discloses exendin derivatives whose amino acids are substituted with nonnatural aminoacids, e.g., pentyl glycine, homoproline or tert-butylglycine, and US2008/0119390 discloses exendin derivatives consisting of shorter amino sequences than the native exendin-4 prepared by deleting some amino acid residues of exendin-4, and prepared by substituting some amino acid residues of exendin-4 with other amino acid residues. These publications are incorporated by references.

Specifically, the present invention may also encompass a derivative thereof with removal of the amino group of N-terminal histidine (desamino-histidyl derivative), a derivative thereof prepared by substitution of the amino group with a hydroxyl group (beta-hydroxyimidazoproionyl derivative), a derivative thereof prepared by ~~modification~~ substitution of the amino group with two methyl residues (dimethyl-histidyl derivative), a derivative thereof prepared by substitution of the amino group with a carboxyl group (beta-carboxyimidazopropionyl derivative), or a derivative thereof with removal of the positive charge of the amino group, in which the alpha carbon of N-terminal histidine residue is removed to remain only the imidazoacetyl group (imidazoacetyl

derivative), and other N-terminal amino group modified-derivatives.

Preferably, the present invention provides exendin-4 derivatives having chemically modified N-terminal amino group or amino acid residue, more preferably exendin-4 derivative in which the alpha amino group or alpha carbon of N-terminal histidine residue (the first amino acid of exendin-4) is substituted or removed, and further more preferably desamino-histidyl-exendin-4 (DA-Exendin-4) with removal of the N-terminal amino group, beta-hydroxy imidazopropionyl-exendin-4 (HY-exendin-4) prepared by substitution of the amino group with a hydroxyl group, beta-carboxy imidazopropionyl-exendin-4 (CX-exendin-4) prepared by substitution of the amino group with a carboxyl group, dimethyl-histidyl-exendin-4 (DM-exendin-4) prepared by substitution ~~modification~~ of the amino group with two methyl residues, and imidazoacetyl-exendin-4 (CA-exendin-4) with removal of alpha carbon of N-terminal histidine residue.

CLAIMS

1. An insulinotropic peptide derivative, wherein N-terminal histidine residue of a native insulinotropic peptide is substituted with 4-imidazoacetyl, and wherein the insulinotropic peptide is exendin-4, exendin-3 or derivatives thereof.

2. The insulinotropic peptide derivetive as set forth in claim1, wherein the insulinotropic peptide is exendin-4 or its derivative.

3. The insulinotropic peptide derivative as set forth in claim 1, wherein the insulinotropic peptide derivative consists of an amino acid of the following Formula 1:

R1-X-R2 <Formula 1>

wherein R1 is 4-imidazoacetyl;

R2 is selected from the group consisting of $-NH_2$ or -OH;

X is selected from the group consisting of Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Y-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Z-Asn-Gly-Gly-Pro-

Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser,

Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Y-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Z-Asn-Gly-Gly and

Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Y-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Z-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser;

Y is selected from the group consisting of Lys, Ser, and Arg; and

Z is selected from the group consisting of Lys, Ser, and Arg.

4. The insulinotropic peptide derivative as set forth in claim3, wherein R1 is 4-imidazoacetyl, Y is Lys or Ser, Z is Lys, and R2 is $-NH_2$.

5. A pharmaceutical composition for the treatment of diabetes, comprising the insulinotropic peptide derivative of claim 1.

CLAIMS

1. An insulinotropic peptide derivative, wherein N-terminal histidine residue of a native insulinotropic peptide is substituted with 4-imidazoacetyl, and wherein the insulinotropic peptide is exendin-4 or exendin-3,

wherein the insulinotropic peptide derivative consists of an amino acid of the following Formula 1:

R1-X-R2 <Formula 1>

wherein R1 is 4-imidazoacetyl;

R2 is selected from the group consisting of $-NH_2$ or -OH;

X is selected from the group consisting of Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Y-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Z-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Y-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Z-Asn-Gly-Gly and Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Y-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Z-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser;

Y is selected from the group consisting of Lys, Ser, and Arg; and

Z is selected from the group consisting of Lys, Ser, and Arg.

2. The insulinotropic peptide derivative as set forth in claim 1, wherein the insulinotropic peptide is exendin-4.

3. The insulinotropic peptide derivative as set forth in claim 1, wherein R1 is 4-imidazoacetyl, Y is Lys or Ser, Z is Lys, and R2 is $-NH_2$.

4. A pharmaceutical composition for the treatment of diabetes, comprising the insulinotropic peptide derivative of claim 1.