

Melanocortin receptors in GtoPdb v.2025.3

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Abstract

Melanocortin receptors (**provisional nomenclature as recommended by NC-IUPHAR [41]**) are activated by members of the melanocortin family (α -MSH, β -MSH and γ -MSH forms; δ form is not found in mammals) and adrenocorticotrophin (ACTH). Endogenous antagonists include **agouti** and **agouti-related protein**. ACTH(1-24) was approved by the US FDA as a diagnostic agent for adrenal function test. **setmelanotide** was approved by the US FDA for weight management in patients with POMC, PCSK1 or LEPR deficiency, **bremelanotide** was approved by the US FDA for generalized hypoactive sexual desire disorder in premenopausal women, and NDP-MSH (**afamelanotide**) was approved by the EMA for the treatment of erythropoietic protoporphyria. Several synthetic melanocortin receptor agonists are under clinical development.

Contents

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Melanocortin receptors

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=38>

Introduction to Melanocortin receptors

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Receptors

MC₁ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=282>

MC₂ receptor

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MC₃ receptor

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MC₄ receptor

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MC₅ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=286>

References

1. Adan RA, Szklarczyk AW, Oosterom J, Brakkee JH, Nijenhuis WA, Schaaper WM, Meloen RH and Gispén WH. (1999) Characterization of melanocortin receptor ligands on cloned brain melanocortin receptors and on grooming behavior in the rat. *Eur J Pharmacol* **378**: 249-258 [PMID:10493100]
2. Al-Obeidi F, Hruby VJ, Castrucci AM and Hadley ME. (1989) Design of potent linear α -melanotropin 4-10 analogues modified in positions 5 and 10. *J Med Chem* **32**: 174-179 [PMID:2535874]
3. Argiolas A and Melis MR. (2013) Neuropeptides and central control of sexual behaviour from the past to the present: a review. *Prog Neurobiol* **108**: 80-107 [PMID:23851261]
4. Balse-Srinivasan P, Grieco P, Cai M, Trivedi D and Hruby VJ. (2003) Structure-activity relationships of novel cyclic α -MSH/ β -MSH hybrid analogues that lead to potent and selective ligands for the human MC3R and human MC5R. *J Med Chem* **46**: 3728-33 [PMID:12904077]
5. Bednarek MA, MacNeil T, Kalyani RN, Tang R, Van der Ploeg LH and Weinberg DH. (2001) Selective, high affinity peptide antagonists of α -melanotropin action at human melanocortin receptor 4: their synthesis and biological evaluation in vitro. *J Med Chem* **44**: 3665-72 [PMID:11606131]
6. Benoit SC, Schwartz MW, Lachey JL, Hagan MM, Rushing PA, Blake KA, Yagaloff KA, Kurylko G, Franco L and Danhoo W *et al.*. (2000) A novel selective melanocortin-4 receptor agonist reduces food intake in rats and mice without producing aversive consequences. *J Neurosci* **20**: 3442-8 [PMID:10777807]
7. Bertolini A, Tacchi R and Vergoni AV. (2009) Brain effects of melanocortins. *Pharmacol Res* **59**: 13-47 [PMID:18996199]
8. Boman A, Jonassen TEN and Lundstedt T. (2007) Phenyl pyrrole aminoguanidine derivatives Patent number: WO2007141343A1. Assignee: Action Pharma A/S. Priority date: 09/06/2006. Publication date: 13/12/2007.
9. Borowsky B, Durkin MM, Ogozalek K, Marzabadi MR, DeLeon J, Lagu B, Heurich R, Lichtblau H, Shaposhnik Z, Daniewska I, Blackburn TP, Branchek TA, Gerald C, Vaysse PJ and Forray C. (2002) Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist. *Nat Med* **8**: 825-830 [PMID:12118247]
10. Boston BA and Cone RD. (1996) Characterization of melanocortin receptor subtype expression in murine adipose tissues and in the 3T3-L1 cell line. *Endocrinology* **137**: 2043-50 [PMID:8612546]
11. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
12. Butler AA, Kesterson RA, Khong K, Cullen MJ, Pelleymounter MA, Dekoning J, Baetscher M and Cone RD. (2000) A unique metabolic syndrome causes obesity in the melanocortin-3 receptor-deficient mouse. *Endocrinology* **141**: 3518-21 [PMID:10965927]
13. Böhm M, Eickelmann M, Li Z, Schneider SW, Oji V, Diederichs S, Barsh GS, Vogt A, Stieler K and Blume-Peytavi U *et al.*. (2005) Detection of functionally active melanocortin receptors and evidence for an immunoregulatory activity of α -melanocyte-stimulating hormone in human dermal papilla cells. *Endocrinology* **146**: 4635-46 [PMID:16081629]
14. Carla Caruso, L. C., Daniela Durand and Teresa N. Scimonelli and Mercedes Lasaga. (2012) Melanocortins: Anti-Inflammatory and Neuroprotective Peptides *In Neurodegeneration* Edited by L. Miguel Martins: InTech:
15. Caruso V, Lagerström MC, Olszewski PK, Fredriksson R and Schiöth HB. (2014) Synaptic changes induced by melanocortin signalling. *Nat Rev Neurosci* **15**: 98-110 [PMID:24588018]
16. Castejón-Griñán M, Herraiz C, Olivares C, Jiménez-Cervantes C and García-Borrón JC. (2018) cAMP-independent non-pigmentary actions of variant melanocortin 1 receptor: AKT-mediated activation of protective responses to oxidative DNA damage. *Oncogene* **37**: 3631-3646

[PMID:29622793]

17. Castrucci AM, Hadley ME and Hruby VJ. (1984) Melanotropin bioassays: in vitro and in vivo comparisons. *Gen Comp Endocrinol* **55**: 104-11 [PMID:6611282]
18. Catania A, Rajora N, Capsoni F, Minonzio F, Star RA and Lipton JM. (1996) The neuropeptide alpha-MSH has specific receptors on neutrophils and reduces chemotaxis in vitro. *Peptides* **17**: 675-9 [PMID:8804079]
19. Chagnon YC, Chen WJ, Pérusse L, Chagnon M, Nadeau A, Wilkison WO and Bouchard C. (1997) Linkage and association studies between the melanocortin receptors 4 and 5 genes and obesity-related phenotypes in the Québec Family Study. *Mol Med* **3**: 663-73 [PMID:9392003]
20. Chaki S, Funakoshi T, Hirota-Okuno S, Nishiguchi M, Shimazaki T, Iijima M, Grottick AJ, Kanuma K, Omodera K, Sekiguchi Y, Okuyama S, Tran TA, Semple G and Thomsen W. (2005) 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 [PMID:15677346]
21. Chaki S, Hirota S, Funakoshi T, Suzuki Y, Suetake S, Okubo T, Ishii T, Nakazato A and Okuyama S. (2003) Anxiolytic-like and antidepressant-like activities of MCL0129 (1-[(S)-2-(4-fluorophenyl)-2-(4-isopropylpiperidin-1-yl)ethyl]-4-[4-(2-methoxynaphthalen-1-yl)butyl]piperazine), a novel and potent nonpeptide antagonist of the melanocortin-4 receptor. *J Pharmacol Exp Ther* **304**: 818-26 [PMID:12538838]
22. Chen AS, Marsh DJ, Trumbauer ME, Frazier EG, Guan XM, Yu H, Rosenblum CI, Vongs A, Feng Y and Cao L *et al.*. (2000) Inactivation of the mouse melanocortin-3 receptor results in increased fat mass and reduced lean body mass. *Nat Genet* **26**: 97-102 [PMID:10973258]
23. Chen W, Kelly MA, Opitz-Araya X, Thomas RE, Low MJ and Cone RD. (1997) Exocrine gland dysfunction in MC5-R-deficient mice: evidence for coordinated regulation of exocrine gland function by melanocortin peptides. *Cell* **91**: 789-98 [PMID:9413988]
24. Chhajlani V. (1996) Distribution of cDNA for melanocortin receptor subtypes in human tissues. *Biochem Mol Biol Int* **38**: 73-80 [PMID:8932521]
25. Chhajlani V, Muceniece R and Wikberg JE. (1993) Molecular cloning of a novel human melanocortin receptor. *Biochem Biophys Res Commun* **195**: 866-73 [PMID:8396929]
26. Chhajlani V and Wikberg JE. (1996) Molecular cloning and expression of the human melanocyte stimulating hormone receptor cDNA (FEBS 11553). *FEBS Lett* **390**: 238 [PMID:8706868]
27. Chu H, Xia J, Yang Z and Gao J. (2012) Melanocortin 4 receptor induces hyperalgesia and allodynia after chronic constriction injury by activation of p38 MAPK in DRG. *Int J Neurosci* **122**: 74-81 [PMID:21985621]
28. Clark AJ, McLoughlin L and Grossman A. (1993) Familial glucocorticoid deficiency associated with point mutation in the adrenocorticotropin receptor. *Lancet* **341**: 461-2 [PMID:8094489]
29. Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, De Waele K, Farooqi IS, Gonneau-Lejeune J and Gordon G *et al.*. (2020) Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol* **8**: 960-970 [PMID:33137293]
30. Conde-Frieboes K, Thøgersen H, Lau JF, Sensfuss U, Hansen TK, Christensen L, Spetzler J, Olsen HB, Nilsson C and Raun K *et al.*. (2012) Identification and in vivo and in vitro characterization of long acting and melanocortin 4 receptor (MC4-R) selective α -melanocyte-stimulating hormone (α -MSH) analogues. *J Med Chem* **55**: 1969-77 [PMID:22335602]
31. Cone RD. (2005) Anatomy and regulation of the central melanocortin system. *Nat Neurosci* **8**: 571-8 [PMID:15856065]
32. Cone RD, Lu D, Koppula S, Vage DI, Klungland H, Boston B, Chen W, Orth DN, Pouton C and Kesterson RA. (1996) The melanocortin receptors: agonists, antagonists, and the hormonal control of pigmentation. *Recent Prog Horm Res* **51**: 287-317; discussion 318 [PMID:8701084]
33. da Silva AA, do Carmo JM, Wang Z and Hall JE. (2014) The brain melanocortin system, sympathetic control, and obesity hypertension. *Physiology (Bethesda)* **29**: 196-202 [PMID:24789984]
34. Daniels D, Suzuki A, Shapiro E, Luo L, Yee DK and Fluharty SJ. (2005) *Rattus norvegicus* melanocortin 3 receptor: a corrected sequence. *Peptides* **26**: 1835-41 [PMID:15985309]
35. Desarnaud F, Labbe O, Eggerickx D, Vassart G and Parmentier M. (1994) Molecular cloning, functional expression and pharmacological characterization of a mouse melanocortin receptor gene. *Biochem J* **299** (Pt 2): 367-73 [PMID:8172596]
36. Dinulescu DM and Cone RD. (2000) Agouti and agouti-related protein: analogies and contrasts. *J Biol Chem* **275**: 6695-8 [PMID:10702221]
37. Fan W, Boston BA, Kesterson RA, Hruby VJ and Cone RD. (1997) Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. *Nature* **385**: 165-8 [PMID:8990120]
38. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T and O'Rahilly S. (2003) Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N Engl J Med* **348**: 1085-95 [PMID:12646665]
39. Farooqi IS and O'Rahilly S. (2008) Mutations in ligands and receptors of the leptin-melanocortin

- pathway that lead to obesity. *Nat Clin Pract Endocrinol Metab* **4**: 569-77 [PMID:18779842]
40. Fong TM, Mao C, MacNeil T, Kalyani R, Smith T, Weinberg D, Tota MR and Van der Ploeg LH. (1997) ART (protein product of agouti-related transcript) as an antagonist of MC-3 and MC-4 receptors. *Biochem Biophys Res Commun* **237**: 629-31 [PMID:9299416]
 41. Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP, Spedding M and Harmar AJ. (2005) International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-88 [PMID:15914470]
 42. Gantz I and Fong TM. (2003) The melanocortin system. *Am J Physiol Endocrinol Metab* **284**: E468-74 [PMID:12556347]
 43. Gantz I, Konda Y, Tashiro T, Shimoto Y, Miwa H, Munzert G, Watson SJ, DelValle J and Yamada T. (1993) Molecular cloning of a novel melanocortin receptor. *J Biol Chem* **268**: 8246-50 [PMID:8463333]
 44. Gantz I, Miwa H, Konda Y, Shimoto Y, Tashiro T, Watson SJ, DelValle J and Yamada T. (1993) Molecular cloning, expression, and gene localization of a fourth melanocortin receptor. *J Biol Chem* **268**: 15174-9 [PMID:8392067]
 45. Gantz I, Shimoto Y, Konda Y, Miwa H, Dickinson CJ and Yamada T. (1994) Molecular cloning, expression, and characterization of a fifth melanocortin receptor. *Biochem Biophys Res Commun* **200**: 1214-20 [PMID:8185570]
 46. Ghamari-Langroudi M, Digby GJ, Sebag JA, Millhauser GL, Palomino R, Matthews R, Gillyard T, Panaro BL, Tough IR and Cox HM *et al.*. (2015) G-protein-independent coupling of MC4R to Kir7.1 in hypothalamic neurons. *Nature* **520**: 94-8 [PMID:25600267]
 47. Giuliani D, Mioni C, Altavilla D, Leone S, Bazzani C, Minutoli L, Bitto A, Cainazzo MM, Marini H and Zaffe D *et al.*. (2006) Both early and delayed treatment with melanocortin 4 receptor-stimulating melanocortins produces neuroprotection in cerebral ischemia. *Endocrinology* **147**: 1126-35 [PMID:16254026]
 48. Grieco P, Balse PM, Weinberg D, MacNeil T and Hruby VJ. (2000) D-Amino acid scan of gamma-melanocyte-stimulating hormone: importance of Trp(8) on human MC3 receptor selectivity. *J Med Chem* **43**: 4998-5002 [PMID:11150170]
 49. Grieco P, Cai M, Han G, Trivedi D, Campiglia P, Novellino E and Hruby VJ. (2007) Further structure-activity studies of lactam derivatives of MT-II and SHU-9119: their activity and selectivity at human melanocortin receptors 3, 4, and 5. *Peptides* **28**: 1191-6 [PMID:17482720]
 50. Grieco P, Lavecchia A, Cai M, Trivedi D, Weinberg D, MacNeil T, Van der Ploeg LH and Hruby VJ. (2002) Structure-activity studies of the melanocortin peptides: discovery of potent and selective affinity antagonists for the hMC3 and hMC4 receptors. *J Med Chem* **45**: 5287-94 [PMID:12431055]
 51. Griffon N, Mignon V, Facchinetti P, Diaz J, Schwartz JC and Sokoloff P. (1994) Molecular cloning and characterization of the rat fifth melanocortin receptor. *Biochem Biophys Res Commun* **200**: 1007-14 [PMID:8179577]
 52. Hartmeyer M, Scholzen T, Becher E, Bhardwaj RS, Schwarz T and Luger TA. (1997) Human dermal microvascular endothelial cells express the melanocortin receptor type 1 and produce increased levels of IL-8 upon stimulation with alpha-melanocyte-stimulating hormone. *J Immunol* **159**: 1930-7 [PMID:9257858]
 53. Herpin TF, Yu G, Carlson KE, Morton GC, Wu X, Kang L, Tuerdi H, Khanna A, Tokarski JS and Lawrence RM *et al.*. (2003) Discovery of tyrosine-based potent and selective melanocortin-1 receptor small-molecule agonists with anti-inflammatory properties. *J Med Chem* **46**: 1123-6 [PMID:12646021]
 54. Hruby VJ, Lu D, Sharma SD, Castrucci AL, Kesterson RA, al-Obeidi FA, Hadley ME and Cone RD. (1995) Cyclic lactam alpha-melanotropin analogues of Ac-Nle4-cyclo[Asp5, D-Phe7,Lys10] alpha-melanocyte-stimulating hormone-(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**: 3454-61 [PMID:7658432]
 55. Huang RR, Singh G, Van der Ploeg LH and Fong TM. (2000) Species-dependent pharmacological properties of the melanocortin-5 receptor. *J Recept Signal Transduct Res* **20**: 47-59 [PMID:10711496]
 56. Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JH, Fang Q, Berkemeier LR, Gu W, Kesterson RA, Boston BA and Cone RD *et al.*. (1997) Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* **88**: 131-41 [PMID:9019399]
 57. Jayawickreme CK, Jayawickreme SP and Lerner MR. (1998) Generation of multiuse peptide libraries for functional screenings. *Methods Mol Biol* **87**: 107-18 [PMID:9523265]
 58. Kadekaro AL, Kavanagh R, Kanto H, Terzieva S, Hauser J, Kobayashi N, Schwemberger S, Cornelius J, Babcock G and Shertzer HG *et al.*. (2005) alpha-Melanocortin and endothelin-1 activate antiapoptotic pathways and reduce DNA damage in human melanocytes. *Cancer Res* **65**: 4292-9 [PMID:15899821]
 59. Kadekaro AL, Leachman S, Kavanagh RJ, Swope V, Cassidy P, Supp D, Sartor M, Schwemberger S, Babcock G and Wakamatsu K *et al.*. (2010) Melanocortin 1 receptor genotype: an important

determinant of the damage response of melanocytes to ultraviolet radiation. *FASEB J* **24**: 3850-60 [PMID:20519635]

60. Kapas S, Cammas FM, Hinson JP and Clark AJ. (1996) Agonist and receptor binding properties of adrenocorticotropin peptides using the cloned mouse adrenocorticotropin receptor expressed in a stably transfected HeLa cell line. *Endocrinology* **137**: 3291-4 [PMID:8754753]
61. Kask A, Mutulis F, Muceniece R, Pähkla R, Mutule I, Wikberg JE, Rägo L and Schiöth HB. (1998) Discovery of a novel superpotent and selective melanocortin-4 receptor antagonist (HS024): evaluation in vitro and in vivo. *Endocrinology* **139**: 5006-14 [PMID:9832440]
62. Kiefer LL, Veal JM, Mountjoy KG and Wilkison WO. (1998) Melanocortin receptor binding determinants in the agouti protein. *Biochemistry* **37**: 991-7 [PMID:9454589]
63. Kievit P, Halem H, Marks DL, Dong JZ, Glavas MM, Sinnayah P, Pranger L, Cowley MA, Grove KL and Culler MD. (2013) Chronic treatment with a melanocortin-4 receptor agonist causes weight loss, reduces insulin resistance, and improves cardiovascular function in diet-induced obese rhesus macaques. *Diabetes* **62**: 490-7 [PMID:23048186]
64. Kim SH, Han S, Zhao J, Wang S, Kusnetzow AK, Reinhart G, Fowler MA, Markison S, Johns M and Luo R *et al.*. (2024) Discovery of CRN04894: A Novel Potent Selective MC2R Antagonist. *ACS Med Chem Lett* **15**: 478-485 [PMID:38628803]
65. Kingsberg SA, Clayton AH, Portman D, Williams LA, Krop J, Jordan R, Lucas J and Simon JA. (2019) Bremelanotide for the Treatment of Hypoactive Sexual Desire Disorder: Two Randomized Phase 3 Trials. *Obstet Gynecol* **134**: 899-908 [PMID:31599840]
66. Kishi T, Aschkenasi CJ, Lee CE, Mountjoy KG, Saper CB and Elmquist JK. (2003) Expression of melanocortin 4 receptor mRNA in the central nervous system of the rat. *J Comp Neurol* **457**: 213-35 [PMID:12541307]
67. Koch M and Horvath TL. (2014) Molecular and cellular regulation of hypothalamic melanocortin neurons controlling food intake and energy metabolism. *Mol Psychiatry* **19**: 752-61 [PMID:24732669]
68. Kojima I, Kojima K and Rasmussen H. (1985) Role of calcium and cAMP in the action of adrenocorticotropin on aldosterone secretion. *J Biol Chem* **260**: 4248-56 [PMID:2579947]
69. Kopanchuk S, Veiksina S, Petrovska R, Mutule I, Szardenings M, Rinken A and Wikberg JE. (2005) Co-operative regulation of ligand binding to melanocortin receptor subtypes: evidence for interacting binding sites. *Eur J Pharmacol* **512**: 85-95 [PMID:15840392]
70. Krishna R, Gumbiner B, Stevens C, Musser B, Mallick M, Suryawanshi S, Maganti L, Zhu H, Han TH and Scherer L *et al.*. (2009) Potent and selective agonism of the melanocortin receptor 4 with MK-0493 does not induce weight loss in obese human subjects: energy intake predicts lack of weight loss efficacy. *Clin Pharmacol Ther* **86**: 659-66 [PMID:19741604]
71. Kubo M, Ishizuka T, Kijima H, Kakinuma M and Koike T. (1995) Cloning of a mouse adrenocorticotropin receptor-encoding gene. *Gene* **153**: 279-80 [PMID:7875603]
72. Kumar KG, Sutton GM, Dong JZ, Roubert P, Plas P, Halem HA, Culler MD, Yang H, Dixit VD and Butler AA. (2009) Analysis of the therapeutic functions of novel melanocortin receptor agonists in MC3R- and MC4R-deficient C57BL/6J mice. *Peptides* **30**: 1892-900 [PMID:19646498]
73. Labbe O, Desarnaud F, Eggerickx D, Vassart G and Parmentier M. (1994) Molecular cloning of a mouse melanocortin 5 receptor gene widely expressed in peripheral tissues. *Biochemistry* **33**: 4543-4549 [PMID:8161509]
74. Liang J, Li L, Jin X, Xu B, Pi L, Liu S, Zhu W, Zhang C, Luan B and Gong L *et al.*. (2018) Pharmacological effect of human melanocortin-2 receptor accessory protein 2 variants on hypothalamic melanocortin receptors. *Endocrine* **61**: 94-104 [PMID:29704154]
75. Lim BK, Huang KW, Grueter BA, Rothwell PE and Malenka RC. (2012) Anhedonia requires MC4R-mediated synaptic adaptations in nucleus accumbens. *Nature* **487**: 183-9 [PMID:22785313]
76. Lu D, Willard D, Patel IR, Kadwell S, Overton L, Kost T, Luther M, Chen W, Woychik RP and Wilkison WO *et al.*. (1994) Agouti protein is an antagonist of the melanocyte-stimulating-hormone receptor. *Nature* **371**: 799-802 [PMID:7935841]
77. MacNeil DJ, Howard AD, Guan X, Fong TM, Nargund RP, Bednarek MA, Goulet MT, Weinberg DH, Strack AM and Marsh DJ *et al.*. (2002) The role of melanocortins in body weight regulation: opportunities for the treatment of obesity. *Eur J Pharmacol* **440**: 141-57 [PMID:12007532]
78. Mansour AR, Farmer MA, Baliki MN and Apkarian AV. (2014) Chronic pain: the role of learning and brain plasticity. *Restor Neurol Neurosci* **32**: 129-39 [PMID:23603439]
79. Metherell LA, Chapple JP, Cooray S, David A, Becker C, Rüschemdorf F, Naville D, Begeot M, Khoo B and Nürnberg P *et al.*. (2005) Mutations in MRAP, encoding a new interacting partner of the ACTH receptor, cause familial glucocorticoid deficiency type 2. *Nat Genet* **37**: 166-70 [PMID:15654338]
80. Mountjoy KG. (2015) Pro-Opiomelanocortin (POMC) Neurones, POMC-Derived Peptides, Melanocortin Receptors and Obesity: How Understanding of this System has Changed Over the Last Decade. *J Neuroendocrinol* **27**: 406-18 [PMID:25872650]
81. Mountjoy KG, Bird IM, Rainey WE and Cone RD. (1994) ACTH induces up-regulation of ACTH

- receptor mRNA in mouse and human adrenocortical cell lines. *Mol Cell Endocrinol* **99**: R17-20 [PMID:8187950]
82. Mountjoy KG, Kong PL, Taylor JA, Willard DH and Wilkison WO. (2001) Melanocortin receptor-mediated mobilization of intracellular free calcium in HEK293 cells. *Physiol Genomics* **5**: 11-9 [PMID:11161002]
 83. Mountjoy KG, Mortrud MT, Low MJ, Simerly RB and Cone RD. (1994) Localization of the melanocortin-4 receptor (MC4-R) in neuroendocrine and autonomic control circuits in the brain. *Mol Endocrinol* **8**: 1298-308 [PMID:7854347]
 84. Mountjoy KG, Robbins LS, Mortrud MT and Cone RD. (1992) The cloning of a family of genes that encode the melanocortin receptors. *Science* **257**: 1248-51 [PMID:1325670]
 85. Mountjoy KG and Wild JM. (1998) Melanocortin-4 receptor mRNA expression in the developing autonomic and central nervous systems. *Brain Res Dev Brain Res* **107**: 309-14 [PMID:9593962]
 86. Nakanishi S, Inoue A, Kita T, Nakamura M, Chang AC, Cohen SN and Numa S. (1979) Nucleotide sequence of cloned cDNA for bovine corticotropin-beta-lipotropin precursor. *Nature* **278**: 423-7 [PMID:221818]
 87. Naville D, Barjhoux L, Jaillard C, Saez JM, Durand P and Bégeot M. (1997) Stable expression of normal and mutant human ACTH receptor: study of ACTH binding and coupling to adenylate cyclase. *Mol Cell Endocrinol* **129**: 83-90 [PMID:9175632]
 88. Ni XP, Pearce D, Butler AA, Cone RD and Humphreys MH. (2003) Genetic disruption of gamma-melanocyte-stimulating hormone signaling leads to salt-sensitive hypertension in the mouse. *J Clin Invest* **111**: 1251-8 [PMID:12697744]
 89. Nickolls SA, Cismowski MI, Wang X, Wolff M, Conlon PJ and Maki RA. (2003) Molecular determinants of melanocortin 4 receptor ligand binding and MC4/MC3 receptor selectivity. *J Pharmacol Exp Ther* **304**: 1217-27 [PMID:12604699]
 90. Norman D, Isidori AM, Frajese V, Caprio M, Chew SL, Grossman AB, Clark AJ, Michael Besser G and Fabbri A. (2003) ACTH and alpha-MSH inhibit leptin expression and secretion in 3T3-L1 adipocytes: model for a central-peripheral melanocortin-leptin pathway. *Mol Cell Endocrinol* **200**: 99-109 [PMID:12644303]
 91. Ollmann MM, Wilson BD, Yang YK, Kerns JA, Chen Y, Gantz I and Barsh GS. (1997) Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein. *Science* **278**: 135-8 [PMID:9311920]
 92. Oosterom J, Nijenhuis WA, Schaaper WM, Slootstra J, Meloen RH, Gispen WH, Burbach JP and Adan RA. (1999) Conformation of the core sequence in melanocortin peptides directs selectivity for the melanocortin MC3 and MC4 receptors. *J Biol Chem* **274**: 16853-60 [PMID:10358030]
 93. Ozdeslik RN, Olinski LE, Trieu MM, Oprian DD and Oancea E. (2019) Human nonvisual opsin 3 regulates pigmentation of epidermal melanocytes through functional interaction with melanocortin 1 receptor. *Proc Natl Acad Sci USA* **116**: 11508-11517 [PMID:31097585]
 94. Pandit R, van der Zwaal EM, Luijendijk MC, Brans MA, van Rozen AJ, Oude Ophuis RJ, Vanderschuren LJ, Adan RA and la Fleur SE. (2015) Central melanocortins regulate the motivation for sucrose reward. *PLoS ONE* **10**: e0121768 [PMID:25811380]
 95. Rached M, El Mourabit H, Buronfosse A, Blondet A, Naville D, Begeot M and Penhoat A. (2005) Expression of the human melanocortin-2 receptor in different eukaryotic cells. *Peptides* **26**: 1842-7 [PMID:15982783]
 96. Robbins LS, Nadeau JH, Johnson KR, Kelly MA, Roselli-Rehfuss L, Baack E, Mountjoy KG and Cone RD. (1993) Pigmentation phenotypes of variant extension locus alleles result from point mutations that alter MSH receptor function. *Cell* **72**: 827-34 [PMID:8458079]
 97. Roselli-Rehfuss L, Mountjoy KG, Robbins LS, Mortrud MT, Low MJ, Tatro JB, Entwistle ML, Simerly RB and Cone RD. (1993) Identification of a receptor for gamma melanotropin and other proopiomelanocortin peptides in the hypothalamus and limbic system. *Proc Natl Acad Sci USA* **90**: 8856-60 [PMID:8415620]
 98. Rosenfeld RD, Zeni L, Welcher AA, Narhi LO, Hale C, Marasco J, Delaney J, Gleason T, Philo JS and Katta V *et al.* (1998) Biochemical, biophysical, and pharmacological characterization of bacterially expressed human agouti-related protein. *Biochemistry* **37**: 16041-52 [PMID:9819197]
 99. Sawyer TK, Sanfilippo PJ, Hruby VJ, Engel MH, Heward CB, Burnett JB and Hadley ME. (1980) 4-Norleucine, 7-D-phenylalanine-alpha-melanocyte-stimulating hormone: a highly potent alpha-melanotropin with ultralong biological activity. *Proc Natl Acad Sci USA* **77**: 5754-8 [PMID:6777774]
 100. Schimmer BP, Kwan WK, Tsao J and Qiu R. (1995) Adrenocorticotropin-resistant mutants of the Y1 adrenal cell line fail to express the adrenocorticotropin receptor. *J Cell Physiol* **163**: 164-71 [PMID:7896893]
 101. Schiöth HB, Muceniec R, Wikberg JE and Chhajlani V. (1995) Characterisation of melanocortin receptor subtypes by radioligand binding analysis. *Eur J Pharmacol* **288**: 311-317 [PMID:7774675]
 102. Schiöth HB. (2001) The physiological role of melanocortin receptors. *Vitam Horm* **63**: 195-232

[PMID:11358115]

103. Schiöth HB, Haitina T, Ling MK, Ringholm A, Fredriksson R, Cerdá-Reverter JM and Klovins J. (2005) Evolutionary conservation of the structural, pharmacological, and genomic characteristics of the melanocortin receptor subtypes. *Peptides* **26**: 1886-900 [PMID:15985310]
104. Schiöth HB, Muceniece R, Mutulis F, Bouifrouri AA, Mutule I and Wikberg JE. (1999) Further pharmacological characterization of the selective melanocortin 4 receptor antagonist HS014: comparison with SHU9119. *Neuropeptides* **33**: 191-6 [PMID:10657491]
105. Schiöth HB, Muceniece R and Wikberg JE. (1996) Characterisation of the melanocortin 4 receptor by radioligand binding. *Pharmacol Toxicol* **79**: 161-5 [PMID:8884876]
106. Schiöth HB, Muceniece R, Wikberg JE and Szardenings M. (1996) Alternative translation initiation codon for the human melanocortin MC3 receptor does not affect the ligand binding. *Eur J Pharmacol* **314**: 381-4 [PMID:8957262]
107. Schiöth HB, Mutulis F, Muceniece R, Prusis P and Wikberg JE. (1998) Discovery of novel melanocortin4 receptor selective MSH analogues. *Br J Pharmacol* **124**: 75-82 [PMID:9630346]
108. Sebhait IK, Martin WJ, Ye Z, Barakat K, Mosley RT, Johnston DB, Bakshi R, Palucki B, Weinberg DH, MacNeil T, Kalyani RN, Tang R, Stearns RA, Miller RR, Tamvakopoulos C, Strack AM, McGowan E, Cashen DE, Drisko JE, Hom GJ, Howard AD, MacIntyre DE, van der Ploeg LH, Patchett AA and Nargund RP. (2002) Design and pharmacology of N-[(3R)-1,2,3,4-tetrahydroisoquinolinium-3-ylcarbonyl]-(1R)-1-(4-chlorobenzyl)-2-[4-cyclohexyl-4-(1H-1,2,4-triazol-1-ylmethyl)piperidin-1-yl]-2-oxoethylamine (1), a potent, selective, melanocortin subtype-4 receptor agonist. *J Med Chem* **45**: 4589-4593 [PMID:12361385]
109. Serova LI, Laukova M, Alaluf LG and Sabban EL. (2013) Intranasal infusion of melanocortin receptor four (MC4R) antagonist to rats ameliorates development of depression and anxiety related symptoms induced by single prolonged stress. *Behav Brain Res* **250**: 139-47 [PMID:23680165]
110. Shen Y, Fu WY, Cheng EY, Fu AK and Ip NY. (2013) Melanocortin-4 receptor regulates hippocampal synaptic plasticity through a protein kinase A-dependent mechanism. *J Neurosci* **33**: 464-72 [PMID:23303927]
111. Shutter JR, Graham M, Kinsey AC, Scully S, Lüthy R and Stark KL. (1997) Hypothalamic expression of ART, a novel gene related to agouti, is up-regulated in obese and diabetic mutant mice. *Genes Dev* **11**: 593-602 [PMID:9119224]
112. Skuladottir GV, Jonsson L, Skarphedinsson JO, Mutulis F, Muceniece R, Raine A, Mutule I, Helgason J, Prusis P and Wikberg JE *et al.*. (1999) Long term orexigenic effect of a novel melanocortin 4 receptor selective antagonist. *Br J Pharmacol* **126**: 27-34 [PMID:10051117]
113. Slominski A, Ermak G and Mihm M. (1996) ACTH receptor, CYP11A1, CYP17 and CYP21A2 genes are expressed in skin. *J Clin Endocrinol Metab* **81**: 2746-9 [PMID:8675607]
114. Smith AI and Funder JW. (1988) Proopiomelanocortin processing in the pituitary, central nervous system, and peripheral tissues. *Endocr Rev* **9**: 159-179 [PMID:3286233]
115. Spaccapelo L, Bitto A, Galantucci M, Ottani A, Irrera N, Minutoli L, Altavilla D, Novellino E, Grieco P and Zaffe D *et al.*. (2011) Melanocortin MC₄ receptor agonists counteract late inflammatory and apoptotic responses and improve neuronal functionality after cerebral ischemia. *Eur J Pharmacol* **670**: 479-86 [PMID:21946115]
116. Star RA, Rajora N, Huang J, Stock RC, Catania A and Lipton JM. (1995) Evidence of autocrine modulation of macrophage nitric oxide synthase by alpha-melanocyte-stimulating hormone. *Proc Natl Acad Sci USA* **92**: 8016-20 [PMID:7544012]
117. Swords FM, Baig A, Malchoff DM, Malchoff CD, Thorner MO, King PJ, Hunyady L and Clark AJ. (2002) Impaired desensitization of a mutant adrenocorticotropin receptor associated with apparent constitutive activity. *Mol Endocrinol* **16**: 2746-53 [PMID:12456795]
118. Szardenings M, Muceniece R, Mutule I, Mutulis F and Wikberg JE. (2000) New highly specific agonistic peptides for human melanocortin MC(1) receptor. *Peptides* **21**: 239-43 [PMID:10764951]
119. Tan CP, McKee KK, Weinberg DH, MacNeil T, Palyha OC, Feighner SD, Hreniuk DL, Van Der Ploeg LH, MacNeil DJ and Howard AD. (1999) Molecular analysis of a new splice variant of the human melanocortin-1 receptor. *FEBS Lett* **451**: 137-41 [PMID:10371153]
120. Tao YX. (2010) The melanocortin-4 receptor: physiology, pharmacology, and pathophysiology. *Endocr Rev* **31**: 506-43 [PMID:20190196]
121. Vaisse C, Clement K, Durand E, Hercberg S, Guy-Grand B and Froguel P. (2000) Melanocortin-4 receptor mutations are a frequent and heterogeneous cause of morbid obesity. *J Clin Invest* **106**: 253-62 [PMID:10903341]
122. Valverde P, Healy E, Jackson I, Rees JL and Thody AJ. (1995) Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. *Nat Genet* **11**: 328-30 [PMID:7581459]
123. van der Klaauw A, Keogh J, Henning E, Stephenson C, Trowse VM, Fletcher P and Farooqi S. (2015) Role of melanocortin signalling in the preference for dietary macronutrients in human beings. *Lancet* **385 Suppl 1**: S12 [PMID:26312834]

124. van der Kraan M, Adan RA, Entwistle ML, Gispen WH, Burbach JP and Tatro JB. (1998) Expression of melanocortin-5 receptor in secretory epithelia supports a functional role in exocrine and endocrine glands. *Endocrinology* **139**: 2348-55 [PMID:9564844]
125. Van der Ploeg LH, Martin WJ, Howard AD, Nargund RP, Austin CP, Guan X, Drisko J, Cashen D, Sebhat I and Patchett AA *et al.*. (2002) A role for the melanocortin 4 receptor in sexual function. *Proc Natl Acad Sci USA* **99**: 11381-6 [PMID:12172010]
126. Västermarck A and Schiöth HB. (2011) The early origin of melanocortin receptors, agouti-related peptide, agouti signalling peptide, and melanocortin receptor-accessory proteins, with emphasis on pufferfishes, elephant shark, lampreys, and amphioxus. *Eur J Pharmacol* **660**: 61-9 [PMID:21208605]
127. Wachira SJ, Hughes-Darden CA, Taylor CV, Ochillo R and Robinson TJ. (2003) Evidence for the interaction of protein kinase C and melanocortin 3-receptor signaling pathways. *Neuropeptides* **37**: 201-10 [PMID:12906838]
128. Wardlaw SL. (2011) Hypothalamic proopiomelanocortin processing and the regulation of energy balance. *Eur J Pharmacol* **660**: 213-9 [PMID:21208604]
129. Wikberg JE. (1999) Melanocortin receptors: perspectives for novel drugs. *Eur J Pharmacol* **375**: 295-310 [PMID:10443584]
130. Wikberg JE and Mutulis F. (2008) Targeting melanocortin receptors: an approach to treat weight disorders and sexual dysfunction. *Nat Rev Drug Discov* **7**: 307-23 [PMID:18323849]
131. Xia Y and Wikberg JE. (1996) Localization of ACTH receptor mRNA by in situ hybridization in mouse adrenal gland. *Cell Tissue Res* **286**: 63-8 [PMID:8781213]
132. Yang Y. (2011) Structure, function and regulation of the melanocortin receptors. *Eur J Pharmacol* **660**: 125-30 [PMID:21208602]
133. Yang YK, Dickinson C, Lai YM, Li JY and Gantz I. (2001) Functional properties of an agouti signaling protein variant and characteristics of its cognate radioligand. *Am J Physiol Regul Integr Comp Physiol* **281**: R1877-86 [PMID:11705773]
134. Yang YK, Fong TM, Dickinson CJ, Mao C, Li JY, Tota MR, Mosley R, Van Der Ploeg LH and Gantz I. (2000) Molecular determinants of ligand binding to the human melanocortin-4 receptor. *Biochemistry* **39**: 14900-11 [PMID:11101306]
135. Yang YK, Ollmann MM, Wilson BD, Dickinson C, Yamada T, Barsh GS and Gantz I. (1997) Effects of recombinant agouti-signaling protein on melanocortin action. *Mol Endocrinol* **11**: 274-80 [PMID:9058374]
136. Yang YK, Thompson DA, Dickinson CJ, Wilken J, Barsh GS, Kent SB and Gantz I. (1999) Characterization of Agouti-related protein binding to melanocortin receptors. *Mol Endocrinol* **13**: 148-55 [PMID:9892020]
137. Ye Z, Guo L, Barakat KJ, Pollard PG, Palucki BL, Sebhat IK, Bakshi RK, Tang R, Kalyani RN and Vongs A *et al.*. (2005) Discovery and activity of (1R,4S,6R)-N-[(1R)-2-[4-cyclohexyl-4-[(1,1-dimethylethyl)amino]carbonyl]-1-piperidinyl]-1-[(4-fluorophenyl)methyl]-2-oxoethyl]-2-methyl-2-azabicyclo[2.2.2]octane-6-carboxamide (3, RY764), a potent and selective melanocortin subtype-4 receptor agonist. *Bioorg Med Chem Lett* **15**: 3501-5 [PMID:15982875]
138. Yoon YR, Lee TG, Choi MH, Shin SW, Ko YG, Rhyu IJ, Kim DH, Seong JK and Baik JH. (2018) Glucose-regulated protein 78 binds to and regulates the melanocortin-4 receptor. *Exp Mol Med* **50**: 120 [PMID:30209265]
139. Yu J, Gimenez LE, Hernandez CC, Wu Y, Wein AH, Han GW, McClary K, Mittal SR, Burdsall K and Stauch B *et al.*. (2020) Determination of the melanocortin-4 receptor structure identifies Ca²⁺ as a cofactor for ligand binding. *Science* **368**: 428-433 [PMID:32327598]