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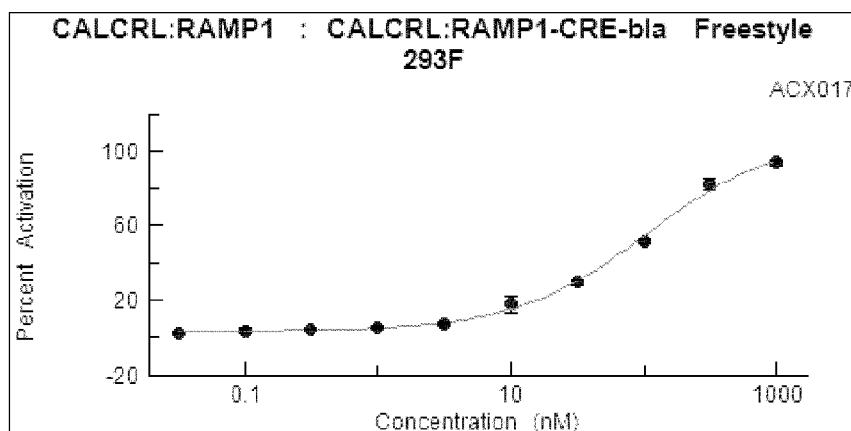


Figure 1

(57) Abstract: The embodiments provide a calcitonin gene-related peptide (CGRP) agonist peptide or pharmaceutically acceptable salt thereof, including pharmaceutical compositions comprising a CGRP agonist peptide. The embodiments further provide treatment methods, including method of treating metabolic disorders and metabolic disorders selected from metabolic syndrome, diabetes and obesity. The methods involve administering to a subject in need thereof an effective amount of CGRP peptide.

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CGRP AGONIST PEPTIDES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application 61/860,244 filed on July 30, 2013 and entitled "CGRP AGONIST PEPTIDES," the entirety of which is hereby incorporated by reference herein.

REFERENCE TO SEQUENCE LISTING

[0002] The present application is being filed along with a sequence listing in Electronic format. The Sequence Listing is provided as a file entitled CSOAR.002WO.TXT, created July 25, 2014 which is approximately 8 kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0003] The present invention relates to peptide agonists of the calcitonin/calcitonin gene-related peptide (CT/CGRP) family of peptide hormones and therapeutic uses thereof.

Description of the Related Art

[0004] The CT/CGRP peptide family includes calcitonin gene-related peptide (CGRP), adrenomedullin (ADM), intermedin (IM), calcitonin (CT) and amylin. The biological actions of these peptides are mediated *via* binding to two closely related type II G protein-coupled receptors, the calcitonin receptor (CTR) and the calcitonin receptor-like receptor (CRLR) (Christopoulos, *et al.* 1999, *Mol. Pharmacol.* **56**:235-242; Poyner *et al.* 2002 *Pharmacol. Rev.* **54**:233-246). Although the calcitonin receptor is the main mediator for calcitonin action, it preferentially binds amylin, when the receptor is associated with a receptor activity modifying protein (RAMP) (see, e.g., Tilikaratne, *et al.* 2000, *J. Pharmacol. Exp. Ther.* **294**(1):61-72). Cloning and functional studies have shown that CGRP, ADM, IM and, to a lesser extent, amylin likewise interact with different combinations of CRLR and the three receptor activity modifying proteins (RAMP-1, RAMP-2 and RAMP-3); see, e.g., McLatchie *et*

et al. 1998, *Nature* 393:333-339 and Roh *et al.* 2004, *JBC* 279(8):7264-7274). In fact, co-expression of the calcitonin receptor-like receptor (CRLR) and receptor activity-modifying proteins (RAMPs) is required to generate functional receptors for calcitonin gene-related peptide (CGRP), adrenomedullin (ADM) and intermedin (IM). The formation of heterodimers between RAMPs and CRLR is essential for the proper cell surface targeting and pharmacological characteristics of CGRP, ADM and IM receptors. Co-expression of RAMP-1 with CRLR leads to the formation of a CGRP receptor, whereas RAMP-2 and RAMP-3 co-expression with CRLR form ADM and IM receptors respectively (Miret, *et al.* 2002, *JBC* 277(9):6881-6887.) IM has been shown to be a nonselective agonist for all three RAMP/CRLR co-receptors.

[0005] The physiological functions of the hormone peptides in the CT/CGRP family are determined by receptor-binding specificity and the tissue expression profiles of individual ligands and their respective receptors and have been shown to be involved in cardiovascular morphogenesis, sensory neurotransmission, inflammatory reactions, nociceptive behavior and glucose homeostasis (see, e.g., Hay, *et al.* 2001, *Trends Pharmacol. Sci.* 22:57-59; Shindo, *et al.* 2001, *Circulation* 104:1964-1971; Zhang *et al.* 2001, *Pain* 89:265-273; Salmon *et al.* (1999) *Neuroreport* 10:849-854; Salmon, *et al.* 2001, *Nat. Neurosci.* 4: 357-358; and Mulder, *et al.* 2000, *Am. J. Physiol.* 278:E684-E691).

[0006] Calcitonin gene-related peptide (CGRP) is a peptide which, in several species, exists in two forms, designated CGRP-alpha and CGRP-beta (or CGRP-I and CGRP-II, respectively). CGRP peptides are highly conserved across species, for example, human and rat CGRP-alpha peptides share 89% amino acid homology (the mature peptides differing by four amino acids) compared to 92% amino acid homology between human alpha- and beta-CGRP (which differ by 3 amino acids). (See for example, Ma, H. 2004, *Nature and Science* 2(3):41-47.) A well-studied peptide in the CT/CGRP family of peptide hormones, CGRP is a 37 amino acid vasoactive neuropeptide that is released from sensory, motor and enteric nerves comprising an amphiphilic α -helical secondary structure in the amino acid sequence between residues 8-25. CGRP has potent vasodilatory and cardiotonic action, as described, for example, in U.S. Pat. No. 4,530,838 to Evans, *et al.* CGRP is present in both the central and peripheral nervous systems and is concentrated in those areas of the body receiving sensory input from the dorsal horn with limited amounts associated with autonomic input. In the brain, the peptide is present in the nuclei of sensory and motor cranial nerves and in cell bodies in the hypothalamus, preoptic area, ventromedial thalamus, hippocampus, and the like (Poyner, D. 1992, *Pharmac. Ther.* 56:23-51).

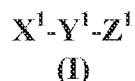
[0007] CGRP is known to be involved in various pharmacological effects, such as: 1) vasodilation, 2) muscle and liver AMP kinase (AMPK) activation and lipolysis and/or fat

oxidation, 3) reduction in food intake, 4) inhibition of gastric emptying and modification of gut function and 5) increased glycolysis and inhibition of glycogen synthesis. The net physiological significance of these effects is not completely understood; however, evidence of CGRP's role in fatty acid oxidation and regulation of lipid availability and utilization has been demonstrated (Danaher, et al, 2008 *Endocrinology* 149(1):154-160). Studies have demonstrated CGRP's role in inhibition of food intake including evidence that its action is via the paraventricular nucleus (PVN) of the hypothalamus. (See for example, Martinez-Alvarez, RM, et al. 2009 *Peptides* 30(4):803-807 and Dhillon, WS, et al. 2002, *Endocrine Abstracts* 3OC43; ISSN1470-3947.) Additionally, it has been shown that CGRP stimulate GLP-1 secretion, a protein known to play an important role in amelioration of diabetes.

[0008] Metabolic syndrome is a disease state manifested by obesity, insulin resistance, dyslipidemia and hypertension. Today, these four manifestations are treated by selective treatment paradigms. Native CGRP has a half-life of less than 30 minutes, and a short duration of pharmacological actions after CGRP infusions is evident. Due to vasodilatory effects of administered CGRP, *in vivo* pharmacological studies of native CGRP can be difficult due to the secondary effects of vasodilation and compensatory vasoconstrictive actions. Thus, the pharmacological usefulness of CGRP, particularly with respect to long-term or chronic use thereof, requires the generation of CGRP analogues with prolonged action and some effects may even only be obtained with longer-acting analogues. Similarly, to be viable as a therapeutic agent, particularly for chronic use, analogues having prolonged action are desirable.

SUMMARY OF THE INVENTION

[0009] In one aspect, the present invention provides calcitonin gene-related peptide (CGRP) agonists comprising the structure of Formula I:



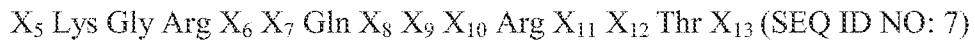
wherein:

\mathbf{X}^1 is an N-terminal fragment comprising at least about five to about seven amino acid residues having the general formula:



wherein \mathbf{X}_1 is Ala or Cys or is not present, \mathbf{X}_2 is Cys, Ser or Gly, provided however that at least one of \mathbf{X}_1 and \mathbf{X}_2 is Cys and only one of \mathbf{X}_1 or \mathbf{X}_2 is Cys, \mathbf{X}_3 is Asp or Asn and \mathbf{X}_4 is Ala or Ser and wherein the terminal Cys of \mathbf{X}^1 is capable of forming a disulfide bridge with the Cys residue in \mathbf{X}_1 or \mathbf{X}_2 ;

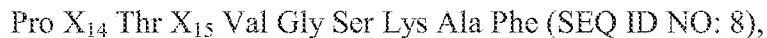
Y^1 is a central core comprising at least about 12 to about 24 and preferably about 15 amino acid residues wherein at least some of the residues of the central core are capable of forming an α -helix under physiological conditions, said central core having the general formula:



wherein X_5 is Val or Met, X_6 is Lys or Tyr, X_7 is Ser or Thr, X_8 is Asp or Glu, X_9 is Phe or Lys, X_{10} is His or Asn, X_{11} is Phe or Lys, X_{12} is His or Gln, X_{13} is Phe or Tyr;

and

Z^1 is a C-terminal fragment comprising at least about six to about twelve amino acid residues, preferably about ten amino acid residues, said C-terminal fragment comprising a C-terminal amide, said fragment having the general formula:



wherein X_{14} is Arg or Gln and X_{15} is Asn or Ala;

or pharmaceutically acceptable salt thereof, wherein said CGRP agonist has a higher binding affinity for human CGRP receptor than does human CGRP.

[0010] In some embodiments, X^1 comprises 6 or 7 amino acids. In some embodiments, Y^1 comprises 15 amino acids. In some embodiments, Z^1 comprises 10 amino acids. In some embodiments, X^1 comprises 6 or 7 amino acids, Y^1 comprises 15 amino acids and Z^1 comprises 10 amino acids.

[0011] In some embodiments, X^1 is Cys, and X^2 is Ser or Gly. In some embodiments, X^2 is Cys, and X^1 is Ala. In some embodiments, X^1 comprises SEQ ID NO: 9. In some embodiments, Z^1 comprises SEQ ID NO: 10.

[0012] In some embodiments, a calcitonin gene-related peptide (CGRP) agonist is provided. In some embodiments, the calcitonin gene-related peptide (CGRP) agonist selected from the group comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 and SEQ ID NO:5 or a pharmaceutically acceptable salt thereof. In some embodiments, the calcitonin gene-related peptide (CGRP) agonist comprises at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 and SEQ ID NO:5 or a pharmaceutically acceptable salt thereof. In some embodiments, the calcitonin gene-related peptide (CGRP) agonist comprises at least 80% sequence identity to the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 and SEQ ID NO:5 or a pharmaceutically acceptable salt thereof.

[0013] In some embodiments, the calcitonin gene-related peptide (CGRP) agonist comprises an N-terminal addition of an XTENS polypeptide. In some embodiments, the

calcitonin gene-related peptide (CGRP) agonist comprises an amino terminus modified with a derivative group. In some embodiments, the derivative group is selected from acetyl, aryl, aralkyl, acyl, epoxysuccinyl and cholestryl groups.

[0014] In some embodiments, the calcitonin gene-related peptide (CGRP) agonist comprises a carboxy-terminus modified with a derivative group. In some embodiments, the derivative group is selected from alcohol, aldehyde, epoxysuccinate, acid halide, carbonyl, halomethane, diazomethane groups and carboxamide. In some embodiments, the calcitonin gene-related peptide (CGRP) agonist comprises a C-terminal carboxy group replaced by an amide group. In some embodiments, the amide group comprises the structure $-\text{C}(\text{O})\text{NH}_2$.

[0015] In some embodiments, a pharmaceutical composition comprising a calcitonin gene-related peptide (CGRP) agonist of the present invention is provided. In some embodiments, the pharmaceutical composition comprises an acceptable excipient and any of the embodiments described above.

[0021] In some embodiments, a method of treating a metabolic disorder is provided. In some embodiments, the method comprises administering to a subject in need thereof an effective amount of the calcitonin gene-related peptide (CGRP) agonist of the present invention. In some embodiments, the subject is human.

[0022] In some embodiments, a method of treating a metabolic disorder selected from the group comprising metabolic syndrome, diabetes and obesity is provided. In some embodiments, the method comprises administering to a subject in need thereof an effective amount of the calcitonin gene-related peptide (CGRP) agonist. In some embodiments, the subject is human.

[0023] In some embodiments, a method of increasing glycolysis in a subject is provided. In some embodiments, the method comprises administering an effective amount of the calcitonin gene-related peptide (CGRP) agonist of the present invention. In some embodiments, a method of increasing AMPK activation in a subject is provided. In some embodiments, the method comprises administering an effective amount of the calcitonin gene-related peptide (CGRP) agonist of the present invention.

[0024] In some embodiments, the subject is suffering from insulin resistance. In some embodiments, the subject is suffering from type-2 diabetes mellitus. In some embodiments, the subject is suffering from hypertension. In some embodiments, the subject is suffering from dyslipidaemia. In some embodiments, the subject is suffering from atherosclerosis. In some embodiments, the subject is suffering from thrombosis.

BRIEF DESCRIPTION OF THE DRAWINGS

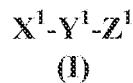
[0025] FIG. 1 provides results of the CALCRL:RAMP1 - CRE-bla Freestyle 293F agonist screen described in **Example 1** below. The graph of concentration of ACX017 (SEQ ID NO: 1) versus percent activation of the CGRP receptor demonstrates that a CGRP agonist of the present invention activated the CGRP receptor with an EC₅₀ concentration of about 105nM.

[0026] FIG. 2 provides results of the CALCRL:RAMP3 - CRE-bla Freestyle 293F agonist screen described in **Example 1** below. The graph of concentration of ACX017 (SEQ ID NO: 1) versus percent activation of the adrenomedullin 2 (AM2) receptor demonstrates that a CGRP agonist of the present invention did not activate the adrenomedullin 2 (AM2) receptor.

[0027] FIGS. 3-6 provide results of the four-day food intake study, described in **Example 2** herein. The effect on cumulative food intake for each of Days 1-4 are shown in FIGS. 3-6, respectively. Graphed is cumulative food intake of each of the test group (single dose of ACX017 (SEQ ID NO:1) and placebo group over the course of eight hours.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0028] In one aspect, the present invention provides calcitonin gene-related peptide agonist having the structure of Formula I:



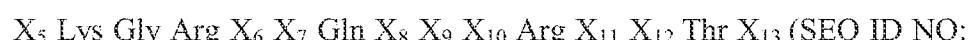
wherein:

\mathbf{X}^1 is an N-terminal fragment comprising at least about five to about seven amino acid residues having the general formula:



wherein \mathbf{X}_1 is Ala or Cys or is not present, \mathbf{X}_2 is Cys, Ser or Gly, provided however that at least one of \mathbf{X}_1 and \mathbf{X}_2 is Cys and only one of \mathbf{X}_1 or \mathbf{X}_2 is Cys, \mathbf{X}_3 is Asp or Asn and \mathbf{X}_4 is Ala or Ser and wherein the terminal Cys of \mathbf{X}^1 is capable of forming a disulfide bridge with the Cys residue in \mathbf{X}_1 or \mathbf{X}_2 ;

\mathbf{Y}^1 is a central core comprising at least about 12 to about 24 and preferably about 15 amino acid residues wherein at least some of the residues of the central core are capable of forming an α -helix under physiological conditions, said central core having the general formula:



wherein X_5 is Val or Met, X_6 is Lys or Tyr, X_7 is Ser or Thr, X_8 is Asp or Glu, X_9 is Phe or Lys, X_{10} is His or Asn, X_{11} is Phe or Lys, X_{12} is His or Gln, X_{13} is Phe or Tyr;

and

Z^1 is a C-terminal fragment comprising at least about six to about twelve amino acid residues, preferably about ten amino acid residues, said C-terminal fragment comprising a C-terminal amide, said fragment having the general formula:

Pro X_{14} Thr X_{15} Val Gly Ser Lys Ala Phe (SEQ ID NO:8),

wherein X_{14} is Arg or Gln and X_{15} is Asn or Ala;

or pharmaceutically acceptable salt thereof, wherein said CGRP agonist has a higher binding affinity for human CGRP receptor than does human CGRP.

[0029] In some embodiments, X^1 comprises the sequence, SEQ ID NO: 9 (ACDTATC).

[0030] In some embodiments, Z^1 comprises the sequence, SEQ ID NO: 10 (PRTNVGSKAF).

[0031] Some CGRP agonists, according to the present invention, comprise: an amino acid sequence having at least 80%, preferably 90%, sequence identity to the amino acid sequence of SEQ ID NOS: 1, 2, 3, 4 or 5 wherein said peptide retains agonist activity.

[0032] Some embodiments provide a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a calcitonin gene-related peptide agonist as disclosed and described herein.

[0033] Some embodiments provide a method of treating a condition associated with insufficient levels of CGRP or that are ameliorated by increased CGRP said method comprising the administration of a calcitonin gene-related peptide agonist as disclosed and described herein, to an individual, the method comprising administering to the individual an effective amount of a calcitonin gene-related peptide agonist as disclosed and described herein.

[0034] Some embodiments provide a calcitonin gene-related peptide agonist having the structure selected from the following peptide sequences, listed in Table 1.

Table 1

| | |
|---|--------------------------------|
| NH ₂ -ACDTATCVLGRLSQELHRLQTYPRTNVGSKAF-NH ₂ ; | (SEQ ID NO: 1)-NH ₂ |
| NH ₂ -ACDTATCVLGRLSQELHRLQTYPTNVGSKAF-NH ₂ ; | (SEQ ID NO: 2)-NH ₂ |
| NH ₂ -CDTATCVLGRLSQELHRLQTYPRTNVGSKAF-NH ₂ ; | (SEQ ID NO: 3)-NH ₂ |
| NH ₂ -CDTATCVLGRLSQELHRLQTYPTNVGSKAF-NH ₂ ; | (SEQ ID NO: 4)-NH ₂ |
| NH ₂ -ACDTATCMLGRYTQDFNRFHTFPRTNVGSKAF-NH ₂ ; | (SEQ ID NO: 5)-NH ₂ |

[0035] In some embodiments, the amino acid sequence of the calcitonin gene-related peptide agonist can be modified, relative to the sequence of SEQ ID NOS: 1, 2, 3, 4 or 5 such that the modification reduces the calcitonin gene-related peptide agonist's susceptibility to

enzymatic proteolysis. In some embodiments this modification may comprise the N-terminal addition of a sequence comprising all or part of the 864 residue XTENS polypeptide, a polypeptide that has been shown to increase protein stability after administration to a subject. See, for example, Schellenberger, *et al.*, 2009, *Nature Biotechnology* 27(12): 1186-1192, which is hereby incorporated by reference in its entirety.

DEFINITIONS

[0036] As used herein, “agonist” refers to a biologically active ligand which binds to its complementary biologically active receptor and activates the latter either to cause a biological response in the receptor or to enhance preexisting biological activity of the receptor.

[0037] As used herein, “C-terminal amide” refers to an amide moiety which replaces the C-terminal hydroxyl moiety usually present at the carboxy-terminus of a polypeptide, such that the polypeptide ends with a carboxamide (i.e., C(=O)-NH₂) rather than a C-terminal carboxy (i.e. C(=O)-OH) moiety. For a description of pharmaceutically acceptable amides as prodrugs, see Bundgaard, H. ed. 1985 *Design of Prodrugs* Elsevier Science Publishers, Amsterdam. These amides are typically formed from the corresponding carboxylic acid and an amine. Generally, amide formation can be accomplished *via* conventional synthetic techniques. See, for example, March, 1992 *Advanced Organic Chemistry*, 4th Ed., John Wiley & Sons, New York, p. 393 and Mark, *et al.* 1980 *Encyclopedia of Chemical Technology*, John Wiley & Sons, New York.

[0038] As used herein, the term “ α -helix” means a structural component that forms an α -helical protein structure or any other structural analogue which results in a similar positioning of the X¹ and Z¹ domains on a receptor.

[0039] As used herein, “pharmaceutically acceptable carrier” refers to a carrier medium which does not interfere with the effectiveness of the biological activity of the active ingredients and which is not toxic to the host or patient.

[0040] As used herein, “pharmaceutically acceptable salt” refers to the non-toxic alkali metal, alkaline earth metal, and ammonium salts commonly used in the pharmaceutical industry including the sodium, potassium, lithium, calcium, magnesium, barium, ammonium, and protamine zinc salts, which are prepared by methods well known in the art. The term also includes non-toxic acid addition salts, which are generally prepared by reacting the modified calcitonin gene-related peptide agonists disclosed herein with a suitable organic or inorganic acid. Representative salts include the hydrochloride, hydrobromide, sulfate, bisulfate, acetate, oxalate, valerate, oleate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate,

fumarate, succinate, tartrate, napsylate, and the like. Thus, the term refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, menthanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. For a description of pharmaceutically acceptable salts as prodrugs, see Bundgaard, H. ed., 1985 *Design of Prodrugs*, Elsevier Science Publishers, Amsterdam.

[0041] As used herein, “therapeutically- or pharmaceutically-effective amount” as applied to the compositions as disclosed herein refers to the amount of composition sufficient to induce a desired biological result. That result can be alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system.

[0042] The amino- and/or carboxy-terminus of the peptide compounds disclosed herein can be unmodified hydrogen. Alternatively, the amino- and/or carboxy-terminus of the peptide compound can be modified with a derivative group. Amino-derivative groups which can be present at the N-terminus of a peptide compound include acetyl, aryl, aralkyl, acyl, epoxysuccinyl and cholesteryl groups. Carboxy-derivative groups which can be present at the C-terminus of a peptide compound include alcohol, aldehyde, epoxysuccinate, acid halide, carbonyl, halomethane, diazomethane groups and carboxamide. In preferred embodiments, the amino terminus is unmodified hydrogen and the carboxy-terminus is modified with a carboxamide derivative group.

[0043] One-letter abbreviations for the canonical amino acids and three-letter abbreviations (in parentheses) are provided in Table 2:

Table 2

| | |
|---------------------|---|
| Alanine (Ala) | A |
| Glutamine (Gln) | Q |
| Leucine (Leu) | L |
| Serine (Ser) | S |
| Arginine (Arg) | R |
| Glutamic Acid (Glu) | E |
| Lysine (Lys) | K |
| Threonine (Thr) | T |
| Asparagine (Asn) | N |
| Glycine (Gly) | G |
| Methionine (Met) | M |
| Tryptophan (Trp) | W |
| Aspartic Acid (Asp) | D |
| Histidine (His) | H |
| Phenylalanine (Phe) | F |
| Tyrosine (Tyr) | Y |
| Cysteine (Cys) | C |
| Isoleucine (Ile) | I |
| Proline (Pro) | P |
| Valine (Val) | V |

[0044] Nomenclature and Symbolism for Amino Acids and Peptides by the UPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN) have been published in the following documents: *Biochem. J.*, 1984, 219, 345-373; *Eur. J. Biochem.*, 1984, 138, 9-5 37; 1985, 152, 1; 1993, 213, 2; *Internat. J. Pept. Prot. Res.*, 1984, 24, following p 84; *J. Biol. Chem.*, 1985, 260, 14-42; *Pure Appl. Chem.*, 1984, 56, 595-624; *Amino Acids and Peptides*, 1985, 16, 387-410; *Biochemical Nomenclature and Related Documents*, 2nd edition, Portland Press, 1992, pages 39-69.

[0045] Amino acids are sometimes referred to herein by the usual three letter codes and/or one letter codes. If, due to typing errors, there are deviations from the commonly used codes, the commonly used codes apply.

[0046] “Percent (%) amino acid sequence identity” with respect to the polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ClustalW2, Kalign, MAFFT, or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters

for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

PREPARTION OF PEPTIDES

Solid Phase Synthesis

[0047] The calcitonin gene-related peptide agonists described herein can be prepared by classical methods known in the art, for example, by using standard solid phase techniques. See, for example, Merrifield, 1963 *J. Am. Chem. Soc.* 85:2149, incorporated herein by reference in their entirety.

[0048] These solid phase peptide synthesis procedures are well known in the art and further described by J.M. Stewart and J.D. Young, 1984 *Solid Phase Peptide Syntheses* 2nd Ed., Pierce Chemical Company and by M. Bodanszky, 1993, *Principles of Peptide Synthesis*, 2nd Ed., Springer Laboratory.

C-Terminal Modifications

[0049] CGRP agonists of the present invention preferably comprise a C-terminal amide, wherein the C-terminal carboxyl group is replaced by an amide $-C(O)NR^3R^4$, wherein R³ and R⁴ are preferably hydrogen (H) but may either or both be a functional group selected, for example, to protect the C-terminal amide from enzymatic degradation and/or to prolong the half-life of the peptide compound *in vivo*, provided however such functional groups do not interfere with, or are modified or removed *in vivo* to permit, binding of the peptide compound to the CGRP receptor. Such functional groups are well known to those of skill in the art; see for example, Kahns, A. and Bundgaard, H. 1991 *Pharmaceutical Research* 8(12):1533-1538. Techniques for synthesis of such C-terminal amides are also well known to those of skill in the art.

[0050] In some embodiments, the calcitonin gene-related peptide agonists as disclosed and described herein may also be prepared by recombinant DNA techniques well known in the art. Such recombinantly produced CGRP peptide agonists may be further modified, for example to replace the C-terminal carboxyl group with an amide, after recombinant production using techniques well known in the art, including for example, enzymatic conversion of the acid to the amide.

Pharmacological Formulations

[0051] The compositions containing the CGRP peptide agonists of the present invention can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, compositions are administered to a patient already suffering from a disease, as

described above, in an amount sufficient to cure or at least partially arrest or ameliorate the symptoms of the disease and/or its complications. An amount adequate to accomplish this is defined as a “therapeutically effective amount” or “therapeutically effective dose”. Amounts effective for this use will depend, for example, on the severity of the disease and the weight and general state of the patient, and can be readily determined by one of ordinary skill in the art.

[0052] In prophylactic applications, compositions containing the compounds disclosed herein are administered to a patient susceptible to or otherwise at risk of a particular disease and are sufficient to prevent, delay or lessen the severity of the disease. Such an amount is defined to be a “prophylactically effective amount” or “prophylactically effective dose.” In this use, the precise amounts again depend, for example, on the patient’s state of health and weight, and can be readily determined by one of ordinary skill in the art.

[0053] In some embodiments, a therapeutically effective amount of a compound of the present invention is administered to a subject (for example, patient or animal) suffering from insulin resistance, type-2 diabetes mellitus, hypertension, obesity, dyslipidaemia, atherosclerosis and/or thrombosis. The dosage ranges for the administration of a compound of this invention are those large enough to produce a therapeutic effect.

[0054] Some embodiments include pharmaceutical compositions comprising, as an active ingredient, at least one of the peptides disclosed herein in association with a pharmaceutical carrier or diluent. These pharmaceutical compositions can be administered by any means, as known to those of skill in the art, and include, without limitation, oral, pulmonary, parenteral (intramuscular, intraperitoneal, intravenous, or subcutaneous injection), inhalational (*via* a fine powder formulation, or aerosol), transdermal, intranasal or sublingual routes of administration and can be formulated in dosage forms appropriate for each route of administration. See, for example, Bernstein, *et al.* PCT Patent Publication No. WO 93/25221, published December 23, 1993; Pitt, *et al.* PCT Patent Publication No. WO 94/17784, published August 18, 1994; and Pitt, *et al.* European Patent Application 613,683, published September 7, 1994, each of which is incorporated herein by reference in its entirety.

[0055] Suitable routes of administration are likewise known to those of skill in the art and may include, for example and without limitation, oral, transmucosal or topical; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, intraperitoneal, intranasal, or intraocular injections, as well as needle-free subcutaneous delivery. The compounds can also be administered in sustained or controlled release dosage forms, including without limitation, depot injections, osmotic pumps, transdermal

(including electrotransport) patches, and the like, for prolonged and/or timed, pulsed administration at a predetermined rate.

[0056] The pharmaceutical compositions of the present embodiments may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes.

[0057] Pharmaceutical compositions for use in accordance with the present embodiments thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically and which are appropriate for the intended route of administration. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

[0058] Although the exact dosage will be determined on a drug-by-drug and disease-by-disease basis, in most cases, some generalizations regarding the dosage can be made, and those of skill in the pharmacology art will understand from the disclosure herein that appropriate doses can be determined using routine techniques. Usually the doses for a compound of this invention would fall in a concentration of from about 10^{-15} M to 10^{-5} M (for example, as measured in one or more of muscle, blood, serum or plasma).

[0059] The amount of a compound of this invention administered to an animal to achieve a desired level or concentration of the compound of this invention will depend on a number of factors well known to practitioners, such as compound half-life (for example, serum half-life), and the frequency and mode of administration. For illustration and not limitation, the dose of a compound of the present invention may be administered in the range from 20 picograms to 1 gram, more often between 3 nanograms and 500 micrograms per dose. In various embodiments, the unit dosage (in some cases daily dosage) is less than about 100 micrograms, less than about 10 micrograms, less than about 1 microgram, less than about 100 nanograms, less than about 10 nanograms, less than about 1 nanogram, less than about 100 picograms, or less than about 10 picograms.

[0060] Other ranges of a compound of this invention will be apparent to the skilled practitioner based on data from initial dose-response curves and other data that can be obtained by routine methods. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. In some embodiments, the composition is administered 1 to 4 times per day or as a single acute dose. In some embodiments, the peptides will be

administered for a period of continuous therapy, for example for a week or more, or for months or years.

[0061] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

[0062] Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[0063] A compound of the present invention can be formulated or co-administered with other active agents that, for example, also treat metabolic or cardiovascular diseases/disorders.

[0064] Throughout the specification, any recitation of a particular compound should be understood to encompass that compound and any (other) pharmaceutically acceptable salts thereof.

Other Utility

[0065] The compounds described herein are useful *in vitro* as unique tools for understanding the biological role of CGRP. The present compounds are also useful in the development of other compounds that bind to and activate CGRP receptors, because the present compounds provide important information on the relationship between structure and activity to facilitate such development.

EXAMPLES

[0066] The following examples are provided to further illustrate the instant embodiments. They are not meant to limit the scope of the embodiments.

EXAMPLE 1

[0067] Cell-based GPCR Profiling Assays. A representative CGRP agonist peptide according to the present invention, ACX017 (SEQ ID NO:1), was profiled against G-Protein Coupled Receptors (GPCRs) in cell-based assays to determine its agonist activity and dose response. Results of the CGRP and adrenomedullin receptor screens are provided below. Assays were performed using the SelectScreen® Cell-based GPCR Profiling Services by Life Technologies, Carlsbad, CA.

CALCRL:RAMP1 - CRE-bla Freestyle 293F - Agonist Screen (CGRP Receptor)

[0068] CALCRL:RAMP1-CRE-bla Freestyle 293F cells were thawed and resuspended in Assay Media (DMEM, 10% dialyzed FBS, 25 mM HEPES pH 7.3, 0.1 mM NEAA, 100 U/mL/100 µg/mL Pen/Strep) to a concentration of 312,500 cells/mL. 32 µL of cell suspension (10,000 cells) was added to each well of a 384-well Poly-D-Lysine assay plate. Cells in Assay Media were incubated for 16-24 hours in the plate at 37°C/5% CO2 in a humidified incubator. 4 µL of a 10X serial dilution of CGRP or ACX017 was added to appropriate wells of the plate. 4 µL of Assay Media was added to all wells to bring the final assay volume to 40 µL. The plate was incubated for 5 hours at 37°C/5% CO2 in a humidified incubator. 8 µL of 1 µM Substrate + Solution D Loading Solution was added to each well and the plate was incubated for 2 hours at room temperature. The plate was read on a fluorescence plate reader.

CALCRL:RAMP3 - CRE-bla Freestyle 293F - Agonist Screen (Adrenomedullin 2 Receptor)

[0069] CALCRL:RAMP3-CRE-bla Freestyle 293F cells were thawed and resuspended in Assay Media (DMEM, 10% dialyzed FBS, 25 mM HEPES pH 7.3, 0.1 mM NEAA, 100 U/mL/100 µg/mL Pen/Strep) to a concentration of 312,500 cells/mL. 32 µL of cell suspension (10,000 cells) was added to each well of a 384-well Poly-D-Lysine assay plate. Cells in Assay Media were incubated for 16-24 hours in the plate at 37°C/5% CO2 in a humidified incubator. 4 µL of a 10X serial dilution of Adrenomedullin or ACX017 were added to appropriate wells of the plate. 4 µL of Assay Media was added to all wells to bring the final assay volume to 40 µL. The plate was incubated for 5 hours at 37°C/5% CO2 in a humidified incubator. 8 µL of 1 µM Substrate + Solution D Loading Solution was added to each well and the plate was incubated for 2 hours at room temperature. The plate was read on a fluorescence plate reader.

[0070] The following controls were run on each plate for each individual cell line:

[0071] Full Agonist control. The full agonist control contained 0.1% DMSO, cells and a maximum concentration of the known agonist. The full agonist control was used to determine the upper end of the assay or 100% activation.

[0072] No Agonist control. The no agonist control contained 0.1% DMSO, cells and assay media in place of the agonist. The no agonist control was used to determine the lower end of the assay or 0% activation.

[0073] Cell-free Control. The cell-free control contained 0.1% DMSO and assay media. It was used to determine the background fluorescence for both coumarin and fluorescein wavelengths. This value was used for background subtraction.

[0074] Known Agonist. A known agonist titration was run on every plate for each cell-line to ensure the cell line was activated within an expected EC50/IC50 range as previously determined.

[0075] Results. As seen in **FIG. 1**, ACX017 demonstrated agonist activity against the CGRP receptor with an approximate EC50 concentration of 105nM. In contrast, **FIG. 2** shows that ACX017 did not activate the adrenomedullin 2 (AM2) receptor. As such ACX017 was shown to exhibit binding and functional specificity to the CGRP receptor in a dose dependent response.

EXAMPLE 2

[0076] Food Intake Study. The effect of a CGRP agonist, in accordance with the present invention, on food intake over time both within and across several days of treatment was evaluated. Study was performed by Explora BioLabs, San Diego, CA and animals treated in accordance with its IACUC standards.

[0077] Sprague Dawley Rats, male, 400g body weight (~12-14wks old) were acclimated for at least seven days to housing environment and a 12 hour light/dark reverse cycle (light overnight/dark during the day. Animals were purpose-bred, specific pathogen-free, and experimentally naïve at the start of the study. Animals had ad libitum access to special Rodent Diet with 60%kcal%fat (D12492, Research Diets, New Brunswick, NJ) and acidified water (pH 2.5-3.0) from arrival throughout the end of the study. Body weight at study initiation was at least 450g. Animals that had: 1) significantly low body weight, 2) severe dehydration, or 3) wounds from fighting were excluded from the study.

[0078] On Day 0, 12 animals were randomized into two groups, Test and Control, to obtain similar body weight averages between groups. Animals were dosed via a single intraperitoneal injection, with either ACX017 (SEQ. ID NO:1) (Test group) or vehicle (Control group) each day, for four days. On each day, dosing was performed in the hour prior to the end of the light phase. ACX017 was dosed at 150 µg/kg in a 10% DMSO aqueous solution. Both ACX017 and vehicle were delivered as 1mL/kg doses.

[0079] Food consumption was measured pre-dose and at 2, 4, 6 and 8 hours post dose. Food intake was measured by weighing food hoppers on Days 1, 2, 3 and four in the hour before end of the light phase and at 2, 4, 6 and 8 hours post dosing.

[0080] Average food intake for each of the Test and Control groups at each time point post dosing was determined. Cumulative food intake for each group over the entire test period (8 hours) is provided in graph form in **FIGS. 1-4** for each of Days 1-4, respectively.

[0081] Consistently, ACX017 suppressed appetite in the Test group for at least about four hours after dosing as evidenced by reduced food intake during that period compared to the Control group at four hours. As such ACX017 (SEQ ID NO: 1) can cause appetite suppression in a subject, as demonstrated.

[0082] All documents cited herein are hereby incorporated by reference in their entirety.

[0083] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity.

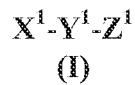
[0084] It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims (e.g., bodies of the appended claims) are generally intended as "open" terms (e.g., the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.). It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to embodiments containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (e.g., "a" and/or "an" should be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should be interpreted to mean at least the recited number (e.g., the bare recitation of "two recitations," without other modifiers, means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to "at least one of A, B, and C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., "a system having at least one of A, B, and C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to

“at least one of A, B, or C, etc.” is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., “a system having at least one of A, B, or C” would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase “A or B” will be understood to include the possibilities of “A” or “B” or “A and B.”

[0085] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

WHAT IS CLAIMED IS:

1. A calcitonin gene-related peptide (CGRP) agonist having the structure of Formula I:



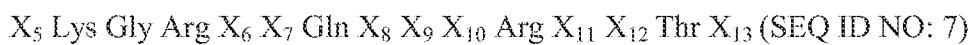
wherein:

\mathbf{X}^1 is an N-terminal fragment comprising at least about five to about seven amino acid residues having the general formula:



wherein \mathbf{X}_1 is Ala or Cys or is not present, \mathbf{X}_2 is Cys, Ser or Gly, provided however that at least one of \mathbf{X}_1 and \mathbf{X}_2 is Cys and only one of \mathbf{X}_1 or \mathbf{X}_2 is Cys, \mathbf{X}_3 is Asp or Asn and \mathbf{X}_4 is Ala or Ser and wherein the terminal Cys of \mathbf{X}^1 is capable of forming a disulfide bridge with the Cys residue in \mathbf{X}_1 or \mathbf{X}_2 ;

\mathbf{Y}^1 is a central core comprising at least about 12 to about 24 and preferably about 15 amino acid residues wherein at least some of the residues of the central core are capable of forming an α -helix under physiological conditions, said central core having the general formula:



wherein \mathbf{X}_5 is Val or Met, \mathbf{X}_6 is Lys or Tyr, \mathbf{X}_7 is Ser or Thr, \mathbf{X}_8 is Asp or Glu, \mathbf{X}_9 is Phe or Lys, \mathbf{X}_{10} is His or Asn, \mathbf{X}_{11} is Phe or Lys, \mathbf{X}_{12} is His or Gln, \mathbf{X}_{13} is Phe or Tyr;

and

\mathbf{Z}^1 is a C-terminal fragment comprising at least about six to about twelve amino acid residues, preferably about ten amino acid residues, said C-terminal fragment comprising a C-terminal amide, said fragment having the general formula:



wherein \mathbf{X}_{14} is Arg or Gln and \mathbf{X}_{15} is Asn or Ala;

or pharmaceutically acceptable salt thereof, wherein said CGRP agonist has a higher binding affinity for human CGRP receptor than does human CGRP.

2. The calcitonin gene-related peptide (CGRP) agonist according to Claim 1, wherein \mathbf{X}^1 comprises 6 or 7 amino acids.
3. The calcitonin gene-related peptide (CGRP) agonist according to Claims 1 or 2, wherein \mathbf{Y}^1 comprises 15 amino acids.
4. The calcitonin gene-related peptide (CGRP) agonist according to any one of Claims 1-3, wherein \mathbf{Z}^1 comprises 10 amino acids.

5. The calcitonin gene-related peptide (CGRP) agonist according to any one of Claims 1-4, wherein X^1 comprises 6 or 7 amino acids, Y^1 comprises 15 amino acids and Z^1 comprises 10 amino acids.
6. The calcitonin gene-related peptide (CGRP) agonist according to any one of Claims 1-5, wherein X^1 is Cys, and X^2 is Ser or Gly.
7. The calcitonin gene-related peptide (CGRP) agonist according to any one of Claims 1-5, wherein X^2 is Cys, and X^1 is Ala.
8. The calcitonin gene-related peptide (CGRP) agonist according to Claim 1, wherein X^1 comprises SEQ ID NO: 9.
9. The calcitonin gene-related peptide (CGRP) agonist according to Claim 1, wherein Z^1 comprises SEQ ID NO: 10.
10. A calcitonin gene-related peptide (CGRP) agonist selected from the group comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 and SEQ ID NO:5 or a pharmaceutically acceptable salt thereof.
11. A calcitonin gene-related peptide (CGRP) agonist comprising at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5, or a pharmaceutically acceptable salt thereof.
12. A calcitonin gene-related peptide (CGRP) agonist comprising at least 80% sequence identity to the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5 or pharmaceutically acceptable salt thereof.
13. The calcitonin gene-related peptide (CGRP) agonist of any one of claims 1-12, wherein the calcitonin gene-related peptide (CGRP) agonist comprises an N-terminal addition of an XTENS polypeptide.
14. The calcitonin gene-related peptide (CGRP) agonist of any one of claims 1-13, wherein the calcitonin gene-related peptide (CGRP) agonist comprises an amino terminus modified with a derivative group.
15. The calcitonin gene-related peptide (CGRP) agonist of claim 14, wherein the derivative group is selected from acetyl, aryl, aralkyl, acyl, epoxysuccinyl and cholesteryl groups.
16. The calcitonin gene-related peptide (CGRP) agonist of any one of claims 1-15, wherein the calcitonin gene-related peptide (CGRP) agonist comprises a carboxy terminus modified with a derivative group.

17. The calcitonin gene-related peptide (CGRP) agonist of claim 16, wherein the derivative group is selected from alcohol, aldehyde, epoxysuccinate, acid halide, carbonyl, halomethane, diazomethane groups and carboxamide.
18. The calcitonin gene-related peptide (CGRP) agonist of any one of claims 1-15, wherein the calcitonin gene-related peptide (CGRP) agonist comprises a C-terminal amide group.
19. The calcitonin gene-related peptide (CGRP) agonist of claim 18, wherein the amide group is $-\text{C}(\text{O})\text{NH}_2$.
20. A pharmaceutical composition comprising:
a pharmaceutically acceptable excipient; and
the calcitonin gene-related peptide (CGRP) agonist of any one of claims 1-19.
21. A method of treating a metabolic disorder comprising administering to a subject in need thereof an effective amount of the calcitonin gene-related peptide (CGRP) agonist according to any one of claims 1-19.
22. The method of claim 21, wherein the metabolic disorder is selected from the group comprising diabetes and obesity.
23. The method of claim 22, wherein the subject is human.

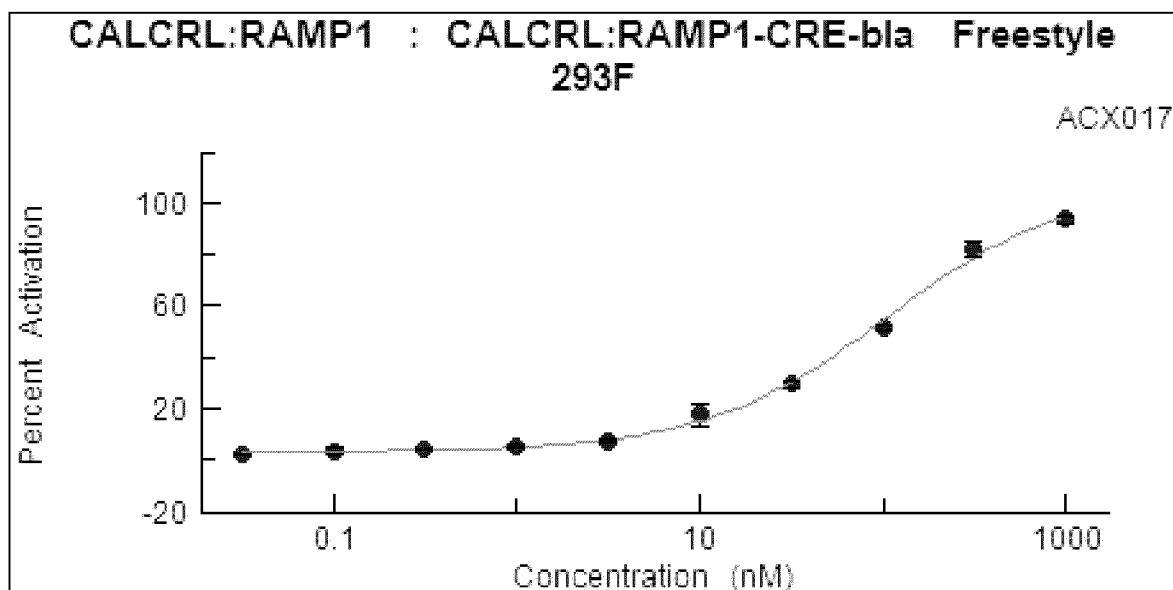


Figure 1

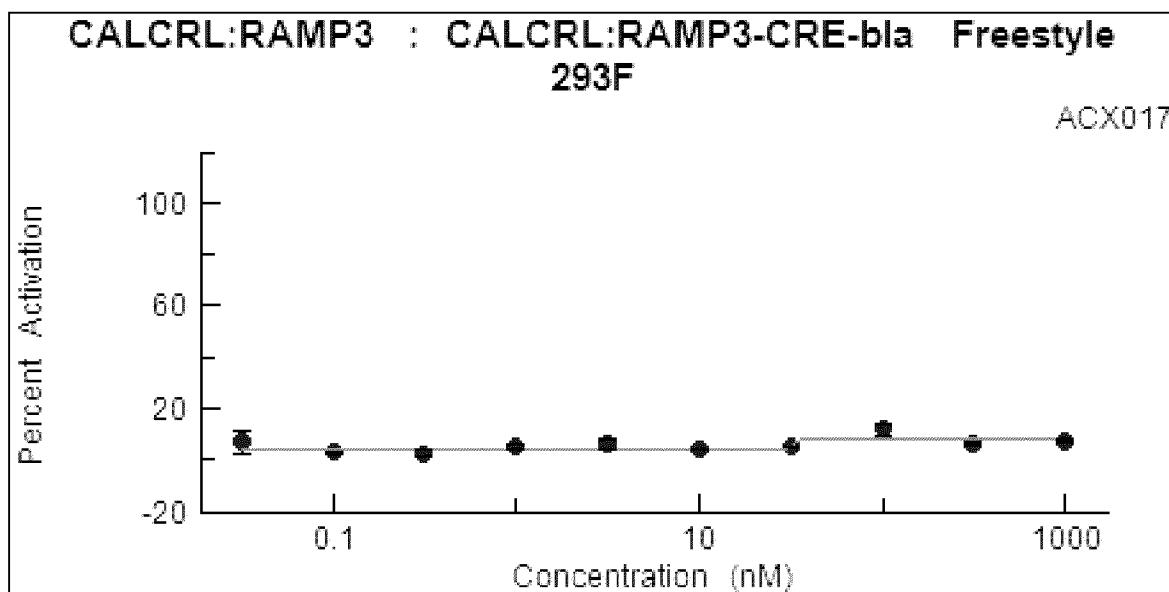


Figure 2

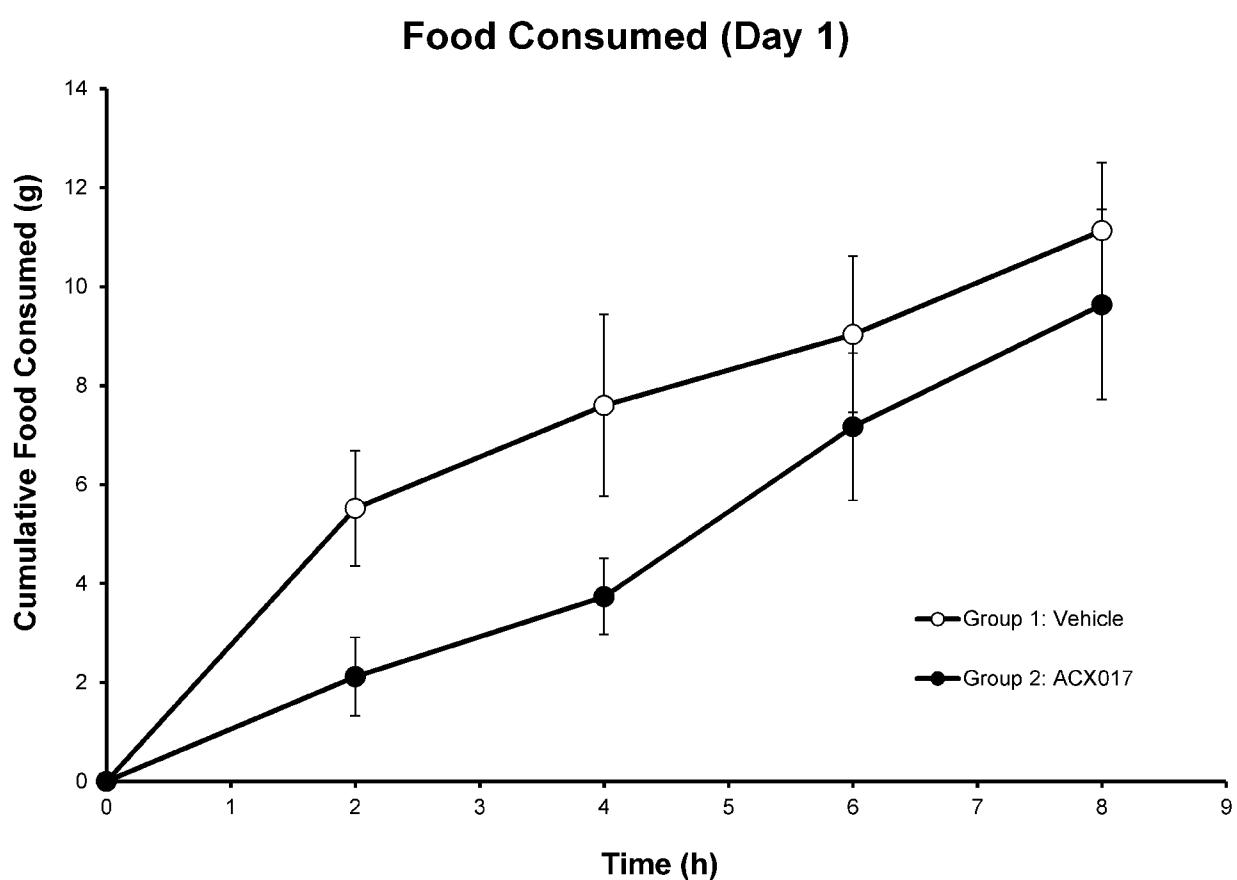


Figure 3

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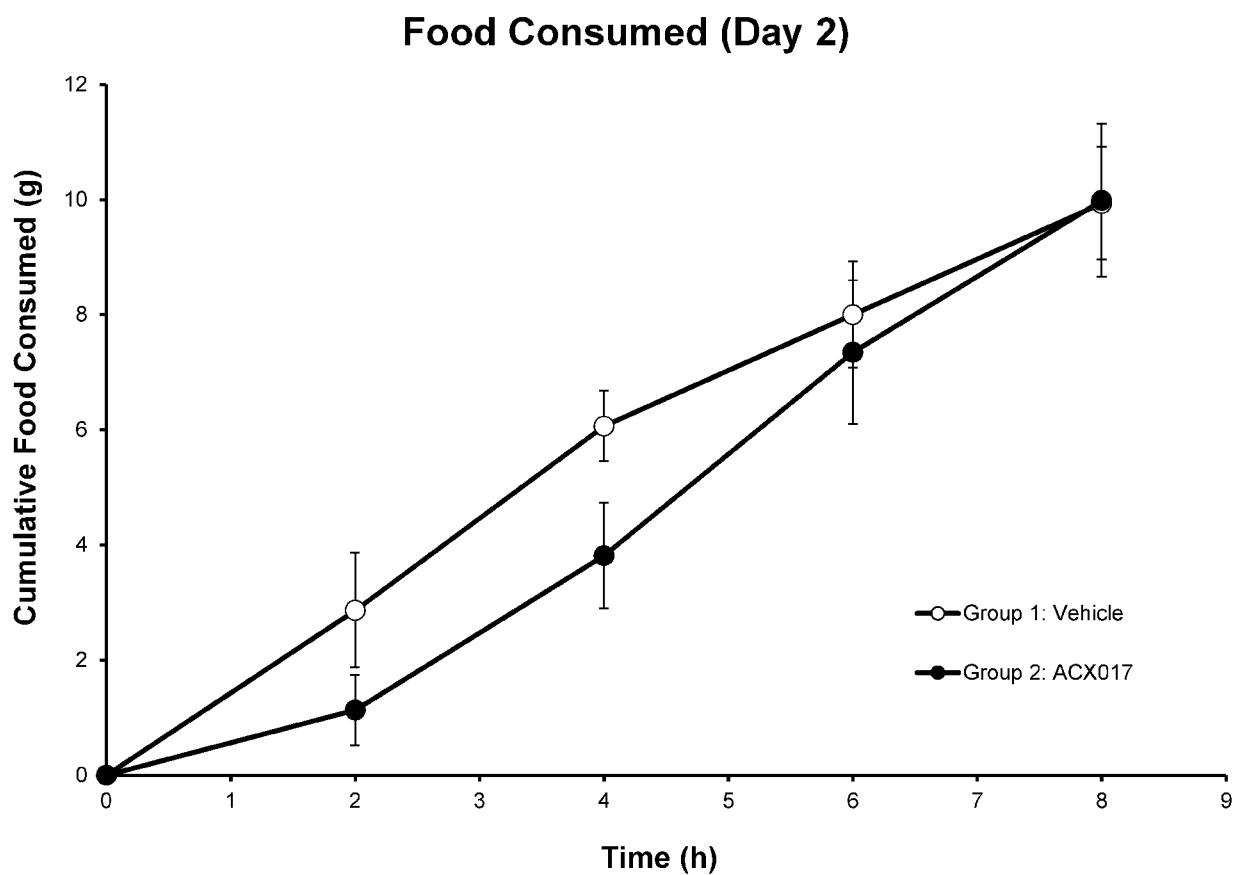


Figure 4

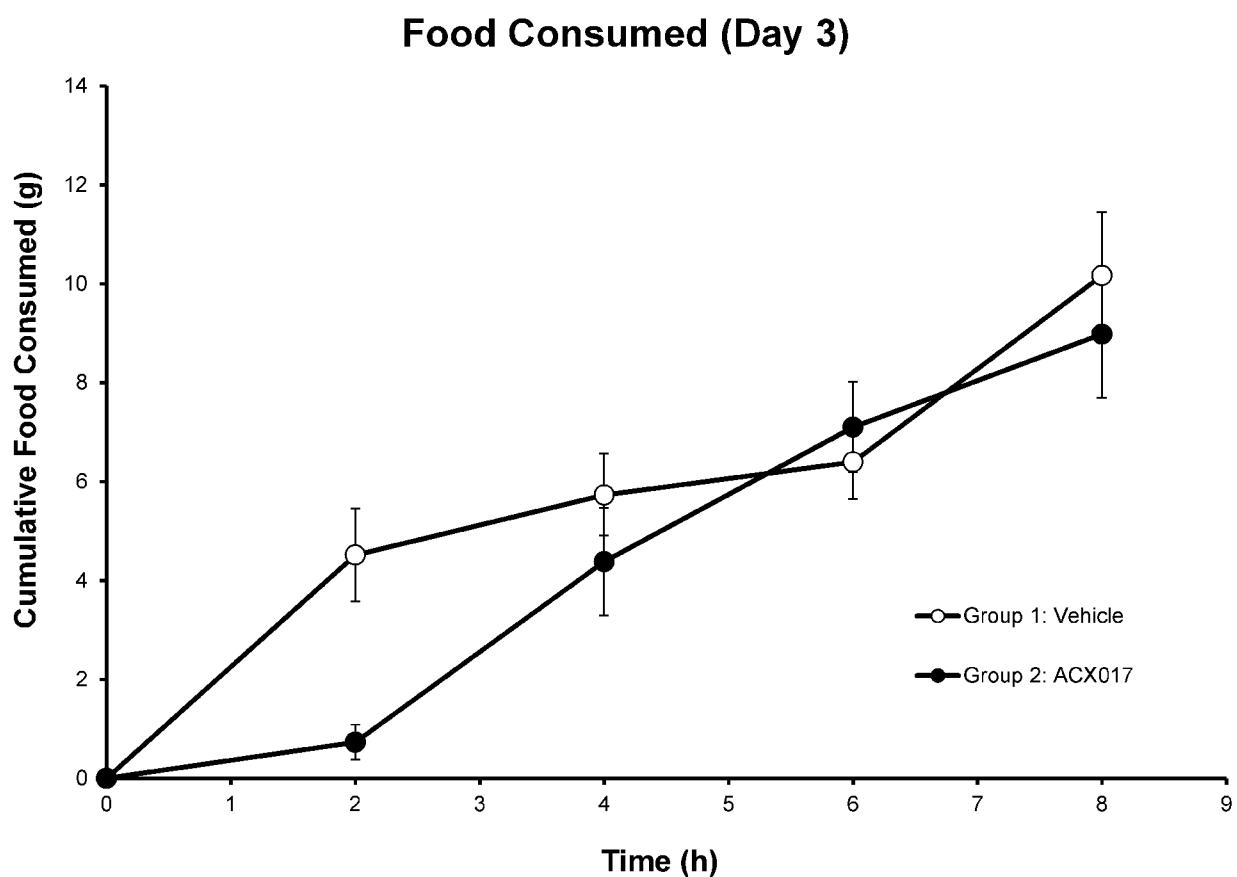


Figure 5

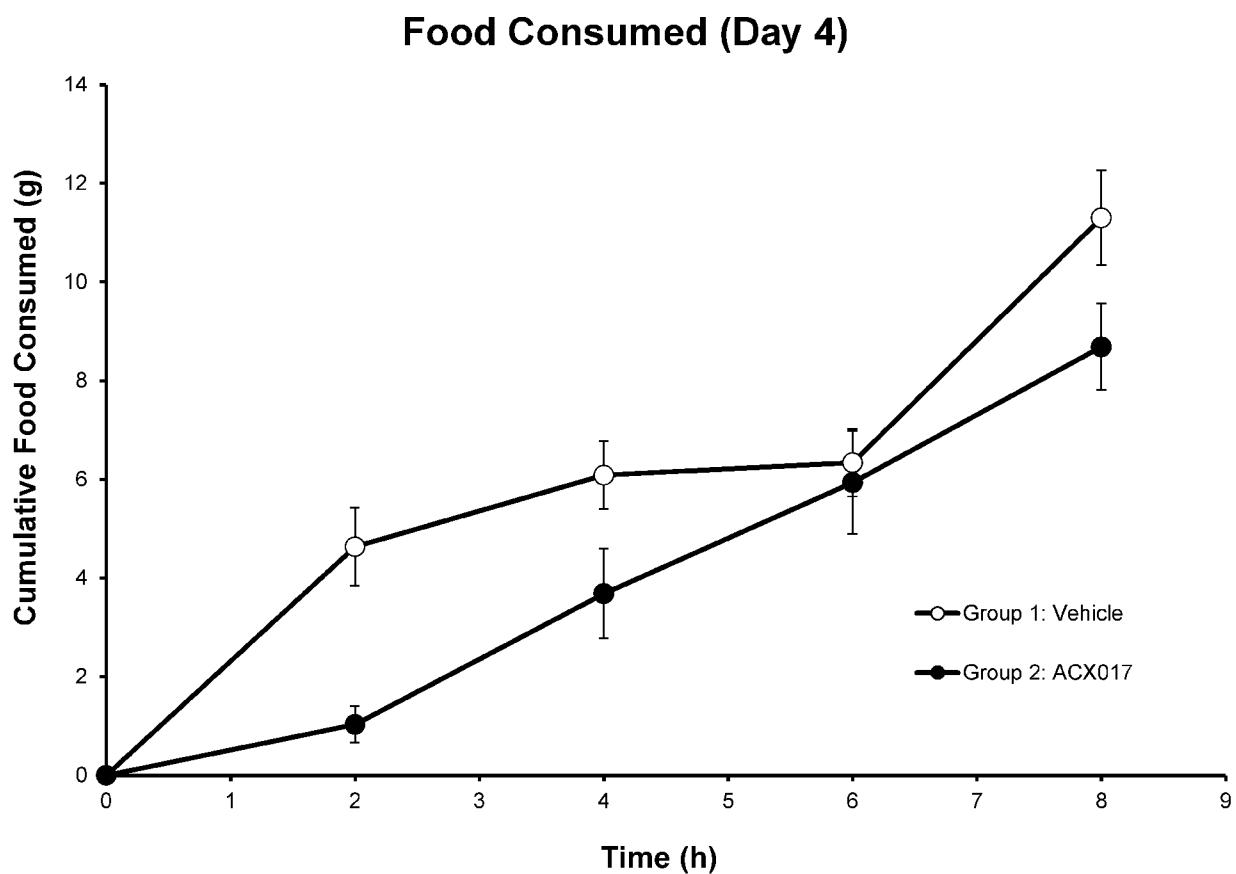


Figure 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/048724

A. CLASSIFICATION OF SUBJECT MATTER

| | | | | |
|-----------------|-----------|----------|----------|----------|
| INV. C07K14/585 | A61K38/23 | A61P3/00 | A61P3/04 | A61P3/10 |
| ADD. | | | | |

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)

C07K

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

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

EPO-Internal, BIOSIS, CHEM ABS Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X | <p>DATABASE Geneseq [Online]</p> <p>11 November 2010 (2010-11-11), "Amylin agonist peptide, SEQ:114.", XP002732365, retrieved from EBI accession no. GSP:AYJ13652 Database accession no. AYJ13652 sequence no.114 -& WO 2010/107874 A2 (AMYLIN PHARMACEUTICALS INC [US]; MACK CHRISTINE M [US]; ROTH JONATHAN) 23 September 2010 (2010-09-23)</p> <p>-----</p> <p>-/-</p> | 11,12, 20-23 |

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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| Date of the actual completion of the international search | Date of mailing of the international search report |
| 13 November 2014 | 28/11/2014 |
| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016 | Authorized officer Le Cornec, Nadine |

INTERNATIONAL SEARCH REPORT

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|------------------------------|
| International application No |
| PCT/US2014/048724 |

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | <p>DATABASE Geneseq [Online]</p> <p>11 November 2010 (2010-11-11), "Amylin agonist peptide, SEQ:106.", XP002732366, retrieved from EBI accession no. GSP:AYJ13644 Database accession no. AYJ13644 sequence ID No.106 & WO 2010/107874 A2 (AMYLIN PHARMACEUTICALS INC [US]; MACK CHRISTINE M [US]; ROTH JONATHAN) 23 September 2010 (2010-09-23)</p> <p>-----</p> | 11,12, 20-23 |
| X | <p>HEINO PAIVI ET AL: "Binding of CGRP analogs and their effect on adenylate cyclase activity in porcine iris-ciliary body", JOURNAL OF OCULAR PHARMACOLOGY AND THERAPEUTICS, vol. 14, no. 6, December 1998 (1998-12), pages 543-554, XP002732367, ISSN: 1080-7683 page 548; table 1 page 550, paragraph first</p> <p>-----</p> | 1-23 |
| X | <p>WO 2013/059336 A1 (AMYLIN PHARMACEUTICALS LLC [US] AMYLIN PHARMACEUTICALS LLC [US]; ASTRA) 25 April 2013 (2013-04-25) sequence 145</p> <p>-----</p> | 11,12, 20-23 |
| X,P | <p>WO 2013/112912 A1 (SOARES CHRISTOPHER J [US]) 1 August 2013 (2013-08-01) page 6; claims; table 1; sequence 2</p> <p>-----</p> | 11,12,20 |
| A | <p>VOLKER SCHELLENBERGER ET AL: "A recombinant polypeptide extends the in vivo half-life of peptides and proteins in a tunable manner", NATURE BIOTECHNOLOGY, vol. 27, no. 12, 1 December 2009 (2009-12-01), pages 1186-1190, XP002665891, NATURE PUBLISHING GROUP, NEW YORK, NY, US ISSN: 1087-0156, DOI: 10.1038/NBT.1588 [retrieved on 2009-11-15] cited in the application the whole document</p> <p>-----</p> | 13 |
| X | <p>WO 2006/083254 A1 (AMYLIN PHARMACEUTICALS INC [US]) 10 August 2006 (2006-08-10) page 28 - page 30; sequences 105,113</p> <p>-----</p> <p>-/-</p> | 11,12 |

INTERNATIONAL SEARCH REPORT

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|------------------------------|
| International application No |
| PCT/US2014/048724 |

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
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