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α-Melanocyte-Stimulating Hormone Inhibits the Nuclear Transcription Factor NF-κB Activation Induced by Various Inflammatory Agents

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α-Melanocyte-stimulating hormone (α-MSH) is a tridecapeptide found mainly in the brain, pituitary, and circulation. It inhibits most forms of inflammation by a mechanism that is not known. As most types of inflammation require activation of NF-κB, we investigated the effect of α-MSH on the activation of this transcription factor by a wide variety of inflammatory stimuli. Electrophoretic mobility shift assay showed that α-MSH completely abolished TNF-mediated NF-κB activation in a dose- and time-dependent manner. It also suppressed NF-κB activation induced by LPS, okadaic acid, and ceramide. The effect was specific, as the activation of the transcription factor activating protein-1 by TNF was unaffected. Western blot analysis revealed that TNF-dependent degradation of the inhibitory subunit of NF-κB, IκBα, and nuclear translocation of the p65 subunit of NF-κB were also inhibited. This correlated with suppression of NF-κB-dependent reporter gene expression induced by TNF. The inhibitory effect of α-MSH appeared to be mediated through generation of cAMP, as inhibitors of adenylate cyclase and of protein kinase A reversed its inhibitory effect. Similarly, addition of membrane-permeable dibutyryl cAMP, like α-MSH, suppressed TNF-induced NF-κB activation. Overall, our results suggest that α-MSH suppresses NF-κB activated by various inflammatory agents and that this mechanism probably contributes to its anti-inflammatory effects. The Journal of Immunology, 1998, 161: 2873–2880.
Materials and Methods

Materials

Penicillin, streptomycin, RPMI 1640 medium, and FCS were obtained from Life Technologies (Grand Island, NY). α-MSH, glycine, NaCl, H-7, and BSA were obtained from Sigma (St. Louis, MO). Adenosine cyclic 3′,5′-phosphorothioate triethylammonium salt (Rp-cAMPS) and H-8 (methylamino)ethyl-5-isoquinolinesulfonamide (HCl) were obtained from Calbiochem (San Diego, CA). H-8 was dissolved in water at a concentration of 2 mM and kept at −20°C. Dideoxyadenosine and dibutyryl cAMP were obtained from LC Laboratory (San Diego, CA). Bacteria-derived recombinant human TNF, purified to homogeneity with a sp. act. of 5 × 10^7 U/mg was provided by Genentech (South San Francisco, CA). Abs against IκBα, p50, p65, and c-Rel, and double-stranded oligonucleotide, with AP-1 consensus sequence were obtained from Santa Cruz Biotechnology (Santa Cruz, CA). NF-κB oligonucleotides from the HIV long terminal repeat, were synthesized and supplied by Life Technologies (Grand Island, NY). 5′-TGTTTACAAGGGAGGTGGG, were synthesized and supplied by Life Technologies (Grand Island, NY). 5′-TTGTTACAAGGGAGGTGGG, were synthesized and supplied by Life Technologies (Grand Island, NY). Underlined regions represent a consensus NF-κB binding sequence.

The rat plasminoids -243RMICAT (wild) and -243RMICAT-mut (mutant), containing the chloramphenicol acetyltransferase (CAT) gene with either the wild-type or mutated NF-κB binding site were supplied by Dr. M. Tien Kuo of the M. D. Anderson Cancer Center (Houston, TX). The characterization of these plasmids has been described previously in detail (15). The well-characterized human histiocytic lymphoma U-937 cell line (16) was obtained from American Type Cell Culture Collection (Manassas, VA) and used in mycoplasma-free cultures.

Electrophoretic mobility shift assays (EMSA)

Cells (2 × 10^6/ml) were treated separately with different concentrations of TNF at 37°C. Nuclear extracts were then prepared according to the method of Schreiber et al. (17). Briefly, 2 × 10^6 cells were washed with cold PBS and suspended in 0.4 ml of lysis buffer (10 mM HEPES (pH 7.9), 10 mM KCl, 0.1 mM EDTA, 0.1 mM EGTA, 1 mM DTT, 1 mM PMSF, 2 mM leupeptin, 2 μg/ml aprotinin, and 0.5 mg/ml benzamidine). The cells were allowed to swell on ice for 15 min, after which 12.5 μl of 10% Nonidet P-40 was added. The tube was then vigorously mixed on a vortex machine for 10 s, and the homogenate was centrifuged for 30 s in a microfuge. The nuclear pellet was resuspended in 25 μl of ice-cold nuclear extraction buffer (20 mM HEPES (pH 7.9), 0.4 M NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM DTT, 0.5 mM PMSF, 2 μg/ml leupeptin, 2 μg/ml aprotinin, and 0.5 mg/ml benzamidine). The cells were allowed to swell on ice for 15 min, after which 12.5 μl of 10% Nonidet P-40 was added. The tube was then vigorously mixed on a vortex machine for 10 s, and the homogenate was centrifuged for 30 s in a microfuge. The nuclear pellet was resuspended in 25 μl of ice-cold nuclear extraction buffer (20 mM HEPES (pH 7.9), 0.4 M NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM DTT, 0.5 mM PMSF, 2 μg/ml leupeptin, 2 μg/ml aprotinin, and 0.5 mg/ml benzamidine), and the tube was incubated on ice for 30 min with intermittent mixing. The nuclear pellet was resuspended in 25 μl of ice-cold nuclear extraction buffer (20 mM HEPES (pH 7.9), 0.4 M NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM DTT, 0.5 mM PMSF, 2 μg/ml leupeptin, 2 μg/ml aprotinin, and 0.5 mg/ml benzamidine), and the tube was incubated on ice for 30 min with intermittent mixing. The tube was then centrifuged for 5 min in a microfuge at 4°C, and the supernatant (nuclear extract) was either used immediately or stored at −70°C for later use. The protein content was measured by the method of Bradford (18).

EMSA were performed by incubating 4 μg of nuclear extract with 16 fmol of 32P end-labeled 45-mer double-stranded NF-κB oligonucleotide from the HIV long terminal repeat, 5′-TTGTTACAAGGGAGGTGGG, were synthesized and supplied by Life Technologies (Grand Island, NY). Underlined regions represent a consensus NF-κB binding sequence. The incubation mixture included 2–5 μg of poly (dl-dc) in a binding buffer (25 mM HEPES pH 7.9, 0.5 mM EDTA, 0.5 mM DTT, 1% Nonidet P-40, 5% glycerol, and 50 mM NaCl) (19, 20). The DNA-protein complex formed was separated from free oligonucleotide on 6.6% native polyacrylamide gel using buffer containing 50 mM Tris, 200 mM glycine pH 8.5, and 1 mM EDTA (21), and then the gel was dried. A double-stranded mutated oligonucleotide, 5′-TTGTTACAAGGGAGGTGGG, was used to examine the specificity of binding of NF-κB to the DNA. The specificity of binding was also examined by competition with the unlabeled oligonucleotide.

The EMSAs for AP-1 were performed as described for NF-κB using 32P end-labeled double-stranded oligonucleotides. The specificity of binding was determined routinely by using an excess of unlabeled oligonucleotide for competition as described previously (22).

Visualization and quantitation of radioactive bands were conducted with a PhorImager (Molecular Dynamics, Sunnyvale, CA) using ImageQuant software.

Western blotting for IκBα, p50, and p65

After the NF-κB activation reaction described above, postnuclear extracts were resolved on 10% SDS-polyacrylamide gels for IκBα. To determine the p50 and p65 levels, nuclear and postnuclear (cytoplasmic) extracts were resolved on 8% SDS-PAGE. The proteins were electrotransferred from the gels to nitrocellulose filters; probed with rabbit polyclonal Abs against IκBα, p50, and p65; and then detected by chemiluminescence (ECL, Amersham, Arlington Heights, IL) (23). The bands obtained were quantitated on a Personal Densitometer Scan version 1.30 using ImageQuant software version 3.3 (Molecular Dynamics).

Transient transfection and CAT assay

U-937 cells were transiently transfected with -243RMICAT (wild) and -243RMICAT-mut (mutant) genes for 6 h using the calcium phosphate method, according to the instructions supplied by the manufacturer (Life Technologies). After transfection, the cells were incubated for 24 h at 37°C, treated with α-MSH (50 nM) for 24 h, stimulated with 100 pM TNF for 1 h, then washed with PBS and examined for CAT activity as previously described (24).

Results

We examined the effect of α-MSH on the activation of transcription factor NF-κB. We used human monocytic U937 cells for these studies because their response to NF-κB activation by various stimuli has been well characterized in our laboratory (22, 25). These cells were treated with up to 100 nM α-MSH for 24 h and then examined for cell viability by the trypan blue dye exclusion method. A viability of 94.6% was noted in 100 nM α-MSH-treated cells compared with 97.8% in untreated cells. Thus, the time of incubation and the concentration of hormone used in our studies had no significant effect on cell viability.

α-MSH inhibits TNF-dependent NF-κB activation

U-937 cells were preincubated for 24 h with different concentrations of α-MSH and then treated with TNF (100 pM) for 30 min at 37°C. They were then examined for NF-κB activation by EMSA. The results shown in Figure 1A indicate that 25 to 50 nM hormone inhibited most of the TNF response. α-MSH by itself did not activate NF-κB. We next tested the kinetics of inhibition. Cells were exposed to α-MSH for 0 to 24 h and then activated by TNF for 30 min. TNF-mediated NF-κB activation was inhibited maximally when the cells were pretreated for 24 h with the hormone (Fig. 1B).

Previous studies from our laboratory have shown that at a high concentration, TNF (10 nM) can activate NF-κB within 5 min and that this induction is much more intense than that obtained with cells using 100-fold lower concentrations for longer times (25). To determine the effect of α-MSH on NF-κB activation, both untreated and hormone-pretreated cells were incubated with various concentrations of TNF (0–10,000 pM) for 30 min, and then NF-κB was assayed by EMSA (Fig. 1C). Although the activation of NF-κB by 10,000 pM TNF was strong, α-MSH completely inhibited it, just as it did at 100 pM TNF. These results show that α-MSH is a very potent inhibitor of NF-κB activation.

To determine the effect of α-MSH on the kinetics of NF-κB activation, both untreated and hormone-pretreated cells were incubated with TNF (100 pM) for different times, and then EMSA was conducted. The activation of NF-κB by TNF was detected with the increased time of incubation in control cells, whereas in α-MSH-pretreated cells, no activation of NF-κB was detected even after up to 60 min of TNF stimulation (Fig. 1D).

NF-κB inhibited by α-MSH consists of p50 and p65 subunits

Various combinations of Rel/NF-κB proteins can constitute an active NF-κB heterodimer that binds to specific DNA sequences. To show that the retarded band visualized by EMSA in TNF-treated cells was indeed NF-κB, we incubated nuclear extracts from TNF-activated cells with Ab to either p50 (NF-κB1) or p65 (Rel A) subunits, or both, and then conducted EMSA. Abs to either subunit of NF-κB decreased the migration of the band on the gel (Fig. 2A), thus suggesting that the TNF-activated complex consisted of p50 and p65 subunits.
and p65 subunits. Both Abs together induced the migration of all the activated NF-κB bands to a high m.w. complex. Neither pre-immune serum nor the irrelevant Abs, anti-c-Rel or anti-cyclin DI, had any effect on the mobility of NF-κB. Competition with excess unlabeled NF-κB probe (100-fold) produced complete disappearance of the band, indicating the specificity of NF-κB.

α-MSH does not inhibit TNF-induced AP-1 activation

Whether α-MSH specially blocks the activation of NF-κB or also affects activation of other transcription factors such as AP-1 (26) was investigated. The cells were treated with different concentrations of the hormone, then treated with TNF (1 nM for 1 h) for AP-1 activation; the nuclear extracts were prepared and then assayed for NF-κB as described in Materials and Methods. Figure 2B shows that α-MSH had no effect on the activation of AP-1 transcription factors. Thus, α-MSH specially blocks the activation of NF-κB.

α-MSH blocks LPS-, okadaic acid-, and ceramide-mediated activation of NF-κB

Besides TNF, NF-κB activation is also induced by several other inflammatory stimuli, including phorbol ester, hydrogen peroxide, LPS, okadaic acid, and ceramide. The signal transduction pathway leading to NF-κB activation induced by these agents may differ. We therefore examined the effect of α-MSH on the activation of the transcription factor by these agents. The results shown in Figure 3 indicate that the hormone completely blocked the activation of NF-κB induced by all these agents except PMA and H₂O₂, whose activities were partially inhibited. The partial inhibition observed in some cases could be because the time and dose of α-MSH used were those optimized for TNF. Alternatively, PMA and H₂O₂ may activate NF-κB by a different mechanism. These results also suggest that α-MSH may act at a step where LPS, okadaic acid, and ceramide converge in the signal transduction pathway leading to NF-κB activation.

Inhibition of NF-κB activation by α-MSH is not cell type specific

Besides myeloid cells, we also examined the ability of α-MSH to block TNF-induced NF-κB activation in epithelial (HeLa), glioma (H4), and lymphoid (Jurkat) cells. The results of these experiments (Fig. 4) indicate that α-MSH inhibited NF-κB in all three cell types. Almost complete inhibition was observed with epithelial and glioma cells, and partial inhibition was observed with Jurkat.
cells, thus suggesting that this effect of α-MSH is not cell type specific. The NF-κB binding in all cells was abrogated by a 25-fold molar excess of unlabeled oligonucleotide.

α-MSH inhibits TNF-dependent degradation of IκBa and nuclear translocation of the p65 subunit of NF-κB

The translocation of NF-κB to the nucleus is preceded by the phosphorylation and proteolytic degradation of IκBa (27). To determine whether the inhibitory action of α-MSH was due to its effect on IκBa degradation, the cytoplasmic levels of IκBa proteins was examined by Western blot analysis. Treatment of cells for 24 h with or without α-MSH alone had no effect on the synthesis of IκBa (Fig. 5A). The IκBa band, however, was decreased in intensity within 5 min of TNF treatment of cells and then disappeared within 10 min. The band reappeared by 30 min. When the hormone was present, the band did not diminish, indicating that α-MSH blocked the TNF-mediated degradation of IκBa (Fig. 5A).

Because NF-κB activation also requires nuclear translocation of the p65 subunit of NF-κB, we measured the levels of p65 in the cytoplasm and nucleus. As expected upon TNF treatment, the level of p65 declined in the cytoplasm and concurrently increased in the nucleus (Fig. 5B). Treatment of cells with α-MSH abolished the TNF-dependent change in the nuclear and cytoplasmic p65 levels. These results show that α-MSH inhibited the TNF-induced translocation of p65 to the nucleus, which is consistent with the inhibition of TNF-dependent degradation of IκBa. Besides p65, the effect of the hormone on the cytoplasmic and nuclear pools of the other member of the Rel family of proteins was also examined. The results shown in Figure 5C indicate that neither TNF by itself nor its combination with α-MSH had any effect on the p50 level.

FIGURE 2. A, Supershift and specificity of the NF-κB. Nuclear extracts (NEs) were prepared from untreated or TNF (0.1 nM)-treated U937 cells (2 × 10⁶/ml), incubated for 15 min with different Abs and cold NF-κB, and then assayed for NF-κB on 6.6% acrylamide gels as described in Materials and Methods. B, Effect of α-MSH on AP-1 transcription factor. Cells were treated with different concentrations of α-MSH for 24 h min at 37°C, then treated with 1 nM TNF for 1 h. Nuclear extracts were prepared and then used for EMSA of AP-1 transcription factor as described in Materials and Methods.

FIGURE 3. Effect of α-MSH on activators (PMA, serum-activated LPS, H₂O₂, okadaic acid, and ceramide) of NF-κB. U937 cells (2 × 10⁶/ml) were preincubated for 24 h at 37°C with α-MSH (50 nM); then with PMA (25 ng/ml), serum activated (SA)-LPS (10 μg/ml), H₂O₂ (250 μM), okadaic acid (500 nM), or ceramide (10 μM) for 30 min; and tested for NF-κB activation as described in Materials and Methods.

FIGURE 4. Effect of α-MSH on TNF-induced NF-κB in different cell types. HeLa, Jurkat, or H4 cells (2 × 10⁶/ml) were preincubated for 24 h with or without α-MSH (50 nM), followed by TNF (100 pM) for 30 min. Nuclear extracts were prepared and tested for NF-κB activation as described in Materials and Methods. The specificity of NF-κB binding was determined by performing EMSA in the presence of a 25-fold molar excess of cold NF-κB oligonucleotide.
An equal level of p50 protein noted in Figure 5C also indicates that equal amounts of protein were loaded for the results shown in A, B, and C.

\( \alpha \)-MSH represses reporter-NF-\( \kappa \)B-CAT gene expression

The MDR promoter containing the NF-\( \kappa \)B binding site linked to the CAT gene was used to examine gene expression after stimulation by TNF. We used a transient expression assay to determine the effect of \( \alpha \)-MSH on the TNF-induced MDR gene linked to the CAT gene. Almost a threefold increase in CAT activity was noted upon stimulation with TNF (Fig. 6), but this was reduced by almost 90% when the wild-type gene-transfected cells were pretreated with \( \alpha \)-MSH for 24 h before TNF treatment. As a control, transfection with the reporter gene containing the mutated NF-\( \kappa \)B binding site did not result in induction of CAT by TNF. These results demonstrate that \( \alpha \)-MSH represses NF-\( \kappa \)B-dependent reporter gene expression induced by TNF.

\( \alpha \)-MSH-mediated inhibition of NF-\( \kappa \)B activation is mediated through cAMP

It has been reported that \( \alpha \)-MSH transduces its signal through cAMP. To examine the role of cAMP, we used dideoxyadenosine (ddAdo), a potent inhibitor of adenylate cyclase (28), the enzyme responsible for the generation of cAMP. Cells were exposed to different concentrations of ddAdo for 2 h and then to \( \alpha \)-MSH for 24 h, and then were stimulated with TNF (100 pM) for 30 min. The results shown in Figure 7A show that ddAdo did not interfere with TNF-induced NF-\( \kappa \)B activation, but it protected against \( \alpha \)-MSH-mediated suppression of NF-\( \kappa \)B stimulated by TNF. Treatment of cells with exogenous cAMP (dibutyryl cAMP) mimicked \( \alpha \)-MSH, in that it induced a gradual decrease in TNF-induced NF-\( \kappa \)B activation with increases in its concentration (Fig. 7B).

Since cAMP is known to activate PKA, we also examined the effects of two specific PKA inhibitors, Rp-cAMPS isomer and H8 (29), on the \( \alpha \)-MSH-induced inhibition of NF-\( \kappa \)B activation. For this, cells were pre-exposed to either Rp-cAMPS isomer (100 \( \mu \)M) or 2 \( \mu \)M H-8 for 1 h at 37°C and then treated with \( \alpha \)-MSH for 24 h, were exposed simultaneously to Rp-cAMPS isomer or to 2 \( \mu \)M H-8 and \( \alpha \)-MSH for 24 h, or were treated after the hormone exposure and then examined for TNF-induced NF-\( \kappa \)B activation. Pretreatment with both PKA inhibitors blocked the inhibitory effects of \( \alpha \)-MSH, while coincubation with the hormone was partially effective. After treatment with Rp-cAMPS isomer or of H-8 there was almost no protection of \( \alpha \)-MSH-mediated inhibition of NF-\( \kappa \)B activation (Fig. 7, C and D). These results indicate that the effects of \( \alpha \)-MSH are mediated through activation of PKA. In contrast to PKA inhibitor, the PKC inhibitor H7 had no effect on \( \alpha \)-MSH-mediated inhibition of NF-\( \kappa \)B activation (Fig. 7E), suggesting that the effect of the PKA inhibitor is specific.

Discussion

Although several studies indicate that certain neuropeptides, such as \( \alpha \)-MSH, have anti-inflammatory effects, the mechanism is not understood. In this study we found that \( \alpha \)-MSH specifically downregulates a transcription factor, NF-\( \kappa \)B, whose activation is induced by a wide variety of inflammatory stimuli, including TNF, endotoxin, ceramide, and okadaic acid. This suppression of NF-\( \kappa \)B...
activation by α-MSH was found not to be cell type specific and was mediated through generation of cAMP and activation of PKA. α-MSH is primarily produced by the cells in the brain and pituitary. It stimulates melanocytes and other cell types. This hormone interacts with different cells through five distinct G protein-coupled receptors (MC-1 to MC-5) (30, 31). All except the MC-2 receptor have been found in brain tissue; the MC-2 receptor was found only in the adrenal cortex. Recently, it was reported that both human and murine macrophage cell lines and human neutrophils express MC-1 receptor (8, 9). Thus, it is highly likely that the effects of α-MSH described here in the human monocytic cell line U-937 and others are mediated through activation of the MC-1 receptor. Like other G protein-coupled receptors, it has also been shown that α-MSH mediates its effects in neutrophils and other cell types through an increase in intracellular cAMP. In our studies, we found that inhibitors of adenylate cyclase blocked the suppressive effect of α-MSH, suggesting a critical role of cAMP in inhibition of NF-κB activation. In addition, treatment of cells with dibutyryl cAMP blocked NF-κB activation.

How cAMP generated by activation of cells with α-MSH inhibits NF-κB was also investigated. That inhibitors of PKA reversed the suppressive effect of α-MSH suggests that cAMP may act by activating this kinase. This possibility is intriguing because it has been shown that PKA-mediated phosphorylation of NF-κB is involved in inducible and constitutive activation of NF-κB (32, 33). It was also shown that the catalytic subunit of PKA associates with IκBa, the inhibitory subunit of NF-κB, in the cytoplasm (34). On stimulation of cells with either LPS or IL-1, PKA is activated, leading to phosphorylation of the p65 subunit of NF-κB and, in turn, to NF-κB’s translocation to the nucleus (34). As the PKA activation observed in these studies was cAMP independent, it is unlikely that this is a mechanism of suppression...
of NF-κB activation by α-MSH. Besides, in our studies PKA activation resulted not in activation of NF-κB, as shown by Zhong et al. (34), but, rather, in its suppression. Also, an inhibitor of PKC, H7, had no effect on the suppressive effect of α-MSH, indicating specificity.

Our results, however, are consistent with those of other reports, which show that elevation of cAMP reduces NF-κB activity (35–38). How elevation of cAMP reduces NF-κB activity, however, is controversial. Ollivier et al. (37) found inhibition of NF-κB-mediated transcription by elevated cAMP or by overexpression of PKA without any inhibition of the IkBα degradation or nuclear translocation of p65. In contrast, Chen and Rothenberg (35) and Neumann et al. (36) reported that the effects of cAMP are mediated through stabilization of IkBα and impairment of the nuclear transport of p65. Similar to the latter observations, we found that elevation of intracellular cAMP induced by α-MSH inhibits IkBα degradation and p65 translocation to the nucleus as well as gene transcription. It is possible that cAMP inhibits NF-κB activation through inhibition of the mitogen-activated protein kinase c-Jun N-terminal kinase pathway, as overexpression of mitogen-activated protein kinase kinase reversed the inhibitory effects of cAMP on NF-κB activation (38).

We found that, besides that induced by TNF, NF-κB activation induced by LPS, ceramide, and okadaic acid was also inhibited by α-MSH. That the NF-κB activation induced by PMA and H2O2 was inhibited only partially suggests a difference in the mechanisms of activation. This is in agreement with studies showing that PMA activates NF-κB by a mechanism different from that of TNF and okadaic acid (39). For instance, inhibitors of PKC block PMA-induced, but not TNF-induced, activation of NF-κB (40). Our data indicate that various signals leading to activation of NF-κB converge at or before the IkBα target, which, in turn, suggests the possibility of a common upstream effector.

Although there are several small molecule and nonpeptide inhibitors of cell signaling known to block NF-κB activation, there are very few normal physiologic peptide hormones reported to block NF-κB activation. It was recently shown that IL-4, IL-10, and growth hormone can block NF-κB activation, but their mechanisms of action were not reported (6, 41, 42).

We demonstrated that α-MSH inhibits the NF-κB-dependent gene transcription activated by TNF. There are a large number of genes involved in cellular inflammation that require NF-κB activation, including MHC-1, TNF, IL-1, IL-6, granulocyte colony-stimulating factor, chemokines, cyclo-oxygenase, lipoxygenase, complement receptor, cell adhesion proteins, and nitric oxide synthase (13). α-MSH has been shown to inhibit nitric oxide synthesis (9), TNF production (8), neutrophil migration, and PG synthesis (10), all of which are NF-κB-dependent and are involved in inflammation. In addition, the p65 subunit of NF-κB has been colocalized with α-MSH in the rat brain, suggesting a close relationship (43). As inhibitors of NF-κB activation have been exploited to treat various inflammatory diseases (44), α-MSH may be useful in those situations. Overall, we conclude that because it has no known pharmacologic toxicity and is able to suppress NF-κB activation by various agents, α-MSH has potential for use in conditions initiated through NF-κB activation, such as inflammatory diseases, HIV replication in AIDS, and septic shock.

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References


