Non Patent Literature 9: Watanabe, T.X. et al., Vasopressor activities of N-terminal fragments of adrenomedullin in anesthetized rat. Biochem Biophys Res Commun, 1996, Volume 219, Issue 1, p. 59-63.

Non Patent Literature 10: Kubo, K et al., Biological properties of adrenomedullin conjugated with polyethylene glycol. Peptides, 2014, Volume 57, p. 118-21.

Non Patent Literature 11: Kato, J., Kitamura, K.. Bench-to-bedside pharmacology of adrenomedullin. European Journal of Pharmacology, 2015, Volume 764, p. 140-148.

SUMMARY

TECHNICAL PROBLEM

[0014] As described above, AM derivatives in which other groups such as a PEG group are linked to AM are known in order to improve the pharmacokinetics of AM from the viewpoint of improvement in sustainability in a living body. However, known AM derivatives are susceptible to improvement. For example, in the case of linking a relatively large group such as a PEG group to a relatively small peptide such as AM, various properties of the resulting AM derivative may vary largely depending on the molecular weight of the PEG group. As described in Patent Literatures 4 and 5 and Non Patent Literature 10, when a peptide moiety and other groups are linked through a bond which may be cleaved by a biological reaction, such as an amide bond or an ester bond, the bond may be cleaved in a relatively short time after administration. As in the AM derivative described in Patent Literature 5, in the case of linking other groups to the side chain of an amino acid residue of AM, the conformation of the AM moiety may be changed to reduce the affinity for an AM receptor recognizing AM. In such a case, pharmacological effects as AM of the resulting AM derivative may be reduced.

[0015] AM has a strong vasodilatory effect, in addition to pharmacological effects such as a cardiovascular protective effect, an anti-inflammatory effect, an angiogenic effect, and a tissue repair promoting effect. This strong vasodilatory effect may cause unwanted side effects such as excessive decreased blood pressure when AM or an AM derivative is administered to subjects. The occurrence of such side effects may become a problem when AM or an AM

derivative is used, particularly, in the expectation that pharmacological effects other than a vasodilatory effect are exerted.

[0016] The disclosure, therefore, is intended to provide novel adrenomedullin derivatives sustainable for a long period which are capable of substantially suppressing unwanted side effects while maintaining pharmacological effects of adrenomedullin.

SOLUTION TO PROBLEM

[0017] The present inventors conducted various investigations of means to solve the problems described above. The present inventors have found that linking of the N-terminal α-amino group of adrenomedullin to a PEG group with a specific molecular weight via a methylene group or a urethane group can prolong blood half-life of the resulting adrenomedullin derivative as compared to adrenomedullin while retaining bioactivity at the same level as in adrenomedullin. Furthermore, the present inventors have found that novel adrenomedullin derivatives having the properties described above are capable of substantially suppressing unwanted side effects such as excessive decreased blood pressure. The present inventors have achieved the disclosure based on the finding described above.

[0017a] In one aspect, there is provided a compound represented by formula (I):

$A\text{-}CH_2\text{-}B$ (I)

wherein

A is a modifying group comprising one or more polyethylene glycol groups, and

B is a peptide moiety derived from adrenomedullin or a modified form thereof with adrenomedullin activity,

wherein the peptide moiety B is linked to the other moieties through a covalent bond of the nitrogen atom of the N-terminal α-amino group of the peptide moiety B to the carbon atom of the methylene group,

or a salt thereof, or a hydrate thereof.

[0017b] In another aspect, there is provided a method for producing the compound as defined herein or a salt thereof, or a hydrate thereof, comprising a linking step of reacting a precursor of peptide moiety B derived from adrenomedullin or a modified form thereof with a precursor

aldehyde of modifying group A comprising one or more polyethylene glycol groups in the presence of a reducing agent to form the compound represented by formula (I), wherein the precursor aldehyde is represented by formula (I-1):

A-CHO (I-1).

[0017c] In another aspect, there is provided a pharmaceutical composition comprising the compound as defined herein or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof and one or more pharmaceutically acceptable carriers.

[0017d] In another aspect, there is provided the pharmaceutical composition as defined herein for use in therapy.

[0017e] In another aspect, there is provided use of the compound as defined herein or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof for manufacturing a medicament for the prevention or treatment of a cardiovascular disease, an inflammatory disease, or a peripheral vascular disease.

[0018] That is to say, the embodiment of the present disclosure is as the following:

(1) A compound represented by formula (I):

A-CH_2-B (I)

wherein

A is a modifying group comprising one or more polyethylene glycol groups, and

B is a peptide moiety derived from adrenomedullin or a modified form thereof with adrenomedullin activity,

wherein the peptide moiety B is linked to the other moieties through a covalent bond of the nitrogen atom of the N-terminal α-amino group of the peptide moiety B to the carbon atom of the methylene group,

or a salt thereof, or a hydrate thereof.

(2) The compound according to the embodiment (1), wherein A is a modifying group represented by the following formula (II):

embodiments (1) to (10) and (12) or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof.

(19) The method according to the embodiment (18) wherein the condition, disease, and/or disorder is a cardiovascular disease, an inflammatory disease, or a peripheral vascular disease.

(20) The compound according to any of the embodiments (1) to (10) and (12) or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof for use in the prevention or treatment of a condition, disease, and/or disorder.

(21) The compound according to the embodiment (20) wherein the condition, disease, and/or disorder is a cardiovascular disease, an inflammatory disease, or a peripheral vascular disease.

(22) Use of the compound according to any of the embodiments (1) to (10) and (12) or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof for manufacturing a medicament for the prevention or treatment of a condition, disease, and/or disorder.

(23) The use according to the embodiment (22) wherein the condition, disease, and/or disorder is a cardiovascular disease, an inflammatory disease, or a peripheral vascular disease.

ADVANTAGEOUS EFFECTS OF INVENTION

[0019] The disclosure provides novel adrenomedullin derivatives sustainable for a long period which are capable of substantially suppressing unwanted side effects while maintaining pharmacological effects of adrenomedullin.

[0020] The present specification includes contents described in the specification and/or drawings of Japanese patent application No. 2015-184685 to which the present application claims priority.

BRIEF DESCRIPTION OF DRAWINGS

[0021]

R^1, $R^{1'}$, $R^{1''}$ and $R^{1'''}$ are each independently hydrogen, substituted or unsubstituted C_1-C_{20} alkyl, substituted or unsubstituted C_2-C_{20} alkenyl, substituted or unsubstituted C_2-C_{20} alkynyl, substituted or unsubstituted C_3-C_{20} cycloalkyl, substituted or unsubstituted C_4-C_{20} cycloalkenyl, substituted or unsubstituted C_4-C_{20} cycloalkynyl, substituted or unsubstituted 3- to 6-membered heterocycloalkyl, substituted or unsubstituted C_7-C_{20} cycloalkylalkyl, substituted or unsubstituted 3- to 6-membered heterocycloalkyl-C_1-C_{20} alkyl, substituted or unsubstituted C_4-C_{20} aryl, substituted or unsubstituted C_5-C_{20} arylalkyl, substituted or unsubstituted 5- to 15-membered heteroaryl, substituted or unsubstituted 5- to 15-membered heteroaryl-C_1-C_{20} alkyl, or substituted or unsubstituted acyl,

R^2 is a bond, substituted or unsubstituted C_1-C_{20} alkylene, substituted or unsubstituted C_2-C_{20} alkenylene, substituted or unsubstituted C_2-C_{20} alkynylene, substituted or unsubstituted C_3-C_{20} cycloalkylene, substituted or unsubstituted C_4-C_{20} cycloalkenylene, substituted or unsubstituted C_4-C_{20} cycloalkynylene, substituted or unsubstituted 3- to 6-membered heterocycloalkylene, substituted or unsubstituted C_7-C_{20} cycloalkylalkylene, substituted or unsubstituted 3- to 6-membered heterocycloalkyl-C_1-C_{20} alkylene, substituted or unsubstituted C_4-C_{20} arylene, substituted or unsubstituted C_5-C_{20} arylalkylene, substituted or unsubstituted 5- to 15-membered heteroarylene, or substituted or unsubstituted 5- to 15-membered heteroaryl-C_1-C_{20} alkylene (the divalent hydrocarbon groups optionally comprise one or more heteroatoms, an amide group (-CO-NH-), an ester group (-CO-O-), or a urethane group (-O-CO-NH-)), an amide group (-CO-NH-), an ester group (-CO-O-), or a urethane group (-O-CO-NH-),

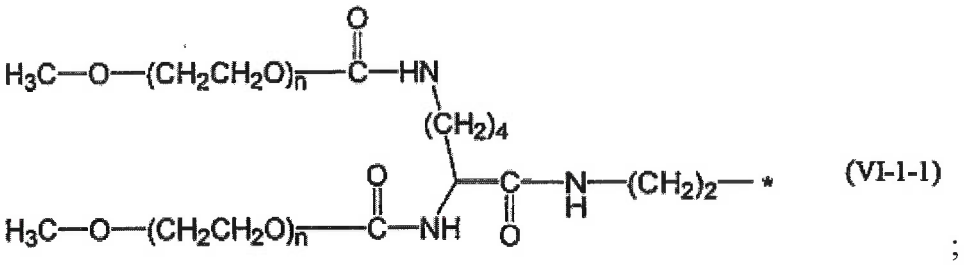
R^3, $R^{3'}$ and $R^{3''}$ are each independently a bond, substituted or unsubstituted C_1-C_{20} alkylene, substituted or unsubstituted C_2-C_{20} alkenylene, substituted or unsubstituted C_2-C_{20} alkynylene, substituted or unsubstituted C_3-C_{20} cycloalkylene, substituted or unsubstituted C_4-C_{20} cycloalkenylene, substituted or unsubstituted C_4-C_{20} cycloalkynylene, substituted or unsubstituted 3- to 6-membered heterocycloalkylene, substituted or unsubstituted C_7-C_{20} cycloalkylalkylene, substituted or unsubstituted 3- to 6-membered heterocycloalkyl-C_1-C_{20} alkylene, substituted or unsubstituted C_4-C_{20} arylene, substituted or unsubstituted C_5-C_{20} arylalkylene, substituted or unsubstituted 5- to 15-membered heteroarylene, or substituted or unsubstituted 5- to 15-membered heteroaryl-C_1-C_{20} alkylene (the divalent hydrocarbon groups optionally comprise

one or more heteroatoms, an amide group (-CO-NH-), an ester group (-CO-O-), or a urethane group (-O-CO-NH-)), an amide group (-CO-NH-), an ester group (-CO-O-), or a urethane group (-O-CO-NH-), wherein when a plurality of R^3, $R^{3'}$ or $R^{3''}$ are present, the plurality of R^3, $R^{3'}$ or $R^{3''}$ are the same as or different from each other, and

* is a binding position to the other moieties.

4. The compound according to any one of claims 1-3, wherein A is a modifying group represented by the following formula (V-1-1), (VI-1-1), (VII-1-1), (VII-1-2), (VII-2-1), or (VIII-1-1):


(V-1-1)
;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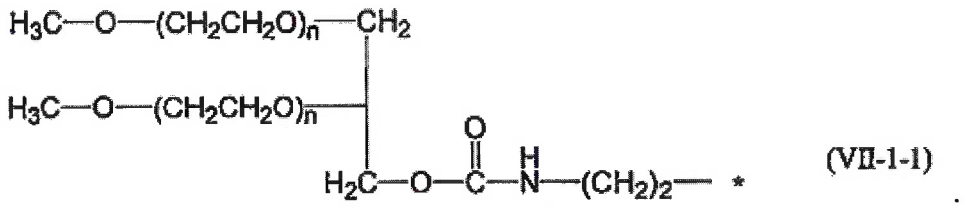
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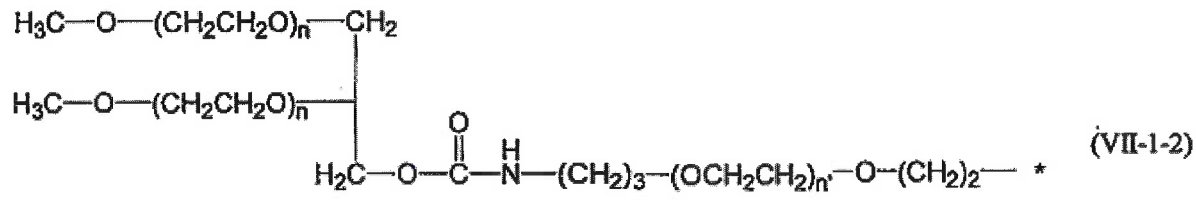
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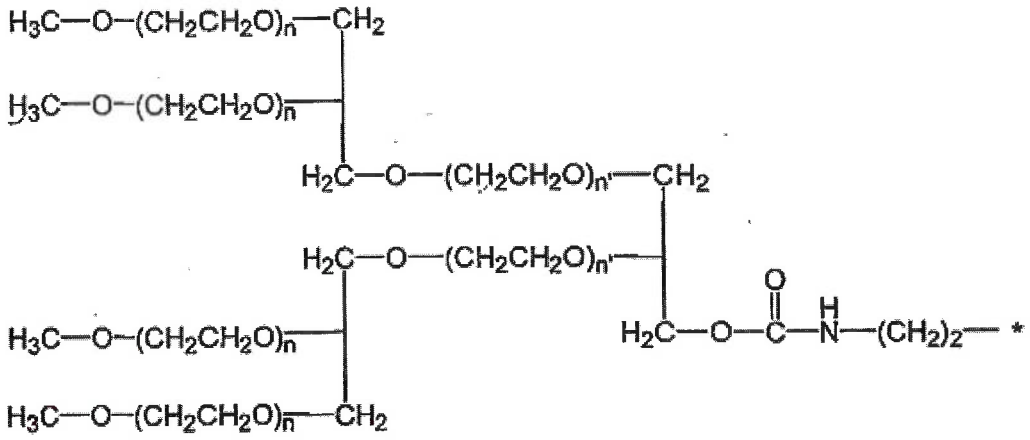

(VII-2-1)

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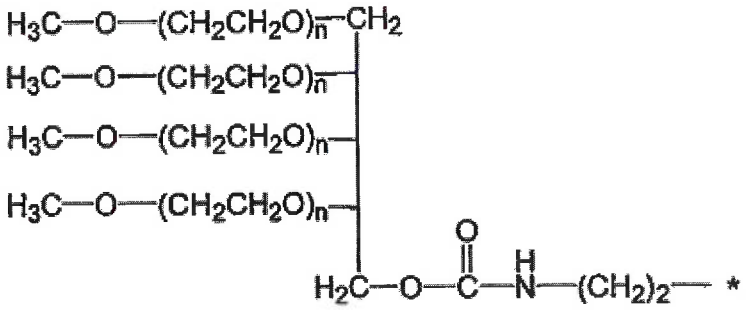

(VIII-1-1)

,

wherein

n is as defined claim 2 or 3,

n' is as defined above about n, and

* is a binding position to the other moieties.

5. The compound according to any one of claims 1 to 4, wherein the polyethylene glycol group represented by formula (III) has a weight-average molecular weight ranging from 1 to 100 kDa in total.

6. The compound according to any one of claims 1 to 5, wherein the adrenomedullin or the modified form thereof with adrenomedullin activity is a peptide selected from the group consisting of:

(i) a peptide consisting of an amino acid sequence of adrenomedullin,

(ii) a peptide that consists of an amino acid sequence of adrenomedullin and has a disulfide bond formed by two cysteine residues in the amino acid sequence,

(iii) the peptide of (ii) wherein the disulfide bond of the peptide is substituted with an ethylene group and the peptide has adrenomedullin activity,

(iv) any peptide of (i) to (iii) wherein the peptide has the amino acid sequence comprising deletion, substitution, or addition of one to fifteen amino acid residues and has adrenomedullin activity,

(v) any peptide of (i) to (iv) wherein the peptide is amidated at the C-terminus thereof, and

(vi) any peptide of (i) to (iv) wherein the peptide has a glycine residue added to the C-terminus thereof.

7. The compound according to claim 6, wherein the adrenomedullin or the modified form thereof is a peptide selected from the group consisting of:

(i) a peptide consisting of an amino acid sequence of adrenomedullin,

(ii) a peptide that consists of an amino acid sequence of adrenomedullin and has a disulfide bond formed by two cysteine residues in the amino acid sequence,

(v) the peptide of (i) or (ii) wherein the peptide is amidated at the C-terminus thereof, and

(vi) the peptide of (i) or (ii) wherein the peptide has a glycine residue added to the C-terminus thereof.

8. The compound according to claim 6, wherein the adrenomedullin or the modified form thereof is a peptide selected from the group consisting of:

(iv') any peptide of (i) to (iii) wherein the peptide has deletion of amino acid residues at positions 1 to 15, positions 1 to 10, or positions 1 to 5 from the N-terminus thereof and has adrenomedullin activity,

(v) the peptide of (iv') wherein the peptide is amidated at the C-terminus thereof, and

(vi) the peptide of (iv') wherein the peptide has a glycine residue added to the C-terminus thereof.

7. The compound according to any one of claims 1 to 6, wherein the adrenomedullin or the modified form thereof is a peptide selected from the group consisting of:

(a) a peptide consisting of the amino acid sequence of SEQ ID NO: 1, or a peptide consisting of the amino acid sequence of SEQ ID NO: 1 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(b) a peptide consisting of the amino acid sequence of the SEQ ID NO: 3, or a peptide consisting of the amino acid sequence of the SEQ ID NO: 3 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(c) a peptide consisting of the amino acid sequence of SEQ ID NO: 5, or a peptide consisting of the amino acid sequence of SEQ ID NO: 5 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(d) a peptide consisting of the amino acid sequence of SEQ ID NO: 7, or a peptide consisting of the amino acid sequence of SEQ ID NO: 7 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(e) a peptide consisting of the amino acid sequence of SEQ ID NO: 9, or a peptide consisting of the amino acid sequence of SEQ ID NO: 9 and having a disulfide bond formed by the cysteine residues at positions 14 and 19;

(f) a peptide consisting of the amino acid sequence of SEQ ID NO: 11, or a peptide consisting of the amino acid sequence of SEQ ID NO: 11 and having a disulfide bond formed by the cysteine residues at positions 14 and 19;

(g) any peptide of (a) to (f) wherein the disulfide bond of the peptide is substituted with an ethylene group and the peptide has adrenomedullin activity;

(h) any peptide of (a) to (g) wherein the peptide has the amino acid sequence comprising deletion, substitution, or addition of one to fifteen amino acids and has adrenomedullin activity;

(i) any peptide of (a) to (h) wherein the peptide is amidated at the C-terminus thereof; and

(j) any peptide of (a) to (h) wherein the peptide has a glycine residue added to the C-terminus thereof.

10. The compound according to claim 9, wherein the adrenomedullin or the modified form thereof is a peptide selected from the group consisting of:

(a) a peptide consisting of the amino acid sequence of SEQ ID NO: 1, or a peptide consisting of the amino acid sequence of SEQ ID NO: 1 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(b) a peptide consisting of the amino acid sequence of SEQ ID NO: 3, or a peptide consisting of the amino acid sequence of SEQ ID NO: 3 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(c) a peptide consisting of the amino acid sequence of SEQ ID NO: 5, or a peptide consisting of the amino acid sequence of SEQ ID NO: 5 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(d) a peptide consisting of the amino acid sequence of SEQ ID NO: 7, or a peptide consisting of the amino acid sequence of SEQ ID NO: 7 and having a disulfide bond formed by the cysteine residues at positions 16 and 21;

(e) a peptide consisting of the amino acid sequence of SEQ ID NO: 9, or a peptide consisting of the amino acid sequence of SEQ ID NO: 9 and having a disulfide bond formed by the cysteine residues at positions 14 and 19;

(f) a peptide consisting of the amino acid sequence of SEQ ID NO: 11, or a peptide consisting of the amino acid sequence of SEQ ID NO: 11 and having a disulfide bond formed by the cysteine residues at positions 14 and 19;

(i) any peptide of (a) to (f) wherein the peptide is amidated at the C-terminus thereof; and

(j) any peptide of (a) to (f) wherein the peptide has a glycine residue added to the C-terminus thereof.

11. The compound according to claim 9, wherein the adrenomedullin or the modified form thereof is a peptide selected from the group consisting of:

(h') any peptide of (a) to (d) wherein the peptide has deletion of amino acid residues at positions 1 to 15, positions 1 to 10, or positions 1 to 5 from the N-terminus thereof and has adrenomedullin activity, or the peptide of (e) or (f) wherein the peptide has deletion of amino acid residues at positions 1 to 13, positions 1 to 8, or positions 1 to 5 from the N-terminus thereof and has adrenomedullin activity;

(i) the peptide of (h') wherein the peptide is amidated at the C-terminus thereof; and

(j) the peptide of (h') wherein the peptide has a glycine residue added to the C-terminus thereof.

12. A method for producing the compound according to any one of claims 1 to 11 or a salt thereof, or a hydrate thereof, comprising a linking step of reacting a precursor of peptide moiety B derived from adrenomedullin or a modified form thereof with a precursor aldehyde of modifying group A comprising one or more polyethylene glycol groups in the presence of a reducing agent to form the compound represented by formula (I), wherein the precursor aldehyde is represented by formula (I-1):

A-CHO (I-1).

13. A pharmaceutical composition comprising the compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof and one or more pharmaceutically acceptable carriers.

14. The pharmaceutical composition of claim 13 for use in therapy.

15. Use of the compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable hydrate thereof for manufacturing a medicament for the prevention or treatment of a cardiovascular disease, an inflammatory disease, or a peripheral vascular disease.

LONG-ACTING ADRENOMEDULLIN DERIVATIVE

ABSTRACT

The invention provides a novel adrenomedullin derivative sustainable for a long period which is capable of substantially suppressing unwanted side effects while maintaining pharmacological effects of adrenomedullin. In an exemplary embodiment, the invention relates to a compound represented by formula (I): A-CH_2-B (I) [wherein A is a modifying group comprising one or more polyethylene glycol groups, and B is a peptide moiety derived from adrenomedullin or a modified form thereof with adrenomedullin activity, wherein the peptide moiety B is linked to the other moieties through a covalent bond of the nitrogen atom of the N-terminal α-amino group of the peptide moiety B to the carbon atom of the methylene group] or a salt thereof, or a hydrate thereof.

[No suitable fig.]