Adrenomedullin as a renal regulator peptide

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Introduction

In 1993, Kitamura et al. discovered a novel hypotensive factor by means of monitoring the ability of extracted fractions of human pheochromocytoma to increase platelet cyclic adenosine 3',5'-monophosphate (cAMP) [1]. This factor is named adrenomedullin (ADM), as it is abundant in normal adrenal medulla as well as in pheochromocytoma. ADM is a 52-amino acid peptide with a ring structure and C-terminal amidation. ADM mediates vasodilating properties through cAMP and nitric oxide (NO). ADM immunoreactivity and gene expressions are widely distributed in mammalian organs, including the kidney [2,3]. ADM is present in human plasma and urine, and urinary levels are higher than plasma levels, indicating that the kidney may be one of the major organs for ADM production [4]. In addition to the vasodilating effect, ADM has diuretic and natriuretic actions, which are mediated by increases in glomerular filtration rate (GFR) and a decrease in distal tubular sodium reabsorption [2]. Clinically, plasma ADM levels are increased in patients with chronic renal failure. Current observations suggest that ADM plays an important role in renal regulation including fluid and electrolyte homeostasis. In this paper, we focus on the study of ADM in the kidney, and review the current knowledge about renal ADM research.

Structure and molecular biology of ADM

ADM consists of 52 amino acids and has a unique 6-amino acid residue ring structure and C-terminal amidation, which is similar to calcitonin gene related peptide (CGRP) and amylin. Actually, ADM shows 27% homology with CGRP, suggesting that ADM belongs to the CGRP superfamily. The human ADM precursor (preproADM) is 185 amino acids in length and is processed to 164-amino acid peptide, proADM, and then to a 52-amino acid peptide, the biologically active form of ADM. The genomic DNA of human ADM consists of 4 exons and 3 introns, and the fourth exon codes for the mature form of ADM [5]. There are also multiple binding sites for activator protein-2 and a cAMP-regulated enhancer element. The ADM gene is located in a single locus of chromosome 11.

Distribution and synthesis of ADM in the kidney

ADM immunoreactivities and gene expressions are widely distributed in mammalian tissues, including kidney. We have demonstrated immunohistochemical stainings for ADM in glomeruli, cortical distal tubules and medullary collecting duct cells [2]. We also found that ADM was present in mesangial cells and microvascular areas of rat glomeruli [3]. The intensities of ADM immunoreactivity in the glomerulus, cortical collecting duct cells, and medullary collecting duct cells were increased in the canine model of congestive heart failure as compared with normal dogs, suggesting renal activation of ADM in congestive heart failure [6]. Other investigators reported that ADM mRNA was expressed in the glomerulus, cortical collecting duct cells, outer collecting duct cells and inner collecting duct cells using the reverse transcription–polymerase chain reaction (RT–PCR) technique [7]. Northern blot analysis revealed high expression of ADM mRNA in mesangial cells [7]. In-situ hybridization also showed ADM gene expression in the glomerulus and cortical distal tubules [8].

Although it is established that ADM is synthesized and secreted from vascular endothelial and smooth muscle cells, ADM is also synthesized and secreted from cultured mesangial cells [3,9]. ADM is detected in human urine, and urinary ADM levels are much higher than plasma levels, suggesting that kidney may be one of the major tissues for ADM production [4].

ADM receptor in the kidney

Receptor autoradiography revealed specific binding sites of [125I]ADM in renal artery and glomeruli.
indicating the presence of a specific receptor for ADM in the kidney [10]. Edwards et al. reported that the effects of the CGRP antagonist, CGRP₈₋₃₇ on ADM-mediated cAMP generation were different between the glomeruli and distal convoluted tubules in the kidney [11]. CGRP₈₋₃₇ had no effect on ADM-mediated increases in cAMP in the glomeruli, however CGRP₈₋₃₇ inhibited ADM-mediated increases in cAMP in the distal convoluted tubules. These findings suggested that glomeruli have ‘ADM-like’ receptors that have a high affinity for ADM but a low affinity for CGRP and CGRP₈₋₃₇, whereas the distal convoluted tubules have ‘CGRP-like’ receptors with a high affinity for CGRP and CGRP₈₋₃₇ but a low affinity for ADM. Recently, McLatchie et al. reported that the calcitonin-receptor-like receptor (CRLR) with seven transmembrane domains and receptor-activity-modifying protein 2 (RAMP₂) with single transmembrane domain generated an ADM receptor [12]. RAMP₂ plays a role in transporting CRLR to the plasma membrane.

Renal physiology

Actions on the renal vessels
ADM is a potent vasodilator in the regulation of vascular tone. In organ chamber studies, ADM induced a concentration-dependent vasodilatation in canine renal arteries [13]. The vasodilating effects were slightly greater in endothelium-intact arteries than in denuded arteries. ADM elicited a concentration-dependent vasodilating response which was blocked by CGRP₈₋₃₇ in the rat isolated perfused kidney [14].

Natriuretic actions
We have elucidated that ADM is a new natriuretic peptide [2]. Intrarenal infusion of ADM resulted in marked diuretic and natriuretic responses, which were associated with an increase in GFR and a decrease in distal tubular sodium reabsorption. ADM-mediated natriuresis was completely abolished by inhibition of prostaglandin synthesis [15].

Other investigators also reported that ADM produced natriuretic actions in dogs [16,17] and in rats [18–20]. The renal response to ADM was attenuated by inhibition of NO synthesis, indicating that renal vasodilating, diuretic and natriuretic responses to ADM may be mediated by the release of endogenous NO [17,21]. Hirata et al. directly showed that ADM increased the release of endogenous NO in the isolated kidney utilizing chemiluminescence assay [19].

Mesangial cell proliferation
ADM inhibited the proliferation of mesangial cells, and ADM decreased the activation of mitogen-activated protein kinase (MAPK) induced by platelet-derived growth factor (PDGF), indicating that ADM can suppress mesangial cell mitogenesis [22]. ADM inhibited both [³H]thymidine incorporation into cultured rat mesangial cells and cell proliferation in a concentration-dependent manner [23]. ADM also inhibited endothelin-1-induced activation of MAPK in cultured mesangial cells [24].

Renin release
Intravenous administrations of ADM in conscious rabbits [25] and conscious sheep [26] resulted in a decrease in mean arterial blood pressure and an increase in plasma renin activity. Jensen et al. investigated the effect of ADM on renin secretion and renin gene expression in renal juxtaglomerular granular cells [27]. Renin release from isolated perfused rat kidney was dose-dependently increased by ADM. In primary cultures of mouse granular cells ADM augmented renin release, renin mRNA accumulation and cAMP production in a concentration- and time-dependent manner. ADM may act as an autocrine and/or paracrine stimulatory factor in the regulation of renin secretion and renin gene expression. However, other investigators reported that chronically infused ADM had a hypotensive effect accompanied by significant reductions of plasma renin activity in conscious two-kidney, one-clip hypertensive and sham-operated rats [28].

Clinical implications in renal diseases
Plasma ADM concentration was increased in patients with chronic renal failure [4,29–31]. There was a positive correlation between circulating ADM and plasma creatinine levels [29]. There was also a positive correlation between plasma ADM concentration and mean arterial blood pressure in both patients before haemodialysis and healthy subjects [30]. However, plasma ADM concentration was not altered by haemodialysis [4,30].

ProADM N-terminal 20 peptide (PAMP)
In addition to ADM, the precursor of ADM (proADM) contains another vasodilating peptide, named proADM N-terminal 20 peptide (PAMP) in its N-terminal portion. Interestingly, the C-terminus of PAMP is amidated like ADM. Tissue localization of PAMP is similar to that of ADM, supporting the theory that its origin is in the same gene as ADM. The mechanism of vasodilatation induced by PAMP is different from that induced by ADM. Shimosawa et al. reported that PAMP inhibits neural transmission at peripheral sympathetic nerve endings [32]. PAMP is present in plasma and its plasma concentration is increased in patients with chronic renal failure [33].

Conclusion
ADM is a 52-amino acid vasodilating and natriuretic peptide, originally isolated in human pheochromocytoma.
ADM is considered to play an important role through its vasodilating and natriuretic properties to regulate vascular tone and renal homeostasis. ADM research has just begun, and further investigations are required to address the importance of ADM under various physiological and pathophysiological conditions.

References