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Adrenomedullin as a Novel Promising Therapeutic Approach

Samara M. Ali *, Sarmad M. H. Mohammed**
*Department of Pharmacology ; College of Dentistry; Baghdad University.
** Department of Microbiology; College of Medicine; Baghdad University.

ABSTRACT

Since 1993, the year on which adrenomedullin was discovered, a none- stop researches were established to identify this promising peptide: its source, fate, pathway, mechanism of action inside the body, how can we involve this peptide into therapeutic field of medicine. This review handled several original papers that covered several brunches of medicine; all of them shared the therapeutic approach of adrenomedullin besides sharing the puzzle of being short in duration of action and its final fate.

Keywords: adrenomedullin, therapy, novel peptide

INTRODUCTION

Adrenomedullin, a novel peptide was discovered in human in 1993, consisting of 52 amino acids, has one intra-molecular disulfide bond and shows slight homology with calcitonin gene related peptide. It was discovered when a group of scientists in Japan were screening a panel of peptides extracted from a pheochromocytoma[(1)]. The Adrenomedullin (AM) gene belongs to the calcitonin super family of peptides, which includes calcitonin, calcitonin gene related peptides (CGRP), amyline and intermedin [(2,3)].

AM is produced in several tissues (kidney, lung, and heart) [(4)], and its production is upregulated by several factors such as oxidative stress, pro-inflammatory cytokines, angiotensin II, hypoxia, hyperglycemia, natriuretic peptide, and aldosterone, among other factors[(5)]. AM can also bind to specific AM receptors [(7)]. McLatchie, et al. [(6)] demonstrated that the combination of calcitonin receptor-like receptor (CALCRL) and receptor activity-modifying protein (RAMP) isoforms determines the ligand selectivity for AM.

Receptor activity-modifying proteins (RAMPs) are a class of protein which interact with and modulate the activities of several Class of G Protein-Coupled Receptors (GPCR) including the receptors for secretin, calcitonin (CT), glucagon, and vasoactive intestinal peptide (VIP)[(8)]. There are three distinct types of RAMPs, designated RAMP1, RAMP2, and RAMP3, each encoded by a separate gene [(9)] .

Currently the function of RAMPs is divided into classes activities. When associated with the Calcitonin receptor (CTR) or Calcitonin receptor-like (CALCRL) (below) RAMPs can change the selectivity of the receptor for a specific hormone [(9)].

GPCR	RAMP isoform	resultant receptor
CALCRL	RAMP1	CGRP
	RAMP2	Adrenomedullin (AM) receptor, designated AM1
	RAMP3	dual CGRP/AM receptor, designated AM2
CT receptor	RAMP1	amylin receptor AMY1
	RAMP2	amylin receptor AMY2
	RAMP3	amylin receptor AMY3

Normal levels of immune-reactive AM have been determined in the human urine, plasma, cerebrospinal fluid, amniotic fluid, and saliva [(1)]. AM have a hypotensive, vasodilator [(10)], paracrine/ apocrine effects [(11)], in addition it inhibit myocyte protein synthesis and cardiac fibroblast proliferation [(12, 13)], AM is also an angiogenic factor [(14)] that is induced by hypoxia [(15)] and can alter the permeability of vascular endothelial cells [(16)]. Also the potent effects of AM on cell migration, growth, and apoptosis have led to the hypothesis that AM may be a key player in tumor growth and metastasis [(17, 18)]. 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 [(18–20)]. Finally, AM is highly expressed in the skin and oral mucosa, and this expression pattern has been linked to its potent effect as an antimicrobial peptide [(21)]. According to what mentioned above AM is a multifunctional peptide that can exert many important and interrelated biological functions under both normal and disease conditions. Many researches recently tried to present Adrenomedullin as new promising therapeutic approach. This review will shed the light on several of them.

AM as An Accelerator of Pressure Ulcer Healing

AM has been shown to have proliferative, migrative and anti-apoptotic effects on various cells including vascular endothelial

cells [22, 23]. smooth muscle cells [24], fibroblasts [25], and keratinocytes [26].

Furthermore, AM is produced in these cells including endothelial cells [27], fibroblasts [28], and keratinocytes [26, 29] Considering that the healing process of pressure ulcers involves granulation tissue, with invasion of the wound space in association with proliferation and migration of endothelial cells and fibroblasts, AM may contribute to the healing process of pressure ulcers. This was approved in a study done on a 5-weak old male ICR mice by inducing pressure ulcer on skin, 3 types of sustained release AM prepared the best was of anionic hydrogel base in which its release was during 24 hr.s instead of 22 min.s which is the half-life of AM. Treatment applied in (2 µg AM in 50 mg hydrogel) twice a day, and measured the wound area for two weeks. AM significantly accelerated wound healing on days 5 to 7 after injury, compared to that in without ointment and ointment only groups, Therefore, sustained-release AM ointment may be a novel therapeutic agent for pressure ulcers.[30]

AM In Septic Shock

AM has been proved to be elevated in human inflammatory disease, including sepsis and septic shock [31]. In experimental sepsis in mice overexpressing AM in their vasculature [32] and in AM-treated septic rats [33, 34] this peptide turned out to possess a high therapeutic potential. Besides anti-inflammatory effects, resulting in reduced liberation of pro-inflammatory cytokines in vivo [35], and anti-apoptotic effects, as shown on vascular endothelial cells [36], AM enhances cardiac output and maintains cardiovascular stability in AM-treated rats and sheep, thereby contributing to improved animal survival [34, 37]. According to this a study by Bettina Temmesfeld-Wollbrück et al (2007) hypothesized that therapeutic in vivo administration of AM in septic shock would improve endothelial barrier function and reduce plasma fluid loss. The study done on Male Sprague–Dawley rats by induction of septic shock then injection of 24 µg/kg per hourAM, the results reveal that AM have a therapeutic effect in increasing survival rate of experimental animal through abolishing of S. aureus α- toxin and reduces endothelial permeability in vivo [38]

AM in Morphine Tolerance

AM is a newly identified pronociceptive peptide with 52 amino acids and a member of the CGRP family which also consists of calcitonin, CGRP, amylin, calcitonin receptor stimulating peptides [39]. AM is distributed in the CNS [40, 41] including dorsal root ganglia (DRG) and superficial layers of the spinal cord [42]. Intrathecal (i.t.) administration of AM receptor agonisthAM1–50 produces long lasting Hyperalgesia These observations suggest that targeting AM receptors could be a promising approach to preserve the analgesic potency of opioids. In a study of Dongmei Wang et al 2011 Adult male Sprague–Dawley rats. Intrathecal injection of morphine sulphate in a dose 20 µg for 6 days to generate tolerance to morphine antinociception, injection of AM22–52 (selective AM receptor antagonist) was given at times as indicated. The results proved that AM significantly attenuated morphine tolerance compared to control group. Acute treatment with AM22–52 (35.8_g) on day 7 completely reversed the hyper-algesia reflected by a significant difference between pre- and post-treatments of AM22–52 ($p < 0.001$). One of the novel findings of this study was to demonstrate that AM was an upstream molecule in a cascade underlying the maintenance of morphine tolerance. Study demonstrates that the blockade of AM receptors quickly leads to the reversal of morphine tolerance. Therefore, it can be proposed that AM receptors could be an effective therapeutic target to restore the potency of opioids following the induction of tolerance [43].

AM in Liver Transplantation

Donor organ preservation remains one of the most important issues in liver transplantation. Cold injury, which contributes to both early and late liver graft dysfunction [44,45,46], is the main challenge that must be overcome. The process involves a set of interconnected events that include Kupffer cell activation, oxidative stress, cholestasis, sinusoidal microthrombosis, hepatocellular ballooning, neutrophil infiltration, and cell death of both liver sinusoidal endothelial cells (LSECs) and hepatocytes [47, 48, 49, 50].

Among these, cold preservation of liver grafts most easily damages LSECs [51, 52]. AM reportedly exerts a protective effect against organ damage in several disease models [53, 54]. Nobuyoshi Iinuma et al in a study finished and published in 2010, worked on C57BL/6J mice. Primary adult mice liver sinusoidal endothelial cells (LSECs) and hepatocytes were isolated, cultured and assayed. The cells were then subjected to a cold storage protocol then seeds were incubated with or without 0.1µg AM. Following results found:

1. AM reduces apoptotic damage to LSECs caused by cold storage.
2. AM attenuates cell adhesion and inflammatory reactions in LSECs.
3. AM shows protective effects on cold stored liver.

Results suggest that AM and its receptor system are expressed in liver by LSECs and exert protective effects through the modulation of apoptosis, immune responses, and cellular adhesion. Based on these findings, we suggest that AM protects LSECs and has the potential to improve the preservation of donor organs for liver transplantation[55].

AM in Obstructive Jaundice

A deficiency of AMBP-1 (AM binding protein) in humans is associated with higher susceptibility to recurrent infections [56]. Previous studies have shown that AMBP-1 levels decrease significantly at the late stage of sepsis, which appears to be responsible for the transition from the hyperdynamic phase to the hypodynamic phase during the progression of polymicrobial sepsis [57, 58].

A study on Male Sprague-Dawley rats (275–325 g) in which Obstructive jaundice was induced by common bile duct ligation (BDL). At 5 h after the onset of sepsis in jaundiced rats, the left femoral vein was cannulated with a polyethylene-50 tubing under isoflurane anesthesia. Human AM (24 mg/kg BW, Phoenix Pharmaceuticals, Belmont, CA) in combination with human AMBP-1 (80 mg/kg BW, Cortex Biochem, San Leandro, CA), or vehicle (i.e., human albumin, 104 mg/kg BW) were administered via the femoral vein catheter over 30 min at a constant infusion rate. The results revealed that Treatment with human AM/AMBP-1 at 5 h after the onset of sepsis in jaundiced rats significantly reduced pulmonary, hepatic and intestinal myeloperoxidase activities and improves survival rate to 87%. The study recommended that administration of human AM/AMBP-1 may provide a novel approach to the treatment of sepsis in patients with pre-existing liver diseases such as obstructive jaundice [(59)].

Mechanisms of Adrenomedullin Antimicrobial Action

Adrenomedullin molecule has a single intramolecular disulphide bond between residues 16 and 21, along with an amidated tyrosine at the carboxyl terminus. In common with other antimicrobial peptides, permits bacterial membrane intercalation. Chemically, therefore AM does resemble an antimicrobial peptide.

Variant modes of antimicrobial activity have been proposed for cationic antimicrobial peptides, including critical membrane depolarization, creation of physical holes in membranes, induction of hydrolytic enzymes that degrade the cell wall, disturbance of membrane function and disruption of critical intracellular processes [(60)].

A study held in 2006 by Allaker R. P. et al in Queen marry university of London aimed to gain insights into the mechanism of antimicrobial action of adrenomedullin against the Gram-negative bacterium Escherichia coli and the Gram positive bacterium Staphylococcus aureus [(61)]. E. coli BUE55 was used as an indicator organism to assess the structure–function relationship of AM and AM fragments. This strain was originally isolated because of its increased sensitivity to polymyxin B. E. coli (NCTC 9001), S. aureus (Oxford antibiotic sensitive strain; NCTC 6571) and C. albicans (ATCC 24433) were also used. Microorganisms were grown in Tryptone Soy Broth (TSB; Lab M) at 37 8C in air with 5% CO2.

Synthetic AM and AM fragments (residues 1–12, 1–21, 13–52, 16–21, 16–52, 22–52, 26–52 and 34–52) were obtained from Phoenix Pharmaceuticals (Karlsruhe, Germany). MIC determinations of peptides and fragments were determined in a broth micro-dilution assay against E. coli BUE55 [(62)]. MBCs of peptides were determined by inoculating samples from MIC determination wells onto blood agar base (Oxoid CM271) with defibrinated horse blood (5%, v/v). Plates were then incubated at 37 C in air with 5% CO2 for 24 h. cultures were then transmitted to be examined by electron microscope.

Growth of E. coli was shown to be significantly reduced in the presence of AM and lysozyme, in comparison to AM alone. While, growth of S. aureus was not significantly reduced in the presence of AM and lysozyme, in comparison to AM alone (Allaker, unpublished observations) [(60)]. It is generally agreed that the AM concentration to inhibit bacterial growth is in excess of the levels normally found in the systemic circulation [(63)].

Adrenomedullin receptors on human T cells

Increases in plasma concentrations of AM are well documented in association with inflammatory and infectious disease states. Indeed, endothelial cells and vascular smooth muscle cells, as well as macrophages, monocytes and neutrophils augment AM production when exposed to IL-1, TNF-α and LPS [(64)]. Similarly, astrocytes, which can secrete AM under normal conditions, were shown to increase AM production after cytokine treatment (TNF-α, IL-1 and INF-γ) [(65)]. AM could clearly influence other macrophage cytokine expression, down-regulating its own inducer TNF-α, indicating a further anti-inflammatory effect during inflammation [(66)]. Importantly, AM has also shown its ability to reduce inflammation level, in a variety of animal models: in experimental arthritis where it successfully reduced both incidence and severity of disease [(67)] and in two different models of sepsis by decreasing levels of immuno-inflammatory mediators [(68)]. Glucocorticoids (GC) are the best-known immunosuppressant, exerting an important role during the inflammatory process [(69)]. In order to clarify AM's role during inflammation and relation between AM and glucocorticoids Liverani E. et al in 2012 [(70)] held on an experiment to assess the protein expression of AM receptor components in T cells.

To accomplish this aim, expression of AM receptor proteins RAMP2, RAMP3 and CLR was investigated in a T cell line and human primary CD3+ T cells before and following activation. Furthermore, they assessed RAMP2, RAMP3 and CLR sensitivity to AM and GC exposure. Their results underline the importance of AM in the inflammatory process, suggesting that AM1 and AM2 expression and functionality are closely related to the T cell activation state, as is the influence exerted by GC's on T cell AM-sensitivity. The study went on buy preparing fresh PBMNCs peripheral blood mononuclear cells from heparinized blood of healthy , CD14− PBMCs were isolated using a monocyte isolation kit, CD14− PBMC were maintained at 37 °C and 5% CO2 in RPMI 1640 media, fully supplemented with penicillin–streptomycin (0.8 mM) , Amphotericin B (0.03 μM) and glutamine (2mM).

For activation, the T cell fraction (1×106 cells/ml) was incubated with 5 μg/ml Phytohemagglutinin (PHA) for 48 h. The Jurkat T cell line was maintained in fully supplemented RPMI media at 37 °C and 5% CO2. Cells were treated with human Adrenomedullin (AM — 10−6 M) or Dexamethasone (Dex — 10−6 M) or AM/ Dex (10−6/10−7 M respectively) or AM plus AM antagonist (human AM 22–52 10−6/10−6 Mrespectively) in fully supplemented media and incubated for 24 h. Control cells received an equivalent amount of vehicle.

Finally the following analysis were done respectively Flow cytometry analysis, Measurement of cAMP levels, Calcium mobilization assay, Real-time PCR amplification.
Statistics were collected and studied and the results proved that AM receptor presentation in T cells is GC-sensitive, which is highly dependent on stimulation state.

The importance of the activation state-dependent sensitivity of the human T cell to this peptide and how this links to its protective capabilities under hypoxic conditions on the one hand and to the known anti-inflammatory properties of AM on the other, will require further consideration and provides an intriguing paradox to resolve.

CONCLUSION

Chemical, multifunctional properties of AM opened new scopes for researchers to utilize these features in the field of diagnosis and therapy. Till now researches are done either laboratory or on animal models this may be due to incomplete picture about its fate, its short half-life (22 min.s), high cost, limitation of routs of administration ..etc. to the best of our knowledge if these obstacles are removed AM will be promising therapeutic approach that will surely leave a thumb print in medicine and put the answer to questions remained unanswered for long time..

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