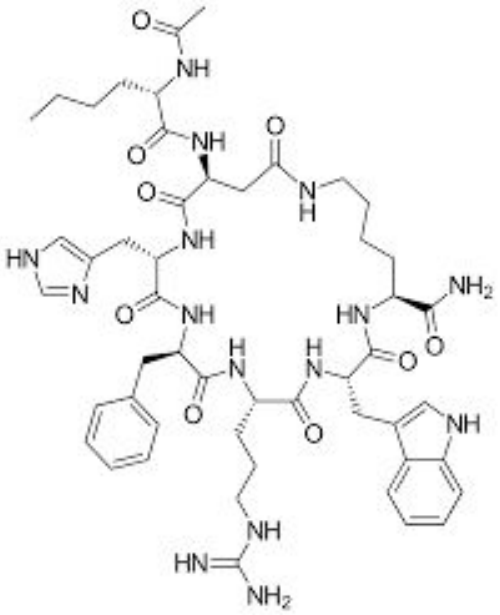
Professional Monograph

Melanotan II



SUMMARY

- Meltanotan II - synthetic alpha melanocyte stimulating hormone (α -MSH)
- Non-specific central melanocortin receptor agonist – MC1R, MC3R, MC4R, MC5R
- Melanotan I (afamelanotide) has the same mechanism of action as Melantotan II, however Melanotan I doesn't cross the BBB so no central effects (the metabolism support and sexual stimulation) like Melanotan II
- Supports melanogenesis
- Photoprotective
- Improves libido
- Immune – activates Treg cells and improves Th1/Th17 balance
- Reduces appetite and improves lipid and glucose regulation
- Neuroprotective – decreases neuroinflammation

- Dopamine modulating

Uses

- Tanning
- Protection from phototoxicity
  - Erythropoietic protoporphyria
- Metabolic Support
  - Lipolytic, appetite control, anti-inflammatory, decreases oxidative stress
- Conditions requiring immune balance
  - Autoimmune conditions
- Libido enhancement
- Potential use in alcohol and drug abuse, including opioids, cocaine (reward cascade supportive)

DOSAGE

- General dosage
  - Tanning
    - 200 mcg SubQ daily for 1 week
    - Adjust according to pigment changes
    - After pigment stabilizes, 100 mcg SC 2 x a week
  - Metabolic Enhancement
    - 50 mcg daily SubQ and adjust
  - Immunity
    - 200 mcg daily SubQ for 6-8 weeks
    - Use until clinical effects are pronounced
  - Sexual stimulation
    - More of a Side effect so occurs with any dosage regimen
    - Higher doses (ie 500 – 1,000 mcg) can lead to more pronounced stimulation
    - Melanotan sexual stimulation occurs gradually so more long term benefits
    - PT-141 (bremelanotide) doses 2x weekly leads to desensitization more frequently

Name(s): Melanotan II

Sequence: Ac-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]-NH2

Molecular formula: C50H69N15O9

Molar Weight: 1024.18 Daltons

Dosage: SubQ General Dosage

- Tanning
  - 200 mcg SC daily for 1 week
  - Adjust according to pigment changes
  - After pigment stabilizes, 100 mcg SC 2 x a week
- Metabolic Enhancement
  - 50 mcg daily and adjust
- Immunity
  - 200 mcg daily for 6-8 weeks
  - Use until clinical effects are pronounced
- Sexual stimulation occurs as a Side Effect for most dosages

- Pronounced effects occur at higher doses

Potential Side Effects and/or Contraindications

- Melanotan II peptide given subcutaneously is reported safe and efficacious in recommended dosages.
- As with all injections, redness and pain at the site of injection may be present.
- Only purchase 98% purity and greater
- Side effects reported with melanotan II include nausea, vomiting, yawning, and a delayed onset of erection (approximately 2 hours).[1]
- Do not use if there is a personal or family history of melanoma or non-melanoma skin cancer.
    - Changes in melanocytic lesions have been reported when using melanotan injections and tanning beds concurrently.[2]
    - There has been a report of rapidly growing new moles after self-administration of MTII in a male with a previous history of malignant melanoma.[3]
- Use with caution if a history of hypertension is present.[4]
    - Anecdotal reports of short-term increases in blood pressure after injection are also reported, especially in those pre-disposed to hypertension.
- It is not recommended to use melanotan I or II If using laser treatments, micro needle, micro abrasion, chemical peels, or getting a tattoo due to increased melanocyte activation which can lead to darker spots around treatment areas.
- There is a case report of systemic toxicity and rhabdomyolysis.[5] The dosage was very high (6 mg) and the product was purchased from the internet without a prescription.

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Dorr RT, Lines R, Levine N, et al. Evaluation of melanotan II a superpotent cyclic melanotropic peptide in a pilot phase-1 clinical study. Life Sci. 1996;58(20):1777-84.
[2] Sivyer GW. Changes of melanocytic lesions induced by melanotan injections and sun bed use in teenage patient with FAMMM syndrome. Dermatol Pract Concept. 2012;2(3):0203a10.
[3] Page S, Chandoke V, Baranova A. Melanin and melanogenesis in adipose tissue: possible mechanisms for abating oxidative stress and inflammation? Obes Rev. 2011;12(5):e21-31.
[4] White WB, Myers MG, Jordan R, et al. Usefullness of ambulatory blood pressure monitoring to assess the melanocortin receptor agonist bremelanotide. J Hypertens. 35(4):761-68.
[5] Nelson ME, Bryant SM, Aks SE. Melanotan II injection resulting in systemic toxicity and rhabdomyolysis. Clin Toxicol (Phila.). 2012;50(10):1169-73.

- Melanotan II use may result in priapism in men if recommended dosage not followed.[6]
    - A report in 60 year old man using a dosage of 10 mg of melanotan II led to a severe case of priapism that required surgery (a Winter shunt) to correct.
    - Discontinue use if priaprism develops in men (an erection lasting longer than 4 hours).
    - It is **NOT** recommended to use PT-141 injection concurrently with a PDE5 inhibitor in men due to risk of priapism.
- NOTE: A number of products are sold online, in gyms and in beauty salons as "melanotan". Only use peptide products that are made by professional pharmacies that use FDA Quality Control Procedures to manufacture this or any peptide.
- With concern on sourcing, IPS is working with FDA accredited compounding pharmacies that are (1) providing an environment for legal use of peptides, and (2) providing a quality product that has been tested for potency, purity and sterility that must comply 100% with US FDA requirements. Illegal and unregulated sources need to stop.
- Melanotan I (afamelanotide) has the same mechanism of action as Melantotan II except does not cross the blood-brain-barrier.

Background

The melanocortin system consists of five seven-trans membrane spanning G-protein coupled (GPCRs) receptors (MC1R-MC5R), the endogenous agonists a-, B- and melanocyte stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), and the endogenous antagonists Agouti and Agouti-related protein (AGRP). The melanocortins are a group of small protein hormones derived by post-translational cleavage of the proopiomelanocortin (POMC) gene product. The known melanocortin hormones include alpha-melanocyte stimulating hormone (MSH), beta-MSH, gamma-MSH and adrenocorticotropic hormone (ACTH).

Five melanocortin receptors (MC1R through MC5R) have been identified and most of these show tissue-specific expression patterns, as well as different binding affinities for each of the melanocortin hormones (see Table 1).[7] The central melanocortin system consists of alpha-MSH, agouti-related protein (AGRP), MC3R and MC4R. AGRP and alpha-MSH are believed to be the natural antagonist and agonist respectively of MC3R and MC4R. This central melanocortin system is thought to play a fundamental role in the control of feeding and body weight. Knock-out mice models and genetic studies have pointed to the importance of the melanocortins in complex human pathways such as pigmentation, lipolysis, food intake, thermogenesis, sexual behaviour, memory and inflammatory response.

[6] Devlin J, Pomerleau A, Foote J. Melanotan II overdose associated with priapism. Clin Toxicol (Phila). 2013;51(4):383.

[7] Adan RAH, Tisesjema B, Hillebrand JJG, et al. The MC4 receptor and control of appetite. Br J Pharmacol. 2006;149(7):815-27.

Recently the melanocortins and their receptors have been the target for drug-based treatment of human physiological processes. MC3R and MC4R are likely targets for controlling body weight; MCIR may be used in the treatment of inflammation and MC2R for the treatment of glucocortical deficiency. A role for MC5R still remains unclear, but the evidence suggests an exocrine gland function.

Melanotan I and II

Melanotan II is a synthetic cyclic lactam analog of naturally occurring α-MSH (melanocyte-stimulating hormone), a truncated version of melanotan I (afamelanotide) with a longer half-life. Melanotan I [Nle4,D-Phe7] α-MSH is a potent non-selective analog of α-MSH with activity at the MC1R, MC3R, MC4R, and MC5R receptors and good *in vivo* stability and biodistribution, but poor blood–brain barrier permeability.[8] Melanotan II (MTII), Ac-Nle-c[Asp5,DPhe7,Lys10] α-MSH-NH2, is of similar potency and range of effects as MTI but enhanced *in vivo* stability (T1/2: 1–2 h) and blood–brain barrier

[8] Hruby VJ, Cai M, Cain J, et al. Design of novel melanocortin receptor ligands: multiple receptors, complex pharmacology, the challenge. Eur J Pharmacol. 2011;660:88–93.

permeability because of its cyclic structure.[9] Melatnotan II is reported to engage signaling pathways in a manner more similar to endogenous melanocortins. Melanotan I (Afamelanotide, Scenesse) is FDA approved as an implant under the skin for prevention of phototoxicity in patients with erythropoetic protoporphyria.[10],[11]

Melanotan II is a non-selective agonist of the melanocortin receptors MC1R, MC3R, MC4R, and MC5R.[12],[13] Melanotan II was originally developed as a "tanning" hormone, and researchers also reported increased libido in patients. Melanotan II produces melanogenesis mainly through peripheral MC1R binding. Sexual stimulation and metabolic effects are central MC4R and MC3R.[14],[15],[16] Early clinical trials of the drug were abandoned when it was found to have adverse reactions including vomiting, nausea and facial flushing.[17] Melanocortin II is a very important therapeutic alternative not only for tanning and sexual dysfunction, but also for metabolic and immune support.

Unlicensed and untested products called melanotan are sold on the internet, but many governmental agencies, including the US FDA, have condemned the use of these agents.

Melanogensis

The pigment melanin is produced in melanosomes by melanocytes in a complex process called melanogenesis. Melanin is the primary determinant of skin, hair, and eye color. Besides defining an important human phenotypic trait, it has a critical role in photoprotection due to its ability to absorb ultraviolet radiation (UVR).[18] The melanocyte interacts intrinsically with endocrine, immune, inflammatory and central nervous systems, and its activity is also regulated by extrinsic factors (such as ultraviolet radiation and drugs).

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[9] Cai M, Mayorov AV, Ying J, et al. Design of novel melanotropin agonists and antagonists with high potency and selectivity for human melanocortin receptors. Peptides. 2005;26:1481–1485.

[10] Kim ES, Garnock-Jones KP. Afamelanotide: A review in erythropoietic protoporphyria. Am J Clin Dermatol. 2016;17(2):175-85.

[11] Langendock JG, Balwani M, Anderson KE, et al. Afamelatotide for Erythropoietic Protoporphyria. N Eng J Med. 2015;373(1):48-59.

[12] Adan RAH, Tisesjema B, Hillebrand JJG, et al. The MC4 receptor and control of appetite. Br J Pharmacol. 2006;149(7):815-27.

[13] Wikberg JE. Melanocortin receptors: new opportunities in drug discovery. Expert Opinion on Therapeutic Patents. 2001;**11**(1): 61–76.

[14] Wessells H, Levine N, Hadley ME, et al. Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. Int J Impot Res. 2000;12 (Suppl 4):S74-9.

[15] King SH, Mayorov AV, Balse-Srinivasan P, et al. Melanocortin receptors, meotropic peptides and penile erection. Curr Top Med Chem. 2007;7(11):1098-1106.

[16] Ven der Ploeg LHT, Martin WJ, Howard AD, et al. A role for the melanocortin 4 receptor in sexual function. PNAS.2002;99(17):11381-11386.

[17] Wessells H, Levine N, Hadley ME, et al. : Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. Int J Impot Res. 2000;12(Suppl 4):S74–9.

[18] Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. Nature. 2007;445:843–50.

Photoprotective effects occur by triggering a 'signaling cascade' via activation of the MC1R on melanocytes (See Figure 1). Melanocytes favor production of eumelanin (photoprotective black/brown pigment).

- Binding of melanotan I or II to MCR1 leads to activation of adenylate cyclase (AC) and stimulation of cyclic adenosine monophosphate (cAMP).
- cAMP then activates protein kinase A (PKA), which results in phophorylation of cAMP response element binding (CREB).
- Phosphorylated CREB will bind to the cAMP response element (CRE) on the microphthalmia-associated transcription factor (MITF) gene leading to the synthesis of the MITF protein.
- This cascade results in increased concentrations of the melanogenic enzymes within the melanocyte.

Figure 1

The result is darkening of the skin and increases photo-protection from UV rays and increased protection from melanoma. MC1R genetic polymorphisms are responsible

for ethnic differences of constitutive pigmentation and for different responses to UVR exposure.[19,20]

Sexual Dysfunction and Erectile Dysfunction

Central melanocrotin receptors are also implicated in the control of sexual function, stimulating lordosis in female rats and erectile activity in male rats as well as in human subjects.[21] Both central and peripheral MC4R are associated with erectile function and MC3R is associated with lordosis. Melanocortins have been studied in clinical trials for the treatment of erectile dysfunction and for female sexual dysfunction.[22,23,24] In laboratory studies, administration of bremelanotide (PT-141, another melanocortin MC4R specific) significantly promoted solicitational behavior in female rats, and appears to be the first "true" aphrodisiac.[25] Studies using animal models have demonstrated that pre-copulatory behaviors in female rats analogous to sexual arousal are evoked, and preliminary clinical data also suggest a role in promoting sexual desire and arousal in women.[26] Studies have also reported that melanocortin peptides also affect dopaminergic neurotransmission, which can also affect sexuality via reward-based neuropharmacology.[27] Current human research and clinical trials validate the use of central melanocortin agonists for the treatment of both male and female sexual dysfunction.[28]

Immune Support

Inflammation and proinflammatory mediators are initially a beneficial host immune response. However, chronic, unresolved inflammatory processes play a pathogenic role in numerous inflammatory diseases, including inflammatory bowel diseases (ulcerative colitis, irritable bowel syndrome, Crohn's). There is research supporting

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[19] Park HY, Kosmadaki M, Yaar M, Gilchrest BA. Cellular mechanisms regulating human melanogenesis. Cell Mol Life Sci. 2009;66:1493–506.

[20] Rouzaud F, Kadekaro AL, Abdel-Malek ZA, Hearing VJ. MC1R and the response of melanocytes to ultraviolet radiation. Mutat Res. 2005;571:133–52.

[21] Martin WJ, MacIntyre DE. Melanocortin receptors and erectile dysfunction. Eur Urol. 2004l;45;706-13.

[22] Clayton AH, Althof SE, Kingsberg S, et al. Bremelanotide for female sexual dysfunctions in premenopausal women: a randomized, placebo-controlled dose-finding trial. Women's Health. 2-16;12(3):325-337.

[23] Wessells H, Levine N, Hadley ME, et al. Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. Int J Impot Res. 2000;12 (Suppl 4):S74-9.

[24] Shadiack AM, Sharma SD, Earle DC, Spana C, Hallam TJ. Melanocortins in the treatment of male and female sexual dysfunction. Curr Top Med Chem. 2007;7(11):1137-44.

[25] Pfaus JG, Shadiack A, Soest TV, et al. Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist. PNAS. 2004;101(27):10201-1020.4

[26] Shadiack AM, Sharma SD, Earle DC, et al. Melanocortins in the treatment of male and female sexual dysfunction. Curr Top Med Chem. 2007;7(11):1137-44.

[27] Shadiack AM, Althof S. Preclinical effects of melanocortins in male sexual dysfunction. Int J Impot Res. 2008;20(Suppl 1):S11-6.

[28] Shadiack AM, Sharma SD, Earle DC, Spana C, Hallam TJ. Melanocortins in the treatment of male and female sexual dysfunction. Curr Top Med Chem. 2007;7(11):1137-44.

that MC1R, MC3R , MC4R and MC5R plays a key role in resolving chronic inflammation.[29,30]

Inflammatory cells including lymphocytes, monocytes/ macrophages, and neutrophils as well as tissue-based cells including mast cells express melanocortin receptors. Monocyte/macrophages as well as microglia express MC1R, MC3R and MC5R and lymphocytes express MC1R, MC3R and MC5R as well.[31] Signaling through these receptors inhibits inflammatory processes and has been associated with shifts from proinflammatory to inhibitory effects of lymphocytes, perhaps in part through effects on antigen presenting cells such as monocytes/macrophages.

Melanocortin receptor signaling is reported to lead to antiinflammatory and immunomodulatory effects in a variety of In-vitro and In-vivo models.[32] *In vitro*, α-MSH reduces the expression or secretion of the pro-inflammatory cytokines interferon-γ, TNF-α, IL-1, IL-6, IL-8 and growth regulated oncogene-α (Gro-α), typically with the aid of mediating molecules such as IL-1β and in the presence of a pro-inflammatory stimulus.[33] α-MSH has additional anti-inflammatory activities in cultured cells, including:

1. Reducing the expression of the IL-8 receptor and non-cytokine pro-inflammatory mediators such as NO2- and iNOS
2. Reducing inflammatory cell migration and the expression of cell adhesion molecules (e.g. ICAM-1);
3. Increasing the expression of the anti-inflammatory cytokine IL-10;
4. Inhibiting activation of the NF-κB pro-inflammatory pathway.[34,35]
5. Also suppression of the chemotaxis of neutrophils, through the inhibition of superoxide radicals produced from neutrophils.[36]

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[29]

[30] Taylor AW, Yee DG, Nishida T, et al. Neuropeptide regulation of immunity. The immunosuppressive activity of alpha-melanocyte stimulating hormone (alpha-MSH). Ann NY Acad Sci. 2000;917;239-47.

[31] Arnason B.G., Berkovich R., Catania A., Lisak R.P., Zaidi M. Mechanisms of action of adrenocorticotropic hormone and other melanocortins relevant to the clinical management of patients with multiple sclerosis. Mult. Scler. 2013;19:130–136.

[32] Loram LC, Culp ME, Connolly-Strong EC, et al. Melanocortin peptides: potential targets in systemic lupus erythematosus. Inflammation. 2015;38(1):260-71.

[33] Brzoska T, Luger TA, Maaser C, Abels C, Bohm M. A-melanocyte-stimulating hormone and related tripeptides: biochemistry, antiinflammatory and protective effects in vitro and in vivo, and future perspectives for the treatment of immune-mediated inflammatory diseases. Endocr Rev. 2008;29:581–602.

[34] Yoon SW, Chun JS, Sung MH, Kim JY, Poo H. alpha-MSH inhibits TNF-α-induced matrix metalloproteinase-13 expression by modulating p38 kinase and nuclear factor kappaB signaling in human chondrosarcoma HTB-94 cells. Osteoarthritis and cartilage/OARS, Osteoarthritis Research Society. 2008;16:115–124.

[35] Manna SK, Sarkar A, Sreenivasan Y. A-melanocyte-stimulating hormone down-regulates CXC receptors through activation of neutrophil elastase. Eur J Immunol. 2006;36:754–769.

[36] Oktar BK, Yuksel M, Alican I. The role of cyclooxygenase inhibition in the effect of α-melanocyte-stimulating hormone on reactive oxygen species production by rat peritoneal neutrophils. Prostaglandins Leukot Essent Fatty Acids. 2004;71:1–5.

MC1r is upregulated in a number of inflammatory diseases, including inflammatory bowel diseases (ulcerative colitis, irritable bowel syndrome, Crohn's), nephritis, rheumatoid arthritis, ocular inflammatory conditions such as uveitis and dry eye, and dermatologic indications. MC1r peptides have an anti-inflammatory effect and can work to regulate the immune system and resolve pro-inflammatory responses.

MC1R agonists are reported to improve Treg function and prevent immune cell infiltration into the CNS by restoring the integrity of the blood-brain-barrier (BBB), which can be beneficial in progressive neuroinflammatory disorders such as multiple sclerosis (MS).[37]

Another mechanism of melanocortin agonists having anti-inflammatory activity is involved with the cholinergic anti-inflammatory pathway (see figure 2). This pathway is a neural mechanism that inhibits pro-inflammatory cytokine release via signals that require the vagus nerve and $\alpha 7$ receptors. This is critical in the regulation of inflammation through brain-immune balance. MC3R and MC4R agonists activate this pathway.[38,39] Benefits include autoimmune regulation, ischemic heart and brain conditions, neuroprotection.

Figure 2

[37] Mykicki N, Herrmann AM, Schwab N, et al. Melanocortin-1 receptor activation is neuroprotective in mouse models of neuroinflammatory disease. Sci Transl Med. 2016;8(362):362ra146.
[38] Guiliani D, et al. Melanocortins and the cholinergic anti-inflammatory pathyway. Adv Exp Med Biol. 2010;681:71-87.
[39] Pavlov VA, et al. Controlling inflammation: the cholinergic Anti-inflammatory pathway. Biochem Soc Trans. 2006;19(6):493-9.

Pavlov VA, et al. Controlling inflammation: the cholinergic Anti-inflammatory pathway. Biochem Soc Trans. 2006;19(6):493-9.

Metabolic Support

Laboratory studies report that Melanotan II induces enhanced thermogenic and anorexic responses via MC4R binding, and helps improve glucose and cholesterol metabolism.[40] Although there have been some laboratory reports of MC3R binding that contributed to body weight regulation and helped prevent salt sensitivity of blood pressure, the MC4R, a G-protein-coupled 7 transmembrane receptor that is activated mainly by α-MSH, is thought to be the dominant efferent arm of the brain melanocortin system's actions on body weight homeostasis, SNS activation, and BP regulation.[41] Impaired MC4R activation caused by mutations of the MC4R or the POMC gene is estimated to account for as many as 5–6% of early onset morbid obesity in humans.[42]

Pharmacological antagonists of MC4R have been reported in laboratory studies to cause hyperphagia, rapid weight gain, and pronounced obesity in rodents, whereas activation of MC4R using synthetic agonists promotes weight loss by reducing appetite and increasing energy expenditure.[43] Conversely, chronic MC4R activation is reported to lead to sustained increases in BP despite reducing food intake and promoting weight loss, and the rise in BP can be prevented by adrenergic receptor blockade.[44] It is reported that a functional MC4R is necessary for excess weight gain to increase SNS activity and elevate BP, and that MC4R also modulates sympathetic responses to stress.

Studies report an expression of the components of the melanogenic pathway and the presence of melanin in visceral adipose.[45] Melanin has antioxidant and anti-inflammatory properties, and there is a larger amount of melanin in the adipose tissue of obese patients relative to lean ones. Melanin is produced in these individuals due to the increased amount of oxidative stress and inflammation, as melanin decreases ROS (reactive oxygen species) and produces increased amounts of anti-inflammatory cytokines in relation to pro-inflammatory cytokines.

Brain Inflammation

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[40] Li G, Zhang Y, Wilsey JT, et al. Unabated anorexic and enhanced thermogenic responses to melanotan II in diet-induced obese rates despite reduced melanocortin 3 and 4 receptor expression. J Endocrinol. 2004;182(1):123-32.

[41] Do Carmo JM, Da Silva AA, Wang Z, et al. Role of the brain melanocortins in blood pressure regulation. Biochem Biophys Acta. 2017;1863(10, pt A):2508-2514.

[42] Da Silva AA, do Carmo JM, Wang Z, et al. The brain melanocortin system, sympathetic control, and obesity hypertension. Physiology (Bethesda). 2014;29(3):196-202.

[43] Da Silva AA, do Carmo JM, Wang Z, et al. The brain melanocortin system, sympathetic control, and obesity hypertension. Physiology (Bethesda). 2014;29(3):196-202.

[44] Da Silva AA, do Carmo JM, Wang Z, et al. The brain melanocortin system, sympathetic control, and obesity hypertension. Physiology (Bethesda). 2014;29(3):196-202.

[45] Page S, Chandoke V, Baranova A. Melanin and melanogenesis in adipose tissue: possible mechanisms for abating oxidative stress and inflammation? Obes Rev. 2011;12(5):e21-31.

There is a wide distribution of at least three melanocortin receptor subtypes (MC1R, MC3R and MC4R) in neural, glial and endothelial cells. Melanocortins reduce production of pro-inflammatory agents in brain cells after injury by modulation of NF-kappaB-mediated transcription.[46] During brain ischemia, alpha-MSH and other melanocortins exert long-term protective influences. Melanocortins protect neurons insulted by various excitotoxins, accelerate neurophysiological recovery after spinal cord injury and increase regenerative capacity of peripheral nerves in post lesion repair.

MC1R activation is involved in neuroprotection and helping decrease neuroinflammation.[47] The non-selective melanocortin receptor agonist afamelanotide (Melanotan I) (NDP-α-MSH) has been reported in laboratory animal studies to induce brain-derived neurotrophic factor (BDNF) expression via activation of the MC4R receptor and mediate profound neurogenesis and cognitive recovery in an animal model of Alzheimer's disease.[48] Also of note, MC4R receptor antagonists produce pronounced antidepressant and antianxiety effects in animal models.

MC4R receptor agonist, such as melanotan II, is reported to activate the central oxytocin system and promote pair bond formation and other prosocial effects, suggesting as possible treatments for social deficits in autism spectrum disorders and schizophrenia.[49] MC4R activation MC4R activation also induces dopamine release in the nucleus accumbens (NAc).[50]

Drug and Alcohol Abuse

There is a large body of research reporting on the role of melanocortins and AgRP systems in neurobiological responses to drugs of abuse, in particular, neurobiological responses to ethanol.[51] Ethanol exposure can lead to a marked reduction in hypothalamic levels of ACTH, a precursor to alpha-melanocyte stimulating hormone. Several laboratory studies report that the MC system modulates neurobiological response to ethanol and decreases ethanol consumption.

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[46] Catania A. Neuroprotective actions of melanocortins: a therapeutic opportunity. Trends Neurosci. 2008;31(7):353-60.

[47] Mykicki N, Herrmann AM, Schwab N, et al. Melanocortin-1 receptor activation is neuroprotective in mouse models of neuroinflammatory disease. Sci Transl Med. 2016;8(362):362ra146.

[48] Guiliani D, Neri L, Canalini F, et al. NDP-α-MSH induces intense neurogenesis and cognitive recovery in Alzheimer transgenic mice through activation of melanocortin MC4 receptors. Mol Cell Neurosci. 2015;67:13-21.

[49] Modi ME, Inoue K, Barrett CE, et al. Melanocortin receptor agonists facilitate oxytocin-dependent partnet preference formation in the prairie vols. Neuropsychopharmacology. 2015;40(8):1856-65.

[50] Lindblom J, Opmane B, Mutulis F, et al. The MC4 receptor mediates alpha-MSH induced release of nucleus accumbens dopamine. Neuroreport. 2001;12: 2155–2158.

[51] Navarro M. The role of the melanocortin system in drug and alcohol abuse. Int Rev Neurobiol. 2017;136:121-150.

[52,53,54] Evidence supports MC4R plays the largest role in blunting ethanol consumption.[55]

Melanocortin peptides are also reported to antagonize opiate dependence and tolerance.[56,57] Studies have reported the participation of melanocortin (MC) system in the development of tolerance to antinociceptive effect of morphine.[58] MC4R and opioid receptors show overlapping distribution in spinal cord and different brain regions like ventral tegmental area (VTA), nucleus accumbens (NAC) and periaqueductal grey (PAG). This provides a neuroanatomical basis for the potential interactions between these two receptor systems in nociceptive processes.[59,60]

A laboratory study reported that Melanotan II helped to improve the ability of Naltrexone to blunt ethanol intake, suggesting use of Melanotan II in opioid addiction and alcohol addiction may help improve current treatment methods.[61]

There is also laboratory evidence that melanocortin agonists regulate the mesocorticolimbic and mesotriatal dopamine systems, possibly supporting reward-based addiction and overeating processes.[62]

Cardiovascular Applications

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[52] Jansone B. Rumaks J, Dzirkale Z, et al. Gamma1- and gamma2-melanocyte stimulating hormones induce central anxiogenic effects and potentiate ethanol withdrawal responses in the elevated plus-maze test in mice. Pharmacol Biochem Behav.2009;92:267–271.
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[58] Kalange AS, Kokare DM, Singru PS, et al. Central administration of selective melanocortin 4 receptor antagonists
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Melanocortins have been described as having a variety of cardiovascular effects, including anti-inflammation, reperfusion and blood pressure elevation.[63] Both alpha- and gamma-MSH acutely elevate blood pressure and heart rate through central stimulation of sympathetic nervous outflow.[64] This action of alpha-MSH is mediated by the melanocortin 4 receptor (MC4R), while sympathetic nervous stimulation by gamma-MSH does not involve the MC3R but rather is likely due to activation of a sodium channel in the central nervous system.

Melanocortin peptides have been reported to elicit anti-inflammatory actions and to promote vascular endothelial function by activating MC1R and MC3R, with the cholinergic anti-inflammatory pathway being a primary mechanism.[65] Studies report melanocortins prevent myocardial reperfusion injury by activating melanocortin MC(3) receptors.[66]

Clinical Studies

- The University of Arizona conducted a pilot Phase I clinical trial on three males published in 1996. The authors concluded that, "Melanotan II has tanning activity in humans given only 5 low doses every other day by subcutaneous injection." The side effects reported were mild nausea and a "stretching and yawning complex" that correlated with spontaneous penile erections.[67]

- A human study that involved ten men who suffered from psychogenic erectile dysfunction was conducted at The Department of Pharmacology, University of Arizona College of Medicine and a study was published in 1998. The authors concluded that, "Melanotan-II is a potent initiator of erections in men with psychogenic erectile dysfunction and has manageable side effects at a dose of 0.025 mg./kg."[68]

- A clinical study at the Section of Urology of The University of Arizona

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College of Medicine using 20 men with psychogenic and organic erectile dysfunction was published in 2000. The authors concluded that, "Melanotan II is a potent initiator of penile erection in men with erectile dysfunction."[69]

DISCLAIMER: Statements made are for educational purposes and have not been evaluated by the US Food and Drug Administration (FDA). They are not intended to diagnose, treat, cure, or prevent any disease. Peptides should only be administered by licensed and qualified health care professionals.

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