ADRENOUREDULLIN ANTAGONIST INFUSION CAUSES UTEROIMPLANTATION GROWTH RESTRICTION

K. R. Padma and Dr. P. Josthna*

Assistant Professor, Department of Biotechnology, Sri Padmavati Mahila Visvavidyalayam (Women’s University) Tirupati- 517 502 Andhra Pradesh, India.

ABSTRACT

The Adrenomedullin peptide hormone has a potent vasorelaxant activity. This novel peptide has shown to be almost a ubiquitous peptide, with the number of tissues and cell types synthesizing adrenomedullin. The pattern of ADM level and gene expression of ADM, its receptor components from early pregnancy has been studied in our present work. In our previous papers we have studied whether antagonism of endogenous adrenomedullin in rats during early gestation period emanated in diminished uterus and implantation growth and found whether this causes through induction of apoptosis. Rats on gestational day 2 were implanted subcutaneously with osmotic (Alzet) minipumps delivering 125 and 250µg rat/day of AM22-52 and were killed on gestational day 9. This review summarizes a clear cut view of Adrenomedullin receptor and significance of ADM in circulation during gestation period.

KEYWORDS: Adrenomedullin, Osmotic mini pumps, Implantation, Uterus, Gestation.

INTRODUCTION

A Novel multiregulatory ubiquitous peptide was discovered when a group of scientists in Japan were screening for a panel of peptides extracted from a pheochromocytoma from adrenal glands. They were looking for biological activity by testing whether these peptides could raise platelet cAMP levels. The scientists exploited a peptide with this activity, purified and sequenced it and termed it “Adrenomedullin” as it was derived from the adrenal medulla.\[1\] The first paper on adrenomedullin, published by (Kitumara et al., 1993). A new field of endocrine and exocrine research had begun. The growth of significance in
adrenomedullin has been exponential, with more than 630 papers published in this field to date including a number of reviews.[2–7] This review aims to summarize the present state of our knowledge of adrenomedullin biology and to focus on issues that are currently unresolved, with an indication of likely areas for future research.

Circulating adrenomedullin
After the initial report of levels of adrenomedullin circulating in plasma[8], several research groups have developed several assays to measure plasma adrenomedullin levels. These levels are essential to sustain pregnancy. The adrenomedullin has a unique six amino acid residue ring structure and C-terminal amidation similar to CGRP[9] and amylin. The six –membered amino acid ring structure connected by one disulfide bond between (between cys16 and cys21) along with receptor modifying protein (RAMP) was found to be responsible for vasodilator activity in human ADM as shown in Figure 1. Intracellular cAMP generation by ADM and other CT supergene family has been recognized as a major signal transduction for their biological effects.

Figure: 1 Model for functional adrenomedullin receptor

Intrauterine growth restriction
Numerous rodent models have provided evidence for the necessity of ADM in normal fetal growth. Yallampalli et.al. and penchalneni et.al., found that antagonism of ADM during pregnancy emanated in intrauterine growth restriction (IUGR), abnormal placental vascularization, and increased fetal resorption, in the rat.[10–11] In the present study, the ADM-antagonist22-52 was profusely infused during Days 2–8 of gestation and on Day 9, we have
sacrificed the animals to observe uteroimplantation site which showed fetal resorption\[12\] and in modest the uterus and implanted weights have been reduced considerably. This proves ADM hormone significance in gestation period.

ADM structure and relation with CGRP family

Figure: 2 Structure of Adrenomedullin

Human adrenomedullin (hAM) cDNA was cloned and sequenced and found to be having 1.6kb long message which in turn encodes for a predicted 185 amino acid. Human adrenomedullin gene sequenced and established which contains 3 introns and 4 exons and maps to 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.\[13\]

ADM in uteroimplantation growth

In our present study, we assessed the role of ADM in the regulation of uteroimplantation growth during pregnancy. There are a multitude of genetic, physiologic and environmental factors that must all work in perfect harmony throughout pregnancy to produce the so-called “miracle” that is a healthy, full-term baby.\[14\] Any aberration in this process may result in pregnancy complications, which can include implantation failure, miscarriage, fetal growth restriction, gestational diabetes, preeclampsia (PE) and preterm birth. Thus there is currently major interest and effort in the field, to expand our understanding of the factors that contribute to healthy versus unhealthy pregnancies. To demonstrate how an environmental changes affects during early pregnancy, an antagonist of ADM 22-52, was continuously infused through osmotic minipumps beginning on gestational day 2 in rats. These animals
received either 125 or 250 µg rat/day of AM\textsubscript{22-52} or vehicle only and were sacrificed on day 9 of gestation to assess uterus and implant weights as shown in figure-3.

![Figure: 3 Osmotic(Alzet) mini pumps](image)

**CONCLUSION**

Adrenomedullin has a range of biological actions including vasodilatation, cell growth, regulation of hormone secretion and antimicrobial effects. Its mechanism of action, however, represented in the previous work of Yallampalli et.al. and Penchalaneni et.al., cAMP is the second messenger in the majority of adrenomedullin actions. Since its discovery as a potential vasodilator, there have been extensive analyses revealing pleiotropic effects of AM. Recent discovery of CRLR/RAMP system that confers ligand selectivity for ADM and CGRP facilitates the understanding of new-facet of ADM/CGRP receptors and their signaling pathways. Development of receptor antagonists highly selective for ADM with higher raffinity and their application in experimental and clinical settings helped us in the understanding of complex pharmacology of ADM in vivo. Here, we have emphasized that both maternal and fetal-derived ADM is important for establishing and maintaining a successful pregnancy.\textsuperscript{[15]}

**Funding**

These studies were supported by DST-SERB, New Delhi for providing financial support in project by releasing funds timely **Project ref. no.: SB/SO/AS-080 /2013.**

**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

Not applicable.
Ethics approval and consent to participate
Animal studies were performed as per institute animal ethics committee regulations and approved by the committee (Reg. No. 1677/PO/a/12/CPCSEA/SPMVV-IEC/2014).

REFERENCES

