homeostasis. Osteocalcin has also been reported to function as a hormone in the body, causing beta cells in the pancreas to release more insulin, and at the same time directing fat cells to release the hormone adiponectin, which increases sensitivity to insulin.

One disadvantage associated with the therapeutic use of bioactive peptides such as osteocalcin, GIP, glucagon, GLP-1 and oxyntomodulin is their extremely short half-life (approximately two minutes for glucagon and GLP-1) in plasma. Accordingly, to obtain reasonable glycemic control, native glucagon-related peptides would need to be administered continuously for a prolonged period of time. The short half life of glucagon and GLP-1 related peptides results from the rapid degradation by Dipeptidyl Peptidase IV (DPP-IV), which cleaves between the second and third amino acids. This cleavage not only inactivates the native peptides but in the case of glucagon and GLP-1 the shortened forms could be functional antagonists at their respective receptors. Accordingly, there is a need for longer-acting variants of GIP, glucagon, GLP-1, and oxyntomodulin, and related peptides, to realize the full therapeutic potential of these mechanisms of drug action

SUMMARY

In a first aspect, the present invention refers to a prodrug comprising the structure:

A-B-Q;

wherein Q is a glucagon superfamily peptide;

A is an amino acid or a hydroxy acid;

B is an N-alkylated amino acid linked to Q through an amide bond between A-B and an amine of Q;

wherein A, B, or the amino acid of Q to which A-B is linked is a non-coded amino acid, further wherein chemical cleavage half-life ($t_{1/2}$) of A-B from Q is at least about 1 hour to about 1 week in PBS under physiological conditions, with the proviso that A-B is not Gly-(N-Methyl-Gly).

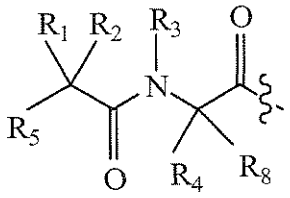
In accordance with some ~~embodiments~~examples a prodrug derivative of a bioactive polypeptide selected from the group consisting of glucagon, exendin-4, GLP-1, GLP-2, GIP, vasoactive intestinal peptide (VIP), Pituitary adenylate cyclase-activating polypeptide 27 (PACAP-27), peptide histidine methionine (PHM), oxyntomodulin, secretin, osteocalcin, growth hormone releasing hormone, as well as analogs, derivatives and conjugates of the foregoing is provided. The prodrug derivative comprises a dipeptide prodrug element covalently linked to an active site of the bioactive polypeptide via an amide linkage. In some ~~embodiments~~examples the dipeptide is covalently bound to the bioactive polypeptide at a position that interferes with the bioactive polypeptide's ability to interact with its corresponding receptor or cofactor. In some ~~embodiments~~examples the dipeptide prodrug element is linked to the amino-terminus of the bioactive peptide. Subsequent removal of the dipeptide, under physiological conditions and in the absence of enzymatic activity, restores full activity to the polypeptide.

In some ~~embodiments~~examples a prodrug is provided having the general structure of A-B-Q. In this ~~embodiment~~example Q is a bioactive peptide, selected from the group of glucagon superfamily peptides, including glucagon-related peptides, osteocalcin, as well as analogs, derivatives and conjugates of the foregoing; and A-B represents a dipeptide prodrug linked to the bioactive peptide through an amide bond. More particularly, in some ~~embodiments~~examples A is an amino acid

or a hydroxy acid and B is an N-alkylated amino acid linked to Q through formation of an amide bond between a carboxyl of B (in A-B) and an amine of Q. Furthermore, in some ~~embodiments~~examples, A, B, or the amino acid of Q to which A-B is linked, is a non-coded amino acid, and chemical cleavage of A-B from Q is at least about 90% complete within about 1 to about 720 hours in PBS under physiological conditions. In another ~~embodiment~~example, chemical cleavage of A-B from Q is at least about 50% complete within about 1 hour or about 1 week in PBS under physiological conditions.

In some ~~embodiments~~examples A and B are selected to inhibit enzymatic cleavage of the A-B dipeptide from Q by enzymes found in mammalian serum. In some ~~embodiments~~examples A and/or B are selected such that the cleavage half-life of A-B from Q in PBS under physiological conditions, is not more than two fold the cleavage half-life of A-B from Q in a solution comprising a DPP-IV protease (i.e., cleavage of A-B from Q does not occur at a rate more than 2x faster in the presence of DPP-IV protease and physiological conditions relative to identical conditions in the absence of the enzyme). In some ~~embodiments~~examples A and/or B is an amino acid in the D stereoisomer configuration. In some exemplary ~~embodiments~~examples, A is an amino acid in the D stereoisomer configuration and B is an amino acid in the L stereoisomer configuration. In some exemplary ~~embodiments~~examples, A is an amino acid in the L stereoisomer configuration and B is an amino acid in the D stereoisomer configuration. In some ~~exemplary embodiments~~examples, A is an amino acid in the D stereoisomer configuration and B is an amino acid in the D stereoisomer configuration.

In some embodiments the dipeptide prodrug element (A-B) comprises a compound having the general structure of Formula I:



I

wherein

R_1, R_2, R_4 and R_8 are independently selected from the group consisting of H, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, (C_1-C_{18} alkyl)OH, (C_1-C_{18} alkyl)SH, (C_2-C_3 alkyl)SCH_3, (C_1-C_4 alkyl)$CONH_2$, (C_1-C_4 alkyl)COOH, (C_1-C_4 alkyl)NH_2, (C_1-C_4 alkyl)$NHC(NH_2^+)NH_2$, (C_0-C_4 alkyl)(C_3-C_6 cycloalkyl), (C_0-C_4 alkyl)(C_2-C_5 heterocyclic), (C_0-C_4 alkyl)(C_6-C_{10} aryl)R_7, (C_1-C_4 alkyl)(C_3-C_9 heteroaryl), and C_1-C_{12} alkyl(W_1)C_1-C_{12} alkyl, wherein W_1 is a

R_7 is selected from the group consisting of hydrogen, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, (C_0-C_4 alkyl)$CONH_2$, (C_0-C_4 alkyl)COOH, (C_0-C_4 alkyl)NH_2, (C_0-C_4 alkyl)OH, and halo.

As described above, in some ~~aspects there is provided~~examples describe a prodrug having the general structure of A-B-Q, wherein Q is a glucagon superfamily peptide (e.g. a glucagon related peptide, Growth Hormone Releasing Hormone (GHRH; SEQ ID NO: 719), vasoactive intestinal peptide (VIP; SEQ ID NO: 720), Pituitary adenylate cyclase-activating polypeptide 27 (PACAP-27; SEQ ID NO: 721), peptide histidine methionine (PHM; SEQ ID NO: 722), or Secretin (SEQ ID NO: 723), and/or and analogs, derivatives and conjugates thereof). Glucagon superfamily peptides may have common structural characteristics, including but not limited to homology within the N-terminal amino acids and/or alpha-helical structure within the C-terminal portion. It is believed that the C-terminus generally functions in receptor binding and the N-terminus generally functions in receptor signaling. A few amino acids in the N-terminal portion and C-terminal portion are highly conserved among members of the glucagon superfamily, for example, His1, Gly4, Phe6, Phe22, Val23, Trp25, and Leu26, with amino acids at these positions showing identity, conservative substitutions or similarity in amino acid side chains. In some ~~embodiments~~examples Q is a glucagon related peptide, e.g. glucagon (SEQ ID NO: 701), oxyntomodulin (SEQ ID NO: 706), exendin-4 (SEQ ID NO: 718), Glucagon-like peptide -1 (GLP-1) (amino acids 7-37 provided as SEQ ID NOs: 703 and 707), Glucagon-like peptide -2 (GLP-2) (SEQ ID NO: 708), GIP (SEQ ID NO: 707) or analogs, derivatives and conjugates of the foregoing. In some ~~embodiments~~examples Q as a glucagon related peptide comprises an amino acid sequence that is at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% identical to the corresponding sequence of native glucagon, native oxyntomodulin, native exendin-4, native (7-37)GLP-1, native GLP-2, or native GIP over the length of the native peptide (or over the positions which correspond to glucagon, see e.g., Figure 10). In other ~~embodiments~~examples, a glucagon superfamily peptide (Q) comprises an amino acid sequence of native glucagon, native exendin-4, native (7-37)GLP-1, native GLP-2, native GHRH, native VIP, native PACAP-27, native PHM, native Oxyntomodulin, native Secretin, or native GIP with up to 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid modifications. In still further ~~embodiments~~examples, Q comprises an amino acid sequence which is a chimera of two or more native glucagon related peptide sequences. In some ~~embodiments~~examples, Q comprises an amino acid sequence at least about 50% identical to native

glucagon (SEQ ID NO: 701) that retains the alpha-helix conformation of the amino acids corresponding to amino acids 12-29 of SEQ ID NO: 701.

Q may be any of the glucagon superfamily peptides that are known in the art, including for example, any glucagon related peptides as known in the art, some of which are disclosed herein by way of nonlimiting examples. A variety of GLP-1 analogs are known in the art and are a glucagon-related peptide according to the current invention, see, e.g., WO 2008023050, WO 2007030519, WO 2005058954, WO 2003011892, WO 2007046834, WO 2006134340, WO 2006124529, WO 2004022004, WO 2003018516, WO 2007124461 each incorporated herein by reference in its entirety for each of its sequence or formula disclosures of GLP-1 analogs or derivatives. In certain ~~embodiments~~examples, Q is a Class 1, 2, 3, 4 or 5 glucagon related peptide as detailed herein. In any of the ~~embodiments~~examples described herein, Q is any of SEQ ID NOs: 1-684, 701-742, 801-919, 1001-1262, 1301-1371, 1401-1518, 1701-1776, and 1801-1908.

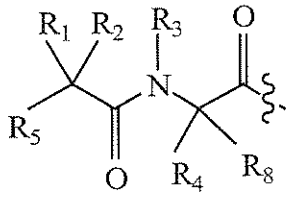
While the dipeptide prodrug, e.g. A-B, may be linked to Q at any position that interferes with the activity of Q, ~~embodiments~~examples disclosed herein illustrate examples of positions that are suitable for linkage of A-B. When position numbers are named herein by referring to the position in the native glucagon sequence (SEQ ID NO: 701), the corresponding position in glucagon analogs or in other glucagon superfamily peptides can be determined by alignment. See, e.g., Figure 10 which shows an alignment of certain glucagon superfamily peptides. For example, position 24 based on native glucagon corresponds to position 24 of (7-37) GLP-1.

In certain ~~embodiments~~examples a glucagon superfamily peptide may comprise a C-terminus or a C-terminal amino acid sequence including but not limited to: COOH, $CONH_2$, GPSSGAPPPS (SEQ ID NO: 710), GPSSGAPPPS-$CONH_2$ (SEQ ID NO: 711), a oxyntomodulin carboxy terminal extension, KRNRNNIA (SEQ ID NO: 714) or KGKKNDWKHNITQ (SEQ ID NO: 713). Additional, C-terminal amino acid sequences for glucagon superfamily peptides are further detailed below.

In other examples~~aspects~~, Q comprises osteocalcin (SEQ ID NO: 709), or an amino acid sequence that is at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% identical to native osteocalcin over the length of the native peptide. Q may comprise an analog of osteocalcin with up to 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid modifications relative to native osteocalcin. In yet other examples~~aspects~~, Q comprises growth hormone releasing hormone (GHRH) (SEQ ID NO: 719), or an amino acid sequence that is at least about 40%,

45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% identical to native GHRH over the length of the native peptide. Q may comprise an analog of GHRH with up to 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid modifications relative to native GHRH. In some ~~embodiments~~examples, Q may be any analog of osteocalcin or GHRH known in the art.

In a further ~~embodiments~~examples, there is provided a prodrug having the general structure of A-B-Q, wherein Q is a glucagon superfamily peptide, osteocalcin or an analog, derivative or conjugate thereof and A-B comprises the general structure:



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wherein R_1 and R_8 are independently selected from the group consisting of H and C_1-C_8 alkyl;

R_2 and R_4 are independently selected from the group consisting of H, C_1-C_8 alkyl, C_2-C_8 alkenyl, (C_1-C_4 alkyl)OH, (C_1-C_4 alkyl)SH, (C_2-C_3 alkyl)SCH_3, (C_1-C_4 alkyl)$CONH_2$, (C_1-C_4 alkyl)COOH, (C_1-C_4 alkyl)NH_2, (C_1-C_4 alkyl)$NHC(NH_2^+)$ NH_2, (C_0-C_4 alkyl)(C_3-C_6 cycloalkyl), (C_0-C_4 alkyl)(C_6-C_{10} aryl)R_7, CH_2(C_5-C_9 heteroaryl), or R_1 and R_2 together with the atoms to which they are attached form a C_3-C_6 cycloalkyl;

R_3 is selected from the group consisting of C_1-C_8 alkyl, (C_1-C_4 alkyl)OH, (C_1-C_4 alkyl)NH_2, (C_1-C_4 alkyl)SH, (C_3-C_6)cycloalkyl or R_4 and R_3 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring;

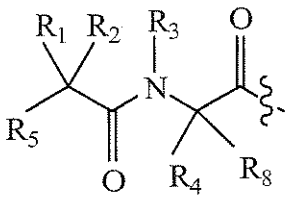
R_5 is NHR_6 or OH;

R_6 is H, or R_6 and R_2 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring; and

R_7 is selected from the group consisting of H and OH.

Provided that when R_4 and R_3 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring, both R_1 and R_2 are other than H.

In other ~~embodiments~~examples, there is provided a prodrug having the general structure of A-B-Q, wherein Q is a glucagon superfamily peptide, osteocalcin or an analog, derivative or conjugate thereof and A-B comprises the general structure:



I

wherein

R_1 and R_8 are independently H or C_1-C_8 alkyl;

R_2 and R_4 are independently selected from the group consisting of H, C_1-C_8 alkyl, C_2-C_8 alkenyl, (C_1-C_4 alkyl)OH, (C_1-C_4 alkyl)SH, (C_2-C_3 alkyl)SCH_3, (C_1-C_4 alkyl)$CONH_2$, (C_1-C_4 alkyl)COOH, (C_1-C_4 alkyl)NH_2, (C_1-C_4 alkyl)$NHC(NH_2+)$ NH_2, (C_0-C_4 alkyl)(C_3-C_6 cycloalkyl), (C_0-C_4 alkyl)(C_2-C_5 heterocyclic), (C_0-C_4 alkyl)(C_6-C_{10} aryl)R_7, and CH_2(C_3-C_9 heteroaryl), or R_1 and R_2 together with the atoms to which they are attached form a C_3-C_{12} cycloalkyl;

R_3 is selected from the group consisting of C_1-C_8 alkyl, (C_1-C_4 alkyl)OH, (C_1-C_4 alkyl)NH_2, (C_1-C_4 alkyl)SH, (C_3-C_6)cycloalkyl or R_4 and R_3 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring;

R_5 is NHR_6 or OH;

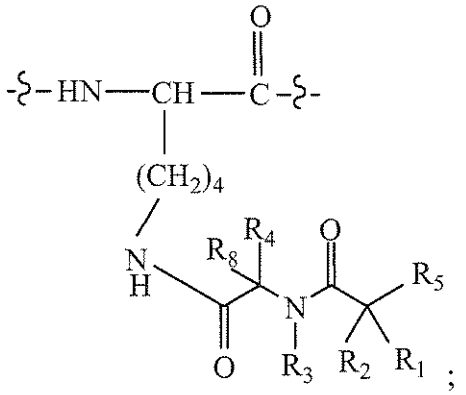
R_6 is H, C_1-C_8 alkyl, or R_6 and R_2 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring; and

R_7 is selected from the group consisting of hydrogen, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, (C_0-C_4 alkyl)$CONH_2$, (C_0-C_4 alkyl)COOH, (C_0-C_4 alkyl)NH_2, (C_0-C_4 alkyl)OH, halo, provided that when R_4 and R_3 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring, both R_1 and R_2 are not H.

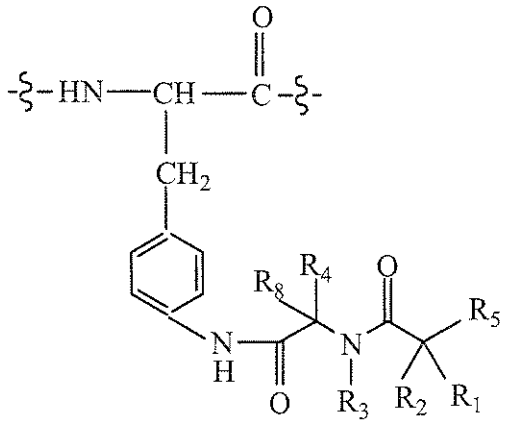
In some ~~embodiments~~examples Q is a peptide selected from the group consisting of Growth Hormone Releasing Hormone (GHRH; SEQ ID NO: 719), vasoactive intestinal peptide (VIP; SEQ ID NO: 720), Pituitary adenylate cyclase-activating polypeptide 27 (PACAP-27; SEQ ID NO: 721), peptide histidine methionine (PHM; SEQ ID NO: 722), or Secretin (SEQ ID NO: 723), glucagon (SEQ ID NO: 701), exendin-4 (SEQ ID NO: 718), Glucagon-like peptide -1 (GLP-1) (amino acids 7-37 provided as SEQ ID NOs: 703 and 704), Glucagon-like peptide -2 (GLP-2) (SEQ ID NO: 708), GIP (SEQ ID NO: 707), or analogs, derivatives and conjugates of the foregoing. In some ~~embodiments~~examples, Q is a glucagon related peptide.

In another ~~embodiment~~example a prodrug analog of a glucagon superfamily peptide, or osteocalcin, or an analog, derivative or conjugate thereof, is provided wherein the prodrug moiety (A-B) is covalently linked to Q at one or more internal amino acid residues in the

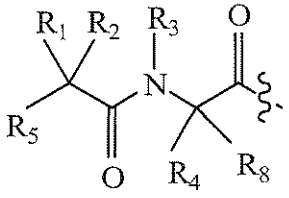
sequence of Q, e.g., at a position of Q corresponding to position 12, 16, 17, 18, 20, 28, or 29 of native glucagon (SEQ ID NO: 701). For example, in certain ~~embodiments~~examples the prodrug moiety (A-B) is linked, directly or via a linker, to a substituted Lys at position 20 of Q. In such ~~embodiments~~examples, Q may comprise at position 20 (relative to the native glucagon sequence), a substitution comprising the structure:



In other ~~embodiments~~examples, the prodrug moiety (A-B) is linked, directly or via a linker, to a substituted amino-Phe at position 22. In such ~~embodiments~~examples, Q may comprise at position 22 (relative to the native glucagon sequence), a substitution comprising the structure:



Alternatively or additionally, the prodrug moiety (A-B) is linked, directly or via a linker, to the amino terminus of Q, wherein A-B comprises the structure:



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wherein R_1 and R_8 are independently selected from the group consisting of H and C_1-C_8 alkyl;

R_2 and R_4 are independently selected from the group consisting of H, C_1-C_8 alkyl, C_2-C_8 alkenyl, (C_1-C_4 alkyl)OH, (C_1-C_4 alkyl)SH, (C_2-C_3 alkyl)SCH_3, (C_1-C_4 alkyl)$CONH_2$, (C_1-C_4 alkyl)COOH, (C_1-C_4 alkyl)NH_2, (C_1-C_4 alkyl)$NHC(NH_2^+)$ NH_2, (C_0-C_4 alkyl)(C_3-C_6 cycloalkyl), (C_0-C_4 alkyl)(C_6-C_{10} aryl)R_7, CH_2(C_5-C_9 heteroaryl), or R_1 and R_2 together with the atoms to which they are attached form a C_3-C_6 cycloalkyl;

R_3 is selected from the group consisting of C_1-C_8 alkyl, (C_1-C_4 alkyl)OH, (C_1-C_4 alkyl)NH_2, (C_1-C_4 alkyl)SH, (C_3-C_6)cycloalkyl or R_4 and R_3 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring;

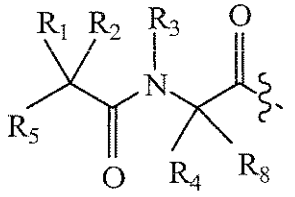
R_5 is NHR_6 or OH;

R_6 is H, or R_6 and R_2 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring; and

R_7 is selected from the group consisting of H and OH,

with the proviso that R_1 and R_2 are each other than H when R_4 and R_3 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring.

In other ~~embodiments~~examples, the prodrug moiety (A-B) is linked, directly or via a linker, to the amino terminus of Q, wherein A-B comprises the structure:



I

wherein

R_1 and R_8 are independently H or C_1-C_8 alkyl;

R_2 and R_4 are independently selected from the group consisting of H, C_1-C_8 alkyl, C_2-C_8 alkenyl, (C_1-C_4 alkyl)OH, (C_1-C_4 alkyl)SH, (C_2-C_3 alkyl)SCH_3, (C_1-C_4 alkyl)$CONH_2$, (C_1-C_4 alkyl)COOH, (C_1-C_4 alkyl)NH_2, (C_1-C_4 alkyl)$NHC(NH_2+)$ NH_2, (C_0-C_4 alkyl)(C_3-C_6 cycloalkyl), (C_0-C_4 alkyl)(C_2-C_5 heterocyclic), (C_0-C_4 alkyl)(C_6-C_{10} aryl)R_7, and CH_2(C_3-C_9 heteroaryl), or R_1 and R_2 together with the atoms to which they are attached form a C_3-C_{12} cycloalkyl;

R_3 is selected from the group consisting of C_1-C_8 alkyl, (C_1-C_4 alkyl)OH, (C_1-C_4 alkyl)NH_2, (C_1-C_4 alkyl)SH, (C_3-C_6)cycloalkyl or R_4 and R_3 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring;

R_5 is NHR_6 or OH;

R_6 is H, C_1-C_8 alkyl, or R_6 and R_2 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring; and

R_7 is selected from the group consisting of hydrogen, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, (C_0-C_4 alkyl)$CONH_2$, (C_0-C_4 alkyl)COOH, (C_0-C_4 alkyl)NH_2, (C_0-C_4 alkyl)OH, halo, with the proviso that R_1 and R_2 are both not H when R_4 and R_3 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring.

In some ~~embodiments~~examples, only one prodrug moiety is linked to Q. For example, in such ~~embodiments~~examples, when the prodrug moiety (A-B) is linked to Q at the N-terminus, there are no prodrug moieties (A-B) linked to an internal amino acid residue in the sequence of Q, and *vice versa*. In some ~~embodiments~~examples, two or three prodrug moieties are linked to Q, e.g. at the N-terminus and at one or more internal sites.

In a second aspect, the present invention refers to a prodrug as defined above, wherein Q is selected from the group consisting of SEQ ID NOs: 1-564, 566-570, 573-575, 577, 579-580, 585-612, 616, 618-632, 634-642, 647, 657-684, 701-732, 801-878, 883-919, 1001-1262, 1301-1371, 1401-1518, 1701-1708, 1710, 1711, 1731-1734, 1738, 1740, 1741, 1745, and 1747-1776.

In a third aspect, the present invention refers to a sterile pharmaceutical composition comprising the prodrug as defined above, and a pharmaceutically acceptable carrier.

In a fourth aspect, the present invention refers to the use of a pharmaceutical composition as defined above in the manufacture of a medicament for treating hyperglycemia or diabetes.

In a fifth aspect, the present invention refers to the use of a pharmaceutical composition as defined above in the manufacture of a medicament for treating obesity.

In a sixth aspect, the present invention refers to the use of a pharmaceutical composition as defined above in the manufacture of a medicament for causing temporary paralysis of the intestinal.

In a seventh aspect, the present invention refers to the use of a pharmaceutical composition as defined above in the manufacture of a medicament for treating or preventing hypoglycemia.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the change in body weight in diet-induced obesity (DIO) mice injected intraperitoneally with a single weekly dose of 15 or 70 nmol/kg of a glucagon analog. Mice were weighed daily (N=8) after the initial injection with the following: vehicle only ▼, Glucagon Superfamily Peptide A ("Peptide A") at 15 nmol/kg (▷) or 70 nmol/kg (▶), or a prodrug derivative of Peptide A wherein a dipeptide is linked to the N-terminus of Peptide A via an amide bond wherein the dipeptide is Aib^{-1} Pro^{0} (administered at 15 nmol/kg (○) or 70 nmol/kg (●)), Aib^{-1} $dPro^{0}$ (administered at 70 nmol/kg (◇)), Lys^{-1} Sar^{0} (administered at 70 nmol/kg (◆)), $dAla^{-1}$ Pro^{0} (administered at 70 nmol/kg (◀)) or Ac-Aib^{-1} Pro^{-1} (administered at 70 nmol/kg (■)).

Fig. 2 is a graph showing the change in body weight in diet-induced obesity (DIO) mice injected intraperitoneally with a single weekly dose of 0.5, 3, 15 or 70 nmol/kg of either vehicle only (◆), Peptide A, (at 0.5 ▲, 3 ▶, 15 ▼ or 70 ◀ nmol/kg/day) or Lys^{-1} Sar^{0}-Peptide A (at 0.5 △, 3 ▷, 15 ▽ or 70 ◁ nmol/kg/day).

Fig. 3 is a graph of blood glucose levels (mg/dL) in DIO mice (N=8) injected first with a glucagon related peptide and then a glucose solution. Mice were injected intraperitoneally at the -60 min time point with vehicle only (▲), or a 15 or 70 nmol/kg dose of one of the following:

(A) Peptide A, (at 15 ◁ or 70 ◀ nmol/kg/day),

(B) Lys^{-1} Sar^{0} Peptide A, (at 15 ▷ or 70 ▶ nmol/kg/day), or

(C) $dLys^{-1}$ Sar^{0} Peptide A, (at 15□, or 70 ■ nmol/kg/day).