

Claims

1. A glucose-dependent insulintropic peptide (GIP) analogue comprising a GIP(3-30) amino acid sequence consisting of:

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3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
E/pyroE – G – T – F – I – S – E/D – Y – S – I/Aib – A/Aib – L/Nle/M – E/D – K – I –

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18 19 20 21 22 23 24 25 26 27 28 29 30
K/Orn – Q – Q – E/D – F – V – E/D – W – L – L – A – Q – K – Z,

wherein a fatty acid molecule is attached, directly or via a linker, to the K/Orn amino acid residue at position 18 of said GIP(3-30) amino acid sequence, wherein **Z** is a peptide consisting of one or more consecutive amino acid residues of GKKNDWKHNITQ (SEQ ID NO: 2), or wherein **Z** is a peptide consisting of one or more consecutive amino acid residues of GPSSGAPPPS (SEQ ID NO: 5), and wherein said GIP analogue is an antagonist of GIPR.

2. The GIP analogue according to claim 1, wherein said GIP analogue inhibits GIPR activity at least 80%, such as at least 85%, such as at least 90%, such as at least 95%, such as about 100%, optionally wherein inhibition of GIPR activity is determined as a decrease in intracellular cAMP.

3. The GIP analogue according to any one of the preceding claims, wherein said GIP analogue has a GIPR antagonistic potency corresponding to an IC₅₀ value of 50 nM or less.

4. The GIP analogue according to any one of the preceding claims, wherein **Z** is a peptide consisting of PSSGAPPPS (SEQ ID NO: 4).

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5. The GIP analogue according to any one of claims 1 to 3, wherein **Z** is a peptide selected from:

- a glycine, a proline,
- GP, PS, PSS, GPS, GPSS (SEQ ID NO: 6), PSSG (SEQ ID NO: 12), PSSGA (SEQ ID NO: 13), GPSSG (SEQ ID NO: 7), PSSGAP (SEQ ID NO: 14),

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- PSSGAPP (SEQ ID NO: 15), GPSSGA (SEQ ID NO: 8), GPSSGAP (SEQ ID NO: 9), GPSSGAPP (SEQ ID NO: 10), PSSGAPPP (SEQ ID NO: 16), PSSGAPPPS (SEQ ID NO: 4), GPSSGAPPP (SEQ ID NO: 11) and GPSSGAPPPS (SEQ ID NO: 5), or
- 5 - GK, GKK, GKKN (SEQ ID NO: 17), GKKND (SEQ ID NO: 18), GKKNDW (SEQ ID NO: 19), GKKKDW (SEQ ID NO: 28), GKKNDK (SEQ ID NO: 29), GKKNDWK (SEQ ID NO: 23), GKKNDWKH (SEQ ID NO: 24), GKKNDWKHN (SEQ ID NO: 25), GKKNDWKHNI (SEQ ID NO: 26), GKKNDWKHNIT (SEQ ID NO: 27) and GKKNDWKHNITQ (SEQ ID NO: 2).
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6. The GIP analogue of any one of the preceding claims, wherein said fatty acid molecule is attached to the side chain amino group of a Lysine (K) amino acid residue at position 18 of said GIP(3-30) amino acid sequence, directly.
- 15 7. The GIP analogue of any one of claims 1 to 5, wherein said fatty acid molecule is attached to the side chain amino group of a Lysine (K) amino acid residue at position 18 of said GIP(3-30) amino acid sequence, via a linker.
- 20 8. The GIP analogue of any one of the preceding claims, wherein said fatty acid molecule is a straight-chain fatty acid or a branched fatty acid; and/or wherein said fatty acid molecule is a monoacyl fatty acid molecule or a diacyl fatty acid molecule; and/or wherein said fatty acid molecule comprises an acyl group of the formula $\text{CH}_3(\text{CH}_2)_n\text{CO}-$, wherein n is an integer of 4 to 24; and/or
- 25 wherein said fatty acid molecule comprises an acyl group of the formula $\text{COOH}(\text{CH}_2)_n\text{CO}-$, wherein n is an integer of 4 to 24.
9. The GIP analogue according to any one of the preceding claims, wherein said fatty acid molecule comprises an acyl group selected from $\text{CH}_3(\text{CH}_2)_6\text{CO}-$, $\text{CH}_3(\text{CH}_2)_8\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{10}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{12}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{14}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{16}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{18}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{20}\text{CO}-$ and $\text{CH}_3(\text{CH}_2)_{22}\text{CO}-$.
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10. The GIP analogue according to any one of the claims 1 to 8, wherein said fatty acid molecule comprises an acyl group selected from $\text{COOH}(\text{CH}_2)_6\text{CO}-$, $\text{COOH}(\text{CH}_2)_8\text{CO}-$, $\text{COOH}(\text{CH}_2)_{10}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{12}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{14}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{16}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{18}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{20}\text{CO}-$ and $\text{COOH}(\text{CH}_2)_{22}\text{CO}-$;
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preferably selected from $\text{COOH}(\text{CH}_2)_{14}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{16}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{18}\text{CO}-$ and $\text{COOH}(\text{CH}_2)_{20}\text{CO}-$.

11. The GIP analogue according to claims 1 to 5 and 7 to 10, wherein said fatty acid molecule is attached via a linker, wherein said linker comprises one or more moieties individually selected from:

 - a. α -amino acid, γ -amino acid, and ω -amino acid,
 - b. one or more amino acids selected from succinic acid, Lys, Glu, and Asp,
 - c. one or more of γ -aminobutanoyl (γ -aminobutyric acid), γ -Glu (γ -glutamic acid), β -Asp (β -asparagyl), β -Ala (β -alanyl), and Gly, and
 - d. [8-amino-3,6-dioxaoctanoic acid]_n (AEEAc_n), wherein n is an integer of 1 to 50, such as an integer of 1-4, 1-3 or 1-2.
12. A pharmaceutical composition comprising a GIP analogue according to any one of the preceding claims.
13. A pharmaceutical composition comprising a GIP analogue according to any one of the preceding claims, having a GIP(3-30) amino acid sequence selected from:

EGTFISEYSIAibMEKIKQQDFVEWLLAQK – Z; (SEQ ID NO: 53) GIP(3-30)
 [D9E;A13Aib;D15E;H18K;N24E],

EGTFISEYSIAibLEKIKQQEFVEWLLAQK – Z; (SEQ ID NO: 81) GIP(3-30)
 [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],

EGTFISEYSIAibNleEKIKQQEFVEWLLAQK – Z; (SEQ ID NO: 82) GIP(3-30)
 [D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],

EGTFISEYSIALEKIKQQEFVEWLLAQK – Z; (SEQ ID NO: 87) GIP(3-30)
 [D9E;M14L;D15E;H18K;D21E;N24E], and

EGTFISEYSIANleEKIKQQEFVEWLLAQK – Z; (SEQ ID NO: 88) GIP(3-30)
 [D9E;M14Nle;D15E;H18K;D21E;N24E],

wherein Z is a peptide consisting of one or more consecutive amino acid residues of GKKN~~D~~WKHNITQ (SEQ ID NO: 2), or wherein Z is a peptide consisting of one or more consecutive amino acid residues of GPSSGAPPPS (SEQ ID NO: 5),

wherein a fatty acid molecule is attached, directly or via a linker, to the lysine (K) amino acid residue at position 18 of said GIP(3-30) amino acid sequence.

14. A pharmaceutical composition comprising a GIP analogue having a GIP(3-30) amino acid sequence selected from:

- 5 EGTFISEYSIAMEKIKQQDFVEWLLAQKPSSGAPPPS (SEQ ID NO: 142),
GIP(3-30)Cex(31-39) [D9E;D15E;H18K;N24E],
- EGTFISEYSAibANleEKIKQQDFVEWLLAQKPSSGAPPPS (SEQ ID NO: 143),
GIP(3-30)Cex(31-39) [D9E;I12Aib;M14Nle;D15E;H18K;N24E],
- 10 EGTFISEYSAibMEKIKQQDFVEWLLAQKPSSGAPPPS (SEQ ID NO: 144),
GIP(3-30)Cex(31-39) [D9E;A13Aib;D15E;H18K;N24E],
- EGTFISEYSAibLEKIKQQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 174),
15 GIP(3-30)Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],
- EGTFISEYSAibNleEKIKQQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 175),
GIP(3-30)Cex(31-39) [D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],
- 20 EGTFISEYSIALEKIKQQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 180),
GIP(3-30)Cex(31-39) [D9E;M14L;D15E;H18K;D21E;N24E], and
- EGTFISEYSIANleEKIKQQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 181),
GIP(3-30)Cex(31-39) [D9E;M14Nle;D15E;H18K;D21E;N24E],
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wherein a fatty acid molecule is attached, directly or via a linker, to the lysine (K) amino acid residue at position 18 of said GIP(3-30) amino acid sequence.

15. A pharmaceutical composition comprising a GIP analogue selected from:
- 30 EGTFISEYSIAMEKIK(C16-diacid)QQDFVEWLLAQKPSSGAPPPS (SEQ ID
NO: 142), GIP(3-30)Cex(31-39) [D9E;D15E;H18K;N24E],
- EGTFISEYSAibANleEKIK(C16-diacid)QQDFVEWLLAQKPSSGAPPPS (SEQ
ID NO: 143), GIP(3-30)Cex(31-39) [D9E;I12Aib;M14Nle;D15E;H18K;N24E],
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EGTFISEY**SI****Aib**MEKIK(C16-diacid)QQDFVEWLLAQKPSSGAPPPS (SEQ ID NO: 144), GIP(3-30)Cex(31-39) [D9E;A13Aib;D15E;H18K;N24E],

5 EGTFISEY**SI****Aib**LEKIK(C16-diacid)QQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 174), GIP(3-30)Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],

10 EGTFISEY**SI****Aib**LEKIK(2xAEAAc+yGlu-C18-diacid)QQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 174), GIP(3-30)Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],

EGTFISEY**SI****Aib**NleEKIK(C16-diacid)QQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 175), GIP(3-30)Cex(31-39) [D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],

15 EGTFISEY**SI****Aib**NleEKIK(2xAEAAc+yGlu-C18-diacid)QQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 175), GIP(3-30)Cex(31-39) [D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],

20 EGTFISEY**SI**ALEKIK(2xAEAAc+yGlu-C18-diacid)QQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 180), GIP(3-30)Cex(31-39) [D9E;M14L;D15E;H18K;D21E;N24E], and

25 EGTFISEY**SI**ANleEKIK(2xAEAAc+yGlu-C18-diacid)QQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 181), GIP(3-30)Cex(31-39) [D9E;M14Nle;D15E;H18K;D21E;N24E].

16. The pharmaceutical composition according to any one of claims 14 to 15, wherein said GIP analogue is

EGTFISEY**SI****Aib**LEKIK(C16-diacid)QQEFVEWLLAQKPSSGAPPPS (SEQ ID NO: 174).

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17. The GIP analogue according to claims 1 to 11, or the pharmaceutical composition according to any one of claims 12 to 16, wherein said GIP analogue is C-terminally amidated or has a free C-terminal carboxylic acid.

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