Calcitonin Gene-Related Peptide Analogues

Technical field

The present invention relates to CGRP peptide analogues which are CGRP receptor agonists.

Background

Calcitonin gene-related peptide (CGRP) is a neuropeptide widely recognized for its pivotal role in various physiological processes, such as vasodilation, neurotransmission modulation, and nociception.

CGRP is a member of the calcitonin family of peptides. The major CGRP receptor is formed by the co-expression of calcitonin receptor-like receptor (CLR) with receptor activity–modifying protein-1 (RAMP1). These receptors are found throughout the cardiovascular system, specifically in blood vessels. Although CGRP is established as a potent vasodilator, there is little evidence that sufficient endogenous CGRP is released to influence physiological blood pressure regulation, although CGRP-containing nerves surround all cardiovascular tissues. CGRP receptor antagonists and antibodies developed as migraine therapies have minimal effect on blood pressure in healthy individuals. Evidence that CGRP plays a role in cardiovascular protection arises from studies where CGRP has been administered in rodent models of hypertension. CGRP is thus known as a potent vasodilator that can reduce blood pressure and therefore potentially treat hypertension and potentially provide benefit to heart diseases driven by hypertension.

The literature demonstrates that CGRP has various pharmacological effects, besides vasodilation, it triggers muscle and liver AMP kinase (AMPK) activation and lipolysis and/or fat oxidation, it reduces food intake, it inhibits gastric emptying and modifies gut function and it increases glycolysis and inhibits glycogen synthesis. The net physiological significance of the referred effects is not completely understood. AMPK activation, fat oxidation and reduced food intake may be beneficial in metabolic diseases, glycolysis and inhibition of glycogen synthesis has been suggested to mediate insulin resistance.

The clinical applicability of native CGRP is limited due to challenges associated with its pharmacokinetics, stability (short half-life), and off-target effects. Thus, continuous effort in identifying CGRP analogues with improved properties is ongoing. Acylated CGRP compounds having prolonged action are disclosed in e.g. WO 2011/051312. Acylation is known to increase half-life at the cost of decreased potency of acylated compounds.

CGRP analogues in the art differ in their pharmacological profile, and changing or removing the amino acids in the N-terminal apart of $CGRP_{1-37}$ is largely known to result in an CGRP receptor antagonist (e.g. $CGRP_{8-37}$, $CGRP_{12-37}$, $CGRP_{27-37}$).

Summary

The present inventors have developed CGRP peptide analogues which are agonists of the CGRP receptor with a potency (EC50) that is comparable or superior to clinically relevant agonist CGRP peptide compounds.

It is an aspect to provide a peptide analogue of CGRP having the sequence ($CGRP_{1-37}$) $X_1CX_3TATCVTHRLAX_{14}LLX_{17}RSGGX_{22}X_{23}KX_{25}NFVPTX_{31}VGSX_{35}AF$ (SEQ ID NO:1), wherein X_1 is Ala or Ser, X_3 is Asp or Asn, X_{14} is Asp or Gly, X_{17} is Arg or Ser, X_{22} is Val or Met, X_{23} is Val or Leu, X_{25} is Asp, Asn or Ser, X_{31} is Asp or Asn, X_{35} is Glu or Lys, and the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of SEQ ID NO:1 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In preferred embodiments of the present disclosure said peptide analogue comprises at least one amino acid substitution selected from: X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro.

Definitions

'CGRP peptide analogue', 'CGRP analogue' and 'peptide analogue' may be used interchangeably herein.

The terms "approximately" and "about" as referred herein are synonymous. In one embodiment, "approximately" and "about" refer to the recited amount, value, or duration ± 5%, ± 4.5%, ± 4%, ±3.5%, ±3%, ±2.5%, ±2%, ±1.75%, ±1.5%, ±1.25%, ±1%, ±0.9%, ±0.8%, ±0.7%, ±0.6%, ± 0.5% ±0.4%, ±0.3%, ±0.2%, ±0.1%, ±0.09%, ±0.08%, ±0.07%, ±0.06%, ±0.05%, ±0.04%, ±0.03%, ±0.02%, or ±0.01%. In one embodiment, "approximately" and "about" refer to the listed amount, value, or duration ±2.5%, ±2%, ±1.75%, ±1.5%, ±1.25%, ±1%, ±0.9%, ±0.8%, ±0.7%, ±0.6%, ± 0.5%. In one embodiment, "approximately" and "about" refer to the listed amount, value, or duration ±1%. In one embodiment, "approximately" and "about" refer to the listed amount, value, or duration ±0.5%. In one embodiment, "approximately" and "about" refer to the listed amount, value, or duration ±0.1%. In the context of an amount or dosage the terms "approximately" and "about" refer to the recited amount or dosage ± 10%, ± 9%, ± 8%, ± 7%, ± 6%, ±5%, ±4%, ±3%, ±2%, ±1.5%, ±1%, ±0.5%.

An "amino acid residue" can be a natural or non-natural amino acid residue linked by peptide bonds or bonds different from peptide bonds. The amino acid residues can be in D-configuration or L-configuration. An amino acid residue comprises an amino terminal part (NH_2) and a carboxy terminal part (COOH) separated by a central part comprising a carbon atom, or a chain of carbon atoms, at least one of which comprises at least one side chain or functional group. NH_2 refers to the amino group present at the amino terminal end of an amino acid or peptide, and COOH refers to the carboxy group present at the carboxy terminal end of an amino acid or peptide. The generic term amino acid comprises both natural and non-natural amino acids. Natural amino acids of standard nomenclature as listed in J. Biol. Chem., 243:3552-59 (1969) and adopted in 37 C.F.R., section 1.822(b)(2) belong to the group of amino acids listed herewith: Y, G, F, M, A, S, I, L, T, V, P, K, H, Q, E, W, R, D, N and C. Non-natural amino acids are those not listed immediately above, including modified amino acid residues.

An “equivalent amino acid residue” refers to an amino acid residue capable of replacing another amino acid residue in a polypeptide without substantially altering the structure and/or functionality of the polypeptide. Equivalent amino acids thus have similar properties such as bulkiness of the side-chain, side chain polarity (polar or non-polar), hydrophobicity (hydrophobic or hydrophilic), charge (acidic, neutral or basic) and side chain organization of carbon molecules (aromatic/aliphatic). As such, “equivalent amino acid residues” can be regarded as “conservative amino acid substitutions”.

Within the meaning of the term “equivalent amino acid substitution” as applied herein, one amino acid may be substituted for another, in one embodiment, within the groups of amino acids indicated herein below:

i) Amino acids having polar side chains (Asp, Glu, Lys, Arg, His, Asn, Gln, Ser, Thr, Tyr, Cys)
ii) Amino acids having non-polar side chains (Gly, Ala, Val, Leu, Ile, Phe, Trp, Pro, Met)
iii) Amino acids having aliphatic side chains (Gly, Ala Val, Leu, Ile)
iv) Amino acids having cyclic side chains (Phe, Tyr, Trp, His, Pro)
v) Amino acids having aromatic side chains (Phe, Tyr, Trp)
vi) Amino acids having acidic side chains (Asp, Glu)
vii) Amino acids having basic side chains (Lys, Arg, His)
viii) Amino acids having amide side chains (Asn, Gln)
ix) Amino acids having hydroxy side chains (Ser, Thr)
x) Amino acids having sulphur-containing side chains (Cys, Met),
xi) Neutral, weakly hydrophobic amino acids (Pro, Ala, Gly, Ser, Thr)
xii) Hydrophilic, acidic amino acids (Gln, Asn, Glu, Asp), and
xiii) Hydrophobic amino acids (Leu, Ile, Val)

Where the L or D form (optical isomers) has not been specified it is to be understood that the amino acid in question has the natural L form, cf. Pure & Appl. Chem. Vol. (56(5) pp 595-624 (1984), alternatively the D form, so that the peptides formed may be constituted of amino acids of L form, D form, or a sequence of mixed L forms and D forms.

A “functional variant” of a peptide is a peptide capable of performing essentially the same functions as the peptide it is a functional variant of. In particular, a functional variant can essentially bind the same molecules as the peptide it is a functional variant of.

Herein, "conservative substitution" refers to a change in the amino acid composition of a peptide in which a residue is replaced with a structurally similar substitute that does not substantially alter the activity of the peptide. Thus, a "conservatively substituted variant" of a particular amino acid sequence refers to an amino acid substitution of an amino acid that is not critical for protein activity, or substitution of an amino acid with another amino acid having similar properties (for example, acidic, basic, positively or negatively charged, polar or non-polar, etc.) such that the substitution of even critical amino acid do not substantially alter activity. Conservative substitution tables providing functionally similar amino acids are well known in the art. The following six groups each contain amino acids that are conservative substitutions for one another: 1) alanine, serine and threonine, 2) aspartic acid and glutamic acid, 3) asparagine and glutamine, 3a) asparagine, glutamine and histidine, 4) arginine and lysine, 5) isoleucine, leucine, methionine and valine, and 6) phenylalanine, tyrosine and tryptophan. One of skill in the art will appreciate that the above-identified substitutions are not the only possible conservative substitutions. For example, one may regard all charged amino acids as conservative substitutions for each other whether they are positive or negative. In addition, individual substitutions, deletions or additions which alter, add or delete a single amino acid or a small percentage of amino acids in an encoded sequence can also be "conservatively substituted variants."

An agonist is a compound that activates a receptor to produce a biological response. A CGRP receptor agonist as used herein is a compound that acts as an agonist on one or more CGRP receptors. In some embodiments a CGRP receptor agonist as used herein is a compound that acts as an agonist on the CGRP receptor comprising one or more of CLR, RAMP1 and RCP. The CGRP receptor may be of human or murine origin, e.g. from a mouse or rat. In some embodiments a CGRP receptor agonist as used herein is a compound that acts as an agonist on the amylin-1 receptor. In some embodiments a CGRP receptor agonist as used herein is a compound that acts as an agonist on the CGRP receptor and the amylin-1 receptor.

“Affinity” refers to the binding between a receptor and its ligand(s).

“Efficacy” is the capacity to produce a maximum receptor response.

Half maximal effective concentration (EC50 or EC_{50}) is a measure of the concentration of a compound or drug which induces a biological response halfway between the baseline and maximum after a specified exposure time. The EC50 is thus the concentration that gives half-maximal response, or a 50% effect. It is commonly used

as a measure of a drug's potency. A drug's potency is dependent on the drug's affinity and efficacy. EC50 is a measure of concentration, expressed in molar units (M), where 1 M is equivalent to 1 mol/L.

The terms “treatment” and “treating” as used herein refer to the management and care of a patient for the purpose of combating a condition, disease or disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient or subject is suffering. The patient to be treated is preferably a mammal, in particular a human being. Treatment of animals, such as mice, rats, dogs, cats, horses, cows, sheep and pigs, is, however, also within the scope of the present context. The patients to be treated can be of various ages. The term ‘subject’, ‘individual’ and ‘patient’ may be used interchangeably herein.

The term "therapeutically effective amount" as used herein refers to an amount sufficient to cure, alleviate, prevent, reduce the risk of, or partially arrest the clinical manifestations of a given disease or disorder and its complications. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary. ‘Amount’ and ‘dosage’ may be used interchangeably herein. Although the particular dose will depend on the molecular structure and chemical properties of the particular compound, those of skill in the art will understand from the disclosure herein that appropriate doses can be determined using routine techniques. The amount of a compound administered to achieve a desired level or concentration of the compound will depend on a number of well-known factors, such as compound half-life and the frequency and mode of administration.

Herein, "prolonged action" means that the half-life or T½ is longer than the T½ of the corresponding native CGRP. Native CGRP has a half-life of less than 30 minutes, and modification by fatty acylation has demonstrated a T½ of up to 8 days. T½ may be determined by the methods described in WO 2011/051312 A1.

Detailed description

Calcitonin gene-related peptide (CGRP), a member of the calcitonin family, exists in 2 isoforms: αCGRP and βCGRP. αCGRP, a 37 amino-acid peptide, is formed by

alternative splicing of the calcitonin gene, in particular in the central and peripheral nervous system, and acts as a potent vasodilator and modulator of cerebrovascular nociception. βCGRP is encoded by a second CGRP gene, predominantly expressed in the enteric sensory system and human βCGRP shares 34 amino acids with human αCGRP. The sequence identity between alpha-CGRP and beta-CGRP is 92% in the human and 97% in the rat.

Both CGRP isoforms act on the CGRP receptor consisting of the 7-transmembrane calcitonin-like receptor (CLR), a receptor activity-modifying protein type 1 (RAMP1), and a receptor component protein (RCP). All 3 components are required for optimal functioning of the receptor. Its major second messenger is cyclic adenosine monophosphate (cAMP). The amylin-1 receptor is suggested to act also as a receptor for CGRP. Native CGRP has a half-life of less than 30 minutes and a short duration of pharmacological actions after infusion.

The sequence of alpha-CGRP and beta-CGRP in human, rat and mouse is as follows:
AC**D**TATCVTHRLAGLLSRSGG**V**VK**N**NFVPTNVGSKAF (alpha-hCGRP; SEQ ID NO:3);
AC**N**TATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF (beta-hCGRP; SEQ ID NO:4);
SC**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (alpha-rCGRP; SEQ ID NO:5);
SC**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGSKAF (beta-rCGRP; SEQ ID NO:6),
SC**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (alpha-mCGRP; SEQ ID NO:7); and
SC**N**TATCVTHRLA**D**LLSRSGG**VL**K**D**NFVPT**D**VGS**E**AF (beta-mCGRP; SEQ ID NO:8).

The consensus sequence of SEQ ID NO:1 covers, for example, CGRP from the following species: pig, mouse, human, dog and rat; in alpha and beta form, where applicable:

$X_1CX_3TATCVTHRLAX_{14}LLX_{17}RSGGX_{22}X_{23}KX_{25}NFVPTX_{31}VGSX_{35}AF$ (SEQ ID NO:1),

wherein X_1 is Ala or Ser, X_3 is Asp or Asn, X_{14} is Asp or Gly, X_{17} is Arg or Ser, X_{22} is Val or Met, X_{23} is Val or Leu, X_{25} is Asp, Asn or Ser, X_{31} is Asp or Asn, X_{35} is Glu or Lys.

Native CGRP has an intramolecular disulfide bridge between the two N-terminal Cys residues in positions 2 and 7, and the carboxy group in the C terminal amino acid residue is amidated.

CGRP peptide analogue of the disclosure

Reference to a CGRP peptide "$CGRP_{1-37}$" refers to a peptide sequence having 37 consecutive amino acids, wherein each amino acid residue is denoted from the N-terminus to the C-terminus as X_1 to X_{37}. Reference to an amino acid at X_1 is thus a reference to the amino acid at position 1, which also is the N-terminal amino acid. Reference to an amino acid at X_{37} is thus a reference to the amino acid at position 37, which also is the C-terminal amino acid. Likewise, reference to an amino acid at X_{10} is thus a reference to the amino acid at position 10, counting from the N-terminus.

It is an aspect of the present disclosure to provide a peptide analogue of a CGRP having the sequence ($CGRP_{1-37}$):

$X_1CX_3TATCVTHRLAX_{14}LLX_{17}RSGGX_{22}X_{23}KX_{25}NFVPTX_{31}VGSX_{35}AF$ (SEQ ID NO:1),

wherein X_1 is Ala or Ser, X_3 is Asp or Asn, X_{14} is Asp or Gly, X_{17} is Arg or Ser, X_{22} is Val or Met, X_{23} is Val or Leu, X_{25} is Asp, Asn or Ser, X_{31} is Asp or Asn, X_{35} is Glu or Lys, and the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of SEQ ID NO:1 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from:

X_1 is Gly or His,
X_3 is His, Arg, Gly, Met or Lys,
X_4 is Ile
X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr,
X_{14} is His, Glu or Asp,
X_{17} is Ala,
X_{19} is His,
X_{22} is Ile, Leu or Val,
X_{23} is Ser or His,
X_{24} is Arg or His,
X_{25} is Lys, Asn, Asp, Glu, Arg or His,

X_{26} is His,
X_{27} is His,
X_{28} is His,
X_{29} is His,
X_{31} is Asp or His,
X_{34} is Pro, and
X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

It is an aspect of the present disclosure to provide a peptide analogue of a calcitonin gene-related peptide (CGRP) having the sequence ($CGRP_{1-37}$):

$X_1CX_3TATCVTHRLAX_{14}LLX_{17}RSGGX_{22}X_{23}KX_{25}NFVPTX_{31}VGSX_{35}AF$ (SEQ ID NO:1),

wherein X_1 is Ala or Ser, X_3 is Asp or Asn, X_{14} is Asp or Gly, X_{17} is Arg or Ser, X_{22} is Val or Met, X_{23} is Val or Leu, X_{25} is Asp, Asn or Ser, X_{31} is Asp or Asn, X_{35} is Glu or Lys, and the carboxy group in the C terminal amino acid residue is optionally amidated,

or a functional variant thereof further comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37} of said peptide,

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His; X_{10} is Asn, Gln or Thr; X_{14} is His; X_{17} is Ala; X_{19} is His; X_{22} is Ile; X_{23} is His; X_{24} is Arg or His; X_{25} is Lys, Asn, Arg or His; X_{28} is His; X_{34} is Pro; and X_{35} is His; wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments of the present disclosure said CGRP peptide ($CGRP_{1-37}$) is selected from human alpha-CGRP (SEQ ID NO:3), human beta-CGRP (SEQ ID NO:4), rat alpha-CGRP (rCGRP; SEQ ID NO:5), rat beta-CGRP (SEQ ID NO:6), mouse alpha-CGRP (SEQ ID NO:7), and mouse beta-CGRP (SEQ ID NO:8), or a functional variant thereof.

In some embodiments there is provided a peptide analogue of a CGRP peptide having

a sequence ($CGRP_{1-37}$) selected from:
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:2),
AC**D**TATCVTHRLAGLLSRSGG**V**VK**N**NFVPTNVGSKAF (SEQ ID NO:3);
ACNTATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF (SEQ ID NO:4);
SCNTATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (SEQ ID NO:5);
SCNTATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGSKAF (SEQ ID NO:6),
SCNTATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (SEQ ID NO:7); and
SCNTATCVTHRLA**D**LLSRSGG**VL**K**D**NFVPT**D**VGS**E**AF (SEQ ID NO:8),

wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:2 to SEQ ID NO:8 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments there is provided a peptide analogue of a beta-CGRP peptide having a sequence ($CGRP_{1-37}$) selected from:
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:2),
ACNTATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF (SEQ ID NO:4);
SCNTATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGSKAF (SEQ ID NO:6),
SCNTATCVTHRLA**D**LLSRSGG**VL**K**D**NFVPT**D**VGS**E**AF (SEQ ID NO:8),

wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 and SEQ ID NO:8 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments there is provided a peptide analogue of a beta-CGRP peptide having the sequence ($CGRP_{1-37}$)
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:2),
wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of SEQ ID NO:2 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments said functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}. In some embodiments said functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises one, two, three, four,

five or six individual conservative amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises at least one amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro. In some embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises two or more amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises one or more amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His and X_{14} is His. In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises one or more amino acid substitution selected from X_{10} is Asp, X_{19} is His and X_{14} is His. In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises one or more amino acid substitution selected from X_{10} is Glu, X_{19} is His and X_{14} is His.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises X_{10} is Asp or Glu. In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises X_{10} is Asp. In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises X_{10} is Glu.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises X_{19} is His.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises X_{14} is His.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises X_1 is Gly.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises X_3 is His.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises X_{34} is Pro.

In some embodiments reference to a CGRP peptide having the sequence $CGRP_{1-37}$ encompass a CGRP peptide having a sequence consisting of $CGRP_{1-37}$ of 37 consecutive amino acids. In some embodiments there is provided a peptide analogue consisting of a CGRP of sequence $bCGRP_{1-37}$ of 37 consecutive amino acids.

In some embodiments there is provided a peptide analogue comprising a CGRP of sequence $bCGRP_{1-37}$ of 37 consecutive amino acids and an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids.

In some embodiments there is provided a peptide analogue consisting of a CGRP of sequence $bCGRP_{1-37}$ of 37 consecutive amino acids and an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from

HCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:9);
SCNTATCVT**Q**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:10);
SCNTATCVT**T**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:11);
SCNTATCVTHRLAGLLSRSGGM**H**KSNFVPTNVGSKAF (SEQ ID NO:12);
SCNTATCVTHRLAGLLSRSGGMV**H**SNFVPTNVGSKAF (SEQ ID NO:13);
SCNTATCVTHRLAGLLSRSGGMVK**N**NFVPTNVGSKAF (SEQ ID NO:14);
SCNTATCVTHRLAGLLSRSGGMVK**R**NFVPTNVGSKAF (SEQ ID NO:15);
SCNTATCVTHRLAGLLSRSGGMVK**H**NFVPTNVGSKAF (SEQ ID NO:16);
SCNTATCVTHRLAGLLSRSGGMVKSNF**H**PTNVGSKAF (SEQ ID NO:17);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**H**AF (SEQ ID NO:18),
GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:19);
SC**H**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:20);
SCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:21);
SCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:22);
SCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:23);
SCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:24);
SCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:25);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:26);

SCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:27);
SCNTATCVTHRLAGLLSRSGGMVKS**H**FVPTNVGSKAF (SEQ ID NO:28);
SCNTATCVTHRLAGLLSRSGGMVKSN**H**VPTNVGSKAF (SEQ ID NO:29);
SCNTATCVTHRLAGLLSRSGGMVKSNFV**H**TNVGSKAF (SEQ ID NO:30);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPT**H**VGSKAF (SEQ ID NO:31);
SC**R**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:32);
SC**G**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:33);
SC**K**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:34);
SC**M**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:35);
SCN**I**ATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:36);
SCNTATCVT**A**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:37);
SCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:38);
SCNTATCVT**G**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:39);
SCNTATCVT**S**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:40);
SCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:41);
GC**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:42);
SC**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:43);
SC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:44);
GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:45);
SC**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:46);
SCNTATCVTHRLAGLLSRSGG**V**VKSNFVPTNVGSKAF (SEQ ID NO:47);
SCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGSKAF (SEQ ID NO:48);
SCNTATCVTHRLAGLLSRSGGMVK**D**NFVPTNVGSKAF (SEQ ID NO:49);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPT**D**VGSKAF (SEQ ID NO:50);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**E**AF (SEQ ID NO:51);
SCNTATCVTHRLA**D**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:52);
SCNTATCVTHRLAGLLSRSGGM**S**KSNFVPTNVGSKAF (SEQ ID NO:53);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**S**AF (SEQ ID NO:54);
SC**H**TATCVT**D**RLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:55);
SCN**I**ATCVTHRLAGLLSR**H**GGMVKSNF**H**PTNVGSKAF (SEQ ID NO:56);
SCN**I**ATCVT**D**RLAGLLSRSGGMVK**K**NFVPTNVGSKAF (SEQ ID NO:57);
SCN**I**ATCVTHRLAGLLSRSGG**I**VKSNF**H**PTNVGSKAF (SEQ ID NO:58);
SCNTATCVT**D**RLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:59);
SCNTATCVT**Q**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:60);
SCNTATCVTHRLA**H**LLSRSGG**I**VK**R**NFVPTNVGSKAF (SEQ ID NO:61);

SCNTATCVTHRLA**H**LL**A**R**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:62);
GCNTATCVTHRLA**H**LLSRSGGMVK**H**NFVPTNVGSKAF (SEQ ID NO:63);
GC**H**TATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:64);
SCNTATCVTHRLAGLLSRSGG**L**VKSNF**H**PTNVG**P**KAF (SEQ ID NO:65);
SCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVG**P**KAF (SEQ ID NO:66);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:67);
GC**H**TATCVT**N**RLA**H**LL**A**R**H**GG**I**VK**K**NFVPTNVG**P**KAF (SEQ ID NO:68);
GC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:69);
GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:70);
GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:71);
GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:72);
GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:73);
GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:74);
GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:75);
GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:76);
GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:77);
GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:78);
GC**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:79);
GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:80);
GCNTATCVTHRLA**D**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:81);
GCNTATCVTHRLA**E**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:82);
GCNTATCVTHRLAGLLSRSGGMVK**E**NFVPTNVGSKAF (SEQ ID NO:83);
GC**H**TATCVTHRLA**D**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:84);
GC**H**TATCVTHRLA**E**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:85);
GC**H**TATCVTHRLAGLLSRSGGMVK**E**NFVPTNVGSKAF (SEQ ID NO:86);
GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGSKAF (SEQ ID NO:87);
GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**R**AF (SEQ ID NO:88); and
GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:89);

wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:9 to SEQ ID NO:89 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide optionally comprises one or more individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10}

is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

Preferably the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 does not comprise an amino acid substitution at the one or more amino acid residues which are indicated in **bold** in said amino acid sequence. The amino acid residues indicated in bold in SEQ ID NO:9 to SEQ ID NO:89 are non-native substitutions of the present disclosure.

In some embodiments said functional variant of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}. In some embodiments said functional variant of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises one, two, three, four, five or six individual conservative amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

In some embodiments said functional variant of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37} at one or more positions outside the one or more amino acid residues which are indicated in **bold** in the amino acid sequence of any one of SEQ ID NO:9 to SEQ ID NO:89.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises at least one amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro. In preferred embodiments the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises at least one amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His and X_1 is Gly.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises X_{10} is Asp or Glu.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises X_{10} is Asp.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises X_{19} is His.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises X_{14} is His.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises X_1 is Gly.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises X_3 is His.

In preferred embodiments the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 comprises X_{34} is Pro.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:8, wherein the carboxy group in the C terminal amino acid residue is amidated,

wherein said peptide comprises one or more individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

wherein said peptide optionally comprises one or more individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:9 to SEQ ID NO:89 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

wherein said peptide comprises one or more individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26}

is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

such as wherein said peptide comprises one or more individual amino acid substitutions selected from: X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:8, and SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8, and SEQ ID NO:9 to SEQ ID NO:89, comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide comprises one or more individual amino acid substitutions selected from: X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure comprises 1 amino acid substitution, such as 2 individual amino acid substitutions, such as 3 individual amino acid substitutions, such as 4 individual amino acid substitutions, such as 5 individual amino acid substitutions, such as 6 individual amino acid substitutions, such as 7 individual amino acid substitutions, such as 8 individual amino acid

substitutions, such as 9 individual amino acid substitutions, wherein each substitution is individually selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises at least two individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser

In some embodiments the peptide analogue of the present disclosure comprises two or more individual amino acid substitutions selected from: X_{10} is Asp or Glu, X_{19} is His, X_1 is Gly, X_{14} is His, X_3 is His and X_{34} is Pro.

In some embodiments the peptide analogue of the present disclosure comprises at least three individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises three or more individual amino acid substitutions selected from: X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro.

In preferred embodiments the peptide analogue of the present disclosure comprises at least one amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro.

In preferred embodiments the peptide analogue of the present disclosure comprises at least one amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly and X_3 is His.

In preferred embodiments the peptide analogue of the present disclosure comprises at least one amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly and X_{34} is Pro.

In preferred embodiments the peptide analogue of the present disclosure comprises at least one amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His and X_1 is Gly.

In preferred embodiments the peptide analogue of the present disclosure comprises at least one amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_3 is His and X_{34} is Pro.

In some embodiments the peptide analogue of the present disclosure comprises at least one amino acid substitution selected from X_{19} is His, X_{10} is Asp, X_{10} is Glu, X_{14} is His, X_{25} is His, X_{25} is Arg, X_{28} is His, X_{35} is Ser, X_1 is His, and X_{23} is His.

In some embodiments the peptide analogue of the present disclosure comprises at least one amino acid substitution to a His amino acid selected from: X_{19} is His, X_{14} is His, X_3 is His, X_{25} is His, X_{28} is His, X_1 is His, X_{23} is His, X_{24} is His, X_{35} is His, X_{26} is His, X_{27} is His, X_{29} is His, and X_{31} is His.

In some embodiments the peptide analogue of the present disclosure comprises at least one amino acid substitution to a His amino acid selected from: X_{19} is His, X_{14} is His, X_{25} is His, X_{28} is His, X_1 is His, and X_{23} is His.

In preferred embodiments the peptide analogue of the present disclosure comprises at least one amino acid substitution to a His amino acid selected from X_{19} is His, X_{14} is His and X_3 is His.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:8, and SEQ ID NO:9

to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8, and SEQ ID NO:9 to SEQ ID NO:89, comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide comprises one or more individual amino acid substitutions selected from X_{19} is His, X_{14} is His and X_3 is His,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{19} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{19} is His, and further comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises a substitution at position 14 wherein X_{14} is His, Glu or Asp.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{14} is His, and further comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn,

Asp, Gln, Glu, Gly, Ser or Thr; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{19} is His and X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{19} is His and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{14} is His and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{19} is His, X_{14} is His and X_3 is His.

In a preferred embodiment one or more of X_{19} is His, X_{14} is His and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_3 is His, and further comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_3 is His and X_{10} is Asp or Glu.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_3 is His, X_{10} is Asp or Glu and X_{19} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_1 is Gly. In a preferred embodiment X_1 is Gly.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:8, and SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8, and SEQ ID NO:9 to SEQ ID NO:89, comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide comprises the amino acid substitution X_1 is Gly,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_1 is Gly, and further comprises one or more amino acid substitutions selected from: X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_1 is Gly, and one or more of X_{19} is His, X_{14} is His and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly and X_{19} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly and X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly, X_{19} is His and X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly, X_{19} is His and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly, X_{14} is His and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly, X_{19} is His, X_{14} is His and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly and X_{34} is Pro.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_1 is Gly, and one or more of X_3 is His, X_{10} is Asp or Glu, X_{19} is His and X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly and X_{10} is Asp.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly and X_{10} is Glu.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly, X_{10} is Asp or Glu, and X_{19} is His,

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly, X_{10} is Asp or Glu, and X_{14} is His,

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_1 is Gly, X_{10} is Asp or Glu, X_{19} is His and X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_1 is His.

In some embodiments the peptide analogue of the present disclosure comprises a substitution at position 10 wherein X_{10} is a negative amino acid selected from Asp or Glu. In a preferred embodiment X_{10} is Asp or Glu.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:8, and SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8, and SEQ ID NO:9 to SEQ ID NO:89, comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide comprises a substitution at position 10 wherein X_{10} is a negative amino acid selected from Asp or Glu,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asp or Glu, and X_1 is Gly.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{10} is Asp.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{10} is Glu.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{10} is Asp, and further comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{10} is Asp and one or more of X_{19} is His, X_3 is His and X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asp and X_{19} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asp and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asp and X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asp, X_{19} is His and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asp and X_1 is Gly.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asp and X_{34} is Pro.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{10} is Glu, and further comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Glu and X_{19} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Glu and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Glu and X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Glu, X_{19} is His and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Glu and X_1 is Gly.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asp and X_{34} is Pro.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{34} is Pro, and further comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; and X_{35} is His, Glu, Arg or Ser;

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{34} is Pro and one or more of X_{14} is His, X_{19} is His, X_1 is Gly, X_3 is His, and X_{10} is Asp or Glu.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{34} is Pro and X_1 is Gly.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{34} is Pro and X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{34} is Pro and X_{19} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{34} is Pro and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{34} is Pro, X_{14} is His and X_{19} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{34} is Pro; and X_{10} is Asp or Glu.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{34} is Pro; X_1 is Gly, X_3 is His and X_{10} is Asp or Glu.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{14} is Glu or Asp, such as wherein X_{14} is Glu, and further comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{14} is Glu or Asp and one or more of X_{19} is His, X_1 is Gly and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{14} is Glu or Asp, and X_{19} is His.
In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{14} is Glu or Asp, and X_1 is Gly.
In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{14} is Glu or Asp, and X_3 is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{10} is Asn and further comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{10} is Asn and one or more of X_3 is His, X_{14} is His, X_{19} is His and X_1 is Gly.
In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asn, X_3 is His, X_{14} is His and X_{19} is His.
In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asn, X_3 is His, and X_1 is Gly.
In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{10} is Asn and X_1 is Gly.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{17} is Ala and one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{17} is Ala and one or more of X_1 is Gly, X_3 is His, X_{10} is Asp or Asn, X_{19} is His, X_{14} is His, and X_{34} is Pro.
In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{17} is Ala and X_{10} is Asp.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{17} is Ala and X_{10} is Asn.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{17} is Ala; and X_{19} is His and/or X_{14} is His.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{17} is Ala and X_1 is Gly.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{22} is Ile or Leu and one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{22} is Ile and one or more of X_1 is Gly, X_{19} is His, X_{14} is His, X_3 is His, X_{10} is Asn, X_{24} is Arg, X_{28} is His, X_{17} is Ala, and X_{34} is Pro.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{22} is Leu and one or more of X_1 is Gly, X_{28} is His and X_{34} is Pro.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{24} is His and said peptide analogue further comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_4 is Ile and said peptide analogue further comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_4 is Ile and one or more of X_{10} is Asp, X_{19} is His, X_{28} is His and X_{22} is Ile.

In some embodiments the peptide analogue of the present disclosure comprises the substitutions X_{24} is Arg and X_{35} is Arg.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{25} is Asp or Glu, such as wherein X_{25} is Glu, and one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{25} is Glu and one or more of X_3 is His and X_1 is Gly.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{24} is Arg with the proviso that X_{25} is not Lys. In some embodiments when X_{24} is Arg then X_{25} is not Lys.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{31} is Asp and one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{28} is His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

In some embodiments the peptide analogue of the present disclosure comprises the substitution X_{35} is His or Arg and one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{28} is His; X_{31} is Asp; and X_{34} is Pro.

In some embodiments the peptide analogue of the present disclosure comprises at least one amino acid substitution selected from: X_1 is His, X_{10} is Thr, X_{14} is His, X_{19} is His, X_{23} is His, X_{25} is Arg or His, and X_{28} is His.

In some embodiments of the present disclosure the peptide analogue comprises at least one amino acid substitution which introduces a His amino acid residue, without reducing the potency of the substituted peptide analogue. In some embodiments of the present disclosure the peptide analogue comprises at least one amino acid substitution which introduces a His amino acid residue, while retaining or even improving the potency of the substituted peptide analogue.

The isoelectric point (pI) is the pH at which a particular molecule is electrically neutral due to the equilibrium of positive and negative charges. In proteins and peptides, this depends on the dissociation constant (pKa) of charged groups of seven amino acids and NH + and COO − groups at polypeptide termini.

Among the natural amino acids, histidine is unique because it has a side chain (R-group) containing an imidazole group, which can act as both a weak acid and a weak base. The side chain pKa of histidine is 6.10, which means that histidine can be positively charged when protonated (at lower pH) and neutral when deprotonated (at higher pH. Thus, introducing or removing one or more histidine residues may determine the activity of a CGRP peptide analogue in biological processes where pH changes can influence its charge state and function, e.g. during ischemic conditions.

Ischemia refers to a condition where there is inadequate blood supply to tissues, leading to a shortage of oxygen and nutrients. When tissues become ischemic, cellular metabolism shifts from aerobic (oxygen-dependent) to anaerobic (oxygen-independent) pathways in an attempt to generate ATP (adenosine triphosphate), the primary energy source for cells. During anaerobic metabolism, glucose is metabolized to produce ATP, but lactic acid is also generated as a byproduct. The accumulation of lactic acid and other metabolic byproducts in the absence of sufficient oxygen leads to a decrease in tissue pH.

In some embodiments of the present disclosure the peptide analogue comprises amino acid substitutions favourable for CGRP receptor potency, binding affinity or efficacy,

and does not comprise amino acid substitutions at positions unfavourable for CGRP receptor potency, binding affinity or efficacy.

The amino acids at position X_2 and position X_7 in the peptide analogue cannot be substituted. The amino acids at position X_2 and X_7 in the peptide analogue are Cys.

In some embodiments of the present disclosure the amino acids at position X_5 and position X_6 are not substituted; such as wherein X_5 is Ala and X_6 is Thr.

In some embodiments of the present disclosure the amino acids of any one of positions X_4, X_5 and X_6 are not substituted; such as wherein X_4 is Thr, X_5 is Ala and X_6 is Thr.

In some embodiments of the present disclosure the amino acids of any one of positions X_4, X_5, X_6 and X_8 are not substituted; such as wherein X_4 is Thr, X_5 is Ala, X_6 is Thr and X_8 is Val.

In some embodiments of the present disclosure the peptide analogue comprises one or more of X_4 is Thr, X_5 is Ala, X_6 is Thr, X_8 is Val, X_9 is Thr, X_{16} is Leu, X_{17} is Ser, X_{22} is Met, X_{30} is Thr, and X_{32} is Val.

In some embodiments of the present disclosure the peptide analogue does *not* comprise an amino acid substitution selected from X_4 is Asp, X_5 is Asp, X_6 is Asp, X_8 is Asp, X_9 is Asp, X_{17} is Asp and X_{22} is Asp.

In some embodiments of the present disclosure in said peptide analogue X_4 is *not* Asp or Glu; X_5 is *not* Asp, Glu or Arg; and X_6 is *not* Asp, Glu, Arg or His.

In some embodiments of the present disclosure in said peptide analogue X_{17} is Ser; such as wherein X_{17} is *not* Asp, Arg or Ile.

In some embodiments of the present disclosure in said peptide analogue X_{22} is Met; such as wherein X_{22} is *not* Asp, Gln or His.

In some embodiments of the present disclosure in said peptide analogue X_{16} is Leu, X_{30} is Thr and X_{32} is Val; such as wherein none of X_{16}, X_{30} and X_{32} is His.

In some embodiments of the present disclosure in said peptide analogue X_{10} is *not* Arg or Lys.

In some embodiments of the present disclosure in said peptide analogue X_{14} is *not* Ile.

In some embodiments of the present disclosure in said peptide analogue X_{19} is *not* Asp or Glu.

In some embodiments of the present disclosure the functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89 comprises 1 to 6 individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

In some embodiments of the present disclosure the functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89 comprises 1 to 5, such as 1 to 4, such as 1 to 3, such as 1 to 2 individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

In some embodiments of the present disclosure the functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89 comprises 6, such as 5, such as 4, such as 3, such as 2, such as 1 individual amino acid substitution(s) at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

In some embodiments of the present disclosure the functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89 comprises 1 to 6 individual amino acid substitutions, such as 1 to 5, such as 1 to 4, such as 1 to 3, such as 1 to 2 individual amino acid substitutions, such as comprises 1, 2, 3, 4, 5 or 6 individual amino acid substitutions, at any one of positions X_4, X_5, X_6, X_8, X_9, X_{11}, X_{21}, X_{13}, X_{15}, X_{16}, X_{18}, X_{20}, X_{21}, X_{26}, X_{27}, X_{29} to X_{33}, X_{36} and X_{37};
such as at any one of positions X_5, X_6, X_8, X_9, X_{11}, X_{12}, X_{13}, X_{15}, X_{16}, X_{18}, X_{20}, X_{21}, X_{30}, X_{32}, X_{33}, X_{36} and X_{37};
such as at any one of positions X_8, X_9, X_{11}, X_{12}, X_{13}, X_{15}, X_{16}, X_{18}, X_{20}, X_{21}, X_{30}, X_{32}, X_{33}, X_{36} and X_{37};
such as at any one of positions X_{11}, X_{12}, X_{13}, X_{15}, X_{18}, X_{20}, X_{21}, X_{33}, X_{36} and X_{37};
such as at any one of positions X_{11}, X_{12}, X_{13}, X_{15}, X_{18}, X_{20}, X_{21} and X_{33}.

In some embodiments of the present disclosure the functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89 comprises 1 to 6 conservative amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor. In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor at systemic pH. Normally, systemic acid-base balance is well-regulated with arterial pH between 7.36 and 7.44; intracellular pH is usually approximately 7.2. In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor at physiological pH, such as a pH of about 7.4, such as a pH of about 7.2 to 7.6, such as a pH of about 7.3 to 7.5.

In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor at ischemic conditions, ischemic pH or acidic pH.

In some embodiments the peptide analogue of the present disclosure has binding affinity to the CGRP receptor.

In some embodiments the peptide analogue of the present disclosure has a potency (EC50) for the CGRP receptor which is equal to or higher than the potency (EC50) of a polypeptide consisting of the amino acid sequence SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:2), having attached to the N-terminal amino acid the acyl group and linker HOOC(CH_2)16CO-isoGlu-AEEA.

In some embodiments the peptide analogue of the present disclosure has a potency (EC50) for the CGRP receptor which is comparable to the potency (EC50) of a polypeptide consisting of the amino acid sequence **A**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:3).

In some embodiments the peptide analogue of the present disclosure has a sequence selected from any one of SEQ ID NO:9 to SEQ ID NO:26, and SEQ ID NO:90 to SEQ ID NO:92,

wherein said peptide optionally comprises one or more individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His; X_{10} is Asn, Gln or Thr; X_{14} is His; X_{17} is Ala; X_{19} is His; X_{22} is Ile; X_{23} is His; X_{24} is Arg or His; X_{25} is Lys, Asn, Arg or His; X_{28} is His; X_{34} is Pro; and X_{35} is His,

or a functional variant thereof comprising one or more individual amino acid substitutions at any one of positions X_4, X_5, X_6, X_8, X_9, X_{11}, X_{21}, X_{13}, X_{15}, X_{16}, X_{18}, X_{20}, X_{21}, X_{26}, X_{27}, X_{29} to X_{33}, X_{36} and X_{37},
wherein the carboxy group in the C terminal amino acid residue is amidated.

In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor with an EC_{50} (nM) value of 16 nM or less, such as of less than 16 nM.

In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor with an EC_{50} (nM) value of 0.01 to 16 nM, such as 0.1 to 16 nM, such as 1 to 16 nM. In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor with an EC_{50} (nM) value of >6 nM to 16 nM.

In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor with an EC_{50} value which is at least 0.5 of the EC50 value of a polypeptide consisting of the amino acid sequence SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:2), having attached to the N-terminal amino acid HOOC(CH_2)16CO-isoGlu-AEEA;
such as an EC_{50} value which is at least 0.8, such as at least 0.75, such as at least 1, such as at least 1.5, such as at least 2, such as at least 2.5, such as at least 3, such as at least 3.5, such as at least 4, such as at least 5 of the EC50 value of HOOC(CH_2)16CO-isoGlu-AEEA-SEQ ID NO:2;
such as an EC_{50} value which is 0.5 to 10; for example 0.5 to 0.6, such as 0.6 to 0.7, such as 0.7 to 0.8, such as 0.8 to 0.9, such as 0.9 to 1.0, such as 1.0 to 1.1, such as 1.1 to 1.2, such as 1.2 to 1.3, such as 1.3 to 1.4, such as 1.4 to 1.5, such as 1.5 to 1.6, such as 1.6 to 1.7, such as 1.7 to 1.8, such as 1.8 to 1.9, such as 1.9 to 2.0, such as 2 to 3, such as 3 to 4, such as 4 to 5, such as 5 to 6, such as 6 to 7, such as 7 to 8, such as 8 to 9, such as 9 to 10, of the EC50 value of HOOC(CH_2)16CO-isoGlu-AEEA-SEQ ID NO:2, such as 0.5 to 5, such as 0.5 to 4, such as 0.5 to 3, such as 0.5 to 2, such as

0.5 to 1.5, such as 1.0 to 10, such as 1.0 to 5 of the EC50 value of HOOC(CH_2)16CO-isoGlu-AEEA-SEQ ID NO:2.

In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor with an EC_{50} (nM) value of 6 nM or less, such as of 5 nM or less, such as of 4 nM or less, such as of 3 nM or less, such as of 2 nM or less, such as of 1 nM or less, such as of 0.5 nM or less, such as of 0.1 nM or less.

In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor with an EC_{50} (nM) value of 0.01 to 6 nM, such as of 0.1 to 6 nM, such as of 1 to 6 nM.

In preferred embodiments the peptide analogue of the present disclosure comprises an intramolecular disulfide bridge between the Cys amino acid residue at position 2 (X_2) and the Cys amino acid residue at position 7 (X_7).

In some embodiments the peptide analogue of the present disclosure comprises a disulfide bridge with a linker, such as a methylene linker, between the Cys amino acid residue at position 2 (X_2) and the Cys amino acid residue at position 7 (X_7), such as -S-[CH_2]-S

Preferably the peptide analogue comprises a disulfide bridge between the Cys amino acid residues at position 2 (X_2) and position 7 (X_7), such as -S-S-, or -S-[CH_2]-S.

In some embodiments the peptide analogue of the present disclosure comprises a Cys amino acid residue at position 2 (X_2) and a Cys amino acid residue at position 7 (X_7).

The carboxy group in the C terminal amino acid residue of the CGRP peptide or peptide analogue is amidated (-COOH to -$CONH_2$), such as the amino acid at position X_{37} is amidated.

In some embodiments of the present disclosure said one or more amino acid substitutions are conservative substitutions or non-conservative substitutions.
In some embodiments of the present disclosure said one or more amino acid substitutions are conservative substitutions.

N-terminal modification

The present disclosure provides a peptide analogue of a CGRP peptide having the sequence ($CGRP_{1-37}$), or a CGRP peptide analogue, having one or more specified amino acid substitutions as disclosed herein, which is an agonist of the CGRP receptor. In some embodiments there is provided a peptide analogue of the present disclosure having attached via a peptide bond to the amino group of the N-terminal amino acid of said CGRP peptide an N-terminal region which is a short peptide.

It is an aspect of the present disclosure to provide a peptide analogue of a CGRP having the sequence ($CGRP_{1-37}$):

$X_1CX_3TATCVTHRLAX_{14}LLX_{17}RSGGX_{22}X_{23}KX_{25}NFVPTX_{31}VGSX_{35}AF$ (SEQ ID NO:1), wherein X_1 is Ala or Ser, X_3 is Asp or Asn, X_{14} is Asp or Gly, X_{17} is Arg or Ser, X_{22} is Val or Met, X_{23} is Val or Leu, X_{25} is Asp, Asn or Ser, X_{31} is Asp or Asn, X_{35} is Glu or Lys, and the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of SEQ ID NO:1 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the present disclosure provides a peptide analogue of a CGRP having a sequence ($CGRP_{1-37}$) selected from any one of SEQ ID NO:2 to SEQ ID NO:8, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:2 to SEQ ID NO:8 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the present disclosure provides a peptide analogue of a beta-CGRP having a sequence ($CGRP_{1-37}$) selected from

SC**N**TATCVTHRLAGLLSRSGGMVK**S**NFVPTNVGSKAF (SEQ ID NO:2),
AC**N**TATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF (SEQ ID NO:4),
SC**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGSKAF (SEQ ID NO:6), and
SC**N**TATCVTHRLA**D**LLSRSGG**VL**K**D**NFVPT**D**VGS**E**AF (SEQ ID NO:8),
wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 and SEQ ID NO:8 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In a particular embodiment the present disclosure provides a peptide analogue of **S**C**N**TATCVTHRLAGLLSRSGGMVK**S**NFVPTNVGSKAF (SEQ ID NO:2), wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of SEQ ID NO:2 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the present disclosure provides a peptide analogue of a CGRP having a sequence ($CGRP_{1-37}$) selected from any one of SEQ ID NO:1 to SEQ ID NO:8, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises one or more amino acid substitutions selected from: X_1 is Gly, X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_3 is His and X_{34} is Pro,

wherein said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the present disclosure provides a peptide analogue of a CGRP having a sequence ($CGRP_{1-37}$) selected from any one of SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:9 to SEQ ID NO:81 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue optionally comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:9 to SEQ ID NO:89 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises one or more amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive

amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:9 to SEQ ID NO:89 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide comprises one or more individual amino acid substitutions selected from: X_1 is Gly, X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_3 is His and X_{34} is Pro,

wherein said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

Reference to a peptide analogue having a peptide sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:89 in some embodiments means a peptide analogue having a peptide sequence consisting of an amino acid sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:89.

Reference to a peptide analogue having a peptide sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:89 in some embodiments means a peptide analogue consisting of a peptide sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:89, and an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, which is attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide sequence.

In some embodiments the present disclosure provides a peptide analogue of a CGRP having a sequence ($CGRP_{1-37}$) selected from any one of SEQ ID NO:9 to SEQ ID

NO:89 comprising an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of any one of SEQ ID NO:9 to 89.

In some embodiments the peptide analogue of the present disclosure comprises an N-terminal single amino acid, an N-terminal dipeptide, an N-terminal tripeptide, or an N-terminal peptide consisting of 2 to 30 consecutive amino acids, which is attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue.

In some embodiments of the present disclosure said N-terminal region consists of naturally occurring amino acid residues. In some embodiments of the present disclosure said N-terminal region consists of naturally occurring amino acid residues individually selected from Y, G, F, M, A, S, I, L, T, V, P, K, H, Q, E, W, R, D, N and C.

In some embodiments said N-terminal peptide consists of 2 to 30 naturally occurring amino acid residues, such as 2 to 30 naturally occurring amino acid residues selected from Y, G, F, M, A, S, I, L, T, V, P, K, H, Q, E, W, R, D, N and C.

In some embodiments said N-terminal peptide consists of 2 to 30 consecutive amino acids individually selected from Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met and Orn. In some embodiments said N-terminal peptide consists of 4 to 30 consecutive amino acid residues individually selected from Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, and Met; such as individually selected from amino acid residues Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Orn, and Met; such as Glu, Lys, and Met.

In some embodiments said N-terminal peptide consists of 6 consecutive Lys amino acids (Lys6). In some embodiments said N-terminal peptide consists of 6 consecutive Ala amino acids (Ala6).

In some embodiments said N-terminal single amino acid is Lys.

In some embodiments said N-terminal single amino acid is an aromatic amino acid. In some embodiments said N-terminal single amino acid is an aromatic amino acid selected from Trp, Tyr, Phe and 3-(l-naphthyl)alanine.

In some embodiments the peptide analogue of the present disclosure comprises

an N-terminal single amino acid which is not an aromatic amino acid, an N-terminal dipeptide or an N-terminal tripeptide, which is attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue, or

an N-terminal peptide consisting of 2 to 30 consecutive amino acids and comprising one or more amino acids selected from: Gly (G), Pro (P), Phe (F) and Val (V), which is attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue.

In some embodiments the peptide analogue of the present disclosure comprises an N-terminal region which is attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said CGRP peptide, wherein said N-terminal region is:
an N-terminal single amino acid which is not an aromatic amino acid and is not a Lys (K), an N-terminal dipeptide, an N-terminal tripeptide, or
an N-terminal peptide consisting of 2 to 30 consecutive amino acid residues and comprising one or more amino acids selected from: Gly (G), Pro (P), Phe (F) and Val (V).

Attachment via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue is equivalent to attachment via a peptide bond to the amino group of the N-terminal amino acid residue of said CGRP peptide analogue.

In some embodiments said N-terminal peptide consists of 2 to 30 consecutive amino acid residues and comprises at least one amino acid selected from: Gly, Pro, Phe and Val. In some embodiments said N-terminal peptide consists of 3 to 30 consecutive amino acid residues and comprises at least one amino acid selected from: Gly, Pro, Phe and Val. In some embodiments said N-terminal peptide consists of 4 to 30 consecutive amino acid residues and comprises at least one amino acid selected from: Gly, Pro, Phe and Val.

In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 3 consecutive amino acid residues, such as 3 to 4, such as 4 to 5, such as 5 to 6, such as 6 to 7, such as 7 to 8, such as 8 to 9, such as 9 to 10, such as 10 to 11, such as 11 to 12, such as 12 to 13, such as 13 to 14, such as 14 to 15, such as 15 to 16, such as 16 to 17, such as 17 to 18, such as 18 to 19, such as 19 to 20, such as 20 to 21, such as 21 to 22, such as 22 to 23, such as 23 to 24, such as 24 to 25, such as 25 to 26, such as 26 to 27, such as 27 to 28, such as 28 to 29, such as 29 to 30 consecutive amino acid residues.

In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 30 consecutive amino acid residues, such as 2 to 25, such as 2 to 20, such as 2 to 19, such as 2 to 18, such as 2 to 17, such as 2 to 16, such as 2 to 15, such as 2 to 14, such as 2 to 13, such as 2 to 12, such as 2 to 11, such as 2 to 10, such as 2 to 9, such as 2 to 8, such as 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3 consecutive amino acid residues.

In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 25 consecutive amino acid residues. In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 20 consecutive amino acid residues. In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 15 consecutive amino acid residues. In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 10 consecutive amino acid residues. In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 9 consecutive amino acid residues. In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 5 consecutive amino acid residues. In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 4 consecutive amino acid residues.

In some embodiments of the present disclosure said N-terminal peptide consists of 2 consecutive amino acid residues, such as 3, such as 4, such as 5, such as 6, such as 7, such as 8, such as 9, such as 10, such as 11, such as 12, such as 13, such as 14, such as 15, such as 16, such as 17, such as 18, such as 19, such as 20, such as 21, such as 22, such as 23, such as 24, such as 25, such as 26, such as 27, such as 28, such as 29, such as 30 consecutive amino acid residues.

In some embodiments of the present disclosure said N-terminal peptide consist of 2 to 30, such as 3 to 30, such as 4 to 30, consecutive amino acids and comprises one or more amino acids selected from: Gly, Pro, Phe and Val.

In some embodiments of the present disclosure said N-terminal peptide comprises one or more amino acids selected from: Gly and Pro.
In some embodiments of the present disclosure said N-terminal peptide comprises at least one amino acid selected from: Gly and Pro.

In some embodiments of the present disclosure said N-terminal peptide comprises one amino acid selected from: Gly and Pro. In some embodiments of the present disclosure said N-terminal peptide comprises two amino acids selected from: Gly and Pro. In some embodiments of the present disclosure said N-terminal peptide comprises two or more amino acids selected from: Gly and Pro. In some embodiments of the present disclosure said N-terminal peptide comprises three amino acids selected from: Gly and Pro. In some embodiments of the present disclosure said N-terminal peptide comprises three or more amino acids selected from: Gly and Pro.

In some embodiments of the present disclosure said N-terminal peptide comprises at least one Gly amino acid. In some embodiments of the present disclosure said N-terminal peptide comprises one Gly amino acid, such as one or more Gly amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises two Gly amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises two or more Gly amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises three Gly amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises three or more Gly amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises four Gly amino acids, such as four or more Gly amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises five Gly amino acids, such as five or more Gly amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises six Gly amino acids, such as six or more Gly amino acids.

In some embodiments of the present disclosure said N-terminal peptide comprises at least one Pro amino acid. In some embodiments of the present disclosure said N-

terminal peptide comprises one Pro amino acid, such as one or more or more Pro amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises two Pro amino acids, such as two or more or more Pro amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises three Pro amino acids, such as three or more or more Pro amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises four Pro amino acids, such as four or more or more Pro amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises five Pro amino acids, such as five or more or more Pro amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises six Pro amino acids, such as six or more or more Pro amino acids.

In some embodiments of the present disclosure said N-terminal peptide comprises one or more amino acids selected from: Phe and Val.

In some embodiments of the present disclosure said N-terminal peptide comprises at least one amino acid selected from: Phe and Val.

In some embodiments of the present disclosure said N-terminal peptide comprises two amino acids selected from: Phe and Val. In some embodiments of the present disclosure said N-terminal peptide comprises two or more amino acids selected from: Phe and Val. In some embodiments of the present disclosure said N-terminal peptide comprises three amino acids selected from: Phe and Val. In some embodiments of the present disclosure said N-terminal peptide comprises three or more amino acids selected from: Phe and Val.

In some embodiments of the present disclosure said N-terminal peptide comprises at least one Phe amino acid.

In some embodiments of the present disclosure said N-terminal peptide comprises at least one Phe amino acid. In some embodiments of the present disclosure said N-terminal peptide comprises one Phe amino acid, such as one or more or more Phe amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises two Phe amino acids, such as two or more or more Phe amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises three

Phe amino acids, such as three or more or more Phe amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises four Phe amino acids, such as four or more or more Phe amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises five Phe amino acids, such as five or more or more Phe amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises six Phe amino acids, such as six or more or more Phe amino acids.

In some embodiments of the present disclosure said N-terminal peptide comprises at least one Val amino acid.

In some embodiments of the present disclosure said N-terminal peptide comprises at least one Val amino acid. In some embodiments of the present disclosure said N-terminal peptide comprises one Val amino acid, such as one or more or more Val amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises two Val amino acids, such as two or more or more Val amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises three Val amino acids, such as three or more or more Val amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises four Val amino acids, such as four or more or more Val amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises five Val amino acids, such as five or more or more Val amino acids. In some embodiments of the present disclosure said N-terminal peptide comprises six Val amino acids, such as six or more or more Val amino acids.

In some embodiments of the present disclosure said N-terminal single amino acid or said N-terminal peptide does not comprises any amino acids with electrically charged side chains selected from Arg, His, Lys, Asp and Glu.

In some embodiments of the present disclosure said N-terminal single amino acid or said N-terminal peptide comprises at the most one amino acid with electrically charged side chains selected from Arg, His, Lys, Asp and Glu.

In some embodiments of the present disclosure said N-terminal single amino acid or said N-terminal peptide comprises one amino acid with electrically charged side chains selected from Arg, His, Lys, Asp and Glu.

In some embodiments of the present disclosure said N-terminal peptide comprises one, and no more than one, Lys amino acid.

In some embodiments of the present disclosure said N-terminal single amino acid or said N-terminal peptide comprises maximum two amino acids with electrically charged side chains selected from Arg, His, Lys, Asp and Glu). In some embodiments of the present disclosure said N-terminal single amino acid or said N-terminal peptide comprises two amino acids with electrically charged side chains selected from Arg, His, Lys, Asp and Glu).

In some embodiments of the present disclosure said N-terminal peptide comprises one or more His amino acids. In some embodiments of the present disclosure said N-terminal single amino acid or said N-terminal peptide comprises one His amino acid. In some embodiments of the present disclosure said N-terminal peptide comprises two His amino acids.

In some embodiments of the present disclosure said N-terminal peptide comprises or consist of one or more amino acids individually selected from Ser, Gly, Arg, Phe, Val, Ala, Pro, Glu, Leu and Lys.

In preferred embodiments of the present disclosure said N-terminal peptide consist of 2 to 30 amino acids individually selected from Ser, Gly, Arg, Phe, Val, Ala, Pro, Glu, Leu and Lys.

In some embodiments of the present disclosure said N-terminal peptide comprises or consist of one or more amino acids individually selected from Ser, Gly, Arg, Phe and Val.

In some embodiments of the present disclosure said N-terminal peptide comprises or consist of one or more amino acids individually selected from Ala, Pro, Glu and Lys.

In some embodiments of the present disclosure said N-terminal peptide consist of 2 to 30 amino acids individually selected from Ser, Gly, Arg, Phe, Val, Ala, Pro, Glu, Leu and Lys, wherein each of said 2 to 30 amino acids selected from Ser, Gly, Arg, Phe, Val, Ala, Pro, Glu, Leu and Lys are present maximum twice.

In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 30 amino acids individually selected from Ser, Gly, Arg, Phe, Val, Ala, Pro, Glu, Leu and Lys, wherein said N-terminal peptide comprises maximum 2 Ser amino acids, maximum 2 Gly amino acids, maximum 2 Arg amino acids, maximum 2 Phe amino acids, maximum 2 Val amino acids, maximum 2 Ala amino acids, maximum 2 Pro amino acids, maximum 2 Glu amino acids, maximum 2 Leu amino acids and maximum 2 Lys amino acids.

In some embodiments of the present disclosure said N-terminal peptide consist of 2 to 30 amino acids individually selected from Ser, Gly, Arg, Phe, Val, Ala, Pro, Glu, Leu and Lys, wherein each of said 2 to 30 amino acids selected from Ser, Gly, Arg, Phe, Val, Ala, Pro, Glu, Leu and Lys are present only once.

In some embodiments of the present disclosure said N-terminal peptide consists of 2 to 30 amino acids individually selected from Ser, Gly, Arg, Phe, Val, Ala, Pro, Glu, Leu and Lys, wherein said N-terminal peptide comprises maximum 1 Ser amino acid, maximum 1 Gly amino acid, maximum 1 Arg amino acid, maximum 1 Phe amino acid, maximum 1 Val amino acid, maximum 1 Ala amino acid, maximum 1 Pro amino acid, maximum 1 Glu amino acid, maximum 1 Leu amino acid and maximum 1 Lys amino acid.

In some embodiments of the present disclosure said N-terminal single amino acid is not an aromatic amino acid. In some embodiments of the present disclosure said N-terminal single amino acid is not an aromatic amino acid selected from Trp, Tyr, Phe and 3-(l-naphthyl)alanine.

In some embodiments of the present disclosure said N-terminal single amino acid is an amino acid selected from: Gly, Pro and Val. In some embodiments of the present disclosure said N-terminal single amino acid is Gly. In some embodiments of the present disclosure said N-terminal single amino acid is Pro. In some embodiments of the present disclosure said N-terminal single amino acid is Val.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence:

$X_{-9}X_{-8}X_{-7}X_{-6}X_{-5}X_{-4}X_{-3}X_{-2}X_{-1}$ (SEQ ID NO:233),

wherein X_{-1} is attached via a peptide bond to the amino group of X_1 of said CGRP peptide or peptide analogue:

X_{-9} is selected from: absent, Ser and Gly,
X_{-8} is selected from: absent, Gly and Ser,
X_{-7} is selected from: absent, Ser and Gly,
X_{-6} is selected from: absent, Gly, Ser, Lys, and Ala,
X_{-5} is selected from: absent, Ser, Gly, Lys and Ala,
X_{-4} is selected from: absent, Gly, Ser, Lys, Ala, Arg and Leu,
X_{-3} is selected from: absent, Ser, Gly, Arg, Pro, Lys, Ala and Leu,
X_{-2} is selected from: Gly, Ser, Arg, Ala, Glu, Lys, Phe and Val, and
X_{-1} is selected from: Ser, Gly, Phe, Val, Lys and Ala;

wherein optionally said N-terminal peptide comprises at least one amino acid selected from: Gly, Pro, Phe and Val.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $X_{-4}X_{-3}X_{-2}X_{-1}$ (SEQ ID NO:234),

wherein X_{-1} is attached via a peptide bond to the amino group of X_1 of said CGRP peptide or peptide analogue, wherein:

X_{-4} is selected from: Gly, Ser, Lys, Ala, Arg and Leu,
X_{-3} is selected from: Ser, Gly, Arg, Pro, Lys, Ala and Leu,
X_{-2} is selected from: Gly, Ser, Arg, Ala, Glu, Lys, Phe and Val, and
X_{-1} is selected from: Ser, Gly, Phe, Val, Lys and Ala;

wherein optionally said N-terminal peptide comprises at least one amino acid selected from: Gly, Pro, Phe and Val.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $X_{-3}X_{-2}X_{-1}$,

wherein X_{-1} is attached via a peptide bond to the amino group of X_1 of said CGRP peptide or peptide analogue,

wherein each of X_{-3}, X_{-2} and X_{-1} is individually selected from Ser, Gly, Arg, Phe, Val, Pro, Glu, Ala, Leu and Lys.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $X_{-3}X_{-2}X_{-1}$,

wherein X_{-1} is attached via a peptide bond to the amino group of X_1 of said CGRP peptide or peptide analogue, wherein

X_{-3} is selected from: Ser, Gly, Arg, Pro, Lys, Ala and Leu,
X_{-2} is selected from: Gly, Ser, Arg, Ala, Glu, Lys, Phe and Val, and
X_{-1} is selected from: Ser, Gly, Phe, Val, Lys and Ala.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of a sequence selected from: SGS, GSG, SG, GS, RSF, RV, PAS and SGSGSGSGS (SEQ ID NO:235).

It is understood that the last-mentioned amino acid in a sequence of more than one amino acid is the amino acid that is attached via a peptide bond to the amino group of the N-terminal amino acid (X_1) of said CGRP peptide or peptide analogue (e.g. the F in the sequence RSF, and the S in the sequence PAS).

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of a sequence selected from: SGS, GSG, SG, GS, RSF, RSFG (SEQ ID NO:237), RV, RVG, LRV, LLRV (SEQ ID NO:238), ES, PAS, SGSG (SEQ ID NO:236), SGSGSGSGS (SEQ ID NO:235), KVG, GKVG (SEQ ID NO:239), KSF and GKSF (SEQ ID NO:240).

In some embodiments of the present disclosure said N-terminal peptide consists of a sequence selected from: SGS, GSG, SG, GS, RSF, RSFG (SEQ ID NO:237), RV, RVG, LRV, LLRV (SEQ ID NO:238), ES, PAS, SGSG (SEQ ID NO:236), SGSGSGSGS (SEQ ID NO:235), KVG, GKVG (SEQ ID NO:239), KSF and GKSF (SEQ ID NO:240).

In some embodiments of the present disclosure said N-terminal peptide consists of a sequence selected from: RSF, RSFG (SEQ ID NO:237), KSF and GKSF (SEQ ID NO:240). In some embodiments of the present disclosure said N-terminal peptide consists of RSF or RSFG (SEQ ID NO:237),

In some embodiments of the present disclosure said N-terminal peptide consists of a sequence selected from: RV, RVG, LRV, LLRV (SEQ ID NO:238), KVG and GKVG (SEQ ID NO:239). In some embodiments of the present disclosure said N-terminal peptide consists of a sequence selected from: RV, RVG, LRV and LLRV (SEQ ID NO:238).

In some embodiments of the present disclosure said N-terminal peptide consists of a sequence selected from:
$S\text{-}(GS)_n$, $(GS)_n$, $G\text{-}(SG)_n$, $(SG)_n$, $(S)_n$, $(G)_n$, $(ES)_n$ and $(RV)_n$ wherein n is an integer of 2 to 12; $(PAS)_n$, $(RSF)_n$, $(KSF)_n$, $(LRV)_n$, $(RVG)_n$ and $(KVG)_n$ wherein n is an integer of 2 to 8; and $(RSFG)_n$, $(GKSF)_n$, $(LLRV)_n$ and $(GKVG)_n$ wherein n is an integer of 2 to 6.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of a sequence selected from: $S\text{-}(GS)_n$, $(GS)_n$, $G\text{-}(SG)_n$, $(SG)_n$, $(S)_n$ and $(G)_n$, wherein n is an integer of 2 to 12; such as
wherein n is an integer of 2 to 11, such as 2 to 10, such as 2 to 9, such as 2 to 8, such as 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 1, such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6, such as wherein n = 7, such as wherein n = 8, such as wherein n = 9, such as wherein n = 10, such as wherein n = 11, such as wherein n = 12.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(PAS)_n$, wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6, such as wherein n = 7, such as wherein n = 8.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(ES)_n$, wherein n is an integer of 2 to 12; such as wherein n is an integer of 2 to 11, such as 2 to 10, such as 2 to 9, such as 2 to 8, such as 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6, such as wherein n = 7, such as wherein n = 8, such as wherein n = 9, such as wherein n = 10, such as wherein n = 11, such as wherein n = 12.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(RSFG)_n$ wherein n is an integer of 2 to 6; such as wherein n is an integer of 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(RSF)_n$ wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6, such as wherein n = 7, such as wherein n = 8.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(GKSF)_n$ wherein n is an integer of 2 to 6; such as wherein n is an integer of 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(KSF)_n$ wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6, such as wherein n = 7, such as wherein n = 8.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(LLRV)_n$ wherein n is an integer of 2 to 6; such as wherein n is an integer of 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(LRV)_n$ wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6, such as wherein n = 7, such as wherein n = 8.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(RV)_n$ wherein n is an integer of 2 to 12; such as wherein n is an integer of 2 to 11, such as 2 to 10, such as 2 to 9, such as 2 to 8, such as 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6, such as wherein n = 7, such as wherein n = 8, such as wherein n = 9, such as wherein n = 10, such as wherein n = 11, such as wherein n = 12.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(RVG)_n$ wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6, such as wherein n = 7, such as wherein n = 8.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(GKVG)_n$ wherein n is an integer of 2 to 6; such as wherein n is an integer of 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6.

In some embodiments of the present disclosure said N-terminal peptide comprises or consists of the sequence $(KVG)_n$ wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3; such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6, such as wherein n = 7, such as wherein n = 8.

In some embodiments of the present disclosure said N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide, contributes to one or more of potency, binding affinity or efficacy of said CGRP peptide to the CGRP receptor, such as increases and/or maintains one or more of potency, binding affinity or efficacy of said CGRP peptide to the CGRP receptor.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:8, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;

such as wherein said peptide comprises at least one amino acid substitution selected from X_1 is Gly, X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_3 is His and X_{34} is Pro,

wherein said peptide analogue comprises an N-terminal region attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue selected from SGS, GSG, SG, GS, RSF, RSFG (SEQ ID NO:237), RV, RVG, LRV, LLRV (SEQ ID NO:238), ES, PAS, SGSG (SEQ ID NO:236), SGSGSGSGS (SEQ ID NO:235), KVG, GKVG (SEQ ID NO:239), KSF and GKSF (SEQ ID NO:240),

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:1 to SEQ ID NO:8, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;

such as wherein said peptide comprises at least one amino acid substitution selected from X_1 is Gly, X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_3 is His and X_{34} is Pro,

wherein said peptide analogue comprises an N-terminal region attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue selected from S-$(GS)_n$, $(GS)_n$, G-$(SG)_n$, $(SG)_n$, $(S)_n$, $(G)_n$, $(ES)_n$ and $(RV)_n$ wherein n is an integer of 2 to 12; $(PAS)_n$, $(RSF)_n$, $(KSF)_n$, $(LRV)_n$, $(RVG)_n$ and $(KVG)_n$ wherein n is an integer of 2 to 8; and $(RSFG)_n$, $(GKSF)_n$, $(LLRV)_n$ and $(GKVG)_n$ wherein n is an integer of 2 to 6;

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:9 to SEQ ID NO:89 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide optionally comprises one or more individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;

such as wherein said peptide optionally comprises one or more individual amino acid substitutions selected from X_1 is Gly, X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_3 is His and X_{34} is Pro,

wherein said peptide analogue comprises an N-terminal region attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue selected from SGS, GSG, SG, GS, RSF, RSFG (SEQ ID NO:237), RV, RVG, LRV, LLRV (SEQ ID NO:238), ES, PAS, SGSG (SEQ ID NO:236), SGSGSGSGS (SEQ ID NO:235), KVG, GKVG (SEQ ID NO:239), KSF and GKSF (SEQ ID NO:240),

wherein said peptide analogue is an agonist of the GCRP receptor.

In some embodiments the peptide analogue of the present disclosure has a peptide sequence selected from any one of SEQ ID NO:9 to SEQ ID NO:89, wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:9 to SEQ ID NO:89 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}, such as comprising one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide optionally comprises one or more individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;

such as wherein said peptide optionally comprises one or more individual amino acid substitutions selected from X_1 is Gly, X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_3 is His and X_{34} is Pro,

wherein said peptide analogue comprises an N-terminal region attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue selected from S-$(GS)_n$, $(GS)_n$, G-$(SG)_n$, $(SG)_n$, $(S)_n$, $(G)_n$, $(ES)_n$ and $(RV)_n$ wherein n is an integer of 2 to 12; $(PAS)_n$, $(RSF)_n$, $(KSF)_n$, $(LRV)_n$, $(RVG)_n$ and $(KVG)_n$ wherein n is an integer of 2 to 8; and $(RSFG)_n$, $(GKSF)_n$, $(LLRV)_n$ and $(GKVG)_n$ wherein n is an integer of 2 to 6;

wherein said peptide analogue is an agonist of the GCRP receptor.

In preferred embodiments said N-terminal region is selected from SGS, RSF, RSFG (SEQ ID NO:237), RV, RVG, LRV, LLRV (SEQ ID NO:238), ES, PAS, SGSG (SEQ ID NO:236), SGSGSGSGS (SEQ ID NO:235), KVG, GKVG (SEQ ID NO:239), KSF and GKSF (SEQ ID NO:240).

In some embodiments said N-terminal region is selected from SGS, RSF, RSFG (SEQ ID NO:237), RV, RVG, LRV, LLRV (SEQ ID NO:238), PAS, SGSG (SEQ ID NO:236), SGSGSGSGS (SEQ ID NO:235), KVG, GKVG (SEQ ID NO:239), KSF and GKSF (SEQ ID NO:240).

In some embodiments said N-terminal region is selected from SGS, RSF, RSFG (SEQ ID NO:237), RV, RVG, LRV, LLRV (SEQ ID NO:238), SGSG (SEQ ID NO:236), SGSGSGSGS (SEQ ID NO:235), KVG, GKVG (SEQ ID NO:239), KSF and GKSF (SEQ ID NO:240).

In some embodiments of the present disclosure said N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide, is a linker, such as an inactive linker.

In some embodiments said linker largely does not affect the potency of the CGRP peptide. In some embodiments said linker largely does not affect the agonistic potency of the CGRP peptide agonist (EC50).

In some embodiments N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide contributes to one or more of potency, binding affinity or efficacy of said CGRP peptide analogue to the CGRP receptor, such as increases and/or maintains one or more of potency, binding affinity or efficacy of said CGRP peptide analogue to the CGRP receptor.

In some embodiments said linker largely does not affect the T½ of the CGRP peptide. In some embodiments said linker largely does not affect the solubility of the CGRP peptide.

In some embodiments of the present disclosure said N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide, is a linker capable of connecting said CGRP peptide analogue to another entity.

In some embodiments of the present disclosure said N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide, is a linker capable of connecting said CGRP peptide analogue to another peptide or protein; such as a therapeutic peptide, a therapeutic protein, a circulating peptide or a circulating protein.

In some embodiments of the present disclosure said CGRP peptide analogue comprises another peptide or protein attached to the N-terminus of said CGRP peptide analogue; such as attached to the N-terminus of the N-terminal single amino acid, N-

terminal dipeptide, N-terminal tripeptide or N-terminal peptide of said CGRP peptide analogue.

In some embodiments of the present disclosure said CGRP peptide analogue comprises a therapeutic peptide, a therapeutic protein, a circulating peptide or a circulating protein attached to the N-terminus of said CGRP peptide analogue; such as attached to the N-terminus of the N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide of said CGRP peptide analogue.

In some embodiments of the present disclosure said CGRP peptide analogue comprises another peptide or protein attached via its C-terminus to the N-terminus of said CGRP peptide analogue; such as attached via its C-terminus to the N-terminus of the N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide of said CGRP peptide analogue.

In some embodiments of the present disclosure said CGRP peptide analogue comprises a therapeutic peptide, a therapeutic protein, a circulating peptide or a circulating protein attached via its C-terminus to the N-terminus of said CGRP peptide analogue; such as attached via its C-terminus to the N-terminus of the N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide of said CGRP peptide analogue.

The term “its C-terminus” here refers to the C-terminus of the ‘another protein’, such as the C-terminus of said therapeutic peptide, therapeutic protein, circulating peptide or circulating protein.

In some embodiments of the present disclosure said another peptide or protein is albumin, an Fc domain or Albumin-binding domain (ABD).
In some embodiments of the present disclosure said circulating protein or peptide is selected from albumin, an Fc domain or Albumin-binding domain (ABD).

The fragment crystallizable domain (Fc domain) is the tail region of an antibody that interacts with cell surface receptors called Fc receptors and some proteins of the complement system. This region allows antibodies to activate the immune system, for example, through binding to Fc receptors. The albumin-binding domain (ABD) is a

small, three-helical protein domain found in various surface proteins expressed by gram-positive bacteria.

In some embodiments of the present disclosure there is provided a peptide analogue having a sequence selected from:

SGS-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO: 90);
RSF-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO: 91);
RV-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO: 92);
SGSGSGSGS–GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:93);
PAS-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:94);
ES-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:95);
KKKKKK-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:96);
AAAAAA-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:97);
PAS-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:98);
SGSG-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:99);
RSFG-GCHTATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:100);
RVG-GCHTATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:101);
PAS-SC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:102);
SGSG-SC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:103);
LRV-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:104);
RSF-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:105);
SGS-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:106);
SGSG-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:107);
LLRV-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:108);
SGS-GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:109);
RSF-GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:110);
RV-GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:111);
PAS-GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:112);
LRV-GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:113);
SGS-GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:114);
RSF-GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:115);
RV-GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:116);
PAS-GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:117);
LRV-GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:118);

SGS-GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:119);
RSF-GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:120);
RV-GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:121);
PAS-GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:122);
LRV-GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:123);
SGS-GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:124);
RSF-GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:125);
RV-GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:126);
PAS-GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:127);
LRV-GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:128);
SGS-GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:129);
RSF-GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:130);
RV-GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:131);
PAS-GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:132);
LRV-GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:133);
SGS-GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:134);
RSF-GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:135);
RV-GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:136);
PAS-GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:137);
LRV-GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:138);
SGS-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:139);
RSF-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:140);
RV-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:141);
PAS-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:142);
LRV-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:143);
SGS-GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:144);
RSF-GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:145);
RV-GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:146);
PAS-GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:147);
LRV-GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:148);
SGS-GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:149);
RSF-GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:150);
RV-GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:151);
PAS-GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:152);
LRV-GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:153);

SGS-GCHTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:154);
RSF-GCHTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:155);
RV-GCHTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:156);
PAS-GCHTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:157);
LRV-GCHTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:158);
SGS-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:159);
RSF-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:160);
RV-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:161);
PAS-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:162);
LRV-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:163);
SGS-GCHTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:164);
RSF-GCHTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:165);
RV-GCHTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:166);
PAS-GCHTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:167);
LRV-GCHTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:168);
SGS-GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:169);
RSF-GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:170);
RV-GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:171);
PAS-GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:172);
LRV-GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:173);
RVG-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:174);
KVG-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:175);
GKVG-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:176);
K-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:177);
KSF-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:178);
KSF-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:179); and
GKSF-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:180);

wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:90 to SEQ ID NO:180 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide optionally comprises one or more individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His;

X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein said analogue is an agonist of the GCRP receptor.

Preferably the peptide analogue of any one of SEQ ID NO:90 to SEQ ID NO:180 does not comprise an amino acid substitution at the one or more amino acid residues which are indicated in **bold** in said amino acid sequence.

In some embodiments said functional variant of any one of SEQ ID NO:90 to SEQ ID NO:180 comprises one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}. In some embodiments said functional variant of any one of SEQ ID NO:90 to SEQ ID NO:180 comprises one, two, three, four, five or six individual conservative amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

In some embodiments said functional variant of any one of SEQ ID NO:90 to SEQ ID NO:180 comprises one, two, three, four, five or six individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37} at one or more positions outside the one or more amino acid residues which are indicated in **bold** in the amino acid sequence of any one of SEQ ID NO:90 to SEQ ID NO:180.

In some embodiments the peptide analogue of any one of SEQ ID NO:90 to SEQ ID NO:180 comprises at least one amino acid substitution selected from X_1 is Gly, X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_3 is His and X_{34} is Pro. In some embodiments the peptide analogue of any one of SEQ ID NO:90 to SEQ ID NO:180 comprises at least one amino acid substitution selected from X_1 is Gly, X_{10} is Asp or Glu, X_{19} is His and X_{14} is His.

<u>CGRP peptide analogue with Acylation/Linker</u>

In some embodiments the CGRP analogue of the present disclosure comprises an acyl group (“Z”) connected to an amino group present in an amino acid residue in the CGRP analogue.

In some embodiments the CGRP analogue of the present disclosure comprises a linker ("Y") and an acyl group ("Z") that forms an Y-Z moiety connected to an amino group present in an amino acid residue in the CGRP analogue.

In some embodiments of the present disclosure a hydrogen has been removed from one of the amino groups present in an amino acid residue of the CGRP peptide analogue, wherein a linker ("Y") and an acyl group ("Z") forms an Y-Z moiety which is connected to an amino group present in an amino acid residue in the CGRP peptide analogue "X"

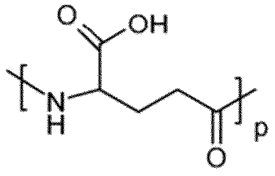
In some embodiments the acyl group (designated Z) and/or the acyl group connected to the linker (designated Y) shall have a sufficient albumin binding affinity. In some embodiments addition of an -Y-Z-moiety will increase the half-life of the CGRP peptide X or CGRP peptide analogue ('prolonged action').

In some embodiments the peptide analogue of the present disclosure comprises an acyl group, Z.

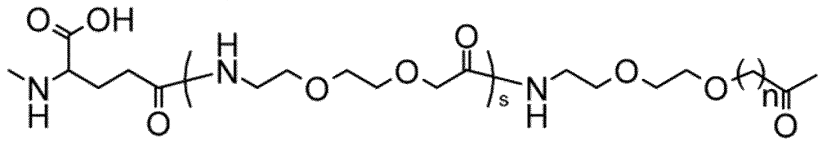
In some embodiments the peptide analogue of the present disclosure comprises an acyl group, Z, connected to an amino group of the N-terminal amino acid residue of the peptide analogue.

In some embodiments the peptide analogue of the present disclosure comprises a linker, Y.

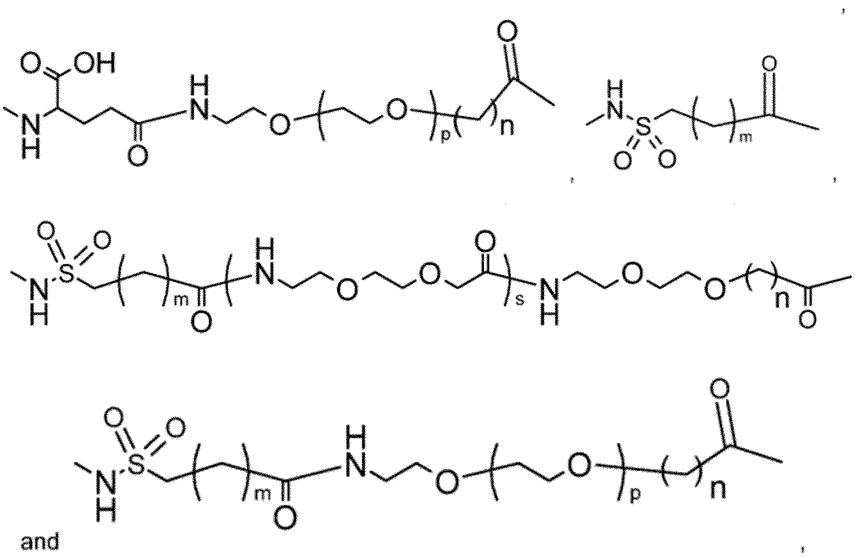
In some embodiments the linker, Y, is selected from the following formulae:



,



,



and

wherein m is an integer of 0 to 6, such as wherein m is 0, 1, 2, 3, 4, 5, or 6;
n is an integer of 1 to 3, such as wherein n is 1, 2, or 3;
s is an integer of 0 to 3, such as wherein s is 0, 1, 2, or 3; and
p is an integer of 1 to 23, such as wherein p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23,
and wherein the carbonyl end of the linker is connected to the N-terminal amino acid residue of the peptide analogue.

In some embodiments the peptide analogue of the present disclosure comprises a linker, Y, wherein said linker comprises one or more moieties individually selected from

i. α-amino acid, γ-amino acid, and ω-amino acid,
ii. Glu, gamma-Glu, iso-Glu, beta-Asp, Asp, beta-Ala, Lys, gamma-aminobutyric acid, and Gly, and
iii. [8-amino-3,6-dioxaoctanoic acid]$_n$ (AEEA$_n$), wherein n is an integer of 1 to 20, such as an integer of 1 to 5, of 1 to 4, of 1 to 3, or of 1 to 2; such as an integer of 1, 2, 3, 4 or 5, preferably 1 or 2.

In some embodiments the peptide analogue of the present disclosure comprises a linker, Y, selected from AEEA, 2AEEA, isoGlu-AEEA, isoGlu-2AEEA, gammaGlu-AEEA and gammaGlu-2AEEA.

In some embodiments the linker, Y, is connected to an amino group of the N-terminal amino acid residue of the peptide analogue.

In some embodiments the acyl group, Z, or the linker, Y, is connected to an amino group of the N-terminal amino acid residue of the CGRP peptide analogue selected from the amino group of position X_{-9}, the amino group of X_{-8}, the amino group of X_{-7}, the amino group of X_{-6}, the amino group of X_{-5}, the amino group of X_{-4}, the amino group of X_{-3}, the amino group of X_{-2}, the amino group of X_{-1}, and the amino group of X_1.

In some embodiments the amino end of the linker, Y, is connected to the acyl group, Z.

In some embodiments the acyl group of Z originates from a fatty acid or fatty diacid.
In some embodiments the acyl group of Z originates from a fatty diacid with an alpha and omega carboxy group.

In some embodiments the acyl group of Z comprises an acyl group of the formula $CH_3(CH_2)_nCO$-, wherein n is in an integer of 4 to 24; such as wherein n is an integer of 8 to 20, of 10 to 20, of 12 to 20, of 14 to 20, or of 14 to 18.

In some embodiments the acyl group of Z comprises an acyl group of the formula COOH(CH2)nCO-, wherein n is an integer of 4 to 24; such as wherein n is an integer of 8 to 20, of 10 to 20, of 12 to 20, of 14 to 20, or of 14 to 18.

In some embodiments the acyl group of Z originates from a fatty acid or fatty diacid with 12-22 carbon atoms.
In some embodiments the acyl group of Z originates from a fatty acid or fatty diacid with 14 carbon atoms.In some embodiments the acyl group of Z originates from a fatty acid or fatty diacid with 16 carbon atoms.
In some embodiments the acyl group of Z originates from a fatty acid or fatty diacid with 18 carbon atoms.
In some embodiments the acyl group of Z originates from a fatty acid or fatty diacid with 20 carbon atoms.

In some embodiments the acyl group is selected from $HOOC(CH_2)14CO$, $HOOC(CH_2)16CO$, $HOOC(CH_2)18CO$, $CH_3(CH_2)14CO$, $CH_3(CH_2)16CO$ and $CH_3(CH_2)18CO$.

In preferred embodiments the N-terminal amino acid of the CGRP peptide analogue of the present disclosure comprises an acyl group and a linker.

In some embodiments the N-terminal amino acid of the peptide analogue of the present disclosure comprises an acyl group and a linker selected from $HOOC(CH_2)16CO$-isoGlu-AEEA, $HOOC(CH_2)16CO$-isoGlu-2AEEA, $HOOC(CH_2)14CO$-isoGlu-AEEA, $HOOC(CH_2)14CO$-isoGlu-2AEEA, $HOOC(CH_2)16CO$-isoGlu-AEEA and $HOOC(CH_2)16CO$-isoGlu-2AEEA.

In some embodiments the N-terminal amino acid of the peptide analogue of the present disclosure comprises an acyl group selected from $HOOC(CH_2)16CO$-isoGlu, $HOOC(CH_2)14CO$-isoGlu and $HOOC(CH_2)18CO$-isoGlu.

In some embodiments the N-terminal amino acid of the peptide analogue of the present disclosure comprises an acyl group selected from $CH_3(CH_2)14CO$-gamma-Glu, $CH_3(CH_2)16CO$-gammaGlu and $CH_3(CH_2)18CO$-gammaGlu.

In preferred embodiments the N-terminal amino acid of the CGRP peptide analogue of the present disclosure comprises $HOOC(CH_2)16CO$-isoGlu-AEEA.

In some embodiments the peptide analogue of the present disclosure further comprises polyethylene glycol (PEG). In some embodiments the CGRP peptide analogue of the present disclosure further comprises a biomarker, such as a fluorescent marker.

Composition and administration

A peptide analogue of the present disclosure may be administered by oral, parenteral (for example, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic

pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

While it is possible for a peptide analogue of the present disclosure to be administered alone, it is often preferable to present it as a pharmaceutical formulation. Formulations typically comprise the active ingredient together with one or more acceptable carriers thereof. Each carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the subject. Therapeutic formulations can be prepared by any methods well known in the art of pharmacy.

It is an aspect to provide a composition comprising a CGRP peptide analogue of the present disclosure, optionally further comprising a carrier.

Also disclosed is a pharmaceutical composition comprising a CGRP peptide analogue of the present disclosure, optionally comprising a pharmaceutically acceptable carrier, excipient or diluent.

Medical use

It is also an aspect to provide a CGRP peptide analogue, a composition, and a pharmaceutical composition according to the present disclosure, for use as a medicament.

In some embodiments there is provided a CGRP peptide analogue of the present disclosure for use in a method of treating a disease selected from: a cardiovascular disease; a neurological disorder; an infection: a renal disease; a metabolic disease; a bone disease: an ischemic disease; an inflammatory disease; a gastrointestinal disease; and pain, such as nociceptive pain and/or neuropathic pain.

In some embodiments there is provided a method of treating a disease selected from: a cardiovascular disease; a neurological disorder; an infection: a renal disease; a metabolic disease; a bone disease: an ischemic disease; an inflammatory disease; a gastrointestinal disease; and pain, such as nociceptive pain and/or neuropathic pain, said method comprising one or more steps of administering a therapeutically effective

amount of a CGRP peptide analogue of the present disclosure to an individual in need thereof.

In some embodiments there is provided use of a CGRP peptide analogue of the present disclosure for the manufacture of a medicament for treating a disease selected from: a cardiovascular disease; a neurological disorder; an infection: a renal disease; a metabolic disease; a bone disease: an ischemic disease; an inflammatory disease; a gastrointestinal disease; and pain, such as nociceptive pain and/or neuropathic pain.

In some embodiments the cardiovascular disease is ischemic heart disease.

Examples

Example 1: Peptide synthesis

A peptide analogue may for instance be produced by classical peptide synthesis, for example, solid phase peptide synthesis using t-Boc or Fmoc chemistry or other well established techniques, see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1999.

The peptide analogues may be covalently connected by a disulfide bridge (—S—S—) between the Cysteine residues at positions 2 and 7. The cyclization of the disulfide bridge may be performed after purification of the peptides or prior to cleavage from the resin in the solid-phase peptide synthesis, optionally in the presence of suitable protecting groups. The disulfide bridge may be formed spontaneously by stirring the peptide in the presence of oxygen or may be formed by treating the peptides with another suitable oxidant such as iodine (I_2), optionally in the presence of a base.

To stabilise the disulfide bridge a disulfide stapling procedure performed under mild, biocompatible reaction conditions (aqueous media, low to ambient temperature and mild pH) can be used directly with unprotected peptides. A key aim of this strategy is to insert a minimal linker (such as methylene) into the disulfide bond and maintain the structural integrity necessary for the biological activity of the peptides.

WO 2011/051312 describes the synthesis of the CGRP analogue HOOC(CH_2)16CO-isoGlu-AEEA-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:2).

Example 2: Determination of Potency in Cell Based Assay

The potency of the peptide analogues was determined in a cell-based CGRP receptor assay detecting cAMP accumulation using a cAMP Detection Kit (VKEY-BIO-A010012).

HEK293 cells were transfected with CGRP receptor subunits and frozen in aliquots.
Peptide analogues were dissolved in DMSO and 4-fold serial diluted 10 times in Assay Buffer (HBSS (Gibco-14025-076) 20 mM HEPES, 0.1% HSA (Sigma-A1653), 500 µM IBMX (Sigma-I5879), pH 7.4).
100 nL solution was added to each well in 384 well assay plates (PerkinElmer-6007299) using a liquid handler (Labcyte, Echo 555).
Cells were thawed, washed twice with HBSS and resuspended in Assay Buffer.
5.000 cells were added to each well (in 10 µl).
The assay plate was shaken for 20 seconds, centrifuged (1000 rpm) for 10 seconds and incubated (23ºC) for 60 minutes.
10 µl Eu2 labelled antibody/cAMP tracer solution (50 µl Eu2 labeled antibody + 50 µl cAMP tracer in 5 ml Detection buffer) were then added to each well.
The assay plate was shaken for 20 seconds, centrifuged (1000 rpm) for 10 seconds and incubated (23ºC) for 1 hour before the plate was read using the Envision microplate reader (Perkin Elmer).

All peptide analogues were assayed in duplicate and potency (EC_{50}) values were calculated using curve-fitting (4-parameter non-linear regression) assisted by GraphPad Prism 10.1.0. Each assay plate contained the comparator sequences SEQ ID NO:2 (acylated) and SEQ ID NO:3, to account for inter-plate and inter-assay variations.

All tested CGRP peptide analogues include a linker/fatty acylation (HOOC(CH_2)16CO-isoGlu-AEEA) attached to the N-terminal amino acid, unless specified otherwise in the below table. All tested CGRP peptide analogues have a C-terminal amidation (-NH_2), unless specified otherwise in the below table.

Results obtained by the method described above are reproduced in the table below:

++++: EC_{50} 6 nM or less

+++: EC_{50} >6 to 16 nM

++: EC_{50} >16 to 200 nM

+: EC_{50} >200 nM

-: EC_{50} >1000 nM

SEQ ID NO	EC50	CGRP Analogue
2	++++	**S**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
3	++++	AC**D**TATCVTHRLAGLLSRSGG**V**VK**N**NFVPTNVGSKAF
4	++++	AC**N**TATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF
5	++++	**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF
6	++++	**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGSKAF
7	++++	**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF
8	++++	**S**C**N**TATCVTHRLA**D**LLSRSGG**V**L**K**D**N**FVPT**D**VGS**E**AF
9	+++	**H**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
10	+++	SCNTATCVT**Q**RLAGLLSRSGGMVKSNFVPTNVGSKAF
11	+++	SCNTATCVT**T**RLAGLLSRSGGMVKSNFVPTNVGSKAF
12	++++	SCNTATCVTHRLAGLLSRSGGM**H**KSNFVPTNVGSKAF
13	+++	SCNTATCVTHRLAGLLSRSGGMV**H**SNFVPTNVGSKAF
14	+++	SCNTATCVTHRLAGLLSRSGGMVK**N**NFVPTNVGSKAF
15	+++	SCNTATCVTHRLAGLLSRSGGMVK**R**NFVPTNVGSKAF
16	+++	SCNTATCVTHRLAGLLSRSGGMVK**H**NFVPTNVGSKAF
17	+++	SCNTATCVTHRLAGLLSRSGGMVKSNF**H**PTNVGSKAF
18	+++	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**H**AF
19	++++	**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
20	++++	SC**H**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
21	++++	SCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
22	++++	SCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF
23	++++	SCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF
24	++++	SCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF
25	++++	SCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF
26	++++	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF
27	++++	SCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF
28	++	SCNTATCVTHRLAGLLSRSGGMVKS**H**FVPTNVGSKAF
29	+++	SCNTATCVTHRLAGLLSRSGGMVKSN**H**VPTNVGSKAF
30	++	SCNTATCVTHRLAGLLSRSGGMVKSNFV**H**TNVGSKAF
31	++	SCNTATCVTHRLAGLLSRSGGMVKSNFVPT**H**VGSKAF
32	++++	SC**R**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
33	++++	SC**G**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF

34	++++	SC**K**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
35	++++	SC**M**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
36	++++	SCN**I**ATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
37	++++	SCNTATCVT**A**RLAGLLSRSGGMVKSNFVPTNVGSKAF
38	++++	SCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF
39	++++	SCNTATCVT**G**RLAGLLSRSGGMVKSNFVPTNVGSKAF
40	++++	SCNTATCVT**S**RLAGLLSRSGGMVKSNFVPTNVGSKAF
41	++++	SCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF
42	++++	**G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
43	++++	SC**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
44	++++	SC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
45	++++	**G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
46	++++	SC**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
47	++++	SCNTATCVTHRLAGLLSRSGG**V**VKSNFVPTNVGSKAF
48	++++	SCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGSKAF
49	++++	SCNTATCVTHRLAGLLSRSGGMVK**D**NFVPTNVGSKAF
50	++++	SCNTATCVTHRLAGLLSRSGGMVKSNFVPT**D**VGSKAF
51	++++	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**E**AF
52	++++	SCNTATCVTHRLA**D**LLSRSGGMVKSNFVPTNVGSKAF
53	++++	SCNTATCVTHRLAGLLSRSGGM**S**KSNFVPTNVGSKAF
54	++++	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**S**AF
55	++++	SC**H**TATCVT**D**RLAGLLSR**H**GGMVKSNFVPTNVGSKAF
56	++++	SCN**I**ATCVTHRLAGLLSR**H**GGMVKSNF**H**PTNVGSKAF
57	++++	SCN**I**ATCVT**D**RLAGLLSRSGGMVK**K**NFVPTNVGSKAF
58	++++	SCN**I**ATCVTHRLAGLLSRSGG**I**VKSNF**H**PTNVGSKAF
59	++++	SCNTATCVT**D**RLAGLL**A**RSGGMVKSNFVPTNVGSKAF
60	++++	SCNTATCVT**Q**RLAGLLSRSGGMVKSNFVPTNVGSKAF
61	++++	SCNTATCVTHRLA**H**LLSRSGG**I**VK**R**NFVPTNVGSKAF
62	++++	SCNTATCVTHRLA**H**LL**A**R**H**GGMVKSNFVPTNVGSKAF
63	++++	**G**CNTATCVTHRLA**H**LLSRSGGMVK**H**NFVPTNVGSKAF
64	++++	**G**C**H**TATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF
65	++++	SCNTATCVTHRLAGLLSRSGG**L**VKSNF**H**PTNVG**P**KAF
66	++++	SCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVG**P**KAF
67	++++	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF
68	++++	**G**C**H**TATCVT**N**RLA**H**LL**A**R**H**GG**I**VK**K**NFVPTNVG**P**KAF
69	NA	**G**C**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
70	NA	**G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
71	NA	**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF
72	NA	**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF
73	NA	**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF
74	NA	**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF
75	NA	**G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF
76	NA	**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF

77	NA	**G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF
78	NA	**G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF
79	NA	**G**C**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
80	NA	**G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF
81	++++	**G**CNTATCVTHRLA**D**LLSR**H**GGMVKSNFVPTNVGSKAF
82	++++	**G**CNTATCVTHRLA**E**LLSR**H**GGMVKSNFVPTNVGSKAF
83	++++	**G**CNTATCVTHRLAGLLSRSGGMVK**E**NFVPTNVGSKAF
84	++++	**G**C**H**TATCVTHRLA**D**LLSR**H**GGMVKSNFVPTNVGSKAF
85	++++	**G**C**H**TATCVTHRLA**E**LLSR**H**GGMVKSNFVPTNVGSKAF
86	++++	**G**C**H**TATCVTHRLAGLLSRSGGMVK**E**NFVPTNVGSKAF
87	++++	**G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGSKAF
88	++++	**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**R**AF
89	++++	**G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF
90	++++	**SGS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
91	++++	**RSF-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
92	++++	**RV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
93	++++	**SGSGSGSGS–** **G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
94	++++	**PAS**-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
95	+++	**ES**-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
96	++++	**KKKKKK**- SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
97	+++	**AAAAAA**- SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
98	++++	**PAS-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
99	++++	**SGSG**- **G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
100	++++	**RSFG**- **G**C**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
101	++++	**RVG-G**C**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
102	++++	**PAS**-SC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
103	++++	**SGSG**- SC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
104	++++	**LRV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
105	++++	**RSF-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
106	++++	**SGS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
107	++++	**SGSG**- **G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
108	+++	**LLRV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
109	++++	**SGS-G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
110	++++	**RSF-G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
111	++++	**RV-G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
112	++++	**PAS-G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
113	++++	**LRV-G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
114	++++	**SGS-G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF

115	++++	**RSF**-**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF
116	++++	**RV**-**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF
117	++++	**PAS**-**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF
118	++++	**LRV**-**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF
119	++++	**SGS**-**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF
120	++++	**RSF**-**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF
121	++++	**RV**-**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF
122	++++	**PAS**-**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF
123	+++	**LRV**-**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF
124	++++	**SGS**-**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF
125	++++	**RSF**-**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF
126	++++	**RV**-**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF
127	++++	**PAS**-**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF
128	++++	**LRV**-**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF
129	++++	**SGS**-**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF
130	++++	**RSF**-**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF
131	++++	**RV**-**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF
132	++++	**PAS**-**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF
133	++++	**LRV**-**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF
134	++++	**SGS**-**G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF
135	++++	**RSF**-**G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF
136	++++	**RV**-**G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF
137	++++	**PAS**-**G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF
138	++++	**LRV**-**G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF
139	++++	**SGS**-**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF
140	++++	**RSF**-**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF
141	++++	**RV**-**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF
142	++++	**PAS**-**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF
143	++++	**LRV**-**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF
144	++++	**SGS**-**G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF
145	++++	**RSF**-**G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF
146	++++	**RV**-**G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF
147	++++	**PAS**-**G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF
148	++++	**LRV**-**G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF
149	++++	**SGS**-**G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF
150	++++	**RSF**-**G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF
151	++++	**RV**-**G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF
152	++++	**PAS**-**G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF
153	++++	**LRV**-**G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF
154	+++	**SGS**-**G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
155	++++	**RSF**-**G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
156	+++	**RV**-**G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
157	+++	**PAS**-**G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF

158	++++	**LRV-G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
159	++++	**SGS-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
160	++++	**RSF-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
161	++++	**RV-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
162	++++	**PAS-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
163	++++	**LRV-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
164	++++	**SGS-G**C**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
165	++++	**RSF-G**C**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
166	++++	**RV-G**C**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
167	++++	**PAS-G**C**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
168	++++	**LRV-G**C**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF
169	+++	**SGS-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF
170	+++	**RSF-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF
171	+++	**RV-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF
172	+++	**PAS-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF
173	+++	**LRV-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF
174	++++	**RVG-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF
175	++++	**KVG-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF
176	++++	**GKVG-** **G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF; Unspecified lipidation
177	++++	**K-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF
178	++++	**KSF-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF
179	++++	**KSF-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF
180	++++	**GKSF-** **G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF
181	++++	HOOC(CH2)16CO-isoGlu-AEEA- **S**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
182	++++	HOOC(CH2)16CO-isoGlu- **S**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
183	++++	CH3(CH2)16CO-gammaGlu- **S**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
184	++++	HOOC(CH2)16CO-isoGlu-2AEEA- **G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
185	+++	HOOC(CH2)14CO-isoGlu-AEEA- **G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
186	+++	HOOC(CH2)14CO-isoGlu-2AEEA- **G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
187	++++	HOOC(CH2)18CO-isoGlu-AEEA- **G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
188	+++	HOOC(CH2)18CO-isoGlu-2AEEA- **G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF
189	++++	**LRV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF; no lipidation

190	++++	**RSF-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF; no lipidation
191	++++	**SGS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF; no lipidation
192	++++	**SGSG-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF; no lipidation
193	++++	**LLRV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF; no lipidation
194	++	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKA**H**
195	-	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF-**P;** no amidation
196	+	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF-**G**; no amidation
197	-	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF-**GGSGPGA**; no amidation
198	-	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF; no amidation
199	-	VTHRLAGLLSRSGGMVKSNFVPTNVGSKAF-HOOC(CH2)16CO-isoGlu-AEEA (C-terminal lipidation)
200	-	VTHRLAGLLSRSGGMVKSNFVPTNVGSKAF; no lipidation
201	-	HOOC(CH2)16CO-isoGlu-AEEA-VTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
202	+	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF-**P**; no amidation
203	+	SCN**D**ATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
204	+	SCNTA**H**CVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
205	+	SCNTATCV**D**HRLAGLLSRSGGMVKSNFVPTNVGSKAF
206	-	SCNTATCVTHRLAGL**H**SRSGGMVKSNFVPTNVGSKAF
207	+	SCNTATCVTHRLAGLLSRSGG**H**VKSNFVPTNVGSKAF
208	+	SCNTATCVTHRLAGLLSRSGGMVKSNFVP**H**NVGSKAF
209	+	SCNTATCVTHRLAGLLSRSGGMVKSNFVPTN**H**GSKAF
210	+	SCN**E**ATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
211	+	SCNT**E**TCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
212	-	SCNT**R**TCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
213	-	SCNTA**E**CVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
214	+	SCNTA**R**CVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
215	+	SCNTATCVT**R**RLAGLLSRSGGMVKSNFVPTNVGSKAF
216	+	SCNTATCVT**K**RLAGLLSRSGGMVKSNFVPTNVGSKAF
217	++	**S**CNTATCVTHRLAGLL**R**RSGGMVKSNFVPTNVGSKAF
218	+	SCNTATCVTHRLA**I**LLSRSGGMVKSNFVPTNVGSKAF
219	+	SCNTATCVTHRLAGLL**D**RSGGMVKSNFVPTNVGSKAF
220	++	SCNTATCVTHRLAGLL**I**RSGGMVKSNFVPTNVGSKAF
221	+	SCNTATCVTHRLAGLLSRSGG**D**VKSNFVPTNVGSKAF
222	+	SCNTATCVTHRLAGLLSRSGG**Q**VKSNFVPTNVGSKAF

223	+	SCNTATCVTHRLAGLL**R**RSGGMVK**D**NFVPT**K**VGSKAF
224	-	SCNT**D**TCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
225	+	SCNTA**D**CVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF
226	-	SCNTATC**D**THRLAGLLSRSGGMVKSNFVPTNVGSKAF
227	+	**A**C**D**TATCVTHRLAGLLSRSGG**V**VK**N**NFVPTNVGSKAF
228	+	**A**C**N**TATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF
229	+	**G**CNTATCVTHRLA**D**LLSR**D**GGMVKSNFVPTNVGSKAF
230	+	**G**CNTATCVTHRLA**E**LLSR**E**GGMVKSNFVPTNVGSKAF
231	+	**G**C**H**TATCVTHRLA**D**LLSR**D**GGMVKSNFVPTNVGSKAF
232	+	**G**C**H**TATCVTHRLA**E**LLSR**E**GGMVKSNFVPTNVGSKAF

Claims

1. A peptide analogue of a calcitonin gene-related peptide (CGRP) having the sequence ($CGRP_{1-37}$):
$X_1CX_3TATCVTHRLAX_{14}LLX_{17}RSGGX_{22}X_{23}KX_{25}NFVPTX_{31}VGSX_{35}AF$
(SEQ ID NO:1),

wherein X_1 is Ala or Ser, X_3 is Asp or Asn, X_{14} is Asp or Gly, X_{17} is Arg or Ser, X_{22} is Val or Met, X_{23} is Val or Leu, X_{25} is Asp, Asn or Ser, X_{31} is Asp or Asn, X_{35} is Glu or Lys, and the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of SEQ ID NO:1 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from:
X_1 is Gly or His,
X_3 is His, Arg, Gly, Met or Lys,
X_4 is Ile
X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr,
X_{14} is His, Glu or Asp,
X_{17} is Ala,
X_{19} is His,
X_{22} is Ile, Leu or Val,
X_{23} is Ser or His,
X_{24} is Arg or His,
X_{25} is Lys, Asn, Asp, Glu, Arg or His,
X_{26} is His,
X_{27} is His,
X_{28} is His,
X_{29} is His,
X_{31} is Asp or His,
X_{34} is Pro, and
X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide

consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

2. The peptide analogue according to claim 1, wherein said peptide analogue is an analogue of a CGRP having the sequence ($CGRP_{1-37}$) selected from:
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:2),
AC**D**TATCVTHRLAGLLSRSGG**V**VK**N**NFVPTNVGSKAF (SEQ ID NO:3);
ACNTATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF (SEQ ID NO:4);
SCNTATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (SEQ ID NO:5);
SCNTATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGSKAF (SEQ ID NO:6),
SCNTATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (SEQ ID NO:7); and
SCNTATCVTHRLA**D**LLSRSGG**VL**K**D**NFVPT**D**VGS**E**AF (SEQ ID NO:8),
wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:2 to SEQ ID NO:8 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

3. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue is an analogue of a beta-CGRP having the sequence ($CGRP_{1-37}$) selected from:

SCNTATCVTHRLAGLLSRSGGMVK**S**NFVPTNVGSKAF (SEQ ID NO:2),
ACNTATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF (SEQ ID NO:4),
SCNTATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGSKAF (SEQ ID NO:6), and
SCNTATCVTHRLA**D**LLSRSGG**VL**K**D**NFVPT**D**VGS**E**AF (SEQ ID NO:8),
wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6 and SEQ ID NO:8 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

4. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue is an analogue of
SCNTATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF (SEQ ID NO:2),
wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of SEQ ID NO:2 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said peptide analogue comprises at least one amino acid substitution selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

5. The peptide analogue according to any one of the preceding claims having a peptide sequence selected from:

HCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:9);
SCNTATCVT**Q**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:10);
SCNTATCVT**T**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:11);
SCNTATCVTHRLAGLLSRSGGM**H**KSNFVPTNVGSKAF (SEQ ID NO:12);
SCNTATCVTHRLAGLLSRSGGMV**H**SNFVPTNVGSKAF (SEQ ID NO:13);
SCNTATCVTHRLAGLLSRSGGMVK**N**NFVPTNVGSKAF (SEQ ID NO:14);
SCNTATCVTHRLAGLLSRSGGMVK**R**NFVPTNVGSKAF (SEQ ID NO:15);
SCNTATCVTHRLAGLLSRSGGMVK**H**NFVPTNVGSKAF (SEQ ID NO:16);
SCNTATCVTHRLAGLLSRSGGMVKSNF**H**PTNVGSKAF (SEQ ID NO:17);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**H**AF (SEQ ID NO:18),
GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:19);
SC**H**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:20);
SCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:21);
SCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:22);
SCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:23);
SCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:24);
SCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:25);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:26);
SCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:27);
SCNTATCVTHRLAGLLSRSGGMVKS**H**FVPTNVGSKAF (SEQ ID NO:28);
SCNTATCVTHRLAGLLSRSGGMVKSN**H**VPTNVGSKAF (SEQ ID NO:29);
SCNTATCVTHRLAGLLSRSGGMVKSNFV**H**TNVGSKAF (SEQ ID NO:30);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPT**H**VGSKAF (SEQ ID NO:31);
SC**R**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:32);
SC**G**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:33);
SC**K**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:34);

SC**M**TATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:35);
SCN**I**ATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:36);
SCNTATCVT**A**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:37);
SCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:38);
SCNTATCVT**G**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:39);
SCNTATCVT**S**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:40);
SCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:41);
GC**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:42);
SC**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:43);
SC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:44);
GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:45);
SC**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:46);
SCNTATCVTHRLAGLLSRSGG**V**VKSNFVPTNVGSKAF (SEQ ID NO:47);
SCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGSKAF (SEQ ID NO:48);
SCNTATCVTHRLAGLLSRSGGMVK**D**NFVPTNVGSKAF (SEQ ID NO:49);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPT**D**VGSKAF (SEQ ID NO:50);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**E**AF (SEQ ID NO:51);
SCNTATCVTHRLA**D**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:52);
SCNTATCVTHRLAGLLSRSGGM**S**KSNFVPTNVGSKAF (SEQ ID NO:53);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**S**AF (SEQ ID NO:54);
SC**H**TATCVT**D**RLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:55);
SCN**I**ATCVTHRLAGLLSR**H**GGMVKSNF**H**PTNVGSKAF (SEQ ID NO:56);
SCN**I**ATCVT**D**RLAGLLSRSGGMVK**K**NFVPTNVGSKAF (SEQ ID NO:57);
SCN**I**ATCVTHRLAGLLSRSGG**I**VKSNF**H**PTNVGSKAF (SEQ ID NO:58);
SCNTATCVT**D**RLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:59);
SCNTATCVT**Q**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:60);
SCNTATCVTHRLA**H**LLSRSGG**I**VK**R**NFVPTNVGSKAF (SEQ ID NO:61);
SCNTATCVTHRLA**H**LL**A**R**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:62);
GCNTATCVTHRLA**H**LLSRSGGMVK**H**NFVPTNVGSKAF (SEQ ID NO:63);
GC**H**TATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:64);
SCNTATCVTHRLAGLLSRSGG**L**VKSNF**H**PTNVG**P**KAF (SEQ ID NO:65);
SCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVG**P**KAF (SEQ ID NO:66);
SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:67);
GC**H**TATCVT**N**RLA**H**LL**A**R**H**GG**I**VK**K**NFVPTNVG**P**KAF (SEQ ID NO:68);
GC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:69);

GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:70);
GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:71);
GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:72);
GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:73);
GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:74);
GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:75);
GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:76);
GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:77);
GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:78);
GC**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:79);
GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:80);
GCNTATCVTHRLA**D**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:81);
GCNTATCVTHRLA**E**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:82);
GCNTATCVTHRLAGLLSRSGGMVK**E**NFVPTNVGSKAF (SEQ ID NO:83);
GC**H**TATCVTHRLA**D**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:84);
GC**H**TATCVTHRLA**E**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:85);
GC**H**TATCVTHRLAGLLSRSGGMVK**E**NFVPTNVGSKAF (SEQ ID NO:86);
GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGSKAF (SEQ ID NO:87);
GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**R**AF (SEQ ID NO:88); and
GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:89);

wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:9 to SEQ ID NO:89 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein optionally said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue,

wherein said peptide analogue is an agonist of the GCRP receptor.

6. The peptide analogue according to claim 5, wherein said peptide comprises one or more individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or

Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

7. The peptide analogue according to any one of claims 5 and 6, wherein the peptide analogue of any one of SEQ ID NO:9 to SEQ ID NO:89 does not comprise an amino acid substitution at the one or more amino acid residues indicated in **bold** in the amino acid sequence of any one of SEQ ID NO:9 to SEQ ID NO:89.

8. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises at least one individual amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro.

9. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises 1 amino acid substitution, such as 2 individual amino acid substitutions, such as 3 individual amino acid substitutions, such as 4 individual amino acid substitutions, such as 5 individual amino acid substitutions, such as 6 individual amino acid substitutions, such as 7 individual amino acid substitutions, such as 8 individual amino acid substitutions, such as 9 individual amino acid substitutions, wherein each amino acid substitution is individually selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

10. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises at least two individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn,

Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

11. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises two or more individual amino acid substitutions selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro.

12. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises at least three individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

13. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises three or more individual amino acid substitutions selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly, X_3 is His and X_{34} is Pro.

14. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises at least one individual amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly and X_3 is His; or selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_1 is Gly and X_{34} is Pro; or selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His, X_3 is His and X_{34} is Pro.

15. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises at least one individual amino acid substitution selected from X_{10} is Asp or Glu, X_{19} is His, X_{14} is His and X_1 is Gly.

16. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises at least one amino acid substitution selected from X_{10} is Asp, X_{10} is Glu, X_{19} is His, X_{14} is His, X_{25} is His, X_{25} is Arg, X_{28} is His, X_{35} is Ser, X_1 is His, and X_{23} is His.

17. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises at least one amino acid substitution to a His amino acid selected from: X_{19} is His, X_{14} is His, X_3 is His, X_{25} is His, X_{28} is His, X_1 is His, X_{23} is His, X_{24} is His, X_{35} is His, X_{26} is His, X_{27} is His, X_{29} is His, and X_{31} is His.

18. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises at least one amino acid substitution to a His amino acid selected from: X_{19} is His, X_{14} is His, X_{25} is His, X_{28} is His, X_1 is His, and X_{23} is His.

19. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises at least one amino acid substitution to a His amino acid selected from X_{19} is His, X_{14} is His and X_3 is His.

20. The peptide analogue according to any one of the preceding claims, wherein X_{19} is His.

21. The peptide analogue according to any one of the preceding claims, wherein X_{19} is His and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

22. The peptide analogue according to any one of the preceding claims, wherein X_{14} is His, Glu or Asp.

23. The peptide analogue according to any one of the preceding claims, wherein X_{14} is His.

24. The peptide analogue according to any one of the preceding claims, wherein X_{14} is His and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

25. The peptide analogue according to any one of the preceding claims, wherein X_{19} is His and X_{14} is His.

26. The peptide analogue according to any one of the preceding claims, wherein X_{19} is His and X_3 is His.

27. The peptide analogue according to any one of the preceding claims, wherein X_{14} is His and X_3 is His.

28. The peptide analogue according to any one of the preceding claims, wherein X_{19} is His, X_{14} is His and X_3 is His.

29. The peptide analogue according to any one of the preceding claims, wherein X_3 is His.

30. The peptide analogue according to any one of the preceding claims, wherein X_3 is His and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,
such as wherein X_3 is His and X_{10} is Asp or Glu;
such as wherein X_3 is His, X_{10} is Asp or Glu and X_{19} is His.

31. The peptide analogue according to any one of the preceding claims, wherein X_1 is Gly.

32. The peptide analogue according to any one of the preceding claims, wherein X_1 is Gly and one or more of X_{19} is His, X_{14} is His and X_3 is His;
such as wherein X_1 is Gly and X_{19} is His;
such as wherein X_1 is Gly and X_{14} is His;
such as wherein X_1 is Gly, X_{19} is His and X_{14} is His;
such as wherein X_1 is Gly and X_3 is His;
such as wherein X_1 is Gly, X_{19} is His and X_3 is His;
such as wherein X_1 is Gly, X_{14} is His and X_3 is His;
such as wherein X_1 is Gly, X_{19} is His, X_{14} is His and X_3 is His.

33. The peptide analogue according to any one of the preceding claims, wherein X_1 is Gly and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;
such as wherein X_1 is Gly and one or more of X_3 is His, X_{10} is Asp or Glu, X_{19} is His and X_{14} is His;
such as wherein X_1 is Gly and X_{10} is Asp,
such as wherein X_1 is Gly and X_{10} is Glu,
such as wherein X_1 is Gly, X_{10} is Asp or Glu, and X_{19} is His,
such as wherein X_1 is Gly, X_{10} is Asp or Glu, and X_{14} is His,
such as wherein X_1 is Gly, X_{10} is Asp or Glu, X_{19} is His and X_{14} is His.

34. The peptide analogue according to any one of the preceding claims, wherein X_{10} is a negative amino acid selected from Asp or Glu.

35. The peptide analogue according to any one of the preceding claims, wherein X_{10} is a negative amino acid selected from Asp or Glu, and X_1 is Gly.

36. The peptide analogue according to any one of the preceding claims, wherein X_{10} is Asp.

37. The peptide analogue according to any one of the preceding claims, wherein X_{10} is Glu.

38. The peptide analogue according to any one of the preceding claims, wherein X_{10} is Asp and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;
such as wherein X_{10} is Asp and one or more of X_{19} is His, X_3 is His and X_{14} is His;
such as wherein X_{10} is Asp and X_{19} is His;
such as wherein X_{10} is Asp and X_3 is His;
such as wherein X_{10} is Asp and X_{14} is His;
such as wherein X_{10} is Asp, X_{19} is His and X_3 is His;
such as wherein X_{10} is Asp and X_1 is Gly.

39. The peptide analogue according to any one of the preceding claims, wherein X_{10} is Glu and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;
such as wherein X_{10} is Asp and one or more of X_{19} is His, X_3 is His and X_{14} is His;
such as wherein X_{10} is Glu and X_{19} is His;
such as wherein X_{10} is Glu and X_3 is His;
such as wherein X_{10} is Glu and X_{14} is His;
such as wherein X_{10} is Glu, X_{19} is His and X_3 is His;
such as wherein X_{10} is Glu and X_1 is Gly.

40. The peptide analogue according to any one of the preceding claims, wherein X_{34} is Pro and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; and X_{35} is His, Glu, Arg or Ser;
such as wherein X_{34} is Pro; and one or more of X_{14} is His, X_{19} is His, X_1 is Gly, X_3 is His, and X_{10} is Asp or Glu;
such as wherein X_{34} is Pro and X_1 is Gly;
such as wherein X_{34} is Pro and X_{14} is His;
such as wherein X_{34} is Pro and X_{19} is His;
such as wherein X_{34} is Pro and X_3 is His;
such as wherein X_{34} is Pro, X_{14} is His and X_{19} is His;
such as wherein X_{34} is Pro; and X_{10} is Asp or Glu;
such as wherein X_{34} is Pro; X_1 is Gly, X_3 is His and X_{10} is Asp or Glu.

41. The peptide analogue according to any one of the preceding claims, wherein X_{14} is Glu or Asp, such as wherein X_{14} is Glu, and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;
such as wherein X_{14} is Glu or Asp; and one or more of X_{19} is His, X_1 is Gly and X_3 is His;
such as wherein X_{14} is Glu or Asp, and X_{19} is His;
such as wherein X_{14} is Glu or Asp, and X_1 is Gly;
such as wherein X_{14} is Glu or Asp, and X_3 is His.

42. The peptide analogue according to any one of the preceding claims, wherein X_{10} is Asn and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;
such as wherein X_{10} is Asn and one or more of X_3 is His, X_{14} is His, X_{19} is His and X_1 is Gly;
such as wherein X_{10} is Asn, X_3 is His, X_{14} is His and X_{19} is His;
such as wherein X_{10} is Asn, X_3 is His, and X_1 is Gly;
such as wherein X_{10} is Asn and X_1 is Gly.

43. The peptide analogue according to any one of the preceding claims, wherein X_{17} is Ala and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;
such as wherein X_{17} is Ala and one or more of X_1 is Gly, X_3 is His, X_{10} is Asp or Asn, X_{19} is His, X_{14} is His, and X_{34} is Pro;
such as wherein X_{17} is Ala and X_{10} is Asp;
such as wherein X_{17} is Ala and X_{10} is Asn;
such as wherein X_{17} is Ala; and X_{19} is His and/or X_{14} is His;
such as wherein X_{17} is Ala and X_1 is Gly.

44. The peptide analogue according to any one of the preceding claims, wherein X_{22} is Ile or Leu and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is

His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;

such as wherein X_{22} is Ile and one or more of X_1 is Gly, X_{19} is His, X_{14} is His, X_3 is His, X_{10} is Asn, X_{24} is Arg, X_{28} is His, X_{17} is Ala, and X_{34} is Pro;

such as wherein X_{22} is Leu and one or more of X_1 is Gly, X_{28} is His and X_{34} is Pro.

45. The peptide analogue according to any one of the preceding claims, wherein X_{24} is His and said peptide analogue further comprises one or more amino acid substitutions selected from:

X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

46. The peptide analogue according to any one of the preceding claims, wherein X_4 is Ile and said peptide analogue further comprises one or more amino acid substitutions selected from:

X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser;

such as wherein X_4 is Ile and one or more of X_{10} is Asp, X_{19} is His, X_{28} is His and X_{22} is Ile.

47. The peptide analogue according to any one of the preceding claims, wherein X_{24} is Arg and X_{35} is Arg.

48. The peptide analogue according to any one of the preceding claims, wherein X_{25} is Asp or Glu, such as wherein X_{25} is Glu, and said peptide analogue further comprises one or more amino acid substitutions selected from:

X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile,

Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser; such as wherein X_{25} is Glu and one or more of X_3 is His and X_1 is Gly.

49. The peptide analogue according to any one of the preceding claims, wherein when X_{24} is Arg then X_{25} is not Lys.

50. The peptide analogue according to any one of the preceding claims, wherein X_{31} is Asp and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{28} is His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser.

51. The peptide analogue according to any one of the preceding claims, wherein X_{35} is His or Arg and said peptide analogue further comprises one or more amino acid substitutions selected from:
X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{28} is His; X_{31} is Asp; and X_{34} is Pro.

52. The peptide analogue according to any one of the preceding claims, wherein the amino acids at position X_5 and position X_6 are not substituted; such as wherein X_5 is Ala and X_6 is Thr.

53. The peptide analogue according to any one of the preceding claims, wherein the amino acids of any one of positions X_4, X_5 and X_6 are not substituted; such as wherein X_4 is Thr, X_5 is Ala and X_6 is Thr.

54. The peptide analogue according to any one of the preceding claims, wherein the amino acids of any one of positions X_4, X_5, X_6 and X_8 are not substituted; such as wherein X_4 is Thr, X_5 is Ala, X_6 is Thr and X_8 is Val.

55. The peptide analogue according to any one of the preceding claims, wherein one or more of X_4 is Thr, X_5 is Ala, X_6 is Thr, X_8 is Val, X_9 is Thr, X_{16} is Leu, X_{17} is Ser, X_{22} is Met, X_{30} is Thr, and X_{32} is Val.

56. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue does *not* comprise an amino acid substitution selected from X_4 is Asp, X_5 is Asp, X_6 is Asp, X_8 is Asp, X_9 is Asp, X_{17} is Asp and X_{22} is Asp.

57. The peptide analogue according to any one of the preceding claims, wherein X_4 is *not* Asp or Glu; X_5 is *not* Asp, Glu or Arg; and X_6 is *not* Asp, Glu, Arg or His.

58. The peptide analogue according to any one of the preceding claims, wherein X_{17} is Ser; such as wherein X_{17} is *not* Asp, Arg or Ile.

59. The peptide analogue according to any one of the preceding claims, wherein X_{22} is Met; such as wherein X_{22} is *not* Asp, Gln or His.

60. The peptide analogue according to any one of the preceding claims, wherein X_{16} is Leu, X_{30} is Thr and X_{32} is Val; such as wherein none of X_{16}, X_{30} and X_{32} is His.

61. The peptide analogue according to any one of the preceding claims, wherein X_{10} is *not* Arg or Lys.

62. The peptide analogue according to any one of the preceding claims, wherein X_{14} is *not* Ile.

63. The peptide analogue according to any one of the preceding claims, wherein X_{19} is *not* Asp or Glu.

64. The peptide analogue according to any one of the preceding claims, comprising at least one amino acid substitution selected from: X_1 is His, X_{10} is Thr, X_{14} is His, X_{19} is His, X_{23} is His, X_{25} is Arg or His, and X_{28} is His.

65. The peptide analogue according to any one of the preceding claims, wherein the functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89 comprises 1 to 6 individual amino acid substitutions, such as 1 to 5, such as 1 to 4, such as 1 to 3, such as 1 to 2 individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

66. The peptide analogue according to any one of the preceding claims, wherein the functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89 comprises 6, such as 5, such as 4, such as 3, such as 2, such as 1 individual amino acid substitution(s) at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

67. The peptide analogue according to any one of the preceding claims, wherein the functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89 comprises 1 to 6, such as 1 to 5, such as 1 to 4, such as 1 to 3, such as 1 to 2 individual amino acid substitutions,
such as comprises 1, 2, 3, 4, 5 or 6 individual amino acid substitutions,
at any one of positions X_4, X_5, X_6, X_8, X_9, X_{11}, X_{12}, X_{13}, X_{15}, X_{16}, X_{18}, X_{20}, X_{21}, X_{26}, X_{27}, X_{29} to X_{33}, X_{36} and X_{37};
such as at any one of positions X_5, X_6, X_8, X_9, X_{11}, X_{12}, X_{13}, X_{15}, X_{16}, X_{18}, X_{20}, X_{21}, X_{30}, X_{32}, X_{33}, X_{36} and X_{37};
such as at any one of positions X_8, X_9, X_{11}, X_{12}, X_{13}, X_{15}, X_{16}, X_{18}, X_{20}, X_{21}, X_{30}, X_{32}, X_{33}, X_{36} and X_{37};
such as at any one of positions X_{11}, X_{12}, X_{13}, X_{15}, X_{18}, X_{20}, X_{21}, X_{33}, X_{36} and X_{37};
such as at any one of positions X_{11}, X_{12}, X_{13}, X_{15}, X_{18}, X_{20}, X_{21} and X_{33}.

68. The peptide analogue according to any one of the preceding claims, wherein the functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89 comprises 1 to 4, such as 1 to 3, such as 1 to 2, such as 1, individual amino acid substitution(s) at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

69. The peptide analogue according to any one of the preceding claims, wherein the functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89 comprises 1 to 5, such as one, two, three, four, five or six individual conservative amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37}.

70. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue is an agonist of the human GCRP receptor.

71. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue is an agonist of the GCRP receptor at systemic pH or physiological pH.

72. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue is an agonist of the GCRP receptor with an EC_{50} (nM) value of 16 nM or less, such as of less than 16 nM, such as with an EC_{50} (nM) value of 0.01 to 16 nM, such as of 0.1 to 16 nM, such as of 1 to 16 nM, such as of >6 nM to 16 nM.

73. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue is an agonist of the GCRP receptor with an EC_{50} value of 6 nM or less, such as of 5 nM or less, such as of 4 nM or less, such as of 3 nM or less, such as of 2 nM or less, such as of 1 nM or less, such as of 0.5 nM or less, such as of 0.1 nM or less;
such as an EC_{50} value of 0.01 to 6 nM, such as of 0.1 to 6 nM, such as of 1 to 6 nM;
such as an EC_{50} value 0.01 to 1.0, such as 0.1 to 1.0 nM.

74. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue is an agonist of the GCRP receptor with an EC_{50} value which is at least 0.5 of the EC50 value of a polypeptide consisting of the amino acid sequence SEQ ID NO:2 having attached to the N-terminal amino acid $HOOC(CH_2)16CO$-isoGlu-AEEA;
such as an EC_{50} which is at least 0.75, such as at least 1, such as at least 1.5, such as at least 2, such as at least 2.5, such as at least 3, such as at least 3.5, such as at least 4, such as at least 5 of the EC50 value of $HOOC(CH_2)16CO$-isoGlu-AEEA-SEQ ID NO:2;
such as an EC_{50} value which is 0.5 to 10, such as which is 0.5 to 5, such as which is 0.5 to 4, such as which is 0.5 to 3, such as which is 0.5 to 2, such as which is 0.5 to 1.5, such as which is 1.0 to 10, such as which is 1.0 to 5 of the EC50 value of $HOOC(CH_2)16CO$-isoGlu-AEEA-SEQ ID NO:2.

75. The peptide analogue according to any one of the preceding claims comprising an intramolecular disulfide bridge (-S-S-), between the Cys amino acid residue at position 2 (X_2) and the Cys amino acid residue at position 7 (X_7).

76. The peptide analogue according to any one of the preceding claims comprising a disulfide bridge with a linker, such as a methylene linker, between the Cys amino acid residue at position 2 (X_2) and the Cys amino acid residue at position 7 (X_7), such as -S-[CH_2]-S-.

77. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises an N-terminal region selected from an N-terminal single amino acid and an N-terminal peptide consisting of 2 to 30 consecutive amino acids, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue.

78. The peptide analogue according to any one of the preceding claims, wherein said N-terminal region consist of naturally occurring amino acid residues individually selected from Y, G, F, M, A, S, I, L, T, V, P, K, H, Q, E, W, R, D, N and C.

79. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises an N-terminal single amino acid; an N-terminal dipeptide; or an N-terminal tripeptide, attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said peptide analogue.

80. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises an N-terminal peptide consisting of 4 to 30 consecutive amino acid residues individually selected from Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, and Met; such as individually selected from amino acid residues Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Orn, and Met; such as Glu, Lys, and Met.

81. The peptide analogue according to any one of the preceding claims, wherein said peptide analogue comprises an N-terminal single amino acid which is Lys; or an N-terminal single amino acid which is an aromatic amino acid selected from Trp, Tyr, Phe and 3-(l-naphthyl)alanine.

82. The peptide analogue according to any one of the preceding claims, comprising an N-terminal region which is attached via a peptide bond to the amino group of the amino acid residue at position 1 (X_1) of said CGRP peptide, wherein said N-terminal region is:
an N-terminal single amino acid which is not an aromatic amino acid and is not a Lys (K),
an N-terminal dipeptide or an N-terminal tripeptide, or
an N-terminal peptide consisting of 2 to 30 consecutive amino acid residues and comprising one or more amino acids selected from: Gly (G), Pro (P), Phe (F) and Val (V).

83. The peptide analogue according to any one of the preceding claims , wherein said N-terminal peptide consists of 2 to 3 consecutive amino acid residues, such as 3 to 4, such as 4 to 5, such as 5 to 6, such as 6 to 7, such as 7 to 8, such as 8 to 9, such as 9 to 10, such as 10 to 11, such as 11 to 12, such as 12 to 13, such as 13 to 14, such as 14 to 15, such as 15 to 16, such as 16 to 17, such as 17 to 18, such as 18 to 19, such as 19 to 20, such as 20 to 21, such as 21 to 22, such as 22 to 23, such as 23 to 24, such as 24 to 25, such as 25 to 26, such as 26 to 27, such as 27 to 28, such as 28 to 29, such as 29 to 30 consecutive amino acid residues;
such as wherein said N-terminal peptide consists of 2 to 30 consecutive amino acid residues, such as 2 to 25, such as 2 to 20, such as 2 to 19, such as 2 to 18, such as 2 to 17, such as 2 to 16, such as 2 to 15, such as 2 to 14, such as 2 to 13, such as 2 to 12, such as 2 to 11, such as 2 to 10, such as 2 to 9, such as 2 to 8, such as 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3 consecutive amino acid residues;
such as wherein said N-terminal peptide consists of 2 consecutive amino acid residues, such as 3, such as 4, such as 5, such as 6, such as 7, such as 8, such as 9, such as 10, such as 11, such as 12, such as 13, such as 14, such as 15, such as 16, such as 17, such as 18, such as 19, such as 20, such as 21,

such as 22, such as 23, such as 24, such as 25, such as 26, such as 27, such as 28, such as 29, such as 30 consecutive amino acid residues;
such as wherein said N-terminal peptide consists of 2 to 20 consecutive amino acid residues, such as 2 to 15 consecutive amino acid residues, such as 2 to 10 consecutive amino acid residues, such as 2 to 5 consecutive amino acid residues.

84. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises one or more amino acids selected from: Gly and Pro; such as wherein said N-terminal peptide comprises at least one Gly amino acid; such as wherein said N-terminal peptide comprises at least one Pro amino acid.

85. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises one or more amino acids selected from Phe and Val; such as wherein said N-terminal peptide comprises at least one Phe amino acid; such as wherein said N-terminal peptide comprises at least one Val amino acid.

86. The peptide analogue according to any one of the preceding claims, wherein said N-terminal single amino acid or said N-terminal peptide does not comprise any amino acids with electrically charged side chains selected from Arg, His, Lys, Asp and Glu; such as wherein said N-terminal single amino acid or said N-terminal peptide comprises one amino acids with electrically charged side chains selected from Arg, His, Lys, Asp and Glu.

87. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises at least one His amino acids; such as comprises one His amino acid.

88. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises one or more amino acids individually selected from Ser, Gly, Arg, Phe, Val, Ala, Pro, Glu, Leu and Lys;
such as wherein said N-terminal peptide consist of 2 to 30 amino acids individually selected from Ser, Gly, Arg, Phe, Val, Ala, Pro, Glu, Leu and Lys.

89. The peptide analogue according to any one of the preceding claims, wherein said N-terminal single amino acid is not an aromatic amino acid selected from Trp, Tyr, Phe and 3-(l-naphthyl)alanine; such as wherein said N-terminal single amino acid is an amino acid selected from: Gly, Pro and Val.

90. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises or consists of the sequence:
$X_{-9}X_{-8}X_{-7}X_{-6}X_{-5}X_{-4}X_{-3}X_{-2}X_{-1}$ (SEQ ID NO:233),
wherein X_{-1} is attached via a peptide bond to the amino group of X_1 of said peptide analogue,
wherein:
X_{-9} is selected from: absent, Ser and Gly,
X_{-8} is selected from: absent, Gly and Ser,
X_{-7} is selected from: absent, Ser and Gly,
X_{-6} is selected from: absent, Gly, Ser, Lys, and Ala,
X_{-5} is selected from: absent, Ser, Gly, Lys and Ala,
X_{-4} is selected from: absent, Gly, Ser, Lys, Ala, Arg and Leu,
X_{-3} is selected from: absent, Ser, Gly, Arg, Pro, Lys, Ala and Leu,
X_{-2} is selected from: Gly, Ser, Arg, Ala, Glu, Lys, Phe and Val, and
X_{-1} is selected from: Ser, Gly, Phe, Val, Lys and Ala;
wherein said optionally N-terminal peptide comprises at least one amino acid selected from: Gly, Pro, Phe and Val.

91. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises or consists of the sequence:
$X_{-4}X_{-3}X_{-2}X_{-1}$ (SEQ ID NO:234),
wherein X_{-1} is attached via a peptide bond to the amino group of X_1 of said peptide analogue,
wherein:
X_{-4} is selected from: Gly, Ser, Lys, Ala, Arg and Leu,
X_{-3} is selected from: Ser, Gly, Arg, Pro, Lys, Ala and Leu,
X_{-2} is selected from: Gly, Ser, Arg, Ala, Glu, Lys, Phe and Val, and
X_{-1} is selected from: Ser, Gly, Phe, Val, Lys and Ala;

wherein optionally said N-terminal peptide comprises at least one amino acid selected from: Gly, Pro, Phe and Val.

92. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises or consists of the sequence: $X_{-3}X_{-2}X_{-1}$, wherein X_{-1} is attached via a peptide bond to the amino group of X_1 of said peptide analogue, wherein each of X_{-3}, X_{-2} and X_{-1} is individually selected from Ser, Gly, Arg, Phe, Val, Pro, Glu, Ala, Leu and Lys.

93. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises or consists of the sequence: $X_{-3}X_{-2}X_{-1}$, wherein X_{-1} is attached via a peptide bond to the amino group of X_1 of said peptide analogue, wherein:
X_{-3} is selected from: Ser, Gly, Arg, Pro, Lys, Ala and Leu,
X_{-2} is selected from: Gly, Ser, Arg, Ala, Glu, Lys, Phe and Val, and
X_{-1} is selected from: Ser, Gly, Phe, Val, Lys and Ala.

94. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises or consists of a sequence selected from: SGS, GSG, SG, GS, RSF, RSFG (SEQ ID NO:237), RV, RVG, LRV, LLRV (SEQ ID NO:238), ES, PAS, SGSG (SEQ ID NO:236), SGSGSGSGS (SEQ ID NO:235), KVG, GKVG (SEQ ID NO:239), KSF and GKSF (SEQ ID NO:240).

95. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide consists of a sequence selected from: S-$(GS)_n$, $(GS)_n$, G-$(SG)_n$, $(SG)_n$, $(S)_n$, $(G)_n$, $(ES)_n$ and $(RV)_n$ wherein n is an integer of 2 to 12; $(PAS)_n$, $(RSF)_n$, $(KSF)_n$, $(LRV)_n$, $(RVG)_n$ and $(KVG)_n$ wherein n is an integer of 2 to 8; and $(RSFG)_n$, $(GKSF)_n$, $(LLRV)_n$ and $(GKVG)_n$ wherein n is an integer of 2 to 6.

96. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide consists of a sequence selected from: S-$(GS)_n$, $(GS)_n$, G-$(SG)_n$, $(SG)_n$, $(S)_n$ and $(G)_n$, wherein n is an integer of 2 to 12; such as wherein n is an integer of 2 to 11, such as 2 to 10, such as 2 to 9, such as 2 to 8, such as 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3.

97. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide consists of the sequence $(PAS)_n$, wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3.

98. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide consists of the sequence $(ES)_n$, wherein n is an integer of 2 to 12; such as wherein n is an integer of 2 to 11, such as 2 to 10, such as 2 to 9, such as 2 to 8, such as 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3.

99. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide consists of a sequence selected from:
$(RSFG)_n$ wherein n is an integer of 2 to 6; such as wherein n is an integer of 2 to 5, such as 2 to 4, such as 2 to 3;
$(RSF)_n$ wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3;
$(GKSF)_n$ wherein n is an integer of 2 to 6; such as wherein n is an integer of 2 to 5, such as 2 to 4, such as 2 to 3; and
$(KSF)_n$ wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3.

100. The peptide analogue according to any one of the preceding claims, wherein said N-terminal peptide consists of a sequence selected from:
$(LLRV)_n$ wherein n is an integer of 2 to 6; such as wherein n is an integer of 2 to 5, such as 2 to 4, such as 2 to 3;
$(LRV)_n$ wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3;

$(RV)_n$ wherein n is an integer of 2 to 12; such as wherein n is an integer of 2 to 11, such as 2 to 10, such as 2 to 9, such as 2 to 8, such as 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3;
$(RVG)_n$ wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3;
$(GKVG)_n$ wherein n is an integer of 2 to 6; such as wherein n is an integer of 2 to 5, such as 2 to 4, such as 2 to 3; and
$(KVG)_n$ wherein n is an integer of 2 to 8; such as wherein n is an integer of 2 to 7, such as 2 to 6, such as 2 to 5, such as 2 to 4, such as 2 to 3.

101. The peptide analogue according to any one of claims 94 to 99, wherein n = 1, such as wherein n = 2, such as wherein n = 3, such as wherein n = 4, such as wherein n = 5, such as wherein n = 6, such as wherein n = 7, such as wherein n = 8, such as wherein n = 9, such as wherein n = 10, such as wherein n = 11, such as wherein n = 12.

102. The peptide analogue according to any one of the preceding claims having a sequence selected from:
SGS-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:90);
RSF-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:91); and
RV-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:92);
SGSGSGSGS–GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:93);
PAS-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:94);
ES-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:95);
KKKKKK-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:96);
AAAAAA-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:97);
PAS-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:98);
SGSG-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:99);

RSFG-GC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:100);
RVG-GC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:101);
PAS-SC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:102);
SGSG-SC**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:103);
LRV-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:104);
RSF-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:105);
SGS-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:106);
SGSG-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:107);
LLRV-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:108);
SGS-GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:109);
RSF-GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:110);
RV-GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:111);
PAS-GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:112);
LRV-GCNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:113);
SGS-GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:114);
RSF-GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:115);
RV-GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:116);
PAS-GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:117);

LRV-GCNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:118);
SGS-GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:119);
RSF-GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:120);
RV-GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:121);
PAS-GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:122);
LRV-GCNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:123);
SGS-GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:124);
RSF-GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:125);
RV-GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:126);
PAS-GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:127);
LRV-GCNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:128);
SGS-GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:129);
RSF-GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:130);
RV-GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:131);
PAS-GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:132);
LRV-GCNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:133);
SGS-GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:134);
RSF-GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:135);
RV-GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:136);
PAS-GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:137);
LRV-GCNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:138);

SGS-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:139);
RSF-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:140);
RV-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:141);
PAS-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:142);
LRV-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:143);
SGS-GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:144);
RSF-GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:145);
RV-GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:146);
PAS-GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:147);
LRV-GCNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:148);
SGS-GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:149);
RSF-GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:150);
RV-GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:151);
PAS-GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:152);
LRV-GCNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:153);
SGS-GC**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:154);
RSF-GC**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:155);
RV-GC**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:156);
PAS-GC**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:157);

LRV-GCHTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:158);
SGS-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:159);
RSF-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:160);
RV-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:161);
PAS-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:162);
LRV-GCNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:163);
SGS-GCHTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:164);
RSF-GCHTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:165);
RV-GCHTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:166);
PAS-GCHTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:167);
LRV-GCHTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:168);
SGS-GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:169);
RSF-GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:170);
RV-GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:171);
PAS-GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:172);
LRV-GCNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:173);
RVG-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:174);
KVG-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:175);
GKVG-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:176);

K-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:177);
KSF-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:178);
KSF-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:179); and
GKSF-GCNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:180);

wherein the carboxy group in the C terminal amino acid residue is amidated,

or a functional variant of any one of SEQ ID NO:90 to SEQ ID NO:180 comprising one or more individual amino acid substitutions at any one of positions X_1, X_3 to X_6, and X_8 to X_{37},

wherein said analogue is an agonist of the GCRP receptor.

103. The peptide analogue according to claim 102, wherein said peptide comprises one or more individual amino acid substitutions selected from: X_1 is Gly or His; X_3 is His, Arg, Gly, Met or Lys; X_4 is Ile; X_{10} is Ala, Asn, Asp, Gln, Glu, Gly, Ser or Thr; X_{14} is His, Glu or Asp; X_{17} is Ala; X_{19} is His; X_{22} is Ile, Leu or Val; X_{23} is Ser or His; X_{24} is Arg or His; X_{25} is Lys, Asn, Asp, Glu, Arg or His; X_{26} is His; X_{27} is His; X_{28} is His; X_{29} is His; X_{31} is Asp or His; X_{34} is Pro; and X_{35} is His, Glu, Arg or Ser,

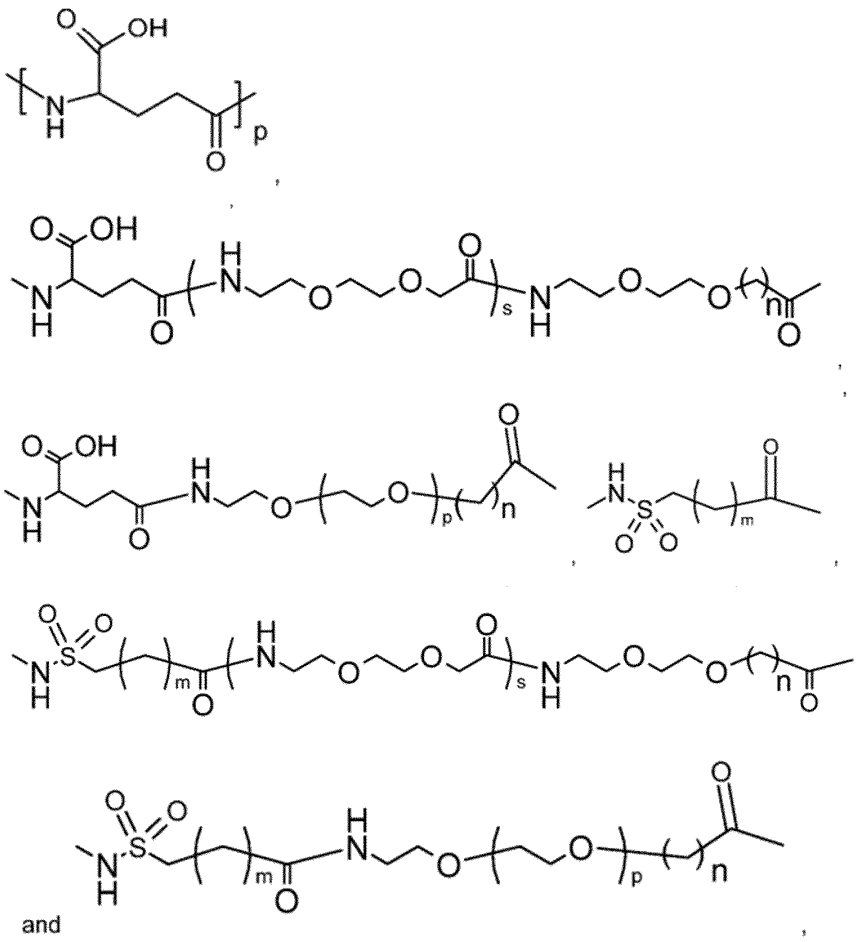
104. The peptide analogue according to any one of claims 102 and 103, wherein the peptide analogue of any one of SEQ ID NO:90 to SEQ ID NO:180 does not comprise an amino acid substitution at the one or more amino acid residues indicated in **bold** in said amino acid sequence.

105. The peptide analogue according to any one of the preceding claims, comprising an acyl group, Z.

106. The peptide analogue according to any one of the preceding claims, comprising an acyl group, Z, connected to an amino group of the N-terminal amino acid residue of the peptide analogue.

107. The peptide analogue according to any one of the preceding claims, comprising a linker, Y.

108. The peptide analogue according to any one of the preceding claims, comprising a linker, Y, selected from:



and

wherein m is an integer of 0 to 6, such as wherein m is 0, 1, 2, 3, 4, 5, or 6;
n is an integer of 1 to 3, such as wherein n is 1, 2, or 3;
s is an integer of 0 to 3, such as wherein s is 0, 1, 2, or 3; and
p is an integer of 1 to 23, such as wherein p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23,
and wherein the carbonyl end of the linker is connected to the N-terminal amino acid residue of the peptide analogue.

109. The peptide analogue according to any one of the preceding claims, comprising a linker, Y, wherein said linker comprises one or more moieties individually selected from

a. α-amino acid, γ-amino acid, and ω-amino acid,
b. Glu, gamma-Glu, iso-Glu, beta-Asp, Asp, beta-Ala, Lys, gamma-aminobutyric acid, and Gly, and
c. [8-amino-3,6-dioxaoctanoic acid]$_n$ (AEEA$_n$), wherein n is an integer of 1 to 20, such as an integer of 1 to 5, of 1 to 4, of 1 to 3, or of 1 to 2; such as an integer of 1, 2, 3, 4 or 5, preferably 1 or 2.

110. The peptide analogue according to any one of the preceding claims, comprising a linker selected from AEEA, 2AEEA, isoGlu-AEEA, isoGlu-2AEEA, gammaGlu-AEEA and gammaGlu-2AEEA,

111. The peptide analogue according to any one of the preceding claims, comprising a linker, Y, connected to an amino group of the N-terminal amino acid residue of the peptide analogue.

112. The peptide analogue according to any one of the preceding claims , wherein the acyl group, Z, or the linker, Y, is connected to an amino group of the N-terminal amino acid residue of the peptide analogue selected from the amino group of X_{-9}, the amino group of X_{-8}, the amino group of X_{-7}, the amino group of X_{-6}, the amino group of X_{-5}, the amino group of X_{-4}, the amino group of X_{-3}, the amino group of X_{-2}, the amino group of X_{-1}, and the amino group of X_1.

113. The peptide analogue according to any one of the preceding claims , wherein the amino end of the linker, Y, is connected to an acyl group, Z.

114. The peptide analogue according to any one of the preceding claims, wherein the acyl group of Z originates from a fatty acid or fatty diacid.

115. The CGRP analogue according to any one of the preceding claims, wherein the acyl group of Z comprises an acyl group of the formula $CH_3(CH_2)_nCO$-, wherein n is in an integer of 4 to 24; or wherein the acyl group

of Z comprises an acyl group of the formula COOH(CH2)nCO-, wherein n is an integer of 4 to 24;
such as wherein n is an integer of 8 to 20, of 10 to 20, of 12 to 20, of 14 to 20, or of 14 to 18.

116. The peptide analogue according to any one of the preceding claims, wherein the acyl group of Z originates from a fatty acid or fatty diacid with 12-22 carbon atoms; such as with 14, 16, 18 or 20 carbon atoms.

117. The peptide analogue according to any one of the preceding claims, where the N-terminal amino acid of said peptide analogue comprises an acyl group selected from $HOOC(CH_2)14CO$, $HOOC(CH_2)16CO$, $HOOC(CH_2)18CO$, $CH_3(CH_2)14CO$, $CH_3(CH_2)16CO$ and $CH_3(CH_2)18CO$.

118. The peptide analogue according to any one of the preceding claims, where the N-terminal amino acid of said peptide analogue comprises an acyl group and a linker selected from $HOOC(CH_2)16CO$-isoGlu-AEEA, $HOOC(CH_2)16CO$-isoGlu-2AEEA, $HOOC(CH_2)14CO$-isoGlu-AEEA, $HOOC(CH_2)14CO$-isoGlu-2AEEA, $HOOC(CH_2)18CO$-isoGlu-AEEA and $HOOC(CH_2)18CO$-isoGlu-2AEEA.

119. The peptide analogue according to any one of the preceding claims, where the N-terminal amino acid of said peptide analogue comprises an acyl group selected from $HOOC(CH_2)16CO$-isoGlu, $HOOC(CH_2)14CO$-isoGlu and $HOOC(CH_2)18CO$-isoGlu.

120. The peptide analogue according to any one of the preceding claims, where the N-terminal amino acid of said peptide analogue comprises an acyl group selected from $CH_3(CH_2)14CO$-gamma-Glu, $CH_3(CH_2)16CO$-gamma-Glu and $CH_3(CH_2)18CO$-gamma-Glu.

121. A composition comprising the peptide analogue according to any one of the preceding claims, optionally further comprising a carrier.

122. A pharmaceutical composition comprising the peptide analogue according to any one of the preceding claims, optionally further comprising a pharmaceutically acceptable carrier, excipient or diluent.

123. A peptide analogue, a composition, and a pharmaceutical composition according to any one of the preceding claims, for use as a medicament.

124. A peptide analogue, a composition, and a pharmaceutical composition according to any one of the preceding claims, for use in a method of treating a disease selected from: a cardiovascular disease, such as ischemic heart disease; a neurological disorder; an infection: a renal disease; a metabolic disease; a bone disease: an ischemic disease; an inflammatory disease; a gastrointestinal disease; and pain, such as nociceptive pain and/or neuropathic pain.