Artykuł przeglądowy *Review*

Role of proopiomelanocortin (POMC) derivatives in body weight regulation: A review of current knowledge and significance in the pathogenesis of obesity in mammals

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Summary

Proopiomelanocortin (POMC) is a polypeptide precursor produced primarily in the cells of the pituitary gland and neurons of the hypothalamus, serving as the precursor to many biologically active peptides, including adrenocorticotropin (ACTH), melanocyte-stimulating hormone (MSH), and β-endorphin (β-EDP). The role of POMC in body weight regulation is a widely studied area in science, as POMC plays a crucial role in the central regulation of appetite, energy metabolism, and body weight homeostasis. Research on POMC in both humans and animals plays a key role in understanding its function, regulation, and impact on the body. These studies may involve genetic analyses and investigations into POMC function in both humans and animals, contributing to a better understanding of the mechanisms of this gene. They also include clinical trials of drugs and other substances that may affect POMC functioning, opening up new perspectives in the treatment of metabolic and hormonal disorders across various species. In this way, research on POMC in both animals and humans collaborates to create a comprehensive picture of the function and significance of this substance in living organisms, potentially leading to advancements in the treatment of various diseases.

This article aims to analyze the latest scientific research on the role of POMC in the regulation of appetite and obesity in both animals and humans, highlighting their interrelationships and significance in understanding metabolic mechanisms.

Keywords: body weight regulation, genetic markers of obesity, obesity pathogenesis, POMC gene expression

Proopiomelanocortin (POMC) is a crucial precursor of numerous hormones and neuropeptides. Its discovery in 1977 is credited to two independent researchers: Roger Guillemin and Andrew W. Schally (35). Many scientific studies have shown the pivotal role of POMC derivatives across various organs, where both the POMC gene and the resulting proteins exhibit profound biological activity (62, 71). POMC is processed through enzymatic cleavage, resulting in the formation of diverse biologically active peptides. This processing occurs primarily in the central nervous system (CNS) but also in other organs and systems, such as the skin, gastrointestinal tract, immune system, and reproductive system. The proteolytic enzymes responsible for converting POMC into its various products include prohormone convertases and carboxypeptidases (35). The products of POMC, including corticotropins, melanotropins, and endorphins, exert their effects by activating distinct receptor classes, such as melanocortin receptors (MCR) and opioid receptors (89). These compounds play diverse and significant roles in various physiological processes, including skin pigmentation, regulation of the body's response to stress and pain, and the modulation of appetite and body weight, with their functions being organ-dependent. The multifunctionality of POMC-derived peptides underscores the biological significance of this precursor in maintaining organismal homeostasis (50, 52). Research on the relationship between POMC and obesity has been the subject of intense clinical investigations for some time, because of the increased risk of premature mortality associated with the presence of coexisting diseases such as cardiovascular disease (CVD), non-alcoholic fatty liver disease, stroke, and type II diabetes (17,

67). Obesity, recognized as a global health problem, has garnered increasing attention from scientists due to its escalating prevalence and consequential health ramifications. It results from a dysregulation of the body's energy balance, leading to excessive adipose tissue accumulation driven by increased energy intake relative to expenditure, influenced by genetic and environmental factors (7, 11, 67). Notably, investigations into the role of POMC in the context of obesity have revealed significant genetic correlations, including mutations in the POMC gene, observed not only in humans but also in animals such as Labrador Retrievers, which exhibit an increased motivation to consume food. This disruption impacts the production of neuroactive peptides β-melanocyte-stimulating hormone (β-MSH) and β-endorphin (β-EDP), which are crucial for regulating satiety. Consequently, individuals of this breed may face an elevated risk of obesity (70). Owing to the high homology of the structure of canine POMC to that of its human counterpart, findings from studies on dogs have been effectively applied to human medicine. This genetic similarity allows dogs to be used as models for scientific research, which can lead to a better understanding of molecular mechanisms and the development of more effective therapeutic strategies for combating obesity in both humans and animals (83).

This article aims to analyze the latest scientific research on the role of POMC in the regulation of appetite and obesity in both animals and humans, highlighting their interrelationships and significance in understanding metabolic mechanisms.

Material and methods

A comprehensive literature review was conducted to examine the role of POMC in body weight regulation and the pathogenesis of obesity. The review involved a systematic search across several scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy utilized specific keywords such as "proopiomelanocortin," "POMC," "body weight regulation," "obesity," "melanocortin 4 receptor" (MC4R), "adrenocorticotropic hormone" (ACTH), and "α-melanocyte-stimulating hormone" (α-MSH), combined with Boolean operators (AND, OR) to refine the search results.

The inclusion criteria were defined to focus on peer-reviewed articles, reviews, and original research studies published in English from January 2000 to June 2024, with two exceptions for pivotal studies where no more recent literature was available. Articles were selected based on their relevance to the biochemical and physiological roles of POMC-derived peptides in body weight regulation and their connection to obesity. Studies were excluded if they were not published in English, lacked a clear focus on POMC or its derivatives, were non-peer-reviewed unless offering critical insights, or were redundant or insufficiently detailed.

The initial search yielded a total of 1,342 articles. These articles underwent an initial screening based on titles and abstracts to exclude studies that were irrelevant to the research focus. A total of 287 articles were then selected for full text review. Each full text article was assessed for relevance using predefined criteria, including the study's focus on the mechanisms by which POMC-derived peptides influence body weight and their implications for obesity. The quality and rigor of the studies were also evaluated, considering factors such as study design, sample size, and the use of appropriate controls.

Among the databases searched, PubMed provided the highest number of relevant articles (652), followed by Scopus (402), Web of Science (205), and Google Scholar (83). Ultimately, 94 articles were selected for inclusion in this detailed review. The selected studies were critically analyzed to synthesize current knowledge on the role of POMC in body weight regulation and obesity, with an emphasis on underlying mechanisms and potential therapeutic implications.

POMC expression

Structure of the POMC gene. The POMC gene in humans is located on the short arm of chromosome 2 (2p23) and consists of three exons containing coding sequences, separated by large introns (71). Exon 1 contains a non-coding sequence, exon 2 encodes the signal peptide and the N-terminal fragment of the peptide, and exon 3 encodes most of the POMC peptide and the signal for the addition of the poly-A tail, including functionally significant peptides such as ACTH, α-/β-MSH, and β-EDP (see Fig. 1) (13). The expression of the POMC gene is complex and regulated by several cis-acting elements in the 5' region and intron 2. POMC transcription in the pituitary is controlled by specific transcription factors, such as homeobox 1 and T-box factor, as well as ubiquitously expressed factors, including members of the orphan nuclear receptor family and NF-κB (8).

The role of insulin and leptin in POMC expression regulation. The regulation of POMC expression is mediated by leptin and insulin signaling. Leptin, produced by adipocytes, acts on POMC and neuropeptide Y/Agouti-related peptide (NPY/AgRP) neurons in the arcuate nucleus (ARC) of the hypothalamus, inhibiting food intake and promoting energy expenditure (69). Insulin, secreted by the pancreas in response to increased blood glucose levels, also affects POMC and NPY/AgRP neurons in the ARC, regulating glucose metabolism and inducing anorectic responses (27). Tyrosine phosphatases PTP1B and TCPTP modulate leptin and insulin signaling, influencing body weight and glucose homeostasis (26). In the fed state, leptin binds to leptin receptors (LEPR) on POMC-expressing neurons (hereafter referred to as "POMC neurons"), activating JAK2 and phosphorylating STAT3, which promotes POMC expression and α-MSH production.

Leptin also activates the PI3K pathway, leading to the generation of PIP3 and the activation of PKCλ, which opens TrpC5 channels, allowing Na+ influx and neuronal firing, as well as the translocation of FOXO1 to the cytosol, enhancing POMC transcription. STAT3 induces the expression of Socs-3 and protein tyrosine phosphatases such as TCPTP, which inhibit LEPR signaling. The insulin receptor and serotonin receptor 5-HT2CR also activate their respective signaling pathways in POMC neurons, leading to TrpC5 channel opening and neuronal firing (4).

Peripheral expression of POMC and the impact of DNA methylation on satiety signaling and obesity. The expression of the POMC gene in peripheral organs differs from its expression in the pituitary gland. The peripheral transcript is truncated to 800 bp, while in the pituitary gland, it is a full-length transcript of 1200 bp. Only the full-length POMC transcript (1200 bp) is functional (18). In GH3 cells, only the full-length POMC mRNA led to the secretion of ACTH and β-EDP, while the short transcript generated unprocessed peptides retained within the cells, suggesting the crucial role of the full sequence in the secretion and function of peptides. GH3 cells transfected with an excess of the short POMC mRNA do not secrete ACTH or β-EDP, which are the only unprocessed forms of POMC, indicating that full processing of this peptide requires specific corticotropic enzymes. These findings raise questions about the role of peripheral POMC, suggesting the possibility of its release in response to organ damage or a potential role in the development of peripheral organs (18). Variable methylation patterns in hypothalamic POMC neurons can affect satiety signaling and obesity (63). A second promoter of the POMC gene has been identified near the intron 2/exon 3 junction, which contains a binding site for the cAMP-response element binding protein (CREB), a transcription factor sensitive to methylation. The activity of this promoter, regulated by DNA demethylation, plays a crucial role in POMC transcription (3). In recent years, studies have shown that diet significantly impacts DNA methylation levels in the hypothalamic feeding center (51). For example, a high fat diet (HFD) and overfeeding lead to changes in the DNA methylation of the POMC and NPY genes in the hypothalamus (91). These findings suggest that diet can modulate the DNA methylation levels of key genes regulating energy homeostasis, which in turn affects their expression and may be linked to susceptibility to obesity. Interestingly, DNA methylation levels in the POMC promoter region correlate with obesity susceptibility; lower methylation levels are associated with greater resistance to developing obesity (78, 91). These studies highlight the importance of epigenetic mechanisms in regulating genes related to energy balance and their role in the pathogenesis of diet-induced obesity (91). Studies have shown that HFD consumption promotes CREB activation in POMC neurons in the ARC of the hypothalamus. Inhibition of CREB activity leads to increased diet-induced weight gain, decreased energy expenditure, and reduced expression of POMC endopeptidases, affecting the production of the key POMC derivative, α-MSH. The activation of CREB by an HFD and its impact on endopeptidase expression suggest a complex mechanism by which a high fat diet can directly modulate the activity of POMC neurons, influencing energy homeostasis and body weight (93).

POMC processing

POMC mRNA is synthesized in the pituitary gland, the ARC in the hypothalamus, the nucleus of the solitary tract (NTS) in the brainstem, and peripheral organs, but as previously mentioned, only in the CNS does it form a single functional protein directed to the Golgi apparatus and then to secretory granules (18, 59). There, posttranslational enzymatic modifications lead to the formation of active peptides (59). The biosynthesis of peptides derived from POMC, according to the „prohormone theory", involves the translation of mRNA into an inactive precursor polypeptide, which then undergoes post-translational proteolysis by various prohormone convertases (PC) (16). Prohormone

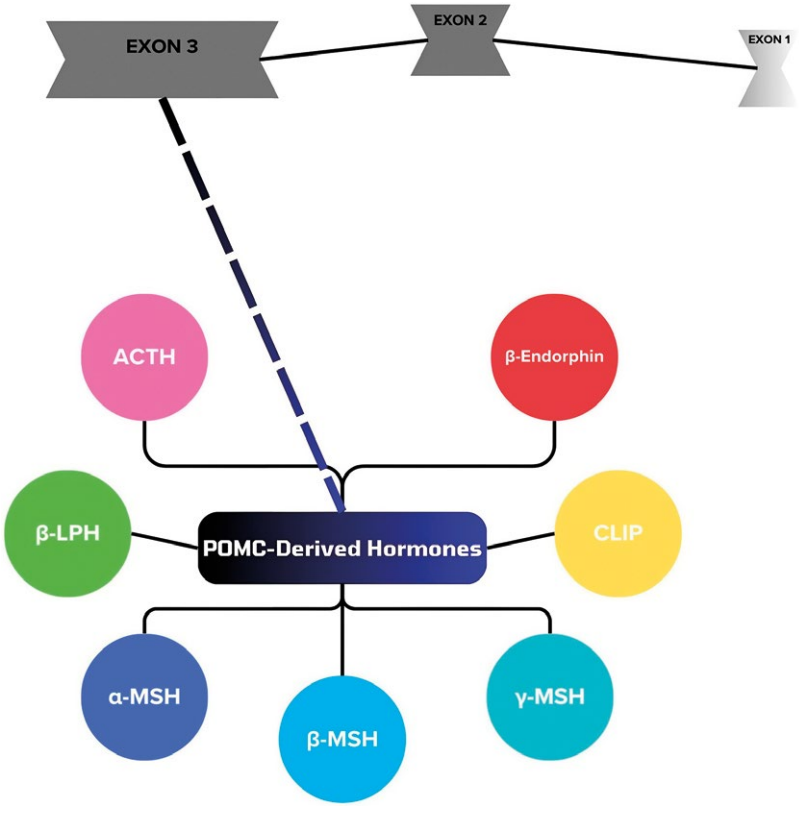

Fig. 1. The post-translational proteolysis of proopiomelanocortin (POMC) in mammals leads to the formation of active hormones such as adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (α-, β-, and γ-MSH), and β-endorphins (β-EDP)

convertases, such as PC1/3 and PC2, along with carboxypeptidase E, work together in the hypothalamus and pituitary gland to process pre-POMC into active peptides, including ACTH, α-MSH, and β-EDP. PC1/3 and PC2 cleave the precursor peptide POMC into smaller, biologically active peptides by cutting at sites containing pairs of dibasic amino acid residues, such as lysine and arginine (22, 80). In addition to cleavage by PC1/3 and PC2, peptides derived from POMC undergo additional post-translational modifications, for example, the acetylation of α-MSH and tissue specific modifications. For instance, in the pituitary gland, different cell populations produce distinct end peptides, with ACTH and α-MSH being synthesized by separate groups of cells (37, 60). Mutations in the PCSK1 gene, which encodes PC1/3, are associated with severe cases of obesity and other endocrinopathies, including growth hormone deficiency, adrenal insufficiency, and hypogonadism. Studies on PC1/3-deficient mice have shown impaired POMC processing, leading to reduced production of α-MSH and metabolic disorders such as obesity (84). In mammals, POMC consists of three main segments: N-POMC, ACTH, and β-lipotropin (β-LPH), which are separated by dibasic amino acid residues (80).

POMC derivatives

ACTH. ACTH is a key hormone that stimulates the adrenal cortex to produce glucocorticoids, such as cortisol, which are essential for regulating metabolism, responding to stress, and maintaining energy homeostasis (82). ACTH is synthesized by corticotropic cells in the anterior pituitary gland and is a post-translational product of the POMC protein. ACTH consists of 39 amino acids and binds to melanocortin 2 receptors (MC2R) on cells in the zona fasciculata of the adrenal cortex, leading to cortisol production. MC2R, part of the G protein-coupled receptors family, requires the presence of the accessory protein melanocortin 2 receptor accessory protein (MRAP) for ACTH activation (53, 73). Mutations in MC2R or MRAP cause familial glucocorticoid deficiency syndrome (2).

Melanotropins. Melanotropins, including α-, β-, and γ-MSH, are key peptides derived from POMC. Among these, α-MSH is the most important, playing a significant role in controlling food intake, body weight, and energy expenditure by interacting with melanocortin 3 and 4 receptors (MC3R and MC4R) in the CNS (53, 73, 90). Melanotropins are also involved in melanogenesis by activating melanocytes to produce melanin, which affects skin pigmentation and eye color. The secretion of melanotropins is strongly inhibited by adrenal hormones, such as cortisol, adrenaline, and noradrenaline (12).

α-MSH. MSH was one of the first peptide hormones isolated from the pituitary gland. Its discovery and functional characterization were conducted by researchers such as Cone et al. and Gantz et al. in the early 1990s (38). It is a potent neuropeptide that can reduce food intake, body weight, and fat mass while increasing energy expenditure. Additionally, it inhibits the release of inflammatory cytokines and chemokines (32). α-MSH influences food intake by binding to MC3R and MC4R in the brain, with each receptor playing different roles in regulating appetite (53, 56). MC3R plays a key role in adapting to dietary changes by regulating appetite and fat mass (1). Its absence leads to increased food intake, reduced locomotor activity, and energy expenditure (5). Mice with inactivated MC3R exhibit compulsive behavioral responses to restricted feeding and have reduced lean mass (86). MC4R is activated by both α- and β-MSH and regulates food intake and energy expenditure. Its deficiency leads to hyperphagia, hyperinsulinemia, hyperglycemia, and obesity. In both humans and animals, the lack of MC4R results in increased food intake and reduced energy expenditure, which leads to increased fat and lean mass, and hyperinsulinemia (85, 86). High levels of α-MSH before therapy are crucial for the effective modulation of anorexigenic and orexigenic pathways in obese adolescents, leading to better control of energy balance and a reduced risk of weight regain. Patients with low levels of α-MSH may have difficulties regulating energy balance, increasing the risk of the yo-yo effect and challenges in maintaining a healthy lifestyle after treatment (48).

β-MSH. β-MSH plays a significant role in body weight regulation by the hypothalamus, influencing energy balance and exhibiting anorexigenic effects. Immunohistochemical studies have shown that β-MSH is the most prevalent peptide in POMC neurons in the ARC, surpassing the number of α-MSH and ACTH-positive neurons. This observation may result from differences in post-translational modification and peptide stability, where β-MSH may have a longer biological half-life than non-acetylated α-MSH, highlighting its importance in regulating appetite and energy homeostasis in humans (6). However, further research demonstrated that β-MSH is not present in the human pituitary gland, questioning its physiological significance (77). In rodents, there is a deficiency of β-MSH (6). In these animals, a critical proteolytic cleavage site in POMC is missing, causing them to produce only α-MSH and never β-MSH, yet they still function normally (25).

γ-MSH. γ-MSH activates the MC3R, influencing energy balance depending on diet (29). It plays a role in the regulation of the cardiovascular and renal systems. In rodents, a high-sodium diet increases γ-MSH levels, which supports sodium excretion by the kidneys and controls blood pressure. A deficiency of γ-MSH leads to salt-sensitive hypertension, which can be corrected by administering the peptide, indicating its crucial role in regulating sodium homeostasis and blood pressure (39).

β-EDP. β-EDP is a peptide that acts as a neurotransmitter and neuromodulator, exerting long-lasting ef-

fects on the body. It functions as a potent analgesic, euphoric, and anti-depressant. β-EDP primarily acts on μ-opioid receptors (MOR) and δ-opioid receptors (DOR), but also affects κ, Σ, and ε receptors, with MOR and DOR playing key roles in the functions of β-EDP (65, 81). β-EDP is part of the opioid receptor agonist system, which also includes α-neoendorphins, enkephalins, and dynorphins. They primarily act on the derivatives, producing potent analgesic effects stronger than morphine, and also influence other opioid receptors. β-EDP decreases cyclic adenosine monophosphate (cAMP) levels and calcium uptake and is released into the periphery in response to pain or stress, suppressing somatosensory fibers, mainly nociceptors (68). β-EDP reduces locomotion and pain, improves slow-wave sleep, and induces analgesia, in contrast to MSH (47).

LPH. LPH is a 91-residue polypeptide that was first isolated by Birk and Li in 1964. It contains an amino acid sequence similar to α-MSH. Initially, β-MSH was thought to be the biologically active equivalent of α-MSH in LPH (77). In the 1970s, it was discovered that hormones such as LPHs, primarily β-LPH, released from POMC, stimulate lipolysis and mobilize lipids through adipocytes (9). Subsequent discoveries revealed that a 31-residue fragment of LPH has potent opioid activity, and LPH itself is a fragment of a larger prohormone. LPH plays a role in the production of biologically active peptides, such as β-EDP (77). β-LPH is a precursor of β-EDP and β-MSH (35).

The role of POMC in body weight regulation

Obesity is a global health issue and the fifth leading cause of death worldwide, resulting from an energy imbalance between calories consumed and calories expended. It significantly increases the risk of many chronic conditions, including CVD, diabetes, and cancer, negatively affecting almost every organ system in the body (74). The POMC gene indirectly plays a crucial role in regulating physiological processes (59). Mutations in POMC lead to metabolic disorders, highlighting the importance of this gene in maintaining health and energy balance in the body (59). Ablation of POMC neurons or a deficiency in POMC or MC4R leads to obesity in rodents and humans (66).

The hypothalamus plays a crucial role in regulating energy and glucose homeostasis by receiving central signals (e.g., α-MSH, β-EDP, ACTH) and peripheral signals (e.g., leptin, insulin, adiponectin, glucagon-like peptide-1, and glucagon-like peptide-2). Understanding the mechanisms of these hormones and signals is crucial for developing new therapies for metabolic disorders associated with obesity (88).

POMC neurons play a complex role in glucose homeostasis. Their activation can either lower or increase glucose levels depending on the physiological context (64). For example, activation of POMC neurons selectively inhibits food intake and weight gain by integrating long-term obesity signals from the hypothalamus with short-term satiety signals from the brainstem (94). These neurons release melanocortins (α-MSH and β-MSH) that activate MC3R and MC4R receptors to reduce food intake and increase energy expenditure (41). Additionally, the function of POMC neurons can be disrupted by an HFD, affecting their ability to detect glucose and leading to changes in mitochondrial dynamics and interactions with the endoplasmic reticulum. This disruption contributes to the dysregulation of the homeostatic activity of these neurons during obesity (41). Moreover, α-MSH is thought to act antagonistically to orexigenic neuropeptides such as NPY and AgRP, which increase appetite (35). While α-MSH activates MCRs to counteract weight gain, AgRP inhibits these receptors, promoting weight gain (87). In addition to reducing appetite, α-MSH stimulates thermogenesis by enhancing sympathetic nervous system activity, which leads to the activation of brown adipose tissue (BAT). In BAT, α-MSH increases the expression of uncoupling protein 1, which plays a crucial role in heat production and energy expenditure. Although the expression of POMC in adipose tissue is not well-defined, POMC-derived peptides, such as α-MSH, may influence lipolysis and lipid metabolism, which are important for regulating body weight and energy storage (35).

The regulation of body weight is a complex process influenced by various hormonal signals, among which the hormone leptin plays a pivotal role. Leptin, produced by adipocytes, activates POMC neurons, which also contribute to the regulation of body weight (30). Activation of POMC neurons by leptin, a satiety hormone, further reduces food intake (59). Leptin acts on LEPR in POMC neurons, which increases energy expenditure and reduces appetite by promoting processes such as thermogenesis in BAT. LEPR activation leads to signaling through the JAK2-STAT3 and PI3K/AKT pathways, which inhibits the expression of orexigenic neuropeptides and stimulates the production of α-MSH (35). Studies have shown that approximately 30% of POMC neurons in the hypothalamus respond to leptin, suggesting their significant role in mediating the metabolic effects of this hormone. Deletion of LEPR from POMC neurons impairs hepatic glucose production without affecting body weight, food intake, or energy expenditure. Furthermore, POMC neurons help regulate leptin levels, particularly during fasting when plasma leptin levels drop. Additionally, changes in adrenergic receptor activity in adipocytes affect leptin expression and production, indicating a complex mechanism of leptin regulation by the CNS (15). Interestingly, while obese individuals typically have reduced levels of adiponectin, Arc POMC −/− mice, particularly females, exhibit elevated adiponectin levels despite obesity. This observation suggests a novel physiological pathway involving POMC neurons and the sympathetic nervous system that affects circulating

adiponectin levels, offering insights into its regulation and role in metabolic disorders (92).

In the fed state, leptin and insulin, released by adipocytes and pancreatic β-cells, cross the blood-brain barrier and bind to receptors on POMC neurons in the ARC of the hypothalamus. This promotes the processing of POMC into α-MSH, which signals reduced food intake and increased energy expenditure by activating MC4R receptors in the paraventricular nucleus (PVN). During fasting, decreased levels of leptin and insulin, along with increased activation of NPY/AgRP neurons, inhibit POMC neurons, leading to reduced firing of MC4R neurons and increased food intake (4).

POMC neurons also express the glucagon-like peptide-1 receptor (GLP-1R) and are stimulated by GLP-1 agonists such as liraglutide. Peripherally administered liraglutide binds to receptors expressed on POMC neurons. Given that it is an analog of GLP-1, it can be inferred that this peptide exhibits a direct stimulatory effect on POMC neurons. GLP-1 may also affect these neurons indirectly by modulating the activity of GLP-1-sensitive presynaptic terminals. This has been confirmed by ultrastructural studies examining the relationship between POMC neurons and GLP-1R-immunoreactive structures, as well as the impact of GLP-1 signaling on the inputs to POMC neurons (66).

Conversely, ghrelin stimulates appetite by activating NPY/AgRP neurons and indirectly inhibiting POMC neurons, thereby reducing the effects of α-MSH on food intake reduction. NPY inhibits α-MSH release, decreasing the conversion of POMC to α-MSH and promoting a positive energy balance, while α-MSH can counteract the orexigenic effects of NPY. AgRP antagonizes α-MSH by blocking MC3R and MC4R, leading to increased food intake and body weight (86). Despite extensive research on the effects of hormones, nutrients, and neuropeptides on POMC neurons, the interactions between these signals are poorly understood (79).

Clinical studies of POMC, significance for the development of therapies in obesity and other diseases

Animal studies play a crucial role in the development of medicine, allowing scientists to better understand the functioning of the human body and discover new therapies. Thanks to these studies, it is possible to develop effective treatments for many diseases, which are later successfully applied to humans (75). Moreover, the knowledge gained from treating humans is often applied in veterinary medicine, contributing to the improvement of animal health (45). This mutual exchange of information between human and veterinary medicine continuously helps refine therapeutic methods for both species (28).

POMC deficiency is an extremely rare, treatable syndrome characterized by three key features that allow for early recognition: adrenal insufficiency, early-onset obesity, and red hair/light skin. However, the phenotype of this syndrome is highly variable and often accompanied by additional endocrine disorders such as central hypothyroidism, and hypogonadotropic hypogonadism, providing new insights into the pathophysiology of POMC deficiency (21). As more case reports emerge, it becomes clear that POMC deficiency is a more complex endocrine disorder, extending beyond the classical triad of symptoms (21, 40). The critical role of POMC in various neuroendocrine functions – such as energy balance, pigmentation, reproductive functions, and growth – stems from its interaction with multiple MCRs and ligands. However, the precise contribution of POMC and its derived peptides to these endocrine functions requires further research, as additional dysfunctions have been observed in some patients (33).

In the context of obesity, mutations in the MC4R gene are notably the most common cause of monogenic obesity, leading to extreme obesity (61). However, in cases of non-monogenic obesity, genome-wide association studies have shown a weak association between obesity and the MC4R gene suggesting that hypothalamic neuron activity in obesity is modulated by polygenic traits and external factors (54). Diet, for instance, is a key factor modulating hypothalamic function. Dietary fats can damage hypothalamic neurons and induce local inflammation, leading to resistance to leptin and insulin. Prolonged exposure to dietary fats can even cause apoptosis of POMC neurons (78).

One of the most significant achievements in the treatment of obesity related to POMC mutations is the development of setmelanotide, an MC4R agonist. In clinical trials, setmelanotide has demonstrated substantial efficacy in reducing body weight in patients with genetically induced obesity caused by POMC mutations. Its mechanism involves the activation of the melanocortin pathway, leading to decreased appetite and increased energy expenditure (19). Research on gene therapies aims to repair mutations in the POMC gene or increase the expression of functional POMC peptides. For example, gene therapy using viral vectors to deliver a correct copy of the POMC gene to the patient's cells has shown early promise, with the potential to restore normal appetite regulation and metabolism (76).

Moreover, studies have shown a link between prenatal exposure to certain chemicals, like triclosan, and the development of an obesity phenotype in male and female rats. Rats exposed to triclosan during early to mid-pregnancy (days 6-14) had lower birth weights but exhibited increased POMC methylation by day 30 (significantly higher in 6 CpGs across the POMC promoter), decreased POMC expression, and later developed early hyperphagic obesity and metabolic syndrome (13). Overall, ongoing clinical research on POMC and its role in obesity and other diseases indicates its significant therapeutic potential. Therapeutic

modulation of POMC pathways can lead to effective treatments not only for obesity but also for various other diseases associated with the dysfunction of this protein. Continued research and the development of gene therapies, as well as drugs targeting MCRs, could bring substantial clinical benefits (78).

Importance of research on POMC in mammals

Dogs and cats. The growing awareness of the prevalence of obesity among domesticated companion animals is becoming increasingly noticeable (72). Obesity in dogs is associated with a shorter lifespan and numerous diseases, similar to those observed in obese humans (58). The increase in the prevalence of obesity in dogs in recent years mirrors a similar trend observed in humans. Environmental factors, such as limited physical activity and easy access to high-calorie food, contribute to this phenomenon (34). Despite the fact that owners have control over their dogs' diet and physical activity levels, susceptibility to obesity varies by breed, indicating a significant role of genetic factors. One notable example is the Labrador Retriever, a breed particularly prone to obesity due to a mutation in the POMC gene (57, 70). This mutation disrupts the production of β-MSH and β-EDP, which play key roles in the regulation of energy in the body and occurs exclusively in Labradors and closely related Flat-Coated Retrievers (70). A 14-base pair deletion in the POMC gene in Labradors is associated with obesity and increased motivation to eat, similar to POMC mutations in humans that increase the risk of type 2 diabetes. Although obesity in dogs is not a major risk factor for diabetes (DM), obese dogs are hyperinsulinemic, and some studies suggest a link between being overweight and the diagnosis of diabetes in dogs (23). The POMC gene mutation in predisposed breeds increases the feeling of hunger between meals. Dogs with this mutation use 25% less energy at rest, meaning they require fewer calories to maintain a healthy weight. Dr. Eleanor Raffan from the University of Cambridge emphasizes that the mutation causes dogs to feel hungry more quickly, leading to overeating. Therefore, owners of these breeds must be particularly cautious about their dogs' diets, as they are more motivated to eat but burn fewer calories (25). Studies also show that obesity is more common in older Labrador Retrievers than in younger ones, while no link was found between coat color and obesity. Assistance/rescue dogs, despite having a greater genetic predisposition to obesity (POMC mutation), were statistically leaner than pet dogs, mainly due to more frequent physical activity and better dietary management. In assistance dogs, regular exercise and lack of access to human food limited the development of obesity (55).

Research on the POMC gene in cats is still underdeveloped and requires further investigation. Studies by Ghielmetti et al. revealed that cats classified as obese at 8 months showed increased food intake. This suggests that kittens with a higher body condition score may have impaired satiety mechanisms, leading to overweight phenotypes. Future research should focus on analyzing genes like MC4R, NPY1R, and POMC, which are related to food intake and activity levels (31). Additionally, a missense variant in POMC (c.28G > C; p.G10R) has been linked to higher body mass and fat content in domestic short-haired cats, potentially influencing fat metabolism and feeding behavior. Further studies are needed to clarify these mechanisms (42).

Cattle and horses. Beef carcass yield affects the profits of distribution companies, while meat quality influences consumer decisions. Current research focuses, among other things, on the factors determining meat quality grades as well as carcass yield (44).

Genes related to the appetite pathway, particularly variants in the proopiomelanocortin (POMC) genethe 12-base pair deletion (c.293_304del) and SNP c.288C > T affect the carcass composition of beef cattle. Genotyping these variants in 386 crossbred steers showed that animals with one copy of the deletion had a significantly smaller longissimus dorsi muscle area, and SNP c.288C > T was associated with body weight, fat content, and marbling. The findings suggest that knowledge of the genotypes of these POMC variants may be beneficial for beef producers when making marketing and selection decisions (24).

In older horses, the most common endocrine disorder is Pituitary Pars Intermedia Dysfunction (PPID), which manifests through symptoms like excessive hair growth, muscle weakness, lethargy, and increased thirst (46). PPID is linked to the loss of dopaminergic inhibition, leading to neurodegeneration in the hypothalamus and overproduction of POMC peptides such as ACTH and α-MSH (14). Excessive secretion of POMC peptides, characteristic of Cushing's disease, often leads to laminitis and elevated cortisol levels (hypercortisolism). Better dietary analysis methods and an understanding of the endocrine impact on hoof health are necessary to prevent laminitis in affected horses (43).

Mouse studies as the key to understanding the mechanisms of human obesity

The relevance of POMC peptides is also evident in mice. Mice lacking peptides derived from POMC exhibit symptoms such as obesity, abnormal adrenal development, and altered pigmentation, which closely resemble those seen in humans with POMC deficiency. Remarkably, treating these mice with a stable α-MSH agonist resulted in a loss of over 40% of their excess body weight within two weeks. These findings not only support the use of POMC mutant mice as models for studying the human POMC deficiency syndrome but also suggest that peripheral melanocortin might offer potential therapeutic applications for treating obesity (52).

The significance of POMC peptides is particularly pronounced in humans. The first cases of POMC mutations in humans were documented by Krude et al. in 1998. These mutations disrupt the production of key peptides such as α-MSH, β-MSH, and ACTH, which are involved in the regulation of appetite, energy homeostasis, and adrenal function. As a result, individuals with POMC mutations experience uncontrolled weight gain from early childhood, evident in early-onset obesity, adrenal hormone deficiencies that can lead to severe metabolic disorders, and characteristic red hair pigmentation due to the lack of α-MSH, which influences melanin production (49). In line with these findings, a recent case described a prepubescent Latino boy with a novel homozygous POMC mutation. This case manifested as severe obesity, hypothyroidism, adrenal insufficiency, and abnormal reddish hair pigmentation. Initial examinations revealed exponential weight gain, central adrenal insufficiency, and a homozygous mutation in exon 3 of the POMC gene. Treatment with metformin, initiated due to insulin resistance, led to a reduction in BMI (36).

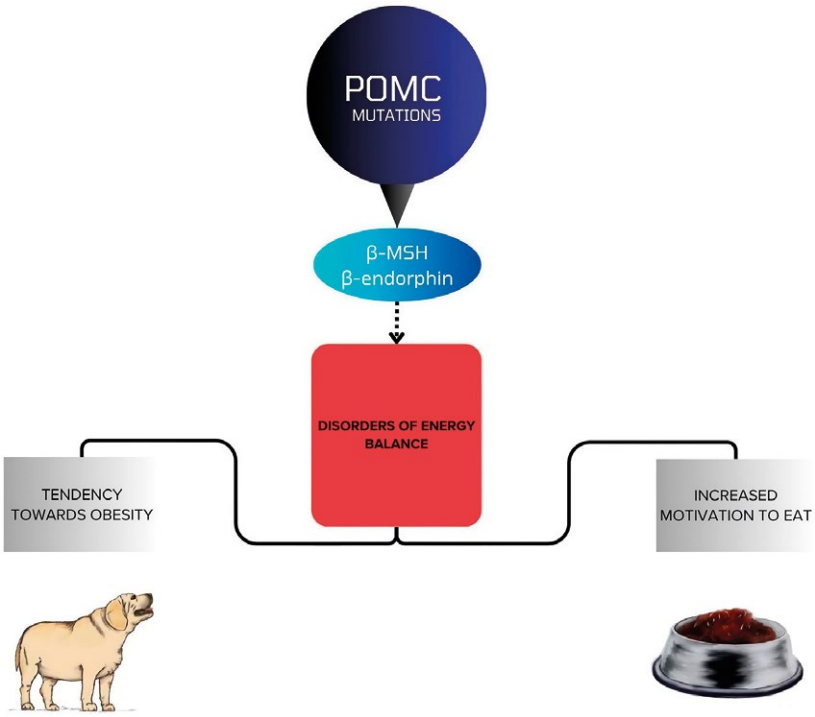

Fig. 2. Mutations in the proopiomelanocortin (POMC) gene in dogs that affect its active hormones, β-melanocyte-stimulating hormone, and β-endorphin (β-EDP), can lead to dysregulation of energy balance and appetite, thereby contributing to obesity

Building on our understanding of POMC's role in human and animal models, recent studies in mice have revealed important insights into how POMC influences energy regulation, with a particular focus on sex differences. POMC expression within 5-HT2CR-expressing neurons regulates energy intake and insulin sensitivity in both male and female mice. However, a significant sex difference exists: only male mice experience restored physical activity, energy expenditure, and normalized body weight, while females remain inactive with compromised BAT and develop obesity despite corrected feeding behavior and insulin levels. This sex-specific response highlights the need to consider sex differences in obesity treatment strategies. The subset of POMC neurons in question constitutes about 40% of all POMC neurons in the ARC (10).

Studies have also shown that faulty regulation of POMC in the hypothalamus is an early marker distinguishing obesity-prone (OP) mice from obesity-resistant (OR) mice, and early inhibition of POMC transforms OR mice into OP mice. The level of β-EDP in the blood after a meal correlates with weight gain in rodents and humans, suggesting it could be a marker of obesity susceptibility. Despite increased POMC expression in OP mice on an HFD, these mice were hyperphagic and gained weight. POMC is processed into α-MSH and β-EDP, which have opposing effects on calorie intake, suggesting that improper processing of POMC into β-EDP influences weight gain (see Fig. 2). In summary, changes in blood β-EDP levels after fat consumption may predict weight gain, necessitating further clinical studies (78).

Conclusions

POMC plays a crucial role in regulating body weight through the integration of neuroendocrine signals that influence appetite, energy expenditure, and overall metabolic balance. Peptides derived from POMC, such as α-MSH, are essential in activating MCRs, which suppress appetite and increase energy expenditure. Disruptions in the POMC pathway, due to genetic mutations, peptide processing changes, or receptor dysfunction, are strongly linked to the development of obesity. Future research on POMC should focus on detailed mapping of the signaling pathways associated with this protein. This is crucial for understanding how POMC regulates various physiological functions, including metabolism and immune response. POMC is a prohormone that, depending on enzymatic processing, can produce at least seven peptide hormones that interact with different MCRs.

Understanding the precise mechanisms by which POMC influences body weight regulation opens new therapeutic possibilities, enabling the development of targeted strategies for treating obesity and related metabolic disorders. Future studies should continue to explore the complexities of POMC signaling and its interactions with other metabolic pathways, which could contribute to fully harnessing the therapeutic potential of these discoveries.

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