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A V2 inhibitor (Tolvaptan) acting as an aquaretic (*i.e.*, a diuretic without natriuresis) had been approved for the treatment of hypervolemic and euvolemic hyponatremia (*i.e.*, serum sodium of 125 mEq/L or less marked hyponatremia), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). Because Tolvaptan is hepatotoxic, it is contraindicated for patient with cirrhosis, hepatorenal, and portal hypertension ascites. *See*, drug warning label for tolvaptan, available at www.accessdata.fda.gov/drugsatfda_docs/label/2018/204441lbl.pdf. Therefore, any innovation that will lower the dose of this medication to avoid hepatotoxicity while improving efficacy will contribute significantly to the long-sought desire to improve treatment of patients with cirrhosis, hepatorenal, and portal hypertension-induced ascites and varices.

There is a need for a V1a receptor agonist that avoids or minimizes the drawbacks or limitations of terlipressin. The V1a receptor agonist should target vascular hydrodynamic imbalance in general, such as blood pressure, blood volume, and electrolyte imbalance seen, for example, in cirrhosis, portal hypertension, bleeding, ascites, sepsis, and hepatorenal syndrome. The therapeutic agent can be 1) a V1a agonist that can be repeatedly administered subcutaneously without causing injection site necrosis, 2) a V1a agonist that limits its activity even at high dose (*i.e.*, a partial agonist

of V1a) such that it will not activate the receptor to its maximum potential, thereby limiting organ ischemia side effects (and thereby having very high therapeutic index), and/or 3) a V1a agonist that does not have significant V2 activity or antidiuretic activity *in vivo*. The present disclosure seeks to fulfill these needs and provides further advantages.

SUMMARY

This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary is not intended to identify key features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

In one aspect, the present disclosure refers to a composition, comprising:

a V1a partial agonist peptide of Formula (A)

[Mpa-Tyr-Phe-Z-Asn-Cys-Pro-B(X)a-Gly-NH2] [SEQ ID NOS. 1-2]

(A)

or a pharmaceutically effective salt thereof,

wherein:

the Mpa and Cys residues are covalently connected with a disulfide bond,

Z is Hgn or Gln;

wherein when Z is Hgn [SEQ ID NO. 1]:

B is any one of L-Lys, D-Lys, L-Orn, D-Orn, L-Dab, D-Dab, L-Dap, or D-Dap, and

X is an amino acid residue pendant to R group of B, wherein the amino acid residue is independently selected at each occurrence from Gly, L-Ala, D-Ala, L-Lys, D-Lys, L-Orn, D-Orn, L-Glu, D-Glu, L-Asp, and D-Asp, and a is an integer from 0 to 10, or

X is a moiety derived from a non-alpha primary amino group-containing C3-12 fatty acid pendant to the R group of B, and a is an integer from 1 to 3;

wherein when Z is Gln [SEQ ID NO. 2]:

B is any one of L-Lys, D-Lys, L-Orn, D-Orn, L-Dab, D-Dab, L-Dap, or D-Dap, and

X is an amino acid residue pendant to the R group of B, wherein the amino acid residue is independently selected at each occurrence from Gly, L-Ala, D-Ala, L-Lys, D-Lys, L-Orn, D-Orn, L-Glu, D-Glu, L-Asp, and D-Asp, and a is an integer from 6 to 10, or

X is a moiety derived from a non-alpha primary amino group-containing C3-12 fatty acid pendant to R group of B, and a is an integer from 1 to 3; and

wherein the composition has a therapeutic index of at least 20.

In another aspect, the present disclosure refers to a use of the composition as described herein in the manufacture of a medicament for treating a subject,

wherein the composition is to be administered to a subject in need thereof in a therapeutically effective dose,

wherein the subject has a condition selected from liver fibrosis, cirrhosis, portal hypertension, ascites, esophageal varices, fundal varices, bleeding, arterial hypotension, hepatorenal syndrome, and any combination thereof, or

wherein the subject has liver fibrosis; or

wherein the subject has cirrhosis; or

wherein the subject has portal hypertension; or

wherein the subject has ascites; or

wherein the subject has refractory ascites; or

wherein the subject has esophageal varices; or

wherein the subject has gastric varices in the fundal region; or

wherein the subject has bleeding varices; or

wherein the subject has arterial hypotension; or

wherein the subject has hepatorenal syndrome.

In another aspect, the present disclosure refers to a use of a pharmaceutical composition comprising a peptide of Formula (B) in the manufacture of a medicament for treating a subject, wherein the pharmaceutical composition comprising a peptide of Formula (B) is to be administered to a subject in need thereof in a therapeutically effective dose, wherein the pharmaceutical composition is to be administered within 1 to 8 hours, preferably 1 to 3 hours, before or after administration of a therapeutically effective dose of a V2 antagonist, preferably after administration of a therapeutically effective dose of the V2 antagonist, wherein the peptide of Formula (B) is

a V1a agonist peptide of Formula (B)

[X'-Tyr-Phe-Gln-Asn-Cys-Pro- Lys(Z)d-Gly-NH2] [SEQ ID NOS. 3-4]

(B)

or a pharmaceutically acceptable salt thereof,

wherein:

X' is (U)c-Cys or Mpa,

wherein when X' is (U)c-Cys and (Z)d is absent [SEQ ID NO. 3],

the 2 Cys residues are covalently connected with a disulfide bond;

U is an amino acid residue and at each occurrence, is independently selected from Gly, L-Ala, D-Ala, L-Lys, D-Lys, L-Orn, D-Orn, L-Glu, D-Glu, L-Asp, and D-Asp, and c is an integer of from 0 to 10; and

wherein when X' is Mpa [SEQ ID NO. 4],

the Mpa and Cys residues are covalently connected with a disulfide bond,

Z is an amino acid residue pendant to R group of Lys and at each occurrence, is independently selected from Gly, D-Ala, L-Ala, D-Lys, L-Lys, D-Orn, L-Orn, D-Glu, L-Glu, D-Asp, and L-Asp, and d is an integer from 0 to 5,

wherein the subject has a condition selected from liver fibrosis, cirrhosis, portal hypertension, ascites, esophageal varices, fundal varices, bleeding, arterial hypotension, hepatorenal syndrome, and any combination thereof; or

wherein the subject has liver fibrosis; or

wherein the subject has cirrhosis; or

wherein the subject has portal hypertension; or

wherein the subject has esophageal varices; or

wherein the subject has fundal varices; or

wherein the subject has bleeding varices; or

wherein the subject has arterial hypotension; or

wherein the subject has hepatorenal syndrome.

In another aspect, the present disclosure refers to the composition as described herein or a pharmaceutical comprising a peptide of Formula (B) for use in therapy.

In one aspect, the present disclosure features a composition, including a V1a partial agonist peptide of Formula (A)

[Mpa-Tyr-Phe-Z-Asn-Cys-Pro-B$(X)_a$-Gly-NH_2] [SEQ ID NOS. 1-2]

(A)

or a pharmaceutically effective salt thereof,

wherein:

the Mpa and Cys residues are covalently connected with a disulfide bond,

Z is Hgn or Gln;

wherein when Z is Hgn [SEQ ID NO. 1]:

B is any one of L-Lys, D-Lys, L-Orn, D-Orn, L-Dab, D-Dab, L-Dap, or D-Dap, and

X is an amino acid residue, wherein the amino acid residue is independently selected at each occurrence from Gly, L-Ala, D-Ala, L-Lys, D-Lys, L-Orn, D-Orn, L-Glu, D-Glu, L-Asp, and D-Asp, and a is an integer from 0 to 10 (*e.g.*, from 0 to 1, from 1 to 2, from 1 to 3, from 1 to 10, from 1 to 6, from 4 to 10, or from 6 to 10), or

X is a moiety derived from a non-alpha primary amino group-containing C_{3-12} fatty acid (*e.g.*, C_{3-6}, C_{3-10}, C_{4-12}, C_{4-6}, C_{4-10}, C_{6-10}, C_{8-10}, or C_{10-12} fatty acid), and a is an integer from 1 to 3;

wherein when Z is Gln [SEQ ID NO. 2]:

B is any one of L-Lys, D-Lys, L-Orn, D-Orn, L-Dab, D-Dab, L-Dap, or D-Dap, and

d is a number of Z and is 0, and

wherein when X' is Mpa [SEQ ID NO. 4],

the Mpa and Cys residues are covalently connected with a disulfide bond,

Z is an amino acid residue and at each occurrence, is independently selected from Gly, D-Ala, L-Ala, D-Lys, L-Lys, D-Orn, L-Orn, D-Glu, L-Glu, D-Asp, and L-Asp, and

d is an integer from 0 to 5.

In some embodiments, the subject has a condition selected from liver fibrosis, cirrhosis, portal hypertension, ascites, esophageal varices, fundal varices, bleeding, arterial hypotension, hepatorenal syndrome, and any combination thereof; or wherein the subject has liver fibrosis; or wherein the subject has cirrhosis; or wherein the subject has portal hypertension; or wherein the subject has esophageal varices; or wherein the subject has fundal varices; or wherein the subject has bleeding varices; or wherein the subject has arterial hypotension; or wherein the subject has hepatorenal syndrome.

Description of the Drawings

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

The foregoing aspects and many of the attendant advantages of this disclosure will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 is an illustration of the stages of liver fibrosis and cirrhosis.

FIGURE 2 is a graph showing the results of EC50 determination of a Formula (I) peptides [Mpa-Tyr-Phe-Hgn-Asn-Cys-Pro-Lys(X)a-Gly [SEQ ID NO. 5]; with disulfide bond between Mpa and Cys] for V1a receptor. A Formula (I) peptide where "(X)a" has X=~~Lys~~Gly and a=0, 3, 6, or 9 has EC50 of 5.2, 53.5, 45.9, or 104.8 nM for V1a receptor (n=2). It is a partial V1a agonist, with 42.8, 32.9, 28.2, or 28.1% highest agonist effect compared with arginine vasopressin (AVP) which is the 100% control (n=2).

FIGURE 3 is a graph of the EC50 of Formula (II) Peptide [Mpa-Tyr-Phe-Gln-Asn-Cys-Pro-Lys(X)a-Gly [SEQ ID NO. 6]; with disulfide bond between Mpa and Cys];

CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A composition, comprising:

a V1a partial agonist peptide of Formula (A)

[Mpa-Tyr-Phe-Z-Asn-Cys-Pro-B$(X)_a$-Gly-NH_2] [SEQ ID NOS. 1-2]

(A)

or a pharmaceutically effective salt thereof,

wherein:

the Mpa and Cys residues are covalently connected with a disulfide bond,

Z is Hgn or Gln;

wherein when Z is Hgn [SEQ ID NO. 1]:

B is any one of L-Lys, D-Lys, L-Orn, D-Orn, L-Dab, D-Dab, L-Dap, or D-Dap, and

X is an amino acid residue pendant to R group of B, wherein the amino acid residue is independently selected at each occurrence from Gly, L-Ala, D-Ala, L-Lys, D-Lys, L-Orn, D-Orn, L-Glu, D-Glu, L-Asp, and D-Asp, and a is an integer from 0 to 10, or

X is a moiety derived from a non-alpha primary amino group-containing C_{3-12} fatty acid pendant to the R group of B, and a is an integer from 1 to 3;

wherein when Z is Gln [SEQ ID NO. 2]:

B is any one of L-Lys, D-Lys, L-Orn, D-Orn, L-Dab, D-Dab, L-Dap, or D-Dap, and

X is an amino acid residue pendant to the R group of B, wherein the amino acid residue is independently selected at each occurrence from Gly, L-Ala, D-Ala, L-Lys, D-Lys, L-Orn, D-Orn, L-Glu, D-Glu, L-Asp, and D-Asp, and a is an integer from 6 to 10, or

X is a moiety derived from a non-alpha primary amino group-containing C_{3-12} fatty acid pendant to R group of B, and a is an integer from 1 to 3; and

wherein the composition has a therapeutic index of at least 20.

2. The composition of Claim 1, wherein Z is Hgn and B is Lys.

3. The composition of Claim 1, wherein Z is Hgn, X is Gly, and a is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

4. The composition of Claim 3, wherein Z is Hgn, X is Gly, and a is 6, 7, 8, 9, or 10.

5. The composition of Claim 1, wherein Z is Gln and B is L-Lys.

6. The composition of Claim 5, wherein Z is Gln, X is Gly, and a is 6, 7, 8, 9, or 10.

7. The composition of Claim 1, wherein Z is Hgn and B is D-Lys.

8. The composition of Claim 1, wherein Z is Hgn and B is L-Orn.

9. The composition of Claim 1, wherein Z is Hgn and B is D-Orn.

10. The composition of Claim 1, wherein Z is Hgn and B is L-Dab.

11. The composition of Claim 1, wherein Z is Hgn and B is D-Dab.

12. The composition of Claim 1, wherein Z is Hgn and B is L-Dap.

13. The composition of Claim 1, wherein Z is Hgn and B is D-Dap.

14. The composition of any one of the preceding claims, further comprising a pharmaceutically acceptable excipient,

wherein the pharmaceutically acceptable excipient optionally comprises a buffer comprising a buffering pH of from 3.5 to 6.5, and

wherein the buffer is optionally selected from an acetate buffer, a citrate buffer, a succinate buffer, a histidine buffer, or any combination thereof.

15. Use of the composition of any one of Claims 1 to 13 in the manufacture of a medicament for~~A method of~~ treating a subject,~~ comprising:~~

wherein the composition is to be administereding to a subject in need thereof in a therapeutically effective dose of a composition of any one of Claims 1 to 13,

wherein the subject has a condition selected from liver fibrosis, cirrhosis, portal hypertension, ascites, esophageal varices, fundal varices, bleeding, arterial hypotension, hepatorenal syndrome, and any combination thereof, or

wherein the subject has liver fibrosis; or

wherein the subject has cirrhosis; or

wherein the subject has portal hypertension; or

wherein the subject has ascites; or

wherein the subject has refractory ascites; or

wherein the subject has esophageal varices; or

wherein the subject has gastric varices in the fundal region; or

wherein the subject has bleeding varices; or

wherein the subject has arterial hypotension; or

wherein the subject has hepatorenal syndrome.

16. The method use of Claims 15, wherein the composition of any one of Claims 2 to 6 is to be comprising administereding to a subject in need thereof in a therapeutically effective dose of a composition of any one of Claims 2 to 6.

17. The method use of Claim 15, wherein Z is Hgn, B is L-Lys, and X is Gly.

18. The usemethod of Claim 17, wherein a is 6.

19. The method use of Claim 15, wherein Z is Gln and B is L-Lys.

20. The method use of any one of Claims 15 to 19, wherein the subject has cirrhosis and portal hypertension.

21. The method use of any one of Claims 15 to 20, wherein the subject has portal hypertension with a hepatic venous pressure gradient of 5 mm Hg and greater.

22. The ~~method~~ use of any one of Claims 15 to 21, wherein the subject has clinically significant portal hypertension with a hepatic venous pressure gradient of 10 mm Hg and greater.

23. The ~~method~~ use of any one of Claims 15 to 22, wherein the subject has ascites.

24. The ~~method~~ use of any one of Claims 15 to 23, wherein the subject has refractory ascites.

25. The ~~method~~ use of any one of Claims 15 to 24, wherein the subject has varices.

26. The ~~method~~ use of any one of Claims 15 to 25, wherein the subject has variceal bleeding.

27. The ~~method~~ use of any one of Claims 15 to 26, wherein the subject has a mean arterial pressure of below 95 mm Hg.

28. The ~~method~~ use of any one of Claims 15 to 27, wherein administration comprises parenteral administration.

29. The ~~method~~ use of any one of Claims 15 to 28, wherein administration comprises intravenous administration.

30. The ~~method~~ use of any one of Claims 15 to 28, wherein administration comprises subcutaneous administration.

31. The ~~method~~ use of any one of Claims 15 to 28, wherein administration comprises slow infusion.

32. The ~~method~~ use of any one of Claims 15 to 30, wherein administration comprises bolus administration.

33. The ~~method~~ use of any one of Claims 15 to 30 and 32, wherein administration comprises a frequency of three times or less a day.

34. The ~~method~~ use of Claim 33, wherein the administration occurs only during daylight hours of between 6:00 and 18:00 at a frequency of once every 4 to 6 hours, and wherein administration does not occur at night between 18:00 and 6:00.

35. The ~~method~~ use of any one of Claims 15 to 34, wherein the subject is to be further administered ~~further comprising administering~~ a V2 antagonist.

36. The ~~method~~ use of Claim 35, wherein the V2 antagonist is to be administered within 1 to 8 hours, preferably 1 to 3 hours, before or after administration of the V1a partial agonist, preferably before administration of the V1a partial agonist.

37. Use of a pharmaceutical composition comprising a peptide of Formula (B) in the manufacture of a medicament for~~A method of~~ treating a subject, ~~comprising:~~wherein the pharmaceutical composition comprising a peptide of Formula (B) is to be administered

~~administering~~ to a subject in need thereof in a therapeutically effective dose ~~of a pharmaceutical composition comprising a peptide of Formula (B)~~, wherein the pharmaceutical composition is to be administered within 1 to 8 hours, preferably 1 to 3 hours, before or after administration of a therapeutically effective dose of a V2 antagonist, preferably after administration of a therapeutically effective dose of the V2 antagonist, wherein the peptide of Formula (B) is

a V1a agonist peptide of Formula (B)

[X'-Tyr-Phe-Gln-Asn-Cys-Pro- $Lys(Z)_d$-Gly-NH_2] [SEQ ID NOS. 3-4]

(B)

or a pharmaceutically acceptable salt thereof,

wherein:

X' is $(U)_c$-Cys or Mpa,

wherein when X' is $(U)_c$-Cys and $(Z)_d$ is absent [SEQ ID NO. 3],

the 2 Cys residues are covalently connected with a disulfide bond;

U is an amino acid residue and at each occurrence, is independently selected from Gly, L-Ala, D-Ala, L-Lys, D-Lys, L-Orn, D-Orn, L-Glu, D-Glu, L-Asp, and D-Asp, and c is an integer of from 0 to 10; and

wherein when X' is Mpa [SEQ ID NO. 4],

the Mpa and Cys residues are covalently connected with a disulfide bond,

Z is an amino acid residue pendant to R group of Lys and at each occurrence, is independently selected from Gly, D-Ala, L-Ala, D-Lys, L-Lys, D-Orn, L-Orn, D-Glu, L-Glu, D-Asp, and L-Asp, and d is an integer from 0 to 5,

wherein the subject has a condition selected from liver fibrosis, cirrhosis, portal hypertension, ascites, esophageal varices, fundal varices, bleeding, arterial hypotension, hepatorenal syndrome, and any combination thereof; or

wherein the subject has liver fibrosis; or

wherein the subject has cirrhosis; or

wherein the subject has portal hypertension; or

wherein the subject has esophageal varices; or

wherein the subject has fundal varices; or

wherein the subject has bleeding varices; or

wherein the subject has arterial hypotension; or

wherein the subject has hepatorenal syndrome.

38. The ~~method~~ use of Claim 37, wherein the V1a agonist peptide of Formula (B) is a V1a agonist peptide of Formula (III)

$[(U)_c$-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-$NH_2]$ [SEQ ID NO. 7]

(III)

or a pharmaceutically effective salt thereof,

wherein:

the 2 Cys residues are covalently connected with a disulfide bond,

U is an amino acid residue and at each occurrence, is independently selected from Gly, L-Ala, D-Ala, L-Lys, D-Lys, L-Orn, D-Orn, L-Glu, D-Glu, L-Asp, and D-Asp, and

c is an integer of from 0 to 10.

39. The ~~method~~ use of Claim 37, wherein the V1a agonist peptide of Formula (B) is a V1a agonist peptide of Formula (IV)

[Mpa-Tyr-Phe-Gln-Asn-Cys-Pro-Lys$(Z)_d$-Gly-NH_2] [SEQ ID NO. 4]

(IV)

or a pharmaceutically effective salt thereof,

wherein:

the Mpa and Cys residues are covalently connected with a disulfide bond,

Z is an amino acid residue pendant to the R group of Lys and at each occurrence, is independently selected from Gly, D-Ala, L-Ala, D-Lys, L-Lys, D-Orn, L-Orn, D-Glu, L-Glu, D-Asp, and L-Asp, and

d is an integer from 0 to 5.

40. The ~~method~~ use of any one of Claims 35 to 39, wherein the V2 antagonist comprises mozavaptan, tolvaptan, tolvaptan phosphate ester, satavaptan, lixivaptan, conivaptan, RWJ-351647, VP-343, VP-393, [PmP1, D-Ile2, Ile4, Arg8, Ala9] vasopressin, [PmP1, D-Ile2, Ile4, Arg8] vasopressin, [PmP1, D-Ile2, Ile4, Arg8, Ala9] vasopressin-(1-8)-OH, or any combination thereof.

41. The ~~method~~ use of any one of Claims 35 to 40, wherein the V2 antagonist is tolvaptan, optionally wherein the V2 antagonist is to be administered parenterally at a dose of from 1 µg/kg to 300 µg/kg.

42. The ~~method~~ use of any one of Claims 35 to 41, wherein the subject is human, and the V2 antagonist is tolvaptan, optionally wherein the V2 antagonist is to be administered parenterally at a dose of from 2 mg to 7 mg.

43. The ~~method~~ use of any one of Claims 38 and 40 to 42, wherein the pharmaceutical composition comprises the V1a agonist peptide of Formula (III), or a pharmaceutically acceptable salt thereof, wherein U is Gly and c is 3;

wherein the V2 antagonist comprises tolvaptan; and

wherein the dose weight ratio of the V1a agonist peptide to tolvaptan is from 1:6 to 1:2.

44. The ~~method~~ use of any one of Claims 15 to 43, wherein V1a partial agonist or V1a agonist is to be administered at a dose less than 150 nmol/dose/Kg.

45. The composition of any one of Claims 1 to 13 or a pharmaceutical composition comprising a peptide of Formula (B) for use in therapy.