# CHAPTER I

## INTRODUCTION

### BACKGROUND AND RATIONALE

Ureteral obstruction (UO) occurs when the kidneys produce urine normally, but the urine is unable to drain out of the afferent ureter into the bladder (Klahr, 2001). The urine backs up causing distention of the kidney structures, including the renal pelvis and calyces (hydronephrosis). A sudden blockade of ureter causes acute UO, while slow, progressive blockade causes chronic UO (Klahr, 2001; Klahr et al., 1998). The most common cause for acute UO is a kidney stone, although a condition that suddenly causes an obstruction of ureter, such as trauma, could result in the disorder. Hydronephrosis in acute UO induces a permanent damage to the kidney (failure of kidney) (Klahr, 2001; Klahr et al., 1998).

UO leads to decrease renal blood flow (RBF), glomerular filtration rate (GFR) (Hammad et al., 2000; Bander et al., 1985), urine output, reabsorption of solutes (sodium) and water (Hammad et al., 2000). The obstruction could impair excretion of hydrogen, potassium, and could induce acidification defect (Vaughanet et al., 1970). The infiltration of the kidney by macrophages (Klahr and Morrissey, 1997), and subsequently fibrosis of the tubulointerstitium (Klahr and Purkerson, 1994) are oftenly observed. These changes involve several vasoactive compounds, such as angiotensin II (ANG II) (Frokiaer, et al., 1992; Ishidoya et al., 1995), nitric oxide (NO) (Pimentel et al., 1993), thromboxane A2 (TBXA2) (Yarger et al., 1980), prostaglandin E2 (PGE2) (Yarger et al., 1980), as well as endothelin (ET) (Hammad et al., 2000).

ANG II, a potent vasoconstrictor that production is rapidly stimulated following the onset of ureteral obstruction (Pimentel et al., 1993). Most of the biological effects of angiotensin are transduced by angiotensin II type 1 (AT1) receptor. (Satoh et al., 2001). These result in increased mean arterial pressure (MAP), induced elevation of afferent and efferent glomerula arterioles leading to RBF and GFR decrement (Klahr and Morrissey, 1998), as well as reduced reabsorption of $Na^+$ by inhibiting of $Na^+$, $K^+$ ATPase (MaLi-jun and Fogo, 2001).

There is an increasing evidence for a pivotal role of ANG II in influencing renal tubular and interstitial function and structure. These include regulation of multiple cytokines and chemokines (Klahr and Morrissey, 1998), and promoting infiltration of monocytes/macrophages (Sharma et al., 1993; Klahr and Morrissey, 1997), transforming growth factor - β1 (TGF - β1) (Kaneto et al., 1993; Pimentel et al., 1995), tumor necrosis factor-α (TNF - α ) (Gou et al., 2001), platelet-derived growth factor (PDGF), and nuclear factor kappa B (NF-kB) (Bander et al., 1985; Hammad et al., 2000) expression. These mediators are important for fibrous tissue formation which can cause renal damage.

Treatments with angiotensin converting enzyme inhibitor (ACEI) or AT1 receptor antagonist (ARA) have been shown to have a beneficial effect in UO (Ishidoya et al., 1995; Klahr and Morrissey, 1997). Both treatments lead to decrease MAP, but increase RBF as well as GFR (Klahr and Morrissey, 1997) and prevent the progression of tubulointerstilial fibrosis (Ishidoya et al., 1995; Kaneto et al., 1994). However, a competitive blockade with ARA could prevent monocyte/macrophage infiltration in kidney with UO (Klahr and Morrissey, 1997).

It has been found that, besides ANG II, NO also is stimulated during UO (Morrissey et al., 1996; Huang et al., 2000; Schulsinger et al., 1997). NO is a highly reactive gas that has a potent effect on renal function including decrease in arterial blood pressure (BP) and increases in renal plasma flow (RPF) and GFR (Moncada et al., 1991; Tolins et al., 1990). In addition, NO could act as an antifibrotic factor in the chronic phase of UO (Morrissey et al., 1996).

NO is synthesized from its precursor, L-arginine, by the enzyme nitric oxide syntheses (NOS). Three distinct NOS isoforms have been identified, including the two constitutive forms of endothelial (eNOS) and neuronal (nNOS) origin. These are transiently activated by agonists inducing elevation of intracellular calcium ($Ca^{2+}$) (Fleming et al., 1998). The third isoform, inducible NOS (iNOS), can be induced by cytokines (Fleming et al., 1998).

NO production is rapidly increased in rats with UO (Pimentel et al., 1993). Both iNOS as well as eNOS mRNA expression and protein are increased in UO rats (Hegarty et al., 2001). The iNOS knockout mice show decreased renal fibrosis and NO production during UO (Huang et al., 2000). On the other hand, the eNOS knockout mice can increase NO production (Chang et al., 2002). Administration of $N^{w}$- nitric- L-arginine methyl ester (L-NAME; non selective NOS inhibitor) significantly increases MAP but decreases RBF and renal function (Chevalier et al., 1992). L-NAME also reduces $Na^{+}$ and water excretion (Lahera et al., 1991). These results are similar to those observed with increased ANG II (Blantz et al., 1976). Both ACEI and ARA prevent most of the changes in renal and glomerular hemodynamics associated with NO inhibition (Nicola et al., 1992). In contrast, an acute suprarenal infusion of ANG II

increases renal eNOS mRNA expression, while a chronic infusion increases eNOS protein expression (Hennington et al., 1998; Moreno et al., 2002). These data suggest that ANG II can stimulate eNOS synthesis and this may be one of the mechanisms which ANG II enhances NO production (Hennington et al., 1998; Moreno et al., 2002).

Both of which interact closely at least in the regulation of renal function and may affect renal dysfunction through many mechanisms. However, at present, there is no study regarding the role of angiotensin system on renal NOS expression as well as NO production during UUO. In the present study, ACEI as well as ARA was used to evaluate the role of ANG II on renal NOS expression and NO production in UUO model.