

Calcitonin Gene-Regulated Peptides

Key References

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Overview

Calcitonin-gene related peptide (CGRP), amylin (AMY), adrenomedullin (AM), calcitonin receptor-stimulating peptide (CRSP) and intermedin/adrenomedullin-2 (IMD/AM-2) are structurally related peptides of the same family. They are characterized by a six to seven amino acid ring structure linked by a disulfide bridge and an amidated C-terminus.

CGRP is a 37 amino acid residue peptide derived from the alternative splicing, in a tissue specific manner, of the calcitonin gene and may exist in two forms α and β with similar biological functions. CGRP is widely distributed in both the central and peripheral nervous systems and exhibits a range of biological actions. Structure-activity studies suggest that these effects are mediated by the activation of at least two CGRP receptor subtypes designated as CGRP₁ and CGRP₂. This classification is based on the preferential affinity of the fragment CGRP(8-37) to antagonize the effect of CGRP (CGRP₁), and the agonistic property of the linear analog [Cys(ACM)^{2,7}]hCGRP α to mimic the effect of CGRP (CGRP₂). The use of BIBN4096BS, the first non-peptide CGRP antagonist having subnanomolar affinity for CGRP receptors, has led to the discovery of further functional CGRP receptor heterogeneity in rodent tissues. BIBN4096BS was much less potent at antagonizing the effects of CGRP proposed to be mediated by the CGRP₂ subtype. An orphan receptor originally described as the calcitonin receptor-like receptor (CLR) has been identified as a CGRP receptor. Its association with the single membrane-spanning receptor-activity-modifying protein 1 (RAMP1) is required for this receptor to behave as a CGRP₁ receptor. It also requires the presence of the receptor component protein (RCP) to generate a complete CGRP's response.

AMY is a 37 amino acid peptide isolated from amyloid deposits of human insulinoma and from the pancreas of type II diabetic patients. AMY-like immunoreactivity is detected in peripheral tissues as well as in hypothalamic areas of the rat brain. In the CNS, AMY induces an anorexic effect similar to that of CGRP. [¹²⁵I]-AMY binding sites have been detected in the rat brain and this distribution profile is distinct from that of [¹²⁵I]-CGRP sites suggesting the existence of unique amylin receptors. AC187, a salmon calcitonin derivative, behaves as a competitive amylin receptor antagonist. At the molecular level, it appears that the calcitonin receptor co-transfected with RAMPs generates three amylin receptor subtypes.

AM is a polypeptide of 50 amino acids in length in the rat and of 52 amino acids in human. AM-like immunoreactivity and corresponding mRNA are present in various rat and human tissues. Administration of AM produces biological effects similar to those reported for CGRP. It was thus proposed that these two peptides were acting via a common CGRP-like receptor since the potent vasodilation action and anorexic effect of AM were antagonized by CGRP (8-37). However, several studies have demonstrated that compared with AM, CGRP is 100- to 1000-times less potent at competing for [¹²⁵I]-AM(1-52) and [¹²⁵I]-AM(13-52) binding sites in various assays. Additionally, structure-activity studies revealed that removing the first 21 N-terminal amino acid residues of hAM, just next to the disulfide bridge (hAM(22-52)), resulted in a peptide with antagonist properties. CLR appears to function as an AM receptor when co-expressed with RAMP2. The existence of additional AM receptor subtypes is supported by functional assays using cells cotransfected with CLR and RAMPs.

New peptides have recently been identified and been added to this peptide family. Three porcine CRSPs are related to CGRP but the biological effects of CRSP-1 are mediated through the calcitonin receptor. CRSP-like immunoreactivity and mRNA have mainly been detected in the brain, pituitary and thyroid gland. CRSPs were also identified in dog, cow and horse but not in human and rodents. IMD/AM-2, a 47 amino acid peptide related to AM, is the most recently discovered member of this peptide family. IMD/AM-2-like immunoreactivity and corresponding mRNA are expressed in various tissues including the submaxillary gland, kidney, lung, heart, gastrointestinal system, pituitary gland and hypothalamus, but not in the adrenal gland. Recent studies have demonstrated that IMD/AM-2 acts on CLR/RAMP-like receptors and exerts biological effects similar to those reported for CGRP and AM, such as cardiovascular regulation and decreased food and water intake.

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CURRENTLY ACCEPTED NAME	CGRP ₁	CGRP ₂	AM1	AM2	AMY
CLONED RECEPTOR AND ASSOCIATED PROTEINS	CLR (464 aa) RAMP1 (148 aa) RCP (146 aa)	Not known	CLR RAMP2 (182 aa)	CLR RAMP3 (148 aa)	CTR (516 aa) + RAMP1 known as AMY1 + RAMP2 known as AMY2 + RAMP3 known as AMY3
POTENCY OF ENDOGENOUS HOMOLOGS	CGRP α (C0167) ~ CGRP β (C1044) > IMD/AM-2 = AM (A3830) \geq AMY > CT	CGRP α (C0167) ~ CGRP β (C1044) > AM (A3830) > AMY	AM (A3830) > IMD/AM-2 = CGRP α (C0167) ~ CGRP β (C1044) \geq AMY > CT	AM (A3830) > IMD/AM-2 = \geq CGRP β (C1044) > CGRP α (C0167) \geq AMY > CT	sCT ~ rAMY >> hCT, CGRP and AM ligand selectivity remains to be fully established
PREFERENTIAL AGONIST	Not known	[Cys(ACM) ^{2,7}]-hCGRP	[Mpr ¹⁴]-rAM(14-50)	Not known	AMY
ANTAGONISTS	BIBN4096BS, CGRP(8-37) (C2806), SB-273779	BIBN4096BS, CGRP(8-37) (C2806)	AM(22-52) > CGRP(8-37)	CGRP(8-37) > AM(22-52)	AC187, AC253, AC413, AC512 sCT(8-32) The antagonist preference for each AMY subtype is still to be established
PROTOTYPICAL TISSUE BIOASSAYS	Atrium, pulmonary artery, spleen, SK-N-MC cells	Vas deferens, urinary bladder, liver, Col-29 cells, HCA-7 cells	Vascular smooth muscle, lung	Not known	Skeletal muscle, MCF-7 cells, ovary cell line CHO-K1
SIGNAL TRANSDUCTION MECHANISMS	G _s (cAMP production)	G _s (cAMP production)	G _s (cAMP production)	G _s (cAMP production)	G _s (cAMP production)
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-[Iodohistidyl ¹⁰]-hCGRP α [¹²⁵ I]-hCGRP(8-37)	[¹²⁵ I]-[Iodohistidyl ¹⁰]-hCGRP α	[¹²⁵ I]-AM(1-52) [¹²⁵ I]-AM(13-52)	[¹²⁵ I]-AM(1-52)	[¹²⁵ I]-Amylin [¹²⁵ I]-Salmon calcitonin
TISSUE EXPRESSION	CNS, PNS, cardiovascular tissues, blood vessels, spleen, Vas deferens, lung, adrenal gland	Coronary arteries, Vas deferens, urinary bladder, liver	CNS, PNS, cardiovascular tissues, spleen, Vas deferens, lung, liver, skeletal muscle	Not known	CNS, lung, stomach, spleen, liver, kidney
PHYSIOLOGICAL FUNCTION	Cardiovascular system: regulation of blood pressure, heart rate, respiratory regulation, calcium homeostasis, control of fluid balance: diuresis, natriuresis, inhibition of gastric acid secretion, inflammation, nociception	Not known	Cardiovascular system: regulation of blood pressure (vasorelaxation), heart rate, control of fluid balance: diuresis, natriuresis, angiogenesis: cell growth, regulation of food intake, nociception	Not known	Reduction of food intake, glucose regulation, inhibition of gastric emptying and acid secretion, inhibition of pancreatic enzymes, calcium homeostasis, memory retention
DISEASE RELEVANCE	Migraine, hypertension, pulmonary hypertension, septic shock	Not known	Hypertension, congestive heart failure, pulmonary hypertension, septic shock, renal failure, cerebral ischemia	Not known	Diabetes, anoxeria

Abbreviations

ACM: Acetamidomethyl

AC187: Acetyl-[Asn³⁰, Tyr³²]-salmon calcitonin (8-32)

AM: Adrenomedullin

AMY: Amylin

BH: Bolton Hunter labeled

BIBN4096BS: [r-(r*,s*)]-N-[2-[[5-Amino-1-[[4-(4-pyridinyl)-1-piperazinyl]carbonyl]pentyl]amino]-1-[[3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-4-(1,4-dihydro-2-oxo-3(2h)-quinazoliny)-,1-piperidinecarboxamide

CGRP: Calcitonin gene-related peptide

CLR: Calcitonin receptor-like receptor

CNS: Central nervous system

CTR: Calcitonin receptor

hCT: human Calcitonin

IMD/AM-2: Intermedin/Adrenomedullin-2

PNS: Peripheral nervous system

RAMP: Receptor-activity-modifying protein

RCP: Receptor component protein

SB-273779: N-Methyl-N-(2-methylphenyl)-3-nitro-4-(2-thiazolylsulfanyl)nitrobenzamide

sCT: Salmon calcitonin

h: human

s: salmon

FOOTNOTES