Review Article

THE ACTIONS OF THE α-MELANOCYTE STIMULATING HORMONE (α-MSH) IN INFLAMMATORY CONDITIONS

Berna K. Oktar, M.Sc. / İnci Alican M.D., Ph.D.

Department of Physiology, School of Medicine, Marmara University, İstanbul, Turkey.

INTRODUCTION

Inflammation, a localized response to tissue injury, and disorders characterized by inflammation are difficult problems in clinical medicine. This difficulty stems in large part from incomplete understanding of inflammatory processes and their regulation. Recent development of the knowledge of the role of the central nervous system and neuroendocrine system in the host responses has provided a new view of the capacity of neuronal and soluble mediators in these systems to influence inflammation. One of these mediators is the endogenous neuropeptide α-MSH, which is an N-acetyl tridecapeptide derived from the cleavage of a larger precursor molecule, pro-opiomelanocortin (POMC). It was originally isolated and characterized from the intermediate lobe of the pituitary and it was first recognized by its effect on skin melanophores in lower vertebrates (1).

α-MSH is widely distributed in tissues of higher organisms; it has been identified in the pituitary, various brain regions, skin, circulation and other sites (2). The plasma half-life of α-MSH is 20-25 min in humans; but its biological half-life is unknown (3). It has been shown that plasma and local α-MSH concentrations increase in certain inflammatory disorders and stress (2,4). Despite its similarity in peptide structure to adrenocorticotropic hormone (ACTH), α-MSH has no major influence on glococorticoid secretion (5).

Binding sites for the peptide are widespread and α-MSH receptors have been characterized and cloned in various tissues (6,7). The receptors for α-MSH and related melanocortins are specific G protein-coupled receptors containing seven transmembrane helixes that activate adenylate cyclase. Five subtypes of melanocortin receptor family have been recognized to date (MC-1 to MC-5). MC-1 receptor is the first receptor that is identified on immune/inflammatory cells (8). Cultured mouse and human macrophages and melanocytes contain mRNA for MC-1 receptor (9,10). MC-1, MC-3, MC-4 and MC-5 receptors have been in the brain tissue (11); whereas, MC-2 receptor is only found in the adrenal cortex (12). MC-1 is also expressed in human neutrophils which may account for the inhibitory influence of the peptide on neutrophil migration in the initial phase of inflammation (13).

There is recent evidence that murine mast cell line expresses mRNA for MC-1 receptor and that α-MSH modulates mast cell responsiveness (14). In these experiments, it has been suggested that α-MSH may exert an inhibitory effect on the mast cell-dependent component of

(Accepted 18 February, 2001) *Marmara Medical Journal 2001;14(2):113-118*

Correspondance to: İnci Alican, M.D., Ph.D – e.mail address: ialican@usa.net

a specific inflammatory response which is characterized by the release of cytokines, chemokines and chemical mediators including histamine and prostaglandins.

Anti-inflammatory Effects of α-MSH in Animal Models

In addition to its well-known effect on pigmentation, α-MSH also mediates other biologic functions such as control of inflammation and fever (15). The anti-inflammatory and antipyretic effects of the peptide are associated with the COOH-terminal tripeptide sequence, Lys-Pro-Val (α-MSH [11-13]) (16) (Fig.1). α-MSH has anti-inflammatory effects in all of the major forms of inflammation: acute, chronic, systemic, allergic and central nervous system (CNS) inflammations. The evidence of the potent influence of α-MSH on acute inflammation are mostly derived from experiments in which inflammation was caused by injection of exogenous inflammatory agents. Recent evidence of anti-inflammatory effect of the peptide has been obtained from the experiments in which mice were pretreated with *Corynebacterium Parvum* or bacterial lipopolysaccharide (LPS), a regimen that results in severe hepatitis (17). In this study, a-MSH prevents hepatic injury and increase of plasma nitrate / nitrite levels. It also decreases LPS-induced cytokine (TNF-α) and chemokine (IL-8) mRNA accumulation and neutrophil infiltration even when it is administered 30 min after LPS challenge (17).

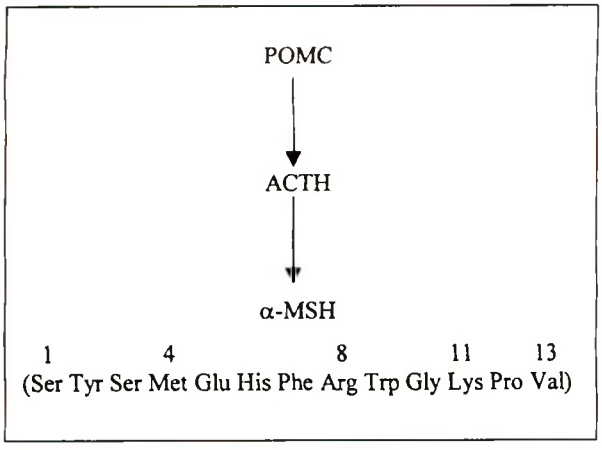

Fig.1 : The structure of the α-MSH (1-13)

Recent observations on delayed type hypersensitivity reactions indicate that a-MSH inhibits induction of contact hypersensitivity and leads to hapten-specific tolerance (18). These effects of α-MSH are presumed to involve an IL-10 "anti-inflammatory cytokine" intermediate because treatment with the IL-10 antibody reduces the effects of the peptide (18).

α-MSH prevents development of chronic inflammation by inhibiting cellular infiltration in a rat model of mycobacterium-induced arthritis (19). It improves several aspects of systemic inflammatory response syndrome, including white blood cell migration into the lungs after endotoxin infusion (20). In addition, it increases survival in experimental peritonitis / endotoxemia in the rats (20).

The peptide promotes functional recovery in CNS ischemia/reperfusion. Recent evidence indicates that α-MSH modulates production of TNF-α in the brain tissue of mice following central LPS injection (21). From these observations, it is clear that the peptide is effective in inflammatory processes that occur in widespread regions of the body.

It is also remarkable that the peptide concentration increases in various clinical and experimental inflammatory disorders. The concentration of α-MSH has been determined in synovial tissues and synovial fluid of patients with rheumatoid arthritis, myocardial infarction, endotoxemia or HIV infection. Peptide concentration ranged from 10^{-10} and 10^{-8} M in these pathological conditions (22-25).

Mechanisms of the Peripheral Effects of α-MSH

The neuropeptide α-MSH is important to the natural limitation of fever, which is an early host response to endotoxin. α-MSH given centrally or systemically reduces fever and this indicates that the peptide reaches the brain. During fever there is pulsatile release of the peptide from septal areas of the brain. α-MSH given exogenously causes antipyresis; whereas blockade of the endogenous α-MSH with antiserum augments the febrile response to pyrogens (26).

The capacity of IL-1 to elicit a pyrogenic response can be effectively inhibited by central administration of α-MSH in rabbits and this suggests that the peptide may also be involved in the actions of IL-1 (27). This peptide is antipyretic when given centrally, intravenously or intragastrically. It is 25,000 times more potent than acetaminophen, as an antagonist of IL-1 induced fever when given centrally and 20,000 times more potent when given intravenously (28). Robertson et al. demonstrated that intravenous injection of α-MSH abrogates fever, neutrophilia and elevation of hepatic serum amyloid protein followed by injection of IL-1 (29). In contrast, ACTH is unable to block either the neutrophilia or the serum amyloid protein elevation seen in response to IL-1, but it reduces fever by 67% (29). It has been indicated that the antipyretic action of ACTH is not related to glucocorticoid release because ACTH effectively reduces fever in adrenalectomized rabbits (30). Thus, these data indicate that both ACTH and α-MSH may serve as regulators of IL-1 related responses *in vivo*.

In addition to its action within the brain to reduce fever, α-MSH inhibits proinflammatory cytokine (e.g., IL-1β, IL-6, IFN-γ and TNF-α)- or chemoattractive chemokine (e.g., IL-8)-dependent reactions both *in vitro* and *in vivo*. For example, it inhibits TNF-α production by human mononuclear cells and IFN-γ production by antigen-stimulated murine lymph node cells and peripheral blood monocytes (31,32). It down-regulates the production of IFN-γ by human T cells and modulates IgE synthesis by human B cells (33). It has been shown that it completely abolishes mRNA expression for IL-8, TNF-α, and monocyte chemoattractant protein-1 in endotoxin-induced liver inflammaton (17). It also inhibits the activation of NF-kB which is an important factor for the induced transcription of TNF-α (34).

Although the mechanism is not clear, it has been shown that α-MSH down-modulates the transcription of IL-1β, TNF-α but not those of IL-4 and IL-6. Cannon et al. found that α-MSH inhibits IL-1-induced murine thymocyte proliferation and fibroblast PGE production *in vitro* (35). Moreover, the peptide and its analog Nle4-d-Phe7-MSH block responses to IL-1 *in vivo*, but not thymocyte proliferation or PGE production stimulated by IL-1 *in vitro* (36).

Previous studies have shown that α-MSH prevents acute inflammation after intradermal injection of LPS, cytokines or irritants including carrageenan and picryl chloride. It prevents LPS-induced liver damage even when it is administered 30 min after LPS (17). It also inhibits IL-1-, TNF-α-, or pyrogen-induced edema *in vivo* (37). It has shown that plasma a-MSH concentration increases within 1 h following the peripheral administration of endogenous pyrogen and this suggests that the peptide is important in the early phase of host defense (38).

Systemic administration of the peptide also reduces some biological responses of the cytokines and inhibits neutrophil migration both *in vitro* and *in vivo*. It has been demonstrated that chemotactic migration of human neutrophils in IL-8 and N-formyl-methionl-leucyl-phenylalanine (fMLP) gradients was inhibited by α-MSH in a dose-related fashion (13). This effect is presumably the result of stimulation of MC-1 receptors expressed by neutrophils. However, unlike murine and human macrophages, neutrophils are unable to produce either the POMC-the precursor of α-MSH- or the peptide itself. Any influence of α-MSH on neutrophils would therefore occur through its paracrine or endocrine actions (Fig.2).

More recently, it has been demonstrated that α-MSH inhibits the production of nitric oxide (NO) which is considered as a potent inflammatory agent produced in large amounts by monocytic

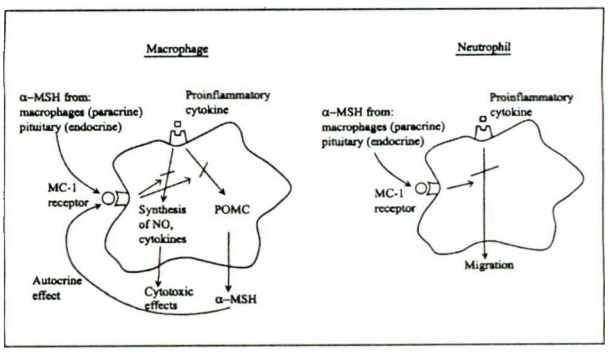

Fig.2 : The mechanisms of the effect of α-MSH on macrophages and neutrophils. (Modified from Lipton JM et al. Immunol Today 1997;18:140-145).

cells, particularly murine macrophages. α-MSH stimulates cAMP production and inhibits LPS/cytokine-stimulated NO and inducible NO synthase (NOS) production in murine and human macrophages (9). These cells have mRNA both for the MC-1 receptor and POMC and they secrete α-MSH when stimulated with TNF-α. α-MSH inhibits LPS-induced increases in serum nitrate/nitrite in both LPS and *C. Parvum*/LPS-induced liver injury models (17). It also prevents the induction of i NOS after renal ischemia in mice and rats (39). Recently, we and other investigators have shown that α-MSH has a protective effect on colonic lesions in a rat model of experimental colitis through the inhibition of NO (40). Rajora et al has demonstrated that a-MSH treatment significantly inhibits increased colonic nitrite values and TNF-α production in dextran sulfate sodium-induced colitis in mice (41). Similarly, α-MSH has been found to reduce the production of NO and TNF-α by cultured murine microglia stimulated with β-amyloid protein *in vitro* (42).

Mechanisms of the Central Effects of α-MSH

In addition to its actions within the brain to reduce fever, it is likewise clear that α-MSH can act centrally to inhibit peripheral inflammation induced by local application of irritants. For example, in the observations of mice with picryl chloride induced ear inflammation, it has been reported that central α-MSH administration- in doses that are ineffective intraperitoneally (0.1-10 μg)- reduces edema formation (43). Subsequent studies have shown that central administration of α-MSH attenuates skin inflammation in mice caused by intradermal injection of the proinflammatory mediators such as IL-1β, IL-8, LTB_4 and PAF (44). These observations indicate that the anti-inflammatory effect of the peptide in the periphery may be mediated by the α-MSH receptors in the brain.

It is clear that intact descending neural pathways are essential to the anti-inflammatory action of centrally administered α-MSH. Transection of the spinal cord in mice with hind paw inflammation prevents the anti-inflammatory action of the centrally administered peptide (45). In addition, intraperitoneal injection of a-MSH in mice with spinal transection has a smaller and delayed anti-inflammatory effect. By contrast, administration of the tripeptide $\alpha\text{-MSH}_{11\text{-}13}$ in the same model has strong and rapid influence on inflammation (45). These observations suggest that the tripeptide $\alpha\text{-MSH}_{11\text{-}13}$ can act directly in the periphery to inhibit inflammation whereas, $\alpha\text{-MSH}_{1\text{-}13}$ presumably requires the activation of descending inhibitory pathways for full expression of its anti-inflammatory effect.

Centrally administered α-MSH must therefore mediate its anti-inflammatory effects through activation of neural pathways that require specific neurotransmitters. In the mouse ear edema model, nonspecific blockade of the β-adrenergic receptors or specific blockade of the β_2 -receptors in the periphery inhibits the anti-inflammatory effect of centrally administered α-MSH (45). However, blockade of cholinergic (muscarinic) receptors or a- or β_1-adrenergic receptors has no effect (45). These results suggest that peripheral β_2-adrenergic neurotransmission is essential to the effect of central α-MSH on peripheral inflammation.

With regard to changes in the peripheral site of inflammation caused by the central α-MSH, it is possible that α-MSH can inhibit local neurogenic components of the inflammatory response. That is, the stimulation of the central MC receptors by the peptide may modulate the release of neurogenic inflammatory mediators (e.g., substance P or calcitonin gene-related peptide) at the site of injury after transmission of inhibitory signals in the descending anti-inflammatory pathways which require the presence of peripheral β_2- adrenergic receptors.

CONCLUSION

The evidence sited above indicates that α-MSH has potent and broad anti-inflammatory effects in many forms of inflammation. The anti-inflammatory actions of the peptide through the activation of central and/or peripheral melanocortin receptors might be useful in the treatment of some clinical cases in the future. Low toxicity of the peptide in animals, its brief duration of action and the lack of evidence of tolerance to repeated administration support further investigations on the peptide.

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