Claims:

1. A glucagon peptide comprising the sequence of SEQ ID NO: 33 or an analog of SEQ ID NO: 33, wherein said analog differs from SEQ ID NO: 33 by one to three amino acid substitutions, said amino acid substitutions located at one or more positions selected from positions 1, 2, 5, 7, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21 and 24 of the analog, with the proviso that said glucagon peptide comprises an amino acid at position 28 or 29 different from that found at the corresponding position in SEQ ID NO: 1, or an additional acidic amino acid added to the carboxy terminus of the peptide.

2. The glucagon peptide of claim 1 wherein the glucagon peptide comprises the sequence of SEQ ID NO: 34.

3. The glucagon peptide of claim 1 wherein the peptide comprises the sequence of SEQ ID NO: 10.

4. The glucagon peptide of claim 1 wherein the glucagon peptide comprises an analog of SEQ ID NO: 34, wherein amino acid at position 2 of the peptide of SEQ ID NO: 34 is other than serine

5. The glucagon peptide of claim 4 wherein position 2 of the peptide is an amino acid selected from the group consisting of d-serine, alanine, glycine, n-methyl serine and amino isobutyric acid.

6. The glucagon peptide of claim 1 wherein the glucagon peptide comprises an analog of SEQ ID NO: 34, wherein amino acid at position 1 of the peptide of SEQ ID NO: 34 is selected from the group consisting of d-histidine, desaminohistidine, hydroxyl-histidine, acetyl-histidine and homo-histidine.

7. The glucagon peptide of claim 1 further comprising a hydrophilic moiety covalently bound at position 16, 17, 21 or 24 of the glucagon peptide.

8. The glucagon peptide of claim 7 wherein said hydrophilic moiety is polyethylene glycol.

9. The glucagon peptide of claim 8 wherein the polyethylene glycol chain has a molecular weight selected from the range of about 1,000 to about 5,000 Daltons.

10. The glucagon peptide of claim 8 wherein the polyethylene glycol chain has a molecular weight of at least about 20,000 Daltons.

11. A glucagon peptide of claim 1 wherein the glucagon peptide further comprises a sequence selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22 bound to the carboxy terminus of said glucagon peptide.

12. A purified glucagon peptide comprising the sequence of SEQ ID NO: 7 or a glucagon agonist analog thereof.

13. The glucagon peptide of claim 12 wherein the peptide comprising a sequence selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 38.

14. The glucagon peptide of claim 13 further comprising an additional amino acid, selected from the group consisting of Asp and Glu, added to the carboxy terminus of the glucagon peptide.

15. The glucagon peptide of claim 12 further comprising a hydrophilic moiety covalently bound to an amino acid residue at a position selected from the group consisting of 16, 17, 21 and 24, and pharmaceutically acceptable salts of said glucagon peptide.

16. The glucagon peptide of claim 15, wherein said hydrophilic moiety is polyethylene glycol.

17. The glucagon peptide of claim 16 wherein the polyethylene glycol chain has a molecular weight selected from the range of about 1,000 to about 5,000 Daltons.

18. The glucagon peptide of claim 16 wherein the polyethylene glycol chain has a molecular weight of at least about 20,000 Daltons.

19. The glucagon peptide of claim 12 wherein the glucagon peptide comprises the sequence of SEQ ID NO: 11 or SEQ ID NO: 38.

20. The glucagon peptide of claim 19 further comprising an extension peptide bound to amino acid 29 of said glucagon peptide, said amino acid sequence selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22.

21. A purified glucagon peptide comprising the sequence of SEQ ID NO: 33, with the proviso that when the amino acid at position 28 is asparagine and the amino acid at position 29 is threonine, the peptide further comprises one to two amino acids, independently selected from the group consisting of Lys, Arg, His, Asp or Glu, added to the c-terminus of the glucagon peptide.

22. The glucagon peptide of claim 21 wherein the glucagon peptide comprises a sequence selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 13 and SEQ ID NO: 32.

23. The glucagon peptide of claim 22, wherein the peptide further comprises one to two amino acids, independently selected from the group consisting of Lys, Arg, His, Asp or Glu, added to the c-terminus of the glucagon peptide.

24. The glucagon peptide of claim 21 further comprising an extension peptide bound to amino acid 29 of said glucagon peptide, said amino acid sequence selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22.

25. The glucagon peptide of claim 21 further comprising a polyethylene glycol chain covalently bound to an amino acid residue at a position selected from the group consisting of 16, 17, 21 and 24, and pharmaceutically acceptable salts of said glucagon peptide.

26. A homo dimer comprising two glucagon peptides bound to one another through a linker, wherein each of said glucagon peptides comprises the sequence of SEQ ID NO: 11.

27. The homo dimer of claim 26 wherein the linker is selected from the group consisting of bifunctional thiol crosslinkers and bi-functional amine crosslinkers.

28. A dimer comprising a first glucagon peptide bound to a second glucagon peptide via a linker, wherein said first glucagon peptide comprises a peptide selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10 and SEQ ID NO: 11 and the second glucagon peptide comprises SEQ ID NO: 33, with the proviso that with regards to the second glucagon peptide, when the amino acid at position 28 is asparagine and the amino acid at position 29 is threonine, the second glucagon peptide further comprises one to two amino acids, independently selected from the group consisting of Lys, Arg, His, Asp or Glu, added to the carboxy terminus of the second glucagon glucagon peptide, and pharmaceutically acceptable salts of said glucagon polypeptides.

29. A pharmaceutical composition comprising the glucagon agonist of claim 12, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

30. A pharmaceutical composition comprising a glucagon agonist that comprises the sequence of SEQ ID NO: 11 or SEQ ID NO: 38, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

31. A kit for administering a glucagon agonist to a patient in need thereof, said kit comprising

a pharmaceutical composition of claim 29; and

a device for administering said composition to a patient.

32. The kit of claim 31 wherein said device is an aerosol dispensing device, wherein the composition is prepackaged within the aerosol device.

33. The kit of claim 31 wherein said device comprises a syringe and a needle, wherein the composition is prepackaged within the syringe.

34. A method of treating hypoglycemia using a pre-formulated aqueous composition, said method comprising the steps of administering an effective amount of a pharmaceutical composition of claim 29.

35. A method of causing temporary paralysis of the intestinal tract, said method comprising administering an effective amount of a pharmaceutical composition of claim 29.

36. A method of reducing weight gain or inducing weight loss, said method comprising administering an effective amount of a composition comprising a glucagon agonist comprising a glucagon peptide selected from the group consisting of SEQ ID NO: 8, wherein amino acid 29 of the glucagon peptide is bound to a second peptide through a peptide bond, and said second peptide comprises sequence selected from the group consisting of SEQ ID NO: 20 (GPSSGAPPPS), SEQ ID NO: 21 (KRNRNNIA) and SEQ ID NO: 22 (KRNR).

37. A method of reducing weight gain or inducing weight loss, said method comprising administering an effective amount of a composition comprising a glucagon agonist comprising a glucagon peptide selected from the group consisting of SEQ ID NO: 8.

Claims

1. A glucagon peptide with improved solubility relative to native glucagon (SEQ ID NO: 1), that is an analog of SEQ ID NO: 1 comprising (a) one, two, or three charged amino acid(s) C-terminal to the amino acid at position 27 of the glucagon peptide, (b) a Leu or Nle at position 27, and (c) up to 4 additional amino acid modifications relative to SEQ ID NO: 1, wherein the glucagon peptide retains improved solubility and glucagon activity.

2. The glucagon peptide of claim 1, wherein said one, two, or three charged amino acid are negatively charged amino acids.

3. The glucagon peptide of claim 2, wherein the negatively charged amino acids are selected from the group consisting of Glu and Asp.

4. The glucagon peptide of claim 3, wherein (i) the amino acid at position 28 is Asp, or (ii) the amino acid at position 29 is Glu, or both (i) and (ii).

5. The glucagon peptide of claim 4, wherein the additional amino acid modifications are: amino acid substitutions at positions 1, 2, 5, 7, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, and 24 relative to SEQ ID NO: 1.

6. A homo dimer comprising two glucagon peptides of claim 5 bound to one another through a linker.

7. The glucagon peptide of claim 2, wherein two or more charged amino acids C-terminal to the amino acid at position 27 are negatively charged.

8. The glucagon peptide of claim 7, comprising a. a substitution of the amino acid at position 15 with Glu, homo-Glu, cysteic acid, homo cysteic acid; b. a hydrophilic moiety covalently bound at position 16, 17, 20, 21, 24 or 29 of said glucagon peptide; c. a sequence selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22

bound to the carboxy terminus of said glucagon peptide; d. an amino acid at position 2 selected from the group consisting of d-serine, alanine, glycine, n-methyl serine and amino isobutyric acid; or the amino acid at position 1 is selected from the group consisting of dhistidine, desaminohistidine, hydroxyl-histidine, acetyl-histidine and homo-histidine; or e. a combination thereof.

9. A glucagon peptide with improved solubility relative to native glucagon (SEQ ID NO: 1) comprising the sequence of SEQ ID NO: 33 or an analog of SEQ ID NO: 33, wherein said analog differs from SEQ ID NO: 33 by one to three amino acid substitutions, said amino acid substitutions located at one or more positions selected from positions 1, 2, 5, 7, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21 and 24 of the analog, with the proviso that said glucagon peptide comprises a charged amino acid at position 28 or 29, or an additional acidic amino acid added to the carboxy terminus of the peptide.

10. The glucagon peptide of claim 1 wherein the glucagon peptide comprises the sequence of any one of SEQ ID NOs: 7, 8, 9, 11, 12, 13, 32, 33, 34, or 38.

11. A pharmaceutical composition comprising the glucagon peptide of claim 5, 9, or 7 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

12. The glucagon peptide of claim 9 further comprising a hydrophilic moiety covalently bound at position 16, 17, 21 or 24 of the glucagon peptide.

13. The glucagon peptide of claim 12 wherein the hydrophilic moiety is polyethylene glycol (PEG).

14. The glucagon peptide of claim 13 wherein the glucagon peptide further comprises a sequence selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 21, and SEQ ID NO: 22 bound to the carboxy terminus of said glucagon peptide.

15. A solution comprising the glucagon peptide of claim 1, 5, or 9 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier; said solution at pH of about 5.5 to about 8.0.

16. A kit for administering a glucagon agonist to a patient in need thereof, said kit comprising the solution of claim 15; and a device for administering said composition to a patient.

17. The kit of claim 16 wherein said device: is an aerosol dispensing device, wherein the composition is prepackaged within the aerosol device; or comprises a syringe and a needle, wherein the composition is prepackaged within the syringe.