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(54) Titre : AGONISTES SELECTIFS DU RECEPTEUR DE TYPE 1 DE L'HORMONE DE MELANO-CONCENTRATION
(54) Title: SELECTIVE MELANIN-CONCENTRATING HORMONE TYPE -1 RECEPTOR AGONISTS

(57) Abrégé/Abstract:
The present invention features truncated hMCH analogs selectively active at MCH-1R over MCH-2R. Using amino acid numbering provided in hMCH, the featured analogs contain an X^{6} which is either a D-amino acid, 5-guanidinopropionic acid or its lower or higher homolog, or a derivative thereof; and a X^{10} which is either asparagine, glutamine, alanine, leucine, isoleucine, valine, norleucine, cyclohexylalanine, phenylalanine, (2')-naphthylalanine, tyrosine, histidine, tryptophan, lysine, serine, threonine, methionine, or a derivative thereof.

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(54) Title: SELECTIVE MELANIN-CONCENTRATING HORMONE TYPE -1 RECEPTOR AGONISTS

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TITLE OF THE INVENTION

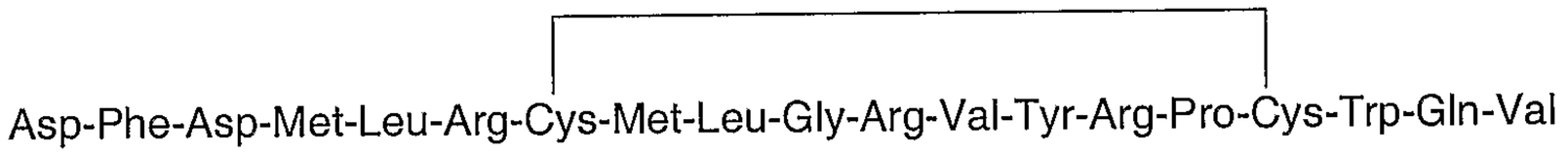
SELECTIVE MELANIN-CONCENTRATING HORMONE TYPE -1 RECEPTOR AGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to provisional application U.S. Serial No. 60/347,191, filed January 9, 2002, hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

Neuropeptides present in the hypothalamus play a major role in mediating the control of body weight. (Flier *et al.,* 1998, *Cell, 92*, 437-440.) Melanin-concentrating hormone (MCH) produced in mammals is a cyclic 19-amino acid neuropeptide synthesized as part of a larger pre-prohormone precursor in the hypothalamus which also encodes neuropeptides NEI and NGE. (Nahon *et al.,* 1990, *Mol. Endocrinol. 4*, 632-637; Vaughan *et al.,* U.S. Patent No. 5,049,655; and Vaughan *et al.,* 1989, *Endocrinology 125*, 1660-1665.) Human MCH (hMCH) has the following structure (SEQ. ID. NO. 1):



MCH was first identified in salmon pituitary, and in fish MCH affects melanin aggregation thus affecting skin pigmentation. In trout and eels MCH has also been shown to be involved in stress induced or CRF–stimulated ACTH release. (Kawauchi *et al.,* 1983, *Nature 305*, 321-323.)

In humans two genes encoding hMCH have been identified that are expressed in the brain. (Breton *et al.,* 1993, *Mol. Brain Res. 18*, 297-310.) In mammals MCH has been localized primarily to neuronal cell bodies of the hypothalamus which are implicated in the control of food intake, including perikarya of the lateral hypothalamus and zona inertia. (Knigge *et al.,* 1996, *Peptides 17*, 1063-1073.)

Pharmacological and genetic evidence suggest that the primary mode of MCH action is to promote feeding (orexigenic). MCH mRNA is up regulated in fasted mice and rats, in the *ob/ob* mouse and in mice with targeted disruption in the gene for neuropeptide Y (NPY). (Qu *et al.,* 1996, *Nature 380,* 243-247 and Erickson

et al., 1996, *Nature 381*, 415-418.) Injection of MCH centrally (ICV) stimulates food intake and MCH antagonizes the hypophagic effects seen with α melanocyte stimulating hormone (αMSH). (Qu *et al.,* 1996, *Nature 380*, 243-247.) MCH deficient mice are lean, hypophagic and have an increased metabolic rate. (Shimada *et al.,* 1998, *Nature 396*, 670-673.) The administration of MCH has been indicated to be useful for promoting eating, appetite or the gain or maintenance of weight. (Maratos-Flier, U.S. Patent No. 5,849,708.)

MCH action is not limited to modulation of food intake as effects on the hypothalamic-pituitary-axis have been reported. (Nahon, 1994, *Critical Rev. in Neurobiol. 8*, 221-262.) MCH may be involved in the body response to stress as MCH can modulate the stress-induced release of CRF from the hypothalamus and ACTH from the pituitary. In addition, MCH neuronal systems may be involved in reproductive or maternal function.

Human MCH can bind to at least two different receptors: MCH-1R and MCH-2R. (Chambers *et al.,* 1999, *Nature 400*, 261-265; Saito *et al.,* 1999, *Nature 400*, 265-269; Bächner *et al.,* 1999, *FEBS Letters 457*:522-524; Shimomura *et al.,* 1999, *Biochemical and Biophysical Research Communications 261*, 622-626; Sailer *et al., Proc. Natl. Acad. Sci. 98*:7564-7569, 2001.) The amino acid identity between MCH-2R and MCH-1R is about 38%. (Sailer *et al., Proc. Natl. Acad. Sci. 98*:7564-7569, 2001.)

SUMMARY OF THE INVENTION

The present invention features truncated hMCH analogs selectively active at MCH-1R over MCH-2R. Using amino acid numbering provided in hMCH, the featured analogs contain an X^6 which is either a D-amino acid, 5-guanidinopropionic acid or its lower or higher homolog, or a derivative thereof; and a X^{10} which is either asparagine, glutamine, alanine, leucine, isoleucine, valine, norleucine, cyclohexylalanine, phenylalanine, (2')-naphthylalanine, tyrosine, histidine, tryptophan, lysine, serine, threonine, methionine, or a derivative thereof.

Human MCH analogs selective for MCH-1R exert a greater activity at MCH-1R than at MCH-2R. MCH activities at MCH-1R and MCH-2R include receptor binding and receptor activation. MCH analogs selectively active at MCH-1R can have an increased binding, an increased activity, or both an increased binding and an increased activity at MCH-1R. Preferred MCH analogs have both an increased binding and an increased activity at MCH-1R. In different embodiments, the

difference between the levels of activity at MCH-1R compared to MCH-2R is at least about 2, 5, 10, or 20 fold.

Thus, a first aspect of the present invention describes an optionally substituted peptide having the structure:

Z^1- X^1-X^2-X^3-X^4-X^5-X^6-X^7-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-Z^2

wherein X^1 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof;

X^2 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof;

X^3 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof;

X^4 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, glutamic acid, or norleucine, or a derivative thereof;

X^5 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof;

X^6 either is a D-amino acid, 5-guanidinopropionic acid or its lower or higher homolog, or a derivative thereof;

X^7 is either lysine, cysteine, homocysteine, 3-mercaptopropionic acid or its higher homolog, penicillamine, 2,3 diamino proprionic acid or its higher homolog, or aspartic acid or its higher homolog, or a derivative thereof;

X^8 is either methionine, norleucine, leucine, isoleucine, valine, methioninesulfoxide, or methioninesulfone, or a derivative thereof;

X^9 is either leucine, isoleucine, valine, alanine, methionine, or 5-aminopentanoic acid, or a derivative thereof;

X^{10} is either asparagine, glutamine, alanine, leucine, isoleucine, valine, norleucine, cyclohexylalanine, phenylalanine, (2')-naphthylalanine, tyrosine, histidine, tryptophan, lysine, serine, threonine, methionine, or citrulline, or a derivative thereof;

X^{11} is either arginine, lysine, citrulline, histidine, homoarginine, norarginine, or nitroarginine, or a derivative thereof;

X^{12} is either valine, leucine, isoleucine, alanine, or methionine, or a derivative thereof;

X^{13} is either phenylalanine, tyrosine, D-(*p*-benzoylphenylalanine), tryptophan, (1')- and (2')-naphthylalanine, cyclohexylalanine, or mono and multi-substituted phenylalanine wherein each substituent is independently selected from the group consisting of O-alkyl, alkyl, OH, NO_2, NH_2, F, I, and Br; or a derivative thereof;

X^{14} is either arginine, lysine, histidine, norarginine, homoarginine, nitroarginine, or 5-aminopentanoic acid, or a derivative thereof;

X^{15} is either proline, alanine, valine, leucine, isoleucine, methionine, sarcosine, or 5-aminopentanoic acid, or a derivative thereof;

X^{16} is an optionally present amino acid that if present is either cysteine, homocysteine, cysteamine, penicillamine, 2,3 diamino propionic acid or its higher homolog, or aspartic acid or its higher homolog, or a derivative thereof;

X^{17} is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof;

Z^1 is an optionally present protecting group that, if present, is covalently joined to the N-terminal amino group;

Z^2 is an optionally present protecting group that, if present, is covalently joined to the C-terminal carboxy group;

provided that if X^{16} is present, X^{16} and X^7 together form a cyclic group joined by either a disulfide bond or an amide bond, wherein if X^7 is either

cysteine, homocysteine, 3-mercaptopropionic acid or its higher homolog, or penicillamine, then X^{16} is either cysteine, homocysteine, cysteamine, or penicillamine; if X^7 is 2,3 diamino proprionic acid or its higher homolog then X^{16} is aspartic acid or its higher homolog; and if X^7 is aspartic acid or its higher homolog then X^{16} is 2,3 diamino proprionic acid or its higher homolog;

further provided that if X^{16} is not present, then X^{17} is not present, Z^2 is not present, X^7 is lysine, and X^{15} and X^7 together form a cyclic group joined by the X^7 Lys epsilon amino group and the X^{15} carboxyl group;

or a labeled derivative of the peptide;

or a pharmaceutically acceptable salt of the peptide or of the labeled derivative.

Unless otherwise stated, those amino acids with a chiral center are provided in the L-enantiomer. Reference to "a derivative thereof" refers to the corresponding D-amino acid, N-alkyl-amino acid, β-amino acid, and ω-amino acid.

Another aspect of the present invention describes a method of screening for a compound able to bind MCH-1R. The method comprises the step of measuring the ability of the compound to affect binding of a hMCH analog to MCH-1R.

Another aspect of the present invention describes a method of selectively producing MCH-1R activity comprising the step of providing a cell functionally expressing MCH-1R with a hMCH analog. The method can be performed using cultured cells expressing MCH-1R or mammals.

Another aspect of the present invention features a method of screening for a MCH-1R antagonist. The method comprises the steps of:

a) combining together MCH-1R or a functional derivative thereof, a test compound, and a selectively active MCH-1R agonist,

b) measuring the ability of the test compound to inhibit an MCH-1R activity as an indication of the ability of the test compound to act as a MCH-1R antagonist.

Another aspect of the present invention describes a method for increasing weight or appetite in a subject. The method comprises the step of administering to the subject an effective amount of a hMCH analog that activates MCH-1R to produce a weight increase.

Another aspect of the present invention describes a method for measuring the ability of a compound to decrease weight or appetite in a subject. The

method involves administering to the subject an effective amount of a hMCH analog that would produce a weight or appetite increase and measuring the effect of the compound on weight or appetite.

Other features and advantages of the present invention are apparent from the additional descriptions provided herein including the different examples. The provided examples illustrate different components and methodology useful in practicing the present invention. The examples do not limit the claimed invention. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present invention.

DETAILED DESCRIPTION OF THE INVENTION

MCH-1R selective analogs were identified containing particular amino acids in position 6 and in position 10 of a truncated hMCH. Based on the identified amino acids different size MCH analogs can be provided. Preferred MCH analogs are smaller length analogs based on AC-hMCH6-16-NH_2 (SEQ. ID. NO. 2). AC-hMCH6-16-NH_2 provides a core region facilitating MCH-1R activity. Smaller length peptides offer advantages over larger peptides such as ease of synthesis and/or increased solubility in physiological buffers.

Preferred hMCH analogs have significant activity at MCH-1R. Significant activity at MCH-1R is activity that is at least about 50%, at least about 75%, or at least about 100% of activity compared to the activity obtained using hMCH. Activity at MCH-1R can be assayed using techniques measuring binding or G-protein activity such as those described in the Example provided below.

Uses of hMCH analogs include research tool and therapeutic applications. Research tool applications generally involve the use of a MCH analog and MCH-1R. MCH-1R can be present in different environments such as a mammalian subject, a whole cell, and membrane fragments. Examples of research tool applications of MCH analogs include screening for compounds active at MCH-1R, determining whether MCH-1R may be present in a sample or preparation, examining the role or effect of MCH and MCH-1R activation, and examining the role or effect of MCH antagonists.

Human MCH analogs selectivity active at MCH-1R have additional uses related to the selective activity. Examples of additional uses include being used to explore differences between MCH-1R and MCH-2R and to distinguish between the presence of MCH-1R and MCH-2R.

Human MCH analogs can be used to screen for both MCH agonists and MCH antagonists. Screening for MCH agonists can be performed, for example, by using a MCH analog in a competition experiment with test compounds. Screening for MCH antagonists can be performed, for example, by using a MCH analog to produce MCH-1R activity and then measuring the ability of a test compound to alter such activity.

Therapeutic applications of hMCH analogs involve administration to a subject containing an MCH-1R. Subjects possessing MCH-1R include humans, mice, rats, dogs, ferrets, and rhesus monkeys.

Reference to subject does not necessarily indicate the presence of a disease or disorder. The term subject includes, for example, humans being treated to help alleviate a disease or disorder, and humans being treated prophylactically to retard or prevent the onset of a disease or disorder.

MCH agonists can be used to achieve a beneficial effect in a subject. For example, a MCH agonist can be used to facilitate weight gain, maintenance of weight and/or appetite increase. Such effects are particularly useful for a patient having a disease or disorder, or under going a treatment, accompanied by weight loss. Examples of diseases or disorders accompanied by weight loss include anorexia, AIDS, wasting, cachexia, and frail elderly. Examples of treatments accompanied by weight loss include chemotherapy, radiation therapy, and dialysis.

MCH antagonists can also be used to achieve a beneficial effect in a patient. For example, a MCH antagonist can be used to facilitate weight loss, appetite decrease, weight maintenance, cancer (*e.g.,* colon or breast) treatment, pain reduction, stress reduction and/or treatment of sexual dysfunction.

MCH-1R Selectively Active Analogs

Selectively active hMCH analogs can be designed based on the disclosure provided herein concerning the importance of particular groups in positions 6 and 10 of hMCH. The remaining amino acids in a MCH analog can correspond to those amino acid present in naturally occurring MCH or can differ from the naturally occurring amino acids.

The importance of different MCH amino acids for providing MCH-1R activity is evaluated by references such as Bednarek *et al.,* 2001, *Biochemistry 40*:9379-9386, Bednarek, International Publication No. WO 01/57070, and Audinot *et al.,* 2001, *The Journal of Biological Chemistry 276*:13554-13562. Techniques

described in these references can be employed to further evaluate amino acid alterations to MCH analogs.

Human MCH-1R analogs featured herein are optionally modified peptides having the structure:

Z^1- X^1-X^2-X^3-X^4-X^5-X^6-X^7-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-Z^2

wherein X^1 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof; preferably, X^1 if present is aspartic acid or glutamic acid; more preferably, X^1 if present is aspartic acid; and more preferably, X^1 is not present;

X^2 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof; preferably, X^2 if present is phenylalanine or tyrosine; more preferably, X^2 if present is phenylalanine; and more preferably, X^2 is not present;

X^3 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof; preferably, X^3 if present is aspartic acid or glutamic acid; more preferably, X^3 if present is aspartic acid; and more preferably, X^3 is not present;

X^4 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, glutamic acid, or norleucine, or a derivative thereof; preferably, X^4 if present is methionine, leucine, isoleucine, valine, alanine or norleucine; more preferably, X^4 if present is methionine; and more preferably, X^4 is not present;

X^5 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine,

serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof; preferably, X^5 if present is leucine, methionine, isoleucine, valine or alanine; more preferably, X^5 if present is leucine; and more preferably, X^5 is not present;

X^6 either is a D-amino acid, 5-guanidinopropionic acid or its lower or higher homolog, or a derivative thereof; preferably, X^6 is either D-arginine, D-alanine, D-norleucine, D-α-aminobutyric acid, D-valine, D-leucine, D-isoleucine, D-proline, D-methionine, D- phenylalanine, D-asparagine, D-glutamine, D-serine, D-threonine, D-glutamic acid, D-aspartic acid, D-lysine, D-histidine, D-tryptophan, D-tyrosine, D-cyclohexylalanine, D-(2')naphthylalanine, D-ornithine, D-homoarginine, D-nitroarginine, D-norarginine, D-citrulline or 5-guanidinopropionic acid; more preferably X^6 is either D-arginine, D-alanine, D-norleucine, D-proline, D-phenylalanine, D-asparagine, D-serine, D-glutamic acid, D-lysine, or D-citrulline;

X^7 is either lysine, cysteine, homocysteine, 3-mercaptopropionic acid or its higher homolog, penicillamine, 2,3 diamino proprionic acid or its higher homolog, or aspartic acid or its higher homolog, or a derivative thereof; preferably, X^7 is either cysteine, homocysteine, 3-mercaptopropionic acid or its higher homolog, penicillamine, 2,3 diamino proprionic acid or its higher homolog, aspartic acid or its higher homolog, or a derivative thereof, more preferably, X^7 is cysteine, 2,3 diamino proprionic acid or aspartic acid;

X^8 is either methionine, norleucine, leucine, isoleucine, valine, methioninesulfoxide, or methioninesulfone, or a derivative thereof; preferably, X^8 is methionine, norleucine or N-methyl norleucine;

X^9 is either leucine, isoleucine, valine, alanine, methionine, or 5-aminopentanoic acid, or a derivative thereof; preferably, X^9 is leucine;

X^{10} is either asparagine, glutamine, alanine, leucine, isoleucine, valine, norleucine, cyclohexylalanine, phenylalanine, (2')-naphthylalanine, tyrosine, histidine, tryptophan, lysine, serine, threonine, methionine, or citrulline, or a derivative thereof; preferably, X^{10} is either asparagine or glutamine;

X^{11} is either arginine, lysine, citrulline, histidine, homoarginine, norarginine, or nitroarginine, or a derivative thereof; preferably, X^{11} is arginine;

X^{12} is either valine, leucine, isoleucine, alanine, or methionine, or a derivative thereof; preferably, X^{12} is valine;

X^{13} is either phenylalanine, tyrosine, D-(*p*-benzoylphenylalanine), tryptophan, (1')- and (2')-naphthylalanine, cyclohexylalanine, or mono and multi-

substituted phenylalanine wherein each substituent is independently selected from the group consisting of O-alkyl, alkyl, OH, NO_2, NH_2, F, I, and Br; or a derivative thereof; preferably, X^{13} is phenylalanine, (2')napthylalanine, p-fluoro-phenylalanine, tyrosine, or cyclohexylalanine;

X^{14} is either arginine, lysine, histidine, norarginine, homoarginine, nitroarginine, or 5-aminopentanoic acid, or a derivative thereof; preferably, X^{14} is arginine;

X^{15} is either proline, alanine, valine, leucine, isoleucine, methionine, sarcosine, or 5-aminopentanoic acid, or a derivative thereof; preferably, X^{15} is proline or sarcosine;

X^{16} is an optionally present amino acid that if present is either cysteine, homocysteine, cysteamine, penicillamine, 2,3 diamino propionic acid or its higher homolog, or aspartic acid or its higher homolog, or a derivative thereof; preferably, X^{16} is present; more preferably, X^{16} is either cysteine, D-cysteine, aspartic acid, or diamino proprionic acid; more preferably, X^{16} is cysteine or D-cysteine;

X^{17} is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof; preferably, X^{17} if present is tyrosine or tryptophan; more preferably, X^{17} is not present;

Z^1 is an optionally present protecting group that, if present, is covalently joined to the N-terminal amino group;

Z^2 is an optionally present protecting group that, if present, is covalently joined to the C-terminal carboxy group;

provided that if X^{16} is present, X^{16} and X^7 together form a cyclic group joined by either a disulfide bond or an amide bond, wherein if X^7 is either cysteine, homocysteine, 3-mercaptopropionic acid or its higher homolog, or penicillamine, then X^{16} is either cysteine, homocysteine, cysteamine, or penicillamine; if X^7 is 2,3 diamino proprionic acid or its higher homolog then X^{16} is aspartic acid or its higher homolog, and if X^7 is aspartic acid or its higher homolog then X^{16} is 2,3 diamino proprionic acid or its higher homolog; preferably the cyclic group is from 32-36 atoms, more preferably it is 32 atoms;

further provided that if X^{16} is not present, then X^{17} is not present, Z^2 is not present, X^7 is lysine, and X^{15} and X^7 together form a cyclic group joined by the X^7 Lys epsilon amino group and the X^{15} carboxyl group;

or a labeled derivative of the peptide;

or a pharmaceutically acceptable salt of the peptide or of the labeled derivative.

The present invention comprehends diastereomers as well as their racemic and resolved enantiomerically pure forms. hMCH analogs can contain D-amino acids, L-amino acids, or a combination thereof.

In different embodiments, hMCH analogs contain a preferred (or more preferred) group at one or more different locations. More preferred embodiments contain preferred (or more preferred) groups in more of the different locations.

A protecting group covalently joined to the N-terminal amino group reduces the reactivity of the amino terminus under *in vivo* conditions. Amino protecting groups include optionally substituted -C_{1-10} alkyl, optionally substituted -C_{2-10} alkenyl, optionally substituted aryl, -C_{1-6} alkyl optionally substituted aryl, -C(O)-$(CH_2)_{1-6}$-COOH, -C(O)- C_{1-6} alkyl, -C(O)-optionally substituted aryl, -C(O)-O-C_{1-6} alkyl, and -C(O)-O-optionally substituted aryl. Preferably, the amino terminus protecting group is acetyl, propyl, succinyl, benzyl, benzyloxycarbonyl or *t*-butyloxycarbonyl.

A protecting group covalently joined to the C-terminal carboxy group reduces the reactivity of the carboxy terminus under *in vivo* conditions. The carboxy terminus protecting group is preferably attached to the α-carbonyl group of the last amino acid. Carboxy terminus protecting groups include amide, methylamide, and ethylamide.

A protecting group covalently joined to the N-terminal amino group reduces the reactivity of the amino terminus under *in vivo* conditions. Amino protecting groups include optionally substituted -C_{1-10} alkyl, optionally substituted -C_{2-10} alkenyl, optionally substituted aryl, -C_{1-6} alkyl optionally substituted aryl, -C(O)-$(CH_2)_{1-6}$-COOH, -C(O)- C_{1-6} alkyl, -C(O)-optionally substituted aryl, -C(O)-O-C_{1-6} alkyl, and -C(O)-O-optionally substituted aryl. Preferably, the amino terminus protecting group is acetyl, propyl, succinyl, benzyl, benzyloxycarbonyl or *t*-butyloxycarbonyl.

A protecting group covalently joined to the C-terminal carboxy group reduces the reactivity of the carboxy terminus under *in vivo* conditions. The carboxy terminus protecting group is preferably attached to the α-carbonyl group of the last amino acid. Carboxy terminus protecting groups include amide, methylamide, and ethylamide.

"Alkyl" refers to an optionally substituted hydrocarbon, or optionally substituted hydrocarbon group joined by carbon-carbon single bonds. The alkyl hydrocarbon group may be straight-chain or contain one or more branches or cyclic groups. Preferably, the alkyl group is 1 to 4 carbons in length. Examples of alkyl include methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, and t-butyl. Alkyl groups may be substituted with one or more substituents selected from the group consisting of halogen (preferably -F or –Cl), -OH, -CN, -SH, $-NH_2$, $-NO_2$, $-C_{1-2}$ alkyl substituted with 1 to 6 halogens (preferably -F or -Cl, more preferably -F), $-CF_3$, $-OCH_3$, or $-OCF_3$. In different embodiments the alkyl has none or one substituent.

"Alkenyl" refers to an optionally substituted hydrocarbon group containing one or more carbon-carbon double bonds. The alkenyl hydrocarbon group may be straight-chain or contain one or more branches or cyclic groups. Preferably, the alkenyl group is 2 to 4 carbons in length. Alkenyl groups may be substituted with one or more substituents selected from the group consisting of halogen (preferably -F or -Cl), -OH, -CN, -SH, $-NH_2$, $-NO_2$, $-C_{1-2}$ alkyl substituted with 1 to 5 halogens (preferably -F or -Cl, more preferably -F), $-CF_3$, $-OCH_3$, or $-OCF_3$. In different embodiments the alkenyl has none or one substituent.

"Aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi- electron system, containing up to two conjugated or fused ring systems. Aryl includes carbocyclic aryl, heterocyclic aryl and biaryl groups. Preferably, the aryl is a 5 or 6 membered ring, more preferably benzyl. Aryl groups may be substituted with one or more substituents selected from the group consisting of $-C_{1-4}$ alkyl, $-C_{1-4}$ alkoxy, halogen (preferably -F or -Cl), -OH, -CN, -SH, $-NH_2$, $-NO_2$, $-C_{1-2}$ alkyl substituted with 1 to 5 halogens (preferably -F or -Cl, more preferably -F), $-CF_3$, or $-OCF_3$. In different embodiments the aryl group has three, two, one, or zero, substituents.

A labeled derivative indicates the presence of a detectable label. Examples of detectable labels include luminescent, enzymatic, and radioactive labels. A preferred radiolabel is ^{125}I. Both the type of label and the position of the label can affect MCH activity. Labels should be selected so as not to substantially alter the

activity of the MCH analog at MCH-1R. The effect of a particular label on MCH activity can be determined using assays measuring MCH activity and/or binding.

In preferred embodiments X^{16} is present, X^{17} is optionally present and the optionally modified peptide has the structure:

$$Z1\text{-}\ X6\text{-}X7\text{-}X8\text{-}X9\text{-}X10\text{-}X11\text{-}X12\text{-}X13\text{-}X14\text{-}X15\text{-}X16\text{-}X17\text{-}Z2$$

wherein the different groups, and preferred groups, are as described above. More preferred embodiments can be produced having different combinations and numbers of preferred and/or more preferred groups.

Production of Human MCH analogs

Human MCH analogs can be produced using techniques well known in the art. For example, a polypeptide region of a MCH analog can be chemically or biochemically synthesized and, if desired, modified to produce a blocked N-terminus and/or blocked C-terminus. Techniques for chemical synthesis of polypeptides are well known in the art. (See *e.g.*, Vincent, *Peptide and Protein Drug Delivery*, New York, N.Y., Dekker, 1990.) Examples of techniques for biochemical synthesis involving the introduction of a nucleic acid into a cell and expression of nucleic acids are provided in Ausubel, *Current Protocols in Molecular Biology,* John Wiley, 1987-1998, and Sambrook *et al.*, in *Molecular Cloning, A Laboratory Manual,* 2nd Edition, Cold Spring Harbor Laboratory Press, 1989.

MCH-1R

MCH-1R is a G-protein coupled receptor that responds to hMCH. Functional MCH-1R activity can be produced using naturally occurring human MCH-1R and functional derivatives thereof. Naturally occurring MCH-1R and functional derivatives thereof are activated by hMCH and can be identified by the presence of at least 12 contiguous amino acids as that present in human MCH-1R of SEQ. ID. NO. 35.

Reference to at least 12 contiguous amino acids present in SEQ. ID. NO. 35 provides a tag for an MCH-1R functional derivative. In different embodiments, functional derivatives comprise at least about 30 consecutive amino acids present in SEQ. ID. NO. 35, or comprise or consist of SEQ. ID. NO. 35.

In an embodiment of the present invention the MCH-1R is a mammalian MCH-1R. Examples of mammalian MCH-1R include MCH-1R found a human, ferret, mouse, rat, dog, and rhesus monkey.

MCH-1R derivatives can be produced, for example, by starting with human MCH-1R. Functional derivatives of MCH-1R can be produced, for example, by introducing amino acid substitutions, additions and deletions. The ability of a polypeptide to have MCH-1R activity can be confirmed using techniques such as those measuring G-protein activity.

Differences in naturally occurring amino acids are due to different R groups. An R group affects different properties of the amino acid such as physical size, charge, and hydrophobicity. Amino acids can be divided into different groups as follows: neutral and hydrophobic (alanine, valine, leucine, isoleucine, proline, tyrptophan, phenylalanine, and methionine); neutral and polar (glycine, serine, threonine, tryosine, cysteine, asparagine, and glutamine); basic (lysine, arginine, and histidine); and acidic (aspartic acid and glutamic acid).

Generally, in substituting different amino acids it is preferable to exchange amino acids having similar properties. Substituting different amino acids within a particular group, such as substituting valine for leucine, arginine for lysine, and asparagine for glutamine are good candidates for not causing a change in polypeptide functioning.

Changes outside of different amino acid groups can also be made. Preferably, such changes are made taking into account the position of the amino acid to be substituted in the polypeptide. For example, arginine can substitute more freely for nonpolor amino acids in the interior of a polypeptide then glutamate because of its long aliphatic side chain. (*See*, Ausubel, *Current Protocols in Molecular Biology,* John Wiley, 1987-1998, Supplement 33 Appendix 1C.)

MCH Receptor Binding Assay

Assays measuring the ability of a compound to bind to MCH-1R employ a MCH-1R polypeptide comprising a hMCH binding site. MCH-1R polypeptides include full-length human MCH-1R and functional derivatives thereof, MCH-1R fragments containing the MCH binding site, and chimeric polypeptides comprising such MCH-1R fragments. A chimeric polypeptide comprising a MCH-1R fragment that binds hMCH also contains one or more polypeptide regions not found in

a naturally occurring MCH-1R. Preferably, assays measuring MCH binding employ full length MCH-1R of SEQ. ID. NO. 35.

The MCH-1R amino acid sequence involved in hMCH binding can be identified using labeled hMCH or hMCH analogs and different receptor fragments. Different strategies can be employed to select fragments to be tested to narrow down the binding region. Examples of such strategies include testing consecutive fragments about 15 amino acids in length starting at the N-terminus, and testing longer length fragments. If longer length fragments are tested, a fragment binding hMCH can be subdivided or mutated to further locate the hMCH binding region. Fragments used for binding studies can be generated using recombinant nucleic acid techniques.

Binding assays can be performed using individual compounds or preparations containing different numbers of compounds. A preparation containing different numbers of compounds having the ability to bind to the MCH-1R can be divided into smaller groups of compounds that can be tested to identify the compound(s) binding to the receptor. In an embodiment of the present invention a test preparation containing at least 10 compounds is used in a binding assay.

Binding assays can be performed using recombinantly produced MCH-1R polypeptides present in different environments. Such environments include, for example, cell extracts and purified cell extracts containing a MCH-1R polypeptide expressed from recombinant nucleic acid or naturally occurring nucleic acid; and also include, for example, the use of a purified MCH-1R produced by recombinant means or from naturally occurring nucleic acid which is introduced into a different environment.

Screening for MCH-1R Active Compounds

Screening for MCH-1R active compounds is facilitated using recombinant nucleic acid expressing a polypeptide having MCH-1R activity. Recombinantly expressed receptors offers several advantages in screening for receptor active compounds, such as the ability to express the receptor in a defined cell system so that responsiveness to receptor active compounds can more readily be differentiated from responses to other receptors. For example, MCH-1R can be expressed in a cell line such as HEK 293, COS 7, and CHO using an expression vector, wherein the same cell line without the expression vector can act as a control.

A recombinant "nucleic acid" refers to an artificial combination of two or more nucleotide sequence regions. The artificial combination is not found in

nature. Recombinant nucleic acid includes nucleic acid having a first coding region and a regulatory element or a second coding region not naturally associated with the first coding region. Preferred recombinant nucleotide sequences are those where a coding region is under the control of an exogenous promoter, and where a second coding region is a selectable marker. The recombinant nucleotide sequence can be present in a cellular genome or can be part of an expression vector.

Preferably, expression is achieved in a host cell using an expression vector. An expression vector contains recombinant nucleic acid encoding a polypeptide along with regulatory elements for proper transcription and processing. The regulatory elements that may be present include those naturally associated with the recombinant nucleic acid and exogenous regulatory elements not naturally associated with the recombinant nucleic acid. Exogenous regulatory elements such as an exogenous promoter can be useful for expressing recombinant nucleic acid in a particular host.

Screening for MCH-1R active compounds is facilitated through the use of a hMCH analog in the assay. The MCH analog provides for MCH-1R activity. The effect of test compounds on such activity can be measured to identify, for example, allosteric modulators and antagonists. Additionally, such assays can be used to identify agonists.

MCH Receptor Activity

MCH-1R and MCH-2R are G protein coupled receptors. MCH-1R couples to both Gi and Gq, while MCH-2R couples to Gq. Coupling of Gi results in the inhibition of adenylate cyclase and subsequent reductions in cAMP levels. Coupling to Gq leads to activation of phospholipase C and subsequent elevation of intracellular Ca^{2+}.

Techniques for measuring different G-protein activities, such as Gi, Gs, and Gq are well known in the art. Gi and Gs activity can be measured using techniques such as a melonaphore assay, assays measuring cAMP production, assays measuring inhibition of cAMP accumulation, and assays measuring binding of ^{35}S-GTP. cAMP can be measured using different techniques such as a radioimmunoassay and indirectly by cAMP responsive gene reporter proteins.

Gq activity can be measured using techniques such as those measuring intracellular Ca^{2+}. Examples of techniques well known in the art that can be employed to measure Ca^{2+} include the use of dyes such as Fura-2 and the use of Ca^{2+}-

bioluminescent sensitive reporter proteins such as aequorin. An example of a cell line employing aequorin to measure G-protein activity is HEK293/aeq17. (Button *et al.*,1993, *Cell Calcium 14*, 663-671, and Feighner *et al.*, 1999, *Science 284*, 2184-2188, both of which are hereby incorporated by reference herein.)

Chimeric receptors containing a hMCH binding region functionally coupled to a G protein can also be used to measure MCH receptor activity. A chimeric MCH receptor contains an N-terminal extracellular domain; a transmembrane domain made up of transmembrane regions, extracellular loop regions, and intracellular loop regions; and an intracellular carboxy terminus. Techniques for producing chimeric receptors and measuring G protein coupled responses are provided for in, for example, International Application Number WO 97/05252, and U.S. Patent Number 5,264,565.

Weight or Appetite Alteration

Human MCH analogs can be used in methods to increase or maintain weight and/or appetite in a subject. Such methods can be used, for example, as part of an experimental protocol examining the effects of MCH antagonists to achieve a beneficial effect in a subject or to further examine the physiological effects of MCH.

Experimental protocols examining the effects of MCH antagonists can be performed, for example, by using a sufficient amount of a hMCH analog to produce a weight or appetite increase in a subject and then examining the effect of a test compound. Changes in weight and appetite can be measured using techniques well known in the art.

Increasing weight or appetite can be useful for maintaining weight or producing a weight or appetite gain in an under weight subject, or in a patient having a disease or undergoing treatment that affects weight or appetite. In addition, for example, farm animals possessing MCH-1R can be treated to gain weight.

Under weight subjects include those having a body weight about 10% or less, 20% or less, or 30% or less, than the lower end of a "normal" weight range or Body Mass Index ("BMI"). "Normal" weight ranges are well known in the art and take into account factors such as a patient age, height, and body type.

BMI measures your height/weight ratio. It is determined by calculating weight in kilograms divided by the square of height in meters. The BMI "normal" range is 19-22.

Administration

Human MCH analogs can be formulated and administered to a subject using the guidance provided herein along with techniques well known in the art. The preferred route of administration ensures that an effective amount of compound reaches the target. Guidelines for pharmaceutical administration in general are provided in, for example, *Remington's Pharmaceutical Sciences 18th Edition*, Ed. Gennaro, Mack Publishing, 1990, and *Modern Pharmaceutics 2nd Edition*, Eds. Banker and Rhodes, Marcel Dekker, Inc., 1990, both of which are hereby incorporated by reference herein.

Human MCH analogs can be prepared as acidic or basic salts. Pharmaceutically acceptable salts (in the form of water- or oil-soluble or dispersible products) include conventional non-toxic salts or the quaternary ammonium salts that are formed, *e.g.*, from inorganic or organic acids or bases. Examples of such salts include acid addition salts such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate; and base salts such as ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine and lysine.

Human MCH analogs can be administered using different routes such as by injection. When administered by injection, the injectable solution or suspension may be formulated using suitable non-toxic, parenterally-acceptable diluents or solvents, such as Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Suitable dosing regimens are preferably determined taking into account factors well known in the art including type of subject being dosed; age, weight, sex and medical condition of the subject; the route of administration; the renal and hepatic function of the subject; the desired effect; and the particular compound employed.

Optimal precision in achieving concentrations of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. The daily dose for a subject is expected to be between 0.01 and 1,000 mg per subject per day.

Human MCH analogs can be provided in kit. Such a kit typically contains an active compound in dosage forms for administration. A dosage form contains a sufficient amount of active compound such that a weight or appetite increase can be obtained when administered to a subject during regular intervals, such as 1 to 6 times a day, during the course of 1 or more days. Preferably, a kit contains instructions indicating the use of the dosage form for weight or appetite increase and the amount of dosage form to be taken over a specified time period.

Examples

Examples are provided below to further illustrate different features of the present invention. The examples also illustrate useful methodology for practicing the invention. These examples do not limit the claimed invention.

Example 1: MCH Receptor Sequences

Human MCH-1R and MCH-2R amino acid and encoding cDNA sequences are as follows:

MCH-1R Amino Acid Sequence (SEQ. ID. NO. 35)

MDLEASLLPTGPNASNTSDGPDNLTSAGSPPRTGSISYINIIMPSVFGTICLLGIIG
NSTVIFAVVKKSKLHWCNNVPDIFIINLSVVDLLFLLGMPFMIHQLMGNGVWH
FGETMCTLITAMDANSQFTSTYILTAMAIDRYLATVHPISSTKFRKPSVATLVI
CLLWALSFISITPVWLYARLIPFPGGAVGCGIRLPNPDTDLYWFTLYQFFLAFA
LPFVVITAAYVRILQRMTSSVAPASQRSIRLRTKRVTRTAIAICLVFFVCWAPY
YVLQLTQLSISRPTLTFVYLYNAAISLGYANSCLNPFVYIVLCETFRKRLVLSV
KPAAQGQLRAVSNAQTADEERTESKGT

MCH-1R cDNA Sequence (SEQ. ID. NO. 36)

ATGGACCTGGAAGCCTCGCTGCTGCCCACTGGTCCCAACGCCAGCAACAC
CTCTGATGGCCCCGATAACCTCACTTCGGCAGGATCACCTCCTCGCACGG
GGAGCATCTCCTACATCAACATCATCATGCCTTCGGTGTTCGGCACCATCT

GCCTCCTGGGCATCATCGGGAACTCCACGGTCATCTTCGCGGTCGTGAAG
AAGTCCAAGCTGCACTGGTGCAACAACGTCCCCGACATCTTCATCATCAA
CCTCTCGGTAGTAGATCTCCTCTTTCTCCTGGGCATGCCCTTCATGATCCA
CCAGCTCATGGGCAATGGGGTGTGGCACTTTGGGGAGACCATGTGCACCC
TCATCACGGCCATGGATGCCAATAGTCAGTTCACCAGCACCTACATCCTG
ACCGCCATGGCCATTGACCGCTACCTGGCCACTGTCCACCCCATCTCTTCC
ACGAAGTTCCGGAAGCCCTCTGTGGCCACCCTGGTGATCTGCCTCCTGTGG
GCCCTCTCCTTCATCAGCATCACCCCTGTGTGGCTGTATGCCAGACTCATC
CCCTTCCCAGGAGGTGCAGTGGGCTGCGGCATACGCCTGCCCAACCCAGA
CACTGACCTCTACTGGTTCACCCTGTACCAGTTTTTCCTGGCCTTTGCCCTG
CCTTTTGTGGTCATCACAGCCGCATACGTGAGGATCCTGCAGCGCATGAC
GTCCTCAGTGGCCCCCGCCTCCCAGCGCAGCATCCGGCTGCGGACAAAGA
GGGTGACCCGCACAGCCATCGCCATCTGTCTGGTCTTCTTTGTGTGCTGGG
CACCCTACTATGTGCTACAGCTGACCCAGTTGTCCATCAGCCGCCCGACCC
TCACCTTTGTCTACTTATACAATGCGGCCATCAGCTTGGGCTATGCCAACA
GCTGCCTCAACCCCTTTGTGTACATCGTGCTCTGTGAGACGTTCCGCAAAC
GCTTGGTCCTGTCGGTGAAGCCTGCAGCCCAGGGGCAGCTTCGCGCTGTC
AGCAACGCTCAGACGGCTGACGAGGAGAGGACAGAAAGCAAAGGCACCT
GA

MCH-2R Amino Acid Sequence (SEQ. ID. NO. 37)

MNPFHASCWNTSAELLNKSWNKEFAYQTASVVDTVILPSMIGIICSTGLVGNI
LIVFTIIRSRKKTVPDIYICNLAVADLVHIVGMPFLIHQWARGGEWVFGGPLCTI
ITSLDTCNQFACSAIMTVMSVDRYFALVQPFRLTRWRTRYKTIRINLGLWAAS
FILALPVWVYSKVIKFKDGVESCAFDLTSPDDVLWYTLYLTITTFFFPLPLILVC
YILILCYTWEMYQQNKDARCCNPSVPKQRVMKLTKMVLVLVVVFILSAAPY
HVIQLVNLQMEQPTLAFYVGYYLSICLSYASSSINPFLYILLSGNFQKRLPQIQR
RATEKEINNMGNTLKSHF

MCH-2R cDNA Sequence (SEQ. ID. NO. 38)

ATGAATCCATTTCATGCATCTTGTTGGAACACCTCTGCCGAACTTTTAAAC
AAATCCTGGAATAAAGAGTTTGCTTATCAAACTGCCAGTGTGGTAGATAC
AGTCATCCTCCCTTCCATGATTGGGATTATCTGTTCAACAGGGCTGGTTGG
CAACATCCTCATTGTATTCACTATAATAAGATCCAGGAAAAAAAACAGTCC
CTGACATCTATATCTGCAACCTGGCTGTGGCTGATTTGGTCCACATAGTTG

GAATGCCTTTTCTTATTCACCAATGGGCCCGAGGGGGAGAGTGGGTGTTT
GGGGGGCCTCTCTGCACCATCATCACATCCCTGGATACTTGTAACCAATTT
GCCTGTAGTGCCATCATGACTGTAATGAGTGTGGACAGGTACTTTGCCCTC
GTCCAACCATTTCGACTGACACGTTGGAGAACAAGGTACAAGACCATCCG
GATCAATTTGGGCCTTTGGGCAGCTTCCTTTATCCTGGCATTGCCTGTCTG
GGTCTACTCGAAGGTCATCAAATTTAAAGACGGTGTTGAGAGTTGTGCTTT
TGATTTGACATCCCCTGACGATGTACTCTGGTATACACTTTATTTGACGAT
AACAACTTTTTTTTTCCCTCTACCCTTGATTTTGGTGTGCTATATTTTAATT
TTATGCTATACTTGGGAGATGTATCAACAGAATAAGGATGCCAGATGCTG
CAATCCCAGTGTACCAAAACAGAGAGTGATGAAGTTGACAAAGATGGTGC
TGGTGCTGGTGGTAGTCTTTATCCTGAGTGCTGCCCCTTATCATGTGATAC
AACTGGTGAACTTACAGATGGAACAGCCCACACTGGCCTTCTATGTGGGT
TATTACCTCTCCATCTGTCTCAGCTATGCCAGCAGCAGCATTAACCCTTTT
CTCTACATCCTGCTGAGTGGAAATTTCCAGAAACGTCTGCCTCAAATCCAA
AGAAGAGCGACTGAGAAGGAAATCAACAATATGGGAAACACTCTGAAAT
CACACTTTTAG

Example 2: Synthesis of Human MCH Analogs

Human MCH analogs were produced using the procedures described below and varying the stepwise addition of amino acid groups. Other procedures for producing and modifying peptides are well known in the art.

Elongation of peptide chains on 4-(2',4'-dimethoxyphenyl-Fmoc-aminomethyl)-phenoxy resin (0.65 meq/g substitution) was performed with a 431A ABI peptide synthesizer. Manufacture-supplied protocols were applied for coupling of the hydroxybenzotriazole esters of amino acids in N-methylpyrrolidone (NMP). The fluorenylmethyloxycarbonyl (Fmoc) group was used for the semipermanent protection of α-amino groups, whereas the side chains were protected with: tert-butyl for aspartic acid and tyrosine residue, 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) for arginine, and trityl for cysteine.

Peptides were cleaved from the resin with TFA containing 5% of anisole. After 2 hours at room temperature the peptidyl resin was filtered, washed with TFA and the combined filtrates were evaporated to dryness in vacuo. The residue was triturated with ether, the precipitate which formed was filtered, washed with ether, and dried. The crude peptides were dissolved in 5% acetic acid in water, and the pH of the solutions were adjusted to pH about 8.2 with dilute ammonium

hydroxide. The reaction mixtures were stirred vigorously while a 0.05% solution of potassium ferricyanide ($K_3Fe(CN)_6$) in water was added dropwise till the solution remained yellow for about 5 minutes. After an additional 20 minutes, oxidation was terminated with ca. 1 ml of acetic acid and the reaction mixtures were lyophilized.

The lyophilized crude peptides were analyzed by analytical reverse-phase high-pressure liquid chromatography (RP HPLC) on a C18 Vydac column attached to a Waters 600E system with automatic Wisp 712 injector and 991 Photodiode Array detector. A standard gradient system of 0-100% buffer B in 30 minutes was used for analysis: buffer A was 0.1% trifluoroacetic acid in water and buffer B was 0.1% triflouroacetic acid in acetonitrile. HPLC profiles were recorded at 210 nm and 280 nm. Preparative separations were performed on a Waters Delta Prep 4000 system with a semipreparative C18 RP Waters column. The above-described solvent system of water and acetonitrile, in a gradient of 0-70% buffer B in 60 minutes, was used for separation. The chromatographically homogenous products (purity > 97%) were analyzed by electrospray mass spectrometry.

Example 3: Radioligand Binding Assays

Membrane binding assays were performed on transiently-transfected COS-7 cells expressing human MCH-2R from the plasmid vector pCI-neo (Promega, Madison, WI), on a Chinese hamster ovary (CHO) cell line stably expressing the MCH-2R from the plasmid vector pEF1/V5-HisB (Invitrogen, Carlsbad, CA), or a CHO cell line stably expressing human MCH-1R from pcDNA3.1. For transient expression, COS-7 cells were cultured in Dulbecco's modified Eagle medium (Gibco BRL, Rockville, MD) with 10% heat inactivated fetal calf serum.

A suspension of 7 x 10^6 COS-7 cells were transfected with 20 μg of pCI-neo/MCH-2R plasmid by electroporation and cells were harvested after 60-72 hours. Membranes were prepared from transient and stable transfectants by hypotonic lysis, frozen in liquid nitrogen, and stored at – 80°C.

A scintillation proximity assay (SPA) was developed to measure the specific binding of [^{125}I]-[Phe^{13}Tyr^{19}]-hMCH. (Bednarek *et al.,* 2001, *Biochemistry 40*:9379-9386.) SPA's were carried out using wheat-germ agglutinin-polyvinyltoluene beads (Amersham Corp., Arlington Heights, IL), in 96-well OptiPlates (Packard, Meriden, CT). Each well contained 0.25 mg of SPA beads, 1-10 μg of membrane protein, and 200 μl of binding buffer (50 mM Tris pH 7.4, 10 mM $MgCl_2$, 2 mM EDTA, 12% glycerol, 0.1% BSA). Binding buffer contained 50 mM

Tris pH 7.4, 8 mM $MgCl_2$, 12% glycerol, 0.1% BSA (Sigma, St. Louis, MO) and protease inhibitors: 4 μg/ml of leupeptin (Sigma, St. Louis, MO), 40 μg/ml of Bacitracin (Sigma, St. Louis, MO), 5 μg/ml of Aprotinin (Roche Molecular Biochem., Indianapolis, IN), 0.05M AEBSF (Roche Molecular Biochem., Indianapolis, IN), and 5 mM Phosphoramidon (Boeringer Mannheim)). Assays were optimized with respect to membrane preparations: for CHO/MCH-1R membranes, 1 μg of membranes per well yielded a > 6x specific binding window and for COS or CHO MCH-2R membranes, 8 μg of membrane protein yielded a window of about 3x.

Specific binding is defined as the difference between total binding and non-specific binding conducted in the presence of 500 nM unlabeled hMCH. Beads were coated with membranes for 20 minutes and dispensed to the 96 wells, various concentrations of test compounds in DMSO were added (final DMSO concentration 1% - 2%), then 25 nCi of [^{125}I]-[Phe^{13}Tyr^{19}]-hMCH (~2000 Ci/mmol; NEN Life Sciences, Boston, MA) was added to the wells. After equilibrating at room temperature for 3 hours, the plates were read in a TopCount (Packard, Meriden, CT). IC_{50} calculations were performed using Prism 3.0 (GraphPad Software, San Diego, CA). The IC_{50} values were measured in three different experiments.

Example 4: Aequorin Bioluminescence Functional Assay

The aequorin bioluminescence assay is a reliable test for identifying G-protein-coupled receptors that couple through the G protein subunit family consisting of G_q and G_{11}. G_q and G_{11} coupling leads to the activation of phospholipase C, mobilization of intracellular calcium, and activation of protein kinase C.

Stable cell lines expressing either the MCH-1R or the MCH-2R and the aequorin reporter protein were used. The assay was performed using a Luminoskan RT luminometer (Labsystems Inc., Gaithersburg, MD) controlled by custom software written for a Macintosh PowerPC 6100. 293AEQ17/MCH-1R (or MCH-2R) cells were cultured for 72 hours and the apo-aequorin in the cells was charged for 1 hour with coelenterazine (10 μM) under reducing conditions (300 M reduced glutathione) in ECB buffer (140 mM NaCl, 20 mM KCl, 20 mM HEPES-NaOH, pH 7.4, 5 mM glucose, 1 mM $MgCl_2$, 1 mM $CaCl_2$, 0.1 mg/mL bovine serum albumin).

The cells were harvested, washed once in ECB medium, and resuspended to 500,000 cells/mL. 100 μL of cell suspension (corresponding to 5 × 10^4 cells) was then injected into the test plate containing the hMCH peptides, and the

integrated light emission was recorded over 30 seconds, in 0.5-s units. 20 μL of lysis buffer (0.1% final Triton X-100 concentration) was then injected and the integrated light emission recorded over 10 seconds, in 0.5-s units. The "fractional response" values for each well were calculated by taking the ratio of the integrated response to the initial challenge to the total integrated luminescence including the Triton X-100 lysis response.

Example 5: Position 6 Modifications

Human MCH analogs modified in position 6 were prepared by solid-phase synthesis and evaluated using the techniques described Examples 1-4. Binding and functional data for analogs of Ac-hMCH(6-16)-NH_2 modified in position 6 are compiled in Tables 1 and 2.

TABLE 1: Position 6 Modification Binding Assay

X^6-Cys^7-Met^8-Leu^9-Gly^{10}-Arg^{11}-Val^{12}-Tyr^{13}-Arg^{14}-Pro^{15}-Cys^{16}-NH_2

SEQ. ID. NO.	X6	MCH-1R IC_{50} (nM)	MCH-2R IC_{50} (nM)	Selectivity 2/1
1		0.3	0.5	1
2	Ac-Arg	1.4	2	3
3	Gva	0.4	12	30
4	D-Arg	035	47	130
5	Ac-D-Arg	0.25	650	2600
6	Ac-D-Ala	0.77	2700	3500
7	Ac-D-Nle	4	1460	370
8	Ac-D-Pro	1.6	1260	790
9	Ac-D-Phe	0.9	1250	1380
10	Ac-D-Asn	5.8	4040	700
11	Ac-D-Ser	0.7	3000	4700
12	Ac-D-Glu	16	6900	430
13	Ac-D-Lys	0.3	1030	3800
14	Ac-D-Cit	3	134	43
15	Δ(X^6-Cys^7), Mpr^7	7	3500	500

"2/1" refers to the MCH-2R/MCH-1R IC_{50} binding ratio. SEQ. ID. NO. 1 is human MCH. "Gva" refers to des-amino-arginine (5-guanidinovaleric acid). "Mpr" refers to des-amino-cysteine (3-mercaptopropionic acid). "Cit" refers to citrulline. "Nle" refers to norleucine.

TABLE 2: Position 6 Modification Activity Assay

X^6-Cys^7-Met^8-Leu^9-Gly^{10}-Arg^{11}-Val^{12}-Tyr^{13}-Arg^{14}-Pro^{15}-Cys^{16}-NH_2

SEQ. ID. NO.	X6	MCH-1R EC_{50} (nM)	MCH-1R Activation %	MCH-2R EC_{50} (nM)	MCH-2R Activation %	Selectivity 2/1
1		30.9	100	30.7	100	1
2	Ac-Arg	20	99	6.2	98	0.3
3	Gva	44	49	10	102	0.2
4	D-Arg	107	130	55	83	0.5
5	Ac-D-Arg	36	97	140	83	4
6	Ac-D-Ala	160	109	4900	51	30
7	Ac-D-Nle	91	115	590	69	6.5
8	Ac-D-Pro	78	120	560	82	7
9	Ac-D-Phe	66	117	510	79	7
10	Ac-D-Asn	260	113	5900	42	22
11	Ac-D-Ser	160	114	6070	39	38
12	Ac-D-Glu	630	100	7200	20	11
13	Ac-D-Lys	94	130	2100	55	22
14	Ac-D-Cit	920	91	310	68	0.3
15	$\Delta(X^6\text{-}Cys^7)$, Mpr^7	610	92	3100	47	5

"2/1" refers to the MCH-2R/MCH-1R EC_{50} activity ratio. SEQ. ID. NO. 1 is human MCH. "Gva" refers to des-amino-arginine (5-guanidinovaleric acid). "Mpr" refers to des-amino-cysteine (3-mercaptopropionic acid). "Cit" refers to citrulline. "Nle" refers to norleucine.

Omission of Ac and the amino group of Arg^6, e.g. incorporation of 5-guanidino-valeric acid (des-amino-arginine) in position 6, produced the compound of SEQ. ID. NO. 3. SEQ. ID. NO. 3 was not a fully effective agonist at hMCH-1R (49% activation at 10 μM concentration), but it was a full agonist at hMCH-2R of potency similar to that of the parent compound. In contrast the SEQ. ID. NO. 4 analog lacking an Ac group and containing a D-Arg in position 6 was equipotent to Ac-hMCH(6-16)-NH_2 at hMCH-1R, but at hMCH-2R was more than 10-fold weaker.

Compounds of SEQ. ID. NOs. 6-13 provided D-enantiomers of hydrophobic amino acids, Ala, Nle, Pro and Phe, and hydrophilic amino acids, Asn, Ser, Glu and Lys, in position 6 of hMCH(6-16)-NH_2. These peptides were efficient binders to hMCH-1R but their signal transduction efficacies at the same receptor were more than 10-fold lower than that of Ac-hMCH(6-16)-NH_2. However, these

compounds poorly bound to and activated hMCH-2R, thus indicating that they were more selective for hMCH-1R.

Replacement of Arg^6 with D-enantiomer of yet another hydrophilic amino acid – citrulline, yielded SEQ. ID. NO. 14. SEQ. ID. NO. 14 had a binding affinity for hMCH-1R about 30-fold lower than that of the D-Arg^6 compound. At both receptors, agonist potencies of SEQ. ID. NO. 14 with the urea side chain in position 6 were lower than those of the L-Arg^6 compound.

In the analog SEQ. ID. NO. 15, the Ac-Arg^6 segment of Ac-hMCH(6-16)-NH_2 was eliminated and 3-thio-propionic acid (des-amino-cysteine) was used instead of Cys to form the disulfide ring. SEQ. ID. NO. 15 showed about 5-fold lower binding affinity and 30-fold lower activity at hMCH-1R than Ac-hMCH(6-16)-NH_2. Similarly to the other peptides modified at position 6, SEQ. ID. NO. 15 was a very weak ligand for hMCH-2R (IC_{50} and EC_{50} > 3000 nM).

Example 6: Position 10 Modifications

Human MCH analogs modified in position 10 were prepared by solid-phase synthesis and evaluated using the techniques described Examples 1-4. The disulfide cycle of Ac-hMCH(6-16)-NH_2 encompasses Gly in position 10. Considerable conformational freedom of Gly, in the absence of a constraining side chain, frequently facilitates formation of new peptide conformers (reversed turns). In order to stabilize some of these low-energy conformations of biological significance, Gly is frequently replaced with sterically constraining amino acids such as α-amino acids. Binding and functional data for analogs of Ac-hMCH(6-16)-NH_2 modified in position 10 are compiled in Tables 3 and 4.

TABLE 3: Position 10 Modification Binding Assay

Ac-Arg^6-Cys^7-Met^8-Leu^9-**X**^{10}-Arg^{11}-Val^{12}-Tyr^{13}-Arg^{14}-Pro^{15}-Cys^{16}-NH_2

SEQ. ID. NO.	X10	MCH-1R IC_{50} (nM)	MCH-2R IC_{50} (nM)	Selectivity 2/1
1		0.3	0.5	1
2	Gly	0.5	2	4
16	Ala	0.44	7	16
17	Leu	0.03	27	1900

TABLE 3: Position 10 Modification Binding Assay

Ac-Arg^{6}-Cys^{7}-Met^{8}-Leu^{9}-**X**^{10}-Arg^{11}-Val^{12}-Tyr^{13}-Arg^{14}-Pro^{15}-Cys^{16}-NH_2

SEQ. ID. NO.	X10	MCH-1R IC_{50} (nM)	MCH-2R IC_{50} (nM)	Selectivity 2/1
18	Nle	0.1	1.9	21
19	Cha	5	55	11
20	Phe	0.1	1.9	19
21	Nal(2')	1.3	18	14
22	Pro	760	3500	5
23	Arg	640	420	0.7
24	Lys	17	1460	86
25	Asn	0.28	490	1800
26	Ser	0.54	55	100
27	Cit	3.1	130	42
28	Glu	290	75%@10	

"2/1" refers to the MCH-2R/MCH-1R IC_{50} binding ratio. SEQ. ID. NO. 1 is human MCH. "Cha" refers to 2-cyclohexylalanine. "Nal(2')" refers to 2'-naphthylalanine. "Cit" refers to citrulline. "Nle" refers to norleucine.

TABLE 4: Position 10 Modification Activity Assay

Ac-Arg^{6}-Cys^{7}-Met^{8}-Leu^{9}-**X**^{10}-Arg^{11}-Val^{12}-Tyr^{13}-Arg^{14}-Pro^{15}-Cys^{16}-NH_2

SEQ. ID. NO.	X10	MCH-1R EC_{50} (nM)	MCH-1R Activation %	MCH-2R EC_{50} (nM)	MCH-2R Activation %	Selectivity 2/1
1		30.9	100	30.7	100	1
2	Gly	20	99	6.2	98	4.6
16	Ala	51	121	15	102	0.29
17	Leu	32	123	57	74	1.8
18	Nle	47	115	17	97	0.4
19	Cha	1200	76	300	74	0.25
20	Phe	66	75	50	88	0.75
21	Nal(2')	> 10000	7	81	105	
22	Pro	> 10000	10	>10000	13	
23	Arg	> 10000	7	1660	38	
24	Lys	5700	43	6050	40	1
25	Asn	51	126	240	86	4.7
26	Ser	130	120	89	87	0.7
27	Cit	920	91	310	68	0.3
28	Glu	> 10000	21	>10000	22	

"2/1" refers to the MCH-2R/MCH-1R EC_{50} activity ratio. SEQ. ID. NO. 1 is human MCH. "Cha" refers to 2-cyclohexylalanine. "Nal(2')" refers to 2'-naphthylalanine. "Cit" refers to citrulline. "Nle" refers to norleucine.

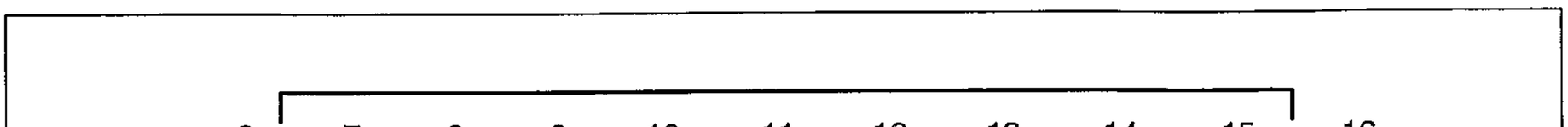
Replacement of Gly^{10} with hydrophobic L-amino acids which possess long, branch or aromatic side chains yielded compounds of SEQ. ID. NOs. 16-21. These analogs bound to hMCH-1R almost as efficiently as the parent compound. At hMCH-2R peptides with Leu, Cha and Nal(2') in position 10 (SEQ. ID. NOs. 17, 19, and 21) were 10- to 70-fold weaker binders. At hMCH-1R, signal transduction efficacies of compounds of SEQ. ID. NOs. 16-18, 20 and 21 were similar to that of Ac-hMCH(6-16)-NH_2, whereas, at hMCH-2R, these compounds were 5 to 10 times less potent. The Cha^{10} analog with the bulky branched side chain in position 10 (SEQ. ID. NO. 19) poorly activated both receptors. Incorporation of the conformationally constraining Pro in place of Gly^{10} was deleterious to agonism at the hMCH receptors; the Pro^{10} analog was virtually inactive at micromolar concentrations (SEQ. ID. NO. 22).

In compounds of SEQ. ID. NOs. 23-27 hydrophilic residues were incorporated in position 10. Peptides with Asn, Ser, Cit and Lys in position 10 were high affinity binders to hMCH-1R, but their affinities for hMCH-2R were 30 to 700 times lower than that of Ac-hMCH(6-16)NH_2. Also, the Asn^{10}, Ser^{10} and Cit^{10} peptides were from 3 to 50-fold weaker agonists at both hMCH receptors than the parent compound, and the Lys^{10} analog was 300 times less potent. The SEQ. ID. NO. 28 analog with an acidic residue in position 10, the Glu^{10} peptide, was practically inactive at hMCH-1R and hMCH-2R.

Example 7: Multiple Modifications

Human MCH analogs modified at least in positions 6 and 10 were prepared by solid-phase synthesis and evaluated using the techniques described in Examples 1-4. Binding and functional data for analogs of Ac-hMCH(6-16)-NH_2 modified in at least positions 6 and 10 are compiled in Tables 5 and 6.

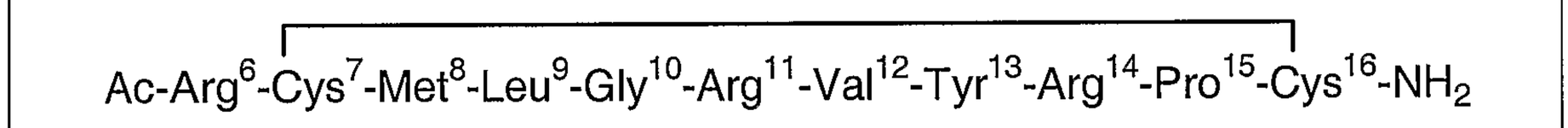
TABLE 5: Multiple Modifications Binding Assay



SEQ. ID. NO.	Modification	MCH-1R IC_{50} (nM)	MCH-2R IC_{50} (nM)	Selectivity 2/1
1		0.3	0.5	1
2	_____	0.5	2	4
29	D-Arg^6, Asn^{10}	0.5	3300	6600
30	D-Arg^6, Gln^{10}	6.1	1400	230
31	D-Arg^6,Nle^8,Asn^{10}	0.28	1600	5700
32	ΔAc,D-Arg^6, Nle^8,Asn^{10}	0.09	250	890
33	D-Arg^6, Asn^{10},Ala^{14}	3.2	48%@10	
34	D-Cit^6,Asn^{10}	8.3	55%@10	

"2/1" refers to the MCH-2R/MCH-1R IC_{50} binding ratio. SEQ. ID. NO. 1 is human MCH. "Cit" refers to citrulline. "Nle" refers to norleucine.

TABLE 6: Multiple Modifications



SEQ. ID. NO.	Modification	MCH-1R EC_{50} (nM)	MCH-1R Activation %	MCH-2R EC_{50} (nM)	MCH-2R Activation %	Selectivity 2/1
1		30.9	100	30.7	100	1
2	_____	20	99	6.2	98	0.3
29	D-Arg^6, Asn^{10}	55	120	8400	20	150
30	D-Arg^6, Gln^{10}	2300	74	>10000	11	
31	D-Arg^6,Nle^8, Asn^{10}	240	130	5500	23	23
32	ΔAc,D-Arg^6, Nle^8,Asn^{10}	350	130	1470	53	4
33	D-Arg^6, Asn^{10},Ala^{14}	260	109	>10000	17	
34	D-Cit^6,Asn^{10}	1460	110	>10000	8	

"2/1" refers to the MCH-2R/MCH-1R EC_{50} activity ratio. SEQ. ID. NO. 1 is human MCH. "Cit" refers to citrulline. "Nle" refers to norleucine.

SEQ. ID. NOs. 29-34 were designed to incorporate changes in the structure of Ac-hMCH(6-16)NH_2 favorable for hMCH-1R selectivity. The D-Arg^6, Asn^{10} and D-Arg^6, Gln^{10} analogs, SEQ. ID. NOs. 29 and 30 activated hMCH-1R almost as efficiently as Ac-hMCH(6-16)NH_2. They were about 150-fold more selective as agonists for hMCH-1R than hMCH-2R. In SEQ. ID. NOs. 31 and 32 Met^8 was replaced with the isosteric Nle. These analogs were potent and selective hMCH-1R agonists.

Omission of the guanidino group in position 14 in Ac-hMCH(6-16)-NH_2, through the replacement of Arg with Ala, yielded SEQ. ID. NO. 33. The SEQ. ID. NO. 33 compound was a 5-fold weaker agonist at hMCH-1R receptor than the parent compound, but was about 50-fold more selective with respect to hMCH-2R.

Other embodiments are within the following claims. While several embodiments have been shown and described, various modifications may be made without departing from the spirit and scope of the present invention.

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tag 1023

WHAT IS CLAIMED IS:

1. An optionally substituted peptide having the structure:

Z^1- X^1-X^2-X^3-X^4-X^5-X^6-X^7-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-Z^2

wherein X^1 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof;

X^2 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof;

X^3 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof;

X^4 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, glutamic acid, or norleucine, or a derivative thereof;

X^5 is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof;

X^6 is either a D-amino acid, 5-guanidinopropionic acid or its lower or higher homolog, or a derivative thereof;

X^7 is either lysine, cysteine, homocysteine, 3-mercaptopropionic acid or its higher homolog, penicillamine, 2,3 diamino proprionic acid or its higher homolog, or aspartic acid or its higher homolog, or a derivative thereof;

X^8 is either methionine, norleucine, leucine, isoleucine, valine, methioninesulfoxide, or methioninesulfone, or a derivative thereof;

X^9 is either leucine, isoleucine, valine, alanine, methionine, or 5-aminopentanoic acid, or a derivative thereof;

X^{10} is either asparagine, glutamine, alanine, leucine, isoleucine, valine, norleucine, cyclohexylalanine, phenylalanine, (2')-naphthylalanine, tyrosine, histidine, tryptophan, lysine, serine, threonine, methionine, or citrulline, or a derivative thereof;

X^{11} is either arginine, lysine, citrulline, histidine, homoarginine, norarginine, or nitroarginine, or a derivative thereof;

X^{12} is either valine, leucine, isoleucine, alanine, or methionine, or a derivative thereof;

X^{13} is either phenylalanine, tyrosine, D-(*p*-benzoylphenylalanine), tryptophan, (1')- and (2')-naphthylalanine, cyclohexylalanine, or mono and multi-substituted phenylalanine wherein each substituent is independently selected from the group consisting of O-alkyl, alkyl, OH, NO_2, NH_2, F, I, and Br; or a derivative thereof;

X^{14} is either arginine, lysine, histidine, norarginine, homoarginine, nitroarginine, or 5-aminopentanoic acid, or a derivative thereof;

X^{15} is either proline, alanine, valine, leucine, isoleucine, methionine, sarcosine, or 5-aminopentanoic acid, or a derivative thereof;

X^{16} is an optionally present amino acid that if present is either cysteine, homocysteine, cysteamine, penicillamine, 2,3 diamino propionic acid or its higher homolog, or aspartic acid or its higher homolog, or a derivative thereof;

X^{17} is an optionally present amino acid that, if present, is either alanine, valine, leucine, isoleucine, proline, tryptophan, phenylalanine, methionine, glycine, serine, threonine, tyrosine, cysteine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid, or glutamic acid, or a derivative thereof;

Z^1 is an optionally present protecting group that, if present, is covalently joined to the N-terminal amino group;

Z^2 is an optionally present protecting group that, if present, is covalently joined to the C-terminal carboxy group;

provided that if X^{16} is present, X^{16} and X^7 together form a cyclic group from 32 to 36 atoms joined by either a disulfide bond or an amide bond, wherein if X^7 is either cysteine, homocysteine, 3-mercaptopropionic acid or its higher homolog, or penicillamine, then X^{16} is either cysteine, homocysteine, cysteamine, or

penicillamine; if X^7 is 2,3 diamino proprionic acid or its higher homolog then X^{16} is aspartic acid or its higher homolog, and if X^7 is aspartic acid or its higher homolog then X^{16} is 2,3 diamino proprionic acid or its higher homolog;

further provided that if X^{16} is not present, then X^{17} is not present, Z^2 is not present, X^7 is lysine, and X^{15} and X^7 together form a cyclic group joined by the X^7 Lys epsilon amino group and the X^{15} carboxyl group;

or a labeled derivative of said peptide;

or a pharmaceutically acceptable salt of said peptide or of said labeled derivative.

2. The peptide of claim 1, wherein X^6 is selected from the group consisting of: D-arginine, D- alanine, D-norleucine, D-α-aminobutyric acid, D-valine, D-leucine, D-isoleucine, D- proline, D-methionine, D- phenylalanine, D- asparagine, D-glutamine, D- serine, D-threonine, D- glutamic acid, D-aspartic acid, D- lysine, D-histidine, D-tryptophan, D-tyrosine, D-cyclohexylalanine, D-(2')naphthylalanine, D-ornithine, D-homoarginine, D-nitroarginine, D-norarginine , D-citrulline and 5-guanidinopropionic acid.

3. The peptide of claim 2, wherein X^{10} is either asparagine or glutamine.

4. The peptide of claim 3, wherein X^1, X^2, X^3, X^4, X^5, X^{16} and X^{17} are not present.

5. The peptide of claim 3, wherein X^{16} is present.

6. The peptide of claim 5, wherein X^1, X^2, X^3, X^4, X^5, are not present and X^{17} is either tyrosine or tryptophan.

7. The peptide of claim 5, wherein X^1, X^2, X^3, X^4, X^5, and X^{17} are not present.

8. The peptide of claim 6, wherein Z^1 is either not present or is $-C(O)CH_3$ and Z^2 is either not present or is $-NH_2$.

9. The peptide of claim 7, wherein Z^1 is either not present or is $-C(O)CH_3$ and Z^2 is either not present or is $-NH_2$.

10. The peptide of claim 7, wherein

X^8 is either methionine, norleucine, or N-methyl norleucine;

X^9 is leucine;

X^{11} is arginine;

X^{12} is valine;

X^{13} is phenylalanine, (2')napthylalanine, p-fluoro-phenylalanine, tyrosine, or cyclohexylalanine;

X^{14} is arginine, or alanine;

X^{15} is either proline or sarcosine; and

X^{16} is either cysteine, D-cysteine, aspartic acid, or diamino proprionic acid.

11. The peptide of claim 10, wherein X^6 is either D-arginine, D-alanine, D-norleucine, D-proline, D-phenylalanine, D-asparagine, D-serine, D-glutamic acid, D- lysine, or D-citrulline.

12. The peptide of claim 11, wherein either X^7 is 2,3 diamino proprionic acid and X^{16} is aspartic acid; or X^7 is aspartic acid and X^{16} is 2,3 diamino proprionic acid.

13. The peptide of claim 12, wherein Z^1 is $-C(O)CH_3$ and Z^2 is $-NH_2$.

14. The peptide of claim 11, wherein X^7 is cysteine and X^{16} is cysteine or D-cysteine.

15. The peptide of claim 14, wherein Z^1 is $-C(O)CH_3$ and Z^2 is $-NH_2$.

16. The peptide of claim 15, wherein X^{10} is glutamine.

17. The peptide of claim 1, wherein said peptide consists of a sequence selected from the group consisting of: SEQ ID NOs: 29, 30, 31, 32, 33, and 34.

18. The peptide of claim 17, wherein said peptide consists of SEQ ID NO: 30.

19. A method of screening for a compound able to bind MCH-1R comprising the step of measuring the ability of said compound to affect binding of the peptide of any one of claims 1-18 to MCH-1R.

20. The method of claim 19, wherein said peptide is radiolabeled.

21. A method of selectively producing MCH-1R activity comprising the step of providing a cell functionally expressing MCH-1R with the peptide of any one of claim 1-18.

22. The method of claim 21, wherein said MCH-1R has the amino acid sequence of SEQ ID NO: 35.

23. A method of screening for a MCH-1R antagonist comprising the steps of:

a) combining together a MCH-1R or a functional derivative thereof, a test compound, and the compound of any one of claims 1-18,

b) measuring the ability of said test compound to inhibit an MCH-1R activity as an indication of the ability of said test compound to act as said MCH-1R antagonist.

24. The method of claim 23, wherein said functional MCH-1R is a mammalian MCH-1R.

25. The method of claim 23, wherein said functional MCH-1R is a human MCH-1R.

26. A method for increasing weight in a subject having an MCH-1R comprising the step of administering to said subject an effective amount of the peptide of any one of claims 1-18.

27. A method for increasing appetite in a subject having an MCH-1R comprising the step of administering to said subject an effective amount of the peptide of any one of claims 1-18.

28. A method for measuring the ability of a compound to decrease weight or appetite in a subject having an MCH-1R comprising the steps of:

a) administering to said subject an effective amount of the peptide of any one of claims 1-18 to produce a weight increase or appetite increase,

b) administering said compound to said subject, and

c) measuring the change in weight or appetite of said subject.