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Effects of Nitric Oxide Synthase (NOS) Blockers on Renal Function

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Over the past 10 years, NOS blockers have been utilized as a major tool to define the role of NO in renal physiology and pathophysiology. Three types of NOS isoforms, neuronal NOS (bNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) are expressed in the different structures of the kidney. The use of more selective NOS blockers has helped our understanding of the function of each one of the three isoforms in various renal physiologic functions. Studies from our and other laboratories several years ago revealed that administration of non specific NOS blockers (L-NMMA) increased systemic blood pressure and modified renal function. At the single nephron level, L-NMMA produced a reduction in nephron filtration rate secondary to reductions in both the ultrafiltration coefficient and nephron plasma flow, the later due to increased afferent and efferent glomerular arteriolar resistances. Studies utilizing angiotensin II receptor blockers revealed that AII blockade suppressed the effect of L-NMMA on efferent arteriolar resistance and ultrafiltration coefficient suggesting the presence of an important interaction between NO and AII in the control of renal hemodynamics. L-NMMA also decreased proximal tubular reabsorption, an effect also abrogated by AII blockade. Follow up studies in our laboratory looking at the interaction between NO and AII demonstrated that administration of non specific NOS blockers (L-NMMA or L-NAME) led to a dissociation between plasma and kidney tissue AII levels where L-NMMA reduced significantly plasma AII levels without modifying kidney AII concentrations. The mechanism responsible for this dissociation remains ill defined but these findings explain the beneficial effects of AII blockade on renal function in the absence of an antihypertensive effect in L-NNMA treated rats. Studies in our laboratory went on to investigate the presence of an interaction between the renal adrenergic system and NO based on our previous findings of renal adrenergic system-AII interaction. Our results demonstrate that renal denervation prevents most of the effects of L-NMMA on glomerular hemodynamics (reduced ultrafiltration coefficient and increased efferent resistance) and tubular function (reduction in proximal reabsorption). Follow up studies in denervated rats revealed that administration of an $\alpha_2$adrenergic receptor agonist restored the glomerular and tubular response to L-NMMA suggesting the presence of an important interaction between AII, renal adrenergic system and NO in the control of normal renal function.

Neuronal NOS is mainly located at the level of the macula densa where NO derived from this enzyme modulates activity of the tubuloglomerular feedback system. We recently investigated the role of neuronal NOS in diabetes-induced hyperfiltration using bNOS blockers. These agents selectively reduced GFR in diabetic rats suggesting that hyperfiltration and decreased tubuloglomerular feedback activity observed in experimental diabetes are mediated by increased bNOS activity. Interestingly, combining bNOS blockers and L-NMMA did not produce any further change in GFR implying that correction of diabetic hyperfiltration with L-NMMA depends on increased bNOS activity and not eNOS as previously suggested.

Our group has also examined the role of iNOS in various renal disease models, including LPS and autoimmune tubulointerstitial nephritis. Both conditions are characterized by significant baseline reductions in GFR and improvement in GFR after administration of iNOS blockers. This unexpected finding where too much NO may be as deleterious as very little NO for kidney function seems rather peculiar to the kidney. It suggests however the presence of highly complex interactions between the three different NOS isoforms with potential autoinhibition phenomenom and between NO and the renal neurohumoral system.