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(54) Title: LONG LASTING INSULINOTROPIC PEPTIDES

(57) Abstract

Modified insulinotropic peptides are disclosed. The modified insulinotropic peptides are capable of forming a peptidase stabilized insulinotropic peptide. The modified insulinotropic peptides are capable of forming covalent bonds with one or more blood components to form a conjugate. The conjugates may be formed *in vivo* or *ex vivo*. The modified peptides are administered to treat humans with diabetes and other related diseases.

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LONG LASTING INSULINOTROPIC PEPTIDES

FIELD OF THE INVENTION

This invention relates to modified insulinotropic peptides. In particular, this invention relates to modified glucagon like peptides and exendin peptides with long duration of action for the treatment of diabetes and other insulinotropic peptide related diseases, gastrointestinal function and activities associated with glucagon levels.

BACKGROUND OF THE INVENTION

The insulinotropic peptide hormone glucagon-like peptide (GLP-1) has been implicated as a possible therapeutic agent for the management of type 2 non-insulin-dependent diabetes mellitus as well as related metabolic disorders, such as obesity. Other useful insulinotropic peptides include exendin 3 and exendin 4. While useful, GLP-1, exendin 3 and exendin 4 suffer from limited duration of action associated with short plasma half-lifes *in vivo*, mainly due to rapid serum clearance and proteolytic degradation. The enzyme responsible for the degradation of GLP-1, dipeptidyl peptidase IV, has been identified. Extensive work has been done in attempts to inhibit the peptidase or to modify GLP-1 in such a way that its degradation is slowed down while still maintaining biological activity. Despite these extensive efforts, a long lasting, active GLP-1 has not been produced. As such, the diabetic community has a tremendous need for improved GLP-1, exendin 3 and exendin 4 peptides.

There is thus a need to modify GLP-1, exendin 3, exendin 4 and other insulinotropic peptides to provide longer duration of action *in vivo*, while maintaining their low toxicity and therapeutic advantages.

SUMMARY OF THE INVENTION

In order to meet those needs, the present invention is directed to modified insulinotropic peptides (ITPs). This invention relates to novel chemically reactive derivatives of insulinotropic peptides that can react with available functionalities on cellular carriers including mobile blood proteins to form covalent linkages. Specifically, the invention relates to novel chemically reactive derivatives of insulinotropic peptides such as glucagon like peptide (GLP) and exendin 3 and exendin 4 that can react with available functionalities on mobile blood proteins to form covalent linkages. The invention also relates to novel chemically reactive derivatives or analogs of insulinotropic peptides that can react with available functionalities on mobile blood proteins to form covalent linkages.

The present invention relates to modified insulinotropic peptides comprising a reactive group which reacts with amino groups, hydroxyl groups or thiol groups on blood compounds to form stable covalent bonds.

The present invention relates to an insulinotropic hormone comprising a modified fragment of GLP-1 and derivatives thereof, especially GLP-1 (7-36) amide. The invention additionally pertains to the therapeutic uses of such compounds, and especially to the use of modified GLP-1 (7-36) amide for the treatment of maturity onset diabetes mellitus (type II diabetes).

The present invention further relates to modified Exendin 3 and Exendin 4 fragments and therapeutic uses of such compounds.

In particular, the present invention is directed to GLP-1(1-36)-Lys^{37} (ε-MPA)-NH_2; GLP-1 (1-36)-Lys^{37} (ε-AAEA-AEEA-MPA)-NH_2; GLP-1 (7-36)-Lys^{37} (ε-MPA)-NH_2; GLP-1 (7-36)-Lys^{37-} (ε-AEEA-AEEA-MPA)-NH_2; D-Ala^2 GLP-1 (7-36)-Lys^{37} (ε-MPA)-NH_2; Exendin-4 (1-39)-Lys^{40} (ε-MPA)-NH_2; Exendin-4 (1-39)-Lys^{40} (ε-AEEA-AEEA-MPA)-NH_2; Exendin-3 (1-39)-Lys^{40} (ε-MPA)-NH_2; Exendin-3 (1-39)-Lys^{40} (ε-AEEA-AEEA-MPA)-NH_2; Lys^{26}(ε-MPA)GLP-1(7-36)-NH_2; GLP-1 (7-36)-EDA-MPA and Exendin-4 (1-39)-EDA-MPA.

The present invention further relates to compositions comprising the derivatives of the insulinotropic peptides and the use of the compositions for treating diabetes in humans.

The invention further pertains to a method for enhancing the expression of insulin which comprises providing to a mammalian pancreatic Beta-type islet cell an effective amount of the modified insulinotropic peptides disclosed above.

The invention further pertains to a method for treating maturity-onset diabetes mellitus which comprises administration of an effective amount of the insulinotropic peptides discussed above to a patient in need of such treatment.

The invention further pertains to the treatment of other insulinotropic peptide related diseases and conditions with the modified insulinotropic peptides of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

To ensure a complete understanding of the invention the following definitions are provided:

Insulinotropic Peptides: Insulinotropic peptides (ITPs) are peptides with insulinotropic activity. Insulinotropic peptides stimulate, or

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