recovering the expression product, and modifying the precursor peptide to yield a compound as disclosed herein.

The precursor peptide may be expressed from a nucleic acid encoding the precursor peptide in a cell or a cell-free expression system comprising such a nucleic acid.

In another aspect, there is provided a compound having the formula: R^1-P^1-R^2 wherein R^1 is hydrogen (Hy), C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl; R^2 is OH or NH_2; P^1 is a peptide having the sequence: H-X2-X3-GTFTSDYSKYLDSΨAAHDFVEWLLSA,

wherein:

X2 is selected from Aib, Ala, D-Ala, Ser, N-Me-Ser, Ac3c, Ac4c and Ac5c;

X3 is selected from Gln and His;

and Ψ is a residue of Lys, Arg, Orn or Cys in which the side chain is conjugated to a substituent selected from:

(i) [17-Carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3;

(ii) [17-Carboxy-heptadecanoyl]-isoGlu

(iii) [13-Carboxy-tridecanoyl]-isoGlu-Peg3-Peg3;

(iv) [Carboxyphenoxynonanoyl]-isoGlu-Peg3-Peg3;

(v) [13-Carboxy-tridecanoyl]-isoGlu-Peg4-Peg4;

(vi) [17-Carboxy-heptadecanoyl]-Peg3-Peg3-isoGlu;

(vii) [17-Carboxy-heptadecanoyl]-isoGlu-GSGSGG; and

(viii) [17-Carboxy-heptadecanoyl]-AA-Peg3-Peg3;

or a pharmaceutically acceptable salt or solvate thereof.

In another aspect, there is provided a compound having the formula:

R^1-P^1-R^2

wherein

R^1 is hydrogen (Hy), C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2;

P^1 is a peptide having the sequence:

His-X2-X3-GTFTSDYSKYL-X15-X16-X17-X18-A-X20-DFI-X24-WLE-X28-A

wherein:

X2 is selected from Aib, Ac3c, Ac4c and Ac5c;

X3 is selected from Gln and His;

X15 is selected from Asp and Glu;

X16 is selected from Glu and Ψ;

X17 is selected from Arg and Ψ;

X18 is selected from Ala and Arg;

X20 is selected from Lys and His;

X24 is selected from Glu and Ψ;

X28 is selected from Ser and Ψ;

wherein the compound contains one and only one Ψ

and wherein said Ψ is a residue of Lys, Arg, Orn or Cys in which the side chain is conjugated to a substituent selected from:

(i) [17-Carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3;

(ii) [17-Carboxy-heptadecanoyl]-isoGlu

(iii) [13-Carboxy-tridecanoyl]-isoGlu-Peg3-Peg3;

(iv) [Carboxyphenoxynonanoyl]-isoGlu-Peg3-Peg3;

(v) [13-Carboxy-tridecanoyl]-isoGlu-Peg4-Peg4;

(vi) [17-Carboxy-heptadecanoyl]-Peg3-Peg3-isoGlu;

(vii) [17-Carboxy-heptadecanoyl]-isoGlu-GSGSGG; and

(viii) [17-Carboxy-heptadecanoyl]-AA-Peg3-Peg3;

or a pharmaceutically acceptable salt or solvate thereof.

In another aspect, there is provided a compound selected from the group consisting of:

Hy-H-Aib-QGTFTSDYSKYLD-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAAKDFIEWLESA-NH2;

Hy-H-Aib-QGTFTSDYSKYLE-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-RAAKDFIEWLESA-NH2;

Hy-H-Ac4c-QGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAKDFIEWLESA-NH2;

Hy-H-Aib-QGTFTSDYSKYLDERAAKDFI-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-WLESA-NH2;

Hy-H-Ac4c-QGTFTSDYSKYLDERAAKDFI-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-WLESA-NH2; and

Hy-H-Ac4c-QGTFTSDYSKYLDERAAKDFIEWLE-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-A-NH2.

DETAILED DESCRIPTION OF THE INVENTION

Throughout this specification, the conventional one letter and three letter codes for naturally occurring amino acids are used, as well as generally accepted abbreviations for other amino

CLAIMS

1. A compound having the formula:

R^1-P^1-R^2

wherein

R^1 is hydrogen (Hy), C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2;

P^1 is a peptide having the sequence:

H-X2-X3-GTFTSDYSKYLDSΨAAHDFVEWLLSA

wherein:

X2 is selected from Aib, Ala, D-Ala, Ser, N-Me-Ser, Ac3c, Ac4c and Ac5c;

X3 is selected from Gln and His;

and Ψ is a residue of Lys, Arg, Orn or Cys in which the side chain is conjugated to a substituent selected from:

(i) [17-Carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3;

(ii) [17-Carboxy-heptadecanoyl]-isoGlu

(iii) [13-Carboxy-tridecanoyl]-isoGlu-Peg3-Peg3;

(iv) [Carboxyphenoxynonanoyl]-isoGlu-Peg3-Peg3;

(v) [13-Carboxy-tridecanoyl]-isoGlu-Peg4-Peg4;

(vi) [17-Carboxy-heptadecanoyl]-Peg3-Peg3-isoGlu;

(vii) [17-Carboxy-heptadecanoyl]-isoGlu-GSGSGG; and

(viii) [17-Carboxy-heptadecanoyl]-AA-Peg3-Peg3;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 wherein P^1 has the sequence:
H-Aib-QGTFTSDYSKYLDSΨAAHDFVEWLLSA

3. A compound according to claim 2 which is:
H-H-Aib-QGTFTSDYSKYLDSΨAAHDFVEWLLSA-NH_2

4. A compound having the formula:
R^1-P^1-R^2
wherein
R^1 is hydrogen (Hy), C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2;
P^1 is a peptide having the sequence:

His-X2-X3-GTFTSDYSKYL-X15-X16-X17-X18-A-X20-DFI-X24-WLE-X28-A

wherein:
X2 is selected from Aib, Ac3c, Ac4c and Ac5c;
X3 is selected from Gln and His;
X15 is selected from Asp and Glu;
X16 is selected from Glu and Ψ;
X17 is selected from Arg and Ψ;
X18 is selected from Ala and Arg;
X20 is selected from Lys and His;
X24 is selected from Glu and Ψ;
X28 is selected from Ser and Ψ;

wherein the compound contains one and only one Ψ

and wherein said Ψ is a residue of Lys, Arg, Orn or Cys in which the side chain is conjugated to a substituent selected from:

(i) [17-Carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3;

(ii) [17-Carboxy-heptadecanoyl]-isoGlu

(iii) [13-Carboxy-tridecanoyl]-isoGlu-Peg3-Peg3;

(iv) [Carboxyphenoxynonanoyl]-isoGlu-Peg3-Peg3;

(v) [13-Carboxy-tridecanoyl]-isoGlu-Peg4-Peg4;

(vi) [17-Carboxy-heptadecanoyl]-Peg3-Peg3-isoGlu;

(vii) [17-Carboxy-heptadecanoyl]-isoGlu-GSGSGG; and

(viii) [17-Carboxy-heptadecanoyl]-AA-Peg3-Peg3;

or a pharmaceutically acceptable salt or solvate thereof.

5. A compound according to claim 4 wherein:

X2 is selected from Aib and Ac4c;

X3 is Gln;

X15 is selected from Asp and Glu;

X16 is Ψ;

X17 is Arg;

X18 is Ala;

X20 is selected from Lys and His;

X24 is Glu;

X28 is Ser.

6. A compound according to claim 4 or claim 5 wherein:

X2 is Ac4c and X20 is Lys;

X2 is Aib and X20 is His.

7. A compound according to any one of claims 4 to 6 wherein

X2 is Aib if X15 is E; or

X15 is D if X2 is Ac4c.

8. A compound according to any one of claims 4 to 7 wherein P^1 has a sequence selected from:

H-Aib-QGTFTSDYSKYLDΨRAAKDFIEWLESA

H-Aib-QGTFTSDYSKYLDΨRAAKDFIEWLESA

H-Aib-QGTFTSDYSKYLEΨRAAKDFIEWLESA

H-Ac4c-QGTFTSDYSKYLDΨRAAKDFIEWLESA and

H-Aib-QGTFTSDYSKYLEΨRAAHDFIEWLESA

9. A compound according to claim 8 which is selected from:

Hy-H-Aib-QGTFTSDYSKYLDΨRAAKDFIEWLESA-NH_2

Hy-H-Aib-QGTFTSDYSKYLDΨRAAKDFIEWLESA-NH_2

Hy-H-Aib-QGTFTSDYSKYLEΨRAAKDFIEWLESA-NH_2

Hy-H-Ac4c-QGTFTSDYSKYLDΨRAAKDFIEWLESA-NH_2 and

Hy-H-Aib-QGTFTSDYSKYLEΨRAAHDFIEWLESA-NH_2

10. A compound according to claim 4 wherein:

X2 is selected from Aib and Ac4c;

X3 is selected from Gln and His;

X15 is Asp;

X16 is Glu;

X17 is selected from Arg and Ψ;

X18 is selected from Ala and Arg;

X20 is Lys;

X24 is selected from Glu and Ψ;

X28 is selected from Ser and Ψ;

11. A compound according to claim 10 wherein, when X28 is Ψ, X2 is Ac4c.

12. A compound according to claim 10 wherein, when X3 is His, X2 is Ac4c and X17 is Ψ.

13. A compound according to claim 10 wherein P^1 has a sequence selected from:

H-Aib-QGTFTSDYSKYLDEΨAAKDFIEWLESA

H-Ac4c-QGTFTSDYSKYLDEΨRAKDFIEWLESA

H-Ac4c-HGTFTSDYSKYLDEΨRAKDFIEWLESA

H-Ac4c-QGTFTSDYSKYLDEΨAAKDFIEWLESA

H-Ac4c-QGTFTSDYSKYLDEΨRAKDFIEWLESA

H-Aib-QGTFTSDYSKYLDERAAKDFIΨWLESA

H-Ac4c-QGTFTSDYSKYLDERAAKDFIΨWLESA

H-Ac4c-QGTFTSDYSKYLDERRAKDFIΨWLESA

H-Ac4c-QGTFTSDYSKYLDERAAKDFIEWLEΨA and
H-Ac4c-QGTFTSDYSKYLDERRAKDFIEWLEΨA

14. A compound according to claim 13 which is selected from:
Hy-H-Aib-QGTFTSDYSKYLDEΨAAKDFIEWLESA-NH_2
Hy-H-Ac4c-QGTFTSDYSKYLDEΨRAKDFIEWLESA-NH_2
Hy-H-Ac4c-HGTFTSDYSKYLDEΨRAKDFIEWLESA-NH_2
Hy-H-Ac4c-QGTFTSDYSKYLDEΨAAKDFIEWLESA-NH_2
Hy-H-Ac4c-QGTFTSDYSKYLDEΨRAKDFIEWLESA-NH_2
Hy-H-Aib-QGTFTSDYSKYLDERAAKDFIΨWLESA-NH_2
Hy-H-Ac4c-QGTFTSDYSKYLDERAAKDFIΨWLESA-NH_2
Hy-H-Ac4c-QGTFTSDYSKYLDERRAKDFIΨWLESA-NH_2
Hy-H-Ac4c-QGTFTSDYSKYLDERAAKDFIEWLEΨA-NH_2 and
Hy-H-Ac4c-QGTFTSDYSKYLDERRAKDFIEWLEΨA-NH_2

15. A compound according to claim 1 wherein P1 has the sequence: H-Aib-QGTFTSDYSKYLDS-K([15-carboxy-pentadecanoyl]-isoGlu)-AAHDFVEWLLSA.

16. A compound according to claim 15 which is: H-H-Aib-QGTFTSDYSKYLDS-K([15-carboxy-pentadecanoyl]-isoGlu)-AAHDFVEWLLSA-NH_2.

17. A compound according to any one of claims 4 to 7 wherein the substituent is [17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3 or [17-carboxy-heptadecanoyl]-isoGlu-GSGSGG.

18. A compound according to claim 10 or claim 12 wherein, when X17 is Ψ, the substituent is [17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3 or [17-Carboxy-heptadecanoyl]-isoGlu.

19. A compound according to claim 10 or claim 11 wherein, when X24 or X28 is Ψ, the substituent is [17-carboxy-heptadecanoyl]-isoGlu-GSGSGG.

20. A compound according to claim 8 wherein P^1 has a sequence selected from:
H-Aib-QGTFTSDYSKYLD-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAAKDFIEWLESA
H-Aib-QGTFTSDYSKYLD-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-RAAKDFIEWLESA
H-Aib-QGTFTSDYSKYLE-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-RAAKDFIEWLESA
H-Ac4c-QGTFTSDYSKYLD-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-RAAKDFIEWLESA and
H-Aib-QGTFTSDYSKYLE-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAAHDFIEWLESA

21. A compound according to claim 20 which is selected from:
Hy-H-Aib-QGTFTSDYSKYLD-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAAKDFIEWLESA-NH_2
Hy-H-Aib-QGTFTSDYSKYLD-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-RAAKDFIEWLESA-NH_2
Hy-H-Aib-QGTFTSDYSKYLE-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-RAAKDFIEWLESA-NH_2
Hy-H-Ac4c-QGTFTSDYSKYLD-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-RAAKDFIEWLESA-NH_2 and
Hy-H-Aib-QGTFTSDYSKYLE-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAAHDFIEWLESA-NH2

22. A compound according to claim 13 wherein P^1 has a sequence selected from:
H-Aib-QGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu)-AAKDFIEWLESA
H-Ac4c-QGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAKDFIEWLESA
H-Ac4c-HGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAKDFIEWLESA
H-Ac4c-QGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu)-AAKDFIEWLESA
H-Ac4c-QGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu)-RAKDFIEWLESA H-Aib-QGTFTSDYSKYLDERAAKDFI-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-WLESA
H-Ac4c-QGTFTSDYSKYLDERAAKDFI-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-WLESA
H-Ac4c-QGTFTSDYSKYLDERRAKDFI-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-WLESA
H-Ac4c-QGTFTSDYSKYLDERAAKDFIEWLE-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-A and

H-H-Ac4c-QGTFTSDYSKYLDERRAKDFIEWLE-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-A-NH_2

23. A compound according to claim 22 which is selected from:

Hy-H-Aib-QGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu)-AAKDFIEWLESA-NH_2

Hy-H-Ac4c-QGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAKDFIEWLESA-NH_2

Hy-H-Ac4c-HGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAKDFIEWLESA-NH_2

Hy-H-Ac4c-QGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu)-AAKDFIEWLESA-NH_2

Hy-H-Ac4c-QGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu)-RAKDFIEWLESA-NH_2

Hy-H-Aib-QGTFTSDYSKYLDERAAKDFI-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-WLESA-NH_2

Hy-H-Ac4c-QGTFTSDYSKYLDERAAKDFI-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-WLESA-NH_2

Hy-H-Ac4c-QGTFTSDYSKYLDERRAKDFI-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-WLESA-NH_2

Hy-H-Ac4c-QGTFTSDYSKYLDERAAKDFIEWLE-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-A-NH_2 and

Hy-H-Ac4c-QGTFTSDYSKYLDERRAKDFIEWLE-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-A-NH_2.

24. A compound which is:

Hy-H-Aib-QGTFTSDYSKYLD-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAAKDFIEWLESA-NH_2.

25. A compound which is:

Hy-H-Aib-QGTFTSDYSKYLE-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-RAAKDFIEWLESA-NH_2.

26. A compound which is:

Hy-H-Ac4c-QGTFTSDYSKYLDE-K([17-carboxy-heptadecanoyl]-isoGlu-Peg3-Peg3)-RAKDFIEWLESA-NH_2.

27. A compound which is:

Hy-H-Aib-QGTFTSDYSKYLDERAAKDFI-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-WLESA-NH_2.

28. A compound which is:
Hy-H-Ac4c-QGTFTSDYSKYLDERAAKDFI-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-WLESA-NH_2.

29. A compound which is:
Hy-H-Ac4c-QGTFTSDYSKYLDERAAKDFIEWLE-K([17-carboxy-heptadecanoyl]-isoGlu-GSGSGG)-A-NH_2.

30. A composition comprising a compound according to any one of the preceding claims in admixture with a carrier.

31. A composition according to claim 30 wherein the composition is a pharmaceutical composition, and the carrier is a pharmaceutically acceptable carrier.

32. A compound according to any one of claims 1 to 29 for use in a method of medical treatment.

33. Use of a compound according to any one of claims 1 to 29 in the manufacture of a medicament for use in a therapeutic method of preventing weight gain or promoting weight loss in an individual in need thereof.

34. Use of a compound according to any one of claims 1 to 29 in the manufacture of a medicament for use in a therapeutic method of lowering circulating LDL levels, and/or increasing HDL/LDL ratio in an individual in need thereof.

35. Use of a compound according to any one of claims 1 to 29 in the manufacture of a medicament for prevention or treatment of obesity, morbid obesity, morbid obesity prior to surgery, obesity linked inflammation, obesity linked gallbladder disease, obesity induced sleep apnea, diabetes, metabolic syndrome, hypertension, atherogenic dyslipidimia, atherosclerois, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke or microvascular disease.

36. The use according to any one of claims 33 to 35 wherein the compound is to be administered as part of a combination therapy together with an agent for treatment of diabetes, obesity, dyslipidemia or hypertension.

37. The use according to claim 36 wherein the agent for treatment of diabetes is a biguanide (e.g. metformin), a sulfonylurea, a meglitinide or glinide (e.g. nateglinide), a DPP-IV inhibitor, an SGLT2 inhibitor, a glitazone, a different GLP-1 agonist, an insulin or an insulin analogue.

38. The use according to claim 36, wherein the agent for treatment of obesity is a glucagon-like peptide receptor 1 agonist, peptide YY receptor agonist or analogue thereof, cannabinoid receptor 1 antagonist, lipase inhibitor, melanocortin receptor 4 agonist, melanin concentrating hormone receptor 1 antagonist, phentermine, a combination of norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (e.g. a combination of phentermine and topiramate), a combination of bupropion and naltrexone, or a serotonergic agent.

39. The use according to claim 36 wherein the agent for treatment of hypertension is an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, diuretic, beta-blocker, or calcium channel blocker.

40. The use according to claim 36 wherein the agent for treatment of dyslipidaemia is a statin, a fibrate, a niacin and/or a cholesterol absorbtion inhibitor.

41. A therapeutic kit comprising a compound according to any of claims 1 to 29 or a composition according to claim 30 or 31.

42. A method of synthesis of a compound according to any one of claims 1 to 29.

43. A method of producing a compound according to any one of claims 1 to 29, the method comprising expressing a precursor peptide sequence from a nucleic acid construct that encodes the precursor peptide, recovering the expression product, and modifying the precursor peptide to yield a compound according to any one of claims 1 to 29.

44. A method according to claim 43 comprising modifying the precursor peptide to introduce the substituent at residue Ψ.