

Melanocortin Receptors

Key References

- Butler, A.A. et al. "A unique metabolic syndrome causes obesity in the melanocortin-3 receptor-deficient mouse." *Endocrinology* **141**, 3518-3521 (2000).
- Chen, W. et al. "Exocrine gland dysfunction in MC5-R deficient mice: Evidence for coordinated regulation of exocrine gland function by melanocortin peptides." *Cell* **91**, 789-798 (1997).
- Cone, R.D. et al. "Melanocortin receptor family." in: *The IUPHAR Compendium of Receptor Characterization and Classification, 2nd edition*, pp. 262-269, IUPHAR Media, London, UK (2000).
- Cone, R.D. "Haploinsufficiency of the melanocortin-4 receptor: Part of a thrifty genotype?" *J. Clin. Invest.* **106**, 185-187 (2000).
- Fong, T.M. et al. "ART (protein product of agouti-related transcript) as an antagonist of MC-3 and MC-4 receptors." *Biochem. Biophys. Res. Commun.* **237**, 629-631 (1997).
- Grieco, P. et al. "D-Amino acid scan of gamma-melanocyte-stimulating hormone: Importance of Trp(8) on human MC3 receptor selectivity." *J. Med. Chem.* **43**, 4998-5002 (2000).
- Hruby, V.J. et al. "Cyclic lactam α -melanotropin analogues of Ac-Nle⁴-c[Asp⁴,D-Phe⁷, Lys¹⁰] α -MSH(4-10)-NH₂ with bulky aromatic amino acids at position 7 show high antagonist potency and selectivity at specific melanocortin receptors." *J. Med. Chem.* **38**, 3454-3461 (1995).
- Huszar, D. et al. "Targeted disruption of the melanocortin-4 receptor results in obesity in mice." *Cell* **88**, 131-141 (1997).
- Lu, D. et al. "Regulation of melanogenesis by the MSH receptor." in *The Pigmentary System*, J. Nordlund, R. Boissy, V. Hearing, R. King and J.-P. Ortonne, (eds). Oxford University Press, NY (1998).
- Lu, D. et al. "Agouti protein is an antagonist of the melanocyte-stimulating hormone receptor." *Nature* **371**, 799-802 (1994).
- Ollmann, M.M. et al. "Antagonism of central melanocortin receptors *in vitro* and *in vivo* by agouti-related protein." *Science* **278**, 135-137 (1997).
- Shutter, J.R. et al. "Hypothalamic expression of ART, a novel gene related to agouti, is upregulated in obese and diabetic mutant mice." *Genes Dev.* **11**, 593-602 (1997).

Overview

The term "melanocortin" refers to peptides derived from the larger pro-opiomelanocortin (POMC) polypeptide precursor that possess melanotropic or adrenocorticotrophic activity. These peptides are produced primarily in the anterior and intermediate lobes of the pituitary and in lower levels in the arcuate nucleus of the hypothalamus and nucleus of the solitary tract in the brainstem, in skin, and a limited number of other sites. In the CNS, POMC-containing neurons project from the arcuate to every brain region, but the densest fiber bundles project intrahypothalamically, and to the brainstem. POMC has also been reported to be expressed in several other tissues, including keratinocytes and hair follicle cells, which may be particularly relevant to pigmentation. The melanocortin peptides are processed from three different regions of POMC, each of which contains a conserved sequence, -His-Phe-Arg-Trp-, that serves as the pharmacophore for melanocortin receptor activation. Peptides derived from the amino terminus of POMC are called γ -MSH (γ -Melanocyte stimulating hormone) peptides. Adrenocorticotrophic hormone (ACTH) and α -MSH are overlapping peptides cleaved from the middle portion and consist of amino acids 1-39 and 1-13 of this middle region, respectively. β -MSH, β -LPH (β -lipotropin) and γ -LPH all derive from the carboxy-terminal portion of the POMC precursor.

Five melanocortin receptors are known to exist, termed MC1-R to MC5-R; each has a single coding exon, and thus no splice variants involving coding sequence have been demonstrated. The peripheral MC1-R, MC2-R, and MC5-R modify cell function by coupling to G_s and elevating intracellular cAMP. While the neuronal MC3-R

and MC4-R couple to G_s in heterologous cells, little data is available regarding their effectors in brain, although elevation of cAMP and stimulation of GABA release have been demonstrated as likely downstream pathways in one model system. A curious feature of the melanocortin receptors is the existence of a family of endogenous antagonists, the agouti proteins. Agouti is a 131 amino acid peptide made by dermal follicular cells that acts as a specific high affinity antagonist of the MC1-R. Agouti related protein (AGRP), a homolog made in the arcuate nucleus of the hypothalamus and the adrenal gland, is an antagonist of the central MC3-R and MC4-R.

The distribution of expression of the melanocortin receptors has been largely determined in the brain and periphery. The MC1-R is nearly exclusively expressed in melanocytes where it regulates the eumelanin-phaeomelanin switch via the cAMP-regulated rate limiting enzyme, tyrosinase. Some data suggest the MC1-R may also be expressed in limited numbers of lymphoid cells. The MC2-R is expressed primarily in the adrenal cortex, where it regulates synthesis and secretion of adrenal corticosteroids. The receptor is also required for development and maintenance of the adrenal cortex. The MC2-R is also seen in adipocytes, although its physiological role is unknown. The MC3-R is expressed primarily in the CNS, in a limited number of hypothalamic and limbic system structures, where it appears to play a role in the regulation of energy homeostasis. Disruption of this receptor causes an obesity syndrome characterized by increased feed efficiency and reduced energy expenditure. The receptor is also found in placenta and gut, and also

appears to be required for the enhanced natriuresis resulting from unilateral nephrectomy. The MC4-R is widely expressed in the CNS, although concentrated expression is seen in the hypothalamus and brainstem. Disruption or antagonism of this receptor causes an obesity syndrome characterized by moderate hyperphagia and obesity, mild hyperinsulinemia, increased linear growth, and otherwise relatively normal neuroendocrine function. This receptor is clearly important in coordinating energy expenditure with energy intake in response to both short term and long term peripheral metabolic signals; haploinsufficiency of the MC4-R is responsible for at least 5% of severe human obesity. The MC5-R is highly expressed in a variety of exocrine glands, where it appears to be involved in regulation of the synthesis and secretion of diverse exocrine gland products. Disruption of the gene results in the defective production of a species of sebaceous lipid. The MC6-R is a putative receptor site that correlates with a novel pressor activity of γ -MSH that cannot be blocked by SHU9119, an antagonist of MC3 and MC4 receptors.

Melanocortin Receptors

CURRENTLY ACCEPTED NAME	MC1-R	MC2-R	MC3-R	MC4-R	MC5-R	MC6-R
ALTERNATE NAMES	MSH-R	ACTH-R	—	—	—	Pressor Receptor
STRUCTURAL INFORMATION	317 aa (human)	297 aa (human)	360 aa (human)	332 aa (human)	325 aa (human)	Not determined
SELECTIVE AGONISTS	SHU9119 (M 4603)	ACTH (A 0423 (h) , A 6303 (p) , A 7075 (r))	γ 2-MSH (M 9638) (in rodents) [D-Trp ⁸]- γ -MSH	Ro 27-4680	SHU9119 (M 4603)	γ -MSH(6-12)
SELECTIVE ANTAGONISTS	Agouti	—	SHU9119 (M 4603) AGRP	SHU9119 (M 4603) Agouti AGRP Ro 27-3225 HS028 (H 4402) HS014 (H 2396)	—	—
SIGNAL TRANSDUCTION MECHANISMS	G _s (increase cAMP)	G _s (increase cAMP)	G _s (increase cAMP)	G _s (increase cAMP), GABA release	G _s (increase cAMP)	
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-[Nle ⁴ -D-Phe ⁷]- α -MSH	[¹²⁵ I]-[Tyr ²³]-ACTH	[¹²⁵ I]-[Nle ⁴ -D-Phe ⁷]- α -MSH	[¹²⁵ I]-[Nle ⁴ -D-Phe ⁷]- α -MSH	[¹²⁵ I]-[Nle ⁴ -D-Phe ⁷]- α -MSH	

ABBREVIATIONS:

ACTH: Adrenocorticotrophic hormone

AGRP: Agouti related protein

HS014: Cyclic [AcCys¹¹,D-Nal¹⁴,Cys¹⁸,Asp-NH₂(22)]- β -MSH(11-22)

HS028: [AcCys¹¹,dichloro-D-phenylalanine¹⁴,cys¹⁸,Asp-NH₂(22)] β -MSH(11-22)

α -MSH: α -Melanocyte stimulating hormone

γ -MSH: γ -Melanocyte stimulating hormone

γ 2-MSH: γ 2-Melanocyte stimulating hormone

Ro 27 3225: N-(1-Oxobutyl)-L-histidyl-L-phenylalanyl-L-arginyl-L-tryptophyl-N2-methyl-glycinamide

Ro 27-4680: N-(1-Oxobutyl)-L-histidyl-3-(2-naphthalenyl)-D-alanyl-L-arginyl-L-tryptophyl-N2-methyl-glycinamide

SHU9119: Ac-Nle⁴-c[Asp⁴,D-Nal⁷,Lys¹⁰]- α -MSH(4-10)-NH₂

h: human

p: porcine

r: rat