CLAIMS

1. Use of a melanocortin-4 receptor (MC4R) agonist in the manufacture of a medicament for treating hypothalamic obesity in a subject wherein the melanocortin-4 receptor (MC4R) agonist is to be administered to the subject, wherein the subject:

(i) has or had been identified as having hypothalamic obesity;

(ii) has or had been identifying as having damage to the brain tissue;

(iii) has or had been identified as having a proliferative brain disease..

2. The use of claim 1, comprising (i).

3. The use of claim 1, comprising (ii).

4. The use of claim 1, comprising (iii).

5. The use of claim 1, wherein the hypothalamic obesity is caused by a neurodevelopmental abnormality or a brain malformation.

6. The use of claim 1, wherein the damage to the brain tissue is present in the hypothalamus.

7. The use of claim 6, wherein the damage to the brain tissue is present in the paraventricular hypothalamic nucleus, ventromedial hypothalamic nucleus, or arcuate hypothalamic nucleus.

8. The use of claim 7, wherein the damage or trauma in the brain occurs in the ventromedial nucleus.

9. The use of claim 1, wherein the subject has hypothalamic obesity.

10. The use of claim 1, wherein the proliferative brain disease comprises a benign tumor, a benign lesion, or a malignant tumor (e.g., cancer).

11. The use of claim 10, wherein the proliferative brain disease is present in the hypothalamus.

12. The use of claim 10, wherein the proliferative brain disease is present in the paraventricular hypothalamic nucleus, ventromedial hypothalamic nucleus, or arcuate hypothalamic nucleus.

13. The use of claim 10, wherein the proliferative brain disease comprises craniopharyngioma or astrocytoma.

14. The use of claim 1, wherein the subject had previously undergone a surgery (e.g., tumor removal or bariatric surgery) or had received radiation.

15. The use of claim 1, wherein the subject is obese, e.g., severely obese.

16. The use of claim 1, wherein the subject is hyperphagic.

17. The use of claim 1, wherein the subject has a body mass index (BMI) greater than 35 kg/m^2 (e.g., ≥36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 kg/m^2 or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

18. The use of claim 1, wherein the subject has a body mass index (BMI) greater than 40 kg/m^2 (e.g., ≥41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55 kg/m^2 or greater) prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

19. The use of claim 1, wherein the subject has failed one or more previous therapies, e.g., exercise, diet, or behavioral therapies, prior to administration of the MC4R agonist, e.g., at the time the MC4R agonist is prescribed, or at the time of the first administration.

20. The use of claim 1, wherein the subject has a lower body weight after administration of the MC4R agonist than before administration of the MC4R agonist.

21. The use of claim 1, wherein the MC4R agonist is has the structure of Formula (I):

$$(R^2R^3)\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1 \quad \text{(I)},$$

wherein:

A^1 is Acc, HN—$(CH_2)_m$—C(O), L- or D-amino acid, or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp, or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid, or deleted;

A^4 is His, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, or (X^1, X^2, X^3, X^4, X^5)Phe;

A^5 is D-Phe, Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1, X^2, X^3, X^4, X^5)Phe, or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn, or HN-CH($(CH_2)_n$-N(R^4 R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, 13-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O), or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn, or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid, or deleted;

R^1 is OH or NH_2;

each of R^2 and R^3 is, independently for each occurrence, selected from the group consisting of H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl, and substituted aryl(C_1-C_{30})acyl;

each of R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl,

aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl, or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6, or 7;

X^1, X^2, X^3, X^4, and X^5 each is, independently for each occurrence, H, F, Cl, Br, I, (C_1-C_{10})alkyl, substituted (C_1-C_{10})alkyl, (C_2-C_{10})alkenyl, substituted (C_2-C_{10})alkenyl, (C_2-C_{10})alkynyl, substituted (C_2-C_{10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN.

22. The use of claim 21, wherein A^1 is selected from Lys, D-Lys, Arg, and D-Arg.

23. The use of claim 21, wherein A^2 and A^9 are each independently selected from Cys, hCys, and Pen.

24. The use of claim 21, wherein A^3 is selected from Ala or D-Ala.

25. The use of claim 21, wherein A^4 is selected from His and D-His.

26. The use of claim 21, wherein A^5 is selected from Phe, D-Phe, D-1-Nal, and D-2-Nal.

27. The use of claim 21, wherein A^6 is Arg.

28. The use of claim 21, wherein A^7 is Trp.

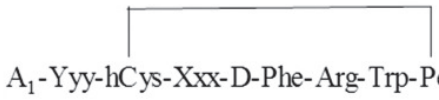
29. The use of claim 21, wherein A^8 and/or A^{10} is deleted.

30. The use of claim 21, wherein R^1 is NH_2.

31. The use of claim 21, wherein one of R^2 and R^3 is independently hydrogen and the other of R^2 and R^3 is independently (C_1-C_{30}) acyl (e.g., acetyl).

32. The use of claim 1, wherein the MC4R agonist is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (SEQ ID NO: 140).

33. The use of claim 1, wherein the MC4R agonist has the structure of Formula (II) or a pharmaceutically acceptable salt thereof:



(II)

where Xxx is Asn, Gln, Ser, or Thr,
where A_1 is H or Ac,
where A_2 is OH or NH_2, and
where Yyy is Lys, Arg, D-Lys, or D-Arg.

34. The use of claim 33, wherein the MC4R agonist is selected from:
SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Dpr)-NH_2;
(SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 642) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 644) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 647) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 648) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 657) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 659) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 662) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 663) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 672) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 674) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 677) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 678) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 687) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 689) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2; and
(SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2,

or a pharmaceutically acceptable salt thereof.

35. The use of claim 1, wherein the MC4R agonist is formulated as a pharmaceutical composition.

36. The use of claim 35, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable excipient.

37. The use of claim 35, wherein the pharmaceutical composition comprises a polyethylene glycol (e.g., a modified polyethylene glycol, e.g., mPEG-DSPE, e.g., mPEG-2,000-DSPE).

38. The use of claim 1, wherein the MC4R agonist is to be administered in a unit dosage suitable for injection, e.g., subcutaneous injection, to the subject.

39. The use of claim 38, wherein the unit dosage form is disposed within a delivery device, e.g., a syringe (e.g., prefilled syringe), an implantable device, a needleless hypodermic injection device, an infusion pump (e.g., implantable infusion pump), or an osmotic delivery system.

40. The use of claim 39, wherein the MC4R agonist is to be administered subcutaneously, e.g., by subcutaneous injection.

41. The use of claim 1, wherein the subject is a human.

42. The use of claim 1, wherein the subject is an adult (e.g., over the age of 18 years old).

43. The use of claim 1, wherein the subject is a pediatric subject, e.g., a child (e.g., under the age of 18, 16, 14, 12, 10, 8, 6, or 4 years).

44. The use of claim 1, wherein prior to administration of the MC4R agonist, the subject had previously received treatment for obesity, e.g., a non-genetic obesity, e.g., hypothalamic obesity.

45. The use of claim 1, wherein after a first administration of the MC4R agonist (e.g., at least 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 4 months, 5 months, 6 months, 8 months, 10 months, 1 year, or longer), the subject exhibits a reduction in BMI.

46. The use of claim 45, wherein the reduction of BMI in the subject is greater than 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 14% 16%, 18%, 20%, or more, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).

47. The use of claim 45, wherein the reduction of BMI in the subject is greater than 0.5%, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).

48. The use of claim 45, wherein the reduction of BMI in the subject is greater than 5%, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).

49. The use of claim 45, wherein the reduction of BMI in the subject is greater than 10%, e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).

50. The use of claim 45, wherein the reduction of BMI in the subject is between 1%-10% (e.g., 1-5%, or 5-10%), e.g., relative to a reference standard (e.g., BMI prior to administration of the MC4R agonist).

51. The use of claim 45, wherein the reduction of BMI in the subject occurs between 8 weeks and 6 months after administration of the MC4R agonist.

52. The use of claim 1, wherein the subject is to be administered an additional agent (e.g., an additional therapeutic agent).

53. The use of claim 1, wherein the MC4R agonist is a compound of Formula (I-a):

$$H\text{-}A^{1}\text{-}c(A^{2}\text{-}A^{3}\text{-}A^{4}\text{-}A^{5}\text{-}A^{6}\text{-}A^{7}\text{-}A^{8}\text{-}A^{9})\text{-}A^{10}\text{-}NH_2 \qquad \text{(I-a)}$$

or a pharmaceutically acceptable salt thereof, wherein:

A^1 is Phe, D-Phe, or Nle;

A^2 is Cys;

A^3 is deleted;

A^4 is His;

A^5 is D-Phe or D-(Et)Tyr;

A^6 is Arg or hArg;

A^7 is Trp or Bip;

A^8 is Ala, β-Ala, Gaba, or Apn;

A^9 is D-Cys; and

A^{10} is Thr or deleted.

54. The use of claim 53, wherein the MC4R agonist of Formula (I-a) is selected from:

(SEQ ID NO: 4) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Ala-D-Cys)-Thr-NH_2;

(SEQ ID NO: 5) D-Phe-c(Cys-His-D-Phe-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

(SEQ ID NO: 6) D-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-D-Cys)-Thr-NH_2;

(SEQ ID NO: 79) D-Phe-c(Cys-His-D-Phe-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

(SEQ ID NO: 80) D-Phe-c(Cys-His-D-(Et)Tyr-Arg-Trp-β-Ala-D-Cys)-Thr-NH_2;

(SEQ ID NO: 81) D-Phe-c(Cys-His-D-Phe-Arg-Bip-β-Ala-D-Cys)-Thr-NH_2;

(SEQ ID NO: 82) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Trp-β-Ala-D-Cys)-Thr-NH_2;

(SEQ ID NO: 83) D-Phe-c(Cys-His-D-Phe-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

(SEQ ID NO: 84) D-Phe-c(Cys-His-D-(Et)Tyr-hArg-Bip-β-Ala-D-Cys)-Thr-NH_2;

(SEQ ID NO: 85) Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2; and

(SEQ ID NO: 105) Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2.

55. The use of claim 1, wherein the MC4R agonist is a compound of Formula (I-b):

$$Ac\text{-}A^1\text{-}c(A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}NH_2 \qquad \text{(I-b)}$$

or a pharmaceutically acceptable salt thereof, wherein:

A^1 is Nle, A6c, D-2-Nal, Cha, Oic, Chg, hCha, D-Cha, D-hCha, Nip, hPro, hLeu, Phe, D-Phe, D-Chg, hPhe, β-hMet, Gaba, Leu, Ile, Val, 2-Nal, Arg or D-Arg;

A^2 is Asp, Cys, D-Cys, or Pen;

A^3 is D-Ala, β-Ala, Gaba, Aib, Gly, Ala, D-Glu, D-Abu, D-Val, D-Ile, D-Leu, D-Tle, D-Cha, deleted;

A^4 His or 3-Pal;

A^5 is Phe, D-Phe, or D-2-Nal;

A^6 is Arg;

A^7 is Trp, 1-Nal, 2-Nal, Bal, or D-Trp;

A^8 is β-Ala, A6c, Ahx, Apn, Gaba, Ala, Aha, D-Ala or deleted;

A^9 is Lys, Cys, D-Cys, or Pen;

A^{10} is deleted.

wherein A^2 and A^9 are pairwise selected to form a disulfide or lactam bridge.

56. The use of claim 55, wherein the MC4R agonist of Formula (I-b) is selected from:

(SEQ ID NO: 1) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-β-Ala-Lys)-NH_2;

(SEQ ID NO: 2) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-A6c-Lys)-NH_2;

(SEQ ID NO: 3) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Ahx-Cys)-NH_2;

(SEQ ID NO: 7) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Apn-Cys)-NH_2;

(SEQ ID NO: 8) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Apn-Lys)-NH_2;

(SEQ ID NO: 9) Ac-A6c-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 10) Ac-D-2-Nal-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 11) Ac-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 12) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 13) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 14) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 15) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 16) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 17) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 18) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 19) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 20) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 21) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 22) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 23) Ac-Nle-c(D-Cys-Gly-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 24) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

(SEQ ID NO: 25) Ac-Nle-c(Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

(SEQ ID NO: 26) Ac-Nle-c(Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

(SEQ ID NO: 27) Ac-Nle-c(Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

(SEQ ID NO: 28) Ac-Nle-c(Cys-Gly-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

(SEQ ID NO: 29) Ac-Nle-c(D-Cys-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

(SEQ ID NO: 30) Ac-Nle-c(D-Cys-D-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

(SEQ ID NO: 31) Ac-Nle-c(D-Cys-β-Ala-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

(SEQ ID NO: 32) Ac-Nle-c(D-Cys-Gaba-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

(SEQ ID NO: 33) Ac-Nle-c(D-Cys-Aib-His-D-Phe-Arg-Trp-D-Cys)-NH_2;

(SEQ ID NO: 34) Ac-Oic-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 35) Ac-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 36) Ac-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 37) Ac-D-Cha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 38) Ac-D-hCha-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 39) Ac-Nip-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 40) Ac-hPro-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 41) Ac-hLeu-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 42) Ac-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 43) Ac-D-Phe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 44) Ac-D-Chg-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 47) Ac-hPhe-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 48) Ac-β-hMet-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 49) Ac-Gaba-c(Asp-His-D-Phe-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 50) Ac-Cha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

(SEQ ID NO: 51) Ac-hCha-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

(SEQ ID NO: 52) Ac-Leu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

(SEQ ID NO: 53) Ac-hLeu-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

(SEQ ID NO: 54) Ac-Phe-c(Asp-His-D-Phe-Arg-D-Trp-Ala-Lys)-NH_2;

(SEQ ID NO: 55) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-D-Ala-Lys)-NH_2;

(SEQ ID NO: 56) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-β-Ala-Lys)-NH_2;

(SEQ ID NO: 57) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 58) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Aha-Lys)-NH_2;

(SEQ ID NO: 59) Ac-Nle-c(Asp-His-D-Phe-Arg-D-Trp-Apn-Lys)-NH_2;

(SEQ ID NO: 60) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Apn-Cys)-NH_2;

(SEQ ID NO: 61) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Gaba-Cys)-NH_2;

(SEQ ID NO: 62) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-Ahx-Cys)-NH_2;

(SEQ ID NO: 63) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-β-Ala-Cys)-NH_2;

(SEQ ID NO: 64) Ac-Nle-c(Cys-His-D-Phe-Arg-D-Trp-D-Ala-Cys)-NH_2;

(SEQ ID NO: 65) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 66) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-2-Nal-Cys)-NH_2;

(SEQ ID NO: 67) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-1-Nal-Cys)-NH_2;

(SEQ ID NO: 70) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-2-Nal-Cys)-NH_2;

(SEQ ID NO: 71) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-1-Nal-Cys)-NH_2;

(SEQ ID NO: 72) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Bal-Cys)-NH_2;

(SEQ ID NO: 73) Ac-Nle-c(Cys-D-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 74) Ac-Nle-c(Asp-His-D-Phe-Arg-Trp-D-Ala-Lys)-NH_2;

(SEQ ID NO: 75) Ac-Nle-c(Cys-D-Ala-His-D-2-Nal-Arg-Bal-Cys)-NH_2;

(SEQ ID NO: 76) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 77) Ac-Nle-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 78) Ac-Nle-c(Pen-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 86) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Trp-Lys)-NH_2;

(SEQ ID NO: 87) Ac-Nle-c(Asp-D-Ala-His-D-Phe-Arg-Bal-Lys)-NH_2;

(SEQ ID NO: 89) Ac-Nle-c(Cys-D-Abu-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 90) Ac-Nle-c(Cys-D-Val-His-D-Phe-Arg-Trp-Cys)- NH_2;

(SEQ ID NO: 91) Ac-Nle-c(Cys-D-Ile-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 92) Ac-Nle-c(Cys-D-Leu-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 93) Ac-Nle-c(Cys-D-Tle-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 94) Ac-Nle-c(Cys-D-Cha-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 95) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

(SEQ ID NO: 96) Ac-Nle-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

(SEQ ID NO: 97) Ac-Nle-c(Pen-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

(SEQ ID NO: 98) Ac-Leu-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

(SEQ ID NO: 99) Ac-Cha-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

(SEQ ID NO: 100) Ac-Ile-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

(SEQ ID NO: 101) Ac-Phe-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

(SEQ ID NO: 102) Ac-Val-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

(SEQ ID NO: 103) Ac-2-Nal-c(Cys-His-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

(SEQ ID NO: 106) Ac-Nle-c(Cys-3-Pal-D-Phe-Arg-Trp-Gaba-Cys)-NH_2;

(SEQ ID NO: 108) Ac-Nle-c(Cys-His-Phe-Arg-D-Trp-Gaba-Cys)- NH_2;

(SEQ ID NO: 109) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-Ala-Lys)-NH_2;

(SEQ ID NO: 110) Ac-Nle-c(Asp-His-D-2-Nal-Arg-Trp-β-Ala-Lys)-NH_2;

(SEQ ID NO: 111) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Gaba-Cys)-NH_2;

(SEQ ID NO: 112) Ac-Nle-c(Cys-His-D-2-Nal-Arg-Trp-Ahx-Cys)-NH_2;

(SEQ ID NO: 113) Ac-hPhe-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 114) Ac-Cha-c(Asp-His-D-2-Nal-Arg-Trp-Gaba-Lys)-NH_2;

(SEQ ID NO: 139) Ac-Arg-c(Cys-D-Ala-His-D-2-Nal-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 140) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 141) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2;

(SEQ ID NO: 142) Ac-D-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 143) Ac-D-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

(SEQ ID NO: 144) Ac-Arg-c(Cys-His-D-Phe-Arg-Trp-Gaba-Pen)-NH_2;

(SEQ ID NO: 145) Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 146) Ac-D-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2; and

(SEQ ID NO: 147) Ac-Arg-c(Asp-His-D-Phe-Arg-Trp-Ala-Lys)-NH_2.

57. The use of claim 1, wherein the MC4R agonist is a compound of Formula (XII-a):

H-Yyy-c(Aaa-Xxx-D-Phe-Arg-Trp-Bbb)-NH_2 (XII-a)

or a pharmaceutically acceptable salt thereof, wherein:

Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;

Xxx is Asn, Gln, Ser, Thr; and

Yyy is Lys, Arg, D-Lys, D-Arg.

58. The use claim 57, wherein the MC4R agonist of Formula (XII-a) is selected from:

(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 643) H-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 646) H-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 658) H-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 661) H-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 673) H-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 676) H-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 688) H-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 691) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2; and
(SEQ ID NO: 693) H-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2.

59. The use of claim 1, wherein the MC4R agonist is a compound of Formula (XII-b):

Ac-Yyy-c(Aaa-Xxx-D-Phe-Arg-Trp-Bbb)-NH_2 (XII-b)

or a pharmaceutically acceptable salt thereof, wherein:

Aaa and Bbb are selected from Cys, hCys, Pen capable of establishing a disulfide bridge; or Glu, Asp, Lys, Orn, Dpr, Dbu capable of establishing a lactam bridge;

Xxx is Asn, Gln, Ser, Thr; and

Yyy is Lys, Arg, D-Lys, D-Arg.

60. The use of claim 59, wherein the MC4R agonist of Formula (XII-b) is selected from:
(SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Apr)-NH_2;
(SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;

(SEQ ID NO: 641) Ac-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 645) Ac-D-Lys-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 656) Ac-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 660) Ac-D-Lys-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 671) Ac-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 675) Ac-D-Lys-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 686) Ac-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 690) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2; and
(SEQ ID NO: 692) Ac-D-Lys-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2.

61. The use of claim 1, wherein the MC4R agonist is a compound of Formula (XII-c):

A_1-Yyy-c(Aaa-Xxx-D-Phe-Arg-Trp-Bbb)-A_2 (XII-c)

or a pharmaceutically acceptable salt thereof, wherein:

A_1 is H or Ac;

A_2 is OH or NH_2;

Yyy is L-Arg or D-Arg;

Aaa and Bbb are selected from Cys, hCys, and Pen capable of establishing a disulfide bridge; or Glu, Asp, Lys, Orn, Dpr, and Dbu capable of establishing a lactam bridge; and

Xxx is Asn, Gln, Ser, or Thr.

62. The use of claim 61, wherein the MC4R agonist of Formula (XII-c) is selected from:
(SEQ ID NO: 629) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 630) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 631) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 632) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 633) Ac-Arg-c(Glu-Gln-D-Phe-Arg-Trp-Apr)-NH_2;
(SEQ ID NO: 634) Ac-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;

(SEQ ID NO: 635) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 636) H-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 637) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 638) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 639) Ac-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 640) H-D-Arg-c(hCys-Asn-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 649) Ac-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 650) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 651) H-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 652) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 653) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 654) Ac-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 655) H-D-Arg-c(hCys-Gln-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 664) Ac-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 665) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 666) H-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 667) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 668) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 669) Ac-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 670) H-D-Arg-c(hCys-Ser-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 679) Ac-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 680) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 681) H-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH;
(SEQ ID NO: 682) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 683) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-NH_2;
(SEQ ID NO: 684) Ac-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH; and
(SEQ ID NO: 685) H-D-Arg-c(hCys-Thr-D-Phe-Arg-Trp-Pen)-OH.

63. The use of claim 1, wherein after administration of the MC4R agonist, the subject experiences a reduction in BMI of between 5-10, e.g., after 16 weeks, relative to the baseline BMI, e.g., the BMI of the subject prior to administration of the MC4R agonist.

64. The use of claim 63, wherein the subject is a pediatric subject between ages 6 and 18.

65. The use of claim 1, wherein after administration of the MC4R agonist, the subject experiences a reduction in weight of between about 5 kg to about 15 kg, e.g., after 16 weeks, relative to the baseline weight, e.g., the weight of the subject prior to administration of the MC4R agonist.

66. The use of claim 65, wherein the subject is a pediatric subject between ages 6 and 18.