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## Decreased Placental Adrenomedullin May Play Role in Preeclampsia

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**Abstract:** Adrenomedullin (AdM) is a novel peptide that elicits a long-lasting vasorelaxant activity. It is expressed in several tissues, including adrenal medulla, heart, lung, kidneys, and cultured vascular smooth muscle cells. Also in large amounts, it is present in amniotic fluid and cord blood. The aim of this study was to assess placental AdM secretion in preeclampsia. Placental tissues were collected from seven preeclamptic patients and ten healthy gravidas. Tissue concentration of rat AdM was measured by using reverse-phase high performance liquid

chromatography (Cecil 1100). Mann Whitney U test was used for statistical significance. Significance was set at  $p < 0.05$ . AdM concentrations were  $144.1 \pm 3.20$  pmol/ml and  $178.7 \pm 4.4$  pmol/ml in preeclamptics and healthy gravidas respectively. This difference was significant ( $p < 0.05$ ). These data suggest that placental synthesis of AdM in preeclampsia is reduced, and low production of AdM may be responsible for placental pathology in preeclampsia.

**Key Words:** Preeclampsia, adrenomedullin, placental pathology.

### Introduction

Preeclampsia is a major cause of maternal and neonatal morbidity and mortality. Despite the ubiquity of the disease and its public health impact, no comprehensive mechanism has been established. The most pathologically significant change in preeclampsia is thought to be arteriolar constriction in general organ systems. Blood pressure is controlled by a complex network of various regulation systems because its homeostatic balance is crucial to the maintenance of vital activity. Among these systems, regulation of vascular tone has been shown to be a major system controlling blood pressure (1,2). AdM is a novel peptide that was first isolated from human pheochromocytoma and it elicits a long-lasting vasorelaxation (3). Several studies suggest that AdM participates in the regulation of blood pressure by different mechanisms (3,4). The immunohistologic distribution of AdM in human tissues has shown the presence of AdM-immunoreactive cells in pancreatic islets, the gastrointestinal neuroendocrine system, and the anterior pituitary gland, indicating that adrenomedullin-positive cells are widely distributed in the

endocrine and neuroendocrine systems where they may play a role in the control of systemic and local circulations and in humoral secretion (5). It was recently isolated from second-trimester human amniotic fluid, amniotic membranes of term pregnancies, and umbilical cord blood (6,7). However, any roles that AdM plays in fetal, placental, or maternal physiology have yet to be elucidated. In this study, we investigated whether or not AdM secretion is altered in the placental unit of those with preeclampsia.

### Materials and Methods

Tissues were collected from 10 healthy gravidas and 7 preeclamptic patients with singleton pregnancies in the third trimester following delivery by elective cesarean section. Samples were immediately stored at  $-30^{\circ}\text{C}$  until analysis. For adrenomedullin measurement, the specimens were minced on ice and then homogenized with a polytron (Kinematica GmbH, Littau, Switzerland) mixer at  $4^{\circ}\text{C}$ , and the homogenate was centrifuged at  $24000g$  for 30 minutes. The supernatant of the extract was loaded onto a Supel-Cosil C-18 column (Sigma, CA),

which was preequilibrated with 1 mol/L acetic acid, and the absorbed materials were eluted with 4 mL of 50% acetonitrile containing 0.1% trifluoroacetic acid. Reverse phase high pressure liquid chromatography was used for measurement. Mann Whitney U test was used for statistical analysis and statistical significance was set at  $p < 0.05$ .

## Results

There was no difference between preeclamptic and healthy gravidas in terms of mean age and gestational age ( $24.3 \pm 3.1$  vs  $26.0 \pm 1.2$  and  $35.9 \pm 2.0$  vs  $37.1 \pm 1.7$ ,  $p > 0.05$ ) respectively. Mean  $\pm$  SE adrenomedullin concentrations were  $144.1 \pm 3.2$  pmol/ml and  $178.7 \pm 4.4$  pmol/ml in preeclamptics and healthy gravidas respectively. This difference was significant ( $p < 0.05$ ).

## Discussion

We found AdM concentration to be markedly lower in placental tissue in preeclamptic patients, than in healthy gravidas. This implies that placental secretion of AdM is decreased in preeclampsia. Recent studies have shown that during pregnancy AdM levels gradually increase and the level of AdM is always higher than in nonpregnant women (8-10). The physiologic significance of highly increased AdM synthesis during pregnancy has yet to be established. It has been demonstrated that AdM exerts natriuretic action on peripheral vasculature and kidneys to control fluid and electrolyte homeostasis and affects angiotensin II (11). Thus it is possible that AdM is involved in the process of adaptation of the vascular system to pregnancy.

Morinoni et al. (8) demonstrated that AdM concentrations detected in fetoplacental tissues is comparable to those found in human adrenal medulla. They showed that immunoreactive AdM staining in the placenta was localized primarily in extravillous trophoblast cells and in scattered areas of the syncytiotrophoblast, although in most villi these results appeared negative. Endothelial cells in chorionic plate and in primary villi vessels also stained for AdM. It was found that arterial and venous umbilical plasma concentrations of AdM did not differ in uncomplicated pregnancies, indicating that in normal state there is neither production nor net clearance of AdM in the placenta (12). AdM,

which is present in amniotic fluid, amnion membranes, and the placenta, may play a role in the modulation of fetal and maternal blood pressure and placental perfusion through its well-known vasoactive properties (13,14).

AdM may affect endocrine secretion (15) and immune response to microbial invasion (16). It was also found to play a role as a modulator of cell growth (17) and to enhance the availability of nutrients to support growth by increasing blood flow (18). These same attributes of AdM in tumor biologic features may also be vital in pregnancy. The failure of normal implantation and development of the placenta may be associated with abnormal fetal growth, including IUGR and preeclampsia. AdM stimulates DNA synthesis and cell proliferation of Swiss 3T3 fibroblasts, acting by means of elevation of intracellular cyclic adenosine monophosphate (19), and inhibits fetal calf serum-stimulated proliferation in cultured rat vascular smooth muscle cells in a paracrine fashion (20). Abnormal immune activation has been suggested as a contributor to the development of preeclampsia. Activated neutrophils and increased plasma interleukin-12 were reported in preeclampsia (10,21,22). From this point of view, one can argue that decreased AdM levels may have deleterious effects as an immunomodulator in preeclampsia. These data are of particular importance in that low levels of placental AdM in preeclampsia may be an explanation for the development of hypertension and IUGR in preeclampsia. Recently, it was reported that plasma AdM was not different in preeclamptic and healthy gravidas, but placental AdM was higher in the preeclamptic group (23). In another study, placental AdM was found to be lower in the preeclamptic rat model (24). Since there are conflicting results in the literature, further studies need to be carried out.

In conclusion, the placental secretion of AdM is itself defective in these patients, and this may play an important role in the development of hypertension and IUGR in preeclampsia. Further research should be done to elucidate the pathophysiologic role of this peptide in pregnancy.

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