

Melanocortin Receptors

Key References

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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 over 100 brain nuclei, 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 MC1R to MC5R; with the exception of the MC1R each has a single coding exon, and no splice variants involving coding sequence. A splice variant of the MC1R, referred to as MC1RB, has been identified that adds an additional 65 amino acids to the intracellular C-terminus. The peripheral MC1R, MC2R, and MC5R

modify cell function by coupling to G_s and elevating intracellular cAMP levels. While the neuronal MC3R and MC4R 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 MC3R and MC4R.

The distribution of expression of the melanocortin receptors has been largely determined in the brain and periphery. The MC1R 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 MC1R may also be expressed in limited numbers of lymphoid cells. The MC2R 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 MC2R is also seen in adipocytes, although its physiological role is unknown. The MC3R 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. MC3R knockout mice also exhibit salt-sensitive hypertension. The MC4R 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 MC4R is responsible for approximately 5% of severe human obesity. The MC4R also plays a role in erectile function. The MC5R 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 MC6R is a putative receptor site that correlates with a novel pressor activity of γ -MSH that cannot be blocked by SHU9119, an antagonist of MC3R and MC4R.

Melanocortin Receptors

CURRENTLY ACCEPTED NAME	MC1R	MC2R	MC3R	MC4R	MC5R	MC6R
ALTERNATE NAMES	MSHR	ACTH-R	—	—	—	Pressor Receptor
STRUCTURAL INFORMATION	317 aa (human) (382 aa splice variant)	297 aa (human)	360 aa (human)	332 aa (human)	325 aa (human)	Not determined
AGONISTS	SHU9119 (M4603), MT-II	Not known	γ2-MSH (M9638) (in rodents), [D-Trp ⁸]-γ-MSH, MT-II	Ro 27-4680, MT-II, [D-Tyr ⁴]-MTII C(β-Ala-His-D-Phe- Arg-Trp-Glu)-NH ₂	MT-II, H-D-Phe-c[Cys-His- D-Phe-Arg-Trp-Pen]- Thr-NH(2), THIQ	γ-MSH(6-12)
ANTAGONISTS	Agouti	Not known	SHU9119 (M4603), AGRP	SHU9119 (M4603), Agouti, AGRP, Ro 27-3225, HS028 (H4402), HS014 (H2396)	Not known	Not known
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)	Not known
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	Not known
TISSUE EXPRESSION	Melanocytes	Adrenal	CNS, gut, kidney	CNS	Exocrine glands	Not known
PHYSIOLOGICAL FUNCTION	Pigmentation	Glucocorticoid synthesis	Energy homeostasis, natriuresis	Energy homeostasis, erectile function	Synthesis and secretion of exocrine gland products	Cardiovascular regulation
DISEASE RELEVANCE	Skin cancer	Familial ACTH resistance	Obesity, hypertension	Obesity, diabetes, erectile dysfunction	Exocrine gland dysfunction	Not known

Abbreviations:

ACTH: Adrenocorticotrophic hormone

AGRP: Agouti related protein

HS014: Ac-Cys-Glu-His-D-2-Nal-Arg-Trp-Gly-Cys-Pro-Pro-Lys-Asp-NH₂

HS028: Ac-Cys-Glu-His-diCl-D-Phe-Arg-Trp-Gly-Cys-Pro-Pro-Lys-Asp-NH₂

α-MSH: α-Melanocyte stimulating hormone

γ-MSH: γ-Melanocyte stimulating hormone

γ2-MSH: γ2-Melanocyte stimulating hormone

MT-II: Ac-Nle⁴-c[Asp⁴,D-Phe,Lys¹⁰]-α-MSH(4-10)-NH₂

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: Acetyl- [Nle⁴,Asp⁵, D-2-Nal⁷,Lys¹⁰]-cyclo-α-MSH(4-10)

THIQ: N-[(3R)-1,2,3,4-tetrahydroisoquinolinium-3-ylcarbonyl]-(1R)-1-(4-chlorobenzyl)-2-[4-cyclohexyl-4-(1H-1,2,4-triazol-1ylmethyl)piperidin-1-yl]-2-oxoethylamine

h: human

p: porcine

r: rat

FOOTNOTES