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(71) Applicant: NOVO NORDISK A/S [DK/DK]; Corporate Patents, Novo Allé, DK–2880 Bagsvaerd (DK).


(54) Title: USE OF HEXAPEPTIDES FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF HOT FLUSHES

(57) Abstract

The present invention relates to the use of hexapeptides for the treatment of migraine, non–insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation and/or vasomotor disturbances.


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TITLE
Use of hexapeptides for the manufacture of a pharmaceutical composition for the treatment of hot flushes.

FIELD OF INVENTION
The present invention relates to the use of compounds of the general formula I for the treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation and/or vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and their pharmaceutical compositions.

BACKGROUND OF THE INVENTION
A “hot flush” is a sudden transient sensation ranging from warmth to intense heat and typically accompanied by flushing and perspiration. It is the classic sign of the menopause and the predominant complaint of menopausal women. Epidemiological studies report that the majority of menopausal women experience hot flushes, although with large variation in frequency and intensity (Treatment of the Postmenopausal Woman, Basic and Clinical Aspects, Raven Press 1994, ed. R.A. Lobo).

A positive correlation between plasma levels of calcitonin gene-related peptide (CGRP) and frequency of hot flushes in women has recently been reported (Chen et al., 1993, Lancet (342) 49), in accordance with the potent vasodilatory effect of CGRP (Brain et al., 1985, Nature, (313) 54-56).

Also, a positive correlation between CGRP antagonists and diabetes, septic shock and inflammation has been described (Feurstein, G, Willette, R and Aiyar, N., 1995, Can. J. Physiol. Pharmacol. 73: 1070-1074).

Recently, a novel heptadeca peptide, nociceptin, was discovered (Meunier et al., 1995, Nature (377) 532-535, Reinscheid et al., 1995, Science (270) 792-794)
Nociceptin and analogues thereof have been disclosed in WO 97/07212, EP 813065 and in WO 97/07208. These peptides and inhibitors thereof are said to be useful for antagonising physiologic effects of an opioid in an animal, and for treating/preventing a disease related to: hyperalgesia, neuroendocrine secretion, stress, locomotor activity, anxiety etc.

Jenck, F et. al. also found, that Orphanin FQ acts as an anxiolytic to attenuate behavioral-responses to stress (PNAS Vol. 94, 1997).


**SUMMARY OF THE INVENTION**

The present invention provides the use of a compound selected from a basic hexapeptide or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of Type II diabetes, septic shock, inflammation and vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes.

Further objects will become apparent from the following description.

**DETAILED DESCRIPTION OF THE INVENTION**

It has been found recently that hexapeptides with L or D basic amino acids in position A¹, A² and/or A³, aromatic L or D amino acids in position A² and/or A³ and/or aromatic or aliphatic L or D amino acids in position A⁴ have the same affinity for the opioid-like receptor ORL1 as nociceptin with binding in the nanomolar range (Dooley, C,T et. al., Binding and In Vitro Activities of Peptides with High Affinity for Nociceptin/Orphanin

Accordingly, in a first aspect, the present invention relates to the use of a compound of the general formula I

\[ A^1 - A^2 - A^3 - A^4 - A^5 - A^6 - Y \]  

(1)

wherein

- \( A^1 \) is Arg, Lys, His, D-Arg, D-Lys, D-His, acylated Arg, acylated Lys, acylated His, acylated D-Arg, acylated D-Lys or acylated D-His;
- \( A^2 \) is Tyr, Trp, Phe, D-Tyr, D-Trp or D-Phe;
- \( A^3 \) is Tyr, Trp, Phe, D-Tyr, D-Trp or D-Phe;
- \( A^4 \) is Lys, Arg, His, D-Arg, D-Lys or D-His;
- \( A^5 \) is Phe, Tyr, Trp, Ile, D-Phe, D-Tyr, D-Trp or D-Ile;
- \( A^6 \) is Arg, Lys, His, D-Arg, D-Lys or D-His and
- \( Y \) is OH or NH₂

or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of Type II diabetes, septic shock, inflammation and vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes.

In one embodiment of the invention the compound of the formula I is selected from the group consisting of

- Ac-Arg-Tyr-Tyr-Arg-Trp-Arg-NH₂,
- Ac-Arg-Tyr-Tyr-Arg-Trp-Lys-NH₂,
- Ac-Arg-Tyr-Tyr-Arg-Ile-Lys-NH₂,
- Ac-Arg-Tyr-Tyr-Lys-Trp-Arg-NH₂ and
Ac-Arg-Tyr-Tyr-Lys-Trp-Lys-NH₂.
(all of which, e.g., are produced using commonly known solid phase peptide synthesis technology).

5  The term Ac is intended to mean acetylated.

In another embodiment of the invention the composition is in a form suitable for oral, nasal, transdermal, pulmonal, or parenteral administration.

10  In a further embodiment of the first aspect the compound of the formula I is administered as a dose in the range from about 0.001 to about 10 g per patient per day, preferably from about 1 to about 1000 mg per patient per day, especially from about 10 to about 100 mg per patient per day, e.g. about 100 mg per patient per day.

15  In still another embodiment of the first aspect the amino acids are all in either the D or L stereochemical configuration, preferably the L stereochemical configuration. However, the compounds of the invention may comprise both L and D amino acids.

In a second aspect the invention relates to a method for the treatment or prevention of migraine, Type II diabetes, sepsis, inflammation and/or vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes, the method comprising administering to a patient in need thereof an effective amount of compound of the formula I or a pharmaceutically acceptable salt thereof.

25  The effective, such as the therapeutically effective amount of a compound of the formula I will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.
In one embodiment of the second aspect the compound of the formula I is administered as a dose with an effective amount in the range from about 0.001 to about 10 g per patient per day, preferably from about 1 to about 1000 mg per patient per day, especially from about 10 to about 100 mg per patient per day, e.g. about 100 mg per patient per day.

Within its scope the invention includes the D and/or L stereochemical configuration of all the amino acids which constitute the compound of the formula I.

As used herein the term “patient” comprises any mammal which may benefit from treatment or prevention of vasomotor disturbances, such as a human, especially if the mammal is a female, such as a woman. However, “patient” is not intended to be limited to a woman.

The compounds intended to be embraced by the present invention are such peptides which are disclosed in Journal of Pharmacology and Experimental Therapeutics, (1997) Vol. 283, No.2: 735-741.

As used herein the term “treatment” is also meant to comprise prophylactic treatment.

Within the present invention, the compound of the formula I may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) which are known to the skilled artisan.
Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds of the formula I are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of the formula I of this invention may form solvates with standard low molecular weight solvents using methods known to a person skilled in the art.

The compound of the formula I may be administered in pharmaceutically acceptable acid addition salt form. Such salt forms are believed to exhibit approximately the same order of activity as the free base forms.

A pharmaceutical composition for use in accordance with the present invention comprises, one or more compound of the formula I as active ingredient(s), or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing compounds of the formula I of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include hexapeptides or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient
which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a
carrier which can be in the form of a capsule, sachet, paper or other container. In
making the compositions, conventional techniques for the preparation of
pharmaceutical compositions may be used. For example, the active compound
will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a
carrier which may be in the form of a ampoule, capsule, sachet, paper, or other
container. When the carrier serves as a diluent, it may be solid, semi-solid, or
liquid material which acts as a vehicle, excipient, or medium for the active
compound. The active compound can be adsorbed on a granular solid container
for example in a sachet. Some examples of suitable carriers are water, salt
solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil,
peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose,
magnesium stearate, talc, gelatine, agar, pectin, acacia, stearic acid or lower alkyl
ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid
monoglycerides and diglycerides, pentaerythritol fatty acid esters,
polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the
carrier or diluent may include any sustained release material known in the art, such as
glycerol monostearate or glycercyl distearate, alone or mixed with a wax. The
formulations may also include wetting agents, emulsifying and suspending
agents, preserving agents, sweetening agents or flavouring agents. The
formulations of the invention may be formulated so as to provide quick,
sustained, or delayed release of the active ingredient after administration to the
patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilised and mixed, if desired, with
auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or
colouring substances and the like, which do not deleteriously react with the acti-
ve compounds.
The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tablettting techniques may contain:
Core:
Active compound (as free compound or salt thereof) 100 mg
Colloidal silicon dioxide (Aerosil) 1.5 mg
Cellulose, microcryst. (Avicel) 70 mg
5 Modified cellulose gum (Ac-Di-Sol) 7.5 mg
Magnesium stearate Ad.

Coating:
HPMC approx. 9 mg
10 *Myvacett 9-40 T approx. 0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

Any novel feature or combination of features described herein is considered essential to this invention.

Pharmacological effects:
Male Sprague Dawley rats (300±25 g) were anaesthetised with pentobarbital sodium (50 mg/kg i.p.) and polyethylene catheters were positioned in both femoral veins for the intravenous administration of drugs, such as nociceptin and analogues, and into the left femoral artery in order to measure arterial blood pressure and heart rate. The trachea was cannulated with polyethylene tubing and the rat was pithed, ventilated and drug treated as described by Nuki Y. et al. (Effects of Dorsal Rhizotomy on Depressor Response to Spinal Cord Stimulation Mediated by Endogenous Calcitonin Gene-related Peptide in the Pithed Rat. J. Neurosurg. 1993; 79:899-904).

Examples:
30 Prior administration of nociceptin and related analogs inhibited the depressor
response to spinal cord stimulation accordingly:

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<th>Structure</th>
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<td></td>
<td>0.3</td>
<td>23 ± 6</td>
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<tr>
<td>Ac-Arg-Tyr-Tyr-Arg-Trp-Lys-NH₂</td>
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<td>0.3</td>
<td>32 ± 7</td>
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A clear dose-response was observed for the hexapeptide, Ac-Arg-Tyr-Tyr-Arg-Trp-Lys-NH₂. In all animals examined, the effect of both nociceptin and the hexapeptide was seen when repeated a second time after a second non-antagonised depressor response.
CLAIMS:

1. Use of a compound of the general formula I

\[ A^1 - A^2 - A^3 - A^4 - A^5 - A^6 - Y \]  

wherein

A\(^1\) is Arg, Lys, His, D-Arg, D-Lys, D-His, acylated Arg, acylated Lys, acylated His, acylated D-Arg, acylated D-Lys or acylated D-His;

A\(^2\) is Tyr, Trp, Phe, D-Tyr, D-Trp or D-Phe;

A\(^3\) is Tyr, Trp, Phe, D-Tyr, D-Trp or D-Phe;

A\(^4\) is Lys, Arg, His, D-Arg, D-Lys or D-His;

A\(^5\) is Phe, Tyr, Trp, Ile, D-Phe, D-Tyr, D-Trp or D-Ile;

A\(^6\) is Arg, Lys, His, D-Arg, D-Lys or D-His and

Y is OH or NH\(_2\)

or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of migraine, Type II diabetes, sepsis, inflammation and/or vasomotor disturbances.

2. Use according to claim 1 wherein said amino acids are all in the L stereochemical configuration.

3. Use according to any one of the claims 1-2 wherein A\(^1\) comprises acetylated Arg.

4. Use according to any one of the claims 1-3 wherein A\(^2\) comprises Tyr.

5. Use according to any one of the claims 1-4 wherein A\(^3\) comprises Tyr.

6. Use according to any one of the claims 1-5 wherein A\(^4\) comprises Arg or Lys.
7. Use according to any one of the claims 1-6 wherein \( A^6 \) comprises Trp or Ile.

8. Use according to any one of the claims 1-7 wherein \( A^6 \) comprises Arg or Lys.

9. Use according to any one of the claims 1-8 wherein \( Y \) is \( \text{NH}_2 \).

10. Use according to claim 1 wherein said amino acids are all in the D stereocchemical configuration.

11. Use according to any one of the claim 1-9 wherein the compound is selected from the group consisting of

\[
\text{Ac-Arg-Tyr-Tyr-Arg-Trp-Arg-NH}_2, \\
\text{Ac-Arg-Tyr-Tyr-Arg-Trp-Lys-NH}_2, \\
\text{Ac-Arg-Tyr-Tyr-Arg-Ile-Lys-NH}_2, \\
\text{Ac-Arg-Tyr-Tyr-Lys-Trp-Arg-NH}_2 \text{ and} \\
\text{Ac-Arg-Tyr-Tyr-Lys-Trp-Lys-NH}_2.
\]

12. Use according to any one of the claims 1-11 wherein said composition is in a form suitable for oral, nasal, transdermal, pulmonal, or parenteral administration.

13. Use according to any one of the claims 1-12 wherein said compound is administered as a dose in the range from about 0.001 to about 10 g per patient per day.

14. Use according to any one of the claims 1-13 wherein said vasomotor disturbances are hot flushes or hot flashes.
15. A method for the treatment of vasomotor disturbances, the method comprising administering to a patient in need thereof an effective amount of a compound of the general formula I

\[ A^1 - A^2 - A^3 - A^4 - A^5 - A^6 - Y \] (I)

wherein

- \( A^1 \) is Arg, Lys, His, D-Arg, D-Lys, D-His, acylated Arg, acylated Lys, acylated His, acylated D-Arg, acylated D-Lys or acylated D-His;
- \( A^2 \) is Tyr, Trp, Phe, D-Tyr, D-Trp or D-Phe;
- \( A^3 \) is Tyr, Trp, Phe, D-Tyr, D-Trp or D-Phe;
- \( A^4 \) is Lys, Arg, His, D-Arg, D-Lys or D-His;
- \( A^5 \) is Phe, Tyr, Trp, Ile, D-Phe, D-Tyr, D-Trp or D-Ile;
- \( A^6 \) is Arg, Lys, His, D-Arg, D-Lys or D-His and

\( Y \) is OH or NH$_2$

or a pharmaceutically acceptable salt thereof.

16. The method according to claim 15 wherein said amino acids are in the L stereochemical configuration.

17. The method according to any one of the claims 15-16 wherein \( A^1 \) comprises acetylated Arg.

18. The method according to any one of the claims 15-17 wherein \( A^2 \) comprises Tyr.

19. The method according to any one of the claims 15-18 wherein \( A^3 \) comprises Tyr.

20. The method according to any one of the claims 15-19 wherein \( A^4 \) comprises Arg or Lys.
21. The method according to any one of the claims 15-20 wherein A\(^5\) comprises Trp or Ile.

22. The method according to any one of the claims 15-21 wherein A\(^6\) comprises Arg or Lys.

23. Use according to any one of the claims 15-22 wherein Y is NH\(_2\).

24. The method according to claim 15 wherein said amino acids are all in the D stereochemical configuration.

25. The method according to any one of the claims 15-23 wherein the compound is selected from the group consisting of

\[
\begin{align*}
&\text{Ac-Arg-Tyr-Tyr-Arg-Trp-Arg-NH}_2, \\
&\text{Ac-Arg-Tyr-Tyr-Arg-Trp-Lys-NH}_2, \\
&\text{Ac-Arg-Tyr-Tyr-Ile-Lys-NH}_2, \\
&\text{Ac-Arg-Tyr-Tyr-Lys-Trp-Arg-NH}_2\text{ and} \\
&\text{Ac-Arg-Tyr-Tyr-Lys-Trp-Lys-NH}_2.
\end{align*}
\]

26. The method according to any one of the claims 15-25 wherein said composition is in a form suitable for oral, nasal, transdermal, pulmonal, or parenteral administration.

27. The method according to any one of the claims 15-26 wherein said compound is administered as a dose in the range from about 0.001 to about 10 g per patient per day.

28. The method according to any one of the claims 15-27 wherein said vasomotor disturbances are hot flushes or hot flashes.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 38/08
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)

IPC6: A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search: 3 August 1999

Date of mailing of the international search report: 03-08-1999

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer
Carolina Palmcrantz/ELY
Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)
INTERNATIONAL SEARCH REPORT

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)(a) for the following reasons:

1. ☒ Claims Nos.: 15–28
   because they relate to subject matter not required to be searched by this Authority, namely:
   "Claims 15–28 relate to methods of treatment of the human or animal body by therapy (Rule.39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds."

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:

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.: 1–13, 14–28

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)
As is stated in Annex B to Administrative Instructions under the PCT, in force July 1, 1992 (PCT GAZETTE 1992, June 25, pages 7062-9, see page 7063 and example 5) unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features"—i.e., features that define a contribution which each of the inventions makes over the prior art (c.f. PCT Rule 13.2).

A search for this "special technical feature" mentioned in PCT Rule 13.2 among the diseases claimed in claim 1 did not reveal such a unifying, novel technical feature. Accordingly, the following inventions were found:

Invention A, claims 1-13 (partly) and 14-28, pertains to the use of a compound of the general formula (1) for the preparation of a pharmaceutical composition for the treatment of vaso-motor disturbances such as migraine.

Invention B, claims 1-13 (partly), pertains to the use of a compound of the general formula (1) for the preparation of a pharmaceutical composition for the treatment of type II diabetes.

Invention C, claims 1-13 (partly), pertains to the use of a compound of the general formula (1) for the preparation of a pharmaceutical composition for the treatment of sepsis.

Invention D, claims 1-13 (partly), pertains to the use of a compound of the general formula (1) for the preparation of a pharmaceutical composition for the treatment of inflammation.

The International Search has been restricted to invention A.