Title: BIOLOGICALLY ACTIVE VASOPRESSIN ANALOGUES

Abstract

Vasopressin analogues of formula (I) wherein X is (S)-2-amino-2-methylbutanoic acid (CarMeAbu) or Valine (Val), Y is Thienylalanine (Thi) or Methionine (Met), Z is D-Phenylalanine (D-Phe) or D-Thienylalanine (Thi) or D-Tyrosine (D-Tyr), are disclosed. Pharmaceutical preparations comprising a vasopressin analogue of the invention as active ingredient are disclosed and exemplified by oral preparations, nasal preparations, and intravenous preparations. The vasopressin analogues of the invention are intended for use as a medicament, specially an antidiuretic agent. The antidiuretic agent is preferably used for the treatment of diabetes insipidus or enuresis.
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5 BIOLOGICALLY ACTIVE VASOPRESSIN ANALOGUES

The present invention relates to biologically active vasopressin analogues. More precisely, the invention relates to vasopressin analogues having specific antidiuretic activity and much improved bioavailability compared to the widely used antidiuretic compound 1-desamino-8-D-arginine vasopressin, also known as desmopressin or DDAVP.

15 Background

DDAVP has now been on the market for about 20 years as a pharmaceutical preparation with antidiuretic activity, at first mainly for the treatment of patients suffering from diabetes insipidus, but, since a few years, also for the treatment of enuresis, specially nocturnal enuresis. It has also successfully been used in the treatment of hemophilia type A, von Willebrand’s disease and prolonged bleeding times of unknown reasons.

25 The intravenous administration of DDAVP gives the best bioavailability of the compound, but is inconvenient to use at home. Therefore, a common way of administration of DDAVP has been by intranasal route. However, the bioavailability of the compound decreases about 10 times. DDAVP may also be administered orally as is disclosed in the European Patent No. 0 163 723. However, the loss in bioavailability is even greater than by administration through the nasal mucosa.
Research efforts have been focused on improved DDAVP analogues. Numerous DDAVP derivatives have been synthesized and tested for bioavailability in the search for compounds with specific antidiuretic activity and with improved absorption through the nasal mucosa and absorption through the intestinal mucosa.

Description of the invention

The present invention provides new vasopressin analogues of the formula

\[ \begin{array}{c}
\text{CH}_2\text{C-Z-Y-X-Asn-NHCHC-Hyp-D-Arg-Gly-NH}_2 \\
\text{123456} 789 \\
\text{CH}_2\text{CH}_2\text{S-CH}_2 \\
\end{array} \]

wherein X is (S)-2-amino-2-methyl-butanoic acid (CoMeAbu) or Valine (Val), Y is Thienylalanine (Thi) or Methionine (Met), Z is D-Phenylalanine (D-Phe) or D-Thienylalanine (D-Thi) or D-Tyrosine (D-Tyr) and Asn is Asparagine, Hyp is 4-trans-Hydroxyproline, D-Arg is D-Arginine, Gly is Glycine.

As is evident from the testing of biological activity disclosed later in the text, the new compounds of the invention have, in
addition to good antidiuretic activity, about 12 to 25 times higher values for gastrointestinal absorption than DDAVP, and 2 to 5 times higher intranasal absorption values. The blood clotting effect of the compounds of the invention has not yet been tested, but it is believed that in analogy with DDAVP, the compounds of the invention will also be useful for the treatment of hemophilia type A, von Willebrand's disease and prolonged bleeding times of unknown reasons.

Another aspect of the invention is directed to a pharmaceutical preparation comprising a vasopressin analogue of the invention as active ingredient. This aspect of the invention is intended to comprise any useful pharmaceutical preparation as long as it contains a vasopressin analogue of the invention as active ingredient. The pharmaceutical preparation is preferably in the form of an oral preparation, such as a tablet or capsula, a nasal preparation, such as a nasal spray or nasal drops, or an intravenous preparation, such as an injectable solution. In a pharmaceutical preparation the active ingredient is in combination with pharmaceutically acceptable additives and/or diluents. A suitable pharmaceutically acceptable diluent is isotonic saline solution. As to the other pharmaceutically acceptable additives and diluents, such can be found in the literature, e.g. the European or US Pharmacopoeia, and these additives shall be chosen in conformity with the specific form of the preparation for a specific administration route.

A further aspect of the invention is directed to a vasopressin analogue of the invention for use as a medicament. The medicament is preferably an antidiuretic agent.
Another aspect of the invention is directed to the use of a vasopressin analogue according to the invention for the preparation of a medicament for the treatment of diabetes insipidus. The invention also comprises the use of a vasopressin analogue according to the invention for the preparation of a medicament for the treatment of enuresis, specially nocturnal enuresis.

Yet another aspect of the invention is directed to a method of treating a diabetes insipidus or enuresis patient comprising administering to said patient an antidiuretically effective amount of a vasopressin analogue of the invention or a pharmaceutical preparation of the invention.

15 General description of the synthesis

The vasopressin (VP) analogues of the invention may be prepared in accordance with known strategies for synthesizing peptides, i.e. step by step, by forming peptide bonds between amino acid residues or modified residues and final ring closure in order to complete the synthesis.

All the VP analogues prepared in the examples given below were synthesized by solid phase technique (J.M. Stewart, J.D. Young, Solid Phase Peptide Synthesis, Pierce Chemical Company, 1984; and E. Atherton, R.C. Sheppard, Solid Phase Peptide Synthesis, 1989).

The peptides were purified by reversed phase chromatography with a mobile phase consisting of acetonitrile/water/0.1% TFA. The pure peptides were then converted to their acetate-salts. The
purity and structure of the peptides were confirmed by HPLC, amino acid analysis and FAB-MS.

The following abbreviations have been used:

- Boc = t-butyloxycarbonyl
- Fmoc = fluorenylmethoxycarbonyl
- H-CoMeAbu-OH = (S)-2-amino-2-methyl-butanolic acid
- Hyp = 4-trans-hydroxyproline
- Thi = 2-thienylalanine
- TBTU = 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate
- DMF = dimethylformamide
- TFA = trifluoroacetic acid

The amino acid derivatives were supplied by Bachem AG, Switzerland, except (S)-2-amino-2-methyl-butanolic acid (H-CoMeAbu-OH) which was supplied by Janssen Chimica (art.nr. 29.005.02). The Fmoc-group was introduced by standard methods (P.B.W. Ten Kortenaar et al., Int. J. Peptide Protein Res. 27, 1986, 398), and NοFmoc-S-(3-t-butyloxycarbonyl propyl)-cysteine was synthesized following the proceeding published by Z. Procházka et al., Collect. Czech. Chem. Commun., 57, 1992, 1335.

The reference compound DDAVP was synthesized by Ferring AB, Malmö, Sweden, in known manner, and the reference compound of Example 3 was also synthesized by Ferring AB, Malmö, Sweden. The last mentioned compound has been disclosed by M. Zaooral et al. in Peptides 1986, p. 468 Table 2. (1987 Walter de Gruyter & Co., Berlin. New York).
Example 1

\[
\begin{align*}
&\text{O} &\text{O} \\
&\text{CH}_2\text{C-D-Phe-Thi-CuMeAbu-Asn-NHCHC-Hyp-D-Arg-Gly-NH}_2 \\
&\text{CH}_2\text{CH}_2 &\text{S} &\text{CH}_2 \\
\end{align*}
\]

The peptide was synthesized with the solid phase technique. Fmoc/tBu-strategy was used, except for Position 2 (D-Phe), where Nα-Boc-amino acid (Boc-D-Phe-OH) was utilized as a derivative. Tentagel-S RAM-resin (1 g, 0.2 mmol/g; RAPP Polymere S 30 023) was used as solid phase. The peptide was cleaved from the resin and deprotected with TFA/ethanedithiol/anisole 95:2.5:2.5 (1.5 h; room temperature). Most of the liquid was evaporated and the peptide was precipitated with diethylether and then freeze-dried from water. The cyclization between positions 1 and 2 was performed in dry DMF with TBTU (1-2 eqv) and N-methyl-morpholine (15-20 eqv). The concentration of the peptide was 1 mg/ml. Reaction time was 4 hours at room temperature. The solvent was evaporated and the peptide was precipitated with diethylether.

Purification was performed on a reversed-phase column with acetonitrile/water/0.1% TFA as an eluent. The fractions of acceptable purity were evaporated and the residue attached to a reversed-phase column. The column was washed with 0.2 M ammonium acetate and water. The peptide was eluted with a mixture of acetonitrile/water/1% acetic acid. Fractions of acceptable purity were evaporated and freeze-dried. The peptide structure was confirmed by HPLC, amino acid analysis and FAB-MS analysis.

Yield 36 mg, 99% purity.
Example 2

\[
\begin{align*}
&\text{O} \\
&\text{CH}_2\text{C-D-Phe-Thi-Val-Asn-NHCHC-Hyp-D-Arg-Gly-NH}_2 \\
&\text{CH}_2\text{CH}_2\text{--S--CH}_2
\end{align*}
\]

The peptide was synthesized and purified by using the same strategy as in Example 1.

Yield 77 mg, 99% purity.

Example 3 (Reference)

\[
\begin{align*}
&\text{O} \\
&\text{CH}_2\text{C-D-Tyr-Phe-Val-Asn-NHCHC-Pro-D-Arg-Gly-NH}_2 \\
&\text{CH}_2\text{CH}_2\text{--S--CH}_2
\end{align*}
\]

The peptide was synthesized and purified by using the same strategy as in Example 1.

Yield 23 mg, 99% purity.

Example 4

\[
\begin{align*}
&\text{O} \\
&\text{CH}_2\text{C-D-Thi-Thi-CoMeAbu-Asn-NHCHC-Hyp-D-Arg-Gly-NH}_2 \\
&\text{CH}_2\text{CH}_2\text{--S--CH}_2
\end{align*}
\]

The peptide was synthesized and purified by using the same strategy as in Example 1.

Yield 30 mg, 99% purity.
Example 5

\[
\begin{align*}
5 \quad & \text{CH}_2 \text{C-D-Tyr-Thi-CuMeAbu-Asn-NHCHC-Hyp-D-Arg-Gly-NH}_2 \\
& \text{CH}_2 \text{CH}_2 \quad \text{S} \quad \text{CH}_2 \\
\end{align*}
\]

The peptide was synthesized and purified by using the same strategy as in Example 1.

10 Yield 34 mg, 99% purity.

Example 6

\[
\begin{align*}
15 \quad & \text{CH}_2 \text{C-D-Thi-Met-Val-Asn-NHCHC-Hyp-D-Arg-Gly-NH}_2 \\
& \text{CH}_2 \text{CH}_2 \quad \text{S} \quad \text{CH}_2 \\
\end{align*}
\]

The peptide was synthesized and purified by using the same strategy as in Example 1.

20 Yield 57 mg, 99% purity.

Biological activity

Compounds were investigated in vivo for the following characteristics:

a) Antidiuretic activity (AD\textsubscript{1v})

30 The antidiuretic activity of the peptides was determined in the well established rat model which is based on continuous measurement of the conductivity of the urine produced by the

b) Gastrointestinal absorption of peptides \([(F_{AD})_v]\]

Absorption of peptides administered in the intestine through a surgically introduced plastic tube (10 cm distal of pylorus) was determined by comparing the antidiuretic effect (area under curve) after intestinal administration with the antidiuretic effect after intravenous administration. The antidiuretic effect was followed as described (J. Medicinal Chem. (1978) 21, 352-356).

c) Intranasal absorption of peptides \((F_{AD})_n\)

Absorption of peptides administered in a volume of 30 μl in the nasal cavity through a PE20 cannula attached to a Hamilton syringe (introduced 10 mm without surgery), was determined by comparing the antidiuretic effect (area under curve) after intranasal administration with the antidiuretic effect after intravenous administration. The antidiuretic effect was followed as described (J. Medicinal Chem. (1978) 21, 352-356).
Results:

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<th>$AD_{IV}$ [IU/μmol]</th>
<th>$(F_{AD})_V$ [%]</th>
<th>$(F_{AD})_{in}$ [%]</th>
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It is evident that the reference compound DDAVP and that of Example 3 have a far lower bioavailability than the compounds of the invention (Ex. 1, Ex. 2, Ex. 4, Ex. 5 and Ex. 6).
CLAIMS

1. A vasopressin analogue of the formula

\[
\begin{array}{c}
\text{CH}_2\text{C-Z-Y-X-Asn-NHCHC-Hyp-D-Arg-Gly-NH}_2 \\
\end{array}
\]

\[
\begin{array}{cccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 \\
\text{CH}_2\text{CH}_2 & \text{S} & \text{CH}_2
\end{array}
\]

wherein X is (S)-2-amino-2-methyl-butanoic acid (CoMeAbu) or Valine (Val),
Y is Thienylalanine (Thi)
or Methionine (Met),
Z is D-Phenylalanine (D-Phe)
or D-Thienylalanine (Thi)
or D-Tyrosine (D-Tyr)
and Asn is Asparagine
Hyp is 4-trans-Hydroxyproline
D-Arg is D-Arginine
Gly is Glycine.

2. A pharmaceutical preparation comprising a vasopressin analogue according to claim 1 as active ingredient.

3. A pharmaceutical preparation according to claim 2, in the form of an oral preparation.

4. A pharmaceutical preparation according to claim 2, in the form of a nasal preparation.
5. A pharmaceutical preparation according to claim 2, in the form of an intravenous preparation.

6. A vasopressin analogue according to claim 1 for use as a medicament.

7. A vasopressin analogue according to claim 6, wherein said medicament is an antidiuretic agent.

8. Use of a vasopressin analogue according to claim 1 for the preparation of a medicament for the treatment of diabetes insipidus.

9. Use of a vasopressin analogue according to claim 1 for the preparation of a medicament for the treatment of enuresis.

10. A method of treating a diabetes insipidus or enuresis patient comprising administering to said patient an anti-diuretically effective amount of a vasopressin analogue according to claim 1 or a pharmaceutical preparation according to claims 2-5.
### INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/SE 94/00594

#### A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07K 7/16, A61K 37/34 // C07K 99:04

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K, C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, EMBASE, WPI, CA, CLAIMS, JAPIO

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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* Further documents are listed in the continuation of Box C. See patent family annex.

**Date of the actual completion of the international search**

15 Sept 1994

**Date of mailing of the international search report**

26 -[19-] 1994

**Name and mailing address of the ISA/ Swedish Patent Office**

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**Box I** Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(c) for the following reasons:

1. **X** Claims Nos.: 10 because they relate to subject matter not required to be searched by this Authority, namely:
   
   See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. **☐** Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- **☐** The additional search fees were accompanied by the applicant’s protest.
- **☐** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)
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