

CLAIMS

1. An isolated polypeptide, comprising the amino acid sequence of SEQ ID NO: 200: HX₂X₃GTX₆X₇X₈X₉X₁₀SX₁₂X₁₃X₁₄EX₁₆X₁₇X₁₈X₁₉X₂₀X₂₁FIX₂₄WLKX₂₈GGPX₃₂SGAPPS-(OH/NH₂) (SEQ ID NO: 200) or a pharmaceutically acceptable salt thereof, wherein:

X₂ is A, 2-aminoisobutyric acid (Aib), or G;

X₃ is E or N-methyl Glu;

X₆ is F or Y;

X₇ is S or T;

X₈ is diaminopimelic acid (Dap), E, K, N, N-methyl Ser, Q, S, s, or Y;

X₉ is D or E;

X₁₀ is I, L, N-methyl Leu, or V;

X₁₂ is E, K, Q, or S;

X₁₃ is Aib, E, K, Q, S, W, or Y;

X₁₄ is E, R, I, K, L, M, Q, or Y;

X₁₆ is 2,4-diaminobutanoic acid (Dab), Dap, E, K, k, or ornithine (Orn);

X₁₇ is E, K, or Q;

X₁₈ is A, K, S, or Y;

X₁₉ is A, K, or V;

X₂₀ is E, K, or R;

X₂₁ is Aib, E, H, K, L, Q, or Y;

X₂₄ is A, Aib, E, K, Q, S, or Y;

X₂₈ is D, E, K, N, Q, S, or Y; and

X₃₂ is Dap, H, K, R, or S;

wherein when X₁₆ is Dab, Dap, K, or Orn, it is covalently bound to a lipophilic substituent, optionally via a spacer;

wherein when X₁₆ is E, at least one of X₁₄, X₁₇, X₁₈, X₁₉, X₂₀, or X₂₁ is selected to be lysine wherein the lysine residue is covalently bound to a lipophilic substituent, optionally via a spacer; and

wherein the peptide optionally further comprises a lactam bridge formed via an amide bond between the side chains of a lysine and a glutamic acid at positions X₁₇ and X₂₁,

respectively; at positions X₂₁ and X₁₇, respectively; at positions X₂₁ and X₂₈, respectively; at positions X₂₈ and X₂₁, respectively; at positions X₂₀ and X₂₄, respectively; at positions X₂₄ and X₂₀, respectively; or at positions X₁₂ and X₁₆, respectively.

2. The isolated polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO: 204:

HX₂EGTFTX₈DX₁₀SX₁₂QX₁₄EX₁₆X₁₇X₁₈X₁₉X₂₀X₂₁FIX₂₄WLKX₂₈GGPX₃₂SGAPPPS-

(OH/NH₂) (SEQ ID NO: 204), or a pharmaceutically acceptable salt thereof, wherein:

X₂ is 2-aminoisobutyric acid (Aib) or G;

X₈ is N or S;

X₁₀ is I, L, or V;

X₁₂ is E, K, or Q;

X₁₄ is M or Y;

X₁₆ is (diaminopimelic acid) Dap covalently bound to a lipophilic substituent, optionally via a spacer, or K covalently bound to a lipophilic substituent, optionally via a spacer;

X₁₇ is E or K;

X₁₈ is A or Y;

X₁₉ is A or V;

X₂₀ is E, K, or R;

X₂₁ is E, K, L, or Q;

X₂₄ is E, K, or S;

X₂₈ is N or Q; and

X₃₂ is H or S;

wherein the peptide optionally further comprises a lactam bridge formed via an amide bond between the side chains of a lysine and a glutamic acid at positions X₁₇ and X₂₁, respectively; at positions X₂₁ and X₁₇, respectively; at positions X₂₀ and X₂₄, respectively; or at positions X₂₄ and X₂₀, respectively.

3. The isolated polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO: 208:

HAibEGTFTSDX₁₀SKQYEX₁₆EAX₁₉X₂₀X₂₁FIX₂₄WLKNGGPSSGAPPPS-(OH/NH₂) (SEQ ID NO: 208), or a pharmaceutically acceptable salt thereof, wherein:

X₁₀ is L or V;

X₁₆ is K covalently bound to a lipophilic substituent, optionally via a spacer;

X₁₉ is A or V;

X₂₀ is E, K, or R;

X₂₁ is K or Q;

X₂₄ is E, K, or S; and

wherein the peptide optionally further comprises a lactam bridge formed via an amide bond between the side chains of a lysine and a glutamic acid at positions X₂₁ and X₁₇, respectively; at positions X₂₀ and X₂₄, respectively; or at positions X₂₄ and X₂₀, respectively.

4. The isolated polypeptide of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein if X₁₄ is M, then X₁₆ is K covalently bound to a lipophilic substituent, optionally via a spacer.

5. The isolated polypeptide of claim 1, or a pharmaceutically acceptable salt thereof, wherein if X₁₆ is E, then X₂₁ is K or E.

6. The isolated polypeptide of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein X₁₄ is Y.

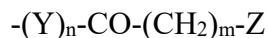
7. The isolated polypeptide of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein X₁₆ is lysine covalently bound to a lipophilic substituent, optionally via a spacer.

8. The isolated polypeptide of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein if X₂₄ is S, then X₁₀ is V.

9. The isolated polypeptide of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein the peptide further comprises a lactam bridge formed via an amide bond between the side chains of a lysine and a glutamic acid at positions X₂₀ and X₂₄, respectively.

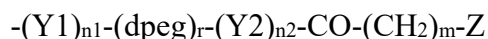
10. The isolated polypeptide of any of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein X₂ is Aib.

11. The isolated polypeptide of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein the lipophilic substituent is covalently bound to the isolated polypeptide via a spacer, and wherein the lipophilic substituent and spacer are of Formula II:



Formula II

or of Formula IV:



Formula IV

wherein,

dpeg is $-[CO(CH_2)O(CH_2)_2O(CH_2)NH]-$;

Y is selected from the group consisting of γ Glu, Asp, Lys and Gly;

Y1 is selected from the group consisting of γ Glu, Asp, and Gly;

Y2 is selected from the group consisting of γ Glu, Asp, and Gly;

Z is $-CH_3$ or $-CO_2H$;

m is from 4 to 24;

n is from 1 to 10;

n1 is from 0 to 10;

n2 is from 0 to 10; and

r is from 1 to 8.

12. The isolated polypeptide of claim 1, comprising the amino acid sequence of any of SEQ ID NOs: 1 to 162, or a pharmaceutically acceptable salt thereof.

13. The isolated polypeptide of any of claims 1-3, comprising an amino acid sequence of any of SEQ ID NOs: 55, 115, 120, and 132, or a pharmaceutically acceptable salt thereof.
14. The isolated polypeptide of claim 13, comprising the amino acid sequence of SEQ ID NO: 115, or a pharmaceutically acceptable salt thereof.
15. The isolated polypeptide of any of claim 13, comprising the amino acid sequence of SEQ ID NO: 120, or a pharmaceutically acceptable salt thereof.
16. A pharmaceutical composition comprising the isolated polypeptide of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.
17. An osmotic delivery device, comprising the isolated polypeptide of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 16.
18. Use of a therapeutically effective amount of the isolated polypeptide of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition of claim 16, in the manufacture of a medicament for treating obesity in a human subject, providing weight loss to the human subject, or suppressing appetite in the human subject.
19. Use of a therapeutically effective amount of the isolated polypeptide of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition of claim 16, in the manufacture of a medicament for treating diabetes in a human subject.
20. Use of a therapeutically effective amount of the isolated polypeptide of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition of claim 16, in the manufacture of a medicament for treating nonalcoholic fatty liver disease (NAFLD) and/or nonalcoholic steatohepatitis (NASH) in a human subject.

21. Use of a therapeutically effective amount of the isolated polypeptide of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition of claim 16, in the manufacture of a medicament for treating a neurological disease or disorder in a human subject.
22. The pharmaceutical composition of claim 16, wherein said pharmaceutical composition is formulated for injection.
23. The pharmaceutical composition of claim 16, wherein said pharmaceutical composition is formulated for oral administration.
24. The pharmaceutical composition of claim 16, wherein said pharmaceutical composition is formulated for administration via an osmotic delivery device.