CALCITONIN GENE-RELATED PEPTIDES

BACHEM

LEADING PARTNER IN TIDES
CGRP

Distribution of CGRP

Calcitonin gene-related peptide (CGRP) is a 37 amino acid peptide which belongs to a family of related peptides including calcitonin, amylin, and adrenomedullin. CGRP peptides are mainly localized in sensory and central neurons and have been implicated in a variety of physiological processes such as cardiovascular homeostasis, calcium metabolism, and control of fetoplacental vascular tone. In this brochure we present a selection of our products for CGRP research.

Introduction

α-CGRP and β-CGRP, also known as CGRP I and II, respectively, belong to the calcitonin family of peptides comprising such members as calcitonin, amylin, calcitonin receptor-stimulating peptide, adrenomedullin 1, and intermedin. The N-terminally truncated analog of intermedin-53 is also known as adrenomedullin 2. At their N-terminus, these peptides have in common a characteristic disulfide loop structure, generally formed by six to seven amino acids. The 37 amino acid peptides α-CGRP and β-CGRP are encoded by different genes on chromosome 11. α-CGRP mRNAs are derived from the calcitonin/CGRP gene by alternative tissue specific splicing of the primary RNA transcripts whereas β-CGRP is encoded by a separate gene with high homology to the calcitonin/CGRP gene. The amino acid sequences of CGRP peptides are well conserved among species, as illustrated in Scheme 1. In humans, α- and β-CGRP differ by three amino acids, in rats, by two amino acids. Both peptides show similar biological activity. In dogs, pigs and numerous other species, variants of the CGRP-like calcitonin receptor-stimulating peptide (CRSP) are expressed in place of β-CGRP. The peptides are similar in their biological activities.

Scheme 1: Amino acid sequences of various CGRP peptides. Positions with high variance as well as amino acids, which differ from the majority of sequences, are highlighted. High variance was arbitrarily assigned to positions, where the major amino acid is present in less than 70% of all sequences.

Distribution of CGRP

CGRP expression is widely distributed in the central and peripheral nervous system. In the brain, it is particularly concentrated in the hypothalamus and in certain nuclei of the brainstem. In the periphery, CGRP is mainly detected in sensory afferents projecting to the spinal cord, in motor neurons at the neuromuscular junctions and in nerve fibers associated with the vasculature. In capsaicin-sensitive sensory neurons, CGRP co-localizes with substance P and other
neuropeptides, in the motor endplate with acetylcholine.

**Physiological Functions**

On the basis of pharmacological studies several physiological functions of CGRP have been suggested. Due to its potent vasodilatory action and its inotropic and chronotropic effects, CGRP is likely to play a role in cardiovascular homeostasis. Furthermore, it influences feeding and digestion since it has been shown to decrease food intake, gastric secretion, and intestinal motility. Based on its ability to modulate substance P signaling, an additional function of CGRP in nociception has been proposed. Additionally, CGRP might be important in processes such as control of fetoplacental vascular tone, regulation of calcium metabolism and insulin secretion, acetylcholine receptor synthesis, peripheral nerve regeneration, and neurogenic inflammation.

**CGRP Receptors**

CGRP receptors have been identified in several tissues, including brain, cardiovascular, endothelial, and smooth muscle tissue. Based on early pharmacological studies, the existence of two classes, CGRP1 and CGRP2 receptors, has been described. According to this historical classification CGRP1 receptors are more sensitive to the antagonistic properties of α-CGRP (8-37) (4013696, 4034544) whereas CGRP2 receptors are more responsive to the agonistic CGRP analogs, (Cys(Acm)2,7-α-CGRP (human) (4039880) and (Cys(Et)2,7)-α-CGRP (human) (4039888). Recent studies have shown that the previously cloned G protein-coupled orphan receptor, named calcitonin receptor-like receptor (CRLR), can interact with members of a new family of three single-transmembrane domain receptor activity-modifying proteins (RAMPs). Interaction with RAMP1 resulted in a CGRP receptor, which is sensitive to α-CGRP (8-37), whereas binding to RAMP2 and RAMP3 led to receptors for adrenomedullin known as AM1 and AM2 receptors, respectively. The AM2 receptor showed considerable affinity for CGRP. Besides their essential role in regulating ligand specificity, RAMPs are also required for membrane trafficking of CRLR. Recently, a receptor component protein (RCP) of the CRLR/RAMP1 complex was described. RCP is an intracellular protein which is highly conserved between species and might be required for G protein-coupled signal transduction.

**CGRP as Cardioprotectant**

CGRP is also present in the heart. Infusion of the peptide induces vasodilation and

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**CGRP Receptor**

CGRP binds to a receptor complex formed by the calcitonin receptor-like receptor (CRLR) and one of three single transmembrane receptor activity modifying proteins (RAMP1). RAMP1 is essential for membrane trafficking of CRLR and for regulation of ligand specificity. An intracellular receptor component protein (RCP) is required for coupling to the cellular signal transduction pathway.
CGRP generates positive inotropic and chronotropic effects, which can be blocked by its antagonist, truncated CGRP 8-37. In case of myocardial ischemia, CGRP is released by cardiac adrenergic cells. In response, an increase of plasma CGRP can be detected. The peptide is involved in protecting the heart against ischemia-reperfusion injury. Unfortunately, the short half-life of CGRP limits its therapeutic use in the treatment of cardiovascular disorders, so long-acting CGRP agonists have gained interest. They also show potential in the management of hypertension. Stabilization of peptidic agonists could be achieved by conjugation of long-chain fatty acids. N-terminally lipidated α-CGRP analogs have been developed and tested in murine models of hypertension and heart failure. Long-time administration of such an analog in vivo eventually resulted in a reduction in food intake and body weight. The modified peptide hormone induced secretion of GLP-1. As an alternative approach for tackling the low metabolic stability of the peptide, controlled-release formulations of α-CGRP for treatment of ischemia due to a myocardial infarction have been developed.

CGRP and Migraine
CGRP has been detected in pericranial vascular nerves and the trigeminal ganglion. The neuropeptide is a potent dilator of cerebral and dural vessels, and it is involved in meningeal dural vasodilation. Migraine is possibly caused by activation of the human trigeminal system and the release of CGRP. Increased cranial CGRP levels have been measured in patients suffering from episodic or chronic migraine. Infusion of the peptide can trigger migraine attacks. Hence, CGRP antagonists could be effective in the treatment of the disease, which afflicts about 15 to 18% of the population worldwide. The recurrent pulsating strong headache and other symptoms turn migraine into a leading cause of disability and a global health problem. Women carry a higher risk of developing the disease than men. A number of small-molecule CGRP receptor antagonists have been evaluated as antimigraine drugs. Clinical studies with the dipeptide mimic olcegepant (BIBN-4096 BS) gave promising results, but the development was discontinued due to low oral bioavailability, rapid clearance and poor physical properties of the compound. Good results were obtained with the D-lysine lactame derivative telcagepant (MK-0974), an antagonist with improved oral bioavailability, in clinical phase III. Its development was discontinued in 2011 due to liver toxicity. More recently, clinical trials have been conducted with atogepant (MK-8031, AGN 241689) (phase II/III), ubrogepant (MK-1602) and rimegepant (BMS-927711) (both phase III, treatment of acute migraine). As an alternative to CGRP receptor antagonists, anti-CGRP antibodies have been developed for the management of both episodic and chronic migraine and cluster headache. As of 2018, three of them, erenumab (AMG-334), fremanezumab (TEV-48125), and galcanezumab (LY2951742), gained FDA approval for the prevention of migraine attacks. Erenumab was approved as well by the European authorities. A further antibody awaiting approval, eptinezumab (ALD403), is still evaluated in clinical studies. Fremanezumab and galcanezumab bind to α- and β-CGRP with about the same affinity. The situation for eptinezumab is not yet clear. Erenumab targets the CGRP receptor instead of the ligand. Application of such antibodies could be contraindicated in case of cerebral and cardiovascular ischemia, which are alleviated by endogenous CGRP due to its cardioprotective activity. In the worst case, CGRP blockade could transform a transient mild ischemic event into a full-blown infarct. Moreover, administration of CGRP antagonists could mitigate other forms of chronic pain such as the joint pain and inflammation afflicting patients suffering from knee arthritis.

Prospects
CGRP has proven to be a molecule which is involved in diverse physiological processes. Future research will contribute to a better understanding of its various properties, the heterogeneity of its receptors, and its physiological interactions with other molecules.
MIGRAINE THERAPY AND CGRP RECEPTOR

Migraine therapy and CGRP receptor, illustration. Monoclonal antibodies (red) being used to block the calcitonin gene-related peptide (CGRP) receptor (blue). The calcitonin gene-related peptide (CGRP, yellow) is designed to bind to its receptor (blue). This occurs on the membranes of neurons and smooth muscle cells in cerebral (brain) blood vessels, activating a signal cascade through G-proteins (dark blue, bottom) that leads to a dilatation of brain blood vessels (vasodilatation). This is a factor in disorders such as migraines. Blocking the CGRP receptor reduces the number of migraine attacks.

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CALCITONIN GENE RELATED PEPTIDES (CGRP)

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CALCITONIN GENE-RELATED PEPTIDES (CGRP) AND FRAGMENTS

CGRP (chicken)
4030455
ACNTATCVTHRLADFLSRSGGV-KNNFVPTNVGSKAF-NH₂
(Disulfide bond)

α-CGRP (human)
4013281
ACDTATCVTHRLAGLLSRSGGV-VKNNFVPTNVGSKAF-NH₂
(Disulfide bond)

Biotinyl-α-CGRP (human)
4038212
Biotinyl-ACDTATCVTHRLAGLLSRSGGV-VKNNFVPTNVGSKAF-NH₂
(Disulfide bond)

(Cys(Acm)²⁻)⁻α-CGRP (human)
4039880
AC(Acm)DTATCVTHRLAGLLSRSGGV-VKNNFVPTNVGSKAF-NH₂
(Disulfide bond)

Tyr-α-CGRP (human)
4030456
YACDTATCVTHRLAGLLSRSGGV-VKNNFVPTNVGSKAF-NH₂
(Disulfide bond)

α-CGRP (mouse, rat)
4025897
SCNTATCVTHRLAGLLSRSGGV-VKDNFVPTNVGSEAF-NH₂
(Disulfide bond)

Biotinyl-α-CGRP (mouse, rat)
4039845
Biotinyl-SCNTATCVTHRLAGLLSRSGGV-VKDNFVPTNVGSEAF-NH₂
(Disulfide bond)

α-CGRP (8-37) (human)
4013696
VTHRLAGLLSRSGGVVKNNFVPNTVGS-KAF-NH₂

α-CGRP (8-37) (mouse, rat)
4034544
VTHRLAGLLSRSGGVVKDNFVPTNVG-SEAF-NH₂

Tyr-α-CGRP (23-37) (mouse, rat)
4015557
YVKDNFVPTNVGSEAF-NH₂

(Tyr²⁻)⁻α-CGRP (27-37) (canine, mouse, rat)
4037183
YVPTNVGSEAF-NH₂

α-CGRP (29-37) (canine, mouse, rat)
4039883
PTNVGSEAF-NH₂

β-CGRP (human)
4015500
ACNTATCVTHRLAGLLSRSGGVMKSN-FVPTNVGSKAF-NH₂
(Disulfide bond)
RELATED
PRODUCTS

For more detailed information please go to shop.bachem.com
Calcitonin (chicken)
4030323
CASLSTCVLGLSQELHKLQTYPTRD- VGAGTP-NH₂
(Disulfide bond)

Calcitonin (eel)
4011079
CSNLSTCVLGLSQELHKLQTYPTRD- VGAGTP-NH₂
(Disulfide bond)

(Des-Cys¹,cyclo(Ser²-Asu⁷))-Calcitonin (eel) acetate salt
4025810
c(SNLST-Asu)VLGKLSQELHKLQTYPTRD- VGAGTP-NH₂

Calcitonin (human)
4014409
CGNLSTCLGLTTYDTQDFNKFHTF- PQTAVGAP-NH₂
(Disulfide bond)

Calcitonin (porcine)
4030443
CSNLSTCVLSAYWRNFLNFRFSGMGF- GPETP-NH₂
(Disulfide bond)

Calcitonin (rat)
4030404
CGNLSTCLGLTTYDTQDLNKFHTFPQT- SIGVGAP-NH₂
(Disulfide bond)

Calcitonin (salmon I)
4033011
CSNLSTCVLGLSQELHKLQTYPTNTGS- GTP-NH₂
(Disulfide bond)

Calcitonin (8-32) (salmon I)
4037182
VLGKLSQELHKLQTYPTNTGSGTP-NH₂

Acetyl-(Asn³⁰,Tyr³²)-Calcitonin (8-32) (salmon I)
4034543
Ac-VLGKLSQELHKLQTYPTNTGSNTY- NH₂

Calcitonin C-Terminal Flanking Peptide (human)
4013739
DMSSDLERDHRPHVSMPQNAN

Calcitonin C-Terminal Flanking Peptide (human)
4102089
DMSSDLERDHRPHVSMPQNAN

Calcitonin N-Terminal Flanking Peptide (human)
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