CALCITONIN GENE-RELATED PEPTIDES

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CALCITONIN GENE-RELATED PEPTIDES (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. It exists in two isoforms α-CGRP (or CGRP I) and β-CGRP (or CGRP II) which are very similar in their biological activities but are encoded by different genes. 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. Receptors for this family of peptides belong to the seven transmembrane G-protein-coupled receptors linked to the activation of adenylate cyclase. Their interaction with receptor activity modifying proteins (RAMPs) is essential for membrane trafficking and for conferring ligand specificity. In this brochure we present a selection of its 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, and adrenomedullin. Recently, the cloning of intermedin-1 added an additional member to this family. 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. In humans α- and β-CGRP differ by 3 amino acids, in rat, by one amino acid. In their biological activities they are very similar.

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 ionotropic and chronotropic effects, CGRP is likely to play a role in cardiovascular homeostasis. Furthermore, it influences feeding and digestion since it has 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 also 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) (H-9895, H-4924) whereas CGRP2 receptors are more responsive to the agonistic CGRP analogs, (Cys(Acm)²⁷)α-CGRP (human) (H-5766) and (Cys(Et)²⁷)α-CGRP (human) (H-5784). 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.

**Therapeutic Implications**

Given the multitude of physiological and pathophysiological effects of CGRP, modulations of its properties represent potential therapeutic interventions in a variety of disease states including cardiovascular disorders and neurogenic inflammation. Clinical trials have indicated that the vasodilatory effect of CGRP might be beneficial in the treatment or prevention of Raynaud’s disease, hypertension, angina pectoris and heart failure. Since CGRP is rapidly metabolized, longer acting CGRP agonists are needed for long-term treatment. CGRP antagonists, for their part, might be useful in the treatment of migraine which involves the activation of the trigeminal system and CGRP-evoked dilatation of cranial vessels. The non-peptidic CGRP antagonist BIBN4096BS (Boehringer Ingelheim) is presently under clinical investigation to assess the importance of CGRP in migraine headache.

**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.
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NEUROPEPTIDE BINDING TO HEART MUSCLE CELL

Neuropeptide binding to a heart muscle cell, composite fluorescence deconvolution micrograph. Stacked images showing calcitonin gene-related peptide (CGRP, red) binding to the contractile fibres (myofibrils, white) of a binucleate cardiomyocyte. The cell’s two nuclei can be seen in blue. Neuropeptides have been found to play a much larger role than initially thought in the control of calcium levels in organs other than the brain.

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CALCITONIN GENE RELATED PEPTIDES (CGRP)

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CALCITONIN GENE-RELATED PEPTIDES (CGRP) AND FRAGMENTS

CGRP (chicken)
H-3352
ACNTATCheetHRLADFLSRSGGV-VKNNFVPNTVGSKAF-NH₂
(Disulfide bond)

α-CGRP (human)
H-1470
ACDTATCVHRLAGLLRSRGGV-VKKNFVPNTVGSKAF-NH₂
(Disulfide bond)

α-CGRP (mouse, rat)
H-2265
SCNTATCVHRLAGLLRSRGGV-VKDNFVPNTVGSEAF-NH₂
(Disulfide bond)

Biotinyl-α-CGRP (human)
H-5688
Biotinyl-ACTATCVHRLAGLLRSRGGV-VKNNFVPNTVGSKAF-NH₂
(Disulfide bond)

Biotinyl-α-CGRP (mouse, rat)
H-5684
Biotinyl-SCNTATCVHRLAGLLRSRGGV-VKDNFVPNTVGSEAF-NH₂
(Disulfide bond)

α-CGRP (8-37) (human)
H-9895
VTHRAGLLRSRGVVKNNFVPNTVGSKAF-NH₂

α-CGRP (8-37) (mouse, rat)
H-4924
VTHRAGLLRSRGVVKDNFVPNTVGSEAF-NH₂
(Disulfide bond)

α-CGRP (8-37) (mouse, rat)
H-4924
VTHRAGLLRSRGVVKDNFVPNTVGSEAF-NH₂
(Disulfide bond)

α-CGRP (9-37) (human)
H-8885
SGGVVKNNFVPNTVGSKAF-NH₂

Acetyl-α-CGRP (19-37) (human)
H-8890
Ac-SGGVVKNNFVPNTVGSKAF-NH₂

α-CGRP (23-37) (human)
H-8895
VKNNFVPNTVGSKAF-NH₂

Tyr-α-CGRP (23-37) (mouse, rat)
H-2270
YVKDNFVPNTVGSEAF-NH₂

(Tyr²⁷)-α-CGRP (27-37) (canine, mouse, rat)
H-5504
YVPTNVGSEAF-NH₂

α-CGRP (29-37) (canine, mouse, rat)
H-5748
PTVGSEAF-NH₂

α-CGRP (30-37) (canine, mouse, rat)
H-5748
TVGSEAF-NH₂

α-CGRP (31-37) (canine, mouse, porcine, rat)
H-5748
VGSEAF-NH₂

α-CGRP (32-37) (canine, mouse, porcine, rat)
H-5742
VGSEAF-NH₂

β-CGRP (human)
H-6730
ACNTATCVHRLAGLLRSRGGMVKNFVPNTVGSKAF-NH₂
(Disulfide bond)
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