty phenotypes indicated that MC3R has a regulator role on the circadian rhythm. Sutton et al. (24) (2008) investigated food anticipatory activities (FAA) on MC3R KO models 3 hours before feeding and they showed significantly less FAA with lower X and Z movements. Then, they examined *Bmal1*, *Npas2*, and *Per2* circadian gene expression patterns on *ad libitum* and restricted feeding conditions on MC3R KO mice. Cortical neuronal mRNA expression patterns showed that *Bmal1* mRNA expression was ten-fold lower in MC3R KO mice during the peak expression vs. WT mice. Restricted feeding was also associated with marked differences in the amplitude of the circadian profile of all three genes in the cortex of MC3R KO vs. WT mice. Accordingly, it was put forward that MC3R was required for normal patterns of the clock activity in the cortex. Therefore, the molecular mechanisms of MC3R on circadian rhythm were partially revealed. However, without clear intracellular trafficking of MC3R, the molecular control mechanisms of MC3R are still not fully understood.

MC3R Protein-protein Interactions and Intracellular Mechanisms

Recent studies have shown that GPCRs are oligomerized in the membrane, paving the way for important studies (31). MC3R and the growth hormone secretagogue receptor (GHSR)-1a belong to the GPCR family and are synthesized in neurons of the hypothalamus (32). Notably, the majority of GHSR-1a-expressing neurons coexpress the MC3R, whereas only a few MC3R-expressing neurons coexpress GHSR-1a in the ARC (31). If α-MSH binds to MC3R in the MC3R signaling pathway, the Gαs protein is activated and increases the cAMP level. Studies have revealed that the dimerization of GHSR-1a and MC3R, as well as basal activation of GHSR-1a, doubled the activity of MC3R stimulated by α-MSH, and the activity of GHSR-1a stimulated with ghrelin decreased by approximately 60%. In this case, MC3R may have different intracellular roles with its ligand-bound and non-ligand forms (31,33). In addition to this interaction, Müller et al. (34) (2016) indicated that GHSR-1a interacts with Gpr83, which regulates the signaling mechanism of GHSR-1a and MC3R heterodimer, and provides ghrelin-dependent and independent energy metabolism control. According to these studies, the molecular regulation of the MC3R signaling could be controlled by GHSR-1a and this control mechanism is dependent on the protein-protein interactions of MC3R.

Subsequently, Müller et al. (34) (2016) revealed the MC3R and MC4R interaction and its intracellular mechanism. According to their study, RING finger protein 11 (RNF11) can make a homodimer and also dimerize with MC3R and MC4R. These heterodimers restricted MC3R and MC4R activation of the secondary messenger pathway system and lowered their activity by about 40%, which may be the reason for decreased MC3R-GHSR-1a heterodimer. In addition, they also specified that the MC3R and MC4R expressions' level remained the same, independent of the RNF11 expression. However, their study lacked confocal microscopy imaging data and the internalization process, which are necessary for a complete understanding of their results. In the literature, most studies consider that MC3R and MC4R may have similar physiological effects and hence called MC3R redundant. However, contrary to what was indicated, they are very different from each other in terms of their phenotypic outcomes, such as more fat mass on HFD and more weight loss in Restriction Feeding Diet in MC3R vs. MC4R, and also the presence of late puberty and poor nutrient partitioning.

Despite MC3R protein-protein interactions, the intracellular trafficking of MC3R is poorly understood. To date, only one publication focused on WT MC3R intracellular trafficking and there are almost no publications studying the loss of function variants intracellular trafficking. The intracellular trafficking of MC3R study published by Wachira et al. (35) in 2007 claimed that MC3R localizes lipid raft regions and endocytic internalization occurs in the presence of γ-MSH. These results are highlighted to understand MC3R intracellular trafficking. However, as a result of the usage of non-specific MC3R antibodies and the lack of quantitative data of the study, MC3R intracellular trafficking is still an unresolved concept and studies with more specific labeling methods are required in order to illuminate MC3R intracellular trafficking.

Conclusion

The GPCR family member of MC3R is responsible for body weight and appetite control and is often mentioned as "redundant". However, recent studies have revealed that MC3R has crucial functions such as regulating hunger, appetite and body weight. The regulations of MC3R on weight control mechanisms also imply that nutrient partitioning mechanisms are affected by MC3R signaling. In addition, growth and puberty onset are also affected and controlled by the MC3R signaling pathway according to patient and mice model studies. Moreover, protein interaction studies have shown that MC3R interacts with GHSR-1a and crucially controls the secondary messenger pathway signaling of MC3R. Surprisingly, the intracellular trafficking of MC3R has not been fully or reliably revealed because of unreliable methodologies which utilize non-specific commercial antibodies. In order to illuminate the intracellular trafficking of MC3R, more specific and reliable approaches should be used. Fully revealing MC3R intracellular trafficking will open up new areas to develop therapeutic approaches in order to treat obesity.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Tulin Yanik, Seyda Tugce Durhan, Design: Tulin Yanik, Seyda Tugce Durhan, Literature Search: Tulin Yanik, Seyda Tugce Durhan, Writing: Tulin Yanik, Seyda Tugce Durhan.

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