Reviews of Literature
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ADRENOMEDULLIN RECEPTORS AND FUNCTIONS OF THIS NOVEL PEPTIDE IN IMPLANTATION

K.R.Padma[1] , Josthna[2] and K.R.Don[3]

[1]Department of Biotechnology, Sri Padmavathi Mahila University(Research Scholar)
[2]Assistant Professor in Sri Padmavathi Mahila University
[3]Doctor in Saveetha Dental college

Abstract:

Adrenomedullin is a novel vasodilatory peptide isolated first in 1993. It was originally isolated from human phaeochromocytoma from adrenal glands of Zona glomerulosa region. This plueripotent hormone increases when implantation occurs and during late gestation decreases. Many promising opportunites for prevention and treatment of aberrant pregnancies made through the introduction of receptors and to manage its clinical treatments in early stage of prenanacy. Adrenomedullin (ADM), Calcitonin Gene related peptide (α- and β-CGRPs),Calcitonin, Amylin and Adrenomedullin -2/intermedin (IMD/ADM) are the six receptors present on the Plasma membrane of the cell. Adrenomedullin contributes to angiogenesis, functions as a growth factor, and helps regulate vascular tone during rat gestation**.** With this understanding the review summarizes a clear cut view of Adrenomedullin receptor and its pathway.

Key words: Adrenomedullin, Calcitonin, Amylin, Preeclampsia, Phaeochromocytoma, Intermedin, fetal resorption,RAMP1,RAMP2,RAMP3.

INTRODUCTION

Adrenomedullin is an alpha amidated peptide and has 52 amino acids,whereas rat has 50 aminoacids. Adrenomedullin is found in bovine, porcine, Canine, humans and rats.The human ADM gene consists of 4exons and maps to chromosomal11.The adrenomedullin is derived from preproadrenomedullin precursor which is of 185 aminoacids.This precursor give rise to active cleavage products.They are PAMP-20,PAMP-12,Adrenotensin and Prodepin. In the year 1993 kitamura et al (1), and his colleagues were the first persons to discover this novel peptide from adrenal medulla, from a pregnant women suffering from phaeochromocytoma which has shown to increase the cAMP levels in a platelet assay. Phaeochromocytoma are tumours derived from adrenal medulla and thus this novel peptide was named as adrenomedullin(2).

Adrenomedullin and tissues it is present:

Adrenomedullin is potent,endogenous vasodilator peptide synthesized and secreted by diverse locations such as columnar epithelium, some gland cells. Neurons of pulmonary parasympathetic nervous system, vascular endothelial cells, chondrocytes, monocytes, macrophages, cardiac ventricular cells, vascular smooth muscle cells and by numerous organs systems including adrenal glands kidneys, brain and pituitary gland. Adrenomedullin is present in human brain in higher concentrations(7). Adrenomedullin like peptides found in echinoderms(starfish), chondrichthyes (shark), Amphibia (necturus).

Adrenomedullin structure:

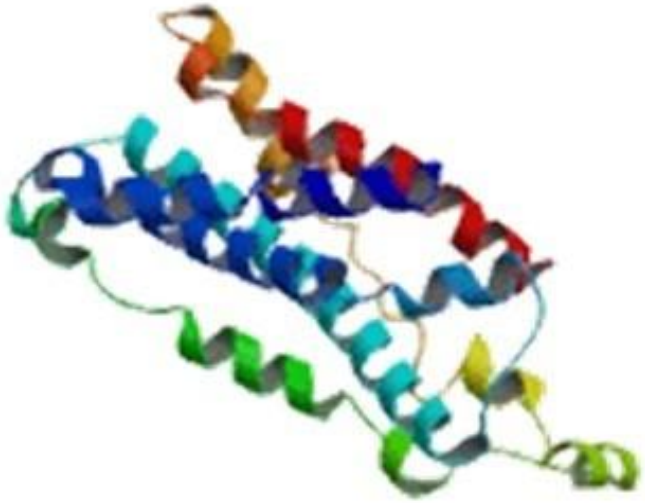
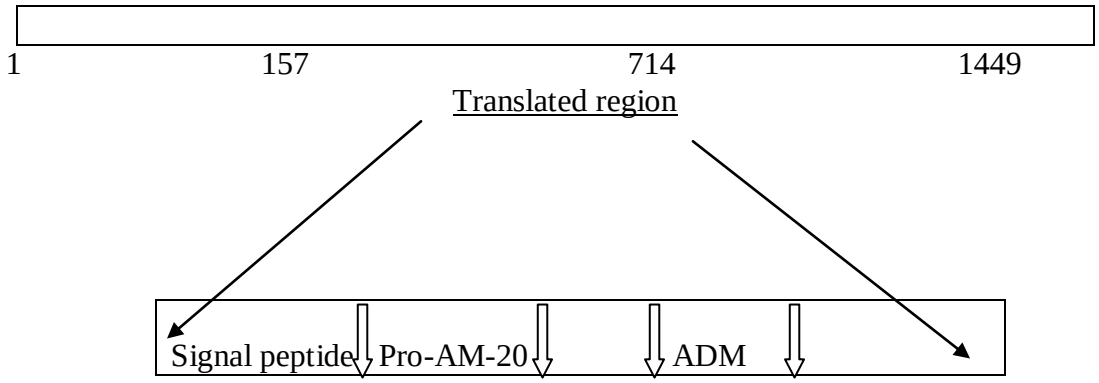


Fig:1 Structure of Adrenomedullin

Human adrenomedullin (hAM) cDNA was cloned and sequenced,its having 1.6kb long message which inturn encodes for a predicted 185 amino acid. Human adrenomedullin gene sequenced and contains 3introns and 4 exons on chromosome 11. Adrenomedullin have structural homology with calcitonin gene related peptide family. This family includes Calcitonin, amylin, Adrenomedullin2/intermedin. They elevate cAMP generation in platelets.CGRP is a 37 amino acid neuropeptide , Calcitonin is a 32 amino acid peptide ,Amylin is a 37 amino acid peptide. Adrenomedullin consists of 52 amino acids and is alpha amidated peptide with intramolecular disulphide bond forming a ring structure of six residues and a carboxy terminal amidated residue(4).

AM mRNA(1.6kb)



Preproadrenomedullin(185aminoacids) 20 74 125 164

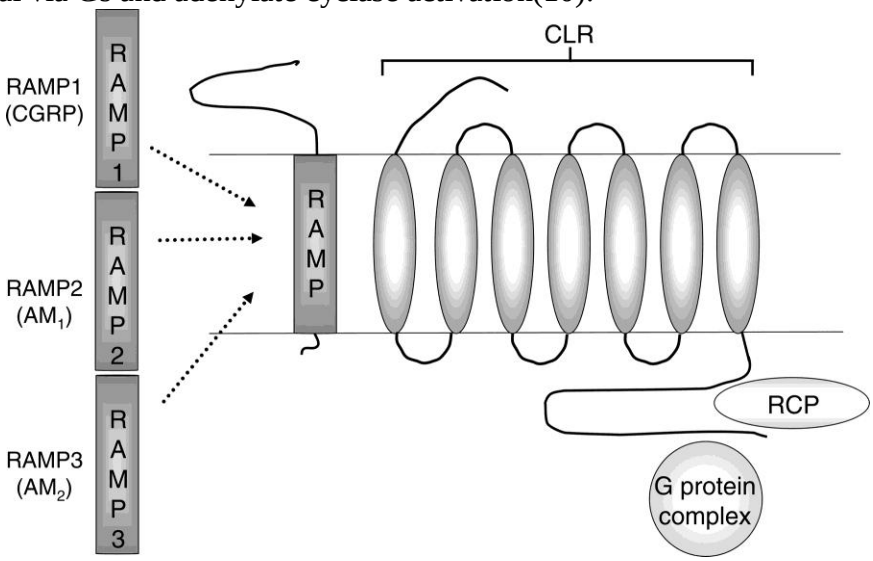
The preproadrenomedullin precursor is 185 aminoacids long. The precursors give rise to cleavage products,they are Adenotensin,PAMP-20, PAMP-12, and prodepin. Adrenomedullin is synthesized and secreted in many cell types. Amylin is also a 37Amino acid peptide present on chromosome 12 instead of chromosome11(5).

Calcitonin gene related peptide family:

The calcitonin family of peptides comprises of six known members. Although homology at the level of primary sequence is weak(6). There are stronger relationships between the secondary structure of the peptides. They all have a six amino acid ring structure and exception is Calcitonin which has seven amino acid ring structure close to their N-termini. The peptides are widely distributed in various organs and tissues and induce multiple biological effects including potent vasodilation. Mainly Vasodilation function is shown by calcitonin gene related peptide and adrenomedullin. Amylin shows reduction in nutrient intake and calcitonin shows decreased bone resorption. Due to their structural similarities, these peptides share some biological activities, that is they interact with similar G-Protein coupled receptors(GPCRs)(6).

Receptor structure:

Although the pharmacology of these receptors is distinct. They are both represented in molecular terms by the type II family G-Protein-coupled receptor , Calcitonin-receptor like receptor (CRLR).The specificity here is defined by co-expression of receptor-activity-modifying proteins(RAMPs).CGRP1 receptors are represented by CRLR and RAMP1,and specific adrenomedullin by receptors CRLR and RAMP2 or RAMP3(9). Here we will be discussing how CRLR/RAMP2 related to adrenomedullin binding. The type II family G-Protein coupled receptors, signal via Gs and adenylate cyclase activation(10).



Structure of Receptors

The CRLR bind with CGRP with high affinity if it was co-transferred with another novel protein called RAMP1.RAMP1 is a single transmembrane protein of 148 amino acids.RAMP family has three isoforms. RAMP1, RAMP2, RAMP3. RAMP1 binds to CGRP, whereas RAMP2 or binds to adrenomedullin receptors(2).

Comparison of adrenomedullin sequences from different Mammalian species and comparison of rat adrenomedullin with other rat calcitonin family peptides.

h, human: p, porcine; b, bovine; m, murine; c, canine; r, rat; AM, adrenomedullin;

AMY, amylin;CT, calcitonin. Dashes (-) denote deleted residue with respect to human

adrenomedullin.

hAM YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVAPRSKISPQGY-NH2

pAM YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDGVAPRSKISPQGY-NH2

bAM YRQSLNNFQGLRSFGCRFGTCTVQKLAHQIYHFTDKDKDGSAPRSKISPQGY-NH2

mAM YRQSMN--QGSRSNGCRFGTCTFQKLAHQIYQLTDKDKDGMAPRNKISPQGY-NH2

cAM YRQSMNNFQGPRSFGCRFGTCTVQKLAHQIYQFTDKDKDGVAPRSKISPQGY-NH2

rAM YRQSMN--QGSRSTGCRFGTCTMQKLAHQIYQFTDKDKDGMAPRNKISPQGY-NH2

rαCGRP SCNTATCVTHRLAGLLSRSGGVVKDNFVPTNVGSEAF-NH2

rβCGRP SCNTATCVTHRLAGLLSRSGGWKDNWPTNVGSKAF -NH2

rAMY KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY-NH2

rCT CSNLSTCMLGTYTQDLNKYHTFPQTSIGVGAP-NH2

ADRENOMEDULLIN IN IMPLANTATION:

Adrenomedullin is a potent endogenous vasodilator peptide synthesized by and secreted by various organs. We noticed the important role of adrenomedullin in placental and fetal growth development in rat as well as human pregnancy. Adrenomedullin (AM) is a 52 amino acid peptide and in rat is 50 amino acid peptide and shares 25% amino acid sequence homology with calcitonin gene related peptide. The adrenomedullin gene and its protein products are highly conserved across species,including human,rat,porcine and bovine.The adrenomedullin has a unique six amino acid residue ring structure and C-terminal amidation similar to CGRP(8) and amylin The six –membered amino acid ring structure (amino-acid 16-21) connected by one disulfide bond between(between cys16 and cys21) was found to be responsible for vasodilator activity in human(h) AM. Thus how we found that adrenomedullin was responsible for Vasodilation and during early pregnancy found to increase the plasma levels and decrease during late gestations.

CONCLUSION:

Thus adrenomedullin and its receptors we are aware of, each receptor has its own unique role. Each has its own action. We are concerned with vasodilation during pregnancy,which is done by adrenomedullin bound with calcitonin receptor like receptor and isoform RAMP2,which is ultimately responsible for increase in plasma levels of adrenomedullin during early pregnancies and the level of adrenomedullin decreases during late gestation(3)(12).

The Type II GPCRs generally signal through Gs and adenylate cyclase(4). The adrenomedullin receptors follow the use of a constitutively active Gs and the protein kinase A inhibitor.Mitogen-activated protein kinases (MAPKs) are responsible in control of cell growth and can be activated in cells by Platelet derived growth factor (PDGF).cAMP can inhibit or stimulate depending upon the cell type. Thus much of work in still on going to see how to increase the fetal growth and prevent abortion during early pregnancy.

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K.R.Padma
Department of Biotechnology, Sri Padmavathi Mahila University(Research Scholar)