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(54) Title: N–TERMINALLY TRUNCATED GLP–1 DERIVATIVES

(57) Abstract

The present invention relates to N–terminally truncated derivatives of human glucagon–like peptide–1 (GLP–1) and analogues thereof having a protracted profile of action, as well as the use of such derivatives in pharmaceutical compositions for the treatment of obesity, insulin dependent or non–insulin dependent diabetes mellitus. The GLP–1 derivatives have a lipophilic substituent attached to at least one amino acid residue.

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N-TERMINALLY TRUNCATED GLP-1 DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel derivatives of human glucagon-like peptide-1 (GLP-1) and fragments analogues thereof having a protracted profile of action and to the use of such derivatives in pharmaceutical compositions.

BACKGROUND OF THE INVENTION

GLP-1 (Glucacon-Like-Peptide-1) is an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism. Human GLP-1 is a 37 amino acid residue peptide originating from preproglucagon which is synthesised *i.a.* in the L-cells in the distal ileum, in the pancreas and in the brain. Processing of preproglucagon to give GLP-1(7-36)amide, GLP-1(7-37) and GLP-2 occurs mainly in the L-cells.

WO 87/06941 (The General Hospital Corporation) disclose peptide fragments which comprises GLP-1(7-37) and functional derivatives thereof and to its use as an insulinotropic agent.

WO 90/11296 (The General Hospital Corporation) disclose peptide fragments which comprise GLP-1(7-36) and functional derivatives thereof and have an insulinotropic activity which exceeds the insulinotropic activity of GLP-1(1-36) or GLP-1(1-37) and to their use as insulinotropic agents.

The amino acid sequence of GLP-1(7-36)amide and GLP-1(7-37) is:

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 7   8   9  10  11  12  13  14  15  16  17  18  19  20  21  22  23
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-

 24  25  26  27  28  29  30  31  32  33  34  35  36                (I)
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X
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wherein X is NH_2 for GLP-1(7-36)amide and X is Gly-OH for GLP-1(7-37).

WO 91/11457 (Buckley *et al.*) discloses analogues of the active GLP-1 peptides 7-34, 7-35, 7-36, and 7-37.

WO 98/08871 discloses GLP-1 derivatives in which a lipophilic substituent is attached to at least one amino acid residue. The lipophilic substituents are in particular long-chain groups containing e.g. 12-24 carbon atoms.

EP 0699686-A2 (Eli Lilly & Co.) discloses certain N-terminal truncated fragments of GLP-1 that are reported to be biologically active.

It is an object of the present invention to provide improved N-terminal truncated fragments of GLP-1.

SUMMARY OF THE INVENTION

In its broadest aspect, the present invention relates to derivatives of GLP-1 and analogues thereof. The derivatives according to the invention have interesting pharmacological properties, including a protracted profile of action. The derivatives also are more metabolically and physically stable, and more soluble.

The GLP-1 derivatives and analogues of the present invention are truncated at the N-terminal end and comprise a lipophilic substituent (optionally via a spacer) attached to at least one amino acid residue. The lipophilic substituent is in particular a long-chain group of the type described in WO 98/08871 (Novo Nordisk A/S).

In particular, the invention relates to an N-terminal truncated GLP-1 derivative comprising a parent peptide of formula II

A – GLP-1(19-B) – X (II)

wherein

A is a peptide comprising the amino acid residues of GLP-1(8-18) or a fragment thereof;

B is an integer in the range of 35-45; and

X is –OH, $–NH_2$, or a C_{1-6} alkyl amide or C_{1-6} dialkyl amide group;

or an analogue thereof;

and wherein a lipophilic substituent is attached to at least one amino acid residue.

DETAILED DESCRIPTION OF THE INVENTION

A simple system is used to describe the GLP-1 derivatives of the present invention. For example, Gly^8-GLP-1(7-37) designates a fragment which relates to GLP-1(1-37) by the deletion of the amino acid residues at positions 1 to 6 and the substitution of the naturally occurring amino acid residue in position 8 (Ala) with Gly. Similarly, $Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37) designates GLP-1(7-37) wherein the ε-amino group of the Lys residue in position 34 has been tetradecanoylated. Where a reference is made to C-terminally extended GLP-1 analogues, the amino acid residue in position 38 is Arg unless otherwise indicated, the amino acid residue in position 39 is also Arg unless otherwise indicated and the amino acid residue in position 40 is Asp unless otherwise indicated. Also, if a C-terminally extended analogue extends to position 41,

42, 43, 44 or 45, the amino acid sequence of this extension is as in the corresponding sequence in human preproglucagon unless otherwise indicated.

The present invention relates to derivatives of native GLP-1 and derivatives of GLP-1 analogs. In a preferred embodiment, the derivatives are derivatives of native GLP-1(8-45) or a fragment thereof. In a more preferred embodiment, the derivatives are derivatives of native GLP-1(8-36). In another more preferred embodiment, the derivatives are derivatives of native GLP-1(8-37). In another more preferred embodiment, the derivatives are derivatives of native GLP-1(8-38).

In a preferred embodiment of GLP-1 derivatives of the present invention, A is a peptide selected from the group consisting of GLP-1(8-18), GLP-1(9-18), GLP-1(10-18), GLP-1(11-18), GLP-1(12-18), GLP-1(13-18), GLP-1(14-18), GLP-1(15-18), GLP-1(16-18), GLP-1(17-18) and GLP-1(18). Preferably, A is GLP-1(8-18), GLP-1(9-18), GLP-1(10-18), GLP-1(11-18) or GLP-1(12-18), and B is 36, 37 or 38. Most preferably, A is GLP-1(8-18).

In a preferred embodiment of GLP-1 derivatives of the present invention, B is 35, 36, 37, 38, 39, 40, 41, 42, 43 or 44. In a more preferred embodiment, B is 36. In another more preferred embodiment. B is 37. In another more preferred embodiment, B is 38.

GLP-1 Analogs

The present invention also relates to derivatives of analogs of GLP-1. The term "analogue" is defined herein as a peptide which relates to a parent peptide by the substitution of one or more amino acid residues of the parent peptide with other amino acid residue(s).

In the GLP-1 derivatives of formula II, up to fifteen, preferably up to ten amino acid residues may be exchanged with any α-amino acid residue, in particular with any α-amino acid residue which can be coded for by the genetic code. Preferred analogues are those in which up to six amino acid residues have been exchanged with any α-amino acid residue which can be coded for by the genetic code.

Preferred GLP-1 derivatives or analogues are those in which:

i) A is selected from the group consisting of GLP-1(8-18), GLP-1(9-18) and GLP-1(10-18); and

ii) B is 36, and the parent peptide comprises one or more amino acid substitutions selected from the group consisting of Arg^{26}, Arg^{34} and Lys^{36};

B is 37, and the parent peptide comprises one or more amino acid substitutions selected from the group consisting of Arg^{26}, Arg^{34}, Lys^{36} and Lys^{37}; or

B is 38, and the parent peptide comprises one or more amino acid substitutions selected from the group consisting of Arg^{26}, Arg^{34}, Lys^{36} and Lys^{38}.

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