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Role of Melanocortins in Inflammation and Other Therapeutic Indications Like Pulmonary Inflammatory, Allergic and Neurological Disorders Like Multiple Sclerosis, Infantile Spasms and Brain Injury-A Systematic Review

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ABSTRACT

After having reviewed the role of melanocortin 4 receptors in obesity here we concentrated on other role of melanocortins in inflammation, other neurological complications. Melanocortins are a collection of adrenocorticotropin hormone (ACTH), α, β as well as ɣ melanocyte stimulating hormone (MSH) along with their receptors, are a part of the old modulatory system. The clinical utility of ACTH was initiated in 1949 by Hench, who initially believed that this action was brought about by the hypothalamo-pituitary-adrenal (H-P-A) Axis and was glucocorticoid (GC)-dependent. It is now well known that the melanocortins bring about the anti-inflammatory as well as immunomodulatory actions by the activation of melanocortin receptors. Having reviewed the role of proopiomelanocortin (POMC) and its peptides in obesity here we tried to unravel the inflammatory and other neurological sequelae of utilization of these melanocortins. Thus, we conducted a systematic review on the melanocortins and their receptors utilizing the Pubmed, Google Scholar, Web of Science, search engines utilizing the MeSH terms melanocortins; melanocortin receptors 1-5; inflammation; actions in various systems; ACTH; Alpha MSH; Gamma and beta MSH; multiple sclerosis (MS); Infantile spasms; head injuries from 1940 till date on 3rd july 2020. We found a total of over 10,000 articles out of which we selected 122 articles for this review. In view of having reviewed MC4R agonism in obesity we did not use betmelinide and setmelanotide being tried for obesity in this review. Thus, we have tried to discuss comprehensively the anti-inflammatory activities that might be utilized clinically after initial enthusiasm lost in this ancient system. Adrenocorticotropin hormone (ACTH) and alpha-Melanocortin stimulating hormone (a-MSH) reduce pro-inflammatory cytokines in several pulmonary inflammatory disorders including asthma, sarcoidosis, and the acute respiratory distress syndrome. They have also been shown to reduce fibrogenesis in animal models with pulmonary fibrosis. By understanding the functions of MCR in macrophages, T-helper cell type 1, and T-helper cell type 17, we may uncover the mechanism of action of melanocortin agonists in sarcoidosis. Further translational and clinical research is needed to define the role of ACTH and a-MSH in pulmonary diseases.

Keywords: Melanocortins, Melanocortin receptors MS: Infantile spasms, ACTH: Alpha MSH: ARDS: Septic shock, pulmonary inflammatory disorders

INTRODUCTION

The melanocortin system is made up of melanocortins, 2 endogenous antagonists, the agouti-signaling s protein (agouti-) as well as agouti-related peptide (Ag RP) along with 5 receptors. The melanocortins consist of ACTH, as well as α, β as well asɣmelanocyte stimulating hormone (MSH), that get produced via post translational processing of a common precursor proopio melanocortin (POMC) (discussed in review no. 1 **(Figure 1)**). Besides the well detailed adrenal responses that get stimulated via adreno corticotropin hormone (ACTH) along with pigmentary

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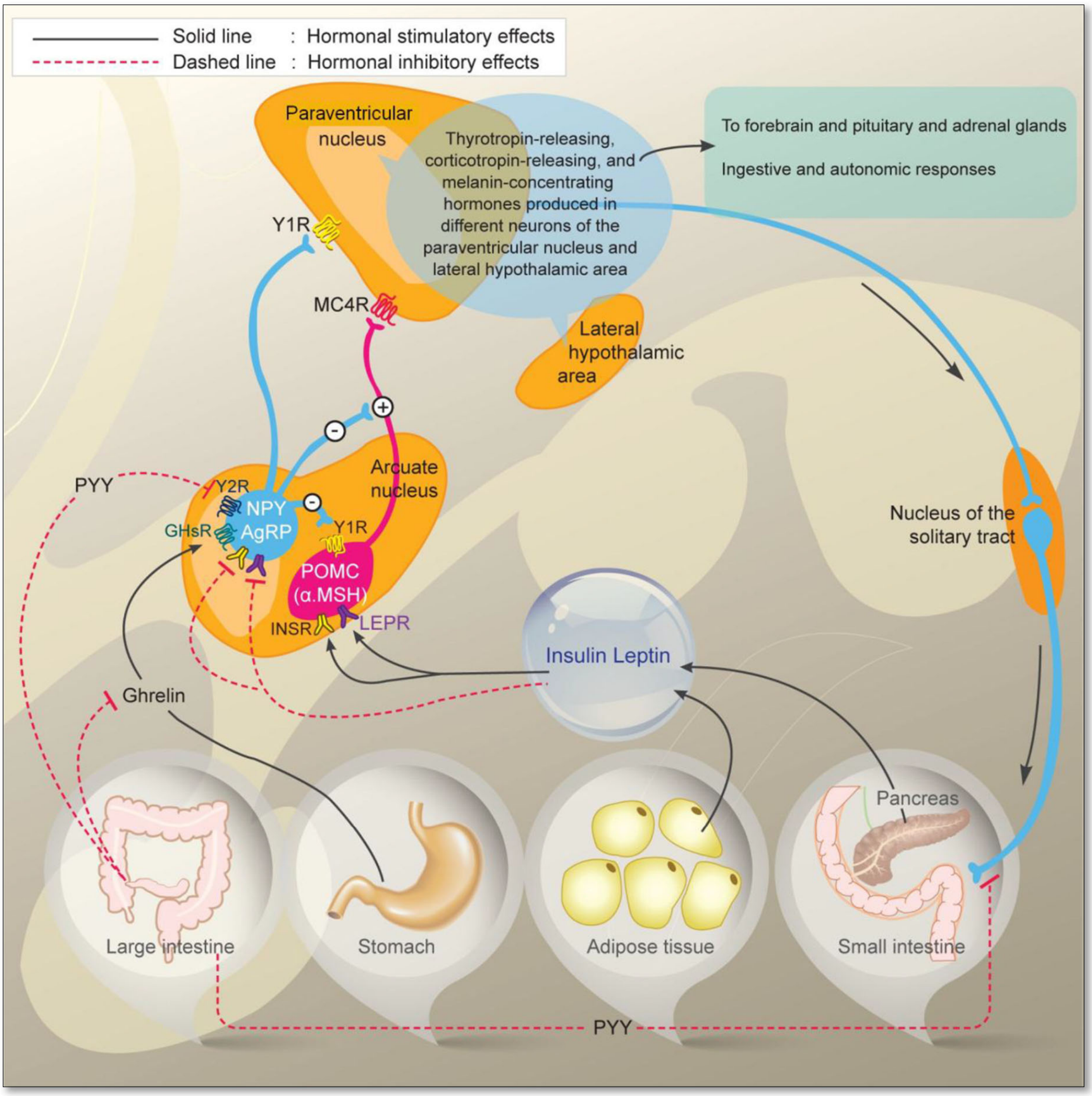

Figure 1. Arcuate nucleus along with paraventriculus nucleus and lateral hypothalamus showing the distribution of POMC/CART and NPY/Ag RP neurons along with MC4R AND NPY Receptors, Leptin and Ghrelin signaling.

actions stimulated through α-MSH, other physiological function like energy homeostasis, sexual activity, exocrine liberation along with anti-inflammatory as well as immune modulatory effects that these neuropeptides have on the host that are markedly versatile have been detailed deeply. We discussed the details of melanocortin in articles related to obesity, and how they are responsible for controlling energy homeostasis [1-3].

1st clinical work utilizing ACTH in the therapy of severer heumatoid arthritis (RA) patients. Rheumatic fever (RF), as well as some other situations was conducted via Hench et al. [4,5] who received the noble prize for physiology as well as medicine in 1950 for the wonderful finding of ACTH as well as cortisol [6]. ACTH helped in the clinical features (CF) of RA along with then via hypothalamo-pituitary-adrenal (HPA) axis getting stimulated as well as generation of glucocorticoids (GC) at that time.

Our insight on melanocortin physiology as well as pharmacology has markedly enhanced following the recognition as well as cloning of melanocortin receptor (MCR). Only in 2002 the local stimulation of MC3R via ACTH, independent of glucocorticoids was shown to be further involved in ACTH being effective in gouty arthritis as well [7]. This significant study pointed that selective MC3R agonists might get used as innovative anti-inflammatory compounds in clinical tackling of chronic inflammatory situations [7]. Here we describe the melanocortin system like melanocortin peptides, MCR as well as intracellular signalling pathways. Subsequently the anti-inflammatory actions of melanocortin, both in vitro as well as in vivo, the mode of action along with potential effectiveness in treatment protocols.

MELANOCORTIN SYSTEM

The melanocortin ligands

Generated through post translational processing of a common precursor protein, POMC **(Figures 1 and 2)**, was initially found in mouse pituitary tumor cells, with later illustration in human non pituitary cells by various independent groups [8]. Nanakhini et al., via Utilization of recombinant technologies documented the nucleotide sequence of the bovine DNA [9], in case of different mammals, amphibian as well as teleosts [10-12]. On contrasting the sequence, a recognizable POMC sequence was illustrated in lamprey the maximum ancient vertebrate which shares structural similarities with higher vertebrates as well as teleosts, pointing that the looks of POMC might be as ancient as 700 million or >years [13].

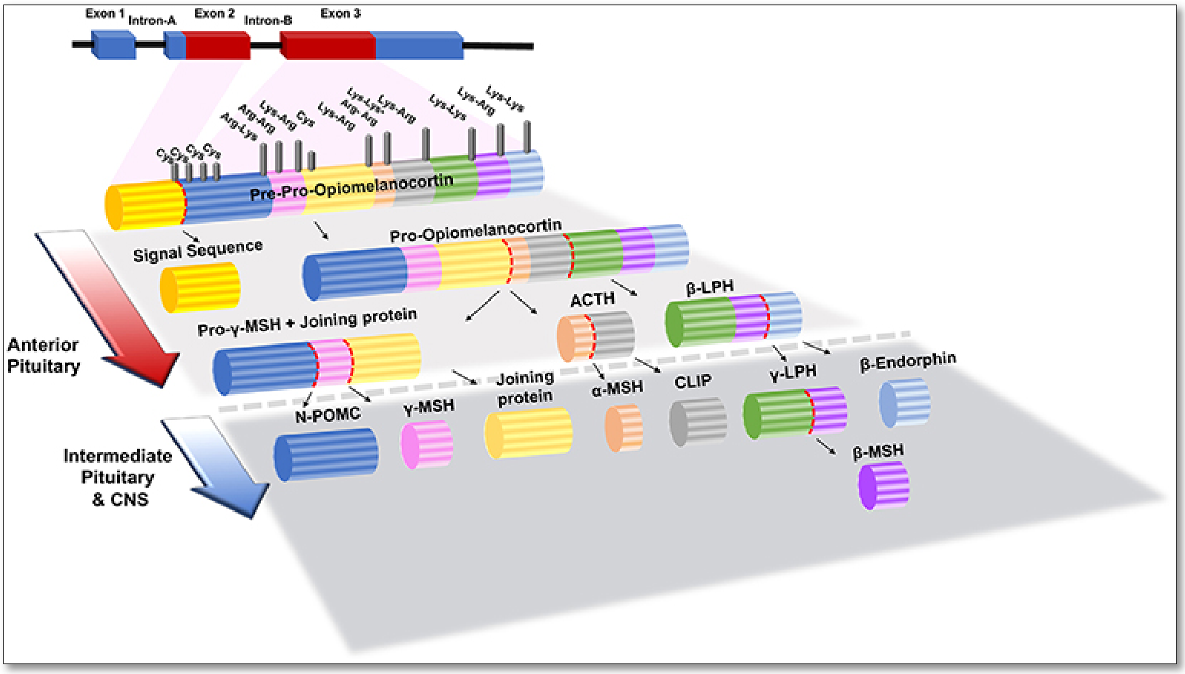

Figure 2. Courtesy ref no-121 Structure of POMC (Pre-Opiomelanocortin) gene and its post-translational processing and modification products in the anterior and intermediate pituitary gland. Lys, Lysine; Arg, Arginine; Cys, Cystine; α-, β- and λ-MSH, α-, β- and λ-Melanocyte Stimulating Hormone; ACTH, Adrenocorticotropic Hormone; β- and λ- LPH, β- and λ-Lipotrophin; N-POMC, N-Pro-Opiomelanocortin. The figure adapted from Bicknell (1) and Mulcahy and Nillni (2) works with modification.

Besides the pituitary as well as melanocytes along with keratinocytes in skin where initially POMC was found, POMC mRNA has been traced in the hypothalamic arcuate nucleus, nucleus of the solitary tract as well as in the caudal brain stem, along with dorsal root ganglion [14,15]. POMC mRNA has been traced in the peripheral immune cells, like lymphocytes as well as monocytes, pointing to a controlling action of POMC obtained peptides in inflammation in these particular immune associated cells [16-19]. Actually, cytokine, interferon, or hormone induced activation of signal transducers as well as activators of transcription signaling cascades escalates POMC expression, as well as Melanocortin generation at places of infection or inflammation [20] **(Figures 1 and 2)**.

The tissue-particular post translational processing of, POMC is mediated via prohormone convertases (PCs), proteolytic enzymes from the family of serine kind of proteases. PC1 cleaves POMC for forming ACTH as well as other peptides in the anterior pituitary gland while in case of lower vertebrates as well as in fetal as well as early infantile times in humans, PC2 present in the pars intermedica, is responsible for the formation of MSH as well as β-endorphin. Additionally, POMC gets digested further into MSH via PC2 in peripheral tissues like skin as well as hair follicles along with the central nervous system (CNS) [21].

All melanocortins possess the same amino acid motif HFRW that is the least sequence needed for receptor binding as well as activation. Noticeably every Melanocortin influences separate capacity for the particular receptor, with ACTH being particular regarding activation of MC2R ,α-MSH possesses maximum capacity for binding MC1R, MC3R, as well as MC4R,while γ-MSH having maximum affinity for MC3R. Melanocortin system is separate in view of presence of 2 natural antagonists, the agouti as well as agouti-related peptide(Ag RP), that work in the form of inverse agonists for blocking the agonistic binding of the MCR as well as reduce the constitutive action(agouti for MC1R as well as Ag RP for MC3R, as well as MC4R). Recently Ag RP via activation of neural MC4R was demonstrated to stimulate Gi activation of potassium channel opening through a Gs independent way [22]. They further demonstrated that Ag RP reduces cAMP action of constitutively active F347A hMC3R, yet stimulates ERK1/2 activation in both wild type as well as laboratory formed mutant F347A hMC3R [23]. In the MC4R, Ag RP is also an inverse agonist for at the Gs cAMP pathway but an agonist at the ERK1/2pathway [24]. These results showed that biased agonism of Ag RP in neural MCRs that adds innovative layer of complicated MCR signaling [25,26].

Melanocortin receptors

Multiple funs of Melanocortin peptides get modulated via 5 MCRs, MC1R to MC5R, whose naming is as per their sequence of their cloning .Being members of Family of G protein coupled receptors (GPCRs), MCRs have a similar basic structure made up of 7-α-helical transmembrane domains, an extracellular (EC) N terminus, as well as intracellular tail that get bound via 3 alternating extracellular C as well as 3 intracellular C loops. Comparing the sequence of human MCRs shows lot of homology from 38% identity among MC2Rsas well as MC4Rs to 60% among MC4R as well as MC5R [20]. MC2R displays variety of expression patterns that might aid in their different types of physiological functions. Being markedly challenging as well as popular drug targets, lot of work has been done to form Melanocortin agonists as well as antagonists that have higher potency as well as greater selectivity.

In skin as well as hair follicles MC1R is the classical MSH receptor expresses along with controls pigmentation. Nevertheless MC1R, possessing the maximum affinity for α -MSH, gets expressed in practically all cell kinds that respond to the anti-inflammatory actions that melanocortins possess. Further normal human monocytes as well as mouse brain were demonstrated to possess very minimal amounts of MC1R binding areas that get up regulated via different stimuli like lipopolysaccharides (LPS) or a combination of cytokines as well as traumatic brain injury, respectively [27]. Additionally, via measurement of ionized calcium binding adapter molecule1 staining (Iba-1) in microglial cells, that is a recognized marker of cerebral inflammation, Schaible et al., demonstrated that α -MSH [9,10], possibly via targeting the MC1R, markedly ameliorates cerebral inflammation, as seen by decrease in activation of Iba-1 positive cells in the ipsilateral hemisphere [27]. 2 synthetic MC1R agonists, BMS-470539 as well as AP1189, were further demonstrated to show anti-inflammatory actions in different inflammation models [28].

The MC2R, i.e the classical–ACTH receptor, gets expressed in the adrenal cortex which controls adrenal steroidogenesis as well as cell proliferation. MC2R further gets expressed in chondrocytes as well as osteoblasts, where it may responsible for controlling local inflammation [29].

The neural MCRs, MC3R, as well as MC4R get primarily expressed in the CNS as well as control energy homeostasis [30]. Nevertheless, the MC3R, gets expressed in human placenta, heart as well as gut along with lymphocytes as well macrophages, where it modulates strong anti-inflammatory actions of MC3R agonists like MTH, D-Trp^{8}γ-MSH, AP214 as well as AP1189 [28,31-34], while MC3R antagonists, SHU-9119 as well as AVM-217, avoids this protective action [31,35].

Detailed localization studies conducted on rodent brains demonstrated the Mc4r mRNA gets expressed in lot of brain areas, that includes brainstem, thalamus, hypothalamus, hippocampus as well as spinal cord [36]. The MC4-R has been illustrated to modulate central anti-inflammatory actions of α-MSH. It was demonstrated by Schaible et al., that MC4-R-modulated activation of anti-apoptotic pathways may partly give the reason of neuroprotective actions characteristic of α-MSH in a mouse model of traumatic brain injury [27] that is just like actions of MC4-R- ligands seen in animal models of cerebral ischemia [37].

The MC5-R gets markedly expressed in the skin, adrenal glands, adipocytes, skeletal muscles, bone marrow, kidney, liver, lungs, spleen, thymus, gonads, uterus along with brain [38,39]. Mc5r knockout mice exhibit a phenotype with impaired water repulsion as well asthermo regulation secondary to reduced sebogenesis, pointing to a part of the receptor in sebum generation as well as thermoregulation [39]. Further studies pointed that this receptor participated in immunomodulatory role of B as well as T lymphocytes along with mast cells [40,41].

Intracellular signaling pathways

On activation by agonists, the, the MCRs, present on the cell surface undergo conformational alterations as well as trigger complicated intracellular networks of pathways that is well agreed upon. The MCRs, are basically coupled to G proteins, resulting in activation of adenylyl cyclase, the enzyme which catalyzes the conversion of cytoplasmic ATP to cAMP. This cAMP in the form of a 2nd messenger activates protein klnase A, that further phosphorylates transcription factor ,cAMP response element-binding protein ,as well as influences the transcription of downstream genes .Besides utilizing the canonical cascade MCRs, have the ability of signaling via other pathways .Like all other MCRs, have been documented to induce ERK1/2 phosphorylation as well as intracellular Ca^{2+}mobilization, though the particular modes not ditto same for all the 5MCRs, [41]. The Gi protein was demonstrated to be correlated with activation of as well as Gq coupled with MC4-R [53,40-42]. Additionally, MC1-R as well as MC2-R were demonstrated to signal via p38 pathways in human HeCaT Keratinocytes on stimulation of Adrenocorticotropin hormone [43]. Phosphorylation of janus kinase/signal transducers and activators of transcription in Ba/F3 cells as well as human cultured IM-9 lymphocytes that express MC5-R [44,45], as well as inhibits c-Jun–N-terminal–kinase activity in HEK293 cells that over express MC4-R were also documented [44,45]. Nevertheless, some of these non-canonical signaling requires independent corroboration by various groups.

Inflammation as well as adrenocorticotropin hormone

***In vitro* actions of ACTH:** That ACTH is better than corticosteroids for the therapy of some inflammatory diseases, has evoked a probabvility that might be utilized in treatment besides liberation of endogenous cortisol. In normal human Keratinocytes $ACTH_{1-39}$ was demonstrated to suppress NFκB activation that gets stimulated by tumor necrosis factor alpha (TNF-α), probably via escalating nuclear translocation of the NFκB inhibitor IκB-α to the nucleus [46]. More immunofluorescent as well as western blot studies that found MC3-R as well as MC2-R in normal Keratinocytes, that modulate the peptide stimulated repression on activation of NFκB [46].

Additionally, the capacity of ACTH for directly manipulating local CNS inflammation that constitutes a factor that probably starts most CNS diseases has been demonstrated in various in vitro studies. Utilizing rat brain cultures that process oligodendroglia, astrocytes as well as microglia, preincubated with cytotoxic substances, $ACTH_{1-39}$,was demonstrated to protect mature oligodendroglia as well as oligodendroglial progenitor cells (OPC) from death stimulated by stauroporine, AMPA,NMDA, Kainate quinolinic acid ,or reactive oxygen species (ROS)[47].In their studies preincubation with cytotoxic substances lead to 50-75%death of mature oligodendroglia but minimal or no death of astrocytes as well as microglia [47]. As oligodendroglia or OPC, differently supply metabolic support to neurons/axons, the protection of oligodendroglia or OPC from excitotoxic and inflammation related insults is of a lot of significance in maintenance of the integrity of CNS [47].

Utilizing the rat glial cultures, this same group of Benjamin et al., demonstrated that $ACTH_{1-39}$, stimulates proliferation and differentiation of oligodendroglial progenitor cells as well as differentiation of platelet derived growth factor receptor alpha (PDGF-α) [that is a phenotypic marker of OPC) positive targeted OPC to a later stage where property of greater expansion of oligodendroglia myelin like sheets as compared to untreated cells [48].

Adenylyl cyclase was pointed to be involved in ACTH modulated growth of proliferation of OPC as well as differentiation, along with anti-inflammatory actions on the basis of these observations. OPC's have delayed maturation as well as exaggerated proliferation on activation of Adenylyl cyclase in vitro [49]. ii) Pituitary Adenylyl cyclise activating polypeptide deficient mice have earlier initiation of myelination, less time for axonal formation, as well as synapse development along with neuronal plasticity [50]. iii) cAMP inducing agents avoid oligodendroglial excitotoxicity, as well as protect mature oligodendroglia from excitotoxic substances [51].

Moreover, ACTH also protect rat forebrain neurons, the most vulnerable cells in CNS, from apoptotic, excitotoxic, as well as inflammation–associated injury in a similar way as mature oligodendroglia, as well as OPC [52]. As excitotoxic substances injury to neurons, is a significant reason for various experimental along with clinical disorders [52]. Still the addition from direct actions of oligodendroglia, OPCs or neurons within the brain and if such advantages can be seen in vivo human patients needs evaluation.

***In Vivo* actions of ACTH**

The efficiency of therapy with ACTH in humans as well as animal RA as well as gouty arthritis have been shown since 1940's .Getting et al., showed in a murine model with monosodium urate (MSU) crystal–stimulated gouty arthritis that $ACTH_{4-10}$ (MEHFRG),that lacked any glucocorticoid stimulated action, inhibited macrophage activation as found by decreased phagocytosis as well as keratinocyte-obtained chemokine (KC)liberation, as well as a neutrophil collection as observed by decrease in IL-1β (that is a pro-inflammatory cytokine)liberated in the inflammatory exudates[36]. As only Mc3r mRNA is found in mouse peritoneal macrophages by RT-PCR, they posited that $ACTH_{4-10}$ (ameliorates KC liberation as well as probably formation of rest of cytokines and ultimately decrease of the host inflammatory actions, with inhibition of 82,88 as well as 75% on neutrophil influx, joint swelling as well as arthritis score, respectively [7]. Similar extent of amelioration of the formation as well as /or liberation in the formation as well as, or liberation of the cytokine IL-1β as well as IL-6 were also seen [7]. Significantly the anti-inflammatory action of $ACTH_{1-39}$ maintain in adrenalectomized rats [7].In combination with the findings that MC3R/MC4R antagonist, SHU9119, blocks anti-inflammatory actions of ACTH, as well as selective MC3R agonist, ү2-MSH, maintains the antiinflammatory actions, it can be posited that partial inflammatory actions of ACTH may be obtained by targeting MC3R expressed in rat knee joint macrophages [7]. Moreover, ACTH was also documented to decrease fever following peripheral delivery [5]. Later Kass et al. showed that intramuscular injections of ACTH decreased markedly leukocytic pyrogen induced fever in humans as well as rabbits [53]. Taken together along with proof that intracerebroventricular delivery of $ACTH_{1-24}$ also causes antipyresis [54]. One can posit that this antipyretic action of ACTH might be obtained through changing the action of hypothalamic heat controlling centers. Nevertheless, more observations that central as well as peripheral actions of $ACTH_{1-24}$ decrease fever in adrenalectomized rats rules out that corticosteroid taking a part is not essential in ACTH–stimulated fever decrease. This is, markedly significant knowing that ACTH stimulated corticosteroids immediately cross the blood brain barrier (BBB) as well as can decrease the fever on delivery in intrahypothalamic way [55].

Mode of anti-inflammatory actions of ACTH

That ACTH modulated antiinflammatory actions can be obtained by both glucocorticoid–dependent as well as independent way is well understood. As per the direct glucocorticoid–dependent action ACTH is the only peptide of the melanocortins that can activate the MC2R. Usually, stimuli in the form of stress or inflammation stimulate the formation as well as liberation of corticotrophin releasing factor(CRF) from the paraventricular nucleus ,that further induces the liberation of ACTH from pituitary .Then ACTH moves to the adrenal gland, where it activates MC2R present on the adrenal cortex as well as stimulates fast formation of cortisol. Then this cortisol activates GC receptors as well as stimulates downstream anti-inflammatory effects via genomic as well as nongenomic pathways, ultimately causing a decline in cytokines, chemokines as well as inducible nitric oxide (NO) formation, escalation of anti-inflammatory modulators as well as phagocytosis of apoptotic neutrophils. Further it has been documented that GC formed in the skin can also manipulate local inflammation, though the basic mode is not clear [56].

Not before 2002, 50 years following the approval of ACTH for the therapy of various inflammatory situations that, maintenance of anti-inflammatory effects in adrenalectomized rats with knee gout was documented via Getting et al., pointing that there is presence of hypothalamo-pituitary-adrenal (H-P-A) as well as GC independent anti-inflammatory mode [7]. Lot of in depth in vitro as well as in vivo studies, have corroborated the posit that ACTH manages to influence the activation of various MCR's directly regarding the anti-inflammatory effects via activation of some MCR's that get expressed in peripheral immune cells as well as hypothalamic neural cells.

Utilization of ACTH in inflammatory diseases for treatment

At present the practical uses of ACTH or its analogues are simply decided on its capacity to stimulate glucocorticoid (GC) formation as well as liberation. Two commercialized ACTH formulations are present in the market in the US. Of these, one is the repository corticotrophin injection (RCI), a markedly purified porcine ACTH analog that has been approved by the FDA for the therapy of multiple autoimmune disorders like Rheumatoid arthritis (RA), Multiple Sclerosis(MS) relapse, symptomatic sarcoidosis, systemic lupus erythematosus (SLE), proteinuria in nephrotic syndrome as well as dermatomyositis/polymyositis, it is used basically as later time treatment of patients whose problem accelerates, or adjunction method in patient fails to be effective or can't tolerate the conventional therapies [57].

In the beginning the use of ACTH for treatment of inflammatory situations like RA was posited by Hench et al. [4], however with the GC treatment emerging, the ACTH treatment became the 2nd line of therapy or as an adjuvant treatment for managing inflammation related to RA. Actually, in a couple of independent clinical trials that were prospective in nature and tried to evaluate the effectiveness as well as safety of RCI in the form of adjuvant treatment in RA subjects, it was demonstrated by Gaylis et al. [58], that 8/10 subjects got methotrexate along with RCI had improvement of the clinical symptomatology as corroborated by enhancement of Clinical Disease Activity Index scores. Two cases had remission of disease as well as 3 had less disease activity. In the same way following subcutaneous injection with RCI at 12 weeks time period, full 6 patients with resistant RA managed to obtain markedly decrease in Disease Activity Index scores, reduced painful as well as swollen joint counts, as well as decrease in global visual analog scale occurred as seen by Gillis et al. [59]. Besides that, marked improvement regarding Health Assessment Questionnaire score in 3/6, ESR in 4/6 as well as C reactive protein (CRP) levels 4/6 [59].

In a variety of clinical studies trying to compare the effectiveness of RCI as well as other conventional treatments regarding infantile spasms therapy, Baram et al. [60], tried to study the effectiveness of RCI as well as prednisone in 29 infants that had been registered, as well as displayed that 86.6% of RCI receiving infants as well as 28.6% of prednisolone-treated infants had total stoppage of spasms as well as removal of hypsarrythmia [60]. Same outcomes were seen by Knupp et al., who conducted a prospective, observational, multicenter study for contrasting the effectiveness of RCI, prednisolone, vigabatrin as well as other standard treatment in 230 registered infants having a diagnosis of infantile spasms. Following 2 wks of therapy, 68% receiving RCI had clear response, as compared to 49 for vibagatrin as well as 22% for nonstandard medicines [61]. The response percentage of RCI therapy receiving infants at 3mths was 55%, much greater than those receiving prednisolone (39%), vigabatrin (36%) as well as for nonstandard medicines (9%) [61]. These outcomes proved with conviction regarding superiority of RCI treatment over other standard treatments regarding infantile spasms. Hence the American Academy of Neurology as well as Child Neurology Society, in the 2004 infantile spasms guideline gave the recommendations that ACTH can be thought of as short-term therapy for infantile spasms [level B evidence].

Seven studies further advocated to the probability of RCI treatment as an alternative method for therapy of MS relapse. In a randomized, double blind, placebo controlled, multisite trial made up of 197 cases the Disability Status Scale, called the golden standard for parameters of results in MS relapse trials, was studied weekly for 4 weeks. 65% of RCI treatments of MS patients had improvement in Disability Status Scale as compared to 48% getting treated with placebo gel as demonstrated by Rose et al. The response rate to RCI treatments of 43% as well as 30%> than those with placebo treatments at week 1 as well as 3 weeks respectively [62,63]. In a prospective, randomized, open -label pilot trial, it was demonstrated by Simsarian et al., that intramuscular as well as subcutaneous delivery of RCI for 5 days lead to comparable amelioration of symptoms [64].

In the last various decades, greater than 2 dozen clinical as well as healthcare use studies of RCI in therapy of autoimmune as well as inflammatory disorders decreased post therapy healthcare use, like hospital admissions, hospital duration of stay, outdoor patients visit, hence improves patient's quality of life (QOL), as well as ameliorates economic problems for families, healthcare system as well as society [57].

The 2nd formulation cosyntropin, is a synthetic analog i.e. made up of 24 aminoacid of ACTH ($ACTH_{1-24}$), is equally potent like the total length peptides regarding steroidogenic activity. But cosyntropin, utilized in ACTH stimulation test is only meant for use for diagnosis of adrenal insufficiency in USA. In UK, $ACTH_{1-24}$), KA Synachen depot ^{R}besides diagnostic use is used as an adjuvant as well as short time treatment for GC therapy in situations where patients can't tolerate GC or respond to that therapy [6].

INFLAMMATION AS WELL AS α-MSH

In vitro actions of α-MSH

The molecular modes of anti-Inflammatory functions of α-MSH modulated inhibition of NFκB activation, as well recognized controller of Inflammation, which regulates the expression of multiple cytokines, cytokine receptors , chemokines, growth factors as well as adhesion molecules was initially demonstrated by Manna as well as Aggarwal, who showed that α-MSH totally ameliorates TNF-α induced the nuclear factor transcription factor-kappa B(NFκB) phosphorylation in a dose as well as time based manner [65]. It further blocks LPS, okadaic acid as well as ceramide modulated activation of NFκB in human monocytic, epithelial, glioma as well as lymphoid cells [65]. Later same action caused by α-MSH were documented in a number of cell kinds that included human microvascular endothelial cells [66]. Human monocytic, as well as melanoma cells [66]. Human glioma cells [68], human pulmonary epithelial cells [69], human keratinocytes [46], mast cells [70], Schwann cells [71], human macrophages as well as neutrophils [72], human dermal fibroblast cells [73], as well as rat small intestine cells [74]. Repression of NFκB translocation is obtained via formation of cAMP, activation of PKA, as well as protection of IκBα from phosphorylation [65]. Recently matrix metalloproteinase 13(MMP-13)–expression via control of p38 as well as NFκB in HTB-94 cells (like human chondrosarcoma cell line expressing MC1R), pointing that α-MSH can be utilized for avoiding MMP-13 modulated collagen breakdown [75].

Deep evaluation showed that α-MSH results in producing anti-Inflammatory actions via repression of pro-Inflammatory cytokines like tumor necrosis factor alpha (TNF-α), interferon gamma (IFNγ), interleukin 1(IL-1), IL-6, IL-8, KC. As per Lipton et al., α-MSH, possibly via action through MC1R, inhibits bacterial endotoxin stimulated TNF-α generation in human glioma cells [76]. In the same way inhibition caused by α-MSH on TNF-α generation was seen in human monocytes as well as macrophages [77], melanoma cells as well as melanocyte [67], as well as human keratinocytes [46], constitutive picomolar α-MSH found in normal aqueous humor in case of humans, rabbits as well as mice was able to repress the formation of antigen stimulated IFNγ was shown by Taylor et al. [78]. Additionally following preincubation of human peripheral blood mononuclear cells (PBMC's) with mitogen as well as various concentrations of α-MSH, it was demonstrated by Lager et al., that mitogen –stimulated transcription as well as biological action of IFNγ was markedly blocked by α-MSH in a dose dependent manner ,as seen by alterations in IFNγ mRNA expression as well as the major HLA class1 antigen expression, respectively[79].The generation of rest of the pro-Inflammatory cytokines, that included IL-1, IL-6, IL-8, Groα as well as KC, on coincubation with or without pro-Inflammatory stimuli, were further inhibited by α-MSH [7,80].

This capacity of α-MSH, in suppression of TNF-α, IFNγ, or intercellular adhesion molecule 1(ICAM-1) have been documented in human normal as well as malignant cells, human dermal papilla, cells as well as fibroblasts, as well as murine mast cells [70,73,81]. The inhibition of LPS-stimulated vascular cell adhesion molecule 1(VCAM1) as well as E-Selectin expression was further documented in human microvascular endothelial cells (HMEC-1), as well as human dermal microvascular endothelial cells (HDMECs)[66,82].Additionally, α-MSH, further controlled the expression of CD86 as well as CD40, cell surface molecules needed for antigen presentation in monocytes as well as dendritic cells. Actually, it was shown that α-MSH, probably working via MC1R, down regulates the surface expression of CD86 in both LPS-treated human monocytes as well as non stimulated human peripheral blood- derived dendritic cells [83].

Furthermore α-MSH, was also illustrated to be a suppressor of pro-Inflammatory non- cytokines controller like nitric oxide (NO) (a well understood inflammatory mediator), prostaglandin E (PGE), as well as reactive oxygen species (ROS).This capacity of α-MSH, in suppression of LPS as well as cytokines stimulated NO formation as well as inducible nitric oxide synthase (NOS) expression was first documented in murine macrophages that expressed MC1R [84]. From that time, same observations were illustrated in cytotoxic agent-stimulated RAW 264.7 cells, THP-1 cells, human melanoma M55 cells, murine microglial cells, rat PBMC's as well as astrocytes [85,86]. It was shown that α-MSH, suppresses cytokines stimulated PGE generation in a cell-particular way ,with inhibitory actions seen in IL-1 induced fetal human lung fibroblasts as well as TNF-α stimulated melanoma M55 cells, but no action was seen in TNF-α stimulated Ha Ca T Keratinocytes[87,88].Additionally, α-MSH was recently illustrated to inhibit LPS or phorbol ester –stimulated generation of superoxide radicals in rat neutrophils [89],as well as IL-18 stimulated oxidative burst in human monocytic cell line[72], pointing to a controlling action on the cellular redox balance as well as apoptotic pathways like that of a radical scavenger [90].

Other modes leading to the anti-Inflammatory effects of α-MSH, has been posited. Like α-MSH, was documented to stimulate the mRNA as well as the protein amounts of IL-10, (a well-known robust cytokine suppressor), in human keratinocytes as well as monocytes respectively [91,92]. Additionally, the capacities of α-MSH, in stimulating CD25 as well as CD24 markers of regulatory T cells, suppressor of IFNy҆, generation from Inflammatory T cells, as well as inhibiting bacterial antigen–stimulated proliferation of T lymphocytres were documented by various groups [92.93].

In vivo actions of α-MSH

Just like ACTH, α-MSH exerts anti-Inflammatory actions, in a lot of animal models showing experimental Inflammation disorders. Like initially it was demonstrated by Glyn & Lipton that α-MSH can inhibit temperature rise in case of rabbits with leukocyte pyrogen –stimulated fever [54]. Following that antipyretic char of α-MSH got affirmed by a lot of animal models (like leukocyte pyrogen–stimulated rabbit and guinea pigs &bacterial endotoxin receiving squirrel monkey) with central delivery of the peptide, peripherally or via intragastric tube [94,95].

After utilization of ACTH, in cases of RA, the anti-Inflammatory effect of α-MSH in experimental RA, has been studied in detail. Ceriani et al. [96], in 1994 demonstrated that intraperitoneal injection of α-MSH, twice daily in experimental adjuvant stimulated arthritis significantly inhibited the clinical as well as histoglogical signs. Although both prednisone as well as α-MSH have same anti-Inflammatory effects on joint Inflammation, the efficacy of prednisone as well as α-MSH on the weight control of experimental rats are seperate with no alterations in weight seen among α-MSH treated as well as un treated animals, however marked weight loss occurred in prednisone group [96].

Further α-MSH has also been demonstrated to act as a robust inhibitor of systemic Inflammation, like sepsis syndrome, septic shock, acute respiratory distress syndrome (ARDS), as well as other situations. Intravenous injection of α-MSH decreases endotoxin stimulated acute phase response in rabbits was demonstrated by Maretin and Lipton [97]. Later same kind of outcomes were illustrated in endotoxemic mice on delivery of the peptide centrally or peripherally [98]. Additionally, Catamia et al. showed that systemic α-MSH or gentamicin injection escalated survival rate in a mouse model of peritonitis, endotoxemia or septic shock [99]. Significantly, it gets even higher survival rates on combination of α-MSH & gentamicin injection together, pointing to an anti-Inflammatory action of α-MSH and gentamicin being independent of each other as well as being additive [99]. In endotoxin-stimulated ARDS rats where there is abundant neutrophil influx into the lung along with injury to lung epithelium, systemic delivery of α-MSH decreases leukocyte amounts in the bronchoalveolar lavage fluid [99]. Similar actions were seen in acute bleomycin stimulated lung damage in rats as well as α-MSH controlled stress Inflammation, as well as fluid homeostasis associated genes that are known to be responsible for the formation of lung damage [100].

Mode of anti- Inflammatory actions of α-MSH

Utilizing the help of a lot of cell culture systems, a lot of modes, that are inhibition of nuclear transcription factor NFκB activation, suppression of pro-Inflammatory cytokines generation as well as adhesion molecule expression, keep the pro-Inflammatory non cytokine controllers, as well as induce cytokine suppressors, besides modulating the lymphocyte function as well as proliferation have been shown to add to the anti-inflammatory actions that get manifested viaα-MSH, and get further checked in animal models of experimentally stimulated fever, RA, ARDS, Inflammatory skin as well as Bowel diseases, along with brain Inflammation [90] **(Figure 3**).

Just akin to ACTH, it is believed that the anti–Inflammatory actions of α-MSH might get modulated via activation of particular MCR's that get expressed in peripheral immune cells along with hypothalamic neurons. Like MC3R was demonstrated to be needed for ACTH as well as α-MSH-stimulated anti–Inflammatory actions in RA [7]. The α-MSH-stimulated Inflammatory modulating signaling pathways in the CNS are believed to be brought about by neural MC4R [101]. MC1R as well as MC5R may be implicated in α-MSH controlled manipulation of pro-Inflammatory cytokines as well as collagens in human articular chondrocytes. Moreover, protective actions of α-MSH in autoimmune uveoretinitis need a functioning MC5R [102].

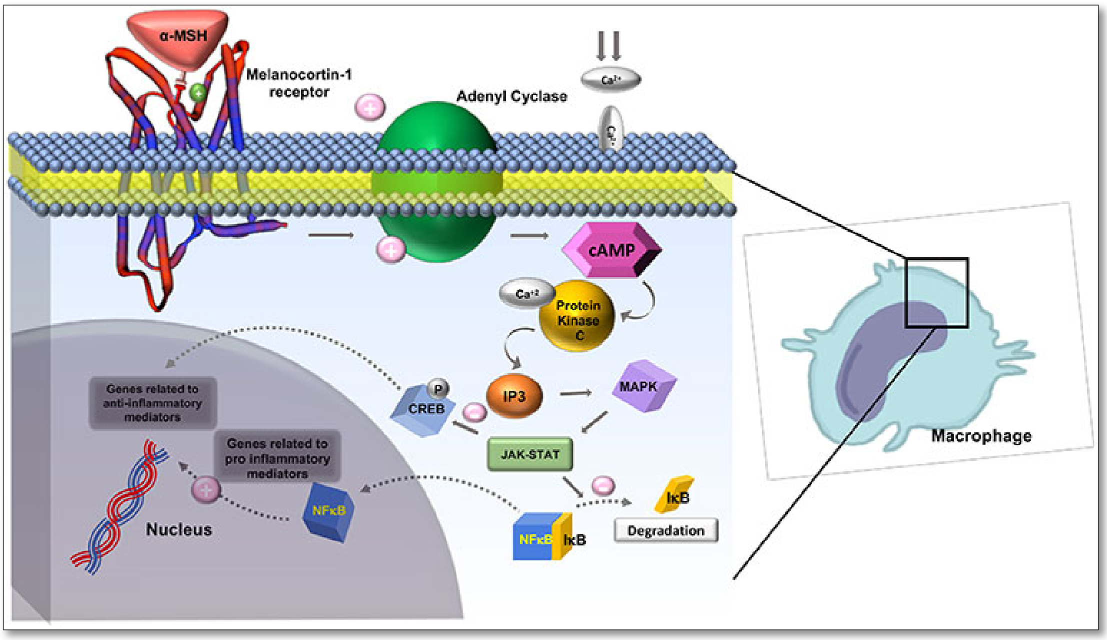

Figure 3. Courtesy ref no-121-Role of Melanocortin-1 receptor on macrophages in inhibiting inflammation. MC1R activates adenyl cyclase and generates cAMP, activating protein kinase-C. This leads to influx of extracellular calcium and activation IP3. IP3 then activates MAPK and JAK-STAT pathways which inhibit the degradation of IκB and activate CREB. CREB is involved in downstream anti-inflammatory effects.

α-MSH and inflammatory diseases-treatment options

At present studies trying to evaluate the utilization of α-MSH regarding therapy of Inflammatory conditions basically concentrate on the C terminal peptide of α-MSH, KPV as well as its derivative KdPT, that sustains anti-inflammatory actions without its pigmentary effects. Actually, KPV as well as KdPT, akin to α-MSH at molecular level, were also demonstrated to control a broad range of signaling pathways that are implicated in Inflammation-associated events like repression of NFκB activation, TNF-α generation, along with IL-10 induction [90].

Moreover, in animal models of experimentally stimulated fever, brain inflammation, RA as well as systemic inflammation, KPV as well as KdPT was documented to decrease leukocytic pyrogen or IL-1 stimulated hyperthermia [95,103], LPS stimulated NFκB activation, picrylic acid, TNF-α, IL-1β, Or IL-6 stimulated ear swelling [104,105] ƴ-carragenan-stimulated hind paw oedema [106]. MSU crystal or IL-1β stimulated peritonitis as well as neutrophil collection [107], as well as dextran sodium sulphate stimulated Colitis with Inflammatory cell infiltration as well as myeloperoxidase activity [108,109], pointing a therapeutic role of α-MSH for therapy of inflammatory disease.

Noticeably intravenous delivered full length α-MSH along with its tripeptides can be there in circulation for just few minutes in view of serum proteases located there [110]. Like neural endopeptidase 24.11, one of the serum proteases expressed on the cell membrane of lot of cell kinds, can cleave α-MSH and thus directly control its biological effect [111]. Though the pharmacokinetics of KPV as well as KdPT in circulation are not known as yet, it might be postulated that D-enantiomers of KPV. In contrast to their stereochemical analogs have greater resistance to proteolysis from peptidases [90]. Hence it is of significance to find better ways of delivering these peptides on the basis of the particular Inflammatory disease.

Regarding safety profiles of α-MSH along with its tripeptides, very little data are present in view of absence of toxicity studies. Nevertheless, the markedly potent analog of α-MSH, [Nle^4-D-Phe^7]-MSH, when delivered intravenous at doses right till 0.6 mg/kg, causes rare GIT upset as well as facial flushing without main harmful actions [112]. Here α-MSH along with its tripeptides would seem to have better safety issues as compared to traditionally used immunosuppressive therapies along with biologics that are understood to result in liver as well as kidney injury, bone marrow suppression, GIT upset, hypertension as well as dyslipidemia.

Significantly, recent studies showed antimicrobial action of α-MSH along with KPV in removing 2 representing pathogens, Staphylococcus aureus as well as Candida albicans [113]. This is reverse of the immunosuppressive as well as anti-inflammatory therapies which have got established and mostly escalate the risk of infection during this continued event. These benefits above the traditional immunosuppressive therapies emphasize that α-MSH along with associated tripeptides as promising agents for the treatment of inflammatory diseases. Nevertheless when contrasted with α-MSH,KPV as well as KdPT might add more benefits in their use for clinical treatment of immune – modulated Inflammatory diseases, as they can be developed with greater ease in view of their small size as well as being cheap, that is theoretical with no pigmentary actions, have greater resistance to bacterial infection, as well as can be delivered with greater ease locally for severe Inflammatory diseases [90].

Special emphasis on Respiratory Inflammatory Diseases

With the finding of MC1R as well as MC3R on wild type alveolar macrophages [114], Getting et al., demonstrated that the melanocortin peptides inhibit leukocyte collection in the case of a mice model of pulmonary allergic as well as non-allergic inflammation. They observed that this protective action correlated with the activation of MC3R on alveolar macrophages [114].

Allergic airway disease has the property of accelerated airway response to substances in the environment. A mice model of asthma was formed by 3 intraperitoneal injections as well as inhalations of 10µg of ovalbumin by Raap et al. [115]. For getting insight on the part of melanocortin signaling in asthma, 1 mg/kg of α-MSH was injected into the tail of mice prior to sensitization. A significant decrease in eosinophil amounts was observed in broncheoalveolar lavage (BAL) ($P<0.001$) along with significant reduction in serum amounts of IgE ($P<0.001$) IL-4 as well as IL-5() (both $P<0.001$) in asthmatic mice in contrast to controls. This study pointed that melanocortin receptors agonists possess anti-Th-2 T cell activity.

Recently Colombo et al. carried out an animal study to find the potential treatment action of α-MSH on acute lung injury (ALI). A rat model of ALI was formed by injecting a 1 mg bleomycin tracheal instillation. 100µg of α-MSH was injected just following bleomycin as well as harvested lung 8, as well as 24h subsequently in both cases along with control groups. They observed α-MSH significantly avoided lung edema (lung weight in control vs. α-MSH group, 5.8±0.5 vs. 3.9±0.1, respectively, $p<0.5$ respectively), along with decreased circulating NO (nitrite) amounts in the case group. Various genes correlated with inflammation that included Cdknla, Hmox 1 as well as Hspala got upregulated in mice having ALI got normalized in the mice receiving α-MSH. Their observations agreed with the potential treatment characteristics of α-MSH in ALI [116].

Further Jiangping et al., found the therapeutic actions of α-MSH in ALI by utilizing a mouse model of ALI. Bilateral renal ischemia for 40 'was done in mice to form ALI. Subsequently the mice were administered 25 mg of α-MSH or saline in case as well as control prior to clamp removal. Therapy with α-MSH was again given 8 as well as 16 h post ischemia. The leukocyte amounts as well as injury score in lung specimens showed significant decrease in case of α-MSH group as compared to saline group. The α-MSH group had significantly lesser expressions of TNFα as well as intercellular adhesion molecule-1 (ICAM-1) genes following renal ischemia [117].

The part of α-MSH was evaluated by Kirstensen et al., in the systemic inflammatory response syndrome (SIRS). They utilized AP214, that is an analog of α-MSH, possessing 6 lysine residues at the N-terminus of native α-MSH, leading to greater binding affinity in receptors. A porcine model of SIRS was formed by them utilizing intravascular injection of lipopolysaccharide (LPS from *Escheriria coli* endotoxin). Then animals got randomized to get either AP214 or saline injections. On exposure to LPS, porcine demonstrated a dose dependent escalation in pulmonary vascular resistance, a known pathophysiologic alteration in acute respiratory syndrome (ARDS) that is seen in sepsis. Acute respiratory distress Syndrome (ARDS) in sepsis setting gets triggered partially by endothelial injury secondary to inflammatory event. Considerably, the peak pulmonary pressure as well as pulmonary vascular resistance got significantly (~33%) decreased in the AP214 group [118].

The mode of action of α-MSH in inhibiting inflammation is not clear. It has been pointed that α-MSH causes its actions in amelioration of the inflammatory response via down regulation of nuclear factor kappa B (NFκB) [119]. NFκB is a nuclear transcription factor having a critical role in cytokine generation. Once inflammatory signals are lacking, NFκB is inactive in the form of a heterodimeric molecule that is made up of 2 subunits, p65 (RclA) as well as p50 ($NF\kappa B_4$) [120]. Moreover, a regulatory protein of NFκB, IκB works as a molecular off switch. In the presence of inflammatory signals, IκB undergoes phosphorylation, ubiqitination, as well as proteolytic degradation that aids in activation of NFκB, especially the p65 subunit [120].It is thought by Moscowitz et al., that the cAMP response element binding protein (CREB) activation has a main part in decreasing the amounts of certain pro inflammatory cytokines like IFN-ɣ́as well as IL-7 (**Figure 3** reviewed in 121).

Organ Fibrosis

Xu et al. [122] evaluated the actions of α-MSH analog on a bleomycin pulmonary fibrosis mice model. They observed that an α-MSH analog decreased the mRNA expression of type I as well as III procollagen along fifth generation of hydroxylproline in the bleomycin treated mice. They further showed that lung generation of TNFα, IL-6, macrophage inflammatory protein 2, as well as transforming growth factor beta 1(TGF-β1) got significantly decreased in the α-MSH analog treated group as compared to controls [122]

Role in sarcoidosis

Sarcoidosis represents a complex, multisystem disorder which has property of non-caseating granulomatous inflammation [123]. Sarcoidosis presentation varies from asymptomatic with incidental imaging observations, to sig morbidity as well as potential mortality in view of basically pulmonary insufficiency as well as cardiac arrhythmia [124]. Despite multiple manifestations of the disease, the lungs as well as thoracic lymph nodes are practically always implicated, resulting in cough, dyspnea, or a decrease in lung function [125]. Immunosuppression remains the best method of treatment since the disease is thought to be modulated mainly through immune system dysregulation [126].

Prednisone as well as ACTH possessing 39 amino acids (repository corticotrophin, a long acting corticotrophin) are the only 2 medicines that are at present approved via the food and drug administration (FDA) for the therapy of Sarcoidosis [127]. ACTH binds with MCRs as well as ameliorates pro inflammatory cytokines, hence having a major role in Sarcoidosis. Utilization of high doses of repository corticotrophin (80 IU) twice a wk for 47 cases presenting with advanced Sarcoidosis was attempted by Baugham et al. [128]. 27/29 subjects that completed 6 months of therapy demonstrated improvement or stabilization of disease. Decrease in oral corticosteroid dose was observed in 27 patients. 18 patients were treated for under 3 months in view of adverse actions, death, or cost. The action seen of repository corticotrophin in this study might be beyond the action of steroidogenesis in the adrenal glands. Repository corticotrophin might further confer anti-inflammatory characteristics on immune cells through MCR agonist actions [129].

It has been demonstrated that the granulomatous inflammation of Sarcoidosis gets controlled by Thelper 1(Th1) activating cytokines that include IFNƴ, as well as interleukin 12. Further a reduction in expression of Thelper 2(Th2) cytokines IL- -4 as well as IL-5[130]. Noticeably IL-12 has been demonstrated to be a crucial controller of the Th1 immune response as well as gets upregulated in lungs of Sarcoidosis. α-MSH has been demonstrated to liberate pro inflammatory Th1 cytokines from alveolar macrophages. On treating macrophages with an inflammatory endotoxin, there is enhanced liberation of interleukin 12 as well as interferon gamma (IFNƴ), as compared to controls. Once these macrophages got exposed to α-MSH. The generation of those Th1 cytokines was significantly reduced [131]. In future one needs to target the actions of melanocortin agonists in pulmonary diseases by integrating them with genomics as well as proteomics for gaining further insight of biologic as well as cellular processes. The part played by MC1R on the lung immune system needs to be further studied. The actions of MC1R agonists that include α-MSH might improve inflammatory lung diseases that include Sarcoidosis. Validation utilizing large multicentre studies is the need of hour for corroborating the therapeutic characteristics of melanocortin agonists in Sarcoidosis, ILD as well as airway diseases.

Role in fetal lung maturation

Glucocorticoids (GCs) are essential to normal lung development. They take part in the control of significant formation processes that include morphological alterations, as well as lung maturation resulting in the surge of surfactant synthesis by type II epithelial cells. Antenatal GC is administered to mothers at risk of premature delivery to reduce the risk of respiratory distress syndrome (RDS). Sex differences were reported in RDS, in the efficiency of antenatal GC treatment independently of surfactant levels, and in surfactant lipid synthesis. Type II epithelial cell maturation is regulated by epithelial-fibroblast cell-cell communication and involves paracrine factors secreted by fibroblasts under the stimulatory effect of GC. This positive action of GC can be inhibited by androgens through the androgen receptor (AR) located in fibroblasts, actually lung formation is controlled not only by GC and androgens but also by GC and androgen metabolisms within the forming lung. Provost and Tremblays group reviewed the metabolism of androgens in the fetal lung earlier. Further, they reviewed multiple parts of GC metabolism in the forming lung that included inactivation as well as re-activation by 11β-HSDs, synthesis from the adrenal-like synthesis pathway expressed within the lung and the putative part of corticotrophin releasing hormone (CRH) and ACTH originating from lung in the control of this pathway [132].

Inflammation as well as other melanocortins

Despite β-MSH as well as ƴ-MSH sharing equivalent affinity for the immunomodulatory MC1R as well as MC3R like ACTH as well as α-MSH, the role of MSH as well as ƴ-MSH in controlling Inflammation are not as clear, in view of absence of experimental proof.

The central antipyretic actions of ƴ2-MSH at the time of inflammatory response got documented through Bock et al., who demonstrated that intraseptal or intravenous infusion of ƴ2-MSH inhibited LPS-stimulated fever in guinea pig [133]. This anti-Inflammatory action of ƴ2-MSH got verified by Getting et al., who showed that in vivo murine models of peritonitis along with in vitro cultured macrophages, ƴ2-MSH caused a dose-based attenuation of polymorphonuclear leukocyte migration [31]. This inhibition correlated with a decrease in KC as well as IL-1β amounts [31]. Additionally, SHU9119 blocked the capacity of ƴ2-MSH to inhibit neutrophil migration, KC as well as IL-1β liberation, pointing to the actions of ƴ2-MSH got manifested via the MC3R or MC4R or both [31]. Nevertheless, only the mRNA along with protein of MC3R, but not MC4R, got verified by RT-PCR as well as western blotting in murine along with rat peritoneal macrophages [31]. This MC3R is functional as it responds to ƴ2-MSH stimulation in starting generation of intracellular cAMP along with this action gets blocked by SHU9119 [31]. Thus, concluding that the experimental inflammatory response got inhibited via selective activation of MC3R on peritoneal macrophages.

Similar observations were seen in a recessive yellow mouse strain that harbored a frame shift mutation in Mc1r gene which caused the generation of a non-functional MC1R protein [134]. Utilizing the benefit of this mouse model as well as more selective MC1R is not essential to evoke the anti-Inflammatory effects of Melanocortins peptides in view ofi), the recessive yellow mice does not show any signs of any continuing inflammatory response, ii) wild type along with recessive yellow mice displayed no separate changes in MSU crystal-stimulated peritonitis as evaluated by polymorphonuclear leukocyte migration as well as liberation of KC's iii) predelivery of y2-MSH decreased MSU crystal-stimulated polymorphonuclear leukocyte migration equally in wild type as well as recessive yellow mice, which was correlated with a decrease in IL-1β amounts iv) the selective MC1R agonist MS05 is inactive in inhibition or any of the Inflammatory properties in both wild type as well as recessive yellow mice [135].

Utilizing male Sprague Dawley rats Xia et al., demonstrated that intravenous infusion of y2-MSH reverses LPS stimulated hypotension along with bradycardia, ameliorates systemic inflammatory response to endotoxin, avoids LPS stimulated IL-1β gene expression in the brain along with peripheral tissues, as well as inhibits LPS stimulated NO amounts, pointing to an innovative method for manipulation of systemic Inflammation via pharmacological modulation of y2-MSH- manipulated autonomic action [136]. The specialized anti-Inflammatory function of β-MSH as well as y-MSH within the brain was documented by Mucience et al. 4 tested melanocortins in an acute mouse neuro inflammation model, were demonstrated to decrease LPS stimulated escalation of NO amounts as measured through electron paramagnetic resonance, with the efficacy order like this β-MSH≥y1-MSH=y2-MSH>α-MSH [137].

CONCLUSIONS

In recent years continuous escalated scientific interest regarding melanocortins as well as its receptors have accumulated in view of their expression widely as well as functions throughout body. A lot of *in vitro* along with *in vivo* as well as clinical studies have shown that the anti-inflammatory function of melanocortins get manifested via a GC-dependent (special for ACTH) as well as independent ways .With greater insight getting accumulated regarding mode of action by which melanocortins control immune responses have given an interest that has got renewed in RCI in the form of a therapeutic method for a variety of inflammatory diseases, as it might improve disease control, quality of life (QOL), as well as decreased healthcare use. Further the benefits of α-MSH-associated tripeptides over and above the traditional melanocortins point that they could be used as novel treatment agents for therapy of inflammatory problems. Further role of melanocortins in therapy of infantile spasms acute exacerbation of MS is to be exploited besides role of melanocortins these days in ARDS of COVID-19 infection currently on. Moreover, lot of rat studies have shown the benefits of activating MC1R, MC3R and MC4R in case of subarachnoid hemorrhage [138-140]. Further Seybold et al. [141], utilized the controlled cortical impact model was used to induce traumatic brain injury (TBI) in mice. Mice were grouped to injury and treatment protocols resulting in four experimental groups including sham + saline, sham + CoSyn, TBI + saline, and TBI + CoSyn. Treatment was delivered via subcutaneous route 3 h post-injury and daily injections were administered for up to 7 days post-injury. The early inflammatory response was examined at 3 days post-injury through the examining of cytokine expression (IL1β and TNFα) as well as immune cell response. Quantification of immune cell response included cell counts of microglia/macrophages (Iba1+ cells) as well as neutrophils (MPO+ cells) in the cortex and hippocampus. Behavioural testing (n=10-14 animals/group) included open field (OF) as well as novel object recognition (NOR) during the first week following injury and Morris water maze (MWM) at 10-15 days post-injury.

Immune cell quantification showed decreased accumulation of Iba1+ cells in the perilesional cortex and CA1 region of the hippocampus for CoSyn-treated TBI animals compared to saline-treated. Reduced numbers of MPO+ cells were also found in the perilesional cortex and hippocampus in CoSyn treated TBI mice compared to their saline-treated counterparts. Moreover, CoSyn therapy decreased IL1β expression in the cortex of TBI mice. Behavioral testing showed a treatment effect of CoSyn for NOR with CoSyn escalating the discrimination ratio in both TBI and Sham groups, indicating increased memory performance. CoSyn also reduced latency to find platform during the initial training period of the MWM when comparing CoSyn to saline treated TBI mice pointing to moderate improvements in spatial memory after CoSyn treatment. Decreased microglia/macrophage collection as well as neutrophil infiltration in addition to moderate improvements in spatial learning in our CoSyn treated TBI mice points to an advantageous anti-inflammatory effect of CoSyn following TBI. Thus, scope for trying these in humans might be there once animal experiments can be replicated in human head injury. Further we have summarized the rejuvenated interest of use of melanocortins in pulmonary diseases including allergic diseases like asthma, acute lung injury and ARDS. Its importance in fetal lung maturation is also highlighted that includes therapy of emergency tuberculosis situations and sarcoidosis.

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