administration, such as subcutaneous or oral route. In particular, there is a desire for compounds that exhibit sufficient efficacy with a favorable side effect profile, and/or stability and bioavailability so that they can be administered orally.

Summary

The polypeptides described herein seek to meet one or more of the needs above. Accordingly, this disclosure describes polypeptides with activity at each of the GIP, GLP-1 and glucagon receptors. The polypeptides described herein allow for administration of doses that provide sufficient activity at each receptor to provide the benefits of agonism of that receptor while avoiding unwanted side effects associated with too much activity. Moreover, the polypeptides described herein have extended duration of action at the GIP, GLP-1 and glucagon receptors allowing for dosing as infrequently as once-a-day, thrice-weekly, twice-weekly, or once-a-week. In this manner, the polypeptides result in enhanced glucose control, metabolic benefits such as body weight lowering and/or improved body composition, lipid benefits, and/or other benefits such as an increase in bone mass or bone formation or a decrease in bone resorption. Furthermore, the polypeptides described herein are suitable for subcutaneous or oral administration. This disclosure also describes effective treatments for disorders or conditions, including obesity, chronic weight management, type 2 diabetes mellitus, NAFLD, NASH, dyslipidemia, metabolic disorder, CKD, OA, OSA and PCOS.

A polypeptide is provided that includes the formula I (SEQ ID NO:4):

$X_1X_2QGTX_6TSDX_{10}X_{11}X_{12}X_{13}LDX_{16}X_{17}AX_{19}X_{20}X_{21}FX_{23}X_{24}X_{25}LX_{27}X_{28}X_{29}X_{30}$
$X_{31}SSX_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}$,

wherein:

X_1 is Y, NMeY or H,

X_2 is Aib,

X_6 is F, αMeF or αMeF(2F),

X_{10} is F, 4-Pal, F(4CN), 3-Pal, F($4NO_2$) or Y,

X_{11} is S or αMeS,

X_{12} is Orn, K, R, Q, Dap, Dab, S, E or I,

X_{13} is αMeL, I or L,

wherein the C-terminal amino acid is optionally amidated;

or a pharmaceutically acceptable salt thereof.

In some examples, the amino acid at position X_{17}, X_{20}, X_{24} or X_{28} with a functional group available for conjugation to a fatty acid is K, C, E or D. In some examples, the amino acid at position X_{17}, X_{20}, X_{24} or X_{28} with a functional group available for conjugation to a fatty acid is K. In some examples, X_{10} is F or 4-Pal. In some examples, X_{12} is Orn, K, R or Q.

In some examples, only one of X_{17}, X_{20}, X_{24} and X_{28} is an amino acid with a functional group available for conjugation to a fatty acid.

In some examples, only one of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid, via a direct bond or via a linker between the amino acid and the fatty acid. In some examples, only one of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid via a linker between the amino acid and the fatty acid. In some examples, the fatty acid is a C_{16}-C_{22} fatty acid.

In one example, a polypeptide is provided that includes the formula I' (SEQ ID NO:1243):

$X_1X_2QX_4TX_6TSDX_{10}X_{11}X_{12}X_{13}LX_{15}X_{16}X_{17}AX_{19}X_{20}X_{21}FX_{23}X_{24}X_{25}LX_{27}X_{28}X_{29}X_{30}X_{31}X_{32}SX_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}X_{43}X_{44}X_{45}X_{46}$, wherein:

X_1 is Y, NMeY or H,

X_2 is Aib,

X_4 is G or D-Ala,

X_6 is F, αMeF or αMeF(2F),

X_{10} is F, 4-Pal, F(4CN), 3-Pal, F($4NO_2$) or Y,

X_{11} is S or αMeS,

X_{12} is Orn, K, R, Q, Dap, Dab, S, E or I,

X_{13} is αMeL, I or L,

X_{15} is D or E,

X_{16} is K, Orn, A or E,

X_{17} is any amino acid with a functional group available for conjugation to a fatty acid, A, I, Q or Orn,

X_{19} is Q or A,

wherein if X_{43} is absent, then X_{44} through X_{46} are also absent, wherein if X_{44} is absent, then X_{45} and X_{46} are also absent; wherein if X_{45} is absent then X_{46} is also absent,

wherein at least one of X_{17}, X_{20}, X_{24} and X_{28} is an amino acid with a functional group available for conjugation to a fatty acid,

wherein the C-terminal amino acid is optionally amidated; or a pharmaceutically acceptable salt thereof.

In some examples, the amino acid at position X_{17}, X_{20}, X_{24} or X_{28} with a functional group available for conjugation to a fatty acid is K, C, E, D or Orn. In some examples, the amino acid at position X_{17}, X_{20}, X_{24} or X_{28} with a functional group available for conjugation to a fatty acid is K. In some examples, the amino acid at position X_{17}, X_{20}, X_{24} or X_{28} with a functional group available for conjugation to a fatty acid is Orn. In some examples, X_{10} is F or 4-Pal. In some examples, X_{12} is Orn, K, R or Q.

In some examples, only one of X_{17}, X_{20}, X_{24} and X_{28} is an amino acid with a functional group available for conjugation to a fatty acid.

In some examples, one of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid, via a direct bond or via a linker between the amino acid and the fatty acid. In some examples, one of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid via a linker between the amino acid and the fatty acid. In some examples, the fatty acid is a C_{16}-C_{22} fatty acid.

In some examples, none of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid.

In one example, a polypeptide is provided that includes the formula II (SEQ ID NO:5):

$YX_2QGTFTSDX_{10}SX_{12}X_{13}LDX_{16}X_{17}AQX_{20}X_{21}FIX_{24}X_{25}LX_{27}X_{28}X_{29}X_{30}X_{31}SSX_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}$,

wherein

X_2 is Aib,

X_{10} is F, 4-Pal or F(4CN),

X_{12} is Orn, K, R, Q, Dap or Dab,

X_{13} is αMeL,

X_{16} is K or Orn,

X_{17} is any amino acid with a functional group available for conjugation to a fatty acid,

X_{20} is Aib, αMe-4-Pal or Q,

X_{21} is A, Q or Orn,

X_{24} is E or Q,

X_{25} is W, Y, 4-Pal, αMeY or αMe-4-Pal,

X_{27} is L or I,

X_{28} is E or A,

X_{29} is G, D-Ala or Aib,

X_{30} is A or G,

X_{31} is P, H, S, 4-Pal, E, T, K(Ac) or Hyp,

X_{34} is G or Aib,

X_{35} is A, Aib, E, H or 4-Pal,

X_{36} is P or Hyp,

$X_{37\ is}$ P or Hyp,

$X_{38\ is}$ P or Hyp,

X_{39} is E, S, G, T, H, 4-Pal or γE,

X_{40} is absent or G, E or S,

wherein if X_{40} is G, E or S, then X_{41} is absent or E, S, T, 4-Pal, D, G, Q or H,

wherein if X_{41} is E, S, T, 4-Pal, D, G, Q or H, then X_{42} is absent or G, E or γE,

wherein if X_{40} is absent, then X_{41} and X_{42} are also absent,

wherein if X_{41} is absent, then X_{42} is also absent,

wherein the C-terminal amino acid is optionally amidated;

or a pharmaceutically acceptable salt thereof.

In some examples of polypeptides of formula II, X_{17} is K, C, E or D. In some examples, X_{17} is K. In some examples, X_{10} is F or 4-Pal. In some examples, X_{12} is Orn, K, R or Q.

In some examples, X_{17} is K and is conjugated to a fatty acid via a direct bond or via a linker between the amino acid and the fatty acid. In some examples, X_{17} is K

and is conjugated to a fatty acid via a linker between the amino acid and the fatty acid. In some examples, the fatty acid is a C_{16}-C_{22} fatty acid.

In some examples, X_{17} is K and is conjugated to a C_{16}-C_{22} fatty acid via a linker between the X_{17} amino acid and the C_{16}-C_{22} fatty acid.

In one example, a polypeptide is provided that includes the formula II' (SEQ ID NO:1244):

$X_1X_2QGTFTSDX_{10}SX_{12}X_{13}LDX_{16}X_{17}AQX_{20}X_{21}FIX_{24}X_{25}LX_{27}X_{28}X_{29}X_{30}X_{31}SSX_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}X_{43}X_{44}$, wherein

X_1 is Y or NMeY

X_2 is Aib,

X_{10} is F, 4-Pal or F(4CN),

X_{12} is Orn, K, R, I, Q, Dap or Dab,

X_{13} is αMeL,

X_{16} is K or Orn,

X_{17} is any amino acid with a functional group available for conjugation to a fatty acid,

X_{20} is Aib, αMe-4-Pal, Q or L-Iva,

X_{21} is A, Q or Orn,

X_{24} is E or Q,

X_{25} is W, Y, 4-Pal, αMeY or αMe-4-Pal,

X_{27} is L or I,

X_{28} is E, Q or A,

X_{29} is G, D-Ala or Aib,

X_{30} is A, S or G,

X_{31} is P, H, S, 4-Pal, E, T, K(Ac) or Hyp,

X_{34} is G or Aib,

X_{35} is A, Aib, E, H or 4-Pal,

X_{36} is P or Hyp,

$X_{37\ is}$ P or Hyp,

$X_{38\ is}$ P or Hyp,

X_{39} is E, S, G, T, H, 4-Pal or γE,

X_{40} is absent or G, E, S or D-Glu,

wherein if X_{40} is G, E, S or D-Glu, then X_{41} is absent or E, S, T, 4-Pal, D, G, Q or H,

wherein if X_{41} is E, S, T, 4-Pal, D, G, Q or H, then X_{42} is absent or G, E or γE,

wherein if X_{42} is G, E, or γE, then X_{43} is absent or E,

wherein if X_{43} is E, then X_{44} is absent or E,

wherein if X_{40} is absent, then X_{41}, X_{42}, X_{43}, and X_{44} are also absent,

wherein if X_{41} is absent, then X_{42}, X_{43} and X_{44} are is also absent,

wherein if X_{43} is absent then X_{44} is also absent,

wherein the C-terminal amino acid is optionally amidated; or a pharmaceutically acceptable salt thereof.

In some examples of polypeptides of formula II', X_{17} is K, C, E or D. In some examples, X_{17} is K. In some examples, X_{10} is F or 4-Pal. In some examples, X_{12} is Orn, K, R or Q.

In some examples, X_{17} is K and is conjugated to a fatty acid via a direct bond or via a linker between the amino acid and the fatty acid. In some examples, X_{17} is K and is conjugated to a fatty acid via a linker between the amino acid and the fatty acid. In some examples, the fatty acid is a C_{16}-C_{22} fatty acid.

In some examples, X_{17} is K and is conjugated to a C_{16}-C_{22} fatty acid via a linker between the X_{17} amino acid and the C_{16}-C_{22} fatty acid.

In some examples, none of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid.

In one example, a polypeptide is provided that includes the formula III (SEQ ID NO:6):

$X_1X_2QGTX_6TSDX_{10}X_{11}X_{12}X_{13}LDX_{16}X_{17}AX_{19}X_{20}X_{21}FX_{23}X_{24}X_{25}LX_{27}X_{28}X_{29}GX_{31}SSX_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}$,

wherein

X_1 is Y, NMeY or H,

X_2 is Aib,

X_6 is F, αMeF or αMeF(2F),

X_{10} is F, 3-Pal, 4-Pal, F(4CN), F($4NO_2$) or Y,

X_{11} is S or αMeS,

X_{12} is Orn, K, R, Q, Dap, S, E or I,

X_{13} is αMeL, I or L,

In some examples of Formula III, the amino acid at position X_{17}, X_{20}, X_{24} or X_{28} with a functional group available for conjugation to a fatty acid is K, C, E or D. In some examples, the amino acid at position X_{17}, X_{20}, X_{24} or X_{28} with a functional group available for conjugation to a fatty acid is K. In some examples, X_{10} is F, 3-Pal, 4-Pal, F(4CN) or $F(4NO_2)$ and X_{12} is I. In some examples, X_{10} is Y and X_{12} is Orn, K, R, Q, Dap, S, E or I.

In some examples, only one of X_{17}, X_{20}, X_{24} and X_{28} is an amino acid with a functional group available for conjugation to a fatty acid.

In some examples, only one of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid, via a direct bond or via a linker between the amino acid and the fatty acid. In some examples, only one of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid via a linker between the amino acid and the fatty acid. In some examples, the fatty acid is a C_{16}-C_{22} fatty acid.

In some examples, only one of X_{17}, X_{20}, X_{24}, or X_{28} is K and is conjugated to a C_{16}-C_{22} fatty acid via a linker between the amino acid and the C_{16}-C_{22} fatty acid.

In one example, a polypeptide is provided that includes the formula III' (SEQ ID NO:1245):

$X_1X_2QX_4TX_6TSDX_{10}X_{11}X_{12}X_{13}LX_{15}X_{16}X_{17}AX_{19}X_{20}X_{21}FX_{23}X_{24}X_{25}LX_{27}X_{28}X_{29}GX_{31}X_{32}SX_{34}X_{35}PX_{37}PX_{39}X_{40}X_{41}X_{42}X_{43}X_{44}X_{45}X_{46}$,

wherein

X_1 is Y, NMeY or H,

X_2 is Aib,

X_4 is G or D-Ala,

X_6 is F, αMeF or αMeF(2F),

X_{10} is F, 3-Pal, 4-Pal, F(4CN), $F(4NO_2)$ or Y,

X_{11} is S or αMeS,

X_{12} is Orn, K, R, Q, Dap, S, E or I,

X_{13} is αMeL, I or L,

X_{15} is D or E,

X_{16} is K, Orn, A or E,

wherein if X_{41} is absent, then X_{42} through X_{46} are also absent,

wherein if X_{42} is absent, then X_{43} through X_{46} are also absent,

wherein if X_{43} is absent, then X_{44} through X_{46} are also absent,

wherein if X_{44} is absent, then X_{45} and X_{46} are also absent,

wherein if X_{45} is absent then X_{46} is also absent,

wherein the polypeptide comprises at least one of the following: X_6 is αMeF or αMeF(2F); X_{10} is F, 3-Pal, 4-Pal, F(4CN) or F($4NO_2$); X_{11} is αMeS; X_{13} is αMeL; X_{24} is D-Glu; and/or X_{25} is αMeY,

wherein if X_{10} is F, 3-Pal, 4-Pal, F(4CN), or F($4NO_2$), then X_{12} is I,

and wherein at least one of X_{17}, X_{20}, X_{24} or X_{28} is an amino acid with a functional group available for conjugation to a fatty acid,

wherein the C-terminal amino acid is optionally amidated; or a pharmaceutically acceptable salt thereof.

In some examples of Formula III', the amino acid at position X_{17}, X_{20}, X_{24} or X_{28} with a functional group available for conjugation to a fatty acid is K, C, E, D or Orn. In some examples, the amino acid at position X_{17}, X_{20}, X_{24} or X_{28} with a functional group available for conjugation to a fatty acid is K. In some examples, the amino acid at position X_{17}, X_{20}, X_{24} or X_{28} with a functional group available for conjugation to a fatty acid is Orn. In some examples, X_{10} is F, 3-Pal, 4-Pal, F(4CN) or F($4NO_2$) and X_{12} is I. In some examples, X_{10} is Y and X_{12} is Orn, K, R, Q, Dap, S, E or I.

In some examples, only one of X_{17}, X_{20}, X_{24} and X_{28} is an amino acid with a functional group available for conjugation to a fatty acid.

In some examples, one of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid, via a direct bond or via a linker between the amino acid and the fatty acid. In some examples, one of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid via a linker between the amino acid and the fatty acid. In some examples, the fatty acid is a C_{16}-C_{22} fatty acid.

In some examples, only one of X_{17}, X_{20}, X_{24}, or X_{28} is K and is conjugated to a C_{16}-C_{22} fatty acid via a linker between the amino acid and the C_{16}-C_{22} fatty acid. In some examples, none of X_{17}, X_{20}, X_{24}, or X_{28} is conjugated to a fatty acid.

In aspect, provided herein is a polypeptide comprising

$X_1X_2QX_4TX_6TSDX_{10}X_{11}X_{12}X_{13}LX_{15}X_{16}X_{17}AX_{19}X_{20}X_{21}FX_{23}X_{24}X_{25}LX_{27}X_{28}X_{29}GX_{31}X_{32}SX_{34}X_{35}PX_{37}PX_{39}X_{40}X_{41}X_{42}X_{43}X_{44}X_{45}X_{46}$,

wherein

X_1 is Y,

X_2 is Aib,

X_4 is G,

X_6 is αMeF(2F),

X_{10} is 4-Pal,

X_{11} is S or αMeS,

X_{12} is I,

X_{13} is αMeL,

X_{15} is D,

X_{16} is Orn,

X_{17} is any amino acid with a functional group available for conjugation to a fatty acid, A, I or Q or Orn,

X_{19} is Q,

X_{20} is αMe-4-Pal,

X_{21} is E or Orn,

X_{23} is I,

X_{24} is D-Glu,

X_{25} is αMeY,

X_{27} is I or V,

X_{28} is E,

X_{29} is G,

X_{31} is P,

X_{32} is S or P,

X_{34} is G,

X_{35} is A or E,

X_{37} is P,

X_{39} is E or S,

X_{40} is G or T,

X_{41} is E, S or G,

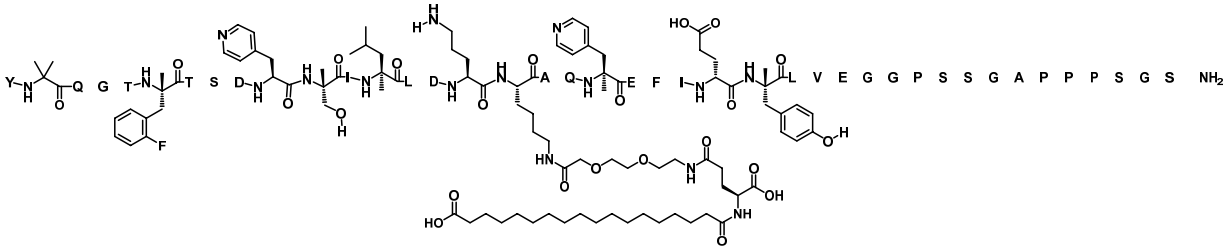
X_{42} is absent, and

X_{43} through X_{46} are absent,

wherein the C-terminal amino acid is optionally amidated; or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a polypeptide comprising a sequence identity of more than 90% to the polypeptide of any of SEQ ID NO's: 692, 700, 702, 705, 706, 716, or 743.

In another aspect, provided herein is a polypeptide having a formula:



(SEQ ID NO: 700), or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a pharmaceutical composition comprising the polypeptide or a pharmaceutically acceptable salt thereof, described herein and at least one pharmaceutically acceptable carrier, diluent, or excipient. In some examples, the pharmaceutical composition is formulated for subcutaneous administration. In some examples, the pharmaceutical composition is formulated for oral administration.

In another example, a method is provided for treating a disease or disorder including obesity, chronic weight management, type 2 diabetes mellitus, NAFLD, NASH, dyslipidemia, metabolic disorder, CKD, OA, OSA and PCOS. Another example provides a method for providing non-therapeutic weight loss comprising administering to a subject in need thereof, an effective amount of a polypeptide described herein or a pharmaceutically acceptable salt thereof. Such methods can include

at least a step of administering to an individual in need thereof an effective amount of a polypeptide a pharmaceutically acceptable salt thereof described herein.

In another example, a polypeptide as described herein is provided for use in therapy. For example, a polypeptide as described herein is provided for use in treating a disease or disorder including obesity, chronic weight management, type 2 diabetes mellitus, NAFLD, NASH, dyslipidemia, metabolic disorder, CKD, OA, OSA and/or PCOS.

In another aspect, provided herein is the polypeptide, or a pharmaceutically acceptable salt thereof, as described herein for use in therapy.

In another aspect, provided herein is a polypeptide, or a pharmaceutically acceptable salt thereof, as described herein for use in treating a disease or condition selected from the group consisting of diabetes mellitus, obesity, chronic weight management, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), dyslipidemia, metabolic syndrome, chronic kidney disease (CKD), osteoarthritis (OA), obesity-related sleep apnea (OSA), polycystic ovary syndrome (PCOS), Parkinson's disease and Alzheimer's disease.

In another aspect, provided herein is use of a polypeptide, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a disease or condition selected from the group consisting of diabetes mellitus, obesity, chronic weight management, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), dyslipidemia, metabolic syndrome, chronic kidney disease (CKD), osteoarthritis (OA), obesity-related sleep apnea (OSA), polycystic ovary syndrome (PCOS), Parkinson's disease and Alzheimer's disease.

In another example, there is provided the use of a polypeptide as described herein in the manufacture of a medicament for treating a disease or disorder including obesity, chronic weight management, type 2 diabetes mellitus, NAFLD, NASH, dyslipidemia, metabolic disorder, CKD, OA, OSA and/or PCOS.

Detailed Description

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of skill in the art to which the disclosure pertains. Although any methods and materials similar to or equivalent to those described

herein can be used in the practice or testing of the polypeptides, pharmaceutical compositions, and methods, the preferred methods and materials are described herein.

Moreover, reference to an element by the indefinite article “a” or “an” does not exclude the possibility that more than one element is present, unless the context clearly requires that there be one and only one element. The indefinite article “a” or “an” thus usually means “at least one.”

CLAIMS

The invention claimed is:

1. A polypeptide comprising:

$X_1X_2QX_4TX_6TSDX_{10}X_{11}X_{12}X_{13}LX_{15}X_{16}X_{17}AX_{19}X_{20}X_{21}FX_{23}X_{24}X_{25}LX_{27}X_{28}X_{29}GX_{31}X_{32}SX_{34}X_{35}PX_{37}PX_{39}X_{40}X_{41}X_{42}X_{43}X_{44}X_{45}X_{46}$,

wherein

X_1 is Y,

X_2 is Aib,

X_4 is G,

X_6 is αMeF(2F),

X_{10} is 4-Pal,

X_{11} is S or αMeS,

X_{12} is I,

X_{13} is αMeL,

X_{15} is D,

X_{16} is Orn,

X_{17} is any amino acid with a functional group available for conjugation to a fatty acid, A, I or Q or Orn,

X_{19} is Q,

X_{20} is αMe-4-Pal,

X_{21} is E or Orn,

X_{23} is I,

X_{24} is D-Glu,

X_{25} is αMeY,

X_{27} is I or V,

X_{28} is E,

X_{29} is G,

X_{31} is P,

X_{32} is S or P,

X_{34} is G,

X_{35} is A or E,

X_{37} is P,

X_{39} is E or S,

X_{40} is G or T,

X_{41} is E, S or G,

X_{42} is absent, and

X_{43} through X_{46} are absent,

wherein the C-terminal amino acid is optionally amidated; or a pharmaceutically acceptable salt thereof.

2. The polypeptide of claim 1, or a pharmaceutically acceptable salt thereof, wherein X_{11} is αMeS.

3. The polypeptide of claim 1, or a pharmaceutically acceptable salt thereof, wherein: X_{11} is S, X_{21} is Orn, X_{27} is I, X_{35} is E, X_{39} is E, X_{40} is T and X_{41} is E.

4. The polypeptide of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein: X_{11} is αMeS, X_{21} is E, X_{27} is V, X_{35} is A, X_{39} is S, X_{40} is G and X_{41} is S.

5. The polypeptide of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein: X_{11} is αMeS, X_{21} is E, X_{27} is I, X_{35} is A, X_{39} is S, X_{40} is G and X_{41} is S.

6. The polypeptide of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein: X_{11} is αMeS, X_{21} is E, X_{27} is I, X_{35} is A, X_{39} is S, X_{40} is G and X_{41} is G.

7. The polypeptide of any of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein: X_{17} is K and is conjugated to a C_{16}-C_{22} fatty acid via a linker between the amino acid and the C_{16}-C_{22} fatty acid.

8. The polypeptide of claim 7, or a pharmaceutically acceptable salt thereof, wherein the linker comprises one to four amino acids.

9. The polypeptide of claim 8, or a pharmaceutically acceptable salt thereof, wherein the amino acids comprised in the linker are Glu, γGlu or a combination thereof.

10. The polypeptide of any of claims 7-9, or a pharmaceutically acceptable salt thereof, wherein the linker comprises one to four (2-[2-(2-amino-ethoxy)-ethoxy]-acetyl) moieties.

11. The polypeptide of claim 10, or a pharmaceutically acceptable salt thereof, wherein the linker comprises a structure of $(\gamma Glu)_a$-(2-[2-(2-amino-ethoxy)-ethoxy]-acetyl)$_b$-$(\gamma Glu)_c$-CO-$(CH_2)_p$-CO_2H, wherein a is 0 or 1, b is 0, 1 or 2, c is 1, 2 or 3, and p is an integer between 14 to 20.

12. The polypeptide of claim 11, or a pharmaceutically acceptable salt thereof, wherein a is 0, b is 1 and c is 1.

13. A polypeptide comprising a sequence identity of more than 90% to the polypeptide of any of SEQ ID NO's: 692, 700, 702, 705, 706, 716, or 743.

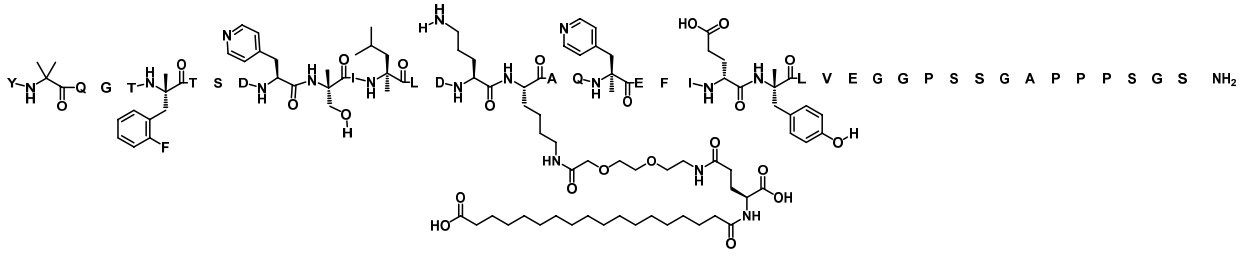
14. The polypeptide of claim 13, or a pharmaceutically acceptable salt thereof, selected from the group consisting of: SEQ ID NO's: 692, 700 and 705.

15. The polypeptide of claim 14 consisting of SEQ ID NO. 692, or a pharmaceutically acceptable salt thereof.

16. The polypeptide of claim 14 consisting of SEQ ID NO. 700, or a pharmaceutically acceptable salt thereof.

17. The polypeptide of claim 14 consisting of SEQ ID NO. 705, or a pharmaceutically acceptable salt thereof.

18. A polypeptide having a formula:



(SEQ ID NO: 700), or a pharmaceutically acceptable salt thereof.

19. The polypeptide of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein the C-terminal is amidated.

20. The polypeptide of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutically acceptable salt is selected from sodium, potassium, trifluoroacetate, hydrochloride or acetate.

21. The polypeptide of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein one or more hydrogen atoms are replaced by deuterium.

22. The polypeptide of any of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein the polypeptide has greater potency at each of the glucagon, GIP and GLP-1 receptors as compared to native glucagon (SEQ ID NO:3), GIP (SEQ ID NO:1) and GLP-$1_{7\text{-}36}$ (SEQ ID NO:2).

23. A pharmaceutical composition comprising the polypeptide or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 22 and at least one pharmaceutically acceptable carrier, diluent, or excipient.

24. The pharmaceutical composition of claim 23, wherein the composition is formulated for oral administration.

25. The pharmaceutical composition of claim 23, wherein the composition is formulated for subcutaneous administration.

26. The polypeptide, or a pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 to 22 for use in therapy.

27. A polypeptide, or a pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 to 22 for use in treating a disease or condition selected from the group consisting of diabetes mellitus, obesity, chronic weight management, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), dyslipidemia, metabolic syndrome, chronic kidney disease (CKD), osteoarthritis (OA), obesity-related sleep apnea (OSA), polycystic ovary syndrome (PCOS), Parkinson’s disease and Alzheimer’s disease.

28. Use of a polypeptide, or a pharmaceutically acceptable salt thereof, as claimed by any one of Claims 1 to 22 in the manufacture of a medicament for treating a disease or condition selected from the group consisting of diabetes mellitus, obesity, chronic weight management, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), dyslipidemia, metabolic syndrome, chronic kidney disease (CKD), osteoarthritis (OA), obesity-related sleep apnea (OSA), polycystic ovary syndrome (PCOS), Parkinson’s disease and Alzheimer’s disease.