Review Article

Curbing Inflammation through Endogenous Pathways: Focus on Melanocortin Peptides

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The resolution of inflammation is now known to be an active process, armed with a multitude of mediators both lipid and protein in nature. Melanocortins are peptides endowed with considerable promise with their proresolution and anti-inflammatory effects in preclinical models of inflammatory disease, with tissue protective effects. These peptides and their targets are appealing because they can be seen as a natural way of inducing these effects as they harness endogenous pathways of control. Whereas most of the information generated about these mediators derives from several acute models of inflammation (such as zymosan induced peritonitis), there is some indication that these mediators may inhibit chronic inflammation by modulating cytokines, chemokines, and leukocyte apoptosis. In addition, proresolving mediators and their mimics have often been tested alongside therapeutic protocols, hence have been tested in settings more relevant to real life clinical scenarios. We provide here an overview on some of these mediators with a focus on melanocortin peptides and receptors, proposing that they may unveil new opportunities for innovative treatments of inflammatory arthritis.

1. Inflammation: Onset and Resolution

One novel approach to the area of inflammation, developed over the last twenty years, is the concept of resolution of inflammation. Current therapies suppress active processes of inflammation, for example, NSAIDs (nonsteroidal anti-inflammatory drugs) block cyclo-oxygenases, glucocorticoids inhibit generation of multiple cytokines, and biologics such as anti-TNFα and anti-CD20 therapies, target specific effectors or antigens. However, this may be only half the story. The story of inflammation begins with a tissue insult originating from an infection, trauma, or damage. The affected tissue secretes signals including autacoids, plasma-derived mediators such as kinins and complement factors, culminating with the now prominent cytokines and chemokines. There are multiple molecules that constitute a distress signal. This leads to an initial recruitment of neutrophils, (or eosinophils, upon parasite attack) which mop up any initial infection and call in macrophages, which are also inflammatory. Once neutrophils and macrophages have cleared the inflammation, the neutrophils undergo apoptosis, the macrophage changes its phenotype into a proresolving and tissue repair one, and then leaves and the tissue should return to its baseline uninflamed state [1]. However this return to baseline is not, as was once thought, characterised solely by absence of the inflammatory insult but it results also from a positive process with its own armamentarium of mediators that bring the tissue from an inflammatory state back into its normal resting state (Figure 1).

There are several processes of clearance of inflammation that lead to the return to the normal state (catabasis) [2]. Exclusion of the primary insult, for example, phagocytosis of invading bacteria, is foremost as this stops the synthesis of proinflammatory mediators. There is then the breakdown
The inflammatory response

Figure 1: The inflammatory response. Stimuli such as tissue injury or microbial invasion trigger the release of chemical mediators (complement, cytokines, eicosanoids, and other autacoids) that activate the leukocyte recruitment (onset). Neutrophils are the first cell type to be recruited, and then peripheral blood monocytes also accumulate at the inflammatory site (acute phase). These monocytes will eventually differentiate into a more phagocytic phenotype helping to neutralize the injurious element and to clear the tissues of apoptotic neutrophils (resolution phase). This proresolving macrophage (and the involvement of stromal cells cannot be excluded here either) orchestrate resolution, by releasing and/or responding to proresolving mediators, some of which have been discussed in this review (see main text). Eventually, fully differentiated cells that have cleared the site by debris, dead cells, and bacteria will leave (via the lymphatic?) and the previously inflamed tissue or organ will regain its functionality, with return to homeostasis.

There is now a host of mediators that are involved in the resolution phase of inflammation. Some of these are autacoids like adenosine, locally generated hormones like melanocortins and somatostatin, bioactive lipids like lipoxins, resolvins, protectins and maresins, proteins like heme oxygenase 1, annexin A1, galectins, and erythropoietin. Due to space limitation, we will discuss here a few examples of proresolving proteins and peptides in the melanocortin system.

2. The Melanocortin System as Archetypal for Proresolving Endogenous Mediators and Targets

In 1950, Philip Hench won the Nobel prize for treating patients with rheumatoid arthritis (RA) with cortisone [6, 7]. What is less well known is that he treated 6 patients with adrenocorticotropic hormone (ACTH) with equally good results, as reported in that seminal paper. ACTH is the prototype of the melanocortins and its anti-inflammatory actions
have been confirmed and formed the basis for its use in the clinical management of inflammatory arthritides such as in the treatment of gout, where it is still used in the USA today. A placebo controlled trial of synacthen, a synthetic form of ACTH, in patients with RA showed an additional benefit which lasted three months after two injections on alternate days [8]. ACTH was evaluated in the treatment of gout patients, with relative contraindications to NSAIDS, ACTH was found to have good effect over and above that which would be expected from the release of endogenous cortisol alone [9]. The later discovery of the proopiomelanocortin system with a number of melanocortins and melanocortin receptors (MCR) has improved our understanding of the biological basis of these effects.

2.1. Melanocortin Receptors. The melanocortin system (Table 1) encompasses five melanocortin receptors, their ligands (agonists and antagonists), and the accessory proteins. The melanocortin receptors are a family of five small stimulatory G protein-coupled receptors, termed MC1 to MC5, initially identified as neuropeptide receptors in mice and humans in the early 1990s [21–27]. Each receptor has seven transmembrane domains, with an extracellular amino-terminus and short cystosolic carboxy-terminus. The melanocortin 2 receptor (MC2) is the only one of the five which has been shown to require an accessory protein for translocation to the cell membrane [28]. However the presence of the accessory proteins (MRAP1 or MRAP2 (melanocortin receptor accessory protein)) may have an effect on the surface expression of the other melanocortin receptors and their ability to be activated by agonists [29, 30].

All melanocortin receptors signal via the cyclic AMP (cAMP) pathway, activating adenylate cyclase resulting in increased intracellular cyclic AMP [31–33]. Activation of certain MCRs has also been shown to mobilise calcium from intracellular stores [34–36] in certain cell types or conditions. For example, activation of MC2 with alpha-MSH can result in increases in intracellular calcium in the presence of the protein kinase A inhibitor H-89 [31]. Similarly, if the cAMP pathway is blocked then MC1 can signal via intracellular calcium mobilisation or the inositol trisphosphate pathway [37, 38]. MC3 has been shown to affect the NFκB pathway by protecting IkBα from degradation leading to a downregulation of inflammatory cytokines and chemokines [33, 39].

In terms of distribution, melanocortin receptors are found in the brain and in peripheral tissues. It is notable that MC1, MC2, and MC3 are expressed on multiple cells of the immune system suggesting a role in inflammation. Of note to the rheumatologist, MC1 and MC3 are present in human articular chondrocytes [40] and rheumatoid synovial fibroblasts. These cells are known to be part of the chronic immune response of rheumatoid arthritis and represent a source of effector cells for endogenous ligand.

2.2. Melanocortin Receptor Ligands. The ligands for the melanocortin receptors are derived from the proopiomelanocortin system. Proopiomelanocortin (POMC) is the precursor protein, from which prohormone convertases cleave the melanocortin stimulating hormones (MSH) alpha-, beta- and gamma-MSH and ACTH as well as the non-melanocortin peptides, beta-lipotropin, gamma-lipotropin, and beta-endorphin. Initially, POMC and its related components were thought to be restricted to the pituitary but now have been shown to have a wider distribution [41]. Table 2 summarizes the endogenous and synthetic melanocortin peptides.

MC5 only responds to ACTH while the other melanocortin receptors respond to the melanocortin stimulating hormones to differing degrees [42]. MC1 responds to alpha-MSH>ACTH>gamma-MSH, as does MC2, whilst MC3 responds to gamma-MSH=ACTH>alpha-MSH. As well as endogenous agonists, there are endogenous antagonists in both the mouse and human system [43]. These are known as agouti and agouti-related protein in the mouse and agouti signalling protein in the human. Other regulators in mice are mahogany, syndecan and the mahogunin ring finger 1 [44].

2.3. Anti-Inflammatory and Antiarthritic Actions of Melanocortin Peptides. The anti-inflammatory actions of alpha-MSH have been shown using in vitro studies on stable cell lines and human primary cells, as well as in vivo models of diseases such as rheumatoid arthritis, colitis or ischaemia reperfusion injury. Alpha-MSH was initially found to be an antipyretic, able to counteract the pyrogenic activities of IL6 and TNFα [45]. Manna and Aggarwal then showed that alpha-MSH suppressed proinflammatory cytokine production by monocytes in response to bacterial lipopolysaccharide, by inhibiting NFκB translocation to the nucleus [33]. Not only does alpha-MSH suppress proinflammatory cytokines, but also it can activate the production of anti-inflammatory cytokines such as IL10 from monocytes [46] and keratinocytes [47]. Alpha-MSH has been shown to be inhibitory in several inflammatory models. It is effective in experimental contact dermatitis and suppresses the sensitisation and elicitation phase of the immune response. Alpha-MSH induces hapten specific tolerance when given intra-venously and this response is dependent on the induction of IL10 [48]. This finding has been taken forward in the nickel-induced contact eczema model in humans where a topical application of alpha-MSH reduced disease [49].

Alpha-MSH has been used in a model of cutaneous vasculitis induced by LPS and the peptide was able to reduce vascular damage and haemorrhage by downregulating cell adhesion molecules crucial for the extravasation of leukocytes to the site of inflammation [50]. Alpha-MSH has been topically applied to an airways model of allergy sensitised to ovalbumin, proallergic cytokines were reduced, and the anti-inflammatory action of alpha-MSH was dependent on IL10 [51].

Melanocortin agonists have been investigated in models of stroke encompassing mouse, rat, and gerbil models and also global and local ischaemic models. Gerbils, given ten minutes of global cerebral ischaemia by the occlusion of both carotid arteries, had reduced neuronal death, hippocampal damage and improved functional recovery if treated with an alpha-MSH derivative with a longer half-life (Nle6, D-Phe7 alpha-MSH, NDP-MSH) between three and nine hours after
Table 1: The melanocortin system.

<table>
<thead>
<tr>
<th>Melanocortin Receptors</th>
<th>MC&lt;sub&gt;1&lt;/sub&gt;</th>
<th>MC&lt;sub&gt;2&lt;/sub&gt;</th>
<th>MC&lt;sub&gt;3&lt;/sub&gt;</th>
<th>MC&lt;sub&gt;4&lt;/sub&gt;</th>
<th>MC&lt;sub&gt;5&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endogenous agonists</strong></td>
<td>αMSH=ACTH&gt;βMSH&gt;γMSH</td>
<td>ACTH</td>
<td>αMSH=ACTH&gt;βMSH&gt;γMSH</td>
<td>αMSH=ACTH&gt;βMSH&gt;γMSH</td>
<td>αMSH&gt;ACTH&gt;βMSH&gt;γMSH</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Skin, Melanocytes, Keratinocytes, Endothelial cells</td>
<td>Adrenal glands, Adipocytes, Chondrocytes, Osteoblasts, Macrophages, Monocytes, Dendritic cells, Mast cells, Neutrophils, CD8+ T cells, B Lymphocytes</td>
<td>Hypothalamus, Macrophages, Monocytes, Dendritic cells, CD4+ T cells, B lymphocytes</td>
<td>Hypothalamus, Dendritic cells, Osteoblasts</td>
<td>Exocrine glands, Sebocytes, Macrophages, Dendritic cells, Mast cells, Chondrocyte, CD4 T cells, B lymphocytes, NK cells</td>
</tr>
<tr>
<td><strong>Signalling pathways</strong></td>
<td>cAMP, cAMP, cAMP</td>
<td>cAMP Intracellular [Ca&lt;sup&gt;2+&lt;/sup&gt;]</td>
<td>cAMP</td>
<td>cAMP Intracellular [Ca&lt;sup&gt;2+&lt;/sup&gt;]</td>
<td>Jak/STAT</td>
</tr>
<tr>
<td><strong>Biological functions</strong></td>
<td>Skin pigmentation, Inflammation, Wound healing</td>
<td>Steroidogenesis</td>
<td>Energy homeostasis, Inflammation</td>
<td>Energy homeostasis, Food intake, Erectile function</td>
<td>Exocrine glands function, Inflammation, Defensive behaviour</td>
</tr>
<tr>
<td><strong>Role in disease/Potential use</strong></td>
<td>Skin cancer, Inflammation, Alopecia areata (?)</td>
<td>Familial glucocorticoid deficiency</td>
<td>Inflammation, Gouty arthritis, Obesity, Tuberculosis (?)</td>
<td>Obesity, Cachexia, Sexual dysfunction</td>
<td>Seborrheic dermatitis, Acne vulgaris, Inflammation</td>
</tr>
</tbody>
</table>

...insult. Interestingly MC<sub>4</sub> blockade abrogated the effects of the NDP-MSH suggesting the activity of MC4R in this process [52]. In human studies, alpha-MSH levels in the plasma have been used as a biomarker for predicting functional recovery from stroke [53].

Alpha-MSH and its analogues have also been used in preclinical models of renal and lung injury, secondary to sepsis or other forms of injury. It has been shown in multiple models to ameliorate injury with improvements in histology and plasma creatinine compared to controls. AP214, a nonselective melanocortin agonist derived from alpha-MSH, has been used in a sepsis-induced kidney injury model. Treatment with AP214 was delayed until six hours after the onset of sepsis and still reduced damage to the kidney as monitored by histological score, tubular damage, and serum creatinine; these effects were associated also with an improved liver function [16]. AP214 also reduced serum TNFxα and IL10 and showed evidence of reduced NFκB activation. There was also an improvement in survival rate in both lethal sepsis groups (improved from 0% survival to 10% survival) and sublethal sepsis groups (an improvement from 40% survival to 70% survival). This has been reflected in other studies of kidney injury models where alpha-MSH was given up to 6 hours after injury, observing increased recovery and protection against renal injury [54].

Alpha-MSH also ameliorates liver inflammation—as assessed following endotoxin induced inflammation in mice— even if given 30 minutes after onset, with decreased neutrophils infiltration and also decreased gene expression of chemotactic cytokines such as MCP1 (monocyte chemoattractant protein) and IL8 as well as TNFα [55]. Severe tissue injury in the lung can lead to acute respiratory distress syndrome as can renal ischaemic reperfusion injury with similar pathways activated in both organs. Alpha-MSH can inhibit lung oedema decrease injury score and leukocyte infiltrate as well as decreasing serum creatinine and improving histology score in the kidney. Gene expression of TNFα and ICAM1 (intercellular adhesion molecule) is reduced in the lung after treatment with alpha-MSH. Alpha-MSH also prevented the degradation of IκB, phosphorylation of p38 mitogen activated protein kinase and decreased API binding suggesting that alpha-MSH can operate through various pathways to modulate the inflammatory response, rather than just triggering one method of dampening inflammation [56].

Melanocortin agonists have been used in the treatment of various experimental arthritis models. AP214 is a peptide
Table 2: State of the art for the development of melanocortin agonists.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Classification</th>
<th>Activity</th>
<th>Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>αMSH</td>
<td>Endogenous</td>
<td>Pan agonist</td>
<td>Anti-inflammatory</td>
<td>[10]</td>
</tr>
<tr>
<td>βMSH</td>
<td>Endogenous</td>
<td>Pan agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>γMSH</td>
<td>Endogenous</td>
<td>Pan agonist with increased MC₃ selectivity</td>
<td>Anti-inflammatory</td>
<td>[11]</td>
</tr>
<tr>
<td>Agouti related peptide</td>
<td>Endogenous</td>
<td>Antagonist, MC₃, MC₄</td>
<td>Skin pigmentation</td>
<td></td>
</tr>
<tr>
<td>Agouti signalling protein</td>
<td>Endogenous</td>
<td>Antagonist, MC₃, MC₄, MC₄</td>
<td>Skin pigmentation</td>
<td></td>
</tr>
<tr>
<td>D-Trp⁶-γMSH</td>
<td>Synthetic peptide</td>
<td>Agonist with increased MC₃ selectivity</td>
<td>Anti-inflammatory (arthritis)</td>
<td>[12]</td>
</tr>
<tr>
<td>NDP-αMSH (MT-I)</td>
<td>Synthetic peptide</td>
<td>Pan agonist</td>
<td>Anti-inflammatory</td>
<td>[10]</td>
</tr>
<tr>
<td>MT-II</td>
<td>Synthetic peptide</td>
<td>Pan agonist</td>
<td>Anti-inflammatory</td>
<td>[13]</td>
</tr>
<tr>
<td>KPV</td>
<td>Synthetic peptide</td>
<td>MC₃ agonist</td>
<td>Anti-inflammatory</td>
<td>[10]</td>
</tr>
<tr>
<td>KPT</td>
<td>Synthetic peptide</td>
<td>Pan agonist</td>
<td>Anti-inflammatory</td>
<td>[10]</td>
</tr>
<tr>
<td>(CKPV)₂</td>
<td>Synthetic peptide</td>
<td>Pan agonist</td>
<td>Anti-inflammatory</td>
<td>[14]</td>
</tr>
<tr>
<td>GKPV</td>
<td>Synthetic peptide on beads</td>
<td>Pan agonist</td>
<td>Anti-inflammatory (melanoma)</td>
<td>[15]</td>
</tr>
<tr>
<td>AP214</td>
<td>Synthetic peptide</td>
<td>Pan agonist</td>
<td>Anti-inflammatory (sepsis and arthritis)</td>
<td>Action Pharma A/S [16, 17]</td>
</tr>
<tr>
<td>HP228</td>
<td>Synthetic peptide</td>
<td>Pan agonist</td>
<td>Protective in acute models of inflammation and organ damage</td>
<td>[18]</td>
</tr>
<tr>
<td>BMS470539</td>
<td>Small molecule</td>
<td>Agonist MC₃</td>
<td>Inhibits LPS response</td>
<td>[19]</td>
</tr>
<tr>
<td>MEI0501</td>
<td>Small molecule</td>
<td>High affinity mMC₃, hMC₄</td>
<td>Neuroprotective</td>
<td>[20]</td>
</tr>
<tr>
<td>Bremelanotide</td>
<td>Small molecule</td>
<td>Agonist MC₃ and MC₄</td>
<td>Prevents organ dysfunction</td>
<td>Palatin Technologies</td>
</tr>
<tr>
<td>SHU-9119</td>
<td>Synthetic peptide</td>
<td>MC₄, agonist for MC₃ and MC₅</td>
<td>Experimental tool</td>
<td></td>
</tr>
<tr>
<td>Afamelanotide</td>
<td>Synthetic peptide</td>
<td>Pan agonist</td>
<td>Vitiligo, acne vulgaris, erythropoietic protoporphyria, solar urticaria</td>
<td>Clinuvel Pharmaceuticals</td>
</tr>
<tr>
<td>RM-493</td>
<td>Synthetic peptide</td>
<td>Agonist MC₄</td>
<td>Obesity</td>
<td>Rhythm Pharmaceuticals, Inc</td>
</tr>
<tr>
<td>Czen001, 002</td>
<td>Synthetic peptide</td>
<td>Agonist</td>
<td>Anti-infective Anti-inflammatory</td>
<td>MSH Pharma</td>
</tr>
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</table>

Pan-agonist which has been shown to reduce the disease score in a mouse model of arthritis and induce proresolving properties (increased phagocytosis) in macrophages [17]. Carrier technology has been applied to alpha- and gamma-MSH and used in the CIA (collagen induced arthritis) and urate peritonitis models showing effective amelioration of inflammatory parameters of the two experimental diseases [11]. This approach aims to facilitate the targeting to inflammatory sites of unstable peptides such as melanocortins, by fusion with the latency-associated peptide (LAP) of TGFβI through a cleavable matrix metalloproteinase linker [57].

Alpha-MSH has been used to treat adjuvant arthritis in rats with an increase in body weight, reduction of the arthritis score, and erosions [58]. POMC gene therapy has been used to treat adjuvant arthritis in rats with a reduction in paw swelling after adjuvant injection as well as thermal hypersensitivity [59]. Melanocortins have also been studied in models of gouty arthritis. Alpha-MSH and a small peptide derivative (CKPV-2) have been shown to inhibit the ability of monocytes to produce neutrophils chemotactants and activating compounds in response to urate crystals [60]. The melanocortin peptide ACTH₄₋₁₀ has been shown to reduce neutrophil accumulation in an in vivo model of crystal-induced peritonitis and to inhibit in vitro macrophage activation with reduced chemokine KC release [61]. By using the mixed MC₃/MC₄ antagonist SHU9119, this study identified MC₃ as being responsible for these actions, since peritoneal macrophages do not express MC₄. Also the agonist...
melanotan II, a stable pan-agonist at all receptors, gave similar results as the alpha-MSH derivative [61, 62]. In the same system, two MC₃ agonists MT-II and gamma-MSH also inhibited neutrophil accumulation and release of cytokine and chemokines from macrophage. Furthermore MC₄ is expressed in the C57BL6 mouse and Sprague Dawley rat peritoneal macrophages, as determined by Western blot. ACTH reduced joint size and inhibited neutrophils accumulation in rat knee joints injected with urate crystals. SHU9119 abrogated the effectiveness of ACTH in this model while gamma-MSH showed similar protective qualities [63]. Further evidence suggesting that MC₃ is important in this model came with the efficacy of nonselective and selective MC₃ agonists in the amelioration of urate crystal-induced peritonitis in a mouse colony bearing a nonfunctional MC₁. This was further supported by presence of MC₃ protein in mouse peritoneal macrophages [64]. [D-Trp⁶]gamma-MSH (a gamma-MSH derivative with preference for activating mouse MC₃) afforded protection when used for the treatment of rat gout arthritis or urate peritonitis, and but not when used in MC₄ deficient mice (only the urate peritonitis model has been tested), again suggesting a role for MC₃ in controlling the inflammation produced by urate crystals [65]. The same compound has been shown to be efficacious in murine peritonitis despite a nonfunctional MC₁, again guiding us to believe that MC₃ might be more relevant in this mouse model of gout [66]. Overall these experiments show the efficacy of ACTH and its derivatives, natural and synthetic, in the treatment of mouse and rat models of gout and suggest that MC₃ is the receptor mediating these effects.

2.4. Melanocortins in Human Arthritis. Little is known about the effects of melanocortins on human arthritis other than the effects of ACTH in rheumatoid arthritis and gout which have been known about since the 1950s [6, 7, 67–72]. The clinical efficacy of ACTH in gouty arthritis was reevaluated in the 1990s [9] and this retrospective study confirmed an efficacy over and beyond what one would expect from the release of endogenous cortisol. In the United States, ACTH is part of the clinical armamentarium for gout, especially for the treatment of patients with contraindications to NSAIDs. Catania et al. discovered elevated levels of alpha-MSH in the synovial fluid of rheumatoid arthritis and juvenile chronic arthritis patients compared to those with osteoarthritis (OA). Using paired samples, these authors also showed that the levels of alpha-MSH were elevated in synovial fluid as compared to serum. The concentrations of alpha-MSH were proportional to the degree of inflammation [73]. Bohm's and Grassel's groups have reported presence of melanocortin receptors 1 and 5 in human chondrocytes and have proposed a role for the melanocortins in the osteoarticular system [74]. Yoon et al. showed a reduction in MMP13 production and p38 kinase phosphorylation when human chondrosarcoma cells were pretreated with alpha-MSH and then stimulated with TNFα. This was independent of ERK and JNK kinases but reliant on p38 kinases and NFκB [75]. Addition of alpha-MSH to TNFα-activated human chondrocytes reduced production of proinflammatory cytokines and increased the release of the anti-inflammatory cytokine IL10 [76].

2.5. Would New Therapeutics Emerge from Research on Melanocortins? We conclude this overview by highlighting the therapeutic potential that the area of the resolution of inflammation may retain. For space limitation, we focus on the melanocortin research only, though it is clear that other effectors of resolution and their targets would also be endowed with promising opportunities. Only the future will tell if new therapeutics will indeed be developed out of this research effort.

Given the data from preclinical models and the success of alpha-MSH and its derivatives as well as de novo agonists, melanocortin ligands have been taken forward into clinical trials for further investigation in humans. The minimum peptide sequence from alpha-MSH that can activate MC receptors is a tri-peptide (KPV). However, although active, it has a very short half-life and much work has been based on modifying alpha-MSH and its derivatives to extend their duration of action. There is much effort on melanocortin peptides, with the aim of producing a preparation, that is, easy to deliver, specific to its target tissue, more selective, and with a longer half-life.

Possible side effects of melanocortin receptor stimulating drugs are skin pigmentation and increased risk of melanoma due to activation of MC₁, hypertension, and behavioural disturbances due to activation of MC₃, MC₄, and MC₅. Pan-agonists may activate the yawning and stretching reflexes stimulated by MC₄. An important aspect to consider for small molecules targeting MC₃ would be their inability to cross the blood brain barrier, thus preventing unwanted actions on food intake and central control of blood pressure [77].

Despite these potential side effects, melanocortin-based therapeutics are generally safe and well tolerated by patients. In addition, ACTH (which activates all melanocortin receptors, as discussed above) is currently used for the treatment of gout, but it displays efficacy also for proteinuric nephropathies [78], exacerbations of multiple sclerosis [79], and several rheumatic disorders [8, 9, 72, 80], indicating that targeting the melanocortin system might be a genuinely valid therapeutic approach. However, the paucity on appropriate randomized, controlled, double-blind trials to evaluate the efficacy of this drug has limited its use as well as development of melanocortin-based therapies.

The perception may be changing right now. In fact, we are experiencing a renaissance of the melanocortin field as many drugs are (or have been) subjected to clinical trials to treat a variety of conditions (http://clinicaltrials.gov). For example, the drug RM-493, a selective MC₄ peptide agonist from Rhythm Pharmaceuticals, Inc. is currently on a phase-II trial to evaluate its antiobesity effects. The drug bremelanotide (Palatin Technologies), which activates MC₁ and MC₄ receptors, is currently under investigation for female sexual arousal disorder, although the effects on blood pressure have questioned the risk/benefit ratio of bremelanotide for this indication. Action Pharma A/S completed a phase-II clinical trial using the compound AP214 (described earlier in this
review) to assess the prevention of kidney injury in patients undergoing cardiac surgery. In addition, the FDA Office of Orphan Products Development is running a trial to assess the effects of alpha-MSH on acute renal failure. A third study (phase II, completed) focused on nephropathies is conducted by Radboud University, in which they aimed to evaluate the effects of a synthetic ACTH on idiopathic membranous nephropathy. Diabetic nephropathy is another indication under evaluation in a phase IV clinical trial conducted by Southeast Renal Research Institute. ACTH is also being evaluated for the treatment of systemic lupus erythematosus and multiple sclerosis (Questcor Pharmaceuticals, Inc., phase IV and I, resp.). The peptide afamelanotide, an alpha-MSH derivative with increased stability and potency developed by Clinuvel Pharmaceuticals Limited, is currently under investigation for the treatment of erythropoietic protoporphyria (phase-III, recruiting), solar urticaria (phase II, completed), and vitiligo (phase I), and for the treatment of acne vulgaris due to its anti-inflammatory properties (phase II, completed). Of note, companies such as MSH Pharma, Inc. include in their pipeline melanocortin drugs to treat conditions such as rheumatoid arthritis and inflammatory bowel disease, highlighting that there is a renewed current interest in developing melanocortin-based therapies for chronic inflammatory diseases and that melanocortin drugs are ready for translation.

Conflict of Interests

The authors have no conflicts of interest.

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