

# Melanin-Concentrating Hormone Receptors

## Key References

- Audinot, V., et al., [125I]-S36057: a new and highly potent radioligand for the melanin-concentrating hormone receptor., *Br. J. Pharmacol.*, **133**, 371-378 (2001).
- Bednarek, M.A., et al., Synthesis and biological evaluation *in vitro* of a selective, high potency peptide agonist of human melanin-concentrating hormone action at human melanin-concentrating hormone receptor 1., *J. Biol. Chem.*, **277**, 13821-13826 (2002).
- Borowsky, B., et al., Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist., *Nat. Med.*, **8**, 825-830 (2002).
- Chaki, S., et al., Anxiolytic- and antidepressant-like profile of ATC0065 and ATC0175: Nonpeptidic and orally active melanin-concentrating hormone receptor 1 antagonists., *J. Pharmacol. Exp. Ther.*, **313**, 831-839 (2005).
- Chen, Y., et al., Targeted disruption of the melanin-concentrating hormone receptor-1 results in hyperphagia and resistance to diet-induced obesity., *Endocrinology*, **143**, 2469-2477 (2002).
- Hervieu, G.J., et al., The distribution of the mRNA and protein products of the melanin-concentrating hormone (MCH) receptor gene, *slc-1*, in the central nervous system of the rat., *Eur. J. Neurosci.*, **12**, 1194-1216 (2000).
- Kowalski, T.J. and McBriar, M.D., Therapeutic potential of melanin-concentrating hormone-1 receptor antagonists for the treatment of obesity., *Expert Opin. Investig. Drugs*, **13**, 1113-1122 (2004).
- Pissios, P. and Maratos-Flier, E., Melanin-concentrating hormone: from fish skin to skinny mammals., *Trends Endocrinol. Metab.*, **14**, 243-248 (2003).
- Saito, Y., et al., Melanin-concentrating hormone receptor: an orphan receptor fits the key., *Trends Endocrinol. Metab.*, **11**, 299-303 (2000).
- Takekawa, S., et al., T-226296: a novel, orally active and selective melanin-concentrating hormone receptor antagonist., *Eur. J. Pharmacol.*, **438**, 129-135 (2002).
- Tan, C.P., et al., Melanin-concentrating hormone receptor subtypes 1 and 2: species-specific gene expression., *Genomics*, **79**, 785-792 (2002).
- Toumaniantz, G., et al., Differential neuronal expression and projections of melanin-concentrating hormone (MCH) and MCH-gene-overprinted-polypeptide (MGOP) in the rat brain., *Eur. J. Neurosci.*, **12**, 4367-4380 (2000).

## Overview

Melanin concentrating hormone (MCH) is a nonadecapeptide with a highly conserved amino acid sequence that is found in a variety of species from fish to mammals. Originally isolated from chum salmon pituitary, MCH changes the distribution of melanosomes by stimulating their aggregation, and functions as a physiological antagonist of  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH). In mammals, MCH is synthesized in the central nervous system, specifically in the magnocellular cell bodies of the lateral hypothalamus and zona incerta. The cell bodies of MCH-containing neurons project widely to the cerebral cortex, amygdala, nucleus accumbens, olfactory tubercle and brainstem nuclei. In mammals, MCH is synthesized from a prepropeptide, encoded by the *Pmch* gene, from which neuropeptide E-I and neuropeptide G-E are also derived. Alternative splicing of *Pmch* also gives rise to additional peptides such as MCH-gene-overprinted-polypeptide (MGOP).

The role of MCH in mammals was elucidated when, using RT-PCR differential display, the expression of the *Pmch* gene was shown to be increased in *ob/ob* mice. These mice provide a genetic model of obesity and suggested a role for MCH in energy homeostasis. The central administration of MCH evokes feeding behavior, and increased expression of *Pmch* is observed in fasted animals. Conversely, feeding as well as leptin treatment to normal and *ob/ob* mice suppresses the expression of *Pmch*. Further studies of the phenotype of mice with targeted gene deletion of *Pmch* confirmed the initial observations and showed a 25% reduction in body weight, by reduction in feeding and increased energy expenditure. The transgenic overexpression of *Pmch* caused an increased propensity to obesity by high fat diet, hyperinsulinemia and insulin resistance.

The effects of MCH are mediated by two G protein-coupled receptors, referred to as MCH<sub>1</sub> and MCH<sub>2</sub>. The MCH<sub>1</sub> receptor was discovered using a reverse pharmacology approach in which MCH was found to increase either intracellular calcium or adenylyl cyclase inhibition in cells expressing the then orphan receptor SLC-1 (or GPR24). MCH<sub>1</sub> couples to multiple G proteins, activating the release of intracellular calcium through coupling to G<sub>q</sub> and suppressing forskolin activation of adenylyl cyclase by coupling to G<sub>i/o</sub> in a pertussis toxin-sensitive manner. The expression of MCH<sub>1</sub> is most abundant in brain (cortex, basal ganglia, hypothalamus and brainstem) with weak expression in muscle, eye, tongue and adipose tissue. The targeted deletion of the gene encoding the MCH<sub>1</sub> receptor in mice yields a lean phenotype with reduced fat mass, increased activity and resistance to diet-induced obesity, suggesting that MCH<sub>1</sub> mediates the effects of MCH on energy homeostasis in rodents. In line with this evidence selective, peptidergic and small molecule, MCH<sub>1</sub> antagonists such as T-226296 and SNAP7941 have also been found to inhibit the feeding response evoked by MCH, and to reduce body weight after chronic administration to rats with diet-induced obesity. In addition, SNAP7941, and recently ATC0065 and ATC0175 were also found to be effective in animal models of anxiety and depression, uncovering a role of MCH in the regulation of mood and emotion, with implications for the use of MCH<sub>1</sub> antagonists in the treatment of affective disorders.

The MCH<sub>2</sub> receptor, which is also activated by MCH and coupled to G<sub>q</sub>, was discovered based on its homology to MCH<sub>1</sub>. With a predominant CNS distribution, MCH<sub>2</sub> is not expressed in rodents and has only been found in dog, ferrets, rhesus monkeys and humans. The current lack of pharmacologi-

cal tools for MCH<sub>2</sub> and the species-specific expression of this receptor have hindered the assessment of its functional role.

# Melanin-Concentrating Hormone Receptors

<b>CURRENTLY ACCEPTED NAME</b>	MCH <sub>1</sub>	MCH <sub>2</sub>
<b>PREVIOUS NAMES</b>	MCH1R, SLC1, MCHR1, MGC32129, GPR24	GPR145, SLT, MCH2R, MCHR2
<b>STRUCTURAL INFORMATION</b>	353 aa (human)	340 aa (human)
<b>PREFERRED ENDOGENOUS PEPTIDE</b>	Melanin-concentrating hormone (human, rat, mouse)	Melanin-concentrating hormone (human, rat, mouse)
<b>SELECTIVE PEPTIDE AGONISTS</b>	[D-Arg <sup>6</sup> ,Asn <sup>10</sup> ]Ac-hMCH(6-16)-NH <sub>2</sub> <sup>a</sup> , [D-Arg <sup>6</sup> ,Gln <sup>10</sup> ]Ac-hMCH(6-16)-NH <sub>2</sub> <sup>a</sup>	Not known
<b>SELECTIVE PEPTIDE ANTAGONISTS</b>	Compound B <sup>b</sup>	Not known
<b>SELECTIVE NON-PEPTIDE ANTAGONISTS</b>	SNAP7941, T-226296, ATC0065, ATC0175	Not known
<b>RADIOLIGANDS OF CHOICE</b>	[ <sup>125</sup> I]-S36057, [ <sup>125</sup> I]-[Phe <sup>13</sup> ,3-iodo-Tyr <sup>19</sup> ]MCH	[ <sup>125</sup> I]-S36057, [ <sup>125</sup> I]-[Phe <sup>13</sup> ,3-iodo-Tyr <sup>19</sup> ]MCH
<b>TISSUE EXPRESSION</b>	CNS: nucleus accumbens, cerebral cortex, amygdala, hippocampus, hypothalamus, striatum, locus coeruleus and medulla oblongata. Pituitary, muscle, eye, tongue, and adipose tissue	CNS: cerebral cortex, nucleus, accumbens, amygdala, hippocampus. Adipose tissue, intestine, spleen, prostate
<b>PHYSIOLOGICAL FUNCTION</b>	Energy homeostasis, neuroendocrine regulation, modulation of mood and appetitive behaviors	Not known
<b>DISEASE RELEVANCE</b>	Obesity, depressive disorders and anxiety	Not known

## Abbreviations:

**ATC0065:** N<sup>2</sup>-[*cis*-4-({2-[4-Bromo-2-(trifluoromethoxy)phenyl]ethyl}amino)cyclohexyl]-N<sup>4</sup>, N<sup>4</sup>-dimethylquinazoline-2,4-diamine dihydrochloride

**ATC0175:** [N-(*cis*-4-[[4-(Dimethylamino)quinazolin-2-yl]amino]cyclohexyl)-3,4-difluorobenzamide hydrochloride

**SNAP 7941:** (+)-Methyl (4S)-3-[[3-(4-[3-(acetylamino)phenyl]-1-piperidinyl)propyl]amino]carbonyl-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate hydrochloride

**T-226296:** (-)-N-[6-(Dimethylamino)-methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide

## FOOTNOTES

**a** see Bednarek, M.A., et al, *J. Biol. Chem.*, **277**, 13821-13826 (2002).

**b** see Bednarek, M.A., et al, *Biochemistry*, **41**, 6383-6390 (2002).