Claims

1. A polypeptide selected from the group consisting of:

(A) SRIF14 consisting of the amino acid sequence represented by SEQ ID NO. 1;

(B) a polypeptide having one or two amino acids deleted, substituted, or added from/to SRIF14 consisting of the amino acid sequence represented by SEQ ID NO. 1;

and

(D) a polypeptide having 80% or more homology with SRIF14 consisting of the amino acid sequence represented by SEQ ID NO. 1;

wherein said polypeptide further comprises (i) N amino acids (wherein N is an integer from 1 or more to 20 or less) at the N-terminal side; and/or

(ii) M amino acids (wherein M is an integer from 1 or more to 6 or less) at the C-terminal side;

characterized in that at least two amino acids are substituted with glycosylated amino acids, and at least one of the amino acids substituted with said glycosylated amino acid is present in any of said N amino acids or in any of said M amino acids; and

the polypeptide has affinity towards somatostatin receptors.

2. A glycosylated polypeptide according to claim 1, characterized in that at least one of the amino acids substituted with said glycosylated amino acid is the amino acid corresponding to position 19 of SRIF14.

3. A glycosylated polypeptide according to claim 1, characterized in that the sequence of said N amino acids added onto the N-terminal is represented by X-Y-,

wherein X means a sequence of any L amino acids (wherein L is an integer from 1 or more to 6 or less), and Y is a sequence selected from the group consisting of:

(1) Lys,

(2) Arg-Lys,

(3) Glu-Arg-Lys,

(4) Arg-Glu-Arg-Lys,

(5) Pro-Arg-Glu-Arg-Lys,

(6) Ala-Pro-Arg-Glu-Arg-Lys,

(7) Met-Ala-Pro-Arg-Glu-Arg-Lys,

(8) Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys,

(9) Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys,

(10) Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys,

(11) Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys,

(12) Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys,

(13) Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys,

(14) Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys, and

(15) a sequence having one or two amino acids deleted, substituted, or added from/to the above sequences (2) - (14).

4. A glycosylated polypeptide according to claim 3, characterized in that at least one of the amino acids substituted with said glycosylated amino acid is present in any of said L amino acids.

5. A polypeptide selected from the group consisting of:

(A) SRIF28 consisting of the amino acid sequence represented by SEQ ID NO. 2;

(B) a polypeptide having one to three amino acids deleted, substituted, or added from/to SRIF28 consisting of the amino acid sequence represented by SEQ ID NO. 2;

(D) a polypeptide having 80% or more homology with SRIF28 consisting of the amino acid sequence represented by SEQ ID NO. 2;

(E) a polypeptide further comprising J amino acids (wherein J is an integer from 1 or more to 15 or less) at the N-terminal side of (A) - (D); and

(F) a polypeptide further comprising K amino acids (wherein K is an integer from 1 or more to 6 or less) at the C-terminal side of (A) - (D);
characterized in that at least two amino acids are substituted with glycosylated amino acids, and
the polypeptide has affinity towards somatostatin receptors.

6. A glycosylated polypeptide according to claim 5, characterized in that at least one of the amino acids substituted with said glycosylated amino acid is an amino acid selected from the group consisting of the amino acid corresponding to position 1, the amino acid corresponding to position 5, the amino acid corresponding to position 9, the amino acid corresponding to position 12, the amino acid corresponding to position 13, the amino acid corresponding to position 14, and the amino acid corresponding to position 19 of SRIF28.

7. A glycosylated polypeptide according to claim 5, characterized in that at least two amino acids are substituted with glycosylated amino acids in said polypeptide (E),

wherein at least one of the amino acids substituted with said glycosylated amino acid is present in said J amino acids at the N-terminal side of said polypeptide (E); or at least one of the amino acids substituted with said glycosylated amino acid is present in said K amino acids of the C-terminal side of said polypeptide (F).

8. A glycosylated polypeptide according to any one of claims 1 to 7, characterized in that it has one or more of the following properties:
- said glycosylated polypeptide has increased stability in blood compared to SRIF28;
- said glycosylated polypeptide has increased half-life in blood by 10-fold or more compared to SRIF28;

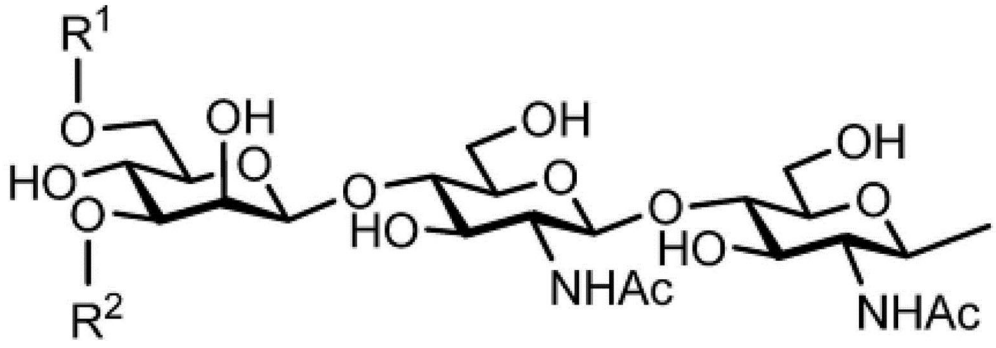
- said affinity towards somatostatin receptors has affinity towards at least two or more receptors selected from the group consisting of SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5;
- said glycosylated polypeptide has affinity towards any one of at least SSTR1 and SSTR4;
- said glycosylated polypeptide has affinity towards both SSTR1 and SSTR4; and
- said glycosylated polypeptide has affinity towards all of SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5.

9. A glycosylated polypeptide according to any one of claims 1 to 8, characterized in that each of said glycosylated amino acids is glycosylated Asn or glycosylated Cys.

10. A glycosylated polypeptide according to any one of claims 1 to 9, characterized in that in each of said glycosylated amino acids, the sugar chain consists of 4 or more sugars.

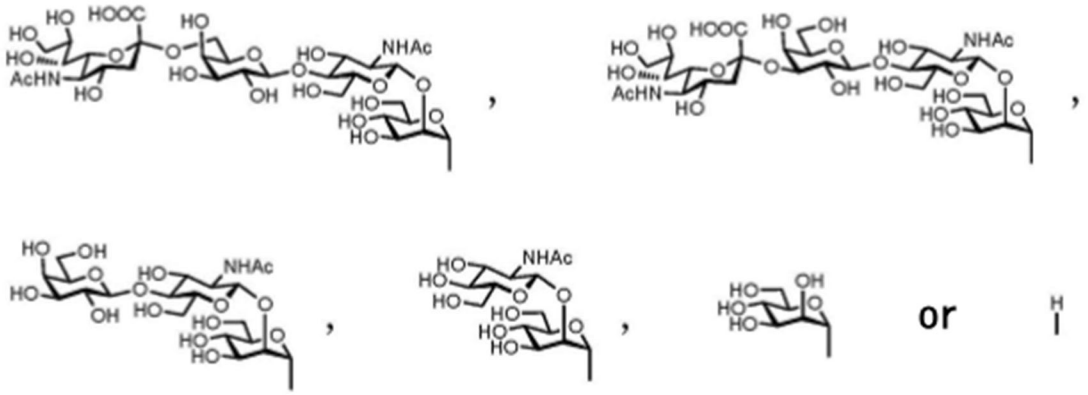
11. A glycosylated polypeptide according to any one of claims 1 to 9, characterized in that in each of said glycosylated amino acids, the sugar chain is a sugar chain represented by the following formula:

[Chemical Formula 1]



[wherein R^1 and R^2 are identical or different and are:

[Chemical Formula 2]



, and Ac is an acetyl group].

12. A glycosylated polypeptide according to any one of claims 1 to 10, characterized in that said sugar chain has at least one sialic acid at the non-reducing terminal, and the carboxy group of said sialic acid is modified by an alkylamino group, a benzyl group, an amino group, or an aminoethylamino group, having 1 - 30 carbons.

13. A pharmaceutical composition characterized in that it comprises:

(I) a glycosylated polypeptide according to any one of claims 1 to 12 and/or a pharmaceutically acceptable salt thereof, and

(II) a pharmaceutically acceptable carrier.

14. A pharmaceutical composition according to claim 13, characterized in that it is for use in the treatment or prevention of a somatostatin-related disease.

15. A pharmaceutical composition according to claim 14, characterized in that said somatostatin-related disease is at least one disease selected from the group consisting of acromegaly, gigantism, Alzheimer's disease and other forms of dementia, cancer, hormone-producing tumor, endocrine

tumor, carcinoid, VIPoma, insulinoma, glucagonoma, Cushing's disease, hormone secretion defect, diabetes and complications thereof, pains, arthritis, diarrhea, gastric ulcer, inflammatory bowel disease, irritable bowel syndrome, gastrointestinal obstruction, ileus, postoperative restenosis, radiation damage, eye disease, dry eye, glaucoma, interstitial keratitis, iritis, cataract, and conjunctivitis.

16. A glycosylated polypeptide selected from the group consisting of:

(A) a SRIF14 consisting of the amino acid sequence of SEQ ID NO:1;

(B) a polypeptide having one or two amino acids deleted from, substituted with, or added to SRIF14, SRIF14 consisting of the amino acid sequence of SEQ ID NO:1;

(D) a polypeptide having 80% or more homology with SRIF14 consisting of the amino acid sequence of SEQ ID NO:1;

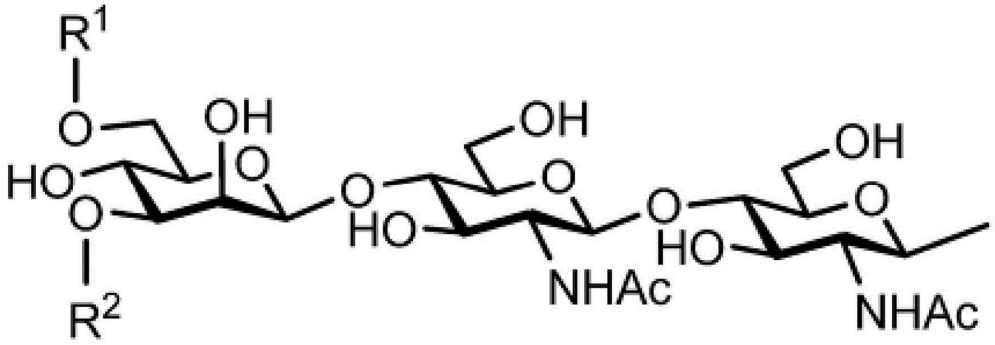
(E) a polypeptide further comprising N amino acids at the N-terminal side of (A) - (D), wherein N is an integer from 1 or more to 20 or less) at the N-terminal side of (A) - (D); and

(F) a polypeptide further comprising M amino acids at the C-terminal side of (A) - (D), wherein M is an integer from 1 or more to 6 or less;

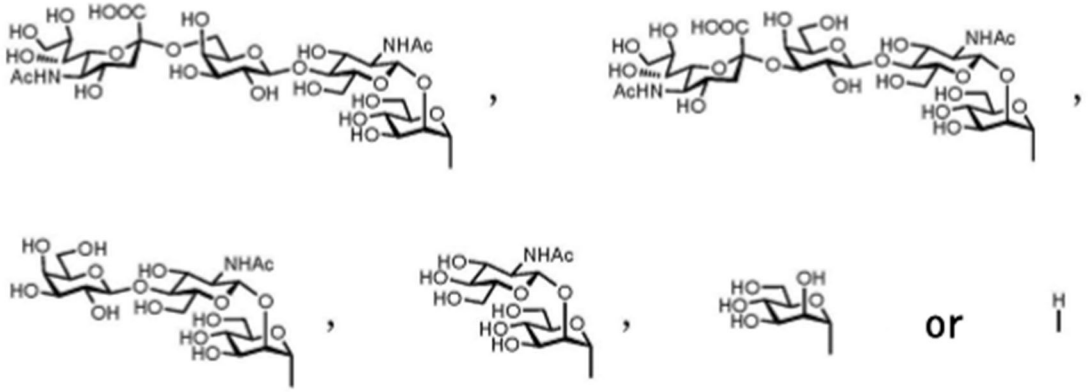
wherein at least two amino acids are substituted with glycosylated amino acids, and the polypeptide has affinity towards somatostatin receptors, and

wherein each of said glycosylated amino acids comprises a sugar chain represented by the following formula:

[Chemical Formula 1]



wherein R^1 and R^2 are identical or different and are:
[Chemical Formula 2]



, and
Ac is an acetyl group.

17. A glycosylated polypeptide selected from the group consisting of:

(A) a SRIF14 consisting of the amino acid sequence of SEQ ID NO:1;

(B) a polypeptide having one or two amino acids deleted from, substituted with, or added to SRIF14, SRIF14 consisting of the amino acid sequence of SEQ ID NO:1;

(D) a polypeptide having 80% or more homology with SRIF14 consisting of the amino acid sequence of SEQ ID NO:1;

(E) a polypeptide further comprising N amino acids at the N-terminal side of (A) - (D), wherein N is an integer

from 1 or more to 20 or less) at the N-terminal side of (A) - (D); and

(F) a polypeptide further comprising M amino acids at the C-terminal side of (A) - (D), wherein M is an integer from 1 or more to 6 or less;

wherein at least two amino acids are substituted with a glycosylated amino acid, and the polypeptide has affinity towards somatostatin receptors, and

wherein said glycosylated polypeptide comprises a sugar chain comprising at least one sialic acid at the non-reducing terminus, and said sialic acid comprises a carboxy group that is modified by an alkylamino group, a benzyl group, an amino group, or an aminoethylamino group, said alkylamino group, benzyl group, amino group, and aminoethylamino group having 1 - 30 carbons.

18. A polypeptide selected from the group consisting of:

(A) a SRIF28 consisting of the amino acid sequence of SEQ ID NO:2;

(B) a polypeptide having one to three amino acids deleted from, substituted with, or added to SRIF28, SRIF28 consisting of the amino acid sequence of SEQ ID NO:2;

(D) a polypeptide having 80% or more homology with SRIF28 consisting of the amino acid sequence of SEQ ID NO:2;

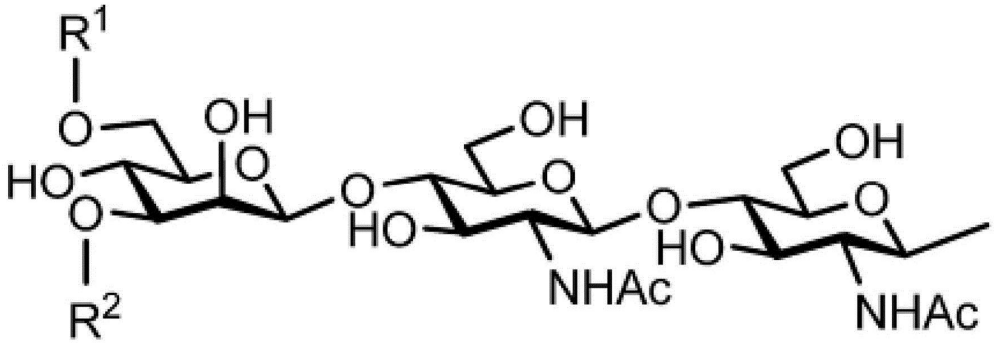
(E) a polypeptide further comprising J amino acids at the N-terminal side of (A) - (D), wherein J is an integer from 1 or more to 6 or less; and

(F) a polypeptide further comprising K amino acids at the C-terminal side of (A) - (D), wherein K is an integer from 1 or more to 6 or less;

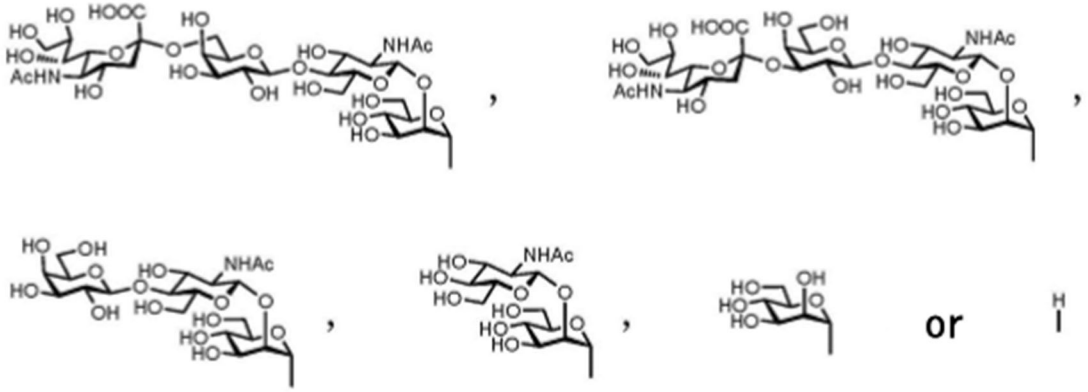
wherein at least two amino acids are substituted with glycosylated amino acids, and the polypeptide has affinity towards somatostatin receptors,

wherein each of said glycosylated amino acids comprises a sugar chain represented by the following formula:

[Chemical Formula 1]



wherein R^1 and R^2 are identical or different and are:
[Chemical Formula 2]



, and
Ac is an acetyl group.

19. A polypeptide selected from the group consisting of:

(A) a SRIF28 consisting of the amino acid sequence of SEQ ID NO:2;

(B) a polypeptide having one to three amino acids deleted from, substituted with, or added to SRIF28, SRIF28 consisting of the amino acid sequence of SEQ ID NO:2;

(D) a polypeptide having 80% or more homology with SRIF28 consisting of the amino acid sequence of SEQ ID NO:2;

(E) a polypeptide further comprising J amino acids at the N-terminal side of (A) - (D), wherein J is an integer from 1 or more to 6 or less; and

(F) a polypeptide further comprising K amino acids at the C-terminal side of (A) - (D), wherein K is an integer from 1 or more to 6 or less;
wherein at least two amino acids are substituted with glycosylated amino acids, and the polypeptide has affinity towards somatostatin receptors,

wherein said glycosylated polypeptide comprises a sugar chain comprising at least one sialic acid at the non-reducing terminus, and said sialic acid comprises a carboxy group that is modified by an alkylamino group, a benzyl group, an amino group, or an aminoethylamino group, said alkylamino group, benzyl group, amino group, and aminoethylamino group having 1 - 30 carbons.

20. A glycosylated polypeptide, selected from the group consisting of SEQ ID NOs: 21-26, 29, 30, 33, 34, 88, 89, 125, 127, 129, 148, 149, 157, 164 and 169.