# N-terminally modified Calcitonin Gene-related Peptide Analogues

## Technical field

The present invention relates to CGRP peptide analogues comprising an N-terminal modification.

## 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.

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. $CGRP_{8-37}$, $CGRP_{12-37}$, $CGRP_{27-37}$).

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.

It is well-known to modify therapeutic proteins to improve various properties, e.g. to improve solubility or increase serum half-life. This includes PEGylation i.e. the addition of poly(ethylene glycol) and XTENs. XTENs are highly hydrophilic, unstructured, nonrepetitive protein polymers consisting of alanine, glutamate, glycine, proline, serine and threonine, designed to prolong the in vivo half-life of pharmaceuticals by introducing a bulking effect similar to that of poly(ethylene glycol).

WO 99/46283 discloses pharmacologically active peptide conjugates having a reduced tendency towards enzymatic cleavage comprising a pharmacologically active protein and a stabilising peptide sequence of 4 to 20 amino acid residues selected from Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn and related amino acids.

**Summary**

The present inventors have developed peptide-based CGRP analogues which comprise a N-terminal region which is a short peptide attached via a peptide bond to the amino group of the N-terminal amino acid residue of a CGRP peptide (i.e. usually at position 1, $X_1$). Surprisingly the attachment of a peptide to the N-terminus of a CGRP peptide does not affect the receptor potency (EC50) of the CGRP peptide, and in some instances even increases CGRP receptor potency. It can thus be used for example as an inactive peptide linker, attaching a CGRP peptide to another entity, or for other purposes e.g. maintaining or increasing potency. In contrast, any modifications made to the C-terminus of the CGRP peptide are poorly tolerated and is demonstrated herein to significantly reduce or abolish CGRP receptor potency.

It is an aspect to provide a CGRP analogue comprising a CGRP peptide of 37 consecutive amino acid residues ($CGRP_{1-37}$), or a functional fragment thereof, and 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 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, Pro, Phe and Val.

In some embodiments said CGRP analogue is an agonist of the CGRP receptor. In some embodiments said CGRP analogue is an antagonist of the CGRP receptor.

**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) or 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 (CGRP-R) 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.

An antagonist is a compound that inhibits or reduces agonist-mediated responses of a receptor. Antagonists usually do not provoke a biological response themselves upon binding to a receptor. Antagonists have affinity but no efficacy for their cognate receptors, and binding will disrupt the interaction and inhibit the function of an agonist at receptors. A CGRP receptor antagonist as used herein is a compound that acts as an antagonist on the CGRP 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 (alpha-CGRP) and βCGRP (beta-CGRP). 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);

**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (alpha-rCGRP; SEQ ID NO:5);
**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGSKAF (beta-rCGRP; SEQ ID NO:6),
**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (alpha-mCGRP; SEQ ID NO:7); and
**S**C**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

The present disclosure provides a CGRP analogue, or CGRP peptide analogue, comprising a CGRP peptide of 37 consecutive amino acid residues ($CGRP_{1-37}$), or a functional fragment thereof, 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.

In some embodiments the present disclosure provides a calcitonin gene-related peptide (CGRP) analogue comprising a CGRP peptide of 37 consecutive amino acid residues ($CGRP_{1-37}$), or a functional fragment thereof, and
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 CGRP peptide, 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 CGRP peptide.

In some embodiments the present disclosure provides a CGRP analogue comprising a CGRP peptide of 37 consecutive amino acid residues ($CGRP_{1-37}$), or a functional fragment thereof, and an N-terminal region attached via a peptide bond to the amino group of the N-terminal amino acid residue 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), or
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).

In some embodiments the present disclosure provides a CGRP analogue comprising a CGRP peptide of 37 consecutive amino acid residues ($CGRP_{1-37}$), or a functional fragment thereof, and 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 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), or
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).

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

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 (G), Pro (P), Phe (F) and Val (V).

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 (G), Pro (P), Phe (F) and Val (V).

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 (G), Pro (P), Phe (F) and Val (V).

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 10 to 30 consecutive amino acid residues, such as 10 to 20 consecutive amino acid residues, wherein said N-terminal peptide does not comprise any amino acids selected from Gly, Asn and Ser.

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 consists of 2 consecutive amino acid residues.

In some embodiments of the present disclosure said N-terminal peptide consists of 3 consecutive amino acid residues.

In some embodiments of the present disclosure said N-terminal peptide consists of 4 consecutive amino acid residues.

In some embodiments of the present disclosure said N-terminal region is an N-terminal dipeptide, or an N-terminal tripeptide. In some embodiments of the present disclosure said N-terminal region is an N-terminal dipeptide. In some embodiments of the present disclosure said N-terminal region is an N-terminal tripeptide.

In some embodiments of the present disclosure said N-terminal peptide consists of naturally occurring amino acid residues. In some embodiments of the present disclosure said N-terminal peptide 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 of the present disclosure said N-terminal peptide consist of 2 to 30, 3 to 30 or 4 to 30 consecutive amino acids and comprises one or more amino acids selected from: Gly (G), Pro (P), Phe (F) and Val (V).

In some embodiments of the present disclosure said N-terminal peptide consist of 4 to 30 consecutive amino acids and comprises more than 25% of an amino acid selected from Gly (G), Pro (P), Phe (F) and Val (V).

In some embodiments of the present disclosure said N-terminal peptide consist of 4 to 30 consecutive amino acids and does not comprise a Lys.

In some embodiments of the present disclosure said N-terminal peptide consist of 4 to 30 consecutive amino acids and comprises one or more amino acids selected from: Gly (G), Pro (P), Phe (F) and Val (V), and comprises a single Lys amino acid.

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 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 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 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 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 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.

In some embodiments of the present disclosure said N-terminal peptide comprises or consist of one or more amino acids 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 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 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 not Lys (K).

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, such as attached to the N-terminal amino acid residue of said CGRP peptide, 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 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 the N-terminal amino acid residue of said CGRP peptide, 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 the N-terminal amino acid residue of said CGRP peptide,
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 the N-terminal amino acid residue of said CGRP peptide, 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 (or C-terminal) 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 (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 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 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.

In some embodiments of the present disclosure said N-terminal peptide comprises or 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.; 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 of the present disclosure said N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide, is a linker.

In some embodiments of the present disclosure said N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide, is 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 said linker largely does not affect the antagonistic potency of the CGRP peptide antagonist (IC50).

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” herein 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.

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 of $CGRP_{1-37}$. 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 of $CGRP_{1-37}$. 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 of $CGRP_{1-37}$. In functional fragments of $CGRP_{1-37}$, wherein one or more amino acids are omitted from the N-terminus of said CGRP peptide, the N-terminal amino acid is the first amino acid, i.e. in the fragment $CGRP_{8-37}$ the amino acid at position $X_8$ is the N-terminal amino acid.

In some embodiments of the present disclosure said CGRP peptide ($CGRP_{1-37}$) has the sequence:

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

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 $X_{37}$.

In some embodiments of the present disclosure said functional variant of SEQ ID NO:1 comprises a Gly (G) amino acid as the N-terminal amino acid, i.e. wherein $X_1$ is Gly.

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 fragment thereof and a functional variant thereof.

In some embodiments of the present disclosure said CGRP peptide ($CGRP_{1-37}$) has a sequence selected from:
**S**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:2),

AC**D**TATCVTHRLAGLLSRSGG**V**VK**N**NFVPTNVGSKAF (SEQ ID NO:3);
AC**N**TATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF (SEQ ID NO:4);
**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (SEQ ID NO:5);
**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGSKAF (SEQ ID NO:6),
**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (SEQ ID NO:7); and
**S**C**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 fragment of any one of SEQ ID NO: 2 to SEQ ID NO:8,

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 $X_{37}$ of said peptide.

In some embodiments the present disclosure provides a CGRP analogue comprising a CGRP peptide ($CGRP_{1-37}$) having a sequence selected from 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 fragment of any one of SEQ ID NO:1 to SEQ ID NO:8,

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 $X_{37}$,

and comprising an N-terminal region attached via a peptide bond to the amino group of the N-terminal amino acid residue 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), or
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).

In some embodiments the present disclosure provides a CGRP analogue comprising a CGRP peptide ($CGRP_{1-37}$) having a sequence selected from 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 fragment of any one of SEQ ID NO:1 to SEQ ID NO:8,

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 $X_{37}$,

and comprising an N-terminal region attached via a peptide bond to the amino group of the N-terminal amino acid residue said CGRP peptide,

wherein said N-terminal region is 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 the present disclosure provides a CGRP analogue comprising a CGRP peptide ($CGRP_{1-37}$) having a sequence selected from 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 fragment of any one of SEQ ID NO:1 to SEQ ID NO:8,

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 $X_{37}$,

and comprising an N-terminal region attached via a peptide bond to the amino group of the N-terminal amino acid residue said CGRP peptide,

wherein said N-terminal region is 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.

In some embodiments said CGRP peptide 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 CGRP peptide.

In preferred embodiments of the present disclosure said functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises a Gly (G) amino acid as the N-terminal amino acid, i.e. wherein $X_1$ is Gly.

In some embodiments said functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises 1 to 6 individual amino acid substitutions at any one of positions $X_1$, $X_3$ to $X_6$, and $X_8$ to $X_{37}$, 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 $X_{37}$; such as 6, such as 5, such as 4, such as 3, such as 2, such as 1 individual amino acid substitutions at any one of positions $X_1$, $X_3$ to $X_6$, and $X_8$ to $X_{37}$. In one embodiment said individual amino acid substitutions are conservative amino acid substitutions.

In some embodiments of the present disclosure a functional fragment of said CGRP peptide ($CGRP_{1-37}$) is a fragment having one or more amino acids omitted from the N-terminus or a fragment having one or more amino acids omitted from the C-terminus of said $CGRP_{1-37}$.

In some embodiments of the present disclosure a functional fragment of said CGRP peptide ($CGRP_{1-37}$) is a fragment having one to ten amino acids omitted from the N-terminus, or a fragment having one to ten amino acids omitted from the C-terminus of said $CGRP_{1-37}$.

In some embodiments of the present disclosure a functional fragment of said CGRP peptide ($CGRP_{1-37}$) is a fragment having 1 to 26 amino acids omitted from the N-terminus, such as 1 to 22 amino acids, such as 1 to 18 amino acids, such as 1 to 11 amino acids, such as 1 to 7 amino acids omitted from the N-terminus.

In some embodiments of the present disclosure a functional fragment of said CGRP peptide ($CGRP_{1-37}$) is a fragment having at least 7 amino acids omitted from the N-terminus.

In some embodiments of the present disclosure a functional fragment of said CGRP peptide ($CGRP_{1-37}$) is a fragment having one or more amino acids omitted from the central part of said $CGRP_{1-37}$, such as one to ten amino acids omitted from the central part of said $CGRP_{1-37}$.

In some embodiments of the present disclosure said CGRP peptide analogue is an antagonist of the GCRP receptor, such as an antagonist of the human CGRP receptor.

In some embodiments of the present disclosure said functional fragment of said CGRP peptide ($CGRP_{1-37}$) is selected from $CGRP_{8-37}$, $CGRP_{12-37}$, $CGRP_{19-37}$, $CGRP_{23-37}$ and $CGRP_{27-37}$.

In some embodiments of the present disclosure said functional fragment of said CGRP peptide ($CGRP_{1-37}$) is selected from:
$CGRP_{8-37}$ including human beta $CGRP_{8-37}$ (SEQ ID NO:200) and human alpha $CGRP_{8-37}$ (SEQ ID NO:243),
$CGRP_{12-37}$ including human beta $CGRP_{12-37}$ (SEQ ID NO:244) and human alpha $CGRP_{12-37}$ (SEQ ID NO:245),
$CGRP_{19-37}$ including human beta $CGRP_{19-37}$ (SEQ ID NO:246) and human alpha $CGRP_{19-37}$ (SEQ ID NO:247),
$CGRP_{23-37}$ including human beta $CGRP_{23-37}$ (SEQ ID NO:248) and human alpha $CGRP_{23-37}$ (SEQ ID NO:249), and
$CGRP_{27-37}$ (SEQ ID NO:250),
or a functional variant of any one of SEQ ID NO:200 and SEQ ID NO:243 to SEQ ID NO:250 having one or more individual amino acid substitutions, such as one, two or three individual amino acid substitutions,
such as a functional variant of any one of SEQ ID NO:200 and SEQ ID NO:243 to SEQ ID NO:250 wherein Ala is substituted with Ser at $X_{36}$, and/or wherein Ser is substituted with Pro at $X_{34}$, and/or wherein Lys is substituted with Phe at $X_{35}$,
wherein optionally said functional fragment is N-terminally acetylated,
wherein said functional fragment is an antagonist of the human CGRP receptor.

In some embodiments the present disclosure provides a CGRP analogue comprising a functional fragment of a CGRP peptide ($CGRP_{1-37}$) having a sequence selected from SEQ ID NO:200 and any one of SEQ ID NO:243 to SEQ ID NO:250, wherein optionally said functional fragment is N-terminally acetylated,

or a functional variant of any one of SEQ ID NO:200 and SEQ ID NO:243 to SEQ ID NO:250 having one or more individual amino acid substitutions, such as one, two or three individual amino acid substitutions,

wherein said functional fragment is an antagonist of the human CGRP receptor,

and comprising an N-terminal region attached via a peptide bond to the amino group of the N-terminal amino acid residue of the functional fragment 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), or
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, Pro, Phe and Val.

In some embodiments the present disclosure provides a CGRP analogue comprising a functional fragment of a CGRP peptide ($CGRP_{1-37}$) having a sequence selected from SEQ ID NO:200 and any one of SEQ ID NO:243 to SEQ ID NO:250, wherein optionally said functional fragment is N-terminally acetylated,

or a functional variant of any one of SEQ ID NO:200 and SEQ ID NO:243 to SEQ ID NO:250 having one or more individual amino acid substitutions, such as one, two or three individual amino acid substitutions,

wherein said functional fragment is an antagonist of the human CGRP receptor,

and comprising an N-terminal region attached via a peptide bond to the amino group of the N-terminal amino acid residue of the functional fragment of said CGRP peptide,

wherein said N-terminal region is 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 the present disclosure provides a CGRP analogue comprising a functional fragment of a CGRP peptide ($CGRP_{1-37}$) having a sequence selected from SEQ ID NO:200 and any one of SEQ ID NO:243 to SEQ ID NO:250, wherein optionally said functional fragment is N-terminally acetylated,

or a functional variant of any one of SEQ ID NO:200 and SEQ ID NO:243 to SEQ ID NO:250 having one or more individual amino acid substitutions, such as one, two or three individual amino acid substitutions,

wherein said functional fragment is an antagonist of the human CGRP receptor,

and comprising an N-terminal region attached via a peptide bond to the amino group of the N-terminal amino acid residue of the functional fragment of said CGRP peptide,

wherein said N-terminal region is 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.

In some embodiments of the present disclosure said CGRP peptide analogue is an agonist of the GCRP receptor, such as an agonist of the human GCRP receptor. In some embodiments the peptide analogue of the present disclosure is an agonist of the GCRP receptor at systemic pH or 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 present disclosure provides a CGRP analogue comprising a CGRP peptide ($CGRP_{1-37}$) having the sequence

$X_1CX_3TATCVTHRLAX_{14}LLX_{17}RSGGX_{22}X_{23}KX_{25}NFVPTX_{31}VGSX_{35}AF$ (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 CGRP 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;

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

In some embodiments of the present disclosure said CGRP peptide ($CGRP_{1-37}$) has a sequence 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 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 is an agonist of the GCRP receptor.

In some embodiments of the present disclosure said CGRP peptide selected from any one of SEQ ID NO:1 to SEQ ID NO:8 comprises 1, 2, 3, 4, 5 or 6 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 of the present disclosure said CGRP peptide comprises 1, 2, 3, 4, 5 or 6 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.

In some embodiments of the present disclosure said CGRP peptide 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 of the present disclosure said CGRP peptide comprises 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 of the present disclosure said CGRP peptide comprises two 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.

In preferred embodiments the peptide analogue of the present disclosure 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 the present disclosure 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.

In some embodiments of the present disclosure said CGRP peptide comprises at least one amino acid substitution individually 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 of the present disclosure said CGRP peptide 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;
such as comprises at least one amino acid substitution selected from $X_{19}$ is His, $X_{14}$ is His and $X_3$ is His.

In some embodiments of the present disclosure said CGRP peptide comprises at least one amino acid substitution wherein $X_{10}$ is a negative amino acid selected from Asp or Glu.

In some embodiments of the present disclosure said CGRP peptide comprises at least one amino acid substitution wherein $X_1$ is Gly.

In some embodiments of the present disclosure in said CGRP peptide 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 the present disclosure provides a CGRP analogue comprising a CGRP peptide ($CGRP_{1-37}$) having a sequence selected from SEQ ID NO:1 to SEQ ID NO:8,

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,

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 $X_{37}$,

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

wherein said analogue is an agonist of the GCRP receptor.

In some embodiments of the present disclosure said CGRP peptide 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 said peptide analogue is an agonist of the GCRP receptor 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 0.01 to 6 nM, such as 0.1 to 6 nM, such as 1 to 6 nM.

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 an acyl group and a linker which is $HOOC(CH_2)16CO$-isoGlu-AEEA.

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

In some embodiments of the present disclosure said CGRP peptide ($CGRP_{1-37}$) has a sequence selected from:
**H**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (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),
**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (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);
**G**C**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);

**G**CNTATCVTHRLA**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);
**G**CNTATCVTHRLA**H**LLSRSGGMVK**H**NFVPTNVGSKAF (SEQ ID NO:63);
**G**C**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);
**G**C**H**TATCVT**N**RLA**H**LL**A**R**H**GG**I**VK**K**NFVPTNVG**P**KAF (SEQ ID NO:68);
**G**C**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:69);
**G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:70);
**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:71);
**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:72);
**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:73);
**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:74);
**G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:75);
**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:76);
**G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:77);
**G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:78);
**G**C**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:79);

**G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:80);
**G**CNTATCVTHRLA**D**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:81);
**G**CNTATCVTHRLA**E**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:82);
**G**CNTATCVTHRLAGLLSRSGGMVK**E**NFVPTNVGSKAF (SEQ ID NO:83);
**G**C**H**TATCVTHRLA**D**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:84);
**G**C**H**TATCVTHRLA**E**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:85);
**G**C**H**TATCVTHRLAGLLSRSGGMVK**E**NFVPTNVGSKAF (SEQ ID NO:86);
**G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGSKAF (SEQ ID NO:87);
**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**R**AF (SEQ ID NO:88); and
**G**CNTATCVTHRLAGLLSRSGGMV**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 said analogue is an agonist of the GCRP receptor.

In some embodiments the CGRP 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.

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

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 said analogue is an agonist of the GCRP receptor.

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

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 analogue is an agonist of the GCRP receptor.

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

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 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;

and comprising 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 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), or
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, Pro, Phe and Val,

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

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

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;

and comprising 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 CGRP peptide,

wherein said N-terminal region is 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 present disclosure provides a CGRP analogue comprising a CGRP peptide ($CGRP_{1-37}$) having a sequence selected from 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 $X_{37}$,

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;

and comprising 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 CGRP peptide,

wherein said N-terminal region is selected from 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 present disclosure provides a CGRP analogue comprising a CGRP peptide ($CGRP_{1-37}$) having a sequence selected from 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 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;

such as wherein said peptide optionally 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;

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 $X_{37}$,

and comprising 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 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), or
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, Pro, Phe and Val,

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

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

wherein said peptide comprises 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;

such as wherein said peptide optionally 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;

and comprising 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 CGRP peptide,

wherein said N-terminal region is 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 present disclosure provides a CGRP analogue comprising a CGRP peptide ($CGRP_{1-37}$) having a sequence selected from 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 $X_{37}$,

wherein said peptide comprises 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;

such as wherein said peptide optionally 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;

and comprising 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 CGRP peptide,

wherein said N-terminal region is selected from 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 said 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 comprises 1 to 6 individual amino acid substitutions at any one of positions $X_1$, $X_3$ to $X_6$, and $X_8$ to $X_{37}$, 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 $X_{37}$; such as 6, such as 5, such as 4, such as 3, such as 2, such as 1 individual amino acid substitutions at any one of positions $X_1$, $X_3$ to $X_6$, and $X_8$ to $X_{37}$. In one embodiment said individual amino acid substitutions are conservative amino acid substitutions.

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), 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 CGRP peptide has a sequence selected from any one of SEQ ID NO:9 to SEQ ID NO:26,
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,
wherein said analogue is an agonist of the GCRP receptor.

In some embodiments the present disclosure provides a CGRP analogue selected from:
**SGS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO: 90);
**RSF-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO: 91);
**RV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO: 92);
**SGSGSGSGS–G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:93);
**PAS**-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:94);

**ES**-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:95);
**PAS**-**G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:98);
**SGSG**-**G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:99);
**RSFG**-**G**C**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:100);
**RVG**-**G**C**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**-**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:104);
**RSF**-**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:105);
**SGS**-**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:106);
**SGSG**-**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:107);
**LLRV**-**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:108);
**SGS**-**G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:109);
**RSF**-**G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:110);
**RV**-**G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:111);
**PAS**-**G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:112);
**LRV**-**G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:113);
**SGS**-**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:114);
**RSF**-**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:115);
**RV**-**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:116);
**PAS**-**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:117);
**LRV**-**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:118);
**SGS**-**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:119);
**RSF**-**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:120);
**RV**-**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:121);
**PAS**-**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:122);
**LRV**-**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:123);
**SGS**-**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:124);
**RSF**-**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:125);
**RV**-**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:126);
**PAS**-**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:127);
**LRV**-**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:128);
**SGS**-**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:129);
**RSF**-**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:130);
**RV**-**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:131);

**PAS-G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:132);
**LRV-G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:133);
**SGS-G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:134);
**RSF-G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:135);
**RV-G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:136);
**PAS-G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:137);
**LRV-G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:138);
**SGS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:139);
**RSF-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:140);
**RV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:141);
**PAS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:142);
**LRV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:143);
**SGS-G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:144);
**RSF-G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:145);
**RV-G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:146);
**PAS-G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:147);
**LRV-G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:148);
**SGS-G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:149);
**RSF-G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:150);
**RV-G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:151);
**PAS-G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:152);
**LRV-G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:153);
**SGS-GC**H**T**ATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:154);
**RSF-GC**H**T**ATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:155);
**RV-GC**H**T**ATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:156);
**PAS-GC**H**T**ATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:157);
**LRV-GC**H**T**ATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:158);
**SGS-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:159);
**RSF-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:160);
**RV-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:161);
**PAS-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:162);
**LRV-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:163);
**SGS-GC**H**T**ATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:164);
**RSF-GC**H**T**ATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:165);
**RV-GC**H**T**ATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:166);

**PAS-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:167);
**LRV-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:168);
**SGS-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:169);
**RSF-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:170);
**RV-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:171);
**PAS-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:172);
**LRV-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:173);
**RVG-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:174);
**KVG-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:175);
**GKVG-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:176);
**K-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:177);
**KSF-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:178);
**KSF-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:179); and
**GKSF-G**CNTATCVTHRLAGLLSRSGGMV**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 $X_{37}$, such as one, two, three or four 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 sequence 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 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 analogue is an agonist of the GCRP receptor.

In some embodiments the CGRP 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 the present disclosure provides a CGRP analogue selected from any one of SEQ ID NO:90 to SEQ ID NO:180, wherein the carboxy group in the C terminal amino acid residue is amidated,

wherein said peptide sequence 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.

In some embodiments the present disclosure provides a CGRP analogue selected from any one of SEQ ID NO:90 to SEQ ID NO:180, wherein the carboxy group in the C terminal amino acid residue is amidated,

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

It is understood that reference to a peptide sequence which is for example **SGS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO: 90) comprising an amino acid substitution at position $X_1$, such as wherein $X_1$ is Gly or His, refers to "$X_1$" as the first amino acid in the CGRP peptide part of the CGRP analogue (here "**G**" in bold), and not to the amino acids in the N-terminal region (here "**SGS-**") which are denoted "$X_{-1}$" and so forth herein.

In some embodiments of the present disclosure said CGRP analogue has a sequence selected from 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 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 optionally amidated, wherein said analogue is an agonist of the GCRP receptor.

In some embodiments of the present disclosure said CGRP peptide or CGRP analogue 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 of the present disclosure said CGRP peptide or CGRP analogue 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 CGRP peptide or CGRP 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.

The carboxy group in the C terminal amino acid residue of the CGRP peptide or CGRP analogue is amidated (-$NH_2$), 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.

<u>CGRP 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 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 analogue “X”.

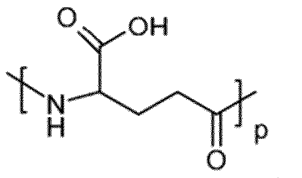
In some embodiments the acyl group (designated Z) and/or the acyl group connected to the linker (designated Y) shall have a sufficient albumin binding affinity. In some embodiments addition of an -Y-Z-moiety will increase the half-life of the CGRP peptide X or CGRP peptide analogue (‘prolonged action’).

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

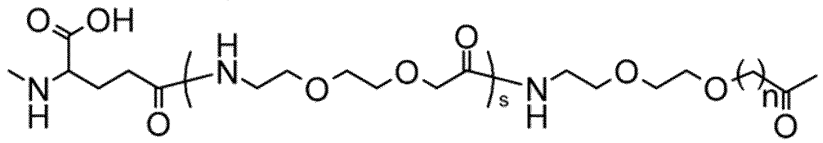
In some embodiments the CGRP peptide analogue of the present disclosure comprises an acyl group, Z, connected to an amino group of the N-terminal amino acid residue of the peptide analogue.

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

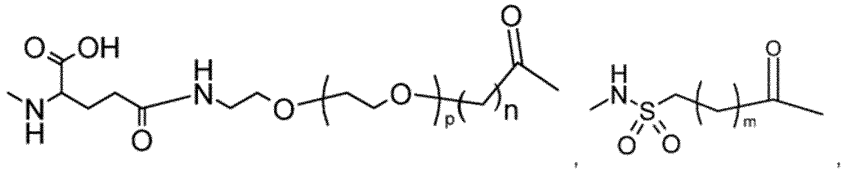
In some embodiments the linker, Y, is selected from the following formulae:



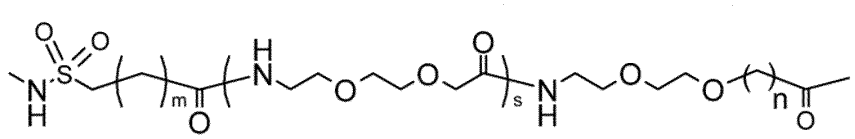
,

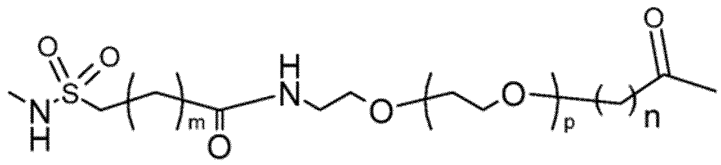


,



,





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 CGRP 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 CGRP 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 $X_{-9}$, 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 $X_{-2}$, 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 CGRP 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 CGRP 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 CGRP 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.

WO2011/051312 describes the synthesis of 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–**<br>**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 94 | ++++ | **PAS**-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 95 | +++ | **ES**-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 96 | ++++ | **KKKKKK**-<br>SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 97 | +++ | **AAAAAA**-<br>SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 98 | ++++ | **PAS-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF |
| 99 | ++++ | **SGSG-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF |
| 100 | ++++ | **RSFG-GCH**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF |
| 101 | ++++ | **RVG-GCH**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 |

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|---|---|---|
| 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-GCH**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 155 | ++++ | **RSF-GCH**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 156 | +++ | **RV-GCH**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 157 | +++ | **PAS-GCH**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 158 | ++++ | **LRV-GCH**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-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF |
| 165 | ++++ | **RSF-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF |
| 166 | ++++ | **RV-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF |
| 167 | ++++ | **PAS-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF |
| 168 | ++++ | **LRV-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF |
| 169 | +++ | **SGS-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF |

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|---|---|---|
| 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-**<br>**G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF;<br>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-<br>**S**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 182 | ++++ | HOOC(CH2)16CO-isoGlu-<br>**S**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 183 | ++++ | CH3(CH2)16CO-gammaGlu-<br>**S**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 184 | ++++ | HOOC(CH2)16CO-isoGlu-2AEEA-<br>**G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 185 | +++ | HOOC(CH2)14CO-isoGlu-AEEA-<br>**G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 186 | +++ | HOOC(CH2)14CO-isoGlu-2AEEA-<br>**G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 187 | ++++ | HOOC(CH2)18CO-isoGlu-AEEA-<br>**G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 188 | +++ | HOOC(CH2)18CO-isoGlu-2AEEA-<br>**G**C**H**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF |
| 189 | ++++ | **LRV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF;<br>no lipidation |
| 190 | ++++ | **RSF-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF;<br>no lipidation |
| 191 | ++++ | **SGS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF;<br>no lipidation |
| 192 | ++++ | **SGSG-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF;<br>no lipidation |
| 193 | ++++ | **LLRV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF;<br>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 calcitonin gene-related peptide (CGRP) analogue comprising

a CGRP peptide of 37 consecutive amino acid residues ($CGRP_{1-37}$), or a functional fragment thereof, and an N-terminal region attached via a peptide bond to the amino group of the N-terminal amino acid residue 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), or
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).

2. The CGRP analogue according to claim 1, 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.

3. The CGRP analogue according to any one of the preceding claims, 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.

4. The CGRP analogue according to any one of the preceding claims, 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.

5. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide consists of 2 to 20 consecutive amino acid residues, such as 2 to 10 consecutive amino acid residues, such as 2 to 9 consecutive amino acid residues, such as 2 to 5 consecutive amino acid residues.

6. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide consists of 4 consecutive amino acid residues.

7. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide consists of 3 consecutive amino acid residues.

8. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide consists of 2 consecutive amino acid residues.

9. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal region is an N-terminal dipeptide, or an N-terminal tripeptide.

10. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide 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.

11. The CGRP 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.

12. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises at least one Gly amino acid.

13. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises at least one Pro amino acid.

14. The CGRP 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.

15. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises at least one Phe amino acid.

16. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises at least one Val amino acid.

17. The CGRP 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, Glu.

18. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises one amino acid with electrically charged side chains selected from Arg, His, Lys, Asp, Glu.

19. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide comprises one, and no more than one, Lys amino acid.

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

21. The CGRP analogue according to any one of the preceding claims, wherein 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.

22. The CGRP analogue according to any one of the preceding claims, 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.

23. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal peptide consist of 2 to 30 amino acids,
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; and/or
wherein 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.

24. The CGRP 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.

25. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal single amino acid is an amino acid selected from: Gly, Pro and Val.

26. The CGRP 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 the N-terminal amino acid residue of said CGRP peptide,
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 optionally said N-terminal peptide comprises at least one amino acid selected from: Gly, Pro, Phe and Val.

27. The CGRP 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 the N-terminal amino acid residue of said CGRP peptide,

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.

28. The CGRP 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 the N-terminal amino acid residue of said CGRP peptide,

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 .

29. The CGRP 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 the N-terminal amino acid residue of said CGRP peptide,
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.

30. The CGRP analogue according to any one of the preceding claims, wherein 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).

31. The CGRP 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.

32. The CGRP 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.

33. The CGRP 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.

34. The CGRP 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.

35. The CGRP 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.

36. The CGRP 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.

37. The CGRP analogue according to any one of claims 31 to 36, 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.

38. The CGRP analogue according to any one of the preceding claims, wherein 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.

39. The CGRP analogue according to any one of the preceding claims, wherein said N-terminal single amino acid, N-terminal dipeptide, N-terminal tripeptide or N-terminal peptide, is a linker, such as an inactive linker.

40. The CGRP analogue according to any one of the preceding claims, wherein 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, such as another peptide or protein.

41. The CGRP analogue according to any one of the preceding claims, comprising 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.

42. The CGRP analogue according to any one of claims 40 to 41, wherein said another peptide or protein is 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, the N-terminal dipeptide, the N-terminal tripeptide or the N-terminal peptide of said CGRP peptide analogue.

43. The CGRP analogue according to any one of claims 40 to 42, wherein said another peptide or protein is a therapeutic peptide, a therapeutic protein, a circulating peptide or a circulating protein.

44. The CGRP analogue according to any one of claims 40 to 43, wherein said another peptide or protein is albumin, an Fc domain or Albumin-binding domain (ABD).

45. The CGRP analogue according to any one of the preceding claims, wherein said CGRP peptide ($CGRP_{1-37}$) is

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

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 $X_{37}$.

46. The CGRP analogue according to any one of the preceding claims, wherein said CGRP peptide ($CGRP_{1-37}$) is selected from:
**S**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:2),
AC**D**TATCVTHRLAGLLSRSGG**V**VK**N**NFVPTNVGSKAF (SEQ ID NO:3);
AC**N**TATCVTHRLAGLLSRSGG**M**VK**S**NFVPTNVGSKAF (SEQ ID NO:4);
**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (SEQ ID NO:5);
**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGSKAF (SEQ ID NO:6),
**S**C**N**TATCVTHRLAGLLSRSGG**V**VK**D**NFVPTNVGS**E**AF (SEQ ID NO:7); and
**S**C**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 fragment of any one of SEQ ID NO: 2 to SEQ ID NO:8,

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 $X_{37}$ of said peptide.

47. The CGRP analogue according to any one of claims 45 and 46, wherein said functional variant of any one of SEQ ID NO:1 to SEQ ID NO:8 comprises a Gly (G) amino acid as the N-terminal amino acid, i.e. wherein $X_1$ is Gly.

48. The CGRP analogue according to any one of the preceding claims, which is an antagonist of the GCRP receptor, such as an antagonist of the human CGRP receptor.

49. The CGRP analogue according to any one of claims 45 to 48, wherein said functional fragment of said CGRP peptide ($CGRP_{1-37}$) is a fragment having one or more amino acids omitted from the N-terminus or a fragment having one or more amino acids omitted from the C-terminus of said $CGRP_{1-37}$, wherein said functional fragment is an antagonist of the human CGRP receptor.

50. The CGRP analogue according to any one of claims 45 to 49, wherein said functional fragment of said CGRP peptide ($CGRP_{1-37}$) is a fragment having at least 7 amino acids omitted from the N-terminus of said $CGRP_{1-37}$, wherein said functional fragment is an antagonist of the human CGRP receptor.

51. The CGRP analogue according to any one of claims 45 to 50, wherein said functional fragment of said CGRP peptide ($CGRP_{1-37}$) is a fragment having one or more amino acids omitted from the central part of said $CGRP_{1-37}$, such as one to ten amino acids omitted from the central part of said $CGRP_{1-37}$, wherein said functional fragment is an antagonist of the human CGRP receptor.

52. The CGRP analogue according to any one of claims 45 to 50, wherein said functional fragment of said CGRP peptide ($CGRP_{1-37}$) is selected from $CGRP_{8-37}$ including human beta $CGRP_{8-37}$ (SEQ ID NO:200) and human alpha $CGRP_{8-37}$ (SEQ ID NO:243),
$CGRP_{12-37}$ including human beta $CGRP_{12-37}$ (SEQ ID NO:244) and human alpha $CGRP_{12-37}$ (SEQ ID NO:245),
$CGRP_{19-37}$ including human beta $CGRP_{19-37}$ (SEQ ID NO:246) and human alpha $CGRP_{19-37}$ (SEQ ID NO:247),
$CGRP_{23-37}$ including human beta $CGRP_{23-37}$ (SEQ ID NO:248) and human alpha $CGRP_{23-37}$ (SEQ ID NO:249), and
$CGRP_{27-37}$ (SEQ ID NO:250),

or a functional variant of any one of SEQ ID NO:200 and SEQ ID NO:243 to SEQ ID NO:250 having one or more individual amino acid substitutions, such as one, two or three individual amino acid substitutions,

such as a functional variant of any one of SEQ ID NO:200 and SEQ ID NO:243 to SEQ ID NO:250 wherein Ala is substituted with Ser at $X_{36}$, and/or wherein Ser is substituted with Pro at $X_{34}$, and/or wherein Lys is substituted with Phe at $X_{35}$,

wherein optionally said functional fragment is N-terminally acetylated,

wherein said functional fragment is an antagonist of the human CGRP receptor.

53. The CGRP analogue according to any one of claims 1 to 47, wherein said analogue is an agonist of the GCRP receptor.

54. The CGRP analogue according to any one of claims 1 to 47, wherein said CGRP peptide ($CGRP_{1-37}$) has the sequence $X_1CX_3TATCVTHRLAX_{14}LLX_{17}RSGGX_{22}X_{23}KX_{25}NFVPTX_{31}VGSX_{35}AF$ (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 CGRP 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,

wherein said N-terminal region 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 analogue is an agonist of the GCRP receptor.

55. The CGRP analogue according to any one of claims 1 to 47 and 54, wherein said CGRP peptide has the sequence ($bCGRP_{1-37}$)
**S**CNTATCVTHRLAGLLSRSGG**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 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 N-terminal region 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 analogue is an agonist of the GCRP receptor.

56. The CGRP analogue according to any one of claims 1 to 47, 54 and 55, wherein said CGRP peptide has a sequence selected from
**H**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (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),
**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (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);
**G**C**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);
**G**CNTATCVTHRLA**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);
**G**CNTATCVTHRLA**H**LLSRSGGMVK**H**NFVPTNVGSKAF (SEQ ID NO:63);
**G**C**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);
**G**C**H**TATCVT**N**RLA**H**LL**A**R**H**GG**I**VK**K**NFVPTNVG**P**KAF (SEQ ID NO:68);
**G**C**H**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:69);
**G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:70);
**G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:71);
**G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:72);
**G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:73);
**G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:74);
**G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:75);
**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:76);
**G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:77);
**G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:78);
**G**C**H**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:79);
**G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:80);
**G**CNTATCVTHRLA**D**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:81);
**G**CNTATCVTHRLA**E**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:82);
**G**CNTATCVTHRLAGLLSRSGGMVK**E**NFVPTNVGSKAF (SEQ ID NO:83);
**G**C**H**TATCVTHRLA**D**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:84);
**G**C**H**TATCVTHRLA**E**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:85);
**G**C**H**TATCVTHRLAGLLSRSGGMVK**E**NFVPTNVGSKAF (SEQ ID NO:86);
**G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGSKAF (SEQ ID NO:87);

**G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGS**R**AF (SEQ ID NO:88); and
**G**CNTATCVTHRLAGLLSRSGGMV**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 thereof 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 N-terminal region 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 analogue is an agonist of the GCRP receptor.

57. The CGRP analogue according to claim 56, 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.

58. The CGRP analogue according to any one of claims 56 and 57, 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 said amino acid sequence.

59. The CGRP analogue according to any one of claims 1 to 47 and 54 to 58, wherein said 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 $X_{37}$; 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 $X_{37}$; such as 6, such as 5, such as 4, such as 3, such as 2, such as 1 individual amino acid substitutions at any one of positions $X_1$, $X_3$ to $X_6$, and $X_8$ to $X_{37}$.

60. The CGRP analogue according to any one of claims 1 to 47 and 54 to 59, wherein said functional variant of any one of SEQ ID NO:1 to SEQ ID NO:89

comprises 1, 2, 3, 4, 5 or 6 individual conservative amino acid substitutions at any one of positions $X_1$, $X_3$ to $X_6$, and $X_8$ to $X_{37}$.

61. The CGRP analogue according to any one of claims 54 to 60, wherein said CGRP peptide comprises 1, 2, 3, 4, 5 or 6 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.

62. The CGRP analogue according to any one of claims 54 to 61, wherein said CGRP peptide 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.

63. The CGRP analogue according to any one of claims 54 to 62, wherein said peptide analogue 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.

64. The CGRP analogue according to any one of claims 54 to 63, wherein said peptide analogue comprises two 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.

65. The CGRP analogue according to any one of claims 54 to 64, wherein said peptide analogue comprises three 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.

66. The CGRP analogue according to any one of claims 54 to 65, wherein said CGRP peptide comprises at least one amino acid substitution individually 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.

67. The CGRP analogue according to any one of claims 54 to 66, wherein said CGRP peptide 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.

68. The CGRP analogue according to any one of claims 54 to 67, wherein said CGRP peptide comprises at least one amino acid substitution selected from $X_{19}$ is His, $X_{14}$ is His and $X_3$ is His.

69. The CGRP analogue according to any one of claims 54 to 68, wherein $X_{10}$ is a negative amino acid selected from Asp or Glu.

70. The CGRP analogue according to any one of claims 54 to 69, wherein $X_1$ is Gly.

71. The CGRP analogue according to any one of claims 54 to 70, 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.

72. The CGRP analogue according to any one of claims 54 to 71, wherein said CGRP peptide 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.

73. The CGRP analogue according to any one of claims 1 to 44 and 53 to 72, wherein said analogue is an agonist of the GCRP receptor with an $EC_{50}$ (nM) value of 16 nM or less; such as 0.01 to 16 nM, such as of 0.1 to 16 nM, such as of 1 to 16 nM, such as 0.01 to 6 nM, such as 0.1 to 6 nM, such as 1 to 6 nM.

74. The CGRP analogue according to any one of claims 1 to 47 and 54 to 73 having a sequence selected from:

**SGS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO: 90);
**RSF-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO: 91);
**RV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO: 92);
**SGSGSGSGS–G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:93);
**PAS**-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:94);
**ES**-SCNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:95);
**PAS-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:98);
**SGSG-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:99);
**RSFG-GCH**TATCVT**N**RLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:100);
**RVG-GCH**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-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:104);
**RSF-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:105);
**SGS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:106);
**SGSG-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:107);
**LLRV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:108);
**SGS-G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:109);
**RSF-G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:110);
**RV-G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:111);

**PAS-G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:112);
**LRV-G**CNTATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:113);
**SGS-G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:114);
**RSF-G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:115);
**RV-G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:116);
**PAS-G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:117);
**LRV-G**CNTATCVTHRLA**H**LLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:118);
**SGS-G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:119);
**RSF-G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:120);
**RV-G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:121);
**PAS-G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:122);
**LRV-G**CNTATCVTHRLAGLL**A**RSGGMVKSNFVPTNVGSKAF (SEQ ID NO:123);
**SGS-G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:124);
**RSF-G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:125);
**RV-G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:126);
**PAS-G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:127);
**LRV-G**CNTATCVTHRLAGLLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:128);
**SGS-G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:129);
**RSF-G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:130);
**RV-G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:131);

**PAS-G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:132);
**LRV-G**CNTATCVTHRLAGLLSRSGG**I**VKSNFVPTNVGSKAF (SEQ ID NO:133);
**SGS-G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:134);
**RSF-G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:135);
**RV-G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:136);
**PAS-G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:137);
**LRV-G**CNTATCVTHRLAGLLSRSGGMV**RK**NFVPTNVGSKAF (SEQ ID NO:138);
**SGS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:139);
**RSF-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:140);
**RV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:141);
**PAS-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:142);
**LRV-G**CNTATCVTHRLAGLLSRSGGMVKSNFVPTNVG**P**KAF (SEQ ID NO:143);
**SGS-G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:144);
**RSF-G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:145);
**RV-G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:146);
**PAS-G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:147);
**LRV-G**CNTATCVT**E**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:148);
**SGS-G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:149);
**RSF-G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:150);
**RV-G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:151);

**PAS-G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:152);
**LRV-G**CNTATCVT**D**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:153);
**SGS-GCH**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:154);
**RSF-GCH**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:155);
**RV-GCH**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:156);
**PAS-GCH**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:157);
**LRV-GCH**TATCVT**N**RLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:158);
**SGS-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:159);
**RSF-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:160);
**RV-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:161);
**PAS-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:162);
**LRV-G**CNTATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:163);
**SGS-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:164);
**RSF-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:165);
**RV-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:166);
**PAS-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:167);
**LRV-GCH**TATCVTHRLA**H**LLSR**H**GGMVKSNFVPTNVGSKAF (SEQ ID NO:168);
**SGS-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:169);
**RSF-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:170);

**RV-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:171);
**PAS-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:172);
**LRV-G**CNTATCVTHRLAGLLSRSGG**L**VKSNFVPTNVGSKAF (SEQ ID NO:173);
**RVG-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:174);
**KVG-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:175);
**GKVG-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:176);
**K-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:177);
**KSF-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:178);
**KSF-G**CNTATCVTHRLAGLLSRSGGMV**R**SNFVPTNVGS**R**AF (SEQ ID NO:179); and
**GKSF-G**CNTATCVTHRLAGLLSRSGGMV**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.

75. The CGRP analogue according to claim 74, wherein said peptide sequence 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

76. The CGRP analogue according to any one of claims 74 to 75, wherein 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.

77. The CGRP analogue according to any one of the preceding claims comprising an intramolecular disulfide bridge between the Cys residue at position 2 ($X_2$) and the Cys residue at position 7 ($X_7$).

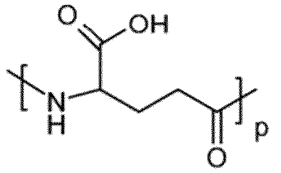
78. The CGRP analogue according to any one of the preceding claims comprising a disulfide bridge with a linker, such as a methylene linker, between the Cys amino acid residue at position 2 ($X_2$) and the Cys amino acid residue at position 7 ($X_7$), such as -S-[$CH_2$]-S.

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

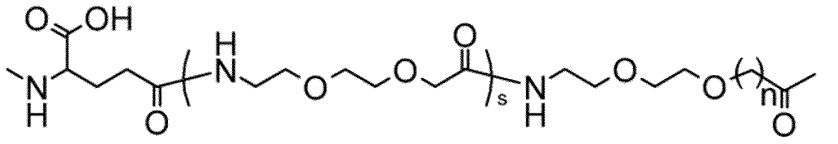
80. The CGRP analogue according to any one of the preceding claims, comprising an acyl group, Z, connected to an amino group of the N-terminal amino acid residue of the peptide analogue.

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

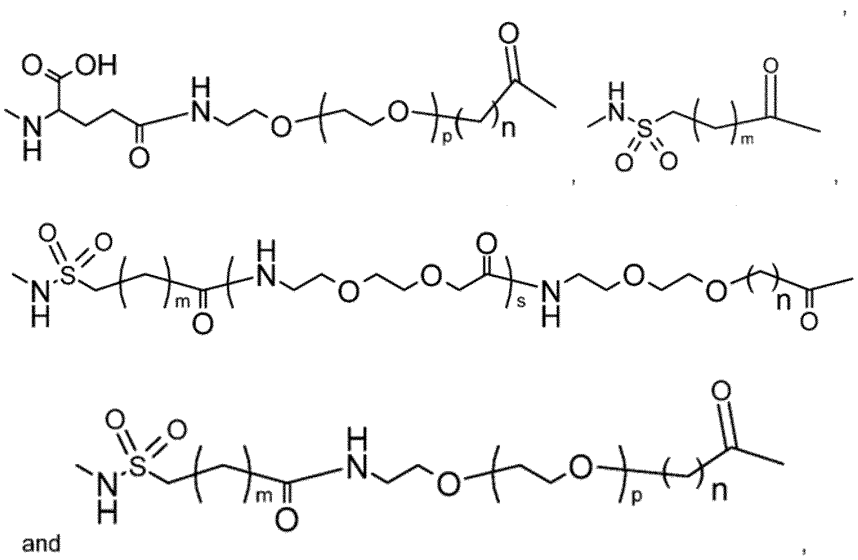
82. The CGRP analogue according to any one of the preceding claims, comprising a linker, Y, selected from:



,



,



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.

83. The CGRP analogue according to any one of the preceding claims, comprising 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.

84. The CGRP 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.

85. The CGRP 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.

86. The CGRP 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 CGRP 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 $X_{-2}$, and the amino group of $X_{-1}$.

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

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

89. 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.

90. The CGRP 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.

91. The CGRP analogue according to any one of the preceding claims, where 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 $CH_3(CH_2)18CO$.

92. The CGRP analogue according to any one of the preceding claims, wherein 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($CH_2$)16CO-isoGlu-AEEA and HOOC($CH_2$)16CO-isoGlu-2AEEA.

93. The CGRP analogue according to any one of the preceding claims, wherein 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.

94. The CGRP analogue according to any one of the preceding claims, wherein 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-gammaGlu and $CH_3$($CH_2$)18CO-gammaGlu.

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

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

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

98. A CGRP 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.