Altered Natriuretic Peptide System in the Kidney in Hypertension

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Diverse control systems are involved in the regulation of blood pressure, including renal, vascular, cardiogenic, neurogenic, and endocrine mechanisms. Among them, the kidney plays the dominant role in the long-term regulation of arterial pressure, in which the volume of extracellular fluid is regulated primarily by excreting or retaining sodium. Therefore, hypertension is usually associated with an altered renal sodium handling. There are mediators between increased renal perfusion pressure and decreased tubular reabsorption of sodium in the kidney. Although a dysfunction of nitric oxide system in the kidney appears to play a major role in the development of salt-sensitive hypertension, the regulation of atrial natriuretic peptide (ANP) may also be altered in hypertension. This review will discuss the altered regulation of ANP system in the kidney in different models of hypertension.

Key Words : Atrial natriuretic peptide, Natriuretic peptide receptor, Kidney, Hypertension

Introduction

The family of natriuretic peptides comprises at least three members of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Molecular cloning studies have characterized three different natriuretic peptide receptors (NPR), i.e., NPR-A, -B, and -C. They differentially recognize the three known natriuretic peptides. ANP and BNP can effectively stimulate NPR-A, whereas NPR-B is efficiently stimulated by CNP[1, 2]. NPR-C binds all three known peptides with high affinity in assuming clearance and buffering functions. In the kidney, ANP receptors are found in the glomerulus[3] and in the papilla, where they are present on vasa recta and collecting ducts[4]. Binding of ANP to the biologically active NPR, coupled to particulate guanylyl cyclase, stimulates cGMP accumulation.

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The natriuretic effect of ANP results from an increase in the filtered load of sodium and from a decrease in reabsorption in the distal segments of the nephron[5, 6]. The renal cortical blood flow, which is usually three times greater than the medullary flow, has been reported to be reduced in volume-expanded, salt-retaining states[7]. The resultant redistribution in renal blood flow, with an increase of juxtamedullary cortical and outer medullary flow, would tend to direct blood away from cortical ANP clearance receptors and reduce renal ANP extraction. This overall reduction would contribute to increased endogenous circulating ANP levels and have a greater effect than a reduction in renal ANP extraction alone.

Natriuretic peptide systems in various models of hypertension

1. Spontaneously hypertensive rats (SHR)

The natriuretic and diuretic response to exogenous ANP is prolonged and exaggerated in SHR[8]. Binding of ANP to NPR-A shows a higher affinity and more efficient production of cGMP in SHR than in WKY rats[9, 10]. Therefore, the exaggerated biological re-

sponse to ANP is related with genetic overexpression of NPR-A and higher activity of particulate guanylyl cyclase in SHR. The upregulation of NPR-A may act as a negative feedback in response to hypertension.

An altered regulation of NPR may also be involved in the development of hypertension in stroke-prone substrain of SHR (SHRSP). The apparent dissociation constant and the maximal binding capacity of the high affinity binding sites are significantly decreased in SHRSP in comparison with those in WKY[11]. However, the progression of hypertension is associated with an enhanced expression of NPR-A in SHRSP, which may have a deterrent role in the development of hypertension and its renal complications[12].

2. Two-kidney, one clip (2K1C) hypertension

Fenoy et al[13] observed that ANP decreased the blood pressure in association with a decreased urinary sodium excretion in 2K1C hypertension. They concluded that the ANP-induced decrease of blood pressure may be responsible for the transitory sodium retention during the administration of the peptide. Nevertheless, their observation suggests an altered renal effect of ANP in 2K1C hypertension.

In fact, ANP produces differential renal effects in 2K1C hypertension : the diuretic and natriuretic effect is blunted in the clipped kidney whereas the excretory function is markedly increased in the contralateral non-clipped kidney[14]. The impaired natriuretic response of the clipped kidney may be related to a downregulation of NPR-A, and the increased sodium excretion and glomerular filtration rate in the contralateral kidney to an increased expression of NPR-A. It was indeed shown that the expression and the number of ANP binding sites were significantly lower in the clipped kidney, and higher in the contralateral non-clipped kidney in 2K1C rats than in the control[15, 16]. In this context, ANP may be of potential advantage in treating this type of hypertension.

3. One-kidney, one clip (1K1C) hypertension

1K1C hypertension is often associated with expanded plasma volume and increased plasma ANP levels. However, the natriuretic and diuretic responses to ANP are blunted[17]. Although a modest augmentation in the density of papillary ANP receptors is observed, the downregulation of glomerular NPR-A and the reduced cGMP response may lead to attenuated renal response to ANP in these rats[18, 19].

The blunted natriuretic and diuretic responses may be restored by a surgical removal of the clip from the renal artery[17]. Accordingly, the unclipping restores the glomerular ANP receptor population in number and affinity in 24 hours[19]. The upregulation and enhanced affinity of glomerular ANP receptors (probably secondary to the decrease in plasma levels of ANP) may contribute to the restoration of natriuresis.

4. Dahl S rats

The papillary collecting duct may differ in guanylyl cyclase activity between Dahl S and Dahl R rats. Prehypertensive Dahl S rats have an intrinsic tendency toward less natriuresis than Dahl R rats when challenged with ANP. The generation of intracellular cGMP in response to ANP of renal papillary collecting tubule cell is reduced in Dahl S rats[20], indicating possible specificity of the reduced responsiveness to ANP in the distal nephron of Dahl S rats. These differences may in part explain the impaired natriuretic responses of Dahl S rats and could represent a factor contributing to the development of salt-sensitive hypertension.

On the contrary, the maximum binding capacity for ^{125}I-ANP in the glomeruli is increased in Dahl S rats at 7 weeks of age by 21% compared with that in Dahl R rats[21]. However, from 7 to 10 weeks of age, Bmax for ^{125}I-ANP in the glomeruli decreases, with no apparent differences between the two strains[21].

Other investigators also have shown that ANP equally enhances intracellular cGMP formation in glomerular mesangial cells between Dahl S and Dahl R rats [20]. Strain or age differences in the affinity constant for ^{125}I-ANP do not occur in the kidney in these rats. The alterations in ANP binding sites in the kidney of Dahl S rats may occur only in response to the sharp increase in blood pressure.

5. DOCA-salt hypertension

Renal ANP synthesis is increased in rats treated with DOCA-salt[22]. The number of ANP receptors is increased and the cGMP formation in response to ANP is exaggerated in the renal papilla, which may account for the increased natriuretic responsiveness of the kidney to ANP in this model of hypertension[23].

However, the translation study demonstrated a decrease of NPR-A mRNA levels in DOCA-salt rats[24], an indication that this mRNA became susceptible to degradation independent of its utilization by the translational machinery. To explain the discrepancy, it has been postulated that the half-life and activity of NPR-A may be prolonged while its biosynthesis is decreased. The apparent upregulation of ANP binding in renal papillae could be attributed to receptor recycling, i.e., even if the overall levels of translatable mRNA are decreased, the protein produced should be less catabolized and constantly mobilized. There may be induction of some protein factors that can direct NPR through the recycling machinery.

On the contrary, the downregulation of glomerular ANP receptors may play a role in the maintenance of high blood pressure in this model of volume-expanded hypertension[23].

6. L-NAME hypertension

Lee et al[25] found that the vascular expression of NPR-A and NPR-C mRNA was decreased, while that of ACE and AT1 receptors was increased in 2K1C and L-NAME hypertension. They also observed that the particulate guanylyl cyclase activity was decreased in these models of hypertension. These findings suggest that the vascular expression of NPR be reciprocally regulated by local RAS activity. Suo et al[26] found that L-NAME treatment increased ventricular ANP and BNP mRNA levels and immunoreactive BNP levels significantly, at least in part, mediated by angiotensin II. It was also demonstrated that the hypertension and renal damage induced by blockade of NOS was prevented by treatment with an ACE inhibitor and/or Ang II receptor antagonist, in which urinary cGMP excretion was significantly increased by L-158,809 (AT1-receptor antagonist)-treated rats[27]. The dysfunctional NO system may be activated by the blockade of AT1-receptor, the stimulated cGMP production then potentially contributing to renal and vascular protection in hypertension and chronic renal disease.

7. Other models of hypertension

In Milan hypertensive rats, saturation experiments with ^{125}I-rat ANP revealed a downregulation of ANP receptors in the glomeruli[28]. In primary aldosteronism, ANP levels are elevated. Furthermore, a widespread reduction of NPR-C numbers would result in a greater reduction in total body extraction of ANP, and downregulation of NPR-A density may limit the biological effectiveness of ANP in primary aldosteronism [29].

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