α -MSH related peptides: a new class of anti-inflammatory and immunomodulating drugs

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α -Melanocyte-stimulating hormone (α -MSH) is a tridecapeptide derived from the proopiomelanocortin by post-translational processing. In addition to its effects on melanocytes, α -MSH has potent anti-inflammatory effects when administered systemically or locally. The anti-inflammatory effects of α -MSH are mediated by direct effects on cells of the immune system as well as indirectly by affecting the function of resident non-immune cells. α -MSH affects several pathways implicated in regulation of inflammatory responses such as NF- κ B activation, expression of adhesion molecules and chemokine receptors, production of pro-inflammatory cytokines and other mediators. Thus α -MSH may modulate inflammatory cell proliferation, activity and migration. The anti-inflammatory effects of α -MSH have been confirmed by means of animal models of inflammation such as irritant and allergic contact dermatitis, cutaneous vasculitis, asthma, inflammatory bowel disease, rheumatoid arthritis, ocular and brain inflammation. Most of the anti-inflammatory activities of α -MSH can be attributed to its C-terminal tripeptide KPV. K(D)PT, a derivative of KPV corresponding to the amino acid 193–195 of IL-1 β , is currently emerging as another tripeptide with potent anti-inflammatory effects. The anti-inflammatory potential together with the favourable physicochemical properties most likely will allow these agents to be developed for the treatment of inflammatory skin, eye and bowel diseases, allergic asthma and arthritis.

The hormone α -melanocyte stimulating hormone (α -MSH) is a tridecapeptide derived from proopiomelanocortin (POMC) by post-translational processing.¹ Numerous studies over the last few years have provided plenty of evidence that α -MSH has potent anti-inflammatory effects when administered systemically or locally.² The anti-inflammatory effects of α -MSH can be elicited via centrally expressed melanocortin receptors which orchestrate descending neurogenic anti-inflammatory pathways. On the other hand, α -MSH can also exert anti-inflammatory effects on cells of the immune system as well as on resident non-immune cell types of peripheral tissues.² Moreover, the C-terminal tripeptide of α -MSH, KPV, and a related tripeptide K(D)PT both exhibit anti-inflammatory properties as seen for α -MSH.² Therefore, the emphasis of this brief review is on in vitro and in vivo anti-inflammatory effects of α -MSH and related peptides as well as their therapeutic potential for the treatment of inflammatory diseases.

ALPHA-MSH AND RELATED PEPTIDES

α -MSH is generated from a precursor hormone called proopiomelanocortin (POMC).³ This molecule serves as the source for several peptide hormones such as adrenocorticotrophin (ACTH), α -MSH, β -MSH and γ -MSH, and the endogenous opioids including β -endorphin. α -MSH is a tridecapeptide which, upon proteolytic cleavage, is generated from its precursor ACTH. POMC is proteolytically cleaved by prohormone convertases that belong to the family of serine proteases of the subtilisin/kexin type. For ACTH, α -MSH, β -MSH and γ -MSH the term melanocortins has been coined to describe the pigment-inducing capacity of these peptides.⁴ Melanocortins elicit their biological effects via binding to specific surface receptors, melanocortin receptors, expressed on target cells. These receptors are distinct from receptors of β -endorphin which belong to the family of opioid receptors. Although POMC peptides were originally considered as neuropeptides, it is now well established that POMC expression and processing may

occur in many 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 (TNF α), as well as exogenous noxious stimuli such as ultraviolet irradiation and microbial agents.¹

C- and N-terminal fragments of α -MSH have significant melanotropic effects. However, the C-terminal peptide fragment of α -MSH (KPV) exerts a similar or even more pronounced anti-inflammatory activity as full-length α -MSH. Other small molecular weight peptides include the N-acetylated and C-amidated tripeptide KPV as well as several stereoisomers.⁵ A structurally related derivative is K(D)PT in which the hydrophobic amino acid valine of KPV is substituted by the more polar amino acid threonine. The all L-form of K(D)PT has first been described as a part of IL1 β . It is colinear to IL1 β _{193–195} and seems to be capable of interacting with the IL1 receptor type I (IL1RI). In order to terminate the pro-inflammatory activity of IL1 β it has to be degraded. During this degradation process the loop containing KPT is revealed and comes to the surface of the protein, allowing interaction with the IL1RI. Thereby KPV exerts an antagonistic activity via blocking IL1 activity, which ultimately contributes to terminating IL1-mediated inflammation.²

MELANOCORTIN RECEPTORS

Melanocortins (α -MSH, β -MSH, γ -MSH and ACTH) bind to melanocortin receptors (MC-Rs) which belong to the superfamily of G-protein coupled receptors with seven transmembrane domains and bind the melanocortin peptides with differential affinity.⁶ Five MC-R subtypes, MC-1R to MC-5R, have been identified and cloned. Human MC-1R and MC-4R

Abbreviations: α -MSH, α -melanocyte-stimulating hormone; ACTH, adrenocorticotrophin; DSS, dextran sodium sulphate; LPS, lipopolysaccharide; MC-Rs, melanocortin receptors; POMC, proopiomelanocortin

discriminate poorly between ACTH and α -MSH, while MC-2R is selective for ACTH. α -MSH is the preferred, though not exclusive, MC-5R ligand, and MC-3R is the least selective receptor of the family.⁷ MC-Rs are more widely expressed throughout the body than originally thought. In particular, MC-1R has been detected in melanocytes and in the majority of non-melanocytic cutaneous human cell types, including inflammatory and immunocompetent cells.¹

The anti-inflammatory effects of α -MSH *in vitro* are mediated mainly via engagement of MC-1R, although a role of MC-3R in this context also has been postulated. Interestingly, the anti-inflammatory effects of α -MSH have been observed in the presence of extremely low, for example subpicomolar, concentrations where based upon the ligand affinity of MC-1R only few receptors would be occupied.^{1,8} It is therefore possible that the anti-inflammatory effects of α -MSH are mediated by MC-Rs and by additional pathways. Accordingly, previous studies could indeed demonstrate that α -MSH potently and selectively reduces surface binding of radiolabelled IL1 β to T cells.⁹

Whether KPV and K(D)PT bind to MC-Rs and utilise the identical signalling pathways as the natural ligands is not yet clear. According to several binding studies, KPV seems not to bind to MC-1R and fails to increase cyclic adenosine monophosphate (cAMP) levels.² Like α -MSH, KPV blocks surface binding of radiolabelled IL1 β to T cells and additionally, like K(D)PT, inhibits the hyperalgesic effect of IL1 β *in vivo*.^{2,9}

ANTI-INFLAMMATORY EFFECTS IN VITRO

An important molecular mechanism underlying the anti-inflammatory effects of α -MSH, such as modulation of pro-inflammatory cytokine and adhesion molecule expression, appears to be the suppression of nuclear factor- κ B (NF- κ B) activation. In several studies using different cell types the effects of α -MSH, KPV or K(D)PT on the lipopolysaccharide (LPS), IL1 β or TNF α mediating the activation of NF- κ B was investigated. A similar reduction of NF- κ B translocation into the nucleus was observed in the presence of α -MSH and either of the tripeptides, regardless of which cell type was investigated. However, the low basal activation level (which can be seen in absence of pro-inflammatory mediators) in these cells remained unchanged on exposure to any of these compounds (fig 1).¹⁰⁻¹²

The investigation of the anti-inflammatory effects of α -MSH at the cellular level was primarily concentrated on the question

whether and to what degree α -MSH suppresses the production of pro-inflammatory cytokines. Accordingly, several studies have shown a significant downregulation of pro-inflammatory cytokines such as IL1 β , IL6 and TNF α , as well as chemokines such as IL8, Gro α and interferon γ (IFN γ) upon treatment with α -MSH.^{2,13} Moreover, chemotaxis induced by IL8 in human neutrophils and monocytic cells is suppressed by α -MSH, indicating that the function of these phagocytic cell types during inflammatory responses is blocked by the peptide via multiple effector pathways.^{2,14} In contrast to the inhibitory effects of α -MSH on the production and activity of pro-inflammatory mediators, α -MSH was found to induce IL10, a cytokine with potent immunosuppressive activities. Exposure of peripheral blood mononuclear cells or human keratinocytes with α -MSH increased both IL10 mRNA and protein.^{15,16}

There is further evidence that additional other mechanisms appear to be responsible for the anti-inflammatory capacity of α -MSH. Accordingly, α -MSH significantly inhibits the IL1, TNF α or LPS mediated expression of several adhesion molecules such as interstitial adhesion molecule-1 (ICAM-1) and P-selectin on dermal vascular endothelial cells. Ultimately, the inhibition of inflammatory cell adhesion and transmigration may contribute to the anti-inflammatory potential of α -MSH.^{17,18} Moreover, α -MSH was found to inhibit the maturation of dendritic cells and to downregulate the expression of costimulatory molecules such as CD86.¹⁹

Few studies have investigated the effect of α -MSH on lymphocyte functions, probably because the overall expression of MC-Rs is low or undetectable in several lymphocyte subsets.²⁰ Recently, there has accumulated some evidence that a subpopulation of regulatory T lymphocytes is induced by α -MSH. They are characterised by the expression of CD25, CD4, CTLA4 and the production of increased levels of TGF β ₂.²¹

α -MSH may also be considered as belonging to the family of antimicrobial peptides and thereby contributing to innate defence. In addition to its anti-inflammatory potential, α -MSH and its C-terminal tripeptide KPV have been discovered to exhibit antimicrobial activity against pathogens such as *Staphylococcus aureus* and *Candida albicans*.^{22,23} The candidacidal activity of α -MSH is believed to be mediated by an increase in cell cAMP.²⁴ Moreover, the candidacidal activity could be further enhanced by inserting a Cys-Cys linker between two units of KPV. These findings indicate that these molecules may be further developed as antimicrobial compounds.

Figure 1 Effect of α -MSH peptides and K(D)PT on NF- κ B activation in endothelial cells (A) and keratinocytes (B). Human dermal microvascular endothelial cells (HDMEC, A) and human keratinocytes (KC, B), respectively, were treated with different mediators as indicated for 15 min. Subsequently, nuclear protein was harvested and used for electrophoretic mobility shift assays detecting NF- κ B homodimers and heterodimers. α -MSH clearly inhibits the nuclear translocalisation of the active p65/p50 NF- κ B heterodimer. In HDMEC, KP and KPV also slightly reduce migration of NF- κ B, while K(D)PT has the most pronounced effect. In KC it can be seen that the octamer MSH₆₋₁₃ reduces nuclear translocalisation of NF- κ B, while the pentamer MSH₉₋₁₃, which lacks most of the described melanocortin receptor-binding domain of α -MSH, has almost no effect. The dipeptide KP on the other hand has a pronounced inhibitory effect, while PV again has not, indicating a certain importance of the lysine residue.

ANTI-INFLAMMATORY EFFECTS IN VIVO

The anti-inflammatory effects of α -MSH in vitro have been confirmed in a variety of animal models. In mice with experimental contact dermatitis elicited by dinitrofluorobenzene or oxazalone, epicutaneous application of α -MSH suppressed both the sensitisation and elicitation phase of the cutaneous immune response (fig 2).²⁵ Studies using intravenously administered α -MSH further confirmed these findings and additionally demonstrated that the peptide induces hapten-specific tolerance. Importantly, in vivo tolerance induction by α -MSH could be abrogated by application of an antibody against IL10, strongly suggesting that this cytokine plays a key role in mediating the molecular anti-inflammatory mechanisms of α -MSH.²⁶ Moreover, the peptides KPV or K(D)PT applied either intravenously or topically like the parent molecule α -MSH were able to suppress the contact dermatitis reaction and to induce hapten-specific tolerance (fig 2).^{27–29} The relevance of the anti-inflammatory potential of α -MSH in murine contact dermatitis is underscored by preliminary findings, demonstrating that α -MSH topically applied in a cream also reduced nickel-induced contact eczema in humans.³⁰

In a model of LPS-induced cutaneous vasculitis (local Shwartzman reaction), a single intraperitoneal injection of α -MSH was able to suppress the vascular damage and haemorrhage via downregulating the sustained expression of vascular E-selectin and vascular cellular adhesion molecule-1, two adhesion molecules crucially required for the diapedesis and activation of leucocytes, ultimately resulting in extravasation, inflammation and haemorrhagic vascular damage.¹⁸

In another murine model α -MSH applied intraperitoneally was shown to inhibit allergic airway inflammation induced by aerosol sensitisation and subsequent challenges with ovalbumin. In addition, levels of both IL4 and IL13, two important pro-allergic cytokines, were found to be decreased in the bronchoalveolar lavage fluid of allergic mice treated with α -MSH. In accordance with the key role of IL10 in α -MSH-mediated suppression of experimental contact dermatitis, the anti-inflammatory action of the peptide in allergic airway inflammation was dependent on the presence of IL10, as IL10 knockout mice were resistant to treatment with α -MSH.³¹

α -MSH has also been tested for its anti-inflammatory potential using animal models of autoimmune uveitis as well as corneal injury. In a murine model of experimental autoimmune uveitis α -MSH given intravenously significantly suppressed the mean uveitis scores.³² Similarly, intravenous application of α -MSH reduced endotoxin-induced uveitis.³³ The anti-inflammatory mechanism of α -MSH in these models appears to be linked to the induction of regulatory T cells since adoptively transferred T cells generated by α -MSH and TGF β ₂ in vitro were also found to suppress experimental autoimmune uveoretinitis.²¹

The anti-inflammatory activity of α -MSH in animal models of arthritis has been of particular interest. Repeated administration

of the peptide intraperitoneally twice daily significantly attenuated the clinical and histological signs of adjuvant-induced experimental arthritis as compared to control animals. α -MSH was similarly effective as prednisolone but did not cause significant weight loss.³⁴ Furthermore, in a rat model of gouty arthritis elicited by intra-articular injection of monosodium urate monohydrate crystals, the MC-3R antagonist SHU9119 blocked the anti-inflammatory action of the α -MSH precursor and structurally related peptide ACTH.³⁵ These data indicate that MC-3R may be a relevant target for the treatment of arthritis.

There is recent evidence that α -MSH has potent anti-inflammatory activity in experimentally induced colitis. In a mouse model of dextran sodium sulphate (DSS)-induced colitis, α -MSH profoundly inhibited weight loss and prevented disintegration of the general condition of the animals.³⁶ In a rat model of trinitrobenzene sulphonic acid-induced colitis, intraperitoneal injection of α -MSH likewise reduced the colonic macroscopic lesions compared to untreated ones in both acute and chronic colitis groups.³⁷ Similar effects have been observed when the mice were treated with the tripeptides KPV or K(D)PT.³⁸ Most interestingly, K(D)PT was significantly more effective in its anti-inflammatory effect than KPV. Moreover, there is evidence for an important role of the MC-1R in the regulation of inflammatory responses of the gut using the DSS model of experimental colitis in mice with a frameshift mutation in the MC-1R gene (MC-1Re/e).³⁸ DSS-induced colitis in MC1Re/e mice was aggravated with higher weight loss and marked histological changes compared to C57BL/6WT, eventually leading to death of all MC1Re/e mice. These findings suggest that MC-1R may be an important regulator of the mucosal innate host defence.

CONCLUSIONS

α -MSH and related tripeptides have been shown to possess promising in vitro as well as in vivo anti-inflammatory effects. In particular the α -MSH-related tripeptides appear to be suited to being developed as anti-inflammatory drugs. Their small molecular size further provides advantages especially for local therapy of inflammatory diseases of skin and mucous membranes. Based on the combined anti-inflammatory and antimicrobial effects of some peptides, the risk for infection may be lower than with conventional immunosuppressive agents. Moreover, the broad anti-inflammatory effect will not result in strong immunosuppression as seen with the corticosteroids or systemic calcineurin inhibitors. Accordingly, activation of NF- κ B as well as subsequent expression of pro-inflammatory molecules is never fully suppressed, but mostly only reduced.¹⁰ In the absence of inflammation or pro-inflammatory stimuli such as LPS or IL1, the anti-inflammatory and immunosuppressive potential of α -MSH and its peptides was usually weak or absent. According to preliminary available toxicity and safety data, the adverse effects of α -MSH-related

Figure 2 Suppression of contact dermatitis reactions and induction of tolerance. Rested female C57BL/6J mice (age: 8 weeks) were sensitised with dinitrofluorobenzene (DNFB). Groups of seven mice were each co-treated with either α -MSH, KPV or K(D)PT by intravenous injection. After five days the animals were challenged with DNFB at the ear. Ear swelling was measured 24 hours later with a spring caliper. Two weeks later this cycle of sensitisation, challenge and measurement of ear swelling was repeated but without the additional application of the peptide mediators.

tripeptides seem to be minimal. Therefore, it is possible that α -MSH-related tripeptides will be developed as novel compounds for the treatment of immune-mediated inflammatory diseases.

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