Factors Influencing Vascular and Natriuretic Responses to ANP

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To explore factors that modulate the magnitude of vasorelaxation and natriuretic/diuretic responses to exogenous ANP, clearance studies were performed in unilateral hydrenephrotic rats with renal vasoconstriction complications. An increase in renal plasma flow associated with a decrease in calculated renal vascular resistance in response to ANP (2 μg·min⁻¹·kg⁻¹, i.v.) was obtained only in the hydrenephrotic kidney. In contrast, the control kidney of the unilateral hydrenephrotic rat had a decrease in glomerular filtration rate and an abolished natriuretic response following ANP administration. A prior renal denervation in the control kidney restored the natriuretic effect of ANP and abolished the lowering of glomerular filtration rate. These data suggest that the vasodilatory effect of ANP may depend on the vascular tone itself, and that renal responses to ANP are significantly modified by renal nerve activity.

Although atrial natriuretic peptide (ANP) has potent vasodilatory and natriuretic activity, the magnitude of these responses seems to be variable among animals. Indeed, an elevation of plasma concentration of ANP is not necessarily accompanied by natriuresis. Factors influencing the response to ANP, however, have not been fully clarified. Until recently, renal perfusion pressure and hydration state are known as modulating factors on the natriuretic/diuretic response.

In a preliminary experiment, we noted a paradoxical response to exogenous ANP in the hydrenephrotic and the control kidney of the same rat. The present study was performed to explore the underlying mechanism.

METHOD

Under ether anesthesia, Wistar male rats (230–300) were prepared for 24 hour unilateral ureter ligation. The animals were cannulated into a femoral artery and vein and a bladder. To release the ureter occlusion, a catheter was also inserted into the ureter just above the ligated site. Renal denervation, if necessary, was carried out by stripping and coating renal nerves with 10% phenol around the renal artery of the intact kidney in the unilateral hydrenephrotic rat. A clearance study was performed during the ureter occlusion or after release of the occlusion in the hydrenephrotic rats, and also in conscious normal rats. ANP (α-human Atrial Natriuretic Polypeptide, a gift from Peptide Institute, Osaka) was infused intravenously at 2 μg·min⁻¹·kg⁻¹.

RESULTS

Hemodynamic effects of ANP (Fig. 1)

In all groups, mean arterial pressure fell from 8 to 17 mmHg. The extent of the decrease was not significantly different among groups. Basal effective renal plasma flow (RPF) in the hydrenephrotic kidney was markedly reduced (5.14 ± 0.47 ml·min⁻¹·g⁻¹ in normal rat kidney, n = 10, and 1.12 ± 0.15 ml·min⁻¹·g⁻¹ in the hydrenephrotic kidney, n = 10). ANP increased RPF about 2 times in the hydrenephrotic kidney.

Key words:
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Fig. 1. Effect of ANP on renal plasma flow. Experiments were carried out in hydronephrotic kidney (HK) 4 hr after release of 24 hr unilateral ureter occlusion and in normal rat kidney (NK). Renal plasma flow was measured by 30 min clearance of p-aminohippuric acid (CPAH), and expressed as per g of kidney wet weight. ANP was infused intravenously at 2 μg·kg⁻¹·min⁻¹. *: p < 0.005, n = 10.

(2.28 ± 0.27 ml·min⁻¹·g⁻¹ during ANP administration, p < 0.001). The changes in calculated renal vascular resistance during ANP infusion showed a negative correlation with the resistance during basal period (y = 27.25 - 1.049x, r = 0.9861, n = 10). In contrast, normal rat kidney or the contralateral control kidney of hydronephrotic rat had a decrease in RPF in response to ANP (-1.76 ml·min⁻¹·g⁻¹, and -1.60 ml·min⁻¹·g⁻¹, respectively).

\textbf{Natriuretic and diuretic effects of ANP in the intact kidney} (Fig. 2)

During ureter occlusion of the opposite kidney, ANP caused natriuresis and diuresis without significant changes in glomerular filtration rate in the remaining kidney (from 2.39 ± 0.19 to 3.10 ± 0.22 μeq·min⁻¹·g⁻¹ for sodium excretion, p < 0.005, and from 18 ± 2 to 36 ± 4 μl·min⁻¹·g⁻¹ for urinary flow, p < 0.001, n = 10). After release of the ureter occlusion, however, neither natriuresis nor diuresis, following systemic infusion of ANP, occurred in the untouched control kidney. Moreover, glomerular filtration rate in the control kidney was significantly reduced in response to ANP (from 1.00 ± 0.09 to 0.76 ± 0.05 ml·min⁻¹·g⁻¹, p < 0.01). Prior renal denervation restored the natriuretic response to ANP (from 1.00 ± 0.22 during basal period to 1.57 ± 0.18 μeq·min⁻¹·g⁻¹ during ANP infusion, p < 0.005). Simultaneously, the renal denervation also unmasked the diuretic effect of ANP, although incompletely (from 7 ± 1 during basal period to 10 ± 1 μl·min⁻¹·g⁻¹ during ANP period, p < 0.005). Furthermore, the decrease in the glomerular filtration rate following ANP infusion was abolished by the prior denervation.

\textbf{DISCUSSION}

The present study clearly shows that at first, the vascular tone itself is a modulating factor for the vasorelaxing effect of ANP: i.e., the more severe the vasoconstriction, the more remarkable the extent of vasodilatory response to ANP. This
may be comparable to the in vitro observation that ANP does relax agonists-induced vasoconstriction, but not basal vascular tension. A decrease in renal plasma flow in response to ANP in the normal rat was compatible with data using pulsed Doppler probe by Lappe et al. This suppressive response may be a compensatory reaction through the activation of sympathetic nerve system to a lowering of blood pressure. Second, renal nerve is involved in the reduction of glomerular filtration rate in the control kidney of the unilateral hydronephrotic rat following intravenous infusion of ANP. Inasmuch as this decrease in glomerular filtration rate was not evoked during ureteral occlusion of the opposite kidney, some action(s) of ANP on urinary excretion in the hydronephrotic kidney appears to be essential for the paradoxical response. The hydronephrotic kidney, after release of the ureteral occlusion, responds to ANP with a twofold increase in renal plasma flow as measured by clearance of paraaminobipyrinic acid. Therefore, it is ANP-induced vasodilation in the hydronephrotic kidney that may be a trigger for the reduction of glomerular filtration rate in the contralateral control kidney. This view is supported by an observation by MacFarlane that intrarenal infusion of acetylcholine, another vasodilatory agent, causes a vasoconstriction of the contralateral renal artery in the dog. The intensity of vasodilation may be more critical than vasorelaxation per se. Acute saline loadings, which moderately increase renal plasma flow in the hydronephrotic kidney, do not affect glomerular filtration rate in the contralateral control kidney (n = 5, unpublished data). The present finding that renal denervation abolishes the paradoxical response to ANP on glomerular hemodynamics might imply that the effect on glomeruli of renal nerve overrides the actions of ANP. Inversely, glomerular hemodynamic effects of ANP could be modulated by renal nerve activity.

The extent of natriuretic and diuretic responses to ANP in the control kidneys were variable. Our study shows that renal nerve also can modify these effects of ANP. This modification by renal nerve would be due to its direct action on proximal tubules to stimulate sodium reabsorption, since the tubules, rather than the renal arterioles and glomeruli, are more sensitive to renal nerve stimulation. Therefore, it is possible that ANP has an inhibitory effect on the anti-natriuresis induced by renal nerve activation. It is not clear from the present data whether or not this interference of renal nerve with the natriuretic action of ANP occurs on the same target tissues.

REFERENCE