physiological conditions while also exhibiting sufficient solubility and chemical and physical stabilities under non-physiological conditions.

Summary

In one aspect of the present disclosure, there is provided a compound comprising the amino acid sequence of His-Ala-Gln-Gly-Thr-Phe-Leu-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Gln-Glu-Phe-Val-Glu-Trp-Leu-Leu-Lys-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Lys-Ser-Lys-NH_2 (SEQ ID NO: 2).

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein and a pharmaceutically acceptable buffer.

In a further aspect of the present disclosure, there is provided a compound disclosed herein for use in a therapy.

In another aspect of the present disclosure, there is provided a compound disclosed herein for use in the treatment of hypoglycemia.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for the treatment of hypoglycemia.

Description

Accordingly, the present invention provides a compound which maintains wild-type glucagon activity but also exhibit sufficient solubility as well as chemical and physical stability. The present invention also provides a compound which is suitable for pump and/or emergency administration. In addition, the present invention provides a compound that can be administered in combination with a fast-acting insulin analog in a dual-chamber pump to provide closed-loop glycemic control.

The present invention provides a compound comprising the amino acid sequence His-Ala-Gln-Gly-Thr-Phe-Leu-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Gln-Glu-Phe-Val-Glu-Trp-Leu-Leu-Lys-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Lys-Ser-Lys-NH_2 (SEQ ID NO: 2). The present invention also provides a compound consisting of the amino acid sequence His-Ala-Gln-Gly-Thr-Phe-Leu-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Gln-Glu-Phe-Val-Glu-Trp-Leu-Leu-Lys-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-

Lys-Ser-Lys-NH_2 (SEQ ID NO: 2). Unexpectedly, it has been found that the compound of the present invention exhibits increased aqueous solubility, increased chemical stability, and reduced fibrillation as compared to human glucagon in aqueous solution. In addition, the compound of the present invention demonstrates enhanced solubility at pH in the 5-7 range. The compound of the present invention also provides similar activity as human glucagon – e.g., potency, time of action, and selectivity at the glucagon receptor as compared to human glucagon. Thus, the compound of the present invention is suitable to treat hypoglycemia, including severe or acute hypoglycemia. The improved properties of the compound of the present invention also allow for the preparation of glucagon in aqueous solutions for pump administration and severe hypoglycemia treatment. .

The present invention further provides a method of treating hypoglycemia in a subject comprising administering a compound comprising the amino acid sequence of SEQ ID NO: 2. The present invention also provides a method of treating hypoglycemia in a subject comprising administering a compound consisting of the amino acid sequence of SEQ ID NO:2. The present invention a further provides a compound comprising the amino acid sequence of SEQ ID NO: 2 for use in therapy. The present invention also provides a compound consisting of the amino acid sequence of SEQ ID NO: 2 for use in

WE CLAIM:

1. A compound comprising the amino acid sequence of His-Ala-Gln-Gly-Thr-Phe-Leu-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Gln-Glu-Phe-Val-Glu-Trp-Leu-Leu-Lys-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Lys-Ser-Lys-NH_2 (SEQ ID NO: 2).

2. The compound of Claim 1, wherein the compound consists of the amino acid sequence of His-Ala-Gln-Gly-Thr-Phe-Leu-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Gln-Glu-Phe-Val-Glu-Trp-Leu-Leu-Lys-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Lys-Ser-Lys-NH_2 (SEQ ID NO: 2).

3. A pharmaceutical composition comprising the compound of Claim 1 or Claim 2 and a pharmaceutically acceptable buffer.

4. The pharmaceutical composition of Claim 3, wherein the pharmaceutically acceptable buffer is histidine-buffered saline.

5. A method of treating hypoglycemia in a subject comprising administering an effective amount of a compound of Claim 1 or Claim 2.

6. A compound of Claim 1 or Claim 2 for use in a therapy.

7. A compound of Claim 1 or Claim 2 for use in the treatment of hypoglycemia.

8. A compound of Claim 1 or Claim 2 for use in the manufacture of a medicament for the treatment of hypoglycemia.

WE CLAIM:

1. A compound comprising the amino acid sequence of His-Ala-Gln-Gly-Thr-Phe-Leu-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Gln-Glu-Phe-Val-Glu-Trp-Leu-Leu-Lys-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Lys-Ser-Lys-NH_2 (SEQ ID NO: 2).

2. The compound of claim 1, wherein the compound consists of the amino acid sequence of His-Ala-Gln-Gly-Thr-Phe-Leu-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-(Aib)-Lys-Lys-Ala-Gln-Glu-Phe-Val-Glu-Trp-Leu-Leu-Lys-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Lys-Ser-Lys-NH_2 (SEQ ID NO: 2).

3. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable buffer.

4. The pharmaceutical composition of claim 3, wherein the pharmaceutically acceptable buffer is histidine-buffered saline.

5. A compound of Claim 1 for use in a therapy.

6. A compound of Claim 1 for use in the treatment of hypoglycemia.

7. Use of a compound of Claim 1 in the manufacture of a medicament for the treatment of hypoglycemia.

8. A pharmaceutical composition comprising the compound of Claim 2 and a pharmaceutically acceptable buffer.

9. The pharmaceutical composition of claim 9, wherein the pharmaceutically acceptable buffer is histidine-buffered saline.

10. A compound of Claim 2 for use in a therapy.

11. A compound of Claim 2 for use in the treatment of hypoglycemia.

12. Use of a compound of Claim 2 in the manufacture of a medicament for the treatment of hypoglycemia.