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REVIEW

Participation of the central melanocortin system in metabolic regulation and energy homeostasis

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Abstract Obesity and metabolic disorders, such as type 2 diabetes and hypertension, have attracted considerable attention as life-threatening diseases not only in developed countries but also worldwide. Additionally, the rate of obesity in young people all over the world is rapidly increasing. Accumulated evidence suggests that the central nervous system may participate in the development of and/or protection from obesity. For example, in the brain, the hypothalamic melanocortin system senses and integrates central and peripheral metabolic signals and controls the degree of energy expenditure and feeding behavior, in concert with metabolic status, to regulate whole-body energy homeostasis. Currently, researchers are studying the mechanisms by which peripheral metabolic molecules control feeding behavior and energy balance through the central melanocortin system. Accordingly, recent studies have revealed that some inflammatory molecules and transcription factors participate in feeding behavior and energy balance by controlling the central melanocortin pathway, and have thus become new candidates as therapeutic targets to fight metabolic diseases such as obesity and diabetes.

Keywords Hypothalamus · Pro-opiomelanocortin · Agouti-related peptide · Neuropeptide Y · Leptin · Transcription factors · Posttranslational modification · Energy balance · Melanocortin pathway

Introduction

The rate of obesity in the worldwide population is rapidly increasing; consequently, it is also gaining attention in many countries as a serious life-threatening factor. Of all adults in the worldwide population, approximately 17 % are obese and 10 % are diabetic. Obesity is a predisposing condition for several other metabolic syndromes, such as hypertension, type 2 diabetes and stroke [1–3]. The development of this obesity epidemic is highly associated with complex and various abnormalities in delicate balance between caloric excess and body weight homeostasis. In other words, the precise coordination of multi-signaling between the peripheral tissues and central nervous system (CNS) is necessary for balancing food intake and energy expenditure, and thus preserves the overall energy standard; this system is compromised in obese individuals.

Many research efforts have primarily focused on the molecular, cellular and systemic integration of the CNS in the regulation of metabolism and feeding behaviors [4–6]. These scientists found that the neuronal networks in the hypothalamus sense a variety of metabolic signals generated by several peripheral systems and transported through the circulating blood stream, and in turn produce an equivalent tone of intra- and intercellular signaling into deep brain regions responsible for coordinated energy expenditure and

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feeding behavior. Specifically, the neurons in the arcuate nucleus of the hypothalamus (ARC), ventromedial hypothalamus (VMH), dorsomedial hypothalamus (DMH), lateral hypothalamic area (LH) and the paraventricular nucleus of the hypothalamus (PVN) are the first cells to respond to the numerous peripheral metabolic inputs, such as leptin and ghrelin. These neurons are anatomically localized around the third ventricle (3v), and they include biochemically discrete types of cells expressing certain receptors specific to the metabolic signal molecules that originate from both the peripheral tissues and CNS [7–11].

The ARC includes two physiologically distinct types of neuronal populations, the proopiomelanocortin (POMC) neurons and the agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons [12, 13]. To date, numerous studies have focused extensively on the mechanisms relying on these neurons that are associated with energy balance. The AgRP/NPY neurons are localized more medio-centrally to the 3v, while most POMC neurons are localized more laterally. The AgRP/NPY neurons sense the hunger-related signal molecules, including ghrelin, and individually play a pivotal role in energy homeostasis [14, 15]. Particulary, recent findings revealed that stimulation of AgRP neuronal activity using channelrhodopsin-2-based photostimulation evoked animals' feeding behavior independent of the melanocortin system [16]. In this study, activation of <1,000 AgRP neurons was sufficient to trigger an animal's food intake, and the degree of change in feeding behavior was positively correlated with either increased duration or frequency of the photostimulation of AgRP neurons. Interestingly, this AgRP neuron-evoked feeding behavior was regulated by the γ-amino-butyric acid (GABA) input to the other brain regions, suggesting that the GABA component of AgRP neuron is crucial in the regulation of feeding behavior, independent of AgRP release from the same neuron.

Among the extra-hypothalamic brain regions, it has been reported that certain nuclei in the brainstem, including the dorsal motor vagal nucleus (DMV), the parabrachial nucleus (PBN) and nucleus of the solitary tract (NTS), also play critical roles in whole-body physiologies related to metabolism regulation, such as feeding behavior, blood pressure and gastric function [17–24]. The PBN has been specifically implicated as a participant in energy homeostasis and feeding behavior, independent of the melanocortin system [25]. The AgRP neurons in the ARC (ARC-AgRP neurons) inhibit the PBN, and, thus, ablation of ARC-AgRP neurons resulted in anorexia and starvation behaviors through the hyperactivation of PBN neurons [24]. However, anatomical and biochemical evidence revealed that a main function of the AgRP/NPY neurons in metabolism regulation is achieved through the melanocortin pathway, which provides inhibitory signals to the melanocortin system [26–28]. In reality, the AgRP/NPY system is a negative counterpart of melanocortin signaling in energy homeostasis. Thus, we next describe in detail the mechanisms how the melanocortin system of the brain affects energy homeostasis and feeding behavior.

The melanocortin system in the regulation of metabolism

The central melanocortin system detects and integrates a variety of hormonal, neuronal and nutritional metabolic signals, such as leptin, insulin, glucose, leucine and serotonin, and regulates energy homeostasis [29, 30] (Fig. 1). Melanocortins are a family of small peptides, which originate from the POMC precursor. A recent study indicated that postnatal ablation of POMC neurons in the brain leads to the development of an obese phenotype with a reduced energy expenditure, similar to that observed in leptin-deficient animal models [31]. A similar metabolic phenotype as with ablation of POMC neurons was observed in a mouse model with *Pomc* gene deletion [32, 33]. Several research groups reported that a mutation in POMC is highly correlated with obesity development in humans [34–36]. On the other hand, studies using animal models overexpressing POMC, either by genetic modification or by virus-associated gene delivery, have demonstrated that these animals were protected from obesity development [37–39]. These studies clearly demonstrated a role of the central POMC system in metabolic regulation and feeding behavior.

In the brain, POMC-producing neurons are localized in several discrete regions including the pituitary, the ARC and the brainstem. In the ARC, it is believed that distinct groups of POMC neurons project into other hypothalamic areas such as the PVN and the LH, as well as the brainstem area, all of which are known to be critical for energy homeostasis [12, 13]. Recently, it has also been reported that in the ARC, POMC neurons expressing leptin receptors do not express serotonin receptors, and vice versa, suggesting the existence of heterogeneous POMC populations in the ARC [40, 41]. POMC-expressing neurons are also found in the NTS of the brainstem [20]. These cells also produce leptin receptors, but do not respond to leptin [21, 42]. It is believed that POMC neurons in the ARC are responsible for the long-term regulation of feeding behavior, which is directly correlated with adiposity, while POMC neurons in the NTS are important for the control of short-term satiety signal [19]. Using the DREAD (designer receptors exclusively activated by designer drugs) method and diphtheria toxin-induced specific ablation of POMC cells either in the ARC or NTS, Zhan et al. [19] also revealed that ablation of POMC cells, only in the ARC and not in the NTS, increased food intake and led to the development of an obese phenotype in animals. As described above, the POMC neurons

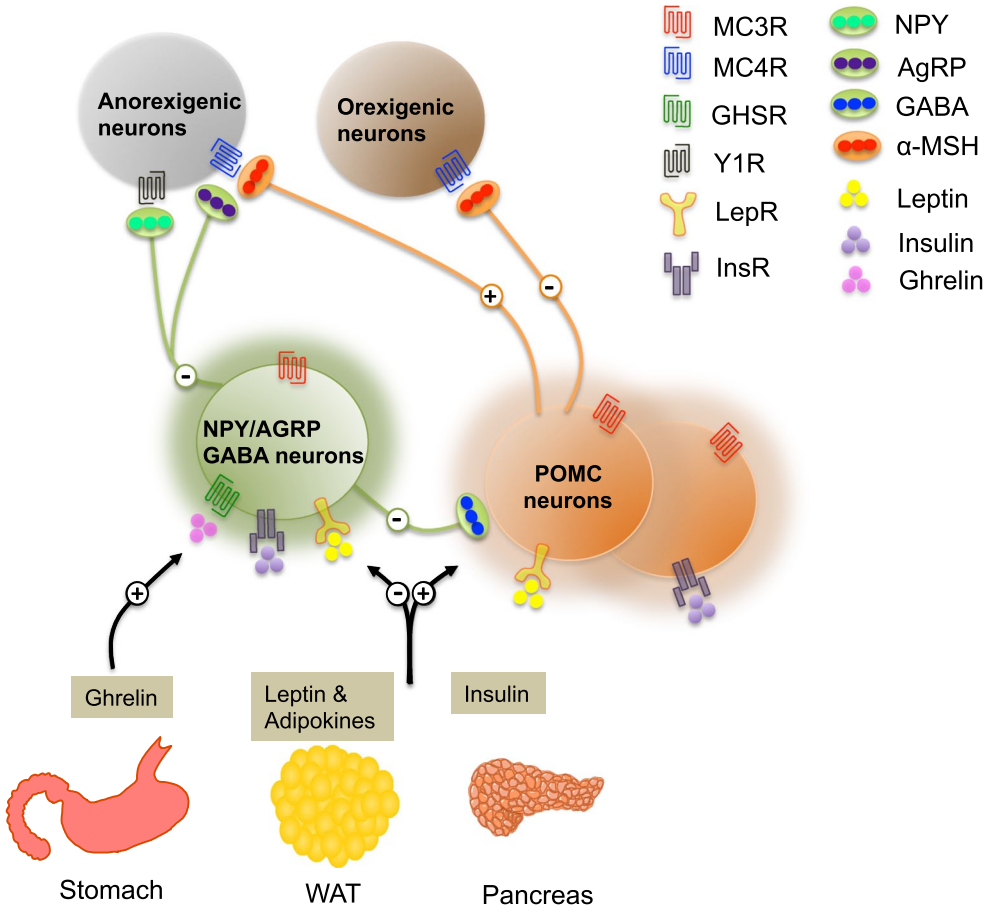

Fig. 1 Hypothalamic melanocortin pathways regulating central energy metabolism. The hypothalamic arcuate nucleus detects a variety of metabolic signals, which originate from several peripheral organs including the gut, adipose tissue and pancreas. For example, the AgRP/NPY neurons express ghrelin receptors, and, thus, specifically detect a gut-derived and hunger-related metabolic molecule, ghrelin, to facilitate energy intake. On the other hand, distinct subtypes of POMC neurons produce either leptin or insulin receptors and respond to the anorexigenic molecules such as adipose-originated leptin or pancreas-derived insulin. Notably, POMC neurons expressing leptin receptors do not co-produce insulin receptors, and vice versa, indicating the existence of heterogeneous subtypes of POMC neurons in the hypothalamus. AgRP/NPY neurons also express leptin and insulin receptors; however, these molecules negatively regulate the AgRP/NPY neuronal activity, unlike POMC cells. POMC and AgRP/NPY neurons project their axon terminals into various brain regions and activate and/or inactivate target cells expressing the dominant melanocortin receptors MC3/4R. Indeed, POMC and AgRP/NPY neurons are in functional opposition to one another. POMC neurons stimulate a satiety response by releasing α-MSH, the most well-known POMC-derived small melanocortin associated with energy balance and feeding behavior, to the anorexigenic system. AgRP/NPY neurons release AgRP and NPY, which are naturally appearing, endogenous antagonists of α-MSH, to the anorexigenic system. Furthermore, AgRP/NPY neurons also create synaptic connections with the POMC system and release GABA to inactivate this system. Overall, a precise coordination of signaling between the POMC and AgRP/NPY systems in the hypothalamus, in concert with metabolic status, is critical for balancing feeding behavior and whole-body energy homeostasis. *NPY* neuropeptide Y, *AgRP* agouti-related peptide, *GABA* gamma-aminobutyric acid, *α-MSH* α-melanocyte-stimulating hormone, *MC3/4R* melanocortin-3/4 receptor, *GHSR* growth hormone secretagogue receptor, *Y1R* neuropeptide Y Y1 receptor, *LepR* leptin receptor, *InsR* insulin receptor, *WAT* white adipose tissue

monitor a variety of circulating signal molecules directly associated with energy balance. However, the detailed relationship between heterogeneous POMC populations with differential projections and their different roles associated with energy homeostasis is not yet understood.

Numerous studies have also shown that cellular signaling within POMC neurons is closely associated with the complex processes for posttranslational modification of POMC protein. POMC is a prohormone that produces several small peptides, such as alpha-melanocyte-stimulating hormone (α-MSH), through a series of protein modification. Therefore, this review will now describe in detail some recently discovered upstream signaling molecules that regulate the POMC system, as well as a special role for leptin as a representative adipokine in this system and the posttranslational modification processes of POMC in

association with energy homeostasis. We will also discuss α-MSH, the most well-known POMC-derived melanocortin in the brain, and its receptor system.

Transcription factors for the melanocortin pathway

A great deal of attention has been paid recently to the identification of new signal molecules in the melanocortin system as potential candidates for the therapeutic treatment of metabolic disorders. Notably, some transcription factors are involved in appetite regulation through the transcriptional control of *Agrp* and *Pomc* genes in the brain (Fig. 2). The promoter regions of both *Pomc* and *Agrp* genes contain binding domains for forkhead protein 1 (Foxo1), which activates AgRP transcription, but inhibit POMC transcription as a downstream transcription factor of insulin signaling [43, 44]. On the contrary, signal transducer and activator of transcription 3 (STAT3) inhibits AgRP transcriptional activity and triggers gene expression of POMC by binding to the leptin-response element [45, 46]. The ablation of STAT3 in POMC neurons resulted in mild

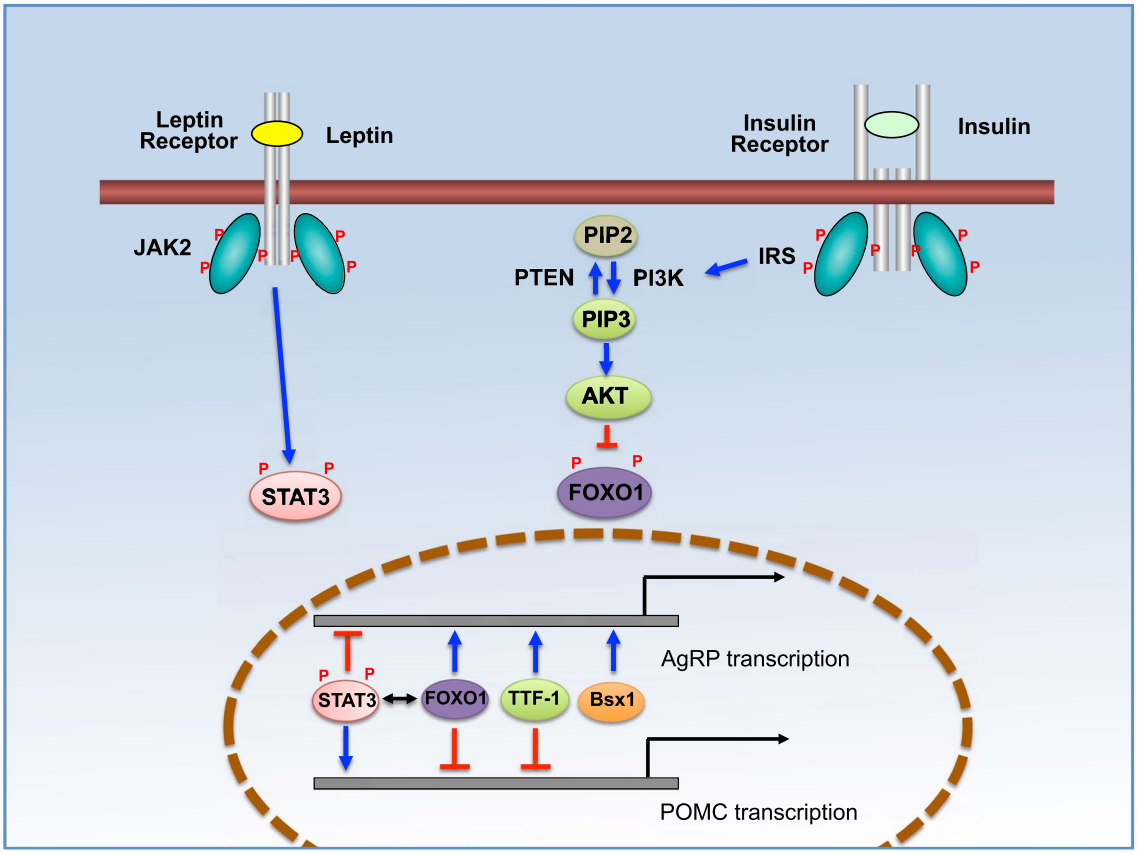

Fig. 2 Intracellular signaling pathways of leptin and insulin receptors in the central melanocortin system. Hypothalamic POMC and AgRP/NPY neurons express both leptin and insulin receptors. Binding of leptin and insulin to their receptors triggers sequential intracellular signaling cascades, finally affecting the transcriptional activity of the melanocortin system. Specifically, the binding of leptin to its receptor induces auto-phosphorylation of the receptor as well as the phosphorylation of JAK (pJAK2) that subsequently activates STAT3 signaling by phosphorylation of STAT3 (pSTAT3). pSTAT3 is then translocated into the nucleus and regulates the expression of genes encoding AgRP and POMC. Independent of leptin signaling, insulin binding to its receptor activates IRS, and further stimulates the PI3K pathway. PI3K phosphorylates PIP2 to produce PIP3 that becomes PIP2 reversely by PTEN-mediated dephosphorylation. PIP3 induces phosphorylation of AKT (pAKT) and pAKT inhibits phosphorylation of FOXO1. The dephosphorylated-FOXO1 directly binds to the promoter region of *Agrp* and *Pomc* genes and regulates their transcriptional activities. Interestingly, STAT3 and FOXO1 compete with each other for the binding domain. Recently, the involvement of some transcription factors in the regulation of central energy balance through the melanocortin system has been determined. Homeobox-containing transcription factors such as TTF-1 and Bsx are expressed in the hypothalamus. TTF-1 activates *Agrp* gene expression, but inhibits *Pomc* transcriptional activity via binding to its specific binding motifs in the *Agrp* and *Pomc* gene promoters. Unlike other transcription factors described above, Bsx1 triggers *Agrp* but not *Pomc* gene expression. *JAK*2 janus kinase 2, *STAT*3 signal transducer and activator of transcription 3, *AKT* serine/threonine-specific protein kinase, *FOXO*1 forkhead box protein O1, *IRS* insulin receptor substrate, *PI3K*, phosphoinositide 3 kinase, *PIP*2 phosphatidylinositol (4,5)-bisphosphate, *PIP*3 phosphatidylinositol (3,4,5)-triphosphate, *PTEN* phosphatase and tensin homolog, *TTF*-1 thyroid transcription factor-1, *Bsx* brain-specific homeobox transcription factor

obesity development with decreased *Pomc* gene expression [45].

Several lines of evidence have also demonstrated that homeobox-containing transcription factors such as thyroid transcription factor-1 (TTF-1) and brain-specific homeobox transcription factor (Bsx) are expressed in the hypothalamus and play a pivotal role in the regulation of *Pomc* and *Agrp* gene expression, thus influencing feeding behavior [47–49]. TTF-1 is also a member of the NKx family of homeodomain genes important for the development of the diencephalic brain region. Knockdown of TTF-1 biosynthesis in the rodent brain inhibited gene expression of *Agrp*, but activated *Pomc* transcription, and further resulted in a decrease in appetite and daily body weight gain of animals [47, 48]. Unlike TTF-1, ablation of Bsx in mice resulted in decreased *Npy* and *Agrp* gene expression as well as reduced locomotion and food-seeking behavior. Furthermore, the deletion of *Bsx* alleviated hyperphagic behavior of animals, which is generally observed in the leptin-deficient mouse model, and thereby prevented the animals from obesity development. Unlike other transcription factors mentioned above, Bsx is required only for *Agrp* gene transcription [49].

Role of inflammatory cytokines in POMC neuron function

In addition to the transcription factors, researchers have recently paid a great deal of attention to the function of inflammatory cytokines in feeding behavior. In rodents, some proinflammatory cytokines such as interleukin 6 (IL6) and tumor necrosis factor alpha (TNFα) were up-regulated, with an increased astrocytic density in the hypothalamus, during early phases of high-fat diet (HFD) treatment [50]. Up-regulation of inflammatory signals in the hypothalamus was also observed in obese humans [50]. An independent study demonstrated in detail the participation of inflammatory signaling in the transcriptional activity of the melanocortin system: rodents receiving lipopolysaccharide (LPS) treatment exhibited an increased level of *Pomc* gene expression in the ARC [51]. In addition, both POMC and AgRP/NPY neurons expressed type 1 interleukin-1 receptor 1 (IL-1R1), and the exogenous administration of IL-1-beta resulted in an increase in the firing rate of POMC neurons [52] and a decrease in the spontaneous release of AgRP [53]. Furthermore, inflammatory signaling in the hypothalamic melanocortin system is strongly associated with disease-related negative energy balance such as anorexia and cachexia [54–56]. These results clearly demonstrate the participation of inflammatory signaling in central regulation of metabolism, primarily through the melanocortin signaling pathway.

Leptin in the control of energy balance

Over the past decade, great scientific progress has been achieved to understand participation of the adipose tissue-derived cytokines (adipokines) in the control of energy homeostasis, including feeding behavior, thermogenesis and other neuroendocrine functions. These adipokines, including adiponectin, visfatin, vaspin, apellin and leptin [57–62], play critical roles for the control of hypothalamic melanocortin pathway. Among them, leptin participates in a variety of physiological and behavioral controls, as a representative adipocyte-derived signal modulator in association with energy homeostasis [13, 63–65]. For example, a mouse model with depletion of leptin ($Lep^{ob/ob}$) displayed a phenotype that was both obese and diabetic, with cold-intolerance, infertility and hyperphagic behavior [13, 64, 66]. Similarly, when leptin receptors in the brain were deleted, the animals displayed a hyperphagic phenotype concomitant with reduced whole-body energy expenditure [67–69]. Indeed, leptin-associated physiological effects are dominantly mediated by the brain [70]. The physiologically active form of leptin receptors is expressed in several regions of the brain including the hypothalamus, midbrain and brainstem of both neonatal and adult animals [71–75]. Among these brain regions, dense leptin receptor expression was detected in the discrete hypothalamic nuclei including the ARC, VMH and PVN. Consequentially, leptin directly modulates neural activity in these hypothalamic regions in a multi-directional manner [7] and influences whole-body energy metabolism in areas such as energy expenditure, feeding behavior and, as a consequence, body weight change [68, 76].

Intracellular signaling in POMC neurons

The mechanisms of intracellular signaling in the POMC system are complex. However, it is understood that both *Pomc* gene expression and the posttranslational modification of precursor protein, POMC, are important for tissue-specific POMC functions. In the ARC, for example, a certain population of POMC neurons produces leptin receptors, and leptin triggers POMC neuronal activity, which can be measured either by an electrophysiological recording or by biochemical determination of the degree of STAT3 phosphorylation and c-fos expression [11, 77–79]. Leptin also activates POMC gene expression in these cells [80]. In addition to leptin, other hormonal and nutritional signaling molecules such as insulin and glucose affect POMC neuronal activity and gene expression. A distinct population of POMC neurons expresses insulin receptors, through which insulin activates the phosphatidylinositol-3 kinase (PI3K) pathway (see Fig. 2) in POMC neurons [81]. Leptin and

insulin activate different intracellular signaling pathways in distinct subtypes of POMC neurons in the ARC, and may act together synergistically, and/or antagonistically, to modulate POMC-associated physiology [82, 83]. POMC neurons also sense circulating glucose, which stimulates ATP production in POMC neurons. Notably, impairment of glucose sensing by POMC neurons is linked to development of type 2 diabetes, partially mediated by mitochondrial uncoupling protein 2 (UCP2) signaling within POMC cells [29].

Alpha-melanocyte-stimulating hormone production by enzymatic processing of POMC

POMC is a prohormone for several small peptides such as adrenocorticotropic hormone (ACTH), α-MSH, γ-MSH and β-endorphin [84–86]. During the posttranslational process, the POMC precursor undergoes several modifications by a variety of proteases and enzymes, such as prohormone convertases (PCs), carboxypeptidase E (CPE) and peptidyl α-amidating monooxygenase (PAM) (Fig. 3). The differential expression of these proteases in distinct tissues and cells leads to the production of a variety of POMC-derived small peptides in the target regions [86]. In the hypothalamus, the POMC precursor is first processed to ACTH, β-lipoprotein (β-LPH) and the N-terminal POMC fragment (N-POC) by the action of PC1/3. Then, ACTH is further processed to α-MSH through sequential modification processes, including participation of several proteases and enzymes such as CPE, PAM and N-acetyltransferase, while β-LPH is processed to β-endorphin by PC2. A majority of POMC synthesized is converted to the physiologically active form of α-MSH in hypothalamic POMC neurons [86].

Of all the POMC products, α-MSH is the best-understood and most abundant signaling molecule in the hypothalamus associated with energy homeostasis. Several groups of scientists have demonstrated a physiological function of α-MSH in the regulation of metabolism [33, 39, 87]. The production of α-MSH in the brain closely coordinates with metabolic status. Studies using animal models, either with acute administration of an α-MSH agonist or with long-term overexpression of α-MSH in the brain,

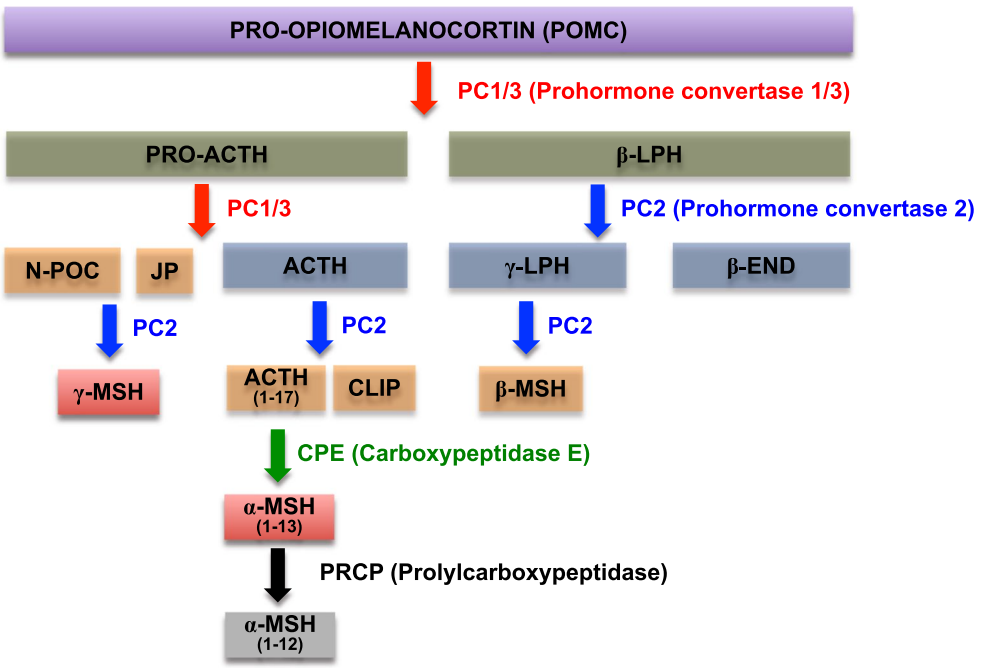

Fig. 3 Posttranslational processing of the POMC precursor protein. POMC is a precursor for several small melanocortin peptides such as α-MSH, γ-MSH and β-endorphins. Various enzymes and proteases responsible for the cleavage of POMC, such as prohormone convertases and carboxypeptidase, are expressed in several tissues. Different combinations of these enzymes are responsible for production of the different tissue-specific melanocortins. In the hypothalamus, POMC predominantly produces a physiologically active form of α-MSH (α-$MSH_{1–13}$), the most well-known melanocortin in the CNS related to metabolic regulation and feeding behavior, through sequential steps of protein cleavages and modifications. Recently, the molecular mechanism responsible for the degradation of α-MSH has also been determined. In this regard, PRCP cleaves one amino acid at the C-terminal end of α-MSH, producing a biologically inactive form of α-MSH (α-$MSH_{1–12}$). *ACTH* adrenocorticotropic hormone, *β- and γ-LPH* β- and γ-lipotropin, *JP* joining peptide, *β-END* β-endorphin, *CLIP* corticotropin-like intermediate lobe peptide, *α-, β- and γ-MSH* α-, β- and γ-melanocyte-stimulating hormone, *PC*1/2/3 prohormone convertase 1/2/3, *CPE* carboxypeptidase E, *N-POC* N-terminal pro-opiomelanocortin, *PRCP* prolylcarboxypeptidase

revealed that α-MSH inhibits feeding behaviors concomitant with an increase in energy expenditure, and therefore counteracts obesity.

Recently, a cellular mechanism responsible for the inactivation of α-MSH has also been reported [88–92]. A small serine peptidase, prolylcarboxypeptidase (PRCP), is expressed in several hypothalamic regions and is released into distinct brain areas where α-MSH is also secreted by POMC-terminals [88]. PRCP effectively cleaves one amino acid from the C-terminal end of α-MSH (Fig. 3), thereby producing a physiologically inactive form of α-MSH [88]. Hypothalamic *PRCP* gene expression was shown to be affected by metabolic status, i.e., an increased level of *PRCP* gene expression was observed in the hypothalamus of fasted animals [92]. Once PRCP expression was abolished ($PRCP^{gt/gt}$), α-MSH levels in the brain were continuously increased. Consequently, $PRCP^{gt/gt}$ animals showed higher energy expenditure, reduced food intake and, as a consequence, lower body weight gain. Therefore, they were protected from diet-induced obesity [89, 90]. These evidences suggest that small population of POMC cells governs multiple physiologies by producing a variety of neuropeptides processed by posttranslational modification.

Melanocortin receptors

Anatomical and functional profiles of the melanocortin receptor subtypes in the mammalian brain have been understood since the 1990s. It was revealed that the melanocortin receptor types 3 and 4 (MC3R and MC4R, respectively) are widely expressed in the brain and play a dominant role as brain-specific melanocortin receptors, although other subtypes of melanocortin receptors are also expressed in the brain of various species [4, 93–97]. Interestingly, genetically modified animals with a deletion of either MC3R or MC4R (*Mc3R* or *Mc4R* knockout mice) matured into an obese phenotype, and thus provided strong evidence for the involvement of MC3R and MC4R in the regulation of metabolism and feeding behavior in concert with melanocortins [1, 4, 98, 99].

Anatomical studies demonstrated that MC3R mRNA expression is abundant and widely present in mammalian brain, including the hypothalamic and limbic regions [100, 101]. Within the hypothalamus, MC3R expression is observed in certain nuclei, such as the ARC and the VMH, to be highly associated with feeding behavior and the regulation of metabolism. Particularly in the ARC, MC3R is produced both by POMC- and AgRP/NPY-ergic neurons [102, 103]. These anatomical evidences indicate the involvement of MC3R in energy homeostasis via transferring the auto-feedback signal of α-MSH on POMC neurons. However, a pathophysiological function of MC3R, in association with metabolic regulation, is ambiguous and still under debate. For example, variants of the *Mc3R* gene were not directly correlated with an obese phenotype in humans [104, 105]. However, a mutation of *Mc3R* in mice leads to the development of a moderately obese phenotype under a standard rodent diet, with an increase in adiposity, a decrease in locomotion and abnormal feeding behavior, without an observed hyperphagic syndrome [106]. In addition, obesity became pronounced in *Mc3R* KO animals when fed a high-fat diet [98, 99]. Recent data also proposed a role of MC3R in adaptation to food restriction [106]. Nevertheless, the pathophysiological significance and the detailed mechanisms by which MC3R plays a role in the control of energy homeostasis have yet to be elucidated.

When compared to other melanocortin receptor subtypes, MC4R has been established as a critical node for body weight homeostasis for a long time [107–109]. MC4R is expressed mostly in the CNS, although its expression is not restricted to the brain [93, 101, 110–114]. Studies profiling a pattern of MC4R expression revealed that gene expression of *Mc4R* is widespread in the brain, although it is predominantly expressed in the hypothalamus, the brainstem and the amygdala [114]. More specifically, the PVN, DMH, VMH and LH in the hypothalamus and the superior colliculus, NTS and DMV in the brainstem showed the highest levels of expression of MC4R, comparatively. This anatomical evidence supports a unique and complex function of MC4R in reproduction, stress, emotional behavior, and cardiovascular function as well as in energy homeostasis. Indeed, rare mutations in the *Mc4R* gene are associated with an obesity syndrome in humans [115–117].

Recently, much effort has also been expended to uncover MC4R-associated intracellular signaling and trafficking mechanisms for a better understanding of MC4R-mediated disease processes, and, accordingly, the participation of melanocortin receptor accessory proteins (MRAPs) was revealed in MC4R signaling [118–121]. MRAP was first identified as an MC2R accessory protein, and MRAP2 is a brain-expressed homologue of MRAP. In the brain, MRAP2 is most abundantly expressed in the hypothalamus and directly interacts with MC4R, influencing the sensitivity of MC4R to α-MSH as well as MC4R-mediated intracellular signaling, both in development and adulthood [120, 121]. In addition, mice with a deletion of MRAP2 developed a severely obese phenotype, clearly demonstrating the participation of MRAP2 in the MC4R-associated energy homeostasis [121]. Overall, the participation of MC4R signaling in energy homeostasis is clear. However, the brain region-specific differential roles of MC4R in metabolic regulation, in association with intracellular signal molecules interacting with MC4R, will require further study in order to provide better understanding of the pathophysiological effect of MC4R dysfunction.

Conclusions and perspectives

As obesity and other diseases associated with metabolic dysfunction, such as hypertension and type 2 diabetes, gain more attention worldwide as potentially life-threatening health factors, scientists have invested significant effort in developing preventative and curative therapies against these metabolic syndromes. In this regard, the participation of the CNS has been a focus in the study of metabolic regulation and whole-body energy homeostasis. In the brain, hypothalamic neural networks including the melanocortin system play an important role in sensing and integrating a variety of metabolic signals, and further triggering signaling cascades into deep brain regions to produce an adequate level of feeding behavior and energy expenditure, thereby preserving whole-body energy balance. Diverse studies have recently been performed to uncover unknown mechanisms underlying the hypothalamic melanocortin system. These studies have found that certain brain-specific transcription factors and inflammatory molecules participate in metabolic regulation through the melanocortin pathway.

Unfortunately, the mechanisms underlying the melanocortin pathway are complex and are still under debate. However, there is no doubt that the central melanocortin pathway plays a fundamental role in controlling whole-body energy homeostasis. Therefore, further investigation is necessary to clearly understand this system, which will in turn aid the fight against obesity and metabolic disorders.

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