We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



6

Melanocortins: Anti-Inflammatory and Neuroprotective Peptides

Carla Caruso, Lila Carniglia, Daniela Durand, Teresa N. Scimonelli and Mercedes Lasaga

Research Institute for Reproduction, School of Medicine, University of Buenos Aires, IFEC-CONICET Department of Pharmacology, School of Chemistry, National University of Córdoba, Córdoba, Argentina

1. Introduction

The melanocortin system includes the melanocortins, their receptors and two endogenous antagonists. This system is involved in several physiological processes in the brain. Melanocortins have potent anti-inflammatory and neuroprotective effects in the central nervous system (CNS). Therefore, they are suitable candidates for the treatment of inflammatory and neurodegenerative disorders within the brain.

2. Melanocortins

Melanocortins include α, β, and γ-melanocyte stimulating homones (MSH), and adrenocorticotropin (ACTH). These neuropeptides derive from pro-opiomelanocortin (POMC) proteolytic cleavage (Fig. 1). POMC is a 31 KDa pro-hormone that is processed by pro-hormone convertases (PCs) in secretory vesicles of the cell. PCs belong to the family of serine proteases and recognize pairs of basic amino acid residues. PC expression is tissue specific and their presence induces secretion of different products generated from POMC, thereby determining melanocortins' selective expression (Bicknell, 2008). Intact POMC was also shown to be released into the circulation (Gibson et al., 1994). α-MSH is produced in the presence of PC1 and PC2 (Benjannet et al., 1991) and additional modifications such as glycosylation, phosphorylation, amidation, and acetylation may occur. For example, acetylation gives α-MSH increased resistance to degradation, this modification resulting in increased biological activity (Wilkinson, 2006).

Although α-MSH is synthesized in several tissues such as skin, placenta, testis, ovary, kidney, and adrenal gland, the main source of α-MSH is the pars intermedia of the pituitary gland (Usategui et al., 1976). In the CNS, α-MSH is produced in the arcuate nucleus of the hypothalamus (O´Donohue & Dorsa, 1982) and in the nucleus of the solitary tract in the brain stem (Bronstein et al., 1992). Melanocortin fibers project from these sites to the paraventricular nucleus, the lateral hypothalamus, and throughout the brain, e.g., amygdala, hippocampus, nucleus accumbes, and spinal cord (Bagnol et al., 1999). ACTH is produced mainly in the anterior pituitary gland and released into circulation, although it is

also expressed in the skin (Wakamatsu et al., 1997). γ-MSH was detected in adrenal medulla (Bjartell et al., 1987), intestine neurons (Wolter, 1985), and the brain (Kawai et al., 1984) whereas β-MSH was found in human hypothalamus (Bertagna et al., 1986), but not in rodent brain. All melanocortins share a conserved sequence of aminoacids: Met-Glu(Gly)-His-Phe-Arg-Trp necessary for their biological activity. Rare mutations in POMC gene have been found in humans, and are associated with severe early-onset obesity, adrenal insufficiency and red hair pigmentation (Krude et al., 1998).

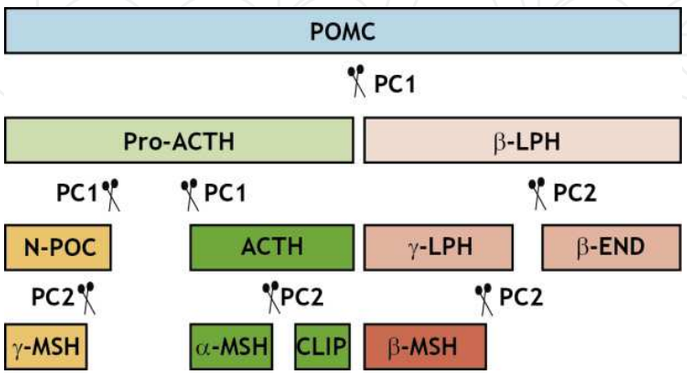


Fig. 1. Hypothalamic post-translational processing of POMC. PC1 (also known as PC3) cleaves POMC protein to generate pro-ACTH and β-lipotropin (β-LPH). Pro-ACTH is further cleaved by PC1 to generate ACTH and N-terminal peptide (N-POC). In the brain and in the intermediate lobe of pituitary, PC2 cleaves ACTH to generate corticotropin-like intermediate peptide (CLIP) and α-MSH. Then, two more peptidases, carboxipeptidase E and peptidyl α-amidating monooxygenase, are needed to produce mature α-MSH. PC2 also generates γ-lipotropin (γ-LPH) and β-endorphin (β-END) from β-LPH cleavage, β-MSH from γ-LPH, and γ-MSH from N-POC cleavage.

2.1 Melanocortin receptors

Cloning of melanocortin receptors (MCRs) led to the characterization of five distinct MCRs which help to explain the wide range of physiological functions of melanocortins. Each receptor is the product of a small, intronless separate gene. MCRs belong to class A of seven transmembrane G protein-coupled receptors (GPCRs) and are positively coupled to adenylate cyclase. MCRs exhibit sequence homology from 40% to 60%. All MCRs have several potential N-glycosylation sites in their N-terminal domains, conserved cysteine residues in their carboxyl termini for potential acetylation with fatty acids, and consensus recognition sites for protein kinase A (PKA) and C. ACTH, α-MSH, and β-MSH are agonists of all MCRs except MC2R which only recognizes ACTH (Schiöth et al., 1996), whereas γ-MSH is a selective MC3R agonist (Roselli-Rehfuss et al., 1993) (Table 1).

MC1R was the first receptor cloned from a melanoma cell line (Chhajlani & Wikberg, 1992) and from normal melanocytes (Mountjoy et al., 1992), and is expressed predominantly in the skin where it mediates α-MSH induction of melanogenesis. MC1R mutations are associated with increased risk of developing melanoma (Kennedy et al., 2001). MC1R is also found in immune cells such as macrophages (Lam et al., 2005), monocytes (Bhardwaj et al., 1997), neutrophils (Catania et al., 1996), and B lymphocytes (Cooper et al., 2005). It is also expressed in endothelial cells (Hartmeyer et al., 1997) and fibroblasts (Böhm et al., 1999).

MC1R is involved in the anti-inflammatory action of α-MSH in leukocytes (Taherzadeh et al., 1999). Indeed, MC1R involvement in the anti-inflammatory effects of melanocortins has been widely studied in peripheral cells (Catania et al., 2004). Recently, MC1R expression was also found in rat heart (Catania et al., 2010). In the CNS, MC1R was detected only in neurons of periaqueductal grey matter (Xia et al., 1995) and in mouse brain (Rajora et al., 1997a). However, nothing is known about the role of MC1R in central effects of melanocortins.

MC2R is present in the adrenal gland and is selectively activated by ACTH leading to production and release of steroids (Mountjoy et al., 1992). Mutations in MC2R gene that produce a non functional receptor are associated with familial glucocorticoid deficiency (Elias et al., 1999), a rare autosomal recessive disorder. MC2R is also present in rodent adipocytes (Boston & Cone, 1996), suggesting a role for melanocortins in lipolysis, although it was not found in human adipocytes (Chhajlani, 1996). MC2R was found in human keratinocytes where its activation by ACTH induced cortisol synthesis (Slominski et al., 1996), and it was recently shown to be present in bone cells as well (Isales et al., 2010).

MC3R is widely distributed in the CNS, highly expressed in the hypothalamus and the limbic system (Roselli-Rehfuss et al., 1993). It has been proposed to function as an auto-receptor since it is expressed in POMC neurons where it might regulate melanocortin release (Jégou et al., 2000). However, MC3R knock-out mice are obese and hyperphagic and have increased fat mass (Chen et al., 2000), indicating that MC3R may have other actions in the brain. MC3R is present in the digestive tract in stomach, duodenum and pancreas and in human placenta (Gantz et al., 1993), as well as in human heart, kidney, testis, ovary, mammary gland, and skeletal muscle (Chhajlani, 1996). Immune cells such as macrophages (Lam et al., 2005) and B lymphocytes (Cooper et al., 2005) express this receptor which is involved in anti-inflammatory effects of melanocortins in macrophages (Getting et al., 2006). MC3R plays a role in sodium homeostasis having natriuretic actions (Lin et al., 1987) and has protective effects in heart ischemia in rats (Guarini et al., 2002).

MC4R is expressed throughout the brain including the cortex, thalamus, hypothalamus, and the spinal cord (Gantz et al., 1994; Mountjoy et al., 1994), and it was shown to be more widely distributed than MC3R in the brain. Outside the CNS, it has been detected in human adipose tissue (Chhajlani, 1996), and it was recently detected in human epidermal melanocytes where it regulates pigmentation (Spencer & Schallreuter, 2009). MC4R is involved in neuroendocrine and autonomic functions, being a key factor in the regulation of food intake and metabolism (Huszar et al., 1997). The anorexigenic effect of α-MSH involves this receptor (Marsh et al., 1999). In this regard, mutations in MC4R gene in humans are associated with obesity (Yeo et al., 1998) and are now considered the most common monogenic cause of obesity. In contrast, no MC3R variants are associated with obesity in humans. MC4R is also involved in the antipyretic actions of α-MSH (Sinha et al., 2004), and it also mediates the neurotrophic effect of α-MSH on cultured neurons (Adan et al., 1996) and on neurite elongation of dorsal root ganglia neurons (Tanabe et al., 2007). MC4R is involved in melanocortins anti-inflammatory action in the brain (Lasaga et al., 2008). MC4R is the only MCR expressed in astrocytes (Selkirk et al., 2007; Caruso et al., 2007) where it exerts anti-inflammatory effects (Caruso et al., 2007). We recently showed that hypothalamic cultured neurons express MC4R and MC3R, and α-MSH also exerts an anti-inflammatory action on these cells (Caruso et al., 2010). Activation of MC4R in astrocytes also induces the

expression of brain-derived neurotrophic factor (BDNF) (Caruso et al., 2011), which suggests that BDNF could mediate melanocortins effects.

MC5R is found in adipocytes, kidney, liver, lung, bone marrow, thymus, mammary gland, testis, ovary, uterus, pituitary, stomach and skin (Chhajlani, 1996; Gantz et al., 1994; Labbé et al., 1994; van der Kraan et al., 1998). Observation of MC5R knock-out mice indicates that its main functions involve regulation of lacrimal glands and of secretion of sebaceous glands (Chen et al., 1997). These mice showed no changes in anti-inflammatory, neuroprotective or analgesic actions induced by administration of α-MSH. MC5R was also found in the adrenal gland (Liakos et al., 1998) where α-MSH induces aldosterone production *in vitro*, although to a lesser extent. MC5R is expressed in B and T lymphocytes, indicating that it could be involved in immune regulation. This receptor has also been detected in some areas of the CNS but its physiological functions are unknown (Griffon et al., 1994).

Receptor subtype	Ligand affinity	Physiological functions	Tissue distribution
MC1	α-MSH= β-MSH ≥ACTH >>γ-MSH	Melanocyte differentiation Synthesis of melanin Pigmentation Anti-inflammatory	Melanocytes, keratinocytes, macrophages,monocytes, neutrophils, endothelial cells
MC2	ACTH	Steroidogenesis	Adrenal cortex, keratinocytes, adipocytes
MC3	γ-MSH = ACTH > α-MSH = β-MSH	Anti-inflammatory Energy homeostasis Natriuretic activity	Hypothalamus and limbic system, digestive tract, heart, kidney, immune cells and placenta
MC4	α-MSH= β-MSH= ACTH >>γ-MSH	Energy homeostasis Sexual behavior Anti-inflammatory Neuroprotection Antipyretic	Widely distributed in the brain
MC5	α-MSH ≥ β-MSH= ACTH >>γ-MSH	Exocrine gland secretion	Widely distributed in peripheral tissues, specially in glands

Table 1. Ligand, function and distribution of MCRs

The melanocortin system is unique in that it is the only system with endogenous antagonists. The Agouti protein (Miller et al., 1993) produced in the skin of rodents is a competitive antagonist of MC1R and also of MC4R albeit with lower affinity (Blanchard et al., 1995). In humans, Agouti is expressed in the skin, adipose tissue, testis, ovary, liver, heart and kidney (Wikberg et al., 2000) and regulates skin pigmentation. The Agouti-related protein (AGRP) was cloned based on its homology with Agouti (Shutter et al., 1997). It is present in the brain only in neurons of the arcuate nucleus (Dinulescu & Cone, 2000) where it promotes increased feeding and decreased energy expenditure by binding MC4R (Cone, 2005). Ubiquitous expression of AGRP causes obesity in mice (Ollman et al., 1997). AGRP is a competitive antagonist of MC3R and MC4R and it was shown to inhibit constitutive MC4R activity (Haskell-Luevano & Monek, 2001).

2.2 MCR signaling pathways

The classical signaling pathway for MCRs couples to stimulatory G protein that activates adenylate cyclase and increases intracellular cyclic AMP (cAMP) production. In turn, cAMP

can activate PKA. This kinase was reported to be involved in melanocortins effects in melanoma cells (Ao et al., 1998) and in adrenal cells (Roy et al., 2011). In Agouti mice PKA constitutive activity even rescued mice from obesity syndrome (Czyzyk et al., 2008). As a result of its activation, PKA can phosphorylate and activate the cAMP responsive element binding protein (CREB), which then acts within the nucleus as a transcription factor. CREB is activated by α-MSH in neurons of the hypothalamic paraventricular nucleus (Sarkar et al., 2002), in neurons of the solitary nucleus (Sutton et al., 2005), in hypothalamic cultured neurons (Caruso et al., 2010), and also in cultured rat astrocytes (Caruso et al., 2011). Apart from the cAMP-PKA-CREB pathway MCRs also activate other signaling pathways. MC3R has been shown to induce inositol phosphate signaling (Konda et al., 1994) and MC5R was reported to activate the Janus kinase/signal transducer and activator of transcription (Jak/STAT) pathway in B cells (Buggy, 1998). Stimulation of all MCRs leads to activation of mitogen-activated protein kinases (MAPK) ERK-1/2 (Chai et al., 2006; Chai et al., 2007; Herraiz et al., 2011; Patten et al., 2007, Rodrigues et al., 2009; Roy et al., 2011). Depending on the cell type this effect may involve phosphoinositol 3 kinase activation (Rodrigues et al., 2009; Vongs et al., 2004). Some reports also show that ERK activation may be PKA-independent in MCR transfected cell lines (Chai et al., 2006; Vongs et al., 2004). Intracellular calcium is also elevated by MC1R, MC3R, and MC4R stimulation (Eves et al., 2003; Konda et al., 1994; Newman et al., 2006). Although these data show some insight into MCR signaling, much work is still needed to fully elucidate signaling pathways of MCRs and to evaluate their importance in *in vivo* models. Pathways may also interact with each other as cross-talk between receptors, adding complexity to the picture. For example, MC4R activation enhances insulin-stimulated mTOR signaling (Chai et al., 2010) and potentiates leptin signaling (Zhang et al., 2009).

In addition to G proteins, MCRs can interact with other proteins that regulate their function. Some accessory proteins help folding and trafficking GPCRs to the cell membrane whereas others are found associated with the receptor and are involved in ligand binding. It is now established that a functional MC2R requires the expression of melanocortin 2 receptor accessory protein (MRAP). MRAP interacts with MC2R and facilitates MC2R cell surface expression, thereby producing an ACTH-responsive receptor (Webb et al., 2009). MRAP has two isoforms, MRAPα and MRAPβ, both expressed in the human adrenal gland (Metherell et al., 2005). Both MRAP isoforms interact directly with MC2R enabling ligand binding and activation (Roy et al., 2007). Individuals lacking MRAP have familial glucocorticoid deficiency disease (Metherell et al., 2005), which highlights the role of MRAP in MC2R functionality. Another accessory protein, MRAP-2, is expressed in the brain and the adrenal gland (Chan et al., 2009). MRAP and MRAP-2 act as negative regulators of MCRs other than MC2R since they reduce cAMP production in response to receptor activation (Chan et al., 2009). In addition, mahoghany, mahoganoid (also called mahogunin ring finger-1), and syndecan-3 were identified as accessory proteins for MCRs. Mahoghany, a transmembrane protein present in the brain and skin, was shown to be a low-affinity receptor for Agouti but not for AGRP (He et al., 2001). Recently, mahoganoid was shown to reduce MC1R and MC4R coupling to cAMP (Perez-Oliva et al., 2009). Finally, syndecan-3 is a proteoglycan that enhances AGRP antagonism of α-MSH at MC4R (Reizes et al., 2003). In spite of all this evidence, interaction between MCRs and accessory proteins is still not fully understood.

2.3 Synthetic compounds acting on MCRs

Some synthetic compounds for MCRs have been developed. (Nle^4, D-Phe^7) α-MSH (NDP-MSH), also known as melanotan I (MTI), is the most potent linear analogue of α-MSH (Sawyer et al., 1980). It shows high affinity for all MCRs and has been widely used in radioligand binding studies. Other agonist peptides are melanotan II (MTII), a small cyclic peptide that is a non selective agonist of all MCRs except MC2R, and HP-228, a linear analogue that is also a non selective agonist for MCRs but shows greater affinity for MC1R (Abou-Mohamed et al., 1995). Several MC4R agonists have also been developed. Ro27-3225 is a full agonist in human cells that express MC4R (Benoit et al., 2000) and was shown to protect against haemorrhagic shock (Giuliani et al., 2007b). Also, THIQ is a MC4R agonist that reduced food intake less effectively than MTII (Muceniece et al., 2007). Antagonists have also been developed. SHU9119 is a potent non-selective antagonist of MC3R and MC4R (Schiöth et al., 1999). HS014 (Schiöth et al., 1999), is the first selective MC4R antagonist since it has 20-fold higher affinity for MC4R over MC3R. HS024 is a competitive analog of α-MSH (Kask et al., 1998) with 100 times more affinity for MC4R over MC3R, although it antagonizes cAMP accumulation induced by all MCRs except MC2R. All antagonists stimulate food intake when administered centrally.

3. Anti-inflammatory effects of melanocortins

Inflammation is a physiological response to infection or tissue damage which, if properly controlled, ultimately leads to the restoration of homeostasis. Cytokines, chemokines, nitric oxide (NO) and prostaglandins (PGs) are mediators of inflammatory processes that induce vasodilation and extravasation of immune cells into injured tissues, activation of pathogen clearance mechanisms and tissue regeneration. These factors have also been linked to the pathology of several CNS disorders with an exacerbated inflammatory component, such as Alzheimer´s disease (AD), Parkinson disease (PD), multiple sclerosis (MS), HIV infection, and brain ischemia/reperfusion. Among their many physiological functions, melanocortins play an important role in the regulation of immune and inflammatory reactions. These effects can be exerted through their binding to centrally expressed MCRs which in turn regulate descending neural anti-inflammatory pathways, or by acting directly on immune cells or non-immune cells present in peripheral tissues (Lasaga et al., 2008), where they modulate the production of inflammatory mediators and the migration of inflammatory cells. Different MCRs may be responsible for the anti-inflammatory properties of melanocortins depending on the tissue or cell type involved. MC1R, MC3R and MC5R are the subtypes most commonly associated with these peripheral effects, whereas MC3R and MC4R are more likely responsible for melanocortins anti-inflammatory action within the CNS. Some studies also indicate that alternative non-MCR-mediated pathways may be involved in the signaling of certain melanocortin peptides such as γ-MSH (Langouche et al., 2002) and α-MSH C-terminal tripeptide Lys-Pro-Val (KPV).

3.1 Peripheral effects

3.1.1 *In vitro* studies

Melanocortins effects on peripheral tissues have been studied in a broad range of *in vitro* systems, particularly in immune cells where they appear to act mainly by decreasing the

production and release of inflammatory mediators and impairing leukocyte activation and infiltration into damaged tissues. For instance, it was shown that α-MSH inhibits synthesis and release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and IL-2 in cells of the immune system (Lipton et al., 1999; Luger et al., 2003; Manna et al., 2006; Star et al., 1995; Taherzadeh et al., 1999). It enhances the release of the anti-inflammatory cytokine IL-10 in monocytes (Bhardwaj et al., 1996) and keratinocytes (Redondo et al., 1998) as well. α-MSH can also inhibit chemokine production in a human retinal epithelial cell line that expresses MC1R (Cui et al., 2005), and IL-8 in fibroblasts and in human adipocytes, (Böhm et al., 1999, 2002). Melanocortins modulate the expression of adhesion molecules in response to inflammatory stimuli. For instance, α-MSH inhibits the expression of adhesion molecules induced by LPS or TNF-α in endothelial cells (Scholzen et al., 2003), leading to impaired lymphocyte adhesion. Another target of melanocortins is the inducible NO synthase (iNOS). This enzyme is induced by inflammatory stimuli and produces a high output of NO, a short-lived molecule which plays a major role in the regulation of immune, nervous and cardiovascular systems. Beyond its many physiological roles, excessive NO production may be harmful and mediate tissue damage and cell death. Several studies indicate that melanocortin peptides exert a protective role by inhibiting iNOS expression in stimulated macrophages, thus leading to decreased NO production (Mandrika et al., 2001; Star et al., 1995; Taylor, 2005). PGs are a family of lipid molecules derived enzymatically from fatty acids with a broad spectrum of physiological functions. They participate in multiple homeostatic effects and play a dual role in immunomodulation, different members of the family being involved in both the onset and resolution of the inflammatory response. Their production is catalyzed by cyclooxygenase (COX) 1 and 2, COX-2 being the isoform specifically activated by inflammation. α-MSH inhibits pro-inflammatory PG synthesis from fibroblasts induced by IL-1β (Cannon et al., 1986). Furthermore, in melanocyte and keratinocyte cell lines α-MSH was shown to reduce the release of PGE_2 induced by TNF-α (Nicolaou et al., 2004).

3.1.2 *In vivo* studies

Some of the *in vivo* anti-inflammatory actions of melanocortins in the periphery are due to ACTH binding to its receptor MC2R in the adrenal cortex which promotes the production of glucocorticoids with a consequent systemic anti-inflammatory response. Melanocortin peptides can have anti-inflammatory effects acting via central MCRs through descending neurogenic pathways or directly on peripheral tissues through other MCR subtypes. Both α-MSH and γ-MSH are capable of inhibiting the effects of IL-1β on the activation of the hypothalamic-pituitary-adrenal axis by acting on central melanocortin receptors (Cragnolini et al., 2004). Several studies show that systemic and/or central administration of α-MSH exerts protective effects in diverse models of peripheral inflammation. Circulating levels of α-MSH have also been shown to be increased in inflammatory diseases such as rheumatoid arthritis, MS, PD, and HIV infection (Catania et al., 2000). Anti-inflammatory actions of melanocortins have been widely studied in animal models of systemic inflammation such as septic shock where α-MSH has been shown to reduce circulating levels of pro-inflammatory cytokines TNF-α and IL-1α (Gonindard et al., 1996) and to improve animals' survival rate from 10% to 50% by 24 h (Lipton et al., 1994). Treatment with ACTH and POMC-derived peptides was also shown to inhibit cytokine release and neutrophil migration in a mouse

model of acute experimental inflammation (Getting et al., 1999). In a model of acute hepatitis induced by LPS, Chiao et al. (1996) showed that α-MSH was able to prevent liver inflammation by inhibiting NO production, TNF-α and IL-8 mRNA increase, and neutrophil infiltration. α-MSH was also shown to reduce chemokine synthesis and prevent damage to lungs and kidneys under hypoxic conditions in a model of renal ischemia (Chiao et al., 1997; Deng et al., 2004). It also reduced heart injury and size of the ischemic area in a rat model of myocardial ischemia, through activation of MC3R (Bazzani et al., 2001; Guarini et al., 2002). Research on experimental inflammatory bowel disease showed that treatment with α-MSH effectively reduces inflammatory mediators in experimental colitis (Rajora et al., 1997b). As for skin inflammation, both centrally and locally administered α-MSH has been shown to modulate the cutaneous immune response in several mouse models of contact dermatitis or cutaneous vasculitis (Brzoska et al., 2008). Furthermore, this peptide was proved to induce hapten-specific tolerance *in vivo* by a mechanism involving IL-10 as a crucial mediator (Grabbe et al., 1996). Since α-MSH and MC1R protein levels are up-regulated in human burns and scars a role in cutaneos injury is also suggested (Muffley et al., 2011). A gene therapy approach based on an α-MSH expression vector has been tested in a model of experimental autoimmune uveitis, in which the treatment was successful in suppressing this condition by a mechanism dependent on MC5R expression, suggesting that this approach might provide effective therapy for uveitis (Lee et al., 2009).

MC1R involvement in the anti-inflammatory effects of melanocortins has been widely observed in peripheral cells (Catania et al., 2004). Recently, it was shown that the selective MC1R agonist BMS-470539 was succesful in inhibiting leukocyte trafficking in the vasculature of mice subjected to mesenteric ischemia-reperfusion. This anti-inflammatory effect was lost when examining the vasculature of mice with mutant inactive MC1Rs (Leoni et al., 2010), indicating that MC1R plays a prominent role in melanocortins effects. In models of allergic and nonallergic lung inflammation, melanocortins inhibited leukocyte accumulation, a protective effect that was associated with MC3R activation (Getting et al., 2008). On the other hand, Ro27-3225, a selective MC4R agonist, reduced the expression of TNF-α and IL-6, and reduced pancreatitis severity, effects that were blocked by HS024, a selective MC4R antagonist (Minutoli et al., 2011). On the other hand, several MCR-independent effects of melanocortin C terminal sequence-derived peptides were described. The melanocortin-derived tripeptide KPV was shown to reduce the inflammatory infiltrate in a model of inflammatory bowel disease, leading to recovery (Kannengiesser et al., 2008). Another synthetic peptide $(CPVK)_2$ also showed anti-inflammatory activity similar to NDP-MSH against endotoxin treatment *in vitro* and *in vivo* by reducing TNF-α and NO production (Gatti et al., 2006). The mechanism of action of these peptides seems to involve interaction with the IL-1 receptor I, thereby preventing IL-1β binding (Mastrofrancesco et al., 2010).

3.2 Central effects

3.2.1 *In vitro* studies

Inflammatory reactions within the CNS constitute a physiological host-defense mechanism by which damaging agents are cleared and tissue homeostasis is restored. As part of this response, glial cells become reactive and release a wide variety of inflammatory mediators such as cytokines, chemokines, complement factors and acute phase reactants. These factors

are necessary for an adequate immune or inflammatory response, but if the response is not properly controlled, they may also lead to tissue damage and cytotoxicity. Therefore, the discovery of compounds with the ability to modulate inflammatory responses in the brain is of paramount importance.

Activation of MCRs in the brain is known to be essential to the anti-inflammatory circuit of melanocortins. Expression of MC1R (Xia et al., 1995; Rajora et al., 1997a) and MC5R (Griffon et al., 1994) has been described but their physiological functions in the CNS are unknown. Considering that α-MSH has anti-inflammatory action in brain of mice with non-functional MC1R (Ichiyama et al., 1999), this receptor may not be an important mediator of anti-inflammatory effects of melanocortins in the CNS. Therefore, the main candidates to mediate central effects of melanocortins are MC3R and MC4R since these are the subtypes expressed in the brain. Astrocytes are the most abundant glial cell population in the brain. The only MCR subtype found in these cells is MC4R (Caruso et al., 2007; Selkirk et al., 2007). On the other hand, subtypes 1, 3, 4 and 5 were detected in a human microglial cell line (Lindberg et al., 2005). Melanocortins were shown to inhibit production of IL-6, TNF-α and NO in a murine microglial cell line, where endogenous α-MSH released from microglial cells was proposed to act as an autocrine immunomodulatory factor (Delgado et al., 1998). They also inhibited the release of both NO and TNF-α from microglia stimulated with β-amyloid peptides and IFN-γ (Galimberti et al., 1999), suggesting that these peptides might modulate the local response to β-amyloid deposition. In human astrocytoma cells, α-MSH inhibits LPS-induced TNF-α release (Wong et al., 1997). We showed that α-MSH attenuates LPS+IFN-γ-induced inflammation in rat astrocytes by decreasing iNOS and COX-2 expression and NO and PGE_2 release (Caruso et al., 2007). These effects were prevented by HS024, strongly suggesting a role for MC4R in brain anti-inflammatory melanocortin effects. However, α-MSH had no effect on basal or IL-1β-induced PGE_2 levels in astrocytes (Katsuura et al., 1989), although it inhibited LPS- or IL-1β-induced PGE_2 production from hippocampus fragments (Weidenfeld et al., 1995), but not IL-1β-induced PGE_2 release from hypothalamic fragments (Mirtella et al., 1995). We recently showed that hypothalamic neurons express MC3R and MC4R and that α-MSH reduces TNF-α expression in these cells where it induces CREB activation (Caruso et al., 2010).

3.2.2 *In vivo* studies

A typical reaction to inflammatory processes in the CNS is the induction of fever as a host-defense response. Melanocortin anti-pyretic action has been known for some time (Tatro, 2000) and is considered adrenal-independent (Murphy et al., 1983). α-MSH central administration reduces fever caused by LPS (Huang et al., 1997), IL-1β (Daynes et al., 1987) and TNF-α (Martin et al., 1991). Also, during fever episodes, levels of α-MSH increase in the brain (Bell & Lipton, 1987) suggesting a physiological role for melanocortins in fever control. α-MSH circulating levels increase in response to endotoxin administration in humans (Catania et al., 1995). Intraperitoneal (i.p.) administration of α-MSH was shown to inhibit fever by activating central MCRs, since their blockade prevented an α-MSH anti-pyretic effect (Huang et al., 1998). This effect was also blocked by HS014, a selective MC4R antagonist, thereby highlighting MC4R involvement in α-MSH effect over LPS-induced fever (Sinha et al., 2004). Central administration of α-MSH in mice reduces the expression of iNOS in lungs and liver and serum TNF-α levels induced by endotoxemia (Delgado

Hernandez et al., 1999). Conversely, i.p. injection of α-MSH has no effect over endotoxemia-induced iNOS expression in lung and liver, supporting the notion that activation of central MCRs is responsible for the peripheral anti-inflammatory effect of α-MSH. Moreover, treatment with α-MSH reduces expression of TNF-α and IL-1β after cerebral ischemia (Huang & Tatro, 2002), lowers TNF-α and NO production induced by LPS+IFN-γ in the CNS (Delgado et al., 1998), and also reduces TNF-α production in brain inflammation (Rajora et al., 1997a). Furthermore, melanocortins inhibit the IL-1β-induced production of NO and PGs in rat hypothalamus (Cragnolini et al., 2006). We demonstrated that α-MSH reduces induction of iNOS and COX-2 gene expression at hypothalamic level in rats during endotoxemia, and that this effect is mediated by MC4R activation (Caruso et al., 2004). Together with α-MSH, γ-MSH and β-MSH were found to exert anti-inflammatory action in a model of neuroinflammation in mice by reducing LPS-induced NO production (Muceniece et al., 2004).

3.3 Mechanisms of anti-inflammatory actions of melanocortins

The nuclear factor-κB (NF-κB) is an essential regulator of the immune response since it drives the expression of several pro-inflammatory genes such as cytokines, chemokines, iNOS and COX-2 induced by diverse inflammatory stimuli (Li & Verma 2002). Under resting conditions it is held within the cytoplasm in an inactive state by its inhibitor (IκB). Upon proper stimulation, IκB is phosphorylated and dissociates from the complex, allowing NF-κB to translocate to the nucleus where it acts as a transcription factor. The most attractive feature of melanocortins is that they reduce production of a variety of inflammatory mediators but do not enterily suppress the inflammatory response. α-MSH is able to inhibit the activation of NF-κB induced by a great diversity of inflammatory stimuli in different cell lines (Manna & Aggarwal, 1998), and in brain inflammation (Ichiyama et al., 1999). This inhibitory action, thought to be the main mechanism responsible for the anti-inflammatory effects of melanocortins, appears to be mediated by cAMP production and PKA activation (Manna & Aggarwal, 1998). α-MSH regulates NF-κB and also p38-MAPK pathways probably through a common upstream element by inducing the binding of the IL-1R-associated kinase 1 (IRAK 1) to its inhibitor IRAK-M in activated macrophages (Taylor, 2005). However, NF-κB inhibition might not be the mechanism of action of melanocortins in all cell types studied. Apart from NF-κB, melanocortins activate CREB, a transcription factor acting on cell proliferation, differentiation and survival. It also regulates the expression of genes involved in immune responses and long term memory. In rat astrocytes, MC4R activation by α-MSH stimulates the cAMP-PKA-CREB pathway without involving inhibition of NF-κB (Caruso et al., 2011). CREB activation by α-MSH occurs in hypothalamic neurons as well, and also without modifying NF-κB activation (Caruso et al., 2010). Similarly, α-MSH failure to modify NF-κB activation was reported in H4 glioma cells (Sarkar et al., 2003).

Another important mediator in α-MSH effects is IL-10, an anti-inflammatory cytokine capable of inhibiting NF-κB activity and the release of many pro-inflammatory mediators such as IL-1, IL-6, TNF-α, and IL-8 (Sabat et al., 2010). This cytokine is induced by α-MSH in monocytes and keratinocytes, and knock-out mice for IL-10 were found to be resistant to α-MSH treatment in a model of allergic inflammation (Raap et al., 2003), strongly supporting a

role for IL-10 as a mediator in melanocortin effect. Furthermore, a MC3R/4R antagonist, SHU9119, reduces LPS-induced IL-10 release in monkeys (Vulliémoz et al., 2006), thereby establishing a physiological role for endogenous melanocortins as modulators of this cytokine's release.

4. Neuroprotective effects of melanocortins

Melanocortins neuroregenerative actions were described long ago. The first reports showed that melanocortin peptides improve nerve regeneration following peripheral nerve injury. ACTH administration improved recovery of adrenalectomized rats subjected to sciatic nerve denervation (Strand & Kung, 1980). α-MSH and ACTH also induced recovery after crushing the sciatic nerve (Bijlsma et al., 1983). α-MSH-like peptides stimulate neurite outgrowth in peripheral nerve injury *in vivo* (Plantinga et al., 1995), and axonal outgrowth from fetal spinal cord slices (van der Neut et al., 1988), and regrowth of injured axons in rat adult spinal cord (Joosten et al., 1999). Endogenous α-MSH also improved recovery of rats with destruction of dopamine neurons of the nucleus accumbens (Wolterink et al., 1990). Its analog MTII also induced nerve regeneration and neuroprotection by preventing toxic neuropathy induced by cisplatin (Ter Laak et al., 2003). Several studies suggested that MC4R is the receptor involved in the neuroregenerative properties of melancortins. α-MSH-induced neurite-like outgrowth in the neuroblastoma cell line 2A was shown to be blocked with a specific MC4R antagonist (Adan et al., 1996). The MC4R agonist ME10501 is neuroprotective in spinal cord injury (Sharma et al., 2006). In mouse dorsal root ganglia neuron cultures, α-MSH promoted neurite outgrowth, an effect entirely inhibited by a selective MC4R blocker, JKC-363 (Tanabe et al., 2007). This study also showed that only MC4R mRNA expression was induced after sciatic nerve injury, suggesting that MC4R could play a central role in nerve regeneration. The mechanism of neurotrophic effects of melanocortins remains largely unknown although it is suggested to be a consequence of the anti-inflammatory effects of these peptides.

Several models of brain injury were shown to improve after melanocortin treatment. In rats subjected to four-vessel occlusion global cerebral ischemia, i.p. administration of α-MSH prevented CA1 pyramidal cell death and reduced glial activation (Forslin Aronsson et al., 2006). NDP-MSH protects hippocampal neurons from dying after cerebral ischemia in gerbils (Giuliani et al., 2006), and after excitotoxicity (Forslin Aronsson et al., 2007). Also, delayed treatment with α-MSH diminished stratial damage and neuronal death after focal cerebral ischemia (Giuliani et al., 2007a). Melanocortins reduced hippocampal damage and improve learning and memory as long as 50 days after ischemia (Giuliani et al., 2009). These studies showed that neuroprotection by melancortins involved MC4R whereas the selective MC3R agonist γ-MSH had no protective effect on cerebral ischemia (Giuliani et al., 2006). In addition, melanocortins through MC4R blocked memory impairment (Gonzalez et al., 2009) as well as memory reconsolidation impairment (Machado et al., 2010) induced by IL-1β administration in the hippocampus. We showed that MC4R activation protects astrocytes from apoptosis induced by LPS+IFN-γ (Caruso et al., 2007), and other authors showed that it also protects hypothalamic neurons from serum deprived-induced apoptosis (Chai et al., 2006). Protection of astrocytes by melanocortins involved decreasing caspase 3 activity induced by LPS+IFN-γ and inducing expression of the anti-apoptotic protein Bcl-2 as well as decreasing expression of the apoptotic protein Bax induced by LPS+IFN-γ (Caruso et al.,

2007). This protective effect was also shown to involve ERK activation in a cell line of hypothalamic neurons (Chai et al., 2006). These data strongly suggest that melanocortins are neuroprotective through MC4R.

A common feature of neurodegenerative diseases is chronic immune activation in the brain. Cytokines have a dual role in inflammation and disease. They contribute to the acute phase of inflammation but also play protective roles in later stages of injury. This is also the case in neurodegeneration: given that IL-1β and TNF-α are increased in neurodegenerative diseases such as AD, PD, and MS, they are believed to be involved in the etiology of these pathologies. However, the role of inflammation in the development of neurodegenerative disorders is not clear. A general understanding indicates that inflammatory processes contribute to the onset of neurodegenerative diseases. Although there is no evidence of melanocortin effects on models of PD or AD, anti-inflammatory therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs) were neuroprotective (Asanuma & Miyazaki, 2008; McGeer & McGeer, 2007). However, the use of NSAIDs for long periods of time can have undesired side effects. Melanocortins could be a better approach for treating these disorders since they could preserve the benefits of the inflammatory response and at the same time prevent its harmful effects. In fact, α-MSH was suggested to be useful in the treatment of inflammatory experimental autoimmune encephalomyelitis (EAE), a T-cell mediated inflammatory autoimmune process that resembles the human demyelinating disease MS. Alterations in plasma concentrations of α-MSH were shown to occur during exacerbation of MS (Sandyk & Awerbuch, 1992). However, in cerebrospinal fluid of MS patients concentrations of α-MSH-like peptides were normal (Pinessi et al., 1992). Orally administered α-MSH can reduce signs of EAE and inhibit CNS inflammation by reducing Th1-cytokines released by CNS lymphocytes (Brod & Hood, 2011). Injection of α-MSH at the onset of EAE also profoundly diminished the severity of EAE in mice (Taylor & Kitaichi, 2008). Furthermore, it was shown that modified T- cells that express and release α-MSH reduce the signs of this disease when they are transferred into mice with EAE, suggesting the possibility of their use in future therapeutic applications (Han et al., 2007).

Astrocytes actions help neurons to perform their physiological functions and contribute to maintain brain homeostasis. They have both beneficial and damaging responses in the CNS. Astrocytes proliferate in response to trauma and provide an environment that can help neurons to survive injury. They are activated by pro-inflammatory agents or by injury and contribute to brain-repair processes, but when inflammation is chronic their sustained activation can have harmful effects. Astrogliosis was found to be present in neurodegenerative diseases (Maragakis & Rothstein, 2006). However, mice deficient in glial fibrillary acidic protein having consequently impaired astrocyte functions develop more severe EAE disease compared to wild type mice (Liedtke et al., 1998). Astrocytes are able to produce neurotrophic factors that can promote neuron survival. We recently showed that MC4R activation induces expression of BDNF in rat astrocytes (Caruso et al., 2011). BDNF has proved to be neuroprotective in AD, MS and PD (Nagahara & Tuszynski, 2011). Indeed, MS patients have decreased levels of BDNF compared to healthy controls (Frota et al., 2009). Therefore, BDNF is a possible mediator of melanocortin action in the brain. It is likely that melanocortins may induce neuroprotective genes such as Bcl-2 and BDNF, thereby contributing to ameliorate neurodegenerative diseases. However, much study is needed to prove this hypothesis.

5. Conclusions

Acute inflammatory response usually ends once the insult is eliminated and tissue is repaired. If this does not occur, inflammation becomes chronic, leading to harmful effects. Since local inflammation is necessary for pathogen clearance, tissue recovery and regeneration, ideal anti-inflammatory agents should prevent exacerbated immune reaction without completely eliminating inflammatory response. Thus, modulation rather than abolishment of inflammation seems to be the best option, and provides an opening to new treatment approaches in acute and chronic diseases of the CNS. Melanocortins are suitable candidates for this task. Their anti-inflammatory properties are well known and they also have neuroregenerative and neuroprotective properties that can help preserve neuron function. However, in view of the variety of effects produced by these peptides, we need to develop more selective and potent agonists for each receptor in order to avoid undesired side effects. Neurodegenerative diseases are tightly linked to chronic inflammation. The extent to which inflammatory mediators functionally impair cognition and memory is largely unknown. Astrocytes in particular might be especially attractive and underappreciated targets for neurodegenerative disease therapeutics. Finally, future studies need to determine the underlying mechanisms of inflammation that lead to neurodegeneration in order to advance towards the development of effective treatments for neurodegenerative diseases.

6. References

Abou-Mohamed, G.; Papapetropoulos, A.; Ulrich, D.; Catravas, J.D.; Tuttle, R.R. & Caldwell, R.W. (1995). HP-228, a novel synthetic peptide, inhibits the induction of nitric oxide synthase in vivo but not in vitro. J Pharmacol Exp Ther, Vol.275, No.2, (November 1995), pp. 584-591, ISSN 0022-3565.

Adan, R.A.; van der Kraan, M.; Doornbos, R.P.; Bar, P.R.; Burbach, J.P. & Gispen, W.H. (1996). Melanocortin receptors mediate α-MSH-induced stimulation of neurite outgrowth in neuro 2A cells. *Brain Res Mol Brain Res*, Vol.36, No.1, (February 1996), pp. 37-44, ISSN 0169-328X.

Ao, Y.; Park, H.Y.; Olaizola-Horn, S. & Gilchrest, B.A. (1998). Activation of cAMP-dependent protein kinase is required for optimal alpha-melanocyte-stimulating hormone-induced pigmentation. *Exp Cell Res*, Vol.244, No.1, (October 1998), pp. 117-124, ISSN 0014-4827.

Asanuma, M. & Miyazaki, I. (2008). Nonsteroidal anti-inflammatory drugs in experimental parkinsonian models and Parkinson's disease. *Curr Pharm Des*, Vol.14, No.14, pp. 1428-1434, ISSN 1381-6128.

Bagnol, D.; Lu, X.Y.; Kaelin, C.B.; Day, H.E.; Ollmann, M.; Gantz, I.; Akil, H.; Barsh, G.S. & Watson, S.J. (1999). Anatomy of an endogenous antagonist: relationship between Agouti-related protein and proopiomelanocortin in brain. *J Neurosci,* Vol.15, No.19, (September 1999), pp. RC26, ISSN 0270-6474.

Bazzani, C.; Guarini, S.; Botticelli, A.R.; Zaffe, D.; Tomasi, A.; Bini, A.; Cainazzo, M.M.; Ferrazza, G.; Mioni, C. & Bertolini, A. (2001). Protective effect of melanocortin peptides in rat myocardial ischemia. *J Pharmacol Exp Ther, Vol.*297, No.3, (June 2001), pp. 1082-1087, ISSN 0022-3565.

Bell, R.C. & Lipton, J.M. (1987). Pulsatile release of antipyretic neuropeptide alpha-MSH from septum of rabbit during fever. *Am J Physiol,* Vol.252, (June 1987), pp. R1152-R1157, ISSN 0002-9513.

Benjannet, S.; Rondeau, N.; Day, R.; Chrétien, M. & Sedah, N.G. (1991). PC1 and PC2 are protein convertases capable of cleaving proopiomelanocortin at distinct pairs of basic residues. *Proc Natl Acad Sci USA*, Vol.88, No.9, (May 1991), pp. 3564-3568, ISSN 0027-8424.

Benoit, S.C.; Schwartz, M.W.; Lachey, J.L.; Hagan, M.M.; Rushing, P.A.; Blake, K.A.; Yagaloff, K.A.; Kurylko, G.; Franco, L.; Danhoo, W. & Seeley, R.J. (2000). A novel selective melanocortin-4 receptor agonist reduces food intake in rats and mice without producing aversive consequences. *J Neurosci*, Vol.20, No.9, (May 2000), pp. 3442-3448, ISSN 0270-6474.

Bertagna, X.; Lenne, F.; Comar, D.; Massias, J.F.; Wajcman, H.; Baudin, V.; Luton, J.P. & Girard, F. (1986). Human beta-melanocyte-stimulating hormone revisited. *Proc Natl Acad Sci USA*, Vol.83, No.24, (December 1986), pp. 9719-9723, ISSN 0027-8424.

Bhardwaj, R.S., Schwarz, A., Becher, E., Mahnke, K., Aragane, Y., Schwarz, T. & Luger, T.A. (1996). Pro-opiomelanocortin-derived peptides induce IL-10 production in human monocytes. *J Immunol*, Vol.156, No.7, (April 1996), pp. 2517-2521, ISSN 0022-1767.

Bhardwaj, R.S.; Becher, E.; Mahnke, K.; Hartmayer, M.; Schwarz, T.; Scholzen, T. & Luger, T.A. (1997). Evidence for the differential expression of the functional alpha-melanocyte-stimulating hormone receptor MC-1 on human monocytes. *J Immunol*, Vol.158, No.7, (April 1997), pp. 3378-33884, ISSN 0022-1767.

Bicknell, A.B. (2008). The tissue-specific processing of pro-opiomelanocortin. *J Neuroendocrinol*, Vol.20, No.6, (June 2008), pp. 692-699, ISSN 0953-8194.

Bijlsma, W.A.; Schotman, P.; Jennekens, F.G.; Gispen, W.H. & De Wied, D. (1983). The enhanced recovery of sensorimotor function in rats is related to the melanotropic moiety of ACTH/MSH neuropeptides. *Eur J Pharmacol*, Vol.92, No.3-4, (September 1983), pp. 231-236, ISSN 0014-2999.

Bjartell, A.; Ekman, R. & Sundler, F. (1987). Gamma 2-[corrected]-MSH-like immunoreactivity in porcine pituitary and adrenal medulla. An immunochemical and immunocytochemical study. *Regul Pept*, Vol.19, No.5-6, (December 1987), pp. 291-306, ISSN 0167-0115.

Blanchard, S.G.; Harris, C.O.; Ittoop, O.R.; Nichols, J.S.; Parks, D.J.; Truesdale, A.T. & Wilkinson W.O. (1995). Agouti antagonism of melanocortin binding and action in the B16F10 murine melanoma cell line. *Biochemistry*, Vol.34, No.33, (August 1995), pp. 10406-10411, ISSN 0006-2960.

Böhm, M.; Schulte, U.; Kalden, H. & Luger, T.A. (1999). Alpha-melanocyte-stimulating hormone modulates activation of NF-kappa B and AP-1 and secretion of interleukin-8 in human dermal fibroblasts. *Ann NY Acad Sci*, Vol.885, (October 1999), pp. 277-286, ISSN 0077-8923.

Böhm, M.; Schiller, M.; Ständer, S.; Seltmann, H.; Li, Z.; Brzoska, T.; Metze, D.; Schiöth, H.B.; Skottner, A.; Seiffert, K.; Zouboulis, C.C. & Luger, T.A. (2002). Evidence for expression of melanocortin-1 receptor in human sebocytes in vitro and in situ. *J Invest Dermatol,* Vol.118, No.3, (March 2002), pp. 533-539, ISSN 0022-202X.

Boston, B.A. & Cone, R.D. (1996). Characterization of melanocortin receptor subtype expression in murine adipose tissues and in the 3T3-L1 cell line. *Endocrinology*, Vol.137, No.5, (May 1996), pp. 2043-2050, ISSN 0013-7227.

Brod, S.A. & Hood, Z.M. (2011). Ingested (oral) ACTH inhibits EAE. *J Neuroimmunol*, Vol.232, No.1-2, (March 2011), pp. 131-135, ISSN 0165-5728.

Bronstein, D.M.; Schafer, M.K.H.; Watson, S.J. & Akil H. (1992). Evidence that β-endorphin is synthesized in cells in the nucleus tractus solitarius: detection of POMC mRNA. *Brain Res*, Vol.587, No.2, (August 1992), pp. 269-275, ISSN 0006-8993.

Brzoska, T.; Luger, T.A.; Maaser, C.; Abels, C. & Böhm, M. (2008). α-Melanocyte-stimulating hormone and related tripeptides: biochemistry, anti-inflammatory and protective effects in vitro and in vivo, and future perspectives for the treatment of immune-mediated inflammatory diseases. *Endocrine Reviews*, Vol.29, No.5, (August 2008), pp. 581-602, ISSN 0163-769X.

Buggy, J. (1998). Binding of alpha-melanocyte-stimulating hormone to its G-protein-coupled receptor on B-lymphocytes activates the Jak/STAT pathway. *Biochemical J*, Vol.331, No.1, (April 1998), pp. 211-216, ISSN 0264-6021.

Cannon, J.G.; Tatro, J.B.; Reichlin, S. & Dinarello, C.A. (1986). α-Melanocyte stimulating hormone inhibits immunostimulatory and inflammatory actions of interleukin 1. *J Immunol,* Vol.137, No.7, (October 1986), pp. 2232-2236, ISSN 0022-1767.

Caruso, C.; Mohn, C.; Karara, A.L.; Rettori, V.; Watanobe, H.; Schiöth, H.B.; Seilicovich, A. &, Lasaga, M. (2004). Alpha-melanocyte-stimulating hormone through melanocortin-4 receptor inhibits nitric oxide synthase and cyclooxygenase expression in the hypothalamus of male rats. *Neuroendocrinology,* Vol.79, No.5, pp. 278-286, ISSN 0028-3835.

Caruso, C.; Durand, D.; Schiöth H.B.; Rey, R.; Seilicovich, A. & Lasaga, M. (2007). Activation of melanocortin 4 receptors reduces the inflammatory response and prevents apoptosis induced by lipopolysaccharide and interferon-gamma in astrocytes. *Endocrinology*, Vol.148, No.10, (October 2007), pp. 4918-4926, ISSN 0013-7227.

Caruso, C.; Sánchez, M.; Durand, D.; Pérez, M.C.; Lasaga, M. & Scimonelli, T. (2010). α-Melanocyte-stimulating hormone modulates lipopolysaccharide plus interferon-γ-induced tumor necrosis factor-α expression but not tumor necrosis factor-α receptor expression in cultured hypothalamic neurons. *J Neuroimmunol*, Vol.227, No.1-2, (October 2010), pp. 52-59, ISSN 0165-5728.

Caruso, C.; Carniglia, L.; Durand, D.; Gonzalez, P.V.; Scimonelli, T. & Lasaga, M. (2011). Melanocortin 4 receptor activation induces brain-derived neurotrophic factor expression in rat astrocytes through cyclic AMP - Protein kinase A pathway. *Mol Cell Endocrinol*, doi:10.1016/j.mce.2011.07.036, in press, ISSN 0303-7207.

Catania, A.; Suffredini, A.F. & Lipton, J.M. (1995). Endotoxin causes release of alpha-melanocyte-stimulating hormone in normal human subjects. *Neuroimmunomodulation*, Vol.2, No.5, (September-October 1995), pp. 258-262, ISSN 1021-7401.

Catania, A.; Rajora, N.; Capsoni, F.; Minonzio, F.; Star, R.A. & Lipton, J.M. (1996). The neuropeptide alpha-MSH has specific receptors on neutrophils and reduces chemotaxis in vitro. *Peptides*, Vol.17, No.4, pp. 675-679, ISSN 0196-9781.

Catania, A.; Airaghi, L.; Colombo, G. & Lipton, J.M. (2000). α-melanocyte-stimulating hormone in normal human physiology and disease states. *Trends Endocrinol Metab,* Vol.11, No.8, (October 2000), pp. 304-308, ISSN 1043-2760.

Catania, A.; Gatti, S.; Colombo, G. & Lipton, J.M. (2004). Targeting melanocortin receptors as a novel strategy to control inflammation. *Pharmacol Rev*, Vol.56, No.1, (March 2004), pp. 1-29, ISSN 0031-6997.

Catania, A.; Lonati, C.; Sordi, A.; Leonardi, P.; Carlin, A. & Gatti, S. (2010). The peptide NDP-MSH induces phenotype changes in the heart that resemble ischemic preconditioning. *Peptides*, Vol.31, No.1, (January 2010), pp. 116-122, ISSN 0196-9781.

Chai, B.; Li, J.Y.; Zhang, W.; Newman, E.; Ammori, J. & Mulholland, M.W. (2006). Melanocortin-4 receptor-mediated inhibition of apoptosis in immortalized hypothalamic neurons via mitogen-activated protein kinase. *Peptides*, Vol.27, No.11, (November 2006), pp. 2846-2857, ISSN 0196-9781.

Chai, B.; Li, J.Y.; Zhang, W., Ammori, J.B. & Mulholland, M.W. (2007). Melanocortin-3 receptor activates MAP kinase via PI3 kinase. *Regul Pept*, Vol.139, No.1-3, (March 2007), pp. 115-121, ISSN 0167-0115.

Chai, B.; Li, J.Y.; Zhang, W., Wu, X.; Zhang, C. & Mulholland, M.W. (2010). Melanocortin-4 receptor activation promotes insulin-stimulated mTOR signaling. *Peptides*, Vol.31, No.10, (October 2010), pp. 1888-1893, ISSN 0196-9781.

Chan, L.F.; Webb, T.R.; Chung, T.T.; Meimaridou, E.; Cooray, S.N.; Guasti, L.; Chapple, J.P.; Egertová, M.; Elphick, M.R.; Cheetham, M.E.; Metherell, L.A. & Clark, A.J. (2009). MRAP and MRAP2 are bidirectional regulators of the melanocortin receptor family. *Proc Natl Acad Sci U S A*, Vol.106, No.15, (April 2009), pp. 6146-6151, ISSN 0027-8424.

Chen, A.S.; Marsh, D.J.; Trumbauer, M.E.; Frazier, E.G.; Guan, X.M.; Yu, H.; Rosenblum, C.I.; Vongs, A.; Feng, Y.; Cao, L.; Metzger, J.M.; Strack, A.M.; Camacho, R.E.; Mellin, T.N.; Nunes, C.N.; Min, W.; Fisher, J.; Gopal-Truter, S.; MacIntyre, D.E.; Chen, H.Y. & Van der Ploeq, L.H. (2000). Inactivation of melanocortin type 3 receptor results in increased fat mass and reduced lean body mass. *Nat Genet*, Vol.26, No.1, (September 2000), pp. 97-102, ISSN 1061-4036.

Chen, W.; Kelly, M.A.; Opitz-Araya, X.; Thomas, R.E.; Low, M.J. & Cone R.D. (1997). Exocrine gland dysfunction in MC5-R-deficient mice: evidence for coordinated regulation of exocrine gland function by melanocortin peptides. *Cell*, Vol.91, No.6, (December 1997), pp. 789-798, ISSN 0092-8674.

Chhajlani, V. & Wikberg, J.E. (1992). Molecular cloning and expression of the human melanocyte stimulating hormone receptor cDNA. *FEBS Lett*, Vol.309, No.3, (September 1992), pp. 417-420, ISSN 0014-5793.

Chhajlani, V. (1996). Distribution of cDNA for melanocortin receptor subtypes in human tissues. *Biochem Mol Biol Int*, Vol.38, No.1, (February 1996), pp. 73-80, ISSN 1039-9712.

Chiao, H.; Foster, S.; Thomas, R.; Lipton, J. & Star, R.A. (1996). Alpha-melanocyte-stimulating hormone reduces endotoxin-induced liver inflammation. *J Clin Invest,* Vol.97, No.9, (May 1996), pp. 2038-2044, ISSN 0021-9738.

Chiao, H.; Kohda, Y.; McLeroy, P.; Craig, L.; Housini, I. & Star, R.A. (1997). Alpha-melanocyte-stimulating hormone protects against renal injury after ischemia in mice and rats. *J Clin Invest,*Vol.99, No.6, (March 1997), pp. 1165-1172, ISSN 0021-9738.

Cone, RD. (2005). Anatomy and regulation of the central melanocortin system. *Nat Neurosci*, Vol.8, No.5, (May 2005), pp. 571-578, ISSN 1097-6256.

Cooper, A.; Robinson, S.J.; Pickard C.; Jackson C.L.; Friedman P.S. & Healy E. (2005). Alpha-melanocyte-stimulating hormone suppresses antigen-induced lymphocyte proliferation in humans independently of melanocortin 1 receptor gene status. *J Immunol*, Vol.175, No.7, (October 2005), pp. 4806-4813, ISSN 0022-1767.

Cragnolini, A.B.; Perelló, M.; Schiöth, H.B. & Scimonelli, T.N. (2004). Alpha-MSH and gamma-MSH inhibit IL-1beta induced activation of the hypothalamic-pituitary-adrenal axis through central melanocortin receptors. *Regul Pept*, Vol.122, No.3, (November 2004), pp. 185-190, ISSN 0167-0115.

Cragnolini, A.; Caruso, C.; Lasaga, M. & Scimonelli, T.N. (2006). alpha-MSH and gamma-MSH modulate early release of hypothalamic PGE2 and NO induced by IL-1beta differently. *Neurosci Lett,* Vol.409, No.3, (December 2006), pp. 168-172, ISSN 0304-3940.

Cui, H.S.; Hayasaka, S.; Zhang, X.Y.; Chi, Z.L. & Hayasaka, Y. (2005). Effect of alpha-melanocyte-stimulating hormone on interleukin 8 and monocyte chemotactic protein 1 expression in a human epithelial cell line. *Ophthalmic Res*, Vol.37, No.5, (September-October 2005), pp. 279-288, ISSN 0030-3747.

Czyzyk, T.A.; Sikorski, M.A.; Yang, L. & McKnight, S. (2008). Disruption of the RIIβ subunit of PKA reverses the obesity syndrome of agouti lethal yellow mice. *Proc Natl Acad Sci U S A*, Vol.105, No.1, (January 2008), pp. 276-281, ISSN 0027-8424.

Daynes, R.A.; Robertson, B.A.; Cho, B.H.; Burnham, D.K. & Newton, R. (1987). Alpha-melanocyte-stimulating hormone exhibits target cell selectivity in its capacity to affect interleukin 1-inducible responses in vivo and in vitro. *J Immunol*, Vol.139, No.1, (July 1987), pp. 103-109, ISSN 0022-1767.

Delgado Hernandez, R.; Demitri, M.T.; Carlin, A.; Meazza, C.; Villa, P.; Ghezzi, P.; Lipton, J.M. & Catania, A. (1999). Inhibition of systemic inflammation by central action of the neuropeptide α-melanocyte-stimulating hormone. *Neuroimmunomodulation,* Vol.6, No.3, (May-June 1999), pp. 187-192, ISSN 1021-7401.

Delgado, R.; Carlin, A.; Airaghi, L.; Demitri, M.T.; Meda, L.; Galimberti, D.; Baron, P.; Lipton, J.M. & Catania, A. (1998). Melanocortin peptides inhibit production of proinflammatory cytokines and nitric oxide by activated microglia. *J Leukoc Biol*, Vol.63, No.6, (June 1998), pp. 740-745, ISSN 0741-5400.

Deng, J.; Xuzhen, H.; Yuen, P. & Star, R. (2004). α-Melanocyte-stimulating hormone inhibits lung injury after renal ischemia/reperfusion. *Am J Respir Crit Care Med,* Vol.169, No.6, (March 2004), pp. 749-756, ISSN 1073-449X.

Dinulescu, D.M. & Cone, R.D. (2000). Agouti and agouti-related protein: Analogies and contrasts. *J Biol Chem,* Vol.275, Nro.10, (March 2000), pp. 6695-6698, ISSN 0021-9258.

Elias, L.L., Huebner, A.; Pullinger, G.S.; Mirtella, A. & Clark, A.J. (1999). Functional characterization of naturally occurring mutations of the human adrenocorticotropin receptor: poor correlation of phenotype and genotype. *J Clin Endocrinol Metab*, Vol.84, No.8, (August 1999), pp. 2766-2770, ISSN 0021-972X.

Eves, P.; Haycock, J.; Layton, C.; Wagner, M.; Kemp, H.; Szabo, M.; Morandini, R.; Ghanem, G.; García-Borrón, J.C.; Jiménez-Cervantes, C. & Mac Neil, S. (2003). Anti-inflammatory and anti-invasive effects of alpha-melanocyte-stimulating hormone in human melanoma cells. *Br J Cancer*, Vol.89, No.10, (November 2003), pp. 2004-2015, ISSN 0007-0920.

Forslin Aronsson, A.; Spulber, S.; Popescu, L.M.; Winblad, B.; Post, C.; Oprica, M. & Schultzberg M. (2006). α-Melanocyte-stimulating hormone is neuroprotective in rat global cerebral ischemia. *Neuropeptides*, Vol.40, No.1, (February 2006), pp. 65-75, ISSN0143-4179.

Forslin Aronsson, A.; Spulber, S.; Oprica, M.; Winblad, B.; Post, C. & Schultzberg, M. (2007). α-MSH rescues neurons from excitotoxic cell death. *J Mol Neurosci*, Vol.33, No.3, pp. 239-251, ISSN 0895-8696.

Frota, E.R.; Rodrigues, D.H.; Donadi, E.A.; Brum, D.G.; Maciel, D.R. & Teixeira AL. (2009). Increased plasma levels of brain derived neurotrophic factor (BDNF) after multiple sclerosis relapse. *Neurosci Lett*, Vol.460, No.2, (August 2009), pp. 130-132, ISSN 0304-3940.

Galimberti, D.; Baron, P.; Meda, L.; Prat, E.; Scarpini, E.; Delgado, R.; Catania, A. & Lipton, J.M. (1999). α-MSH peptides inhibit production of nitric oxide and TNF-α by activated microglial cells activated with β-amyloid and interferon-γ. *Biochem Biophys Res Commun,* Vol.263, No.1, (September 1999), pp. 251-256, ISSN 0006-291X.

Gantz, I.; Konda, Y.; Tashiro, T.; Shimoto, Y.; Miwa, H.; Munzert, G.; Watson, S.J.; DelValle, J. & Yamada T. (1993). Molecular cloning of a novel melanocortin receptor. *J Biol Chem*, Vol.268, No.11, (April 1993), pp. 8246-8250, ISSN 0021-9258.

Gantz, I.; Shimoto, Y.; Konda, Y.; Miwa, H.; Dickinson, C.J. & Yamada, T. (1994). Molecular cloning, expression, and characterization of a fifth melanocortin receptor. *Biochem Biophys Res Commun*, Vol.200, No.3, (May 1994), pp. 1214-1220, ISSN 0006-291X.

Gatti, S.; Carlin, A.; Sordi, A.; Leonardi, P.; Colombo, G.; Fassati, L.R.; Lipton, J.M. & Catania, A. (2006). Inhibitory effects of the peptide (CKPV)2 on endotoxin-induced host reactions. *J Surg Res*, Vol.131, No.2, (April 2006), pp. 209-214, ISSN 0022-4804.

Getting, S.J; Gibbs, L.; Clark, A.J.; Flower, R.J. & Perretti, M. (1999). POMC Gene-Derived Peptides Activate Melanocortin Type 3 Receptor on Murine Macrophages, Suppress Cytokine Release, and Inhibit Neutrophil Migration in Acute Experimental Inflammation. *J Immunol*, Vol.162, No.12, (June 1999), pp. 7446-7453, ISSN 0022-1767.

Getting, S.J.; Lam, C.W.; Leoni, G.; Gavins, F.N.; Grieco, P. & Perretti, M. (2006). [D-Trp8]-gamma-melanocyte-stimulating hormone exhibits anti-inflammatory efficacy in mice bearing a nonfunctional MC1R (recessive yellow e/e mouse). *Mol Pharmacol*, Vol.70, No.6, (December 2006), pp. 1850-1855, ISSN 0026-895X.

Getting, S.J.; Riffo-Vasquez, Y.; Pitchford, S.; Kaneva, M.; Grieco, P.; Page, C.P.; Perretti, M. & Spina, D. (2008). A role for MC3R in modulating lung inflammation. *Pulm Pharmacol Ther*, Vol.21, Nro.6, (December 2008), pp. 866-873, ISSN 1094-5539.

Gibson, S.; Crosby, S.R.; Stewart, M.F.; Jennings, A.M.; McCall, E. & White, A. (1994). Differential release of proopiomelanocortin-derived peptides from the human pituitary: evidence from a panel of two-site immunoradiometric assays. *J Clin Endocrinol Metab*, Vol.78, No.4, (April 1994), pp. 835-841, ISSN 0021-972X.

Giuliani, D.; Mioni, C.; Altavilla, D.; Leone, S.; Bazzani, C.; Minutoli, L.; Bitto, A.; Cainazzo, M.; Marini, H.; Zaffe, D.; Botticelli, A.; Pizzala, R.; Savio, M.; Necchi, D.; Schioth, H.B.; Bertolini, A.; Squadrito, F. & Guarini, S. (2006). Both early and delayed treatment with melanocortin 4 receptor-stimulating melanocortins produces neuroprotection in cerebral ischemia. *Endocrinology*, Vol.147, No.3, (March 2006), pp. 1126-1135, ISSN 0013-7227.

Giuliani, D.;Ottani, A.; Mioni, C.; Bazzani, C.;Galantucci, M.; Minutoli, L.; Bitto, A.; Zaffe, D.; Botticelli, A.R.; Squadrito, F. & Guarini, S. (2007a). Neuroprotection in focal cerebral ischemia owing to delayed treatment with melanocortins. *Eur J Pharmacol*, Vol.570, No.1-3, (September 2007), pp. 57-65, ISSN 0014-2999.

Giuliani, D.; Mioni, C.; Bazzani, C.; Zaffe, D.; Botticelli, A.R.; Capolongo, S.; Sabba, A. Galantucci, M.; Iannone, A.; Grieco, P.; Novellino, E.; Colombo, G.; Tomasi, A.; Catania, A. & Guarini, S. (2007b). Selective melanocortin MC4 receptor agonists reverse haemorrhagic shock and prevent multiple organ damage. *Br J Pharmacol*, Vol.150, No.5, (March 2007), pp. 595-603, ISSN 0007-1188.

Giuliani, D.; Ottani, A.; Minutoli, L.; Stefano, V.D.; Galantucci, M.; Bitto, A.; Zaffe, D.; Altavilla, D.; Botticelli, A.R.; Squadrito, F. & Guarini, S. (2009). Functional recovery after delayed treatment of ischemic stroke with melanocortins is associated with overexpression of the activity-dependent gene Zif268. *Brain Behav Immun*, Vol.23, No.6, (August 2009), pp. 844-850, ISSN 0889-1591.

Gonindard, C.; Goigoux, C.; Hollande, E. & D'Hinterland, L.D. (1996). The Administration of an α-MSH Analogue Reduces the Serum Release of IL-1α and TNFα Induced by the Injection of a Sublethal Dose of Lipopolysaccharides in the BALB/c Mouse. *Pigment Cell Res*, Vol.9, No.3, (June 1996), pp. 148-153, ISSN 0893-5785.

Gonzalez, P.V.; Schiöth, H.B.; Lasaga, M. & Scimonelli, T.N. (2009). Memory impairment induced by IL-1beta is reversed by alpha-MSH through central melanocortin-4 receptors. *Brain Behav Immun*, Vol.23, No.6, (Aug 2009), pp. 817-822, ISSN 0889-1591.

Grabbe, S.; Bhardwaj, R.S.; Mahnke, K.; Simon, M.M.; Schwarz, T. & Luger, T.A. (1996). Alpha-melanocyte-stimulating hormone induces hapten-specific tolerance in mice. *J Immunol*, Vol.156, No.2, (January 1996), pp. 473-478, ISSN 0022-1767.

Griffon, N.; Mignon, V.; Facchinetti, P.; Diaz, J.; Schwartz, J.C. & Sokoloff, P. (1994). Molecular cloning and characterization of the rat fifth melanocortin receptor. *Biochem Biophys Res Commun*, Vol.200, No.2, (April 1994), pp. 1007-1014, ISSN 0006-291X.

Guarini, S.; Schiöth, H.B.; Mioni, C.; Cainazzo, M.; Ferraza, G.; Giuliani, D.; Wikberg, J.E.; Bertoni, A. & Bazzani, C. (2002). MC(3) receptors are involved in the protective effect of melanocortins in myocardial ischemia/reperfusion-induced arrhythmias. *Naunyn Schmiedeberg's Arch Pharmacol*, Vol.366, No.2, (August 2002), pp. 177-182, ISSN 0028-1298.

Han, D.; Tian, Y.; Zhang, M.; Zhou, Z. & Lu, J. (2007). Prevention and treatment of experimental autoimmune encephalomyelitis with recombinant adeno-associated virus-mediated alpha-melanocyte-stimulating hormone-transduced PLP139-151-specific T cells. *Gene Ther, Vol.*14, No.5, (March 2007), pp. 383-395, ISSN 0969-7128.

Hartmeyer, M.; Scholzen, T.; Becher, E.; Bhardwaj, R.S.; Schwarz, T. & Luger, T.A. (1997). Human dermal microvascular endothelial cells express the melanocortin receptor type 1 and produce increased levels IL-8 upon stimulation with α-melanocyte-stimulating hormone. *J Immunol*, Vol.159, No.4, (August 1997), pp. 1930-1937, ISSN 0022-1767.

Haskell-Luevano, C. & Monek, E.K. (2001). Agouti-related protein functions as an inverse agonist at a constitutively active brain melanocortin-4 receptor. *Regul Pept*, Vol.99, No.1, (May 2001), pp. 1-7, ISSN 0167-0115.

He, L.; Gunn, T.M.; Bouley, D.M.; Lu, X.Y.; Watson, S.J.; Schlossman, S.F.; Duke-Cohan, J.S. & Barsh, G.S. (2001). A biochemical function for attractin in agouti-induced pigmentation and obesity. *Nat Genet*, Vol.27, No.1, (January 2001), pp. 40-47, ISSN 1061-4036.

Herraiz, C.; Journé, F.; Abdel-Malek, Z.; Ghanem, G.; Jiménez-Cervantes, C. & García-Borrón, J.C. (2011). Signaling from the human melanocortin 1 receptor to ERK1 and ERK2 mitogen-activated protein kinases involves transactivation of cKIT. *Mol Endocrinol*, Vol.25, No.1, (January 2011), pp. 138-156, ISSN 0888-8809.

Huang, Q.H.; Entwistle, M.L.; Alvaro, J.D.; Duman, R.S.; Hruby, V.J. & Tatro, J.B. (1997). Antipyretic role of endogenous melanocortins mediated by central melanocortin receptors during endotoxin-induced fever. *J Neurosci,* Vol.17, No.9, (May 1997), pp. 3343-3351, ISSN 0270-6474.

Huang, Q.H.; Hruby, V.J. & Tatro, J.B. (1998). Systemic α-MSH suppresses LPS fever via central melanocortin receptors independently of its suppression of corticosterone and IL-6 release. *Am J Physiol,* Vol.275, No.2Pt2, (August 1998), pp. R524-R530, ISSN 0002-9513.

Huang, Q. & Tatro, J.B. (2002). Alpha-MSH suppress intracerebral tumor necrosis factor-α and interleukin-1β gene expression following transient cerebral ischemia in mice. *Neurosci Lett,* Vol.334, No.3, (December 2002), pp. 186-190, ISSN 0304-3940.

Huszar, D.; Lynch, C.A.; Fairchild-Huntress, V.; Dunmore, J.H.; Fang, Q.; Berkemeier, L.R.; Gu, W.; Kesterson, R.A.; Boston, B.A. & Cone, R.D. (1997). Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell*, Vol.88, No.1, (January 1997), pp. 131-141, ISSN 0092-8674.

Ichiyama, T.; Sakai, T.; Catania, A.; Barsh, G.S.; Furukawa, S. & Lipton, J.M. (1999). Systemically administered α-melanocyte-stimulating peptides inhibit NF-kappaB activation in experimental brain inflammation. *Brain Res,* Vol.836, No.1-2, (July 1999), pp. 31-37, ISSN 0006-8993.

Isales, C.M.; Zaidi. M. & Blair, H.C. (2010). ACTH is a novel regulator of bone mass. *Ann N Y Acad Sci*, Vol.1192, (March 2010), pp. 110-116, ISSN 0077-8923.

Jégou, S.; Boutelet, I. & Vaudry, H. (2000). Melanocortin-3 receptor mRNA expression in pro-opiomelanocortin neurones of the rat arcuate nucleus. *J Neuroendocrinol*, Vol.12, Nro.6, (June 2000), pp. 501-505, ISSN 0953-8194.

Joosten, E.A.; Majewska, B.; Houweling, D.A.; Bar, P.R. & Gispen W.H. (1999). Alpha-melanocyte stimulating hormone promotes regrowth of injured axons in the adult rat spinal cord. *J Neurotrauma*, Vol.16, No.6, (June 1999), pp. 543-553, ISSN 0897-7151.

Kask, A.; Mutulis, F.; Muceniece, R.; Pähkla, R.; Mutule, I.; Wikberg, J.S.; Rägo, L. & Schiöth H.B. (1998). Discovery of a novel superpotent and selective melanocortin 4 receptor antagonist (HS024): Evaluation in vitro and in vivo. *Endocrinology*, Vol.139, No.12, (December 1998), pp. 5006-5014, ISSN 0013-7227.

Katsuura, G.; Gottschall, P.E.; Dahl, R.R. & Arimura, A. (1989). Interleukin-1 beta increases prostaglandin E2 in rat astrocyte cultures: modulatory effect of neuropeptides. *Endocrinology,* Vol.124, No.6, (June 1989), pp. 3125-3127, ISSN0013-7227.

Kawai, Y.; Inagaki, S.; Shiosaka, S.; Shibasaki, T.; Ling, N.; Tohyama, M. & Shiotani, Y. (1984). The distribution and projection of gamma-melanocyte stimulating hormone in the rat brain: an immunohistochemical analysis. *Brain Res*, Vol.29, No.1, (April 1984), pp. 21-32, ISSN 0006-8993.

Kennedy, C.; ter Huurne, J.; Berkhout, M.; Gruis, N.; Bastiaens, M.; Bergman, W.; Willemze, R. & Bavinck, J.N. (2001). Melanocortin 1 receptor (MC1R) gene variants are associated with an increased risk for cutaneous melanoma which is largely independent of skin type and hair color. *J Invest Dermatol*, Vol.117, No.2, (August 2001), pp. 294-300, ISSN 0022-202X.

Kannengiesser, K.; Maaser, C.; Heidemann, J.; Luegering, A.; Ross, M.; Brzoska, T.; Böhm, M.; Luger, T.A.; Domschke, W. & Kucharzik, T. (2008). Melanocortin-derived tripeptide KPV has anti-inflammatory potential in murine models of inflammatory bowel disease. *Inflamm Bowel Dis*, Vol.14, No.3, (March 2008), pp. 324-331, ISSN 1078-0998.

Konda, Y.; Gantz, I.; Del Valle, J.; Shimoto, Y.; Miwa, H. & Yamada, T. (1994). Interaction of dual intracellular signaling pathways activated by the melanocortin-3 receptor. *J Biol Chem*, Vol. 269, No.18, (May 1994), pp. 13162-13166, ISSN 0021-9258.

Krude, H.; Biebermann, H.; Luck, W.; Horn, R.; Brabant, G. & Grüters, A. (1998). Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet*, Vol.19, No.2, (June 1998), pp. 155-157, ISSN 1061-4036.

Labbé, O.; Desarnaud, F.; Eggerickx, D.; Vassart, G. & Parmentier, M. (1994). Molecular cloning of a mouse melanocortin 5 receptor gene widely expressed in peripheral tissues. *Biochemistry*, Vol.33, No.15, (April 1994), pp. 4543-4549, ISSN 0006-2960.

Lam, C.W.; Getting, S.J. & Perretti, M. (2005). In vitro and in vivo induction of heme oxygenase 1 in mouse macrophages following melanocortin receptor activation. *J Immunol*, Vol.174, No.4, (February 2005), pp. 2297-2304, ISSN 0022-1767.

Langouche, L.; Pals, K. & Denef, C. (2002). Structure–activity relationship and signal transduction of γ-MSH peptides in GH3 cells: further evidence for a new melanocortin receptor. *Peptides*, Vol.23, No.6, (June 2002), pp. 1077-1086, ISSN 0196-9781.

Lasaga, M.; Debeljuk, L.; Durand, D.; Scimonelli, T.N. & Caruso, C. (2008). Role of alpha-melanocyte stimulating hormone and melanocortin 4 receptor in brain inflammation. *Peptides*, Vol.29, No.10, (October 2008), pp. 1825-1835, ISSN 0196-9781.

Lee, D.J.; Biros, D.J. & Taylor, A.W. (2009). Injection of an alpha-melanocyte stimulating hormone expression plasmid is effective in suppressing experimental autoimmune uveitis. *Int Immunopharmacol*, Vol.9, No.9, (August 2009), pp. 1079-1086, ISSN 1567-5769.

Leoni, G.; Voisin, M.B.; Carlson, K.; Getting, S.; Nourshargh, S. & Perretti, M. (2010). The melanocortin MC(1) receptor agonist BMS-470539 inhibits leucocyte trafficking in the inflamed vasculature. *Br J Pharmacol*, Vol.160, No.1, (May 2010), pp. 171-180, ISSN 0007-1188.

Li, Q. & Verma, I.M. (2002). NF-kappaB regulation in the immune system. *Nat Rev Immunol,* Vol.2, No.10, (October 2002), pp. 725-734, ISSN 1474-1733.

Liakos, P.; Chambaz, E.M.; Feige, J.J. & Defaye, G. (1998). Expression of ACTH receptors (MC2-R and MC5-R) in the glomerulosa and the fasciculata-reticularis zones of bovine adrenal cortex. *Endocr Res*, Vol.24, No.3-4, (Aug-Nov 1998), pp. 427-432, ISSN 0743-5800.

Liedtke, W.; Edelman, W.; Chiu, F-C.; Kucherlapati, R. & Raine, C. (1998). Experimental autoinmune encephalomyelitis in mice lacking glial fibrillary acidic protein is characterized by a more severe clinical course and an infiltrative central nervous system lesion. *Am J Pathol*, Vol.152, No.1, (January 1998), pp. 251-259, ISSN 0002-9440.

Lin, S.Y.; Chaves, C.; Wiedemann, E. & Humphreys, M.H. (1987). A γ-melanocyte stimulating hormone-like peptide causes reflex natriuresis after acute unilateral nephrectomy. *Hypertension*, Vol.10, No.6, (December 1987), pp. 619-627, ISSN 0194-911X.

Lindberg, C.; Hjorth, E.; Post, C.; Winblad, B. & Schultzberg, M. (2005). Cytokine production by a human microglial cell line: effects of β-amyloid and α-melanocyte-stimulating hormone. *Neurotox Res*, Vol.8, No.3-4, (November 2005), pp. 267-276, ISSN 1029-8428.

Lipton, J.M.; Ceriani, G.; Macaluso, A.; McCoy, D.; Carnes, K.; Biltz, J. & Catania, A. (1994). Anti-inflammatory effects of the neuropeptide α-MSH in acute, chronic and systemic inflammation. *Ann NY Acad Sci*, Vol.741, (November 1994), pp. 137-148, ISSN 0077-8923.

Lipton, J.M.; Zhao, H.; Ichiyama, T.; Barsh, G.S. & Catania, A. (1999). Mechanism of antiinflammatory action of α-MSH peptides: in vivo and in vitro evidence. *Ann NY Acad Sci,* Vol.885, (October 1999), pp. 173-182, ISSN 0077-8923.

Luger, T.A.; Scholzen, T.E.; Brzoska, T. & Böhm, M. (2003). New insights into the functions of alpha-MSH and related peptides in the immune system. *Ann NY Acad Sci*, Vol.994, (June 2003), pp. 133-140, ISSN 0077-8923.

Machado, I.; González, P.; Schiöth, H.B.; Lasaga, M. & Scimonelli, T.N. (2010). α-Melanocyte-stimulating hormone (α-MSH) reverses impairment of memory reconsolidation induced by interleukin-1 beta (IL-1 beta) hippocampal infusions. *Peptides*, Vol.31, No.11, (November 2010), pp. 2141-2144, ISSN 0196-9781.

Manna, S.K. & Aggarwal, B.B. (1998). Alpha-melanocyte-stimulating hormone inhibits the nuclear transcription factor NF-kappa B activation induced by various inflammatory agents. *J Immunol,* Vol.161, No.6, (September 1998), pp. 2873-2880, ISSN 0022-1767.

Manna, S.K.; Sarkar, A. & Sreenivasan, Y. (2006). Alpha-melanocyte-stimulating hormone down-regulates CXC receptors through activation of neutrophil elastase. *Eur J Immunol,* Vol.36, No.3, (March 2006), pp. 754-769, ISSN 0014-2980.

Mandrika, I.; Muceniece, R. & Wikberg, J.E. (2001). Effects of melanocortin peptides on lipopolysaccharide/interferon-gamma-induced NF-kappaB DNA binding and nitric oxide production in macrophage-like RAW 264.7 cells: evidence for dual mechanisms of action. *Biochem Pharmacol,* Vol.61, No.5, (March 2001), pp. 613-621, ISSN 0006-2952.

Maragakis, N.J. & Rothstein, J.D. (2006). Mechanism of disease: astrocytes in neurodegenerative disease. *Nat Clin Pract Neurol*, Vol.2, No.12, (December 2006), pp. 679-689, ISSN 1745-834X.

Marsh, D.J.; Hollopeter, G.; Huszar, D.; Laufer, R.; Yagaloff, K.A.; Fisher, S.L.; Burn, P. & Palmiter, R.D. (1999). Response of melanocortin-4 receptor-deficient mice to anorectic and orexigenic peptides. *Nat Genet*, Vol.21, No.1, (January 1999), pp. 119-122, ISSN 1061-4036.

Martin, L.W.; Catania, A.; Hiltz, M.E. & Lipton, J.M. (1991). Neuropeptide α-MSH antagonizes IL-6 and TNF-induced fever. *Peptides,* Vol.12, No.2, (March-April 1991), pp. 119-122, ISSN 0196-9781.

Mastrofrancesco, A.; Kokot, A.; Eberle, A.; Gibbons, N.C.; Schallreuter, K.U.; Strozyk, E.; Picardo, M.; Zouboulis, C.C.; Luger, T.A. & Böhm, M. (2010). KdPT, a tripeptide derivative of alpha-melanocyte-stimulating hormone, suppresses IL-1 beta-mediated cytokine expression and signaling in human sebocytes. *J Immunol*, Vol.185, No.3, (August 2010), pp. 1903-1911, ISSN 0022-1767.

McGeer, P.L. & McGeer, E.G. (2007). NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. *Neurobiol Aging*, Vol.28, No.5, (May 2007), pp. 639-647, ISSN 0197-4580.

Metherell, L.A.; Chapple, J.P.; Cooray, S.;David, A.; Becker, C.; Rüschendorf, F.; Naville, D.; Begeot, M.; Khoo, B.; Nürnberg, P.; Huebner, A.; Cheetham, M.E. & Clark, A.J. (2005). Mutations in MRAP, encoding a new interacting partner of the ACTH receptor, cause familial glucocorticoid deficiency type 2. *Nat Genet*, Vol.37, No.2, (February 2005), pp. 166-170, ISSN 1061-4036.

Miller, M.W.; Duhl, D.M.; Vrieling, H.; Cordes, S.P.; Ollman, M.M.; Winkes, B.M. & Barsh G.S. (1993). Cloning of the mouse agouti gene predicts a secreted protein ubiquitously expressed in mice carrying the lethal yellow mutation. *Genes Dev*, Vol.7, No.3, (March 1993), pp. 454-467, ISSN 0890-9369.

Minutoli, L. ; Squadrito, F. ; Nicotina, P.A. ; Giuliani, D. ; Ottani, A. ; Polito, F. ; Bitto, A. ; Irrera, N. ; Guzzo, G. ; Spaccapelo, L. ; Fazzari, C. ; Macrì, A. ; Marini, H. ; Guarini, S. & Altavilla, D. (2011). Melanocortin 4 receptor stimulation decreases pancreatitis severity in rats by activation of the cholinergic anti-inflammatory pathway. *Crit Care Med*, Vol.162, No.4, (February 2011), pp. 917-928, ISSN 0090-3493.

Mirtella, A.; Tringali, G.; Guerriero, G.; Ghiara, P.; Parente, L.; Preziosi, P. & Navarra, P. (1995). Evidence that the interleukin-1 beta-induced prostaglandin E2 release from rat hypothalamus is mediated by type I and type II interleukin-1 receptors. *J Neuroimmunol*, Vol.61, No.2, (September 1995), pp. 171-177, ISSN 0165-5728.

Mountjoy, K.; Robbins, L.; Mortrud, L. & Cone, R.D. (1992). The cloning of a family of genes that encode the melanocortin receptors. *Science*, Vol.257, No.5074, (August 1992), pp. 1248-1251, ISSN 0036-8075.

Mountjoy, K.; Mortrud, L.; Low, M.J.; Simerkly, R.B. & Cone, R.D. (1994). Localization of the melanocortin-4 receptor (MC4-R) in neuroendocrine and autonomic control circuits in the brain. *Mol Endocrinol*, Vol.8, No.10, (October 1994), pp. 1298-1308, ISSN 0888-8809.

Muceniece, R.; Zvejniece, L.; Kirjanova, O.; Liepinsh, E.; Krigere, L.; Baumane, L.; Kalvinsh, I.; Wikberg, J.E. & Dambrova, M. (2004). Beta- and gamma-melanocortins inhibit lipopolysaccharide induced nitric oxide production in mice brain. *Brain Res*, Vol.995, No.1, (January 2004), pp. 7-13, ISSN 0006-8993.

Muceniece, R.; Zvejniece, L.; Vilskersts, R.; Liepinsh, E.; Baumane, L.; Kalvinsh, I.; Wikberg, J.E. & Dambrova, M. (2007). Functional evaluation of THIQ, a melanocortin 4 receptor agonist, in models of food intake and inflammation. *Basic Clin Pharmacol Toxicol*, Vol.101, No.6, (December 2007), pp. 416-420, ISSN 1742-7835.

Muffley, L.A.; Zhu, Q.K.; Engray, L.H.; Gibran, N.S. & Hocking, A.M. (2011). Spatial and temporal localization of the melanocortin 1 receptor and its ligand α-melanocyte-stimulating hormone during cutaneous wound repair. *J Histochem Cytochem*, Vol.59., No.3, (March 2011), pp. 278-288, ISSN 0022-1554.

Murphy, M.T.; Richards, D.B. & Lipton, J.M. (1983). Antipyretic potency of centrally administered alpha-melanocyte stimulating hormone. *Science*, Vol.221, No.4606, (July 1983), pp. 192-193, ISSN 0036-8075.

Nagahara, A.H. & Tuszynski, M.H. (2011). Potential therapeutic uses of BDNF in neurological and psychiatric disorders. *Nat Rev Drug Discov*, Vol.10, No.3, (March 2011), pp. 209-219, ISSN 1474-1776.

Newman, E.A.; Chai, B.X.; Zhang, W.; Li, J.Y.; Ammori, J.B. & Mulholland, M.W. (2006). Activation of the melanocortin-4 receptor mobilizes intracellular free calcium in immortalized hypothalamic neuron. *J Surg Res*, Vol.132, No.2, (May 2006), pp. 201-2077, ISSN 0022-4804.

Nicolaou, A.; Estdale, S.E.; Tsatmali, M.; Herrero, D.P. & Thody, A.J. (2004). Prostaglandin production by melanocytic cells and the effect of alpha-melanocyte stimulating hormone. *FEBS Lett,* Vol.570, No.1-3, (July 2004), pp. 223-226, ISSN 0014-5793.

O´Donohue, T.L. & Dorsa, D.M. (1982). The opiomelanotropinergic neuronal and endocrine systems. *Peptides*, Vol. 3, Nro.3, (May-June 1982), pp. 353-395, ISSN 0196-9781.

Ollman, M.M.; Wilson, B.D.; Yang, Y.K.; Kerns, J.A.; Chen, Y.; Gantz, I. & Barsh, G.S. (1997). Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein. *Science*, Vol.278, No.5335, (October 1997), pp. 135-138, ISSN 0036-8075.

Patten, C.S.; Daniels, D.; Suzuki, A.; Fluharty, S.J. & Yee, D.K. (2007). Structural and signaling requirements of the human melanocortin 4 receptor for MAP kinase activation. *Regul Pept*, Vol.142, No.3, (August 2007), pp. 111-122, ISSN 0167-0115.

Pérez-Oliva, A.B.; Olivares, C.; Jiménez-Cervantes, C. & García-Borrón, J.C. (2009). Mahogunin ring finger-1 (MGRN1) E3 ubiquitin ligase inhibits signaling from melanocortin receptor by competition with Galphas. *J Biol Chem*, Vol.284, No.46, (November 2009), pp. 31714-31725, ISSN 0021-9258.

Pinessi, L.; Rainero, I.; de Gennaro, T.; Violante, A.; Cassano, D.; Matera, L. & Cesano, A. (1992). Cerebrospinal fluid and plasma concentrations of POMC-related peptides in multiple sclerosis. *Ann N Y Acad Sci*, Vol.650, (April 1992), pp. 351-354, ISSN 0077-8923.

Plantinga, L.C.; Verhaagen, J.; Edwards, P.M.; Hali, M.; Brakkee, J.H. & Gispen, W.H. (1995). Pharmacological evidence for the involvement of endogenous alpha-MSH-like peptides in peripheral nerve regeneration. *Peptides*, Vol.16, pp. 319-324, ISSN 0196-9781.

Raap, U.; Brzoska, T.; Sohl, S.; Päth, G.; Emmel, J.; Herz, U.; Braun, A.; Luger, T. & Renz, H. (2003). Alpha-melanocyte-stimulating hormone inhibits allergic airway inflammation. *J Immunol,* Vol.171, No.1, (July 2003), pp. 353-359, ISSN 0022-1767.

Rajora, N.; Boccoli, G.; Burns, D.; Sharma, S.; Catania, A. & Lipton, J.M. (1997a). α-MSH modulates local and circulating tumor necrosis factor-α in experimental brain inflammation. *J Neurosci*, Vol.17, No.6, (March 1997), pp. 2181-2186, ISSN 0270-6474.

Rajora, N.; Boccoli, G.; Catania, A. & Lipton, J.M. (1997b). α-MSH modulates experimental inflammatory bowel disease. *Peptides*, Vol.18, No.3, pp. 381-385, ISSN 0196-9781.

Redondo, P.; Garcia-Foncillas, J.; Okroujnov, I. & Bandrés, E. (1998). α-MSH regulates interleukin-10 expression by human keratinocytes. *Arch Dermatol Res*, Vol.290, No.8, (August 1998), pp. 425-428, ISSN 0340-3696.

Reizes, O.; Benoit, S.C.; Strader, A.D.; Clegg, D.J.; Akunuru, S. & Seeley, R.J. (2003). Syndecan-3 modulates food intake by interacting with the melanocortin/AgRP pathway. *Ann N Y Acad Sci*, Vol.994, (June 2003), pp. 66-73, ISSN 0077-8923.

Rodrigues, A.R.; Pignatelli, D.; Almeida, H. & Gouveia, A.M. (2009). Melanocortin 5 receptor activates ERK1/2 through a PI3K-regulated signalling mechanism. *Mol Cell Endocrinol*, Vol.303, No.1-2, (May 2009), pp. 74-81, ISSN 0303-7207.

Roselli-Rehfuss, L.; Mountjoy, K.; Robbins, L.; Mortrud, L.; Low, M.; Tatro, J.; Entwistle M.; Simerly, R. & Cone, R. D. (1993). Identification of a receptor for γ melanotropin and other proopiomelanocortin peptides in the hypothalamus and limbic system. *Proc Natl Acad Sci USA*, Vol.90, No.19, (October 1993), pp. 8856-8860, ISSN 0027-8424.

Roy, S.; Rached, M. & Gallo-Payet, N. (2007). Differential regulation of the human adrenocorticotropin receptor [melanocortin-2 receptor (MC2R)] by human MC2R accessory protein isoforms alpha and beta in isogenic human embryonic kidney 293 cells. *Mol Endocrinology*, Vol.21, No.7, (July 2007), pp. 1656-1669, ISSN 0888-8809.

Roy, S.; Pinard, S.; Chouinard, L. & Gallo-Payet, N. (2011). Adrenocorticotropin hormone (ACTH) effects on MAPK phosphorylation in human fasciculata cells and in embryonic kidney 293 cells expressing human melanocortin 2 receptor (MC2R) and MC2R accessory protein (MRAP)β. *Mol Cell Endocrinol*, Vol.336, No.1-2, (April 2011), pp 31-40, ISSN 0303-7207.

Sabat, R.; Grütz, G.; Warszawska, K.; Kirsch, S.; Witte, E.; Wolk, K. & Geginat, J. (2010). Biology of interleukin-10. *Cytokine Growth Factor Rev,* Vol.21, No.5, (October 2010), pp. 331-344, ISSN 1359-6101.

Sandyk, R. & Awerbuch, G.I. (1992). Nocturnal plasma melatonin and alpha-melanocyte stimulating hormone levels during exacerbation of multiple sclerosis. *Int J Neurosci*, Vol.67, No.1-4, (November-December 1992), pp. 173-186, ISSN 0020-7454.

Sarkar, A.; Sreenivasan, Y. & Manna, S.K. (2003). Alpha-melanocyte-stimulating hormone induces cell death in mast cells: involvement of NF-kappa B. *FEBS Lett*, Vol.549, No.1-3, (August 2003), pp. 87-93, ISSN 0014-5793.

Sarkar, S.; Légradi, G. & Lechan, R.M. (2002). Intracerebroventricular of alpha-melanocyte stimulating hormone increases phosphorylation of CREB in TRH- and CRH-neurons of the hypothalamic paraventricular nucleus. *Brain Res*, Vol.945, No.1, (July 2002), pp. 50-59, ISSN 0006-8993.

Sawyer, T.K.; Sanfilippo, P.J.; Hruby, V.J.; Engel, M.H.; Heward, C.B.; Burnett, J.B. & Hadley, M.E. (1980). 4-Norleucine, 7-D-phenylalanine-alpha-melanocyte-stimulating hormone: a highly potent alpha-melanotropin with ultralong biological activity. *Proc Natl Acad Sci USA*, Vol.77, No.10, (October 1980), pp. 5754-5758, ISSN 0027-8424.

Schiöth, H.B.; Chhajlani, V.; Muceniece, R.; Klusa, V. & Wikberg, J.E. (1996). Major pharmacological distinction of the ACTH receptor from other melanocortin receptors. *Life Sci*, Vol.59, No.10, pp. 797-801, ISSN 0024-3205.

Schiöth, H.B.; Muceniece, R.; Mutulis, F.; Bouifrouri, A.A.; Mutule, I. & Wikberg, J.E. (1999). Further pharmacological characterization of the selective melanocortin 4 receptor antagonist HS014: comparison with SHU9119. *Neuropeptides*, Vol.33, No.3, (June 1999), pp. 191-196, ISSN 0143-4179.

Scholzen, T.E.; Sunderkötter, C.; Kalden, D.H.; Brzoska, T.; Fastrich, M.; Fisbeck, T.; Armstrong, C.A.; Ansel, J.C. & Luger, T.A. (2003). Alpha-melanocyte stimulating hormone prevents lipopolysaccharide-induced vasculitis by down-regulating endothelial cell adhesion molecule expression. *Endocrinology*, Vol.144, No.1, (January 2003), pp. 360-370, ISSN 0013-7227.

Selkirk, J.V.; Nottebaum, L.M.; Lee, J.; Yang, W.; Foster, A.C. & Lechner S.M. (2007). Identification of differential melanocortin 4 receptor agonist profiles at natively expressed receptors in rat cortical astrocytes and recombinantly expressed receptors in human embryonic kidney cells. *Neuropharmacology*, Vol.52, No.2, (February 2007), pp. 459-466, ISSN 0028-3908.

Sharma, H.S.; Skottner, A.; Lundstedt, T.; Flärdh, M. & Wiklund, L. (2006). Neuroprotective effects of melanocortins in experimental spinal cord injury. An experimental study in the rat using topical application of compounds with varying affinity to melanocortin receptors. *J Neural Transm*, Vol.113, No.4, (April 2006), pp. 463-476, ISSN 0300-9564.

Shutter, J.R.; Graham, M.; Kinsey, A.C.; Scully, S.; Luthy, R. & Stark, K.L. (1997). Hypothalamic expression of ART, a novel gene related to agouti, is up-regulated in obese and diabetic mice. *Genes Dev*, Vol.11, No.5, (March 1997), pp. 593-602, ISSN 0890-9369.

Sinha, P.; Schiöth, H. & Tatro J. (2004). Roles of the melanocortin-4 receptor in antipyretic and hyperthermic actions of centrally administered alpha-MSH. *Brain Res*, Vol.1001, No. 1-2, (March 2004), pp. 150-158, ISSN 0006-8993.

Slominski, A.; Ermak, G. & Mihm, M. (1996). ACTH receptor, CYP11A1, CYP17 and CYP21A2 genes are expressed in skin. *J Clin Endocrinol Metab*, Vol.81, No.7, (July 1996), pp. 2746-2749, ISSN 0021-972X.

Spencer, J.D. & Schallreuter, K.U. (2009). Regulation of pigmentation in human epidermal melanocytes by functional high-affinity beta-melanocyte-stimulating hormone/melanocortin-4 receptor signaling. *Endocrinology*, Vol.150, No.3, (March 2009), pp. 1250-1258, ISSN 0013-7227.

Star, R.A.; Rajora, N.; Huang, J.; Stock, R.C.; Catania, A. & Lipton, J.M. (1995). Evidence of autocrine modulation of macrophage nitric oxide synthase by alpha-melanocyte-stimulating hormone. Proc *Natl Acad Sci U S A*, Vol.92, No.17, (August 1995), pp. 8016-8020, ISSN 0027-8424.

Strand, F.L. & Kung, T.T. (1980). ACTH accelerates recovery of neuromuscular function following crushing of peripheral nerve. *Peptides*, Vol.1, No.2, pp. 135-138, ISSN 0196-9781.

Sutton, G.M.; Duos, B.; Patterson, L.M. & Berthoud, H-R. (2005). Melanocortinergic modulation of cholecystokinin-induced suppression of feeding through extracellular signal-regulated kinase signalling in rat solitary nucleus. *Endocrinology*, Vol.146, No.9, (September 2005), pp. 3739-3747, ISSN 0013-7227.

Taherzadeh, S.; Sharma, S.; Chhajlani, V.; Gantz, I.; Rajora, N.; Demitri, M.T.; Kelly, L.; Zhao, H.; Ichiyama, T.; Catania, A. & Lipton, J.M. (1999). α-MSH and its receptors in regulation of tumor necrosis factor-α production by human monocyte/macrophages. *Am J Physiol*, Vol.276, No.5Pt2, pp. R1289-R1294, ISSN 0002-9513.

Tanabe, K.; Gamo, K.; Aoki, S.; Wada, K. & Kiyama, H. (2007). Melanocortin receptor 4 is induced in nerve-injured motor and sensory neurons of mouse. *J Neurochem*, Vol.101, No.4, (May 2007), pp. 1145-1152, ISSN 0022-3042.

Tatro, J.B. (2000). Endogenous antipyretics. *Clin Infect Dis*, Vol.31, No.5, (October 2000), pp. S190-S201, ISSN 1058-4838.

Taylor, A.W. & Kitaichi, N. (2008). The diminishment of experimental autoimmune encephalomyelitis (EAE) by neuropeptide alpha-melanocyte stimulating hormone (alpha-MSH) therapy. *Brain Behav Immun*, Vol.22, No.5, (July 2008), pp. 639-646, ISSN 0889-1591.

Taylor, A.W. (2005). The immunomodulating neuropeptide alpha-melanocyte-stimulating hormone (alpha-MSH) suppresses LPS-stimulated TLR4 with IRAK-M in macrophages. *J Neuroimmunol*, Vol.162, No.1-2, (May 2005), pp. 43-50, ISSN 0165-5728.

Ter Laak, M.P.; Brakkee, J.H.; Adan, R.A.; Hamers, F.P. & Gispen, W.H. (2003). The potent melanocortin receptor agonist melanotan-II promotes peripheral nerve regeneration and has neuroprotective properties in the rat. Eur J Pharmacol, Vol.462, No.1-3, (February 2003), pp. 179-183, ISSN 0014-2999.

Usategui, R.; Oliver, C.; Vaudry, H.; Lombardi, G.; Rozenberg, I. & Mourre, A.M. (1976). Immunoreactive alpha-MSH and ACTH levels in rat plasma and pituitary. *Endocrinology*, Vol.98, No.1, (January 1976), pp. 189-196, ISSN 0013-7227.

Van der Kraan, M.; Adan, R.A.; Entwistle, M.L.; Gispen, W.H.; Burbach, J.P. & Tatro, J.B. (1998). Expression of melanocortin-5 receptor in secretory epithelia supports a functional role in exocrine and endocrine glands. *Endocrinology*, Vol.139, No.5, (May 1998), pp. 2348-2355, ISSN 0013-7227.

Van der Neut, R.; Bär, P.R.; Sodaar, P. & Gispen, W.H. (1988). Trophic influences of alpha-MSH and ACTH4-10 on neuronal outgrowth in vitro. *Peptides*, Vol.9, No.5, (September-October 1988), pp. 1015-1020, ISSN 0196-9781.

Vongs, A.; Lynn, N.M. & Rosenblum, C.I. (2004). Activation of MAP kinase by MC4-R through PI3 kinase. *Regul Pept*, Vol.120, No.1-3, (August 2004), pp. 113-118, ISSN 0167-0115.

Vulliémoz, N.R.; Xiao, E.; Xia-Zhang, L.; Ferin, M. & Wardlaw, S.L. (2006). Melanocortin Modulation of Inflammatory Cytokine and Neuroendocrine Responses to Endotoxin in the Monkey. *Endocrinology*, Vol.147, No.4, (April 2006), pp. 1878-1883, ISSN 0013-7227.

Wakamatsu, K.; Graham, A.; Cook, D. & Thody, A.J. (1997). Characterisation of ACTH peptides in human skin and their activation of the melanocortin-1 receptor. *Pigment Cell Res*, Vol.10, No.5, (October 1997), pp. 288-297, ISSN 0893-5785.

Webb, T.R.; Chan, L.; Cooray, S.N.; Cheetham, M.E.; Chapple, J.P. & Clark, A.J. (2009). Distinct Melanocortin 2 Receptor Accessory Protein Domains Are Required for Melanocortin 2 Receptor Interaction and Promotion of Receptor Trafficking. *Endocrinology*, Vol.150, No.2, (February 2009), pp. 720-726, ISSN 0013-7227.

Weidenfeld, J.; Crumeyrolle-Arias, M. & Haour, F. (1995). Effect of bacterial endotoxin and interleukin-1 on prostaglandin biosynthesis by the hippocampus of mouse brain: role of interleukin-1 receptors and glucocorticoids. *Neuroendocrinology*, Vol.62, No.1, (July 1995), pp. 39-46, ISSN 0028-3835.

Wikberg, J.; Muceniece, R.; Mandrika, I.; Prusis, P.; Lindblom, J.; Post, C. & Skottner, A. (2000). New aspects on the melanocortins and their receptors. *Pharmacol Res*, Vol.42, No.5, (November 2000), pp. 393-420, ISSN 1043-6618.

Wilkinson, C.W. (2006). Roles of acetylation and other post-translational modifications in melanocortin function and interactions with endorphins. *Peptides*, Vol.27, No.2, (February 2006), pp. 453-471, ISSN 0196-9781.

Wolter, H.J. (1985). Dynorphin-A (1-8) and gamma-melanotropin exist within different myenteric plexus neurons of rat duodenum. *Biochem Biophys Res Commun*, Vol.131, No.2, (September 1985), pp. 821-826, ISSN 0006-291X.

Wolterink, G.; Van Zanten, E. & Van Ree, J.M. (1990). Functional recovery after destruction of dopamine systems in the nucleus accumbens of rats. IV. Delay by intra-accumbal treatment with ORG2766- or α-MSH antiserum. *Brain Res*, Vol.507, No.1, (January 1990), pp. 115-120, ISSN 0006-8993.

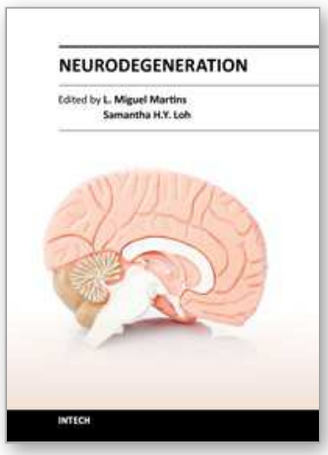
Wong, K.Y.; Rajora, N.; Boccoli, G.; Catania, A. & Lipton, J.M. (1997). A potencial mechanism of local anti-inflammatory action of alpha-melanocyte-stimulating hormone within the brain: modulation of tumor necrosis factor-alpha production by human astrocytic cells. *Neuroimmunomodulation*, Vol.4, No.1, (January-February 1997), pp. 37-41, ISSN 1021-7401.

Xia, Y.; Wikberg, J.E.S. & Chhajlani, V. (1995). Expression of melanocortin 1 receptor in periaqueductal gray matter. *Neuroreport*, Vol.6, No.16, (November 1995), pp. 2193-2196, ISSN 0959-4965.

Yeo, G.S.; Farooqi, I.S.; Aminiam, S.; Halsall, D.J.; Stanhope, R.G. & O'Rahilly, S. (1998). A frameshift mutation in MC4R associated with dominantly inherited human obesity. *Nat Genet*, Vol.20, No.2, (October 1998), pp. 111-112, ISSN 1061-4036.

Zhang, Y.; Wu, X.; He, Y.; Kastin, A.J.; Hsuchou, H.; Rosenblum, C.I. & Pan, W. (2009). Melanocortin potentiates leptin-induced STAT3 signaling via MAPK pathway. *J Neurochem*, Vol.110, No.1, (July 2009), pp. 390-399, ISSN 0022-3042.

IntechOpen



Neurodegeneration

Edited by Dr. L. Miguel Martins

ISBN 978-953-51-0502-2
Hard cover, 362 pages
Publisher InTech
Published online 11, April, 2012
Published in print edition April, 2012

Currently, the human population is on a collision course for a social and economic burden. As a consequence of changing demographics and an increase in human individuals over the age of 60, age-related neurodegenerative disorders are likely to become more prevalent. It is therefore essential to increase our understanding of such neurodegenerative disorders in order to be more pro-active in managing these diseases processes. The focus of this book is to provide a snapshot of recent advancements in the understanding of basic biological processes that modulate the onset and progression of neurodegenerative processes. This is tackled at the molecular, cellular and whole organism level. We hope that some of the recent discoveries outlined in this book will help to better define the basic biological mechanisms behind neurodegenerative processes and, in the long term, help in the development of novel therapeutic approaches.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Carla Caruso, Lila Carniglia, Daniela Durand, Teresa N. Scimonelli and Mercedes Lasaga (2012). Melanocortins: Anti-Inflammatory and Neuroprotective Peptides, Neurodegeneration, Dr. L. Miguel Martins (Ed.), ISBN: 978-953-51-0502-2, InTech, Available from: http://www.intechopen.com/books/neurodegeneration/melanocortins-anti-inflammatory-and-neuroprotective-peptides

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen