

waste accumulates in the body due to impaired kidney function, resulting in high blood pressure, anemia, weakened bones, nerve damage, *etc.*, and an increased risk of cardiovascular disease.

Such chronic renal disease is a progressive disease and is difficult to recognize in the early stages, and therefore, early diagnosis through examination is important. When the treatment time is delayed, it progresses to chronic renal failure, requiring dialysis or a kidney transplant.

Treatment of chronic renal disease consists of reducing risk factors and maintaining or restoring kidney function. In particular, hypertension is closely related to chronic renal disease, as it is known that in 60% of patients, chronic renal disease is accompanied by high blood pressure. Therefore, studies are being conducted on treatment of chronic renal disease using antihypertensive drugs, and treatment methods of using angiotensin converting enzyme inhibitors, angiotensin receptor blockers, *etc.* are being studied. However, upon administration of known antihypertensive drugs, side effects such as abnormal renal function, hyperkalemia, and ischemic renal injury have also been reported.

Accordingly, efforts have been made to develop new therapeutic agents and therapies for chronic renal disease by lowering blood pressure and restoring renal function.

【Summary】

In one aspect, provided herein is a use of of a pharmaceutical composition in the manufacture of a medicament for preventing or treating chronic renal disease, the pharmaceutical composition comprising a glucagon derivative and a pharmaceutically acceptable excipient,

wherein the glucagon derivative is a peptide including an amino acid sequence of the following General Formula 1:

X1-X2-QGTF-X7-SD-X10-S-X12-X13-X14-X15-X16-X17-X18-X19-X20-X21-F-X23-X24-W-L-X27-X28-X29-X30 (General Formula 1, SEQ ID NO: 46)

wherein X1 is tyrosine (Y);

X2 is *alpha*-methyl-glutamic acid (α -methyl-glutamic acid), aminoisobutyric acid (Aib), D-alanine, glycine (G), *N*-methylglycine (Sar), serine (S), or D-serine;

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);
X12 is lysine (K) or cysteine (C);
X13 is tyrosine (Y) or cysteine (C);
X14 is leucine (L) or cysteine (C);
X15 is aspartic acid (D), glutamic acid (E), or cysteine (C);
X16 is glutamic acid (E), aspartic acid (D), serine (S), *alpha*-methyl-glutamic acid, or cysteine (C), or is absent;
X17 is aspartic acid (D), glutamine (Q), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V), or is absent;
X18 is alanine (A), aspartic acid (D), glutamic acid (E), arginine (R), valine (V), or cysteine (C), or is absent;
X19 is alanine (A), arginine (R), serine (S), valine (V), or cysteine (C), or is absent;
X20 is lysine (K), histidine (H), glutamine (Q), aspartic acid (D), arginine (R), *alpha*-methyl-glutamic acid, or cysteine (C), or is absent;
X21 is aspartic acid (D), glutamic acid (E), leucine (L), valine (V), or cysteine (C), or is absent;
X23 is isoleucine (I), valine (V), or arginine (R), or is absent;
X24 is valine (V), arginine (R), alanine (A), cysteine (C), glutamic acid (E), lysine (K), glutamine (Q), *alpha*-methyl-glutamic acid, or leucine (L), or is absent;
X27 is isoleucine (I), valine (V), alanine (A), lysine (K), methionine (M), glutamine (Q), or arginine (R), or is absent;
X28 is glutamine (Q), lysine (K), asparagine (N), or arginine (R), or is absent;
X29 is threonine (T); and
X30 is cysteine (C), or is absent
(with the proviso that when the amino acid sequence of General Formula 1 is identical to SEQ ID NO: 1 or SEQ ID NO: 12, it is excluded).

【Disclosure】

【Technical Problem】

It is necessary that new therapeutic agents and therapies be developed for chronic renal disease by lowering blood pressure and restoring renal function.

【Technical Solution】

An object of the present disclosure is to provide a pharmaceutical composition for preventing or treating chronic renal disease (chronic kidney disease), the pharmaceutical composition including a glucagon derivative or a conjugate thereof.

Another object of the present disclosure is to provide a method of preventing or treating chronic renal disease, the method including the step of administering the glucagon derivative or conjugate thereof; or the composition including the same.

[CLAIMS]

1. Use of a pharmaceutical composition in the manufacture of a medicament for preventing or treating chronic renal disease, the pharmaceutical composition comprising a glucagon derivative and a pharmaceutically acceptable excipient,

wherein the glucagon derivative is a peptide including an amino acid sequence of the following General Formula 1:

X1–X2–QGTF–X7–SD–X10–S–X12–X13–X14–X15–X16–X17–X18–X19–
X20–X21–F–X23–X24–W–L–X27–X28–X29–X30 (General Formula 1, SEQ ID NO: 46)

wherein X1 is tyrosine (Y);

X2 is *alpha*-methyl-glutamic acid (α -methyl-glutamic acid), aminoisobutyric acid (Aib), D-alanine, glycine (G), *N*-methylglycine (Sar), serine (S), or D-serine;

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y) or cysteine (C);

X12 is lysine (K) or cysteine (C);

X13 is tyrosine (Y) or cysteine (C);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D), glutamic acid (E), or cysteine (C);

X16 is glutamic acid (E), aspartic acid (D), serine (S), *alpha*-methyl-glutamic acid, or cysteine (C), or is absent;

X17 is aspartic acid (D), glutamine (Q), glutamic acid (E), lysine (K), arginine (R), serine (S), cysteine (C), or valine (V), or is absent;

X18 is alanine (A), aspartic acid (D), glutamic acid (E), arginine (R), valine (V), or cysteine (C), or is absent;

X19 is alanine (A), arginine (R), serine (S), valine (V), or cysteine (C), or is absent;

X20 is lysine (K), histidine (H), glutamine (Q), aspartic acid (D), arginine (R), *alpha*-methyl-glutamic acid, or cysteine (C), or is absent;

X21 is aspartic acid (D), glutamic acid (E), leucine (L), valine (V), or cysteine (C), or is absent;

X23 is isoleucine (I), valine (V), or arginine (R), or is absent;

X24 is valine (V), arginine (R), alanine (A), cysteine (C), glutamic acid (E), lysine (K), glutamine (Q), *alpha*-methyl-glutamic acid, or leucine (L), or is absent;

X27 is isoleucine (I), valine (V), alanine (A), lysine (K), methionine (M), glutamine (Q), or arginine (R), or is absent;

X28 is glutamine (Q), lysine (K), asparagine (N), or arginine (R), or is absent;

X29 is threonine (T); and

X30 is cysteine (C), or is absent

(with the proviso that when the amino acid sequence of General Formula 1 is identical to SEQ ID NO: 1 or SEQ ID NO: 12, it is excluded).

2. The use of claim 1, wherein the peptide is in the form of a long-acting conjugate, which is represented by the following Formula 1:

[Formula 1]

X–L–F

wherein X represents a peptide including the amino acid sequence of General Formula 1;

L represents a linker containing ethylene glycol repeating units;

F represents an immunoglobulin Fc region; and

– represents covalent linkages between X and L and between L and F, respectively.

3. The use of claim 1 or 2, wherein, in General Formula 1,

X2 is aminoisobutyric acid (Aib);

X7 is threonine (T), valine (V), or cysteine (C);

X10 is tyrosine (Y);

X12 is lysine (K);

X13 is tyrosine (Y);

X14 is leucine (L) or cysteine (C);

X15 is aspartic acid (D);

X16 is glutamic acid (E) or serine (S);

X17 is lysine (K), arginine (R), or cysteine (C);

X18 is arginine (R);

X19 is alanine (A) or cysteine (C);

X20 is glutamine (Q) or lysine (K);

X21 is aspartic acid (D) or glutamic acid (E);

X23 is valine (V);

X24 is glutamine (Q);
X27 is methionine (M);
X28 is asparagine (N);
X29 is threonine (T); and
X30 is cysteine (C) or is absent.

4. The use of claim 1, wherein the peptide includes an amino acid sequence selected from the group consisting of SEQ ID NOS: 7 to 11, and 13 to 25, 27, 29, 31, 33, and 35 to 45.

5. The use of claim 3, wherein the peptide includes an amino acid sequence selected from the group consisting of SEQ ID NOS: 20, 22, 23, 27, 33, 35, 37, 38, 40, 41, 42, and 44.

6. The use of claim 1 or 2, wherein the composition exhibits one or more of the following characteristics of:

- (a) lowering the blood pressure;
- (b) reducing albumin excretion;
- (c) reducing proteinuria; and
- (d) restoring the renal function.

7. The use of claim 1 or 2, wherein the pharmaceutical composition exhibits effects of lowering the blood pressure and restoring the renal function in a subject, when administered to the subject.

8. The use of claim 1 or 2, wherein the C-terminus of the peptide is amidated.

9. The use of claim 1 or 2, wherein the peptide has a ring formed between amino acid residues.

10. The use of claim 2, wherein the immunoglobulin Fc region is aglycosylated.

11. The use of claim 2, wherein the immunoglobulin Fc region is an IgG4 Fc region.

12. The use of claim 2, wherein the immunoglobulin Fc region is a dimer consisting of two polypeptide chains, and one end of L is linked to only one polypeptide chain of the two polypeptide chains.

13. The use of claim 2, wherein, in the long-acting conjugate, L is linked to F and X by covalent linkages formed by reacting one end of L with an amine group or a thiol group of F and by reacting the other end of L with an amine group or a thiol group of X, respectively.

14. The use of claim 2, wherein L is polyethylene glycol.

15. The use of claim 2, wherein the formula weight of a moiety of the ethylene glycol repeating units in L is in the range of 1 kDa to 100 kDa.

16. The use of claim 1 or 2, wherein the pharmaceutical composition further comprises a GLP-1 receptor agonist (glucagon-like peptide 1 receptor agonist).

17. The use of claim 16, wherein the GLP-1 receptor agonist is selected from the group consisting of GLP-1, exendin-3, exendin-4, agonists thereof, derivatives thereof, fragments thereof, variants thereof, and combinations thereof.

18. The use of claim 16, wherein the GLP-1 receptor agonist is a GLP-1 receptor agonist derivative in which the N-terminal histidine residue is substituted with a substance selected from the group consisting of des-amino-histidyl, dimethyl-histidyl, *beta*-hydroxy imidazopropionyl, 4-imidazoacetyl, and *beta*-carboxy imidazopropionyl.

19. The use of claim 16, wherein the GLP-1 receptor agonist is selected from the group consisting of a native exendin-4, an exendin-4 derivative in which the N-terminal amine group of exendin-4 is deleted, an exendin-4 derivative in which the N-terminal amine group of exendin-4 is substituted with a hydroxyl group, an exendin-4 derivative in which the N-terminal amine group of exendin-4 is modified with a dimethyl group, and an exendin-4 derivative in which the *alpha*-carbon of a first amino acid (histidine) of exendin-4 is deleted.

20. The use of claim 16, wherein the GLP-1 receptor agonist is in the form of a long-acting conjugate, in which the GLP-1 receptor agonist is linked to the immunoglobulin Fc region.

21. The use of claim 20, wherein the GLP-1 receptor agonist is an imidazo-acetyl exendin-4 (CA exendin-4) linked to the immunoglobulin Fc region via a linker containing ethylene glycol repeating units.