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Adrenomedullin and its clinical significance: A review

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Abstract
Adrenomedullin is a novel peptide hormone, abundantly found in the adrenal medulla, this accounts the name adrenomedullin. This peptide is a member of the calcitonin gene-related peptide family that include calcitonin, amyline and intermedin. Its production is up-regulated by several factors such as oxidative stress, pro-inflammatory cytokines, angiotensin II, hypoxia, hyperglycemia, natriuretic peptide and aldosterone. Also the potent effects of AM on cell migration, growth, and apoptosis (programmed cell death) have led to the hypothesis that AM may play a key role in tumor growth and metastasis. AM is a multifunctional peptide hormone that can exert many important and interrelated biological functions under both normal and disease conditions like atherosclerosis, septic shock, cardiac failure, renal failure, bronchial asthma, diabetes and neoplasm.

Keywords: Adrenomedullin, apoptosis, calcitonin gene-related peptide, neoplasm

1. Introduction
Adrenomedullin (AM), a peptide hormone that is abundantly found in the adrenal medulla, therefore this accounts for the name adrenomedullin and was discovered by [1], extracted from pheochromocytoma in humans by monitoring the elevated 3' 5' cyclic adenosine monophosphate (cAMP) production in platelets. It forms a ring structure by 52 amino acid residues held by one intra-molecular disulfide bond. This peptide is classified as a member of the calcitonin gene-related peptide (CGRP) superfamily, which includes calcitonin, calcitonin gene related peptides (CGRP), amyline and intermedin. High level of AM is present in the adrenal medulla and circulating AM is most abundant in vascular wall [2]. AM is produced in several tissues like kidney, lung, and heart and its production is up-regulated by several factors such as oxidative stress, pro-inflammatory cytokines, angiotensin II, hypoxia, hyperglycemia, natriuretic peptide and aldosterone. AM have a hypotensive, vasodilator, paracrine / apocrine effect. AM is also an angiogenic factor that is induced by hypoxia and can alter the permeability of vascular endothelial cells. Also the potent effects of AM on cell migration, growth, and apoptosis (programmed cell death) have led to the hypothesis that AM may be a key player in tumor growth and metastasis [3]. AM may also contribute to blood volume regulation through its natriuretic and diuretic functions in the kidney and its effects on central nervous system control of thirst and salt appetite [4]. AM is highly expressed in the skin and oral mucosa, and this expression pattern has been linked to its potent antimicrobial effect [5]. As mentioned above AM is a multifunctional peptide hormone that can exert many important and interrelated biological functions under both normal and disease conditions.

2. Clinical significance of adrenomedullin
2.1. Atherosclerosis
In the atherosclerotic plaque, macrophage produces tumor necrosis factor alpha (TNF-alfa). This production of TNF-alfa stimulus the AM production. Adrenomedullin's action on vascular tone and its inhibitory effects on smooth muscle vascular cells may indicate a future use of this substance as an anti-atherosclerotic treatment [6].

2.2. Septic shock
Acute cardio-circulatory failure during septic shock could also imply adrenomedullin. High AM levels have been measured in the lipopolisaccharide endotoxic shock animal model and it has been suggested that the potent vasodilatory effect of the substance could contribute to shock pathogenesis [7].

2.3. Cardiac failure
Patients with cardiac failure show elevated adrenomedullin plasma levels that are directly correlated with severity of the disease. In acute myocardial infarction, AM levels rise to a fivefold compared to normal values. In patients with MI complicated by cardiac failure, AM levels may rise even more significantly. Elevation of AM levels, like that of ANP, in myocardial infarction and cardiac failure, could represent a compensatory mechanism to the excessive vasoconstriction that follows these pathological events. In this way cardiac function could be ameliorated through a modulation of vascular tone characterized particularly by reduction of the preload and the postload [7].

2.4. Renal failure
In renal failure, AM levels are significantly elevated, probably due to a reduced renal clearance of the substance similarly to what takes place for other low weight polypeptides like insulin and parathormone (Parlapiano *et al*., 1999) [7].

2.5. Bronchial asthma
In hypoxic chronic obstructive pulmonary disease and bronchial asthma high plasma AM levels have been reported. Adrenomedullin plasma levels are also higher during acute asthma attacks compared to stable asthma disease. The cause of this elevation is not known. It seems possible that AM's bronchodilatatory action is a reaction to elevated catecholamine levels present during asthma crisis [7].

2.6. Hepatic cirrhosis
Adrenomedullin plasma levels rise during hepatic cirrhosis and may be they could play a role in the pathogenesis of the altered haemodynamic and electrolyte conditions present in this disease [7].

2.7. Neoplasm
AM was originally purified from human pheochromocytoma, an adrenal tumor (Kitamura *et al*., 1993). Subsequent studies have shown that AM and its receptors are expressed in many types of tumor cells (fig 1). In addition, AM exerts mitogenic effects on some types of tumor cells. These findings suggest the possibility that AM acts as an autocrine/paracrine growth factor in tumors [3].

The role of hypoxia and inflammatory cytokines in regulation of AM expression and secretion by tumour cells *in vivo* has been suggested. Adrenomedullin promotes formation of xenografted tumours by stimulation of autocrine growth and survival of tumour cells and through paracrine effects on surrounding vessels. Possible intracellular signalling mechanisms underlying effects of AM in tumour microenvironment (in endothelial, vascular smooth muscle (VSMC) and tumour cells) suggest its potential role in tumorigenesis, resistance to chemotherapy and tumour progression.

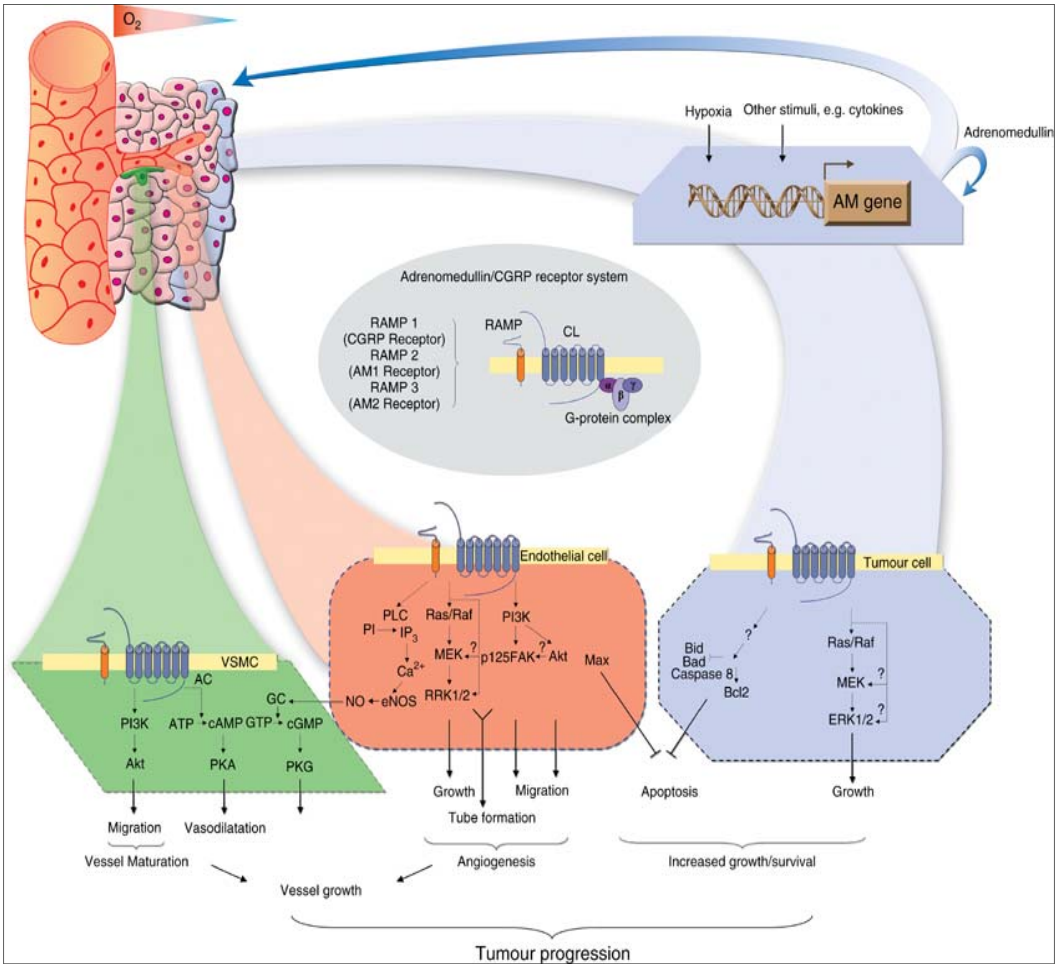

Fig 1: Role of adrenomedullin in tumour progression. AC= Adenylate cyclase; GC= Guanylate cyclase; PKA= Protein kinase A, PKG= Protein kinase-G, PLC= Phospholipase C, MEK= Mitogen-activated protein kinase kinase; ERK= Extracellular signal-regulated kinase (also termed MAPK).

2.8. Diabetes

AM inhibits insulin release after an oral glucose load. Therefore, it can be expected that AM contributes to diabetes and even leads to the development of diabetic complications. Diabetes is characterized by hyperglycemia. It is resulted from dysregulation of insulin secretion or peripherial resistance. Diabetes mellitus causes retinopathy, neuropathy, nephropathy, and atherosclerosis. These complications are the results of prolonged hyperglycemia, altered metabolic pathways and non-enzymatic glycation of proteins. There have been advances in the understanding of the relationship between AM and diabetes. Plasma AM level is elevated in patients with poorly controlled diabetes than in normal subjects, which suggests a direct effect of glucose on AM release. The effect of hyperglycemia on ADM expression is mediated through protein kinase C in vascular smooth muscle cells.

Several studies have been carried out in an attempt to explain the rise in plasma AM level and its implications in diabetic complications. One study showed that plasma AM level was elevated in type 2 diabetes but did not correlate with glucose level in circulation [8].Instead, increased ADM level was correlated with various diabetic complications, and the severity of diabetic nephropathy and retinopathy. Plasma ADM levels were mainly associated with renal failure and retinopathy in type 1 diabetes. On the other hand, plasma ADM levels in type 2 diabetes patients are linked to a wider range of complications. The rise may be attributed to acute hyperinsulinemia, oxidative stress and endothelial damage. This stimulus increases ADM production from pancreatic islets and vascular endothelium. Such a rise may represent a causative factor triggering the onset of disease and insulin resistance [2].

3. Conclusion

Adrenomedullin has a range of biological actions including vasodilatation, cell growth and regulation of hormone secretion, natriuresis, and antimicrobial effects. Its mechanism of action, however, remains unclear. cAMP is the second messenger in the majority of adrenomedullin actions, but other systems must be involved. The role of nitric oxide remains to be elucidated, as does the mechanism of the growth-stimulatory effect of cAMP.

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5. References

1. Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H *et al*. Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. Biochemical and Biophysical Research Communications, 1993; 192:553-560.
2. Wong HK, Tang F, Cheung TT, Cheung BMY. Adrenomedullin and diabetes. World Josurnal of Diabetes. 2014; 5(3):364-371.
3. Zudaire E, Martinez A, Cuttitta F. Adrenomedullin and cancer. Regulatory peptides, 2003; 112:175-183.
4. Nikitenko LL, Fox SB, Kehoe S, Rees MC, Bicknell R. Adrenomedullin and tumour angiogenesis. British Journal of Cancer. 2006; 94:1-7.
5. Brogden KA, Guthmiller JM, Salzet M, Zasloff M. The nervous system and innate immunity: the neuropeptide connection. Nature Immunology. 2005; 6:558-564.
6. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature, 1993; 362:801-809.
7. Parlapiano C, PaolettI V, Campana E, Labbadia G, Giovanniello T, Califano F *et al*. Adrenomedullin assay and its clinical significance. European Review for Medical and Pharmacological Sciences. 1999; 3:53-61.
8. Nakamura T, Honda K, Ishikawa S, Kitamura K, Eto T, Saito T. Plasma adrenomedullin levels in patients with noninsulin dependent diabetes mellitus: close relationships with diabetic complications. Endocrinology Journal. 1998; 45:241-246.