REVIEW ARTICLE

Pigmentation and beyond: An overview of role of melanocyte stimulating hormone

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ABSTRACT

Melanocortins are tridecapeptides derived from proopiomelanocortin (POMC) by post-translational processing. POMC molecule serves as the source for several peptide hormones such as adrenocorticotrophin (ACTH), alpha melanocyte stimulating hormone (α-MSH), β-MSH and γ-MSH, and also the endogenous opioids including β-endorphin. They were originally identified as a product of the pituitary gland. However, recent evidence shows that POMC products are mainly produced by various non-pituitary tissues. Alfa-MSH has many effects beside its main action on melanocyte and melanogenesis. It has a potent anti-inflammatory, immunomodulatory action. It controls obesity, and also has an antimicrobial and a candidicidal activity through its C-terminal peptide fragment (KPV). Five melanocortin receptors (MC-Rs) subtypes, MC-1R to MC-5R, have been identified and cloned. MC-Rs are more widely expressed all over the body than originally thought. In particular, MC-1R not only has been detected in melanocytes but also in the majority of non-melanocytic cutaneous human cell types, including inflammatory and immunocompetent cells. Recently, Afamelanotide, an alpha melanocyte stimulating hormone (α-MSH) agonistic analog has been introduced as first line therapy for treatment of diseases associated with absolute sunlight-intolerance such as erythropoietic protoporphyria (EPP). It has shown promising results, and a favorable risk-benefit profile.

KEYWORDS: MSH, melanogenesis, anti-inflammatory, immunomodulatory, afamelanotide

Melanocyte stimulating hormone (MSH)

Proopiomelanocortin (POMC) is proteolytically cleaved by prohormone convertases belonging to the family of serine proteases of the subtilisin/kexin type. For adrenocorticotrophin (ACTH), alpha melanocyte stimulating hormone (α-MSH), β-MSH and γ-MSH, the term melanocortins has been applied to describe the pigment-inducing capacity of these peptides. Alfa-MSH is a known tridecapeptide generated from its precursor ACTH[1] on proteolytic cleavage.

Alfa-Melanocyte stimulating hormone (α-MSH), Ac-Ser1-Tyr2-Ser3-Met4-Glu5-His6-Phe7-Arg8-Trp9-Gly10-Lys11-Pro12-Val13-NH2, has been originally recognized as an endogenous peptide which affects pigment formation and granules dispersion in the skin of lower vertebrates.[2] In mammals, this peptide has subsequently been implicated in physiological processes such as learning and memory, blood pressure, pigmentation, immune modulation, weight homeostasis, and others.[3] Although POMC peptides were originally considered as neuropeptides, it is now well established that POMC expression and processing may occur in many other peripheral tissues. The generation of melanocortins is controlled by endogenous mediators such as corticotrophin-releasing hormone, pro-inflammatory cytokines such as interleukin 1 (IL1) and tumour necrosis factor α (TNFα), as well as exogenous noxious stimuli such as ultraviolet radiation UVR and microbial agents.[4] C and N-terminal fragments of α-MSH

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both have significant melanotropic effects. Moreover, the C-terminal peptide fragment of α-MSH (KPV) exerts a similar, or even more pronounced anti-inflammatory activity as full-length α-MSH.[5] KPV exerts an antagonistic activity via blocking (IL1) activity, which ultimately contributes to terminating (IL1)-mediated inflammation.[6] The use of this peptide as an anti-inflammatory agent is limited by its low selectivity between the different melanocortin receptors, susceptibility to proteolytic degradation, and rapid clearance from circulation.[7] Even though α-MSH has some effects as a successful anti-inflammatory agent, its use as a systemic therapeutic agent is not appealing because of undesirable effects on hormonal regulation. Energy homeostasis through melanocortin receptor 4 (MC-R4) agonism results in appetite suppression, increased lipid metabolism, and weight loss.[8]

Melanocortin receptors (Table 1)

Melanocortins (α-MSH, β-MSH, γ-MSH and ACTH) bind with melanocortin receptors (MC-Rs) which belong to the superfamily of G-protein coupled receptors with seven transmembrane domains. These receptors bind the melanocortin peptides with differential affinity. Proopiomelanocortin (POMC) peptides have been shown to activate adenylate cyclase upon binding specific G-protein coupled receptors (GPCRs) and result in accumulation of intracellular cyclic adenosine monophosphate (cAMP).[9] Five MC-R subtypes, (MC-1R to MC-5R), have been identified and cloned.[10] (Table 1) MC-1R was the first melanocortin recep-

Table 1 Characteristics of MC-Rs types

Subtypes	Agonist profile	Tissue expression[A]	Identified cell type[b]
MC-1R	α-MSH> ACTH>>γ -MSH	Skin, brain, immune system, gut, testis, ovary, placenta, lung, liver, adrenal gland, skeletal muscle	Melanocytes, keratinocytes, fibroblastic cells, endothelial cells, secretory epithelia, microglia, astrocytes, monocytes/ macrophages, lymphocytes, neutrophils, mast cells, intestinal epithelia, Leydig>s cells, lutein cells, trophoblastic cells, skeletal muscle cells
MC-2R	ACTH	Adrenal glands, testis, skin, adipose tissue, pancreas	Cells of the zona fasciculata and glomerolosa, adipocytes, keratinocytes, lymphocytes, Bpancreas cells
MC-3R	γ-MSH = ACTH ≥α-MSH	Brain, heart, immune system, skeletal muscle	Macrophages, intestinal epithelial cells, lymphocytes
MC-4R	α-MSH =ACTH>>γ-MSH	Brain, skin, skeletal muscle	Dermal papilla cells, skeletal muscle cells, lymphocytes
MC-5R	α-MSH≥ACTH> γ -MSH	Skeletal muscle, brain, skin, exocrine glands, lung, heart, spleen, immune system, kidney, adipose tissue, adrenal gland, uterus, ovary, placenta, bone marrow, skeletal muscle	Adipocytes, mast cells, secretory epithelia, macrophages, skeletal muscle cells, intestinal epithelial cells, lymphocytes

[a] Including immortalized cell lines and tumor cells.

[b] As detected in the murine or human system. Source Brzoska et al[25]

tor cloned from melanocytes, it has been demonstrated that MC-1R plays an important role in the regulation of melanogenesis and pigmentation. Functional mutations of this receptor greatly impact the fur color in mammals as well as hair and skin color in humans.[11] The melanocortin 1 receptor (MC-1R) has been detected on the surface of several types of skin cells (melanocytes, keratinocytes, sebocytes, and others) and also on various melanoma cells. It has been found to control the relative amounts of eumelanin and pheomelanin in mammals.[12] Variants of MC-1R which do not exhibit any function are associated with fair skin, poor tanning, propensity to freckle and increased risk of skin cancer.[13] Moreover, MC-1R has been suggested to be critically involved in melanoma susceptibility since certain mutations in the MC-1R gene are strongly associated with increased melanoma incidence by sensitizing melanocytes to the cytotoxic effects of UVR irradiation.[14] MC-1R has also been detected in other peripheral sites: the pituitary, testis, corpus luteum, placenta, endothelial cells, glioma cells, astrocytes, and in low levels in the brain.[15] Its presence on the surface of various immune cells such as macrophages, fibroblasts, monocytes, mast cells, neutrophils and dendritic cells, suggests its involvement in endogenous control of some inflammatory processes.[16] Human MC-1R is activated equally well by αMSH and ACTH, and to a lesser degree by βMSH and γMSH.[17] MC-2R is selective only for ACTH.[10] Furthermore, human melanocortin 2 receptor (MC-2R) for ACTH binding, and signaling are different from that of other melanocortin receptors.[18]

Humphreys et al[19] found that there are important effects of MSH's, particularly γ-MSH (the melanocortin 3 receptor, MC-3R), on sodium metabolism and blood pressure regulation in rats.

Activation of the MC-4R by α-MSH increases the energy expenditure, decreases the food intake, and promotes sympathetic activity.[20] Mutations in the POMC gene in humans (MC-4R) have resulted in obesity.[21] Spencer and Schallreuter in 2009 got results that imply an important role for the β-MSH/MC4-R cascade in human melanocyte biology, although the function and purpose of this signal in keratinocytes needs furthermore elucidation.[22] In addition, bioavailable small molecule MC-4R antagonists have shown efficacy in erectile dysfunction.[23]

The expression of melanocortin receptor (MC-5R) has been found to be associated with sebocyte differentiation and sebum production. Sebaceous lipids are down-regulated in melanocortin (MC-5R) receptor-deficient mice; consistent with the observation that (α-MSH) acts as a sebotropic hormone in rodents. The melanocortin receptor (MC-5R) antagonists may prove to be clinically useful for the treatment of sebaceous disorders with excessive sebum production, such as acne vulgaris.[24]

Melanogenesis and melanocortins (Fig. 1)

Melanocytes are key components of the skin's pigmentary system by their ability to produce melanin. These cells are found in many locations all over the body. In the skin they are found within the hair follicle and in some mammals, including humans, are also present in the basal layer of the interfollicular epidermis. Mature melanocytes have long dendritic processes that ramify among the neighboring keratinocytes. In this way, each melanocyte makes contact with around 30-40 keratinocytes which constitutes the epidermal-melanin unit. This association enables the melanocyte to transfer melanin into the keratinocytes, where it deter-

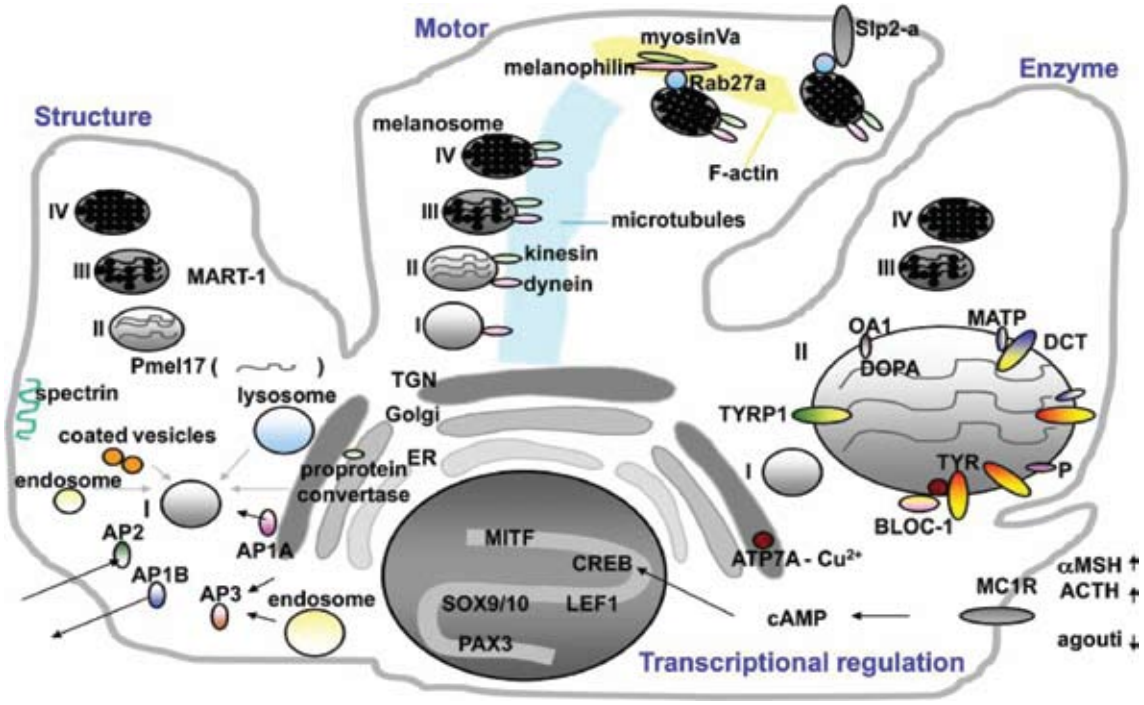

Fig. 1 Factors that affect skin pigmentation within melanocytes.[39]

mines skin color and helps to protect against the damaging effects of ultraviolet radiation (UVR).[26] Melanocytes are the unique cells that produce melanosomes, which are specific melanin-containing intracellular organelles that share several features with lysosomes in that they contain acid-dependent hydrolases and lysosomal-associated membrane proteins (LAMPs).[27] Melanosomes can be classified into four distinct stages (I-IV) according to their degree of maturation. Intraluminal fibrils begin to form in amorphous spherical (stage I) melanosomes and generate a meshwork characteristic of (stage II) melanosomes, both stages lacking melanin pigment and being usually called early melanosomes. Melanin synthesis begins within the fibrillar stage II melanosomes and the melanins are deposited uniformly on the internal fibrils resulting in the production of (stage III) melanosomes. In heavily pigmented melanocytes, all structural detail is eventually obscured due to the presence of copious amounts of melanin in (stage IV) melanosomes. Melanosomes are classified as lysosome-related organelles (LROs), and recent studies characterizing the proteomes of early melanosomes show that they are derived from the endoplasmic reticulum (ER), coated vesicles, lysosomes and endosomes.[28,29]

The main site of α-MSH production is from the pars intermedia of the pituitary gland. However, because of its poorly developed pars intermedia, the pituitary of human secretes only small amounts of α-MSH except under pathological conditions.[30] However, α-MSH and other melanocortin peptides are produced at extrapituitary sites, including the skin.[31] Although they are produced in other cell types in the skin, including melanocytes, and Langerhans cells, epidermal keratinocytes are a major source of these peptides.[32]

When binding of the MC1-R and α-MSH occurs, it activates adenylate cyclase which, in turn, causes an increase in intracellular cAMP. This is the classical pathway by which α-MSH is believed to

mediate its melanogenic effects in melanocytes. Increases in cAMP result, through protein kinase A (PKA), in the activation of tyrosinase, the rate-limiting enzyme in the melanin pathway. Evidence suggests that α-MSH increases the expression, de novo synthesis, and activation of tyrosinase enzymes.[33] The PI3-kinase/p70S6-kinase pathway may be involved in regulating melanogenesis.[34] The possibility that other intracellular pathways are also activated on binding of α-MSH to its receptor must be kept in mind. For example, there is evidence that protein kinase C is involved in mediating the melanogenic actions of α-MSH on melanocyte.[35] Adding to its receptor-mediated effects, there is evidence to suggest that α-MSH is able to regulate tyrosinase activity independently of the MC1-R. α-MSH binds also (6R)-L-erythro 5,6,7,8 tetrahydrobiopterin (6-BH_4) and the latter has been shown to regulate the availability of <sc<L-tyrosine and the activity of tyrosinase in melanocytes.[36] α-MSH serves as a chaperone for 6-BH4, it could, through this interaction, modulate the synthesis of melanin.[37] Alfa-MSH regulates the pattern of melanogenesis by preferentially stimulating the synthesis of eumelanin (eumelanin is the most important and leads to more darkening of the skin) at the expense of phaeomelanin.[38] Alfa-MSH and cAMP, may lead to extensive changes in the ionic equilibrium of melanocytes, resulting in the alkalinization of melanosomes, which in turn leads stimulation of tyrosinase activity and favor melanin synthesis.[39]

There is evidence that α-MSH stimulates melanocyte dendricity in the melanocyte. The regulation of dendricity by α-MSH may be vital for the pigmentary response. This process may be dependent on activation of several intracellular signaling pathways. It appears mostly that cAMP is important, and there is evidence that, by acting on the GTP-binding proteins Rac and Rho, cAMP increases actin disorganization and promotes melanocyte dendricity.[40] Cyclic-AMP also stimulates the transport of melanosomes to the tips of dendrites by controlling Rab27a expression.[41] Other way in which α-MSH affects melanocytes, is by protecting these cells from the damaging effects of free oxygen radicals, such as the superoxide anion.[42]

It has been suggested that the pigmentary effects of UVR are mediated through melanocortin peptides such as α-MSH. Alfa-MSH could act as a paracrine and an autocrine factor in the regulation of melanocytes and skin pigmentation. In addition to its effects on melanocortin peptide secretion, UVR upregulates the expression of the α-MSH receptor[43] and increases the binding of α-MSH to human melanocytes.[44]

Cellular effect of α-MSH

MSH has a great effect on cytokines, inflammatory products, chemokines and others.

1. NF-kB-a known master regulator of inflammation suppressed by α-MSH. The molecular mechanism underlying the antiinflammatory effects of a-MSH, especially the modulation of proinflammatory cytokine and adhesion molecule expression is done by suppression of nuclear factor-KB (NF-kB) activation.[45] NF-kB deactivation by a-MSH is thought to be mediated by increased levels of (cAMP) and correlates with inhibition of the degradation of the inhibitory subunit of NF-kB, (IkBo). As a consequence, nuclear translocation of the p65 subunit of (NF-kB) is suppressed.[46]
2. The anti-inflammatory effect of α-MSH at the cellular level focused on the suppressive effect

of the peptide on expression of proinflammatory cytokines, interferon-y (IFN-y) and TNF- α[47]

3. α-MSH suppresses chemokines IL-8 and Gro α.[48] Also, other proinflammatory cytokines regulated by α-MSH are IL-1, IL-6, and the keratinocyte-derived chemokine (KC).[49] The IL-8 receptor in human neutrophils is also down-regulated by α-MSH. Moreover, chemotaxis induced by IL-8 in both human neutrophils and monocytic cells is suppressed by α-MSH.[50]
4. In contrast to the suppressive effects of α-MSH on several proinflammatory mediators, the peptide was also identified as an inducer of IL-10, a cytokine with potent immunosuppressive activities. Stimulation with α-MSH increases both IL-10 mRNA and protein at a low concentration.[51]
5. Studies on various cell types of human skin including pigment cells, fibroblastic cells, and dermal microvascular endothelial cells as well as murine mast cells have demonstrated that α-MSH is capable of suppressing the expression of intercellular adhesion molecule-1 (ICAM-1) induced by proinflammatory stimuli such as IFN-y, LPS, or TNF-α.[52] Other surface molecules modulated by a-MSH are CD86 and CD40, which are required for antigen presentation by monocytes and dendritic cells.
6. An inhibitory effect of α-MSH on prostaglandins (PGs) production was demonstrated many years ago. α-MSH suppressed PGE synthesis in fetal human lung fibroblasts stimulated with IL-1.[53] The effect of α-MSH on PGE synthesis appears to be cell type-specific.[54] Induction of inducible NO synthase (iNOS) and release of the gaseous vasodilator nitric oxide (NO) after stimulation of cells with various proinflammatory stressors, e.g., LPS, IFN- y, and B-amyloid can also be suppressed by α-MSH.[55]
7. Recently, it has been reported that α-MSH (200 nM) inhibits TNF-α induced matrix metalloproteinase (MMP)-13 expression by modulating p38 kinase and NF-kB activation in the human chondrosarcoma cell line HTB-94.[56]
8. α-MSH on lymphocyte function: The overall expression of MC-Rs is low or undetectable in several lymphocyte subsets.[57] The induction of regulatory T cells Treg (CD25+ve, CD4 +ve) was mostly pronounced when primed T cells were activated in vitro first in the presence of α-MSH, followed by TGF-B2.[58] It was demonstrated that α-MSH suppresses proliferation of human T lymphocytes stimulated with streptokinase/ streptodornase. Streptokinase/ streptodornase is a potent bacterial antigen to which most of the individuals mount a T cell-mediated response.[7] It was also suggested that α-MSH may utilize other signaling pathways than cAMP, i.e., calcium, to maintain its immunosuppressive effect.[25]

Cytoprotective effect

Early studies focused on the protective effect of melanocortins on neuronal cell types, more recent studies have lately extended towards other non-neuronal cell types with fascinating new functional facets of α-MSH as a potent modulator of apoptosis induced by genotoxic stress.[25] A neurotrophic and neuroprotective effect of melanocortins against various forms of nerve damage such as crush injury or neurotoxic drug damage has been reported.[59] Recent studies are focusing on the molecular mechanism by which α-MSH and MC-Rs prevent apoptosis in neuronal and other related cell types. These studies suggest that NDP-MSH via MC-4R activates ERK1/2 and thereby attenu-

ates serum deprivation-induced apoptosis.[60]

Alfa-MSH acts as a suppressor of apoptosis in nonneuronal cells. Cyclosporine A was shown to induce expression of the Fas/Fas ligand system in human kidney-2 cells, an immortalized proximal tubular epithelial cell line. One micromole of α-MSH results in reducing cyclosporine A-induced apoptosis and also attenuated the enhanced levels of Fas, Fas ligand, and the Fas-associated protein with death domain.[61]

Apoptosis induced by UVB irradiation is significantly suppressed by α-MSH in a number of cutaneous cell types. This is linked to reduced amounts of DNA photoproducts, i.e., cyclopyrimidine dimers.[62] Regarding this effect α-MSH analogs have been suggested as a novel melanoma preventive strategy.[63]

Antimicrobial effect

The presence of the old anti-inflammatory peptide α-melanocyte-stimulating hormone [α-MSH (1–13), SYSMEHFRWGKPV] in barrier organs such as gut and skin suggests a role in the nonspecific (innate) host defense.[64] α-MSH and its C-terminal sequence Lys-Pro-Val [α-MSH(11-13)] have antimicrobial effects against two major and representative pathogens: Staphylococcus aureus and Candida albicans.[65] Evidence suggests that the candidacidal effect of α-MSH is mediated through induction of cAMP. As α-MSH- induces cAMP in C. albicans on the other hand the adenyl cyclase inhibitor ddAdo partly reversed the candidacidal effect of α-MSH. It is likely, therefore, that the antimicrobial effect was caused by enhancement of this way.

Carotenuto et al designed and synthesized novel peptide analogues. They focused on the sequence alpha-MSH(6-13), which contains the invariant melanocortin core sequence His-Phe-Arg-Trp (6-9) and also contains the sequence Lys-Pro-Val (11-13) important for antimicrobial activity. These compounds have greater candidacidal activity than α-MSH.[65]

Protective effect against organ damage

It has become apparent that this protective activity of α-MSH is linked to its antiinflammatory action and to common molecular effector pathways e.g., modulation of NF-kB activity.[25]

- Postlesional repair; Studies have addressed the neuroprotective and neurotrophic effects of melanocortins, especially ACTH and related peptides.[66] α-MSH can increase postlesional repair of nerve in rats.[67] α-MSH also proved to reduce inflammation, hypervascularization, and fibrosis.[68]
- Drug-induced neuro- and ototoxicity; α-MSH was evaluated for its protective in vivo effect against cisplatin-induced ototoxicity was superior to ORG 2766 in the speed and extent of the recovery of the auditory nerve compound action potential threshold.[69] It was found that α-MSH reduced kainic acid-induced astrocyte excitotoxicity and reduced elevated IL-10 levels.[70] Daily injection of 50ug of α-MSH reduces apoptosis in the tubules and the interstitium and attenuates tubulointerstitial fibrosis after 48 days of cyclosporine treatment but failed to improve renal function parameters.[71] After drug-induced nephrotoxicity, from gentamycin administration for 7 consecutive days, α-MSH 25ug daily into the peritoneal cavity reduced the severity of renal damage as determined by histology, MPO activity, and concentration of renal glutathione levels, but again failed to improve renal functional parameters.[72]

- Alfa-MSH in experimental ischemia: elevated levels of circulating α-MSH have been detected in patients with congestive heart failure. New York Heart Association class II, suggested participation of melanocortins in distinct forms of human heart disease.[73] In ischemic heart injury demonstrated in rats, all doses of α-MSH reduced infarct size, whereas only at 200 ug/kg of α-MSH were coronary flow, aortic flow, and left ventricular developed pressure significantly increased compared with non α-MSH-treated animals. This reveals beneficial effects of α-MSH as well as of ACTH peptides on cardiovascular function and survival.[74] Studies addressing the effect of α-MSH on post ischemic activation of proinflammatory cytokines demonstrated that the peptide (0.5 mg/kg) given before the start of the ischemia and again 1 h after reperfusion significantly suppressed elevated TNF-α levels in the cerebrocortical territory of the middle cerebral artery after transient unilateral occlusion.[75] Studies showed promising clinical potential use of MC-4R agonists as a future therapeutic approach in ischemic stroke.[76] After mesenteric ischemia, the peptide α-MSH (50-100 ug) had salutary effects on intestinal damage, inflammation, and NF-kB activation.[77] Administration of α-MSH during renal ischemia reduced ischemia-induced renal dysfunction, reduced tubule necrosis and inflammation, and attenuated ischemia- induced expression of KC/IL-8, ICAM-1 and iNOS.[78]
- Experimental ureteral obstruction; It has been shown that IV administration of 50ug of α-MSH in an animal model with bilateral ureteral obstruction almost completely prevented the decrease in glomerular filtration rate and strongly reduced tubular cell apoptosis.[79]
- Experimental acute lung injury; Using mouse model it was demonstrated that IV α-MSH (25ug) not only attenuated NF-kB and p38 activation, as well as DNA binding of activator protein 1 (API) in the kidney, but also had similar distant protective effects, namely in the lung.[80]

Appetite and obesity effect

Obesity is considered as an inflammatory state associated with a modification in the pattern of adipokine secretion.[81] Current biological and pharmacological evidence suggests that the melanocortin 4(MC-4R) and melanocortin 3 receptors (MC-3R) are involved in various aspects of energy balance and feeding behaviors in animals including humans. With those bases, designed agonists and antagonists of these ligands might serve as drugs for the treatment of feeding disorders.[82] Studies confirmed the role of the α-MSH concentration in the peripheral control of energy balance in obese adolescents.[81] The alpha-MSH changes were correlated to weight status changes but not to changes of cortisol, insulin, or homeostasis model assessment of insulin resistance index.[83] Roubert et al in 2010, analyzed effect of two novel melanocortin agonists. Both agonists were able to activate mutated hMC-4R with decreased α-MSH potency, which suggests that those mutations would be the best targets for the MC4R agonists among MC4R mutation-bearing obese patients.[84] On the other hand, Donahoo et al. 2009 found that α-MSH levels did not correlate significantly with any parameter of adiposity or diet composition. Hence, this suggests that endogenous plasma α-MSH levels are not a metric for body composition per se.[85]

Application of α-MSH in vivo[25]

1. α-MSH in experimentally induced fever; α-MSH has shown potent antipyretic activity in experimental fever. Fever is induced by central application of endogenous or exogenous pyrogen, and the efficacy of a co-injected antipyretic substance is subsequently measured.[86] Very small doses (Nanograms) of α-MSH injected intracerebroventricularly were found to be sufficient to suppress the pyrogenic effect induced by central application of bacterial endotoxin (LPS) or (PGE_2). Same results were obtained when exogenous pyrogen or IL-1 was injected IV. The antipyretic effect of α-MSH was operational not only when the peptide was administered centrally but also when given systemically or even intragastrically. The antipyretic effect of centrally administered α-MSH is mediated by MC-Rs, most likely via (MC-3Rs) and (MC-4Rs), which are expressed in autonomic sites in the hypothalamus and brain stem.[87]
2. α-MSH in treatment of experimentally induced autoimmune encephalomyelitis (EAE); The potent anti-inflammatory effects of α-MSH in various cell types of the CNS with the inhibitory effect of α-MSH on NF-kB activation and cytokine production,[88] resulted in attempts to treat experimental autoimmune encephalomyelitis (EAE). This displayed an altered Th1-like cytokine as well as a high frequency of CD4+, CD25+ regulatory T cells, indicating a novel therapeutic approach to treat autoimmune diseases of the CNS.[89]
3. Inhibition of systemic inflammation; In models of systemic inflammation, sepsis, and acute respiratory distress, α-MSH has proved to be a potent agent. Systemic or sc injection of α-MSH reduced circulating levels of IL-1a and TNF- α.[90] Lipton et al[91] showed that in a model of peritonitis/endotoxemia induced by cecal ligation and puncture, systemic α-MSH administration improved the survival rate of the mice, and the effect was similar to systemic administration of the broad-spectrum antibiotic gentamycin.
4. Experimentally induced contact dermatitis and cutaneous vasculitis; Central administration of α-MSH alone was capable of inhibiting skin inflammation induced by local injection of irritants or proinflammatory cytokines.[92] Application of α-MSH suppressed both the sensitization and elicitation limbs of the cutaneous immune response.[93] α-MSH topically applied in a cream may also reduce contact eczema in man.[31] In classical models to study vasculitis which is called Shwartzman reaction, single IP injection of α-MSH suppressed the vascular damage and hemorrhage by inhibiting the sustained expression of vascular E-selectin and vascular cellular adhesion molecule-1.[94]
5. Experimentally induced organ fibrosis; There is evidences that α-MSH also has antifibrogenic/ antifibrotic effects in animal models of fibrosis. It decreased lung fibrosis induced by bleomycin.[95] Alfa-MSH at small doses reduced bleomycin induced collagen type I and type III synthesis in human dermal fibroblasts and up-regulated the expression of the above enzymes, so it is significantly attenuated skin fibrosis.[96]
6. Experimentally induced arthritis; Local, but not systemic, administration of very high amounts of ACTH (100 /ug) reduced neutrophil migration, arthritis score, joint size, and cytokine levels. Mechanism of action of

α-MSH is through locally expressed MC-Rs in particular those expressed in the synovia, in addition to the antiinflammatory action of ACTH.[97]

7. Experimental ocular inflammation; α-MSH (50ug) given IV 10 and 12 d after immunization suppressed the mean induced uveitis scores.[98] IV application of α-MSH (250-1000 /ug per injection) dose-dependently, reduced endotoxin-induced uveitis as determined by the number of infiltrating cells in the anterior chamber and the amounts of protein, NO, TNF-α, IL-6, monocyte chemoattractant protein-1, and macrophage inhibitory protein-2 in the aqueous humor.[99] Interestingly, in another model of corneal trauma and inflammation, α-MSH furthermore turned out to act equipotent with corticosteroids. Treatment with α-MSH, either topically or IM, markedly reduced edema, hyperemia, aqueous protein levels, and aqueous inflammatory cell number.[100]
8. Experimentally induced airway inflammation; α-MSH was shown to inhibit allergic airway inflammation in mice. Microgram doses of IP injected, α-MSH reduced peribronchial airway inflammation as measured by cell numbers and distribution of leukocyte subpopulations. Levels of two important proallergic cytokines IL-4 and IL-13 were also suppressed. The action of the peptide in allergic airway inflammation was dependent on the presence of IL-10.[101]
9. Experimentally induced acute pancreatitis: It has been shown that α-MSH injected IP attenuated cerulein-induced organ inflammation and damage.[102] The precise mechanism by which α-MSH attenuates this form of acute pancreatitis is unclear. Exocrine secretory epithelia are known to express the (MC-5R). It was recently shown that MC-2R is expressed in mouse primary islet tissue.[103]
10. Experimental liver inflammation and colitis; Acute hepatitis induced by LPS and Corynebacterium parvum pretreatment could be prevented by α-MSH when given IP 30 min after LPS administration. α-MSH suppressed systemic NO production, hepatic neutrophil infiltration, and increased hepatic mRNA levels of TNF-α and the chemokines IL-8 and monocyte chemoattractant protein-1.[104] In animal models α-MSH has also potent antiinflammatory activity in experimentally induced colitis. α-MSH daily profoundly reduced the appearance of fecal blood, inhibited weight loss, and prevented disintegration of the general condition of the animals.[105]

Afamelanotide (Scenesse®)

Melanin broadly reduces skin penetration by ultraviolet and visible wave lengths by absorbing, reflecting and refracting these lights. Afamelanotide (Nle(4)-D-Phe(7)-α-MSH), a synthetic linear analog of alpha-melanocyte stimulating hormone and agonist of the melanocortin-1-receptor, promotes melanin synthesis, increasing skin pigmentation.[106] Afamelanotide ([Nle4-D-Phe7]-α-MSH, Scenesse®; Clinuvel Pharmaceuticals Ltd, Melbourne, Vic., Australia) has potential to offer systemic photoprotection in a wide range of patients.[107] It has also been shown to possess immunomodulatory properties in experimental models, with studies in rodents showing reductions in IL-1b, IL-1α and TNF-α.[90] It has been used in solar urticaria and EPP and showed promising results.

Solar urticaria

Although the exact molecular mechanisms underlying solar urticaria have not been elucidated, it is believed that a photoallergen is produced, which is recognized by dermal mast cells, causing degranulation and release of inflammatory mediators such as histamine,[108] leukotrienes, proteoglycans, proteases, and proinflammatory and chemotactic cytokines including tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-4, IL-13 and IL-8.[109] Histamine binds to H1 receptors so activating cytoplasmic transcription factors including NF-kB which further stimulates the transcription of proinflammatory mediators. Localized increases in blood vessel permeability leads to extravasation of eosinophils, erythrocytes and neutrophils. Swelling of nerve fibres has been reported and it is believed that activation of cutaneous nerves results in the release of neuropeptides producing the flare response.[110] Prolonged increase in melanization at exposed and unexposed skin sites in patients with solar urticaria following administration of a single 16mg subcutaneous implant of the α-MSH analogue afamelanotide has been observed.[107] The lower dose implantation route is associated with fewer acute side-effects[106] and the drug is well tolerated.[107]

Erythropoietic protoporphyria (EPP)

A rare inherited disease resulting in accumulation of photosensitizing protoporphyrin in the dermis. It is characterized by severe dermal pain and incapacitating phototoxic reactions when the skin is exposed to visible light, primarily blue light.[111] Afamelanotide sustained release resorbable implant formulation at a dose of 20mg, given twice, at an interval of 60 days in EPP showed both tolerance to artificial light and melanin density increased significantly by day 120 after the start of afamelanotide.[106] Afamelanotide used in patients with EPP showed increase in"Exposure times [multiplied by] Freedom from Pain" (ETFP) that is likely to prove useful in future clinical trials.[112] Afamelanotide is considered one of the agents that are showing promising results in early phases of clinical trials preventing non melanoma skin cancers.[113] It is currently undergoing clinical trials in polymorphous light eruption and repigmentation therapy in nonsegmental vitiligo in combination with narrowband UVB therapy.

Truncated tripeptides such as KDPT which do not bind to MC-1R but have sustained anti-inflammatory properties are currently emerging as another novel therapeutic strategy in dermatology.[114]

It looks obvious that in the next few years the α-MSH and its analogues will be drugs of choice in many diseases whether dealing with the photosensitivity or with anti-inflammatory and immunomodulatory effects.

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