Pathogenesis of Postobstructive Diuresis : Role of Aquaporin Water Channels, Sodium Transporters and Natriuretic Peptide System in the Kidney in Rats

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Although the obstruction is potentially reversible with treatment, marked and sometimes prolonged diuresis and natriuresis associated with an impaired ability to concentrate the urine may follow relief of the obstruction. Various factors contributing to the postobstructive diuresis and natriuresis have been suggested, including decreases of tubular sodium reabsorption, retention of urea and expansion of extracellular fluid volume. Tubular damage as a consequence of obstruction may occur one or more nephron segments and may result in decreased reabsorption of filtrate. The discovery of aquaporin (AQP) membrane water channels and sodium (co)transporters and channels provided insight, at the molecular level, into the fundamental physiology and pathophysiology of water and sodium balance. In addition, recent studies have shown that the kidney per se is also a site of production and release of atrial natriuretic peptide (ANP). The locally synthesized ANP may act in a paracrine manner to increase the urinary excretion of sodium and water. In this context, an altered regulation of ANP in the kidney may result in an altered urinary excretion. The combined interactions of multiple independent mechanisms are thought to be involved in the pathogenesis of postobstructive diuresis and natriuresis. We examined the changes of AQP water channels, sodium (co)transporters and natriuretic peptide system in obstructed kidneys. The expression of AQP water channels and sodium transporters was decreased in the obstructed kidneys, which may at least in part account for the urinary concentration defect associated with postobstructive diuresis and natriuresis. In addition, the postobstructive natriuresis was associated with an enhanced renal expression of ANP mRNA and an increased urinary excretion of ANP. The plasma dendroaspis natriuretic peptide (DNP) level was increased following an experimental ureteral obstruction. The urinary excretion of DNP was increased along with the postobstructive diuresis. An enhanced activity of DNP system may in part play a role in mediating the postobstructive diuresis

Key Words : Aquaporins, Sodium transporters, Natriuretic peptides, Ureteral obstruction

Introduction

Obstruction of the urinary tract is a common cause of loss of renal function. A marked and sometimes prolonged diuresis may follow the relief of severe obstruction of both kidneys. Various factors contributing to the postobstructive diuresis have been suggested, including decreases of tubular sodium reabsorption, retention of urea and expansion of extracellular fluid volume[1]. Tubular damage as a consequence of obstruction may occur one or more nephron segments and may result in decreased reabsorption of filtrate. This is associated with significant sodium and water loss despite a marked decrease in glomerular filtration rate (GFR) and a deficient response to exogenous mineralocorticoid and

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vasopressin. Although a role of atrial natriuretic peptide (ANP) in mediating the postobstructive diuresis has been also suggested[2], the detailed mechanisms remain to be determined. This review aims at providing recent insight into the role of renal aquaporins (AQPs), natriuretic peptide system, and sodium (co)transporters in postobstructive diuresis.

1. Decreased abundance of aquaporin (AQP) water channels

Although the obstruction is potentially reversible with treatment, marked and sometimes prolonged diuresis associated with an impaired ability to concentrate the urine may follow relief of the obstruction. Among patients with chronic partial urinary tract obstructions or with recently relieved partial or complete urinary tract obstructions, decreases in renal concentrating ability can usually be demonstrated[3]. The recent discovery of aquaporin (AQP) channels has increased our understanding of water transport across the permeable epithelial cell membrane. In the kidney, at least six isoforms of AQP proteins have been detected (AQP1, -2, -3, -4, -6, and -7). Among these isoforms, AQP1 is primarily responsible for the constitutive water permeability of proximal tubules and thin descending limbs of Henle[3]. Studies using AQP1-knockout mice revealed a dual role of AQP1 in proximal tubular reabsorption and medullary hypertonicity construction[4]. However, AQP2 to AQP4 are mainly expressed in the collecting duct. AQP2 is specifically located in the principal cells of the collecting duct and is regulated in the short term and long term via the arginine vasopressin (AVP)/cyclic AMP (cAMP) pathway[5]. In addition, the constitutive localization of AQP3 and AQP4 in the basolateral membrane of principal cells confers to the epithelium high water permeability, in concert with AQP2 insertion into the apical membrane. Frøkiaer et al.[6] recently observed a decrease in the expression of AQP2 channels in the kidney after a bilateral ureteral obstruction (BUO). However, detailed mechanisms underlying the altered regulation of AQP2 have not been established. In addition, whether there is altered regulation of AQP channels other than AQP2 has not been determined. Thus, we examined examined whether the postobstructive failure of urinary concentration could be related to altered regulation of AQP water channels in the kidney, and the catalytic activities of different parts of adenylyl cyclase complexes were separately investigated[7, 8]. After ureteral obstruction, the expression of AQP1 to AQP4 proteins was decreased in the cortex, outer medulla, and inner medulla of obstructed kidneys. We demonstrated that cAMP generation in response to AVP was blunted in the obstructed kidneys, with the decrease being more pronounced in the medulla than in the cortex. Furthermore, cAMP generation in response to forskolin, which directly activates the catalytic unit of adenylyl cyclase, was decreased in the medulla of the obstructed kidneys. The cAMP generation in response to sodium fluoride, which activates adenylyl cyclase in a receptor-independent but G protein-dependent manner, was also significantly blunted. Accordingly, the expression of Gs and that of adenylyl cyclase VI were significantly decreased. Not only Gs protein but also the catalytic unit of adenylyl cyclase itself may be impaired in the obstructed kidneys, and the dysregulation of AQP2 channels may be attributable to these impairments. The minimal or absent changes in adenylyl cyclase activity in the cortex may be in line with the previous hypothesis that the cortex is normally not heavily loaded with adenylyl cyclase activity. It is also likely that the impairment may become more extensive in the obstructed kidneys when the degree of local changes, such as tubular pressure changes, becomes greater. However, the reduction of AQP2 channels was parallel in the membrane-enriched and cytoplasmic fractions, suggesting preserved trafficking. Similar findings were noted in rats with several acquired forms of nephrogenic diabetes insipidus syndromes, such as cisplatin-induced nephropathy[9], lithium-induced nephropathy[10],

and ischemic acute renal failure[11]. AQP3 is mainly localized to the basolateral membrane of collecting duct principal cells in the cortex and outer medulla, and AQP3 null mice revealed marked polyuria and urinary concentration defect[12]. Our study demonstrated that AQP3 expression was decreased in the cortex, outer medulla, and inner medulla of the obstructed kidneys, more prominently in the medulla. Recent studies demonstrated long-term regulation of AQP3 (with a marked increase in its expression in the collecting ducts), but not AQP1 or AQP4, in response to water restriction or AVP infusion[13]. This finding suggests that the AVP/cAMP pathway also has a role in the long-term regulation of AQP3. The decrease in AQP3 abundance may also be attributable to an impairment in the activity of the AVP/cAMP pathway. AQP1 is present in large amounts in both apical and basolateral membranes of proximal tubules and descending thin limbs. AQP1 gene-knockout mice demonstrated 80 to 90% reductions in osmotic water permeability in the proximal tubules and descending thin limbs and became severely dehydrated[4]. We demonstrated in this study that AQP1 expression was significantly reduced in the obstructed kidneys, as revealed by both immunohistochemical and Western blot analyses. The decrease in AQP1 expression was more prominent in the cortex and outer medulla than in the inner medulla. Although the altered expression of AQP1 could be causally related to postobstructive diuresis, it may also indicate differential regulation of AQP1, compared with AQP2 and AQP3. Mechanisms regulating AQP1 remain to be further elucidated. Although it is primarily expressed in the brain, AQP4 is also expressed in the basolateral membrane of inner medullary collecting ducts[14]. It presumably provides the exit during AVP-dependent water reabsorption. Recently, transgenic knockout mice lacking AQP4 demonstrated a mild urinary concentration defect and a fourfold reduction of water permeability in the inner medulla[15]. The decreased expression of AQP4 in the inner medulla may also contribute to postobstructive diuresis.

In summary, the expression of AQP water channels was decreased in the ureter-obstructed kidneys, which may at least in part account for the urinary concentration defect associated with postobstructive diuresis. The primary impairment of AQP channels that are regulated via the AVP/cAMP pathway may lie at the level of G proteins and adenylyl cyclase itself.

2. Diminished expression of sodium transporters

The tubular reabsorption of solutes is basically linked to the activity of Na,K-ATPase that is heavily expressed in the basolateral membrane throughout the nephron segments. On the contrary, the sodium transporters in the apical membrane differ in different tubular segments. In the proximal tubule, type-3 Na-H exchanger (NHE3) is apically expressed. On the other hand, the apically expressed bumetanide-sensitive Na-K-2Cl cotransporters (BSC1 or NKCC2) and NHE3 are mainly responsible for the sodium reabsorption in thick ascending of Henle (TAL). In the distal convoluted tubule, the thiazide-sensitive sodium chloride cotransporter (TSC) is involved in the apical movement of sodium[16-18].

The postobstructive natriuresis and diuresis has been attributed to a decreased tubular reabsorption of sodium and water. A reduced expression and activity of Na,K-ATPase in the medullary thick ascending loop of Henle (TAL) has been known[19]. In addition, Li et al. most recently demonstrated a decreased expression of major sodium transporters in the kidney in rats with unilateral ureteral obstruction (UUO)[20]. We demonstrated that the expression of 1 and 1 subunits and the catalytic activity of Na,K-ATPase were decreased in the obstructed kidney in BUO[21]. Accordingly, the expression of NHE3, BSC1 and TSC was also markedly decreased. Immunohistochemistry confirmed the downregulation of these sodium transporters in the obstructed kidney. The immunoreactivities of 1 and 1 subunits were decreased throughout

the tubules from cortex to inner medulla. The NHE3 immunoreactivity expressed on the apical membrane of the proximal tubule and cortical TAL was reduced. The BSC1 immunoreactivity was also reduced in TAL, while the TSC immunoreactivity was markedly decreased in the distal convoluted tubule[21]. The transport of sodium ions is basically linked to Na,K-ATPase activity in the basolateral membrane throughout the tubules. On the other hand, the secondary active secretion of hydrogen is coupled with the transport of sodium into the cell, mediated by NHE3 at the apical membrane. BSC1, localized at the apical domain of the cortical and medullary TAL, mediates sodium and chloride transport in these water impermeable segments, resulting in generation of the hypertonicity in medullary interstitium. TSC is involved in the apical movement of sodium in the distal convoluted tubule. Taken together, the decreased expression and activity of these sodium transporters may be causally related with a diminished urinary concentrating ability and a decreased tubular reabsorption of sodium. The expression of BSC1 may be stimulated by vasopressin/cAMP pathway[22]. However, it has been found that rats with BUO have significantly higher plasma values of vasopressin[23]. It is unlikely that the decreased expression of BSC1 is related with an altered activity of vasopressin/cAMP pathway in BUO. It has also been known that the expression of TSC in the distal tubule is stimulated by mineralocorticoids[24]. Therefore, one may blame an altered activity of mineralocorticoids for the altered expression of TSC. However, a suppression of aldosterone is not apparent in obstructive nephropathy, with its plasma levels remaining within or above the normal range[25]. The expression of these sodium transporters may have been influenced by local factors such as increased tubular pressure, uremic milieu or local hormones rather than systemic mineralocorticoid activity. Indeed, among others, the local atrial natriuretic peptide (ANP) system has been shown to be upregulated in the ureteral obstructed kidney[26, 27]. ANP decreases the sodium-hydrogen exchange in the proximal tubule, inhibits chloride reabsorption in the medullary TAL, increases cGMP in the distal tubule, and inhibits the tubular Na,K-ATPase activity[28]. In this context, the decreased abundance and activity of sodium transporters may at least in part be related with an increased activity of local ANP system. However, the underlying mechanisms remain to be further examined. It has been demonstrated that the abundance of sodium transporters may be decreased in a rat model of renal failure[29]. One may thus argue if there is any influence of renal failure on the expression of transporters in BUO. However, the expression of sodium transporters was similarly decreased in UUO, in which a renal failure was not evident. Our findings are also consistent with those recently shown by Li et al.[20], in which major sodium transporters were downregulated in the kidney in UUO. It is unlikely that the altered expression of these transporters be related with a renal failure in BUO.

In summary, the expression of NHE3, BSC1 and TSC was decreased along with the expression and activity of Na,K-ATPase in the ureteral obstructed kidney. The reduced abundance of these sodium transporters may in part account for the postobstructive natriuresis and diuresis.

3. Increased renal expression of atrial natriuretic peptide

Recent studies have shown that the kidney per se is also a site of production and release of ANP. ANP immunoreactive signals are localized to the distal tubule and intercalated cells of the collecting duct[30]. In addition, in vitro autoradiography and in situ hybridization demonstrated natriuretic peptide receptors (NPRs)-A, -B, and -C, and their respective mRNAs in the kidney[31]. The locally synthesized ANP may act in a paracrine manner to increase the urinary excretion of sodium and water. In this context, an altered regulation of ANP in the kidney may result in

an altered urinary excretion. We demonstrated that urinary volume and sodium excretion increased after release of BUO, along with the increased ANP mRNA expression in the kidney and the urinary ANP excretion. The ANP excretion positively correlated with the urinary volume and sodium excretion. The mRNA expression of both NPR-A and NPR-C was decreased by BUO, the latter being far more prominently affected. The maximal binding capacity of radiolabeled ANP was decreased in the glomerulus and papilla in BUO. ANP-stimulated cGMP generation was reduced in the glomerulus and papilla in BUO animals, which was rapidly resumed following the release of the obstruction[26]. It has been suggested that the endogenous ANP accounts for one fourth of the postobstructive diuresis[32]. The plasma ANP was indeed increased in BUO. An excessive retention of salt and water may occur during the period of obstruction, and hence, an expansion of extracellular fluid volume would account for the increased plasma ANP. When natriuretic and diuretic forces become manifest following the relief of obstruction in our study, however, the plasma ANP was decreased. Total volume excreted during the four-hour period of observation after release of BUO was estimated at up to one half of the plasma volume[26]. Therefore, the increase or the decrease of plasma ANP levels would merely reflect an increase or instant contraction of the extracellular fluid volume and may not be causally related to the postobstructive diuresis. This speculation may be in line with the previous notion that the degree of diuresis does not necessarily correlate with the plasma level of ANP[33].

The locally synthesized ANP in the kidney has been suggested to play a regulatory role in the urinary sodium and water excretion. Furthermore, its role may be altered in various pathophysiological states such as in DOCA-salt treated[34], diabetic[35], and subtotal nephrectomized[36] rats. Postobstructive diuresis may also be attributed to an altered regulation of local ANP system in the kidney. Indeed, the postobstructive diuresis was associated with an enhanced renal expression of ANP mRNA and an increased urinary excretion of ANP. Furthermore, the urinary ANP excretion positively correlated with the urinary flow and sodium excretion[26]. These findings support the hypothesis that an increased local synthesis of ANP is causally related to the postobstructive diuresis.

4. Altered regulation of local renal and vascular natriuretic peptide systems

Natriuretic peptides (NP) have been known to play a role in the cardiovascular homeostasis. Among the subtypes of NP receptor (NPR) thus far known, NPR-A has high affinities both for atrial NP (ANP) and brain NP (BNP), whereas NPR-B is selectively stimulated by C-type NP (CNP). They are linked to the particulate guanylyl cyclase, their activation resulting in a secondary formation of cGMP[37]. On the contrary, NPR-C binds to all the known NP ligands less tightly[38], acting in their metabolic clearance[37]. The biological activity of NP system may be affected by the tissue expression of NPR as well as of NP. The local NP system in its own right may exert an important role. Indeed, we have demonstrated that the postobstructive natriuresis is in part associated with an enhanced activity of local ANP system[26, 27]. In the vasculature, the local NP system plays a role in the vasorelaxation[39]. An altered regulation of vascular NP system may exist in association with ureteral obstruction, since the blood pressure may be increased following the obstruction of the urinary tract[40]. We demonstrated that the mRNA expression of ANP, BNP, and CNP was increased in the obstructed kidney and the thoracic aorta following the ureteral obstruction, along with an increased systemic blood pressure[41]. A substantial vasoconstriction of the renal vascular bed has been predominantly observed after ureteral obstruction, thereby reducing GFR and effective renal plasma flow[42]. The increased synthesis of NP may permit the prolonged diuresis in the pre-

viously obstructed kidney, being as a compensatory mechanism to preserve the renal function. The locally synthesized NP in the vasculature may then compensate for the hypertension induced by fluid volume retention. On the contrary, the expression of different subtypes of NPR was decreased in the kidney and the aorta in BUO. An elevated tubular pressure, hypertension and uremic milieu may be responsible for the reduced functional receptors. However, it has been shown that an exposure to ANP results in a reduction of NPR in cultured vascular smooth muscle cells43). In this context, the down-regulation of NPR may be attributed to an enhanced local synthesis of NP. The altered expression of NPR-A and NPR-B may be manifested by an altered biological effect of NP system. The effects of NP may be dissipated when the expression of its active receptors, NPR-A and NPR-B, is decreased. Indeed, the decreased NPR-A and NPR-B expression was associated with a decreased guanylyl cyclase activity in BUO. However, it has been shown that the decreased guanylyl cyclase activity is rapidly reversible upon releasing the ureteral obstruction[26, 27]. Taken together, enhanced local synthesis of NP along with a rapid recovery of guanylyl cyclase activity may allow an increased natriuresis in the previously obstructed kidney.

In summary, the expression of ANP, BNP and CNP was increased in the kidney and the aorta in BUO. The expression of NPR-A, NPR-B, and NPR-C was decreased, along with decreased guanylyl cyclase activity. They may be causally related with the postobstructive diuresis and the altered hemodynamic regulation and blood pressure in BUO.

5. Role of dendroaspis natriuretic peptide

Dendroaspis natriuretic peptide (DNP) has been recently added among the members of natriuretic peptide family[44]. As with other natriuretic peptides, it has a potent vasorelaxant effect and plays a regulatory role in the urinary sodium excretion, in association with a secondary generation of cyclic guanosine monophosphate (cGMP)[45]. We demonstrated an increase of plasma DNP immunoreactivity following the experimental BUO46). An increase of plasma ANP concentrations has been associated with an increased intravascular volume, such as in congestive heart failure (CHF)[47] and bilateral ureteral obstruction[26]. It has been recently observed that the plasma level of DNP immunoreactivity is also increased in CHF[48]. Immunohistochemistry for DNP also revealed positive staining in the atrial and ventricular myocardium in dogs, which was increased in CHF[49]. It is likely that an expansion of the intravascular volume during the period of ureteral obstruction leads to an increased synthesis and release of DNP as well as of ANP. A decreased number of functioning nephrons and hence impaired clearance of the hormone in the kidney may also contribute to the increase of plasma DNP, since the circulating natriuretic peptides are mainly degraded in the kidney[50]. Although DNP has been detected in the urine[45], its presence in the kidney has not been determined. Our study demonstrated DNP immunoreactivities in the rat kidney, which was not affected by the ureteral obstruction. Nor were the cardiac tissue levels of DNP altered[46]. Although the tissue DNP immunoreactivity in the heart and kidney, unlike that in the plasma, was not significantly affected by the ureteral obstruction, this finding does not necessarily indicate an unaltered production of the hormone. A rapid secretion of the hormone despite an increased synthesis may prevent its pile-up in the tissue. It has been indeed shown that the tissue level of ANP is similar between normal and failing rat atria, although circulating levels of the hormone are increased in association with increased production by the failing myocardium in CHF[47]. In this context, the increased plasma levels of DNP with no significant changes of its tissue levels may be indicative of an increased synthesis followed by a rapid secretion. Natriuretic peptides exert their biological effects through binding to their mem-

brane-bound receptors and subsequently activating particulate guanylyl cyclase, leading to a generation of cGMP. Therefore, measurements of urinary cGMP may be a useful marker indicating the production and release of the natriuretic peptides. We also observed that the urinary excretion of cGMP was significantly higher in the experimental group of rats with ureteral obstruction. The elevated cGMP excretion in the urine in the postobstructed kidney may be a reflection of the higher circulating values of natriuretic peptides including DNP as well as ANP.

In summary, the plasma DNP level was increased following an experimental ureteral obstruction. The urinary excretion of DNP was increased along with the postobstructive diuresis. An enhanced activity of DNP system may in part play a role in mediating the postobstructive diuresis.

Conclusion

The protein abundance of AQP water channels was decreased in the ureter-obstructed kidneys, which may at least in part account for the urinary concentration defect in postobstructive diuresis. The expression of NHE3, BSC1 and TSC was decreased along with the expression and activity of Na,K-ATPase in the ureteral obstructed kidney. The reduced abundance of these sodium transporters may in part account for the postobstructive natriuresis and diuresis. Postobstructive diuresis may also be attributed to an altered regulation of local ANP system in the kidney. Indeed, the postobstructive diuresis was associated with an enhanced renal expression of ANP mRNA and an increased urinary excretion of ANP. Furthermore, the urinary DNP as well as ANP excretion positively correlated with the urinary flow and sodium excretion. These findings support the hypothesis that an increased local synthesis of natriuretic peptide is causally related to the postobstructive diuresis.

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