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Structural Modifications Allow the Removal of Melanocortin Receptor 1 Agonism From Melanocortin Receptor 4 Agonists

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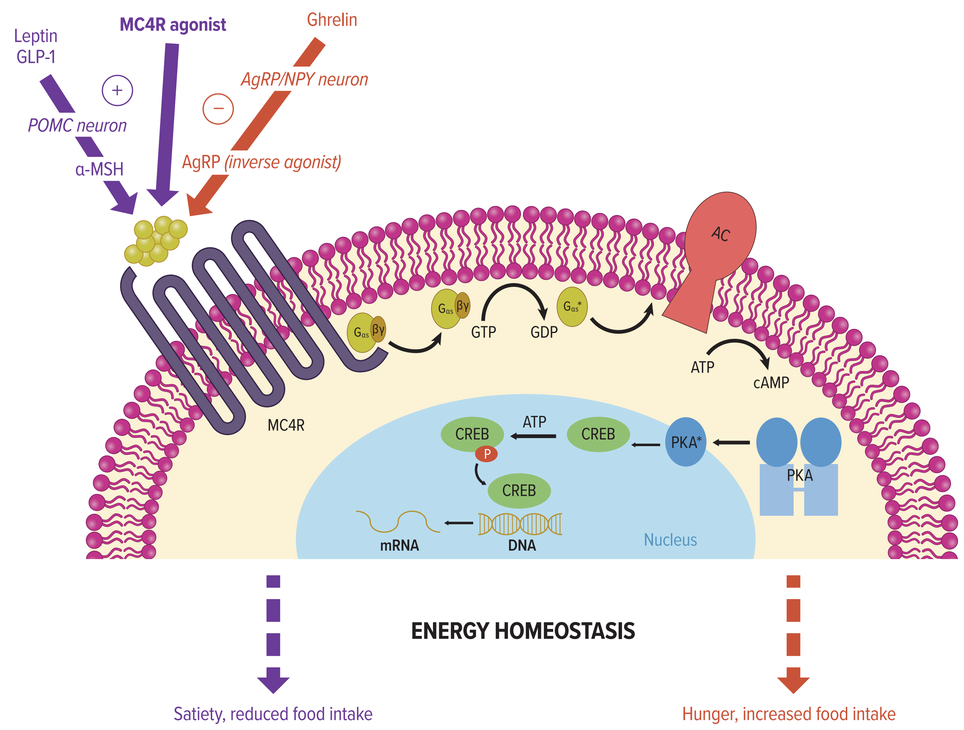
- The melanocortin pathway regulates energy balance.[1-3] The melanocortin receptor 4 (MC4R) gene is the most commonly associated gene found in childhood obesity. Multiple studies have investigated its mechanism of action and the function of different mutations[4]
- MC4R plays an important role in food intake behavior and energy homeostasis largely via the binding of its endogenous agonist α-melanocyte–stimulating hormone, whose release is stimulated by leptin (**Figure**)[2,3,5,6]
- Activating the MC4R pathway is therefore potentially a treatment option for general obesity

Mechanism for Melanocortin-Mediated Regulation of Gene Expression for Energy Homeostasis[6-8]



α-MSH stimulation of MC4R leads to activation of the G protein, Gαs, and the subsequent activation of AC, which converts ATP to cAMP. cAMP-mediated activation of PKA leads to the dissociation of the catalytic subunit of the PKA complex. Upon translocation of the active PKA catalytic subunit (PKA*) into the nucleus, PKA phosphorylates the transcription factor CREB. When bound to upstream consensus DNA sequences (CRE), CREB-P facilitates transcription of a gene by interaction with the core transcriptional machinery.
AC, adenylate cyclase; AgRP, agouti-related protein; α-MSH, α-melanocyte-stimulating hormone; CRE, cAMP response elements; CREB, cAMP response element binding protein; GLP-1, glucagon-like peptide-1; MC4R, melanocortin receptor 4; NPY, neuropeptide Y; PKA, protein kinase A; POMC, proopiomelanocortin.
Adapted from Gonçalves et al 2018[6] and Palmer et al 2017[9].

- Setmelanotide, an MC4R agonist, is approved by the US Food and Drug Administration for chronic weight management in adults and children ≥6 years of age with genetically linked obesity[10]
- Bremelanotide is approved for treatment of acquired, generalized hypoactive sexual desire disorder in premenopausal women,[11] and has demonstrated in 2 phase 1, randomized, placebo-controlled trials that bremelanotide may reduce caloric intake and promote weight loss among women with obesity[12]

- When considering an agonist, a low concentration of the compound that induces the expected response (half maximal effective concentration [EC50]) is not the only property to take into consideration. The selectivity, the ability to activate only the desired pathway with minimal activation of extraneous signaling pathways, should also be assessed
- **Palatin Technologies has identified the peptide structural loci that are responsible for the MC1R agonism found in nonselective MC4R agonists, resulting in the discovery of new MC4R agonists of increasing selectivity (Table)**
  - 4 locations on the cyclic peptide structure act together to impart MC1R agonism
  - Each structural locus has been modified to optimize MC4R activity over MC1R activity
  - When all 4 loci are optimized, the resulting synergy allows MC1R agonism to be eliminated (agonist #3 in the **Table**)

MC4R Agonists Approved and in Development

Agonist	MC1R EC50 (E_{max})	MC4R EC50 (E_{max})	MC4R Selectivity[a]	Structural Loci Modified From Bremelanotide
Bremelanotide	0.23 nM (91.8%)	5.01 nM (91.0%)	0.05	–
Setmelanotide	0.4 nM (106%)	0.66 nM (98.8%)	0.61	Not structurally analogous
PL8905	30.2 nM (78.5%)	4.99 nM (88.3%)	6.05	Loci #1 and 2
1	199.6 nM (98.8%)	2.99 nM (107.4%)	66.76	Loci #1 and 3
2	69.1 nM (89.9%)	0.74 nM (94.9%)	93.38	Loci, #1, 2, and 3
3	352.3 nM (32.5%)	9.69 nM (90.5%)	Undefined[b]	Loci #1, 2, 3, and 4

[a]MC1R EC50/MC4R EC50. [b]cAMP expression was too low to allow the compound to be defined as an MC1R agonist.
cAMP, cyclic adenosine monophosphate; EC50, half maximal effective concentration; E_{max}, maximum effect; MC1R, melanocortin receptor 1; MC4R, melanocortin receptor 4; POMC, proopiomelanocortin.

- An MC4R agonist with high selectivity for the MC4R would potentially reduce skin pigmentation adverse effects[2,13]

The development of these more selective MC4R agonists potentially further improves treatment options for obesity and may help avoid side effects of MC1R stimulation

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Disclosures John H. Dodd, Lakmal Boteju, and Carl Spana are employees of Palatin Technologies, Inc.

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