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REVIEW ARTICLE

ROLE OF ADRENOMEDULLIN IN HUMAN BODY

Nahida Tabassum* and Saima Rasool

Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar, Kashmir, J&K, India-190006.

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***Corresponding author:**
n.tabassum.uk@gmail.com

ABSTRACT

Adrenomedullin (AM), discovered in 1993, is a 52-amino acid vasoactive peptide with multi-functions associated with pheochromocytoma (a tumour arising from adrenal medulla). It is widely distributed in human tissues, especially in cardiovascular and endocrine tissues and is metabolized via aminopeptidase action. It has two specific receptors formed by the calcitonin-receptor-like receptor (CALCRL) and receptor activity-modifying protein (RAMP) 2 or 3 known as AM_1 and AM_2 receptors, respectively. In addition, it has appreciable affinity for the calcitonin gene-related peptide ($CGRP_1$) receptor. At present adrenomedullin is believed to function through combinations of the CALCRL and RAMP2 complexes, as well as CGRP receptors. It is the most potent endogenous vasodilatory peptide found in the body. Its effects include increasing the tolerance of cells to oxidative stress and hypoxic injury and angiogenesis. It shows a positive influence in disorders such as hypertension, myocardial infarction, chronic obstructive pulmonary disease and other cardiovascular diseases. It acts as a local regulator of bone growth and has marked beneficial effects in the host defense mechanism. It increases blood flow in the adrenal gland, causing a gradual release of catecholamines. It is expressed and accumulated in epithelial surfaces (skin, lung, genitourinary tract, digestive system and others) and body fluids (plasma, sweat, milk, saliva, amniotic fluid and others) thereby illustrating its role as an antimicrobial agent. It has a protective role during sepsis and is rendered as an attractive molecule for the treatment of septic shock.

INTRODUCTION

A group of scientists in Japan were screening a panel of peptides extracted from a pheochromocytoma and were looking for biological activity by testing whether the peptides could raise platelet cAMP levels. During this research, they found a new regulatory peptide with this activity, purified and sequenced it and termed it "Adrenomedullin" as it was derived from the adrenal medulla. Adrenomedullin is a ubiquitously expressed alpha-amidated 52-amino acid vasoactive peptide that belongs to

the amylin/ calcitonin family of molecules and was discovered in 1993. It was isolated from a human pheochromocytoma (a tumour arising from adrenal medulla) (Kitamura, 1993). This peptide hormone is expressed in normal adrenal medulla, but is widely distributed throughout the body including lungs, kidney tissues, endothelial cells, brain and embryonic skeleton (Ichiki, 1994). Besides controlling fluid-electrolyte homeostasis, it is a potent vasodilator and can inhibit pituitary ACTH secretion (Kitamura, 1994). It circulates in picomolar concentrations in both rats and humans**.** Recently a second peptide AM2 has been recognised, exhibiting similar functions (Fujisawa *et al.,* 2004).

Structure and Synthesis of Adrenomedullin

Structure: The human adrenomedullin gene is localized to a single locus on Chromosome 11 with 4 exons and 3 introns. It initially codes for a 185-amino acid precursor peptide preproadrenomedullin, which gives rise to several biologically active cleavage products including an inactive 53-amino acid adrenomedullin, e PAMP, adrenotensin and AM95-146. Mature human adrenomedullin is activated to form a 52 amino acid, 6-amino acid ring that shares moderate structural similarity to the calcitonin family of regulatory peptides (calcitonin, CGRP and amylin) (Kitamura, 1993). It is having a single disulfide bridge between residues 16 and 21 and with an amidated tyrosine at the carboxy terminus and shows some homology with calcitonin gene-related peptide (CGRP) (Cheng Hai-Ling Margaret, 2007) and has therefore been added to the calcitonin / CGRP/ amylin peptide family. Circulating adrenomedullin consists of both amidated (mature) and the glycated form (inactive), with the latter comprising the major form (85%).

Synthesis: Adrenomedullin is synthesized and secreted by most tissues of the body, including columnar epithelium, some gland cells, neurons of the pulmonary parasympathetic nervous system, vascular endothelial cells, chondrocytes, monocytes and macrophages, cardiac ventricular cells (myocytes and non-myocytes), vascular smooth muscle cells and by numerous organ systems, including adrenal gland, kidney, brain, pituitary gland and cardiovascular tissues (Hinson *et al.,*2000). Although the gene encoding adrenomedullin is very highly expressed in the adrenal gland, in both zona glomerulosa and the adrenal medulla (Kapas, 1998)**,** there is considerable evidence against the adrenal as the major source of circulating peptide. High concentrations of the protein are observed also in human plasma and in the human brain suggesting that it may act as a neurotransmitter, neuromodulator or neurohormone in humans. Since the discovery that adrenomedullin gene is more highly expressed in endothelial cells than even in the adrenal medulla (Sugo, 1994)**,** this peptide has been regarded as a secretary product of the vascular endothelium, together with nitric oxide (NO) and endothelin. The expression of adrenomedullin transcript increases significantly under hypoxic conditions. This involves regulation by hypoxia-responsive elements localized in the adrenomedullin promoter region (Garayoa *et al.,* 2000). The adrenomedullin gene is a target also for negative regulation by the myc transcription complex.

Regulation of Adrenomedullin Synthesis: Adrenomedullin production has been shown to be regulated, by a variety of substances, in a variety of cell types. It is secreted by the human adrenocortical carcinoma cell line SW-13 and subject to complex regulation by cytokines and other agents. Forskolin and 8-bromo-cAMP suppress production and gene transcription of adrenomedullin (Hattori *et al.,* 1999)**.** Thrombin, VIP (vasoactive intestinal peptide) and IFN-gamma also inhibit its production, while angiotensin - 2, endothelin -1, bradykinin, substance P, adrenalin, dexamethasone, hydrocortisone, aldosterone, phorbol esters and fetal calf serum stimulate its production. Retinoic acid and thyroid hormones also markedly increase adrenomedullin production (Minamino *et al.,* 1995). IL1, TNF and bacterial lipopolysaccharides additively stimulate production of adrenomedullin in vascular smooth muscle cells. Thyroid hormone and phorbol ester increases adrenomedullin and endothelin-1 secretion but to a lesser extent. IFN-gamma inhibits adrenomedullin secretion from endothelial cells,

whereas oxidized LDL stimulates it (Isumi *et al.,* 1998).

Metabolism: Mature adrenomedullin is metabolized initially via metalloproteases to yield adrenomedullins 8–52, 26–52, and 33–52, followed by an aminopeptidase action to yield adrenomedullins 2–52, 27–52, and 28–52 (Lewis LK, 1997). The plasma half-life of adrenomedullin has been reported to be 22.0 ± 1.6 min with a MCR of 27.4 ± 3.6 ml/kg·min and with an apparent volume of distribution of 880 ±150 ml/kg (Meeran, 1997). It has been suggested that the lung may be a major site of adrenomedullin clearance in man.

Receptors of Adrenomedullin

Adrenomedullin has two specific receptors formed by the calcitonin-receptor-like receptor (CALCRL) and receptor activity-modifying protein (RAMP) 2 or 3 complexes. These are known as AM_1 and AM_2 receptors, respectively. In addition, adrenomedullin has appreciable affinity for the $CGRP_1$ receptor, composed of CALCRL and RAMP1.

a) **AM_1 Receptor:** The AM_1 receptor has a high degree of selectivity for adrenomedullin over CGRP and other peptides. $AM_{22–52}$ is an effective antagonist at this receptor.
b) **AM_2 receptor:** AM_2 receptor shows less specificity for adrenomedullin, having appreciable affinity for ßCGRP. $CGRP_{8–37}$ is either equipotent or more effective as an antagonist than $AM_{22–52}$, depending on the species from which the receptor components are derived. βCGRP might be able to activate both $CGRP_1$ and AM_2 receptors and adrenomedullin could activate AM_1 and AM_2 receptors as well as $CGRP_1$ receptors.

Current peptide antagonists are not sufficiently selective to discriminate between these three receptors. Unlike the classical one ligand-one receptor notion of receptor signalling, the interaction of both CALCRL and RAMP at the membrane is required for adrenomedullin to mediate its action. The outcome of adrenomedullin stimulation of its receptor is the cellular production of both cyclic AMP (cAMP) and nitric oxide production. Adrenomedullin seems to have little affinity for receptors for the other two members of the peptide family, calcitonin and amylin (Disa, 1998).

Physiological Functions of Adrenomedullin

Adrenomedullin is commonly identified as a vasodilator that has a remarkable range of actions varying from regulating cellular growth and differentiation, through modulating hormone secretion to antimicrobial effects.

1) Vascular Actions

Adrenomedullin is a circulating hormone and may act as local autocrine and /or paracrine vasoactive hormone. It has hypotensive and vasodilator activity and is thought to play a significant role in cardiovascular and renal homeostasis, mediating vasodilatory and natriuretic properties through the second messenger cAMP, nitric oxide and the renal prostaglandin system**.** Intravenous infusion of adrenomedullin results in a potent and sustained hypotension mainly via NO generation in the vasculature (Hirata, 1995) and is comparable to that of CGRP. Acute or chronic administration of adrenomedullin results in a significant decrease in total peripheral resistance accompanied by a fall in blood pressure. This is concomitant with a rise in heart rate, cardiac output and stroke volume (Khan, 1997). Adrenomedullin lowers vascular resistance in lung, heart, kidney and adrenal gland. Plasma concentrations of adrenomedullin are increased in cardiovascular disease in proportion to the degree of hemodynamic impairment. Plasma adrenomedullin levels in heart failure and in subjects with acute myocardial infarction, have been shown to provide independent prognostic information (Lainchbury, 2001). Experiments with antisense oligonucleotides support a physiologic role for adrenomedullin in the central regulation of sodium homeostasis.

2) Endocrine Actions

Adrenomedullin has significant effects on the endocrine system.

i) The pituitary: Adrenomedullin inhibits basal ACTH secretion. It also inhibits corticotrophin-releasing hormone (CRH)-stimulated ACTH secretion, but does not block the

ability of CRH to stimulate cAMP accumulation in these cells. This suggests that adrenomedullin exerts its effect through an adenylyl cyclase-independent mechanism and also suggests a role in regulating the hypothalamic-pituitary-adrenocortical axis. Increased serum levels of adrenomedullin have been observed also in patients with Cushing's syndrome due to pituitary adenoma or adrenal tumor, with levels normalizing after surgical treatment (Letizia *et al.,* 2000).

ii) Adrenal gland: Like other regulatory peptides present in the adrenal gland adrenomedullin affects the secretory activity of the adrenal cortex. It acts through specific adrenomedullin receptors and stimulates zona glomerulosa cells to produce aldosterone. In addition, it has been reported that CGRP and adrenomedullin exert opposite effects on aldosterone secretion (Hinson, 1998). Adrenomedullin causes an increase in perfusion medium flow rate and in adrenal blood flow. It can stimulate corticosterone secretion and is abundant in adrenal medullary cells (Kapas, 1999).

iii) Reproductive effects: Adrenomedullin has important regulatory roles in reproductive tissues. It is present throughout the female reproductive tract / system. The plasma levels of adrenomedullin are elevated in normal pregnancy and may be involved in the process of adaptation of the vascular system to pregnancy. The presence of adrenomedullin in placenta and fetoplacental tissues (Marinoni 1998) supports a role for adrenomedullin in control of vascular tone at the local level to regulate uteroplacental-fetal circulation. Since it is synthesized in and secreted from vascular endothelial cells, it may play a role as an antiproliferative factor for these cells in a paracrine fashion (Kano *et al.,* 1996).

iv) The pancreas: Adrenomedullin attenuates and delays the insulin response to oral glucose challenge, resulting in initial elevated glucose levels. The vasodilatory effect of adrenomedullin may also have some influence on insulin secretion by elevating pancreatic perfusion rate, which is yet to be proved. However, the existence of a constitutively inhibitory tone in pancreatic islets may play a role in the homeostasis of this organ (Martínez *et al.,* 1996).

3) Growth and development

Adrenomedullin is an autocrine growth factor for human endometrial endothelial cells and is thus involved in endometrial angiogenesis. It is a potent mitogen for Swiss 3T3 cells and stimulates DNA synthesis in synergy with insulin (Withers *et al.,* 1996). In normal and malignant skin, adrenomedullin and the L1 receptor are detected and adrenomedullin increases ^{3}H-thymidine uptake. It also stimulates DNA and cAMP synthesis in human oral keratinocytes. In human normal glial cells and glial cell tumors, adrenomedullin suppresses cell growth and increases intracellular cAMP (Yeung, 1996). Growth of human and rat astrocytomas and human glioblastomas, as well as cultured glioblastoma-derived cell lines, is inhibited by adrenomedullin (Takahashi, 1997). In addition to the possible antiproliferative effects of adrenomedullin, it may also inhibit coronary artery smooth muscle cell migration, perhaps with the two effects combining to inhibit vascular remodeling. It has also been shown to be angiogenic in the chick chorio-allantoic membrane assay and to increase human umbilical vein endothelial cell number (Zhao, 1998). It also has been proposed as an important factor in embryogenesis and differentiation and as an apoptosis survival factor for rat endothelial cells (Kato, 1997).

4) Renal effects

Circulating adrenomedullin can also affect renal functions. Adrenomedullin administration has been shown to have no effect on heart rate or mean arterial blood pressure, but increases renal blood flow (RBF), urine output and urinary Na^{+} excretion in a dose-dependent manner, indicative of direct preglomerular and postglomerular arteriolar effects (Ebara, 1994). Intravenous administration increases Na^{+} excretion without an increase in urine flow or creatine clearance. It has been shown that neutral endopeptidase (NEP) can potentiate the renal natriuretic and diuretic actions of intrarenal adrenomedullin infusion (Lisy, 1998). Adrenomedullin is secreted from renal tubular cell lines and its secretion is stimulated by arginine vasopressin (Sato *et al.,* 1998). It is found in the conditioned medium of cultured mesangial and

glomerular epithelial cells. Its expression is upregulated by TNF-alpha. It also has a role in protecting the kidney glomeruli from inflammatory reactions or immune injuries and in the endocrine function of the kidney. It elevates plasma renin levels, a response thought to be secondary to the hypotensive action of adrenomedullin. In the absence of changes in perfusion pressure or renal nerve activity, it stimulates intrarenal renin release.

5) Other peripheral effects

i) Gastric function: Adrenomedullin has been shown to have profound effects on gastrointestinal motor and secretory functions. Intravenous injection of adrenomedullin (150–600 pmol) decreases gastric emptying of a non-calorific meal in a dose-dependent manner. Peripheral infusion inhibits both basal and pentagastrin- and 2-deoxy-D-glucose-stimulated gastric acid secretion (Rossowski, 1997). In contrast, a bolus intravenous injection stimulates gastric acid output due to increases in the volume of secretion and elevated pepsin levels.

ii) Bone: Adrenomedullin has been shown to be mitogenic for osteoblastic cells and to promote bone growth. Bone remodeling is a complex process of coordinated resorption and formation of bone, which is regulated by systemic hormones and by local factors. The co-expression of adrenomedullin and adrenomedullin receptors in osteoblasts, suggests that adrenomedullin may function as a local regulator of bone growth (Cornish, 1997). It also increases protein synthesis *in-vitro* and the area of mineralized and unmineralized bone *in-vivo* suggesting that adrenomedullin might play a paracrine regulatory role in skeletal growth throughout life.

iv) Lung: Adrenomedullin is released by sub populations of human pulmonary artery smooth muscle cells and inhibits growth and release of endothelin in other cells that do not express adrenomedullin. It may thus function as a paracrine mediator in the inhibition of pulmonary vascular remodeling (Upton *et al.,* 2001). In addition to causing pulmonary vasodilatation, adrenomedullin inhibits bronchoconstriction induced by histamine or acetylcholine. This suggests there may be a relevant role for the increase in circulating levels of adrenomedullin seen during acute attacks of asthma (Kohno, 1996). The adrenomedullin-relaxant response of the vasculature may also provide a protective role in the pulmonary circulation of patients with pulmonary hypertension (Nishikimi, 1997). Adrenomedullin may also have an anti-inflammatory role in the lung. Macrophages secrete neutrophil chemoattractants in response to chemotaxis as part of the inflammatory process, particularly in the lung. It significantly inhibits alveolar macrophage release of neutrophil chemoattractants in response to lipopolysaccharide, in a dose-dependent manner (Kamoi, 1995).

v) Innate immunity/mucosal defense: Neutrophils are usually the first cells arriving to inflammatory sites and represent cardinal cellular effectors of the innate host response. Adrenomedullin is produced by neutrophils and significantly potentiates accumulation of this cell type in skin through an IL-1ß-dependent mechanism. The inhibitory potential of adrenomedullin on neutrophil migration has also been proposed in the context of ischemic brain injury. It is a proinflammatory and anti-inflammatory cytokine (Wong,, 2005) that potently suppress LPS-induced TNF-α production on macrophages. It up-regulates the production of the anti-inflammatory cytokine IL-6 in nonstimulated and LPS-stimulated macrophages (Tilg, 1997). Up-regulation of IL-6 and down-regulation of TNF-α supports its role as an anti-inflammatory factor that suppresses the progression of inflammation. It also has antimicrobial properties against both Gram-positive and Gram - negative bacteria isolated from skin, oral cavity, respiratory tract and the gut. The concentration of adrenomedullin required to kill / inhibit bacterial growth is higher than those levels found in the circulation. It also is an attractive molecule for the treatment of septic shock.

6) CNS effects

Adrenomedullin and its receptors exist in the CNS and its cellular components. Focal brain ischemia is the most common event leading to stroke in

humans and a role for adrenomedullin in this condition has been suggested. Infusion of adrenomedullin (1 µg/kg/min) attenuates the reduction in regional blood flow after middle cerebral arterial occlusion (MCAO) and decreases the degree of ischemic brain injury. It also has a role in preventing ischemic brain injury by increasing collateral circulation. Intra-cerebroventricular (icv) injection of adrenomedullin causes a dose-dependent reduction in feeding and has also been shown to prevent reserpine-induced gastric ulcers in a dose-related manner (Clementi G, 1998). Intra-cerebroventricular injection administration of high doses of adrenomedullin provokes hypertension.

The temporal aspects of CNS-induced hypertension by adrenomedullin parallel those seen after administration of angiotensin II (Saita M, 1998 suggesting that there is a common mechanism underlying the hypertensive action of both these peptides in the brain. For example, phentolamine blocks the actions of both adrenomedullin and angiotensin II in the CNS, lending further support for adrenomedullin and angiotensin II to act within the brain to stimulate sympathetic nervous system function. The central hypertensive actions of adrenomedullin may be cardio protective in that it acts to protect against major cardiovascular collapse such as events encountered during sepsis.

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