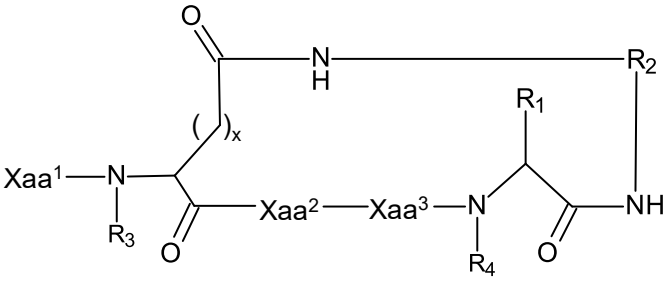
Both agonist and antagonist melanocortin receptor-specific compounds are known, including agonist and antagonist peptides. For example, MC4r agonist peptides are believed to have utility for treatment of obesity or inducing weight loss, and for treatment of various forms of sexual dysfunction, including male erectile dysfunction and female sexual dysfunction. MC4r antagonist peptides are believed to result in weight gain, with potential utility for conditions such as cachexia and other wasting syndromes and conditions.

Peptide analogs of the endogenous agonist alpha-melanocortin stimulating hormone (α-MSH) are known. These include both linear and cyclic peptides. Cyclic melanocortin receptor-specific peptides are typically cyclized through side chains, such as amide or cysteine linkages, and acylated at the N-terminus and amidated at the C-terminus (endogenous α-MSH is acylated at the N-terminus and amidated at the C-terminus), but it is known that α-MSH analogs may have a C-terminus carboxyl group, as disclosed in U.S. Patent 6,579,968.

Notwithstanding the intense scientific and pharmaceutical interest in melanocortin receptor-specific peptides, evidenced by numerous articles in the scientific literature and numerous patent applications and issued patents, the only melanocortin receptor-specific peptide drugs approved in the United States are bremelanotide, sold under the tradename VYLEESI®, indicated for hypoactive sexual desire disorder in premenopausal women, afamelanotide, sold under the tradename SCENESSE®, indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria, and setmelanotide, sold under the tradename INCIVREE™, indicated for treatment of obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency. There remains a significant and substantial need for melanocortin receptor-specific peptides for use in pharmaceutical applications, particularly in treatment of inflammation-related diseases, indications, conditions and syndromes. It is against this background that the present invention was made.

SUMMARY

The present disclosure relates to a side chain-to-tail diamine-linked cyclized peptide of formula I:



(I)

including all enantiomers, stereoisomers or diastereomers thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein:

Xaa^1 is $-R_5-R_6$;

Xaa^2 and Xaa^3 are each independently from one to three L- or D-isomer amino acids, or a combination thereof, linked by backbone amide bonds, wherein any backbone nitrogen atom is optionally alkylated with a C_1 to C_8 linear or branched alkyl, and if optionally alkylated, the alkyl optionally forms a ring with the side chain of the same amino acid if said side chain is aliphatic, wherein the ring is optionally substituted;

R_1 is H or an L- or D-isomer amino acid side chain;

R_2 is $–(CH_2)_u-$ or $–(CH_2)_v-O-(CH_2)_w-$;

R_3 is H or a C_1 to C_9 linear or branched aliphatic chain, optionally comprising one or more C=C double bonds;

R_4 is -H or a C_1 to C_8 linear or branched alkyl;

R_5 is optionally present, and if present, is from one to three L- or D-isomer amino acids, or a combination thereof, linked by backbone amide bonds, wherein any backbone nitrogen atom is optionally methylated;

R_6 is H or a C_1 to C_{17} acyl group comprising optionally substituted linear or branched alkyl, cycloalkyl, alkylcycloalkyl, aryl, aralkyl or heteroaryl;

x is from 1 to 5;

u is from 2 to 8;

v is from 2 to 5; and

w is from 2 to 5.

In the peptide of formula I Xaa^2-Xaa^3 may comprise the amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted. Alternatively, Xaa^2-Xaa^3 may comprise, or may consist of, the amino acid sequence -His-D-Phe-Arg- or -His-Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted and R_1 is a side chain of the L- or D-isomer amino acid Trp.

In another example, R_1 may be a side chain of the L- or D-isomer amino acid Trp.

In yet another aspect, Xaa^2-Xaa^3 may comprise the amino acid sequence -His-D-Phe- or -His-Phe- wherein the phenyl ring of D-Phe or Phe is optionally substituted and R_1 is a side chain of the L- or D-isomer amino acid Arg.

In yet another example of the peptide of formula I, R_5 may be an L- or D-isomer of Nle or Arg. In this example, Xaa^2-Xaa^3 may comprise the amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted. Alternatively, in this example, Xaa^2-Xaa^3 may comprise the amino acid sequence -D-Phe-Arg-or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted and R_1 is a side chain of the L- or D-isomer amino acid Trp.

In another example of the peptide of formula I, R_3 is not present and R_4 is a C_1 to C_{17} acyl group. In this example, Xaa^2-Xaa^3 may comprises he amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted. Alternatively, Xaa^2-Xaa^3 may comprise the amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted and R_1 is a side chain of the L- or D-isomer amino acid Trp.

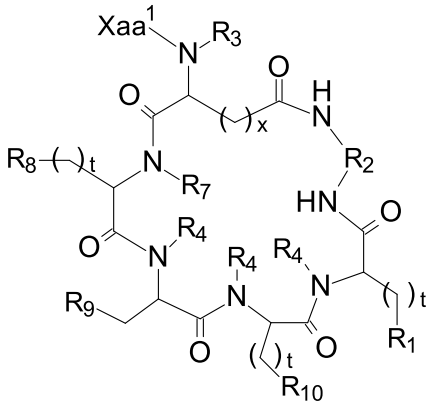
In another example of the peptide of formula I, R_5 is an L- or D-isomer of Nle or Arg and R_6 is a C_1 to C_{17} acyl group. In this example, Xaa^2 and Xaa^3 comprise the amino acid sequence -D-Phe-Arg- or

-Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted. Alternatively, Xaa^2 and Xaa^3 may comprise the amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optinally substituted and R_1 is a side chain of the L- or D-isomer amino acid Trp.

In another example, wherein the phenyl ring of D-Phe or Phe is optionally substituted, it is optionally substituted with between one and three ring substituents wherein the substituents are the same or different, and each independently comprise halo, (C_1-C_{10})alkyl-halo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, aryl, (C_1-C_{10})alkylaryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carbamoyl, carboxy, carbamoyl, alkoxy-carbonyl, or aryloxy-carbonyl.

In the peptide of formula I, the L- or D-isomer amino acids may consist of alpha amino acids, beta amino acids, gamma amino acids or delta amino acids, or a combination thereof.

There is further provided the peptide of formula I which is a peptide of formula II:



(II)

including all enantiomers, stereoisomers or diastereomers thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein:

Xaa^1 is -R_5-R_6;

R_1 is substituted or unsubstituted indole, phenyl or naphthyl;

R_2 is –$(CH_2)_u$- or –$(CH_2)_v$-O-$(CH_2)_w$-;

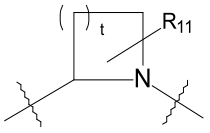
R_3 is H or a C_1 to C_9 linear or branched aliphatic chain, optionally comprising one or more C=C double bonds;

R_4 is -H or -CH_3;

R_5 is optionally present, and if present, is from one to three L- or D-isomer amino acids, or a combination thereof, wherein any backbone nitrogen atom is optionally methylated;

R_6 is H or a C_1 to C_{17} acyl group comprising optionally substituted linear or branched alkyl, cycloalkyl, alkylcycloalkyl, aryl, aralkyl or heteroaryl;

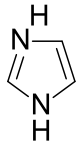
R_7 is -H, -CH_3 or -CH_2-, and if it is -CH_2- forms with R_8 a ring of the general structure

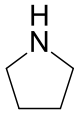


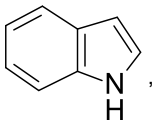
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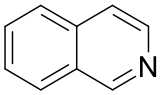
R_8 is -H if R_8 forms the ring with R_7, or R_8 is

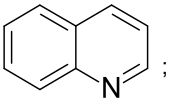
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 , or

;

R_{11} is -O-CH_2-phenyl, where phenyl is substituted or unsubstituted;

R_{12a} and R_{12b} are each independently and independently in each instance H or a C_1 to C_4 linear, branched or cyclic alkyl chain;

t is in each instance independently from 1 to 4;

x is from 1 to 5;

u is from 2 to 8;

v and w are each independently from 2 to 5; and

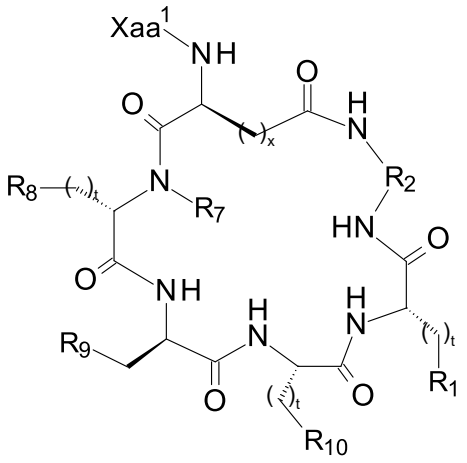
z is from 1 to 3.

In the peptide of formula II, R_9 may be unsubstituted naphthyl.

In another example, in the peptide of formula II, any substituted phenyl or naphthyl may be in each instance independently substituted with between one and three ring substituents wherein the substituents are the same or different, and are each independently halo, (C_1-C_{10})alkyl-halo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, aryl, (C_1-C_{10})alkylaryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carbamoyl, carboxy, carbamoyl, alkoxy-carbonyl, or aryloxy-carbonyl.

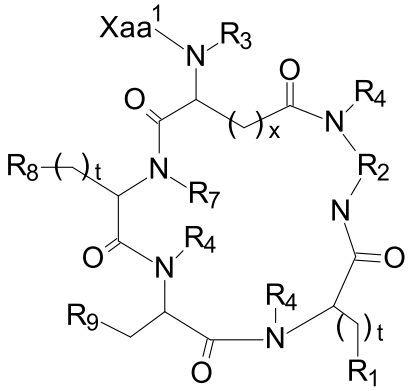
In another example of the peptide of formula II, R_5 comprises at least one L- or D-isomer amino acid, which may be a single L- or D-isomer amino acid with an aliphatic side chain, including wherein the aliphatic side chain is -$(CH_2)_3$-CH_3. Alternatively, in the peptide of formula II R_5 may be a single L- or D-isomer amino acid with a side chain comprising at least one nitrogen atom, including but not limited to where R_5 is an L- or D-isomer of Arg, Lys, Orn, Dab, Dap or Cit.

In another example of the peptide of formula II, the peptide may be of the formula:



In any of the examples of the peptide of formula II, Xaa^1 may be Ac-Arg, Ac-D-Arg, Ac-Nle, Ac-D-Nle, Ac-Trp, cyclopentyl acetyl, hexanoyl, 3-phenylpropanoyl, cyclopentylacetyl, acetyl, 2-naphthylacetyl, or 3-(1-naphthyl)propanoyl; R_1 may be indole or naphthalene; R_7 and R_8 may together comprise pyrrolidine, including wherein pyrrolidine is substituted, including but not limited to wherein the substituent is -O-CH_2-phenyl, where phenyl is substituted or unsubstituted; R_9 may be substituted phenyl.

In an alternative example, the peptide of formula I may be a peptide of formula III:



(III)

including all enantiomers, stereoisomers or diastereomers thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein:

Xaa^1 is -R_5-R_6;

R_1 is

-N(R_{12a})(R_{12b}),

-NH-(CH_2)$_z$-N(R_{12a})(R_{12b}),

-NH-C(=NH)-N(R_{12a})(R_{12b}),

-NH-C(=O)-N(R_{12a})(R_{12b}),

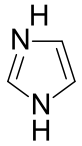
-O(R_{12a}),

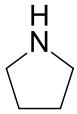
-C_1 to C_{17} linear, branched or cyclic alkyl chain,

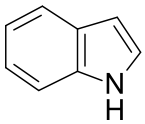
-S(=O)$_2$-CH_3,

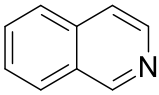
-S(=O)-CH_3,

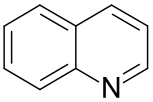

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, or


;

R_9 is substituted or unsubstituted phenyl or naphthyl;

R_{11} is -O-CH_2-phenyl, where phenyl is substituted or unsubstituted;

R_{12a} and R_{12b} are each independently and independently in each instance H or a C_1 to C_4 linear, branched or cyclic alkyl chain;

t is in each instance independently from 1 to 4;

x is from 1 to 5;

u is from 2 to 8;

v and 2 are each independently 2 to 5; and

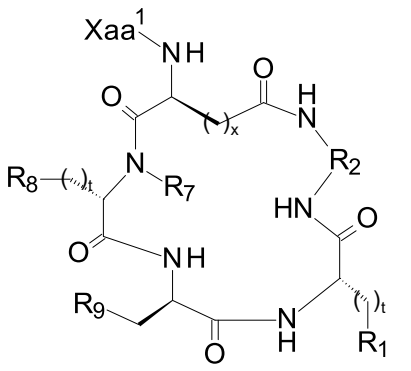
z is from 1 to 3.

In one example of the cyclic peptide of formula III, R_9 is unsubstituted naphthyl. In another example of the peptide of formula III, any substituted phenyl or naphthyl may in each instance independently be substituted with between one and three ring substituents wherein the substituents are the same or different, and are each independently halo, (C_1-C_{10})alkyl-halo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, aryl, (C_1-C_{10})alkylaryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carbamoyl, carboxy, carbamoyl, alkoxy-carbonyl, or aryloxy-carbonyl.

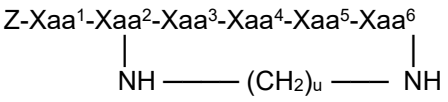
In another example of the peptide of formula III, R_5 may comprise at least one L- or D-isomer amino acid, which may be a single L- or D-isomer amino acid with an aliphatic side chain.

In another example of the peptide of formula III, R_6 may be acetyl, cyclopentyl acetyl, hexanoyl, 3-phenylpropanoyl, cyclopentylacetyl, 2-naphthylacetyl, or 3-(1-naphthyl)propanoyl.

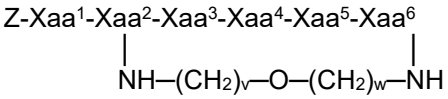
In another example of the peptide of formula III, the peptide is a cyclic peptide of the formula:



In another example, the disclosure provides a cyclic peptide of formula IV or V:



(IV), or



(V),

or a pharmaceutically acceptable salt thereof, wherein

Z is H or an N-terminal group;

Xaa^1 is optionally present, and if present is from one to three amino acids, wherein any backbone nitrogen atom is optionally methylated;

Xaa^2 is an L- or D-isomer of an amino acid with a side chain comprising a carboxyl group forming an amide bond with a first -NH- of the group $-NH-(CH_2)_u-NH-$ or $-NH-(CH_2)_v-O-(CH_2)_w-NH-$;

Xaa^3 is an L- or D-isomer amino acid of Pro, optionally substituted with hydroxyl, halogen, sulfonamide, alkyl, -O-alkyl, aryl, alkyl-aryl, alkyl-O-aryl, alkyl-O-alkyl-aryl, -O-alkyl-aryl, or -O-aryl, or Xaa^3 is an L- or D-isomer amino acid with a side chain comprising at least one primary amine, secondary amine, alkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, ether, sulfide, or carboxyl;

Xaa^4 is an L- or D-isomer amino acid with a side chain comprising substituted or unsubstituted aryl;

Xaa^5 is an L- or D-isomer amino acid with a side chain comprising at least one primary amine, secondary amine, guanidine, urea, alkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, or ether, and if Xaa^6 is not present, with a C-terminal carboxyl group forming an amide bond with a second -NH- of the group $-NH-(CH_2)_u-NH-$ or $-NH-(CH_2)_v-O-(CH_2)_w-NH-$;

Xaa^6 is optionally present, and if present is an L- or D-isomer amino acid with a side chain comprising at least one aryl or heteroaryl, optionally substituted with one or more ring substituents, and when one or more are present, are the same or different and independently hydroxyl, halogen, sulfonamide, alkyl, -O-alkyl, aryl, or -O-aryl, and with a C-terminal carboxyl group forming an amide bond with a second -NH- of the group $-NH-(CH_2)_u-NH-$ or $-NH-(CH_2)_v-O-(CH_2)_w-NH-$;

u is from 2 to 8; and

v and w are each independently from 2 to 5;

wherein the groups -NH-$(CH_2)_u$-NH- and -NH-$(CH_2)_v$-O-$(CH_2)_w$-NH- each comprise a first -NH- and a second -NH-.

In the cyclic peptide of formula IV or V, Z may be an N-terminal group selected from the group consisting of a C_1 to C_{17} acyl group comprising a linear or branched alkyl, cycloalkyl, alkyl cycloalkyl, aryl or aralkyl.

In the cyclic peptide of formula IV or V, Xaa^1 may be a single amino acid residue selected from the group consisting of Gly or an L- or D-isomer of Ala, Nle, Leu, Ile or Val. Alternatively, Xaa^1 may be a single amino acid with a side chain including at least one primary amine, guanidine or urea group, including but not limited to an L- or D-isomer of Arg, Lys, Orn, Dab, Dap or Cit.

In the cyclic peptide of formula IV or V, Xaa^4 may be D-Phe or Phe, optionally substituted with from one to three ring substituents. The ring substituents may be the same or different, and are each independently halo, (C_1-C_{10})alkyl-halo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, aryl, (C_1-C_{10})alkylaryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carboxy, or alkoxy-carbonyl. Alternatively, Xaa^4 may be D-Nal 1 or D-Nal 2.

In the cyclic peptide of formula IV or V, Xaa^5 may be an L- or D-isomer of of Arg, Lys, Orn, Dab or Dap, and Xaa^6 may be an L- or D-isomer of Trp, Nal 1 or Nal 2.

The cyclic peptide of formula IV or V thus includes, but is not limited to, the following substitutions where:

Z is a C_1 to C_7 linear alkyl acyl group;

Xaa^1 is an L- or D-isomer of Nle or Arg;

Xaa^2 is an L- or D-isomer of Asp or Glu wherein the side chain carboxyl group forms an amide bond with a first -NH- of the group -NH-$(CH_2)_u$-NH- or -NH-$(CH_2)_v$-O-$(CH_2)_w$-NH-;

Xaa^3 is an L- or D-isomer of His, Hyp(Bzl), Met(O_2), or Asn**;**

Xaa^4 is an L- or D-isomer of substituted or unsubstituted Phe, Nal 1 or Nal 2;

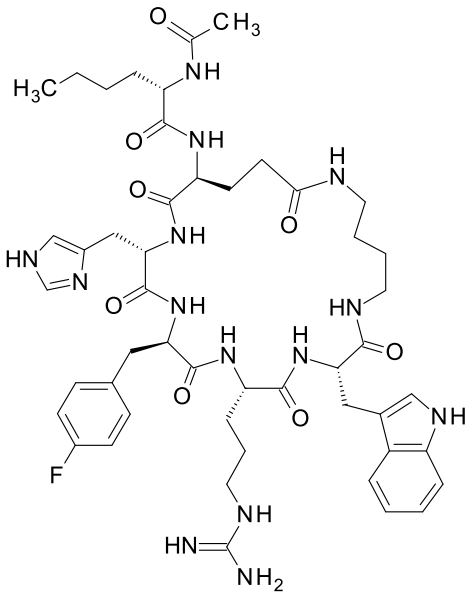
Xaa^5 is an L- or D-isomer of Arg; and

Xaa^6 is an L- or D-isomer of Trp, Nal 1 or Nal 2, wherein the C-terminal carboxyl group thereof forms an amide bond with a second -NH- of the group -NH-$(CH_2)_u$-NH- or -NH-$(CH_2)_v$-O-$(CH_2)_w$-NH-.

There is further provided an example of the cyclic peptide of formula IV, wherein the side chain carboxyl group of Xaa^2 forms an amide bond with a first -NH- of the group -NH-$(CH_2)_u$-NH and the C-terminal carboxyl group of Xaa^6 forms an amide bond with a second -NH- of the group -NH-$(CH_2)_u$-NH-.

In another example of the cyclic peptide of formula IV or V at least one backbone nitrogen atom thereof may comprise a methyl group. In an alternative example, no backbone nitrogen atom thereof comprises a methyl group.

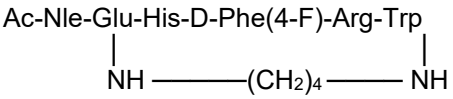
In one aspect, there is provided a cyclic peptide having the structure:



or a pharmaceutically acceptable salt thereof.

In the foregoing cyclic peptide, the pharmaceutically acceptable salt may be an acetate salt or alternatively may be a trifluoroacetate salt.

In another example, there is provided a cyclic peptide which is:



or a pharmaceutically acceptable salt thereof.

In another aspect, there is further provided a pharmaceutical composition comprising the cyclic peptides as set forth above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, there is provided the cyclic peptide as described herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect, there is provided the pharmaceutical composition as described herein for use in therapy.

The disclosure further includes a method for treatment of a melanocortin receptor-mediated disease, indication, condition or syndrome in a human or non-human mammal, comprising the step of administering pharmaceutical composition comprising one or more of the cyclic peptides as set forth above. The disclosure further includes a method for treating a condition responsive to changes in melanocortin receptor function in a human or non-human mammal, comprising the step of administering a pharmaceutical composition comprising the one or more of the cyclic peptides as set forth above. In the method for treating, the melanocortin receptor-mediated disease, indication, condition or syndrome in a human may be ocular inflammation, and the pharmaceutical composition may be an aqueous pharmaceutical composition for administration to the surface of the eye.

In another aspect, there is provided use of the pharmaceutical composition as described herein in the manufacture of a medicament for treatment of a melanocortin receptor-mediated disease, indication, condition or syndrome in a human;

wherein the melanocortin receptor-mediated disease, indication, condition or syndrome in a human is ocular inflammation.

The ocular inflammation responses to changes in melanocortin receptor function may be caused by an ocular condition, wherein the ocular condition is dry eye disease, corneal ulcer, corneal erosion, corneal abrasion, corneal degeneration, corneal perforation, corneal scarring, epithelial defect, keratoconjunctivitis, idiopathic uveitis, corneal transplantation, age-related macular degeneration, diabetic eye, blepharitis, glaucoma, ocular hypertension, post-operative eye pain and inflammation, posterior segment neovascularization, proliferative vitreoretinopathy, cytomegalovirus retinitis, endophthalmitis, choroidal neovascular membrane, vascular occlusive disease, allergic eye disease, tumor, retinitis pigmentosa, eye infection, scleritis, ptosis, miosis, eye pain, mydriasis,

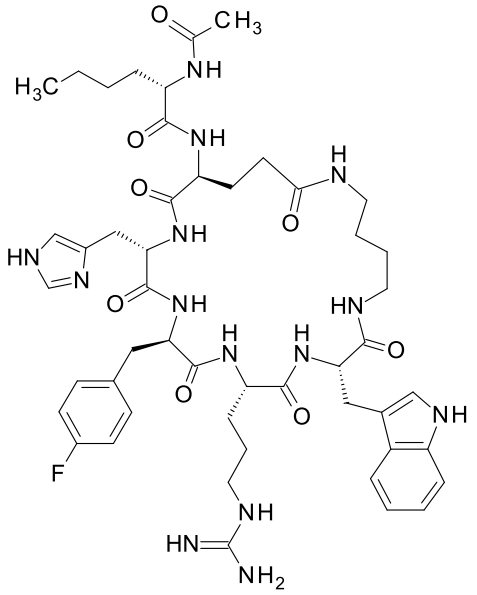
neuralgia, cicatrizing ocular surface disease, ocular infection, inflammatory ocular disease, ocular surface disease, corneal disease, retinal disease, ocular manifestations of systemic diseases, hereditary eye condition, ocular tumor, increased intraocular pressure, herpetic infection, pterygium, a wound sustained to ocular surface, post-photorefractive keratotomy eye pain and inflammation, thermal or chemical burn to the cornea, scleral wound, keratoconus or conjunctival wound. In one example, the inflammation is caused by dry eye disease or keratoconjunctivitis sicca.

In one example, there is provided a pharmaceutical composition for ocular administration wherein the pharmaceutically acceptable carrier is an aqueous solution comprising about 2.79 mg/mL of trisodium citrate dihydrate, about 9 mg/mL of sodium chloride and about 1 mg/mL of polysorbate 80. In the pharmaceutical composition the cyclic peptide may be in a trifluoroacetic acid salt form at a concentration of about 1.0 µg/mL. The pharmaceutical composition may further comprise about 0.10 mg/mL anhydrous citric acid. The pharmaceutical composition aqueous solution is at about pH 6.5, and the composition further comprises sodium hydroxide or hydrochloric acid as needed to adjust pH. The disclosure provides a method of treating dry eye disease or keratoconjunctivitis sicca comprising administering no more than about 50 µL of the pharmaceutical composition no more often than about three times per day. Preferably no more than about 150 ng of cyclic peptide or pharmaceutically acceptable salt thereof is administered per eye per day.

In another aspect, there is provided use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating dry eye disease or keratoconjunctivitis sicca wherein no more than 50 µL of the pharmaceutical composition as described herein is to be administered per eye no more often than three times per day.

In another aspect, there is provided use of an aqueous solution of the cyclic peptide as described herein in the manufacture of a medicament for treating dry eye disease or keratoconjunctivitis sicca wherein the aqueous solution of the cyclic peptide is to be administered to the surface of each eye.

The disclosure provides a method of treating dry eye disease or keratoconjunctivitis sicca comprising administering to the surface of the eye no more than about 150 ng per day of a melanocortin receptor-specific peptide with an EC_{50} value of less than 1 nM at each of MC1r and MC5r per eye in divided doses administered no more than three times per day. The dose administered may be less than 150 ng/eye/day of a peptide of the disclosure, and may be about 100 ng/eye/day or about 50 ng/eye/day of a peptide of the disclosure. The peptide is an agonist or partial agonist at each of MC1rand MC5r, with EC_{50} values determined by cAMP production using the HTRF detection method as performed by CEREP. In one example, the melanocortin receptor-specific peptide is a cyclic peptide of the structure:



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There is provided a cyclic peptide template which may be utilized in making receptor-specific peptides for biological receptors.

There is provided a melanocortin receptor-specific peptide-based pharmaceutical composition for use in treatment of melanocortin receptor-mediated diseases, indications, conditions and syndromes.

There is provided a peptide-based melanocortin receptor-specific pharmaceutical, wherein the peptide is selective and an agonist for MC1r and is an antagonist at MC4r.

There is provided a peptide-based melanocortin receptor-specific pharmaceutical, wherein the peptide is selective and an agonist for MC1r and is a partial agonist at MC4r.

There is provided a receptor-specific peptide which functionally active at one or more melanocortin receptors at subnanomolar EC_{50} values.

There is provided a melanocortin receptor-specific peptide which is an agonist or partial agonist at MC1r and MC5r at EC_{50} values of less than 1 nM.

Other aspects and novel features, and the further scope of applicability of the present disclosure will be set forth in part in the detailed description to follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the disclosure. The aspects of the disclosure may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated into and form a part of the specification, illustrate one or more embodiments of the present invention and, together with the description, serves to explain the principles of the invention. The drawings are only for the purpose of illustrating one or more preferred embodiments of the invention and are not to be construed as limiting the invention.

FIG 1A is a box/whisker plot, indicating the median (line), 25th/75th percentile (box), mean (+) and the (whiskers) of the corneal fluorescein score on day 12, following exposure on day 1 to a controlled desiccating environment with transdermal administration of scopolamine to establish disease prior to any treatment. Individual data points are depicted as filled circles. The number of eyes (n) was 24 per group, except for the untreated group (n =14).

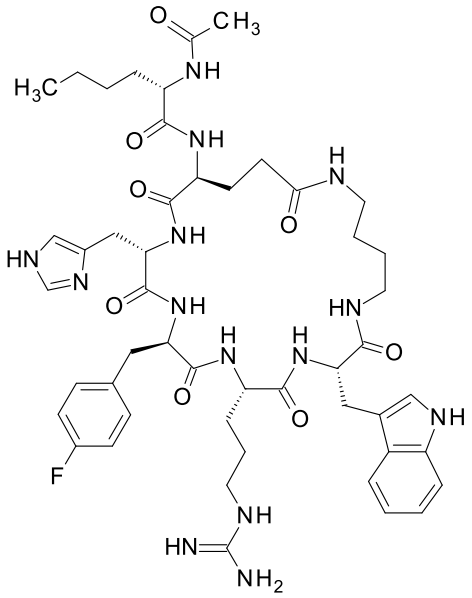
FIG 1B is a box/whisker plot, indicating the median (line), 25th/75th percentile (box), mean (+) and the (whiskers) of the corneal fluorescein score on day 24, following treatment commencing on day 13 of the groups in FIG 1A. Individual data points are depicted as filled circles. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ versus untreated eyes.

FIG 2 are box/whisker plots of the data as in FIG 1A and FIG 1B, showing comparisons by treatment between day 12 (prior to treatment) and day 24 (after 12 days of topical treatment with test compounds) for untreated eyes, PBS (vehicle control phosphate buffered saline) and each test compound. Peptide No. 60 administered at doses between 10^{-2} and 10^{-4} mg/mL resulted in a statistically significantly improvement of corneal fluorescein scores from day 12 to day 24.

CLAIMS

We claim:

1. A cyclic peptide having the structure



or a pharmaceutically acceptable salt thereof.

2. The cyclic peptide according to claim 1, which is an acetate salt or a trifluoroacetate salt.

3. A pharmaceutical composition comprising the cyclic peptide according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

4. Use of the pharmaceutical composition of claim 3 in the manufacture of a medicament for treatment of a melanocortin receptor-mediated disease, indication, condition or syndrome in a human;

wherein the melanocortin receptor-mediated disease, indication, condition or syndrome in a human is ocular inflammation.

5. The use according to claim 4 wherein:

(i) the pharmaceutical composition is an aqueous pharmaceutical composition for administration to the surface of the eye; or

(ii) the inflammation is caused by an ocular condition, wherein the ocular condition is dry eye disease, corneal ulcer, corneal erosion, corneal abrasion, corneal degeneration, corneal perforation, corneal scarring, epithelial defect, keratoconjunctivitis, idiopathic uveitis, corneal transplantation, age-related macular degeneration, diabetic eye, blepharitis, glaucoma, ocular hypertension, post-operative eye pain and inflammation, posterior segment neovascularization, proliferative vitreoretinopathy, cytomegalovirus retinitis, endophthalmitis, choroidal neovascular membrane, vascular occlusive disease, allergic eye disease, tumor, retinitis pigmentosa, eye

infection, scleritis, ptosis, miosis, eye pain, mydriasis, neuralgia, cicatrizing ocular surface disease, ocular infection, inflammatory ocular disease, ocular surface disease, corneal disease, retinal disease, ocular manifestations of systemic diseases, hereditary eye condition, ocular tumor, increased intraocular pressure, herpetic infection, pterygium, a wound sustained to ocular surface, post-photorefractive keratotomy eye pain and inflammation, thermal or chemical burn to the cornea, scleral wound, keratoconus or conjunctival wound.

6. The use according to claim 5 wherein the inflammation is caused by dry eye disease or keratoconjunctivitis sicca.

7. The pharmaceutical composition of claim 3 wherein the pharmaceutically acceptable carrier is an aqueous solution comprising about 2.79 mg/mL of trisodium citrate dihydrate, about 9 mg/mL of sodium chloride and about 1 mg/mL of polysorbate 80.

8. The pharmaceutical composition according to claim 7 wherein the aqueous solution is at about pH 6.5, and the composition further comprises sodium hydroxide or hydrochloric acid as needed to adjust pH.

9. The pharmaceutical composition of claim 7 wherein the cyclic peptide is in a trifluoroacetic acid salt form at a concentration of about 1.0 µg/mL.

10. The pharmaceutical composition of claim 9 further comprising about 0.10 mg/mL anhydrous citric acid.

11. Use of the pharmaceutical composition of claim 9 in the manufacture of a medicament for treating dry eye disease or keratoconjunctivitis sicca wherein no more than 50 µL of the pharmaceutical composition of claim 9 is to be administered per eye no more often than three times per day.

12. The use according to claim 11 wherein no more than 150 ng of cyclic peptide or pharmaceutically acceptable salt thereof is to be administered per eye per day.

13. Use of an aqueous solution of the cyclic peptide according to claim 1 or 2 in the manufacture of a medicament for treating dry eye disease or keratoconjunctivitis sicca wherein the aqueous solution of the cyclic peptide is to be administered to the surface of each eye.

14. The use according to claim 13 wherein no more than 150 ng of the cyclic peptide is to be administered per eye per day as an eye drop.

15. The cyclic peptide according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, for use in therapy.

16. The pharmaceutical composition according to any of claims 3 or 7 to 10 for use in therapy.