Modulation of Host Defense by the Neuropeptide $\alpha$-MSH

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Received June 8, 1989

$\alpha$-melanocyte stimulating hormone (\(\alpha\)-MSH), a peptide that occurs within the brain, the circulation, and other body sites, is a potent antipyretic agent when given centrally or peripherally. The peptide likewise inhibits inflammation and aspects of the acute-phase response. The combined evidence suggests that \(\alpha\)-MSH molecules act as natural modulators of host reactions by antagonizing the central and peripheral actions of cytokines.

It is clear that cytokines released in response to disease, tissue injury, or inflammation are very powerful inducers of cellular and systemic reactions of the host. These cytokines, including interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor (TNF), and so on, can act separately, although in nature they are likely to act together, to induce inflammation, the acute-phase response, and changes in activity of the immune system. No diseases have yet been identified that are associated specifically with surplus cytokine activity, although there is considerable speculation about cytokines in many disorders, including arthritis. The speculation stems from the powerful influence of the cytokines on physiological processes, and this same influence suggests that there must be endogenous modulation of their effects to prevent severe damage and to ensure survival of the host. Neuropeptides, such as \(\alpha\)-melanocyte stimulating hormone (\(\alpha\)-MSH) that exist within the central nervous system (CNS) [1,2] and in other parts of the body and that also increase in the circulation after challenge with endogenous pyrogen or bacterial endotoxin [3], may modulate the effect of cytokines either directly or indirectly.

THE \(\alpha\)-MSH MOLECULE, FUNCTION AND LOCALIZATION

The \(\alpha\)-MSH molecule is ancient and has been found within the CNS of invertebrates and lower vertebrates, such as fish [4], as well as in higher organisms [5]. Detailed analysis of its structure, processing, chemistry, distribution, and the like can be found in a recent extensive review on the peptide by A. Eberle [5]. \(\alpha\)-MSH (1-13) has the same amino acid sequence as ACTH (1-13) (Fig. 1), and in certain tissues (e.g., intermediate lobe of the pituitary, arcuate nucleus, nucleus of the solitary tract) it is derived from ACTH, which in turn is derived from its precursor POMC. In the dorsal hypothalamus, the \(\alpha\)-MSH (1-13) peptide develops de novo without processing of 173 amino acids.
ACTH or other POMC molecules [6]. The molecule is named for its capacity to darken the skin of amphibians (see [5]), but it has little pigmentary activity in man [7]. The effect of \( \alpha \)-MSH on skin chromatophores, which are ontogenetically derived from the neural crest, is to alter color. Melanocytes, melanophores of birds and mammals, primarily synthesize brown/black melanin and may be influenced by \( \alpha \)-MSH, but the physiological role of the peptide in mammalian pigmentation is not clear.

In higher organisms no physiological role for \( \alpha \)-MSH has been clearly established. There is, however, considerable evidence that the peptide can influence learning and memory [5,8]. This influence is more likely the result of actions on attention and arousal rather than on learning and memory processes per se. Evidence is developing that \( \alpha \)-MSH exerts trophic actions within the peripheral and central nervous systems. \( \alpha \)-MSH appears to stimulate neurite outgrowth [9], the initial regeneration or sprouting response to peripheral nerve injury [10,11], and to facilitate recovery from CNS lesions [12,13]. Because such injuries induce host responses such as inflammation, it is important to learn if the trophic effects of \( \alpha \)-MSH in nervous tissue are related to antagonism of cytokines and cytotoxins.

\( \alpha \)-MSH is found in high concentrations within the pituitary (e.g., [2]), and it has been identified as an important component of the neuroendocrine system for many years. The peptide also exists in mammalian skin [14], and \( \alpha \)-MSH receptors are widespread in the body [15]. The peptide occurs naturally in the circulation, and one of the early links between \( \alpha \)-MSH and immune responses was the discovery of the peptide in lymphocytes [16].

**ANTIPYRETIC ACTIVITY OF \( \alpha \)-MSH**

Fever is an aspect of host response to disease and injury. It is an elevation in the level around which body temperature is regulated and is believed to result from the action of cytokines on neurons, particularly thermosensitive neurons that reside primarily within the preoptic/anterior hypothalamic region of the brain, the site of primary temperature control. Indeed, although hyperthermia, a non-regulated rise in temperature, can be induced via peripheral or central actions of certain agents, fever can occur only via an action of pyrogens on CNS temperature controls. It is not certain whether cytokines induce, or always induce, release of prostaglandins of the E series as intermediates in their influence on thermoregulatory neurons. The mechanisms of antipyretic activity of common antipyretic drugs is also uncertain and may involve competitive antagonism of cytokines, inhibition of synthesis of prostaglandin mediators, and so on [17].

\( \alpha \)-MSH, first reported to reduce fever in 1981 ([18]; see reviews [19–24]), has subsequently been found, when given by several routes (Table 1), to inhibit fever caused in rabbits by endogenous pyrogen. The consistency of the antipyretic response to the peptide when it is given by multiple routes is remarkable, and it suggests a uniform activity of the molecule to limit host reaction. The potency of the peptide also suggests a role for endogenous \( \alpha \)-MSH in fever control: on a molar basis, it is more than 25,000 times more potent than acetaminophen in reducing fever when given intracerebroventricularly (icv) and approximately 20,000 times more potent when given intrave...
nously (iv) [28]. The action of the peptide is much like that of antipyretic drugs in that, in antipyretic doses, it reduces fever without altering normal body temperature, even in the cold [29]. The antipyretic influence of α-MSH is not peculiar to the rabbit. It has also been observed in mice [30–32], guinea pigs [33], and squirrel monkeys [34]. Although the bulk of research has been performed with endogenous pyrogens, crude products of incubation of leukocytes with endotoxin that undoubtedly contain interleukins, TNF, and other cytokines, α-MSH is also effective against fever caused by lipopolysaccharide [20] and by IL-1 and TNF [30–32,35]. Our recent research indicates that it also reduces fever caused by IL-6 [Martin LW, Lipton JM: unpublished observation]. In one study [35] α-MSH also antagonized the effect of IL-1β on measures of sleep. It is noted below that, although α-MSH antagonizes the actions of cytokines, it does not inhibit hyperthermia-caused prostaglandin E, a presumed mediator of fever, or that caused by prostaglandin precursor arachidonic acid.

Questions remain about the relative importance of specific neuroanatomical sites to α-MSH modulation of fever control. Although it is hazardous to speculate from comparisons of dose effectiveness when the peptide is injected centrally, the results in Table 1 do suggest some possibilities. It is clear that large amounts of α-MSH are required to reduce fever when the peptide is injected into the PO/AH region, which suggests that this location may not be the primary site of its antipyretic action. Depending on the specific site, nanogram to µg doses are required to reduce fever when α-MSH is injected into the septal region, which suggests that the septum is more important, or at least more sensitive, than the PO/AH region; however, doses of α-MSH in the nanogram range have marked effects on fever when injected into the cerebral ventricles. This latter observation suggests, but does not prove, that the α-MSH receptors that are important to the antipyretic activity of the peptide are widely distributed within the CNS. Indeed, doses less than 1 µg/kg given iv cause marked reductions in fever. It is likely that little of this peptide reaches central sites of action. These observations must be treated with caution, for there is much that is unknown about processing and action of α-MSH within localized CNS sites. It may be that very small amounts of α-MSH within specific sites are important to fever control. Similar observations of differences in potency of peptides injected into CNS tissue and into the cerebral ventricles have been common in neuroendocrine studies. Such observations, alone, can only provide hypotheses about the relative importance of CNS sites of action.

### PHYSIOLOGICAL ROLE OF α-MSH IN FEVER CONTROL

The antipyretic potency of α-MSH and its effectiveness in a number of homeothermic species raised the question of a role of the endogenous peptide in regulation of

| Route          | Dose      | Reference                        |
|----------------|-----------|----------------------------------|
| icv            | ng range  | e.g., Glyn and Lipton [18]       |
| iv             | < 1 µg/kg | e.g., Glyn and Lipton [18]       |
| Intragastric   | < 1 mg/kg | Murphy and Lipton [25]          |
| Intra-septal   | µg        | Glyn-Ballinger et al. [26]       |
| Intra-PO/AH    | 350 µg    | Feng et al. [27]                 |
fever. Three types of evidence were developed that are consistent with the idea that α-MSH is important to a naturally occurring fever modulation system within the CNS. First, it was noted that the concentration of α-MSH within the septal region, but not elsewhere, rose during fever [36,37] but not during hyperthermia induced by exposure to a hot environment [37]. In related experiments (Table 1), microinjection of α-MSH into this region reduced fever [26]. In push-pull studies, the concentration of α-MSH was increased in a pulsatile fashion during fever, but not during normothermia [38]. The timing of onset of the pulses suggested a direct action of cytokines on induction of the pulses. Third, in passive immunoneutralization experiments, antiserum specific for α-MSH enhanced, especially in duration, fever after intravenous (iv) injection of endogenous pyrogen [39]. Thus, binding and inactivation of endogenous α-MSH has a marked effect on fever. The combined results of these experiments, against a background of research on α-MSH administration, suggested that the peptide is a vital feature of an endogenous CNS mechanism that modulates the pyrogenic effect of cytokines and prevents dangerous rises in core temperature.

THE ANTIPYRETIC MESSAGE SEQUENCE OF α-MSH

In initial studies of the effects of neuropeptides on fever, ACTH (1-24) was likewise found to have antipyretic activity [18]; however, because α-MSH was effective, the antipyretic property of the larger ACTH molecule was not studied in detail. It was noted that the antipyretic effect of centrally and peripherally administered ACTH (1-24) does not depend upon release of corticosteroids from the adrenal gland [40], but repeated administration of ACTH can cause Cushing's syndrome, which would limit the usefulness of the molecule for treatment of fever.

In early tests, the focus was upon N-terminal and intermediate fragments of α-MSH, and α-MSH (1-3), α-MSH (1-4), α-MSH (4-8), α-MSH (4-9), and so on, were found to be ineffective [unpublished observations]. α-MSH (1-10) was likewise inactive, as were larger fragments of ACTH such as CLIP (18-39) [19]. The combined results suggest that the COOH-terminal tripeptide, α-MSH (11-13), is the antipyretic message sequence. This fragment was discovered to have antipyretic activity when given centrally or iv, although the doses required were greater than for α-MSH (1-13) [41]. More recently [42], α-MSH (11-13) given icv reduced fever in a dose-related fashion. α-MSH (10-13) was also antipyretic but less potent than α-MSH (11-13); α-MSH (9-13) had previously been found to have little or no antipyretic activity, but α-MSH (8-13) was more potent than the α-MSH (11-13) molecule. Thus, adding amino acids to the tripeptide antipyretic message sequence can both reduce and enhance antipyretic activity. Although the bulk of the research has been upon the α-MSH (1-13) molecule, it may be that COOH-terminal fragments of the peptide are also important to modulation of host responses, with some, such as α-MSH (11-13) and α-MSH (8-13), being more active.

INFLUENCE OF α-MSH ON THE ACUTE-PHASE RESPONSE AND RELATED HOST RESPONSES

As described in detail elsewhere in this issue, cytokines can induce aspects of the acute-phase response in addition to fever when administered centrally or peripherally. The influence of their central administration is remarkable because it demonstrates a link between CNS structures and peripheral responses that are normally attributed to the immune system. Recent evidence indicates that actions of the cytokines can be
α-MSH MODULATION

antagonized by the neuropeptide α-MSH. For example, Robertson et al. [30] found that α-MSH inhibited IL-1-induced fever, neutrophilia, and synthesis of serum amyloid P (SAP) in a time- and dose-dependent fashion in mice; these changes were not inhibited by ACTH or glucocorticoids. In related experiments from the same laboratory [31], α-MSH inhibited fever, neutrophilia, SAP synthesis, and increases in plasma corticosterone induced in mice by iv IL-1 and also depressed contact hypersensitivity; a stable analogue of α-MSH was more effective, but neither peptide altered plasma PGE₂ concentration. α-MSH given icv inhibited fever, leukocyte, and C-reactive protein responses induced by central injection of endogenous pyrogen in rabbits [43]. The neuropeptide likewise inhibited fever and increases in SAP caused by recombinant IL-1 and TNF [32]. Injections of α-MSH into the fourth ventricle inhibited neutrophilia, fever, SAP, and fibrinogen responses caused by the recombinant molecules. Peripheral injection of α-MSH depressed contact hypersensitivity. These results clearly indicate that α-MSH antagonism of cytokine effects is not limited to fever but extends to multiple changes induced by the soluble mediators.

An increase in capillary permeability is a hallmark of inflammation, and it is possible to reliably record this change in shorn rabbits given dye iv before intradermal injections of histamine. At the site of histamine injection, the increase in capillary permeability allows globulin with bound dye to leak through and color the skin. The color intensity and diameter of the spots were less in rabbits given the tripeptide [23]; α-MSH (1-13) had a similar effect. In related experiments, increased capillary permeability was induced by injecting endogenous pyrogen rather than histamine. In these studies as well, α-MSH (1-13) inhibited the increase in capillary permeability [24].

Recently, tests were performed using the mouse ear edema model, in which ear swelling was induced by local application of picryl chloride [44]. α-MSH (11-13) given intraperitoneally (ip) inhibited ear swelling in a dose-related fashion with reduced effects at both low and high doses, a U-shaped relation characteristic of peptide activity. The most effective dose of tripeptide was as effective as a large dose of the corticosteroid prednisolone. These findings thus confirm the anti-inflammatory activity of the tripeptide in a different animal model.

Is it possible that α-MSH acts locally in the skin to inhibit inflammation? Does the peptide migrate to sites of inflammation? The answers to these questions are not complete. Early in our research on the peptide, α-MSH was injected into the skin in doses up to 20 μg along with histamine or endogenous pyrogen. There was no clear inhibition by the peptide of increases in capillary permeability [Lipton JM: unpublished observations]. Likewise, when the tripeptide or α-MSH (1-13) was injected intradermally along with histamine, in two humans, the size of wheals was not affected [Lipton JM, Sullivan T: unpublished observations]. Although the studies were limited and the possibility remains that effective doses were not discovered because of the U-shaped nature of peptide activity, the data suggest that there is no local antagonism between the peptide and histamine or cytokines at sites in the skin.

In separate experiments, endogenous pyrogen was injected intradermally in rabbits; the skins were removed an hour later, aliquots containing the injection sites were punched out of the frozen skin and, after processing, the concentration of α-MSH in each site was determined. Endogenous pyrogen did not cause an influx of peptide: sites injected with pyrogen had the same amount of α-MSH as saline-injected sites [Hiltz ME, et al: unpublished observations]. These preliminary findings suggest that there is
no natural migration of the anti-inflammatory peptide to high concentration of cytokines in the skin.

Recent research on contact hypersensitivity induced in the mouse by picryl chloride indicated that α-MSH (1-13) can inhibit the swelling associated with this response [Hiltz ME, Lipton JM: unpublished observations]. Such hypersensitivity is cell-mediated in man, presumably by T lymphocytes. The swelling in the mouse may, however, be due to migration of cells, particularly polymorphonuclear leukocytes, and the release of soluble agents (cytotoxins) from participating cells. The mechanism of action of α-MSH may occur via an influence on granulocytes per se. Mason and Van Epps [45] noted that neutrophil penetration into subdermal sponges injected with cytokines was inhibited by intraperitoneal injections of α-MSH. It may be that a similar action of α-MSH accounts for the influence on contact hypersensitivity. In these recent studies, α-MSH inhibited neutrophil migration induced by IL-1, TNF, and C5a. The effect on IL-1-induced granulocyte migration was dose-related; ACTH had a lesser effect and β-endorphin was ineffective. α-MSH had no effect on concentrations of circulating neutrophils. The combined results suggest that α-MSH can act to antagonize the actions of specific cytokines that are linked to inflammation and other host defense reactions.

Our findings on anti-inflammatory activity of α-MSH molecules are consistent with previous studies on urate crystal inflammation [46]. When α-MSH was injected along with urate crystals into the hind paw of the rat, a small but consistent inhibition of swelling was noted. In these experiments β-endorphin and somatostatin were also effective inhibitors, whereas neotensin and substance P increased swelling.

There is little in vitro evidence on the effects of α-MSH in host cell responses. Augmentation of murine thymocyte proliferation by IL-1 and IL-1-stimulated production of prostaglandin in fibroblasts was inhibited by α-MSH with a biphasic dose-response relationship [47]. These results, and lack of influence on basal thymocyte proliferation on IL-2-induced proliferation of a cytotoxic T-cell lymphocyte line, led to the conclusion that α-MSH is an endogenous antagonist of IL-1, one that is relatively specific. Others [3] did not observe inhibition by α-MSH of IL-1-induced thymocyte proliferation or proliferation of an IL-1-responsive T-cell line. Although these in vitro results are inconsistent, the marked effects of α-MSH in live animals are clear, and they appear to reflect antagonism by the peptide of several activities of IL-1.

**EFFECTS OF HOST CHALLENGE UPON CIRCULATING α-MSH**

The increased concentration of α-MSH within the septal region after challenge with endogenous pyrogen in both tissue-sampling and push-pull studies raised questions about circulating levels of α-MSH. This peptide has a short half-life in the circulation, generally a few minutes, and there was no reason to believe that increases in the septal region are necessarily associated with changes in concentration of circulating peptide. Rabbits were given endogenous pyrogen icv or iv, and blood samples taken 0, 2, and 4 hours later were processed and assayed for α-MSH [3]. Central injections that caused fever had no significant effect on α-MSH concentration, but iv pyrogen caused a marked increase in the circulating peptide, presumably due to stimulation of both peripheral and central pyrogen receptors. These results are very important to understanding the role of the neuropeptide in host defense, for they indicate that α-MSH becomes available throughout the body in response to challenge, to modulate host responses. It may be that the peptide and its fragments can penetrate the brain to
influence fever and other host responses and that circulating α-MSH inhibits migration of cells in the periphery.

OTHER ACTIVITIES OF α-MSH (11-13)

This fragment of α-MSH has not been studied extensively, perhaps in part because of the cost of producing custom peptides. In general, rather large doses have been given in a limited number of studies and the effects have been small. The fragment does not appear to be involved in pigmentation since it exerts only weak activity in Rana and Anolis melanophore assays [48,49]. It is perhaps not important to attention, learning, and memory effects, unlike N-terminal α-MSH fragments, because it has only about 2.5 percent of the activity of α-MSH (1-13) in delaying extinction in the pole-jumping test [50]. It stimulates inner zone and capsular cells of the adrenal cortex of the rat, but only in very large doses (10^{-5} to 10^{-3} M); therefore this action may not be specific [51]. The molecule has been implicated in stimulation of glycolysis, but not steroidogenesis, in mouse adrenal cortical cells, although α-MSH (11-13) was not tested alone [52]. The activity of dopamine neurons in the arcuate nucleus and the substantia nigra of the rat, estimated from cellular fluorescence intensity, is altered by substantial doses of α-MSH (11-13) [53]. The latter finding may be important to understanding the mechanisms of central action of the tripeptide, although a clear link between dopamine neurons and host responses has not been established. In summary, such research on the α-MSH (11-13) molecule has been limited and mostly negative. The strongest evidence of dose-related effects of α-MSH (11-13) is the research on antipyretic and anti-inflammatory activities described above.

THE MECHANISMS OF ACTION OF α-MSH PEPTIDES
IN HOST DEFENSE

The current working hypothesis is that α-MSH, or its fragments, is released by, or concomitantly with, cytokines. Evidence indicates that α-MSH concentrations within the septum and in the circulation increase in the presence of cytokines. Circulating α-MSH is then available throughout the body to modulate host responses. It may be that circulating α-MSH likewise penetrates into the brain, but, because of barrier systems, it appears more likely that smaller active fragments like α-MSH (11-13) penetrate. How do α-MSH and COOH-terminal fragments antagonize the effects of cytokines? There is as yet no clear answer. It is unlikely that α-MSH acts as an IL-1 receptor antagonist, since it does not appear to displace the cytokine from CNS [54] or lung tissue [Schmidt T; personal communication] receptors. α-MSH appears not to act as a prostaglandin synthesis inhibitor like certain other antipyretics because it did not antagonize hyperthermia induced by sodium arachidonate [55]. In whole-animal models of inflammation, it may inhibit inflammation by preventing migration of neutrophils into sites of high concentration of cytokines [45], although this possibility is unlikely to account for its central antipyretic properties. There is also evidence that neutrophils increase vascular permeability [56]. Thus, an inhibition of leukocytes may be responsible for the inhibitory effects of α-MSH (1-13) and α-MSH (11-13) on histamine- and endogenous pyrogen-induced increases in capillary permeability we have observed, although this hypothesis remains to be determined. Thus, with this bioactive peptide, just as with antipyretic and anti-inflammatory drugs that have been studied for much longer, the picutre is incomplete. Discovery of the cellular and
molecular activities of α-MSH peptides in exerting antipyretic and anti-inflammatory effects is a major aim of future research.

**POTENTIAL FOR THERAPEUTIC USE**

α-MSH and its fragments are widespread in the body, and it may be that such molecules are part of a modulatory system that limits host responses. If this hypothesis is true, then it may be possible to use the α-MSH molecule, or, preferably, the shorter α-MSH (11-13) message sequence, to control responses such as fever, neutrophilia, and inflammation in injury and disease. Although much remains to be learned, it is likely that treatment with a naturally occurring substance would be safer than treatment with exogenous drugs. Indeed, treatment with large doses of α-MSH, relative to antipyretic doses, are required centrally to cause toxic effects in rabbits [56]. Doses greater than 1 mg caused agitation, ataxia, and, in 30 percent of the animals, death, but lesser amounts were not harmful. Thus, although the peptide is toxic when given in large doses, the roughly 5,000-fold difference between antipyretic and lethal doses provides a wide safety margin. In contrast, as little as 10 grams of aspirin taken orally has caused death in man [37], an amount only 15 times the common antipyretic dose (650 mg).

If α-MSH peptides are to be used therapeutically, it is important that there be no development of tolerance. When the antipyretic effect of central α-MSH against endogenous pyrogen fever was tested, the α-MSH injected alone twice daily for ten days, and the effect on fever was tested again, there was no sign of tolerance [58].

The duration of action of α-MSH and the related peptides is relatively brief, perhaps one to 1.5 hours in most cases. This brief action allows more precise control, and there is no concern about the agent remaining in the body for long periods. New molecular configurations may provide a longer duration of action. Several molecular analogues have already been developed, and one, Nle4-D-Phe7 (α-MSH), is even more potent in reducing fever than α-MSH (1-13) when given centrally [59]. Unfortunately, the molecule is not effective against fever when given peripherally. Because of its relative safety, it may be possible to give the natural peptide in large doses and thus increase the duration of effect of a single dose. In brief, the activity of α-MSH molecules and their prima facie safety suggests that such agents might be useful in treatment of clinical disease, injury, and inflammation.

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