Renal Obstruction and Inducible Nitric Oxide Synthase (iNOS) Review

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Abstract: Renal obstructiion is a condition in which the urine flow is blocked. This causes the urine to back up and injure kidneys. Obstructive uropathy occurs when urine cannot drain through a ureter. Urine backs up into the kidney and causes it to become hydronephrosis. Nitric oxide synthases (NOSs, EC 1.14.13.39) are a family of enzymes catalyzing the production of nitric oxide (NO) from L-arginine. NO is an important cellular signaling molecule that helps to modulate the vascular tone, insulin secretion, airway tone and peristalsis, etc, and it is involved in angiogenesis and neural development. It may function as a retrograde neurotransmitter.
[Ma H, Young M. **Inducible Nitric Oxide Synthase (iNOS) and Renal Obstruction Research Literatures.** *Researcher* 2015;7(5):39-44]. (ISSN: 1553-9865). http://www.sciencepub.net/researcher. 8

Key words: inducible nitric oxide synthase (iNOS); obstruction; renal

Introduction

Renal obstructiion is a condition in which the flow of urine is blocked, which causes the urine to back up and injure the kidneys. Obstructive uropathy occurs when urine cannot drain through a ureter. Urine backs up into the kidney and causes it to become hydronephrosis. It can occur suddenly, or be a long-term problem. If the blockage comes on suddenly, kidney damage is less. Long-term damage to the kidneys may occur if the blockage has been present for a long time. If the problem is caused by a blockage in the bladder, the bladder may have long-term damage, which may lead to problems emptying the bladder or leakage of urine.

Nitric oxide synthases (NOSs, EC 1.14.13.39) are a family of enzymes catalyzing the production of nitric oxide (NO) from L-arginine. NO is an important cellular signaling molecule that helps to modulate the vascular tone, insulin secretion, airway tone and peristalsis, etc, and it is involved in angiogenesis and neural development, and it may function as a retrograde neurotransmitter. The inducible isoform, iNOS, is involved in immune response, binds calmodulin at physiologically relevant concentrations, and produces NO as an immune defense mechanism. NO is a free radical with an unpaired electron that is the proximate cause of septic shock and may function in autoimmune disease.

NOSs are unusual in that they require five cofactors. Eukaryotic NOS isozymes are catalytically self-sufficient. The electron flow in the NO synthase reaction is: NADPH → FAD → FMN → heme → O2. Tetrahydrobiopterin provides an additional electron during the catalytic cycle which is replaced during turnover. Arginine-derived NO synthesis has been identified in mammals, fish, birds, invertebrates, and bacteria.

There are three known isoforms in mammals, two are constitutive (cNOS) and the third is inducible (iNOS). Cloning of NOS enzymes indicates that cNOS include both brain constitutive (NOS1) and endothelial constitutive (NOS3); the third is the inducible (NOS2) gene. The inducible isoform iNOS produces large amounts of NO as a defense mechanism.

Induction of the high-output iNOS usually occurs in an oxidative environment, and thus high levels of NO have the opportunity to react with superoxide leading to peroxynitrite formation and cell toxicity. These properties may define the roles of iNOS in host immunity, enabling its participation in anti-microbial and anti-tumor activities as part of the oxidative burst of macrophages. All three isoforms (each of which is presumed to function as a homodimer during activation) share a carboxyl-terminal reductase domain homologous to the cytochrome P450 reductase.

The following introduces recent reports as references in the related studies.

Akgul, T., E. Huri, et al. "Phosphodiesterase 5 inhibitors attenuate renal tubular apoptosis after partial unilateral ureteral obstruction: an experimental study." Kaohsiung J Med Sci. 2011 Jan;27(1):15-9. doi: 10.1016/j.kjms.2010.03.001. Epub 2011 Jan 28.

There were significant differences in apoptotic cell counts between sildenafil group and the other two study groups. The sildenafil group demonstrated lesser apoptotic cell count than the vardenafil (p=0.021) and tadalafil (p=0.009) groups. PUUO increases the renal tubular apoptosis and elevates NOS concentrations in renal tubular tissue after PUUO. Phosphodiesterase 5 inhibitors have a protective effect against the tubular apoptosis.

Broadbelt, N. V., P. J. Stahl, et al. "Early upregulation of iNOS mRNA expression and increase in NO

metabolites in pressurized renal epithelial cells." Am J Physiol Renal Physiol. 2007 Dec;293(6):F1877-88. Epub 2007 Sep 19.

With the use of a designed apparatus, pressure led to an extremely early induction of iNOS and a rapid activation of NOS activity to increase NO and cGMP in proximal tubule epithelial cells. The rapid effects of pressure on iNOS may have important implications in the obstructed kidney.

Chade, A. R., M. Rodriguez-Porcel, et al. "Antioxidant intervention blunts renal injury in experimental renovascular disease." J Am Soc Nephrol. 2004 Apr;15(4):958-66.

Chronic antioxidant intervention in early experimental renovascular disease (RVD) improved renal functional responses, enhanced tissue remodeling, and decreased structural injury. This study supports critical pathogenic contribution of increased oxidative stress to renal injury and scarring in RVD and suggests a role for antioxidant strategies in preserving the atherosclerotic and ischemic kidney.

Cherla, G. and E. A. Jaimes "Role of L-arginine in the pathogenesis and treatment of renal disease." J Nutr. 2004 Oct;134(10 Suppl):2801S-2806S; discussion 2818S-2819S.

L-arginine is reduced in preeclampsia and recent experimental studies indicate that L-arginine supplementation may be beneficial in attenuating the symptoms of preeclampsia. Administration of exogenous L-arginine has been shown to be protective in ischemic acute renal failure. In summary, the role of L-arginine in the pathogenesis and treatment of renal disease is not completely understood and remains to be established.

Chiang, C. W., H. T. Lee, et al. "Genetic deletion of soluble epoxide hydrolase attenuates inflammation and fibrosis in experimental obstructive nephropathy." Mediators Inflamm. 2015;2015:693260. doi: 10.1155/2015/693260. Epub 2015 Jan 22.

The levels of superoxide anion radical and hydrogen peroxide as well as NADPH oxidase activity were also decreased in UUO kidneys of sEH (-/-) mice compared to that observed in WT mice. Collectively, our findings suggest that sEH plays an important role in the pathogenesis of experimental obstructive nephropathy and may be a therapeutic target for the treatment of obstructive nephropathy-related diseases.

Chow, B. S., M. Kocan, et al. "Relaxin requires the angiotensin II type 2 receptor to abrogate renal interstitial fibrosis." Kidney Int. 2014 Jul;86(1):75-85. doi: 10.1038/ki.2013.518. Epub 2014 Jan 15.

Relaxin's antifibrotic actions were significantly blocked by PD123319 in vitro and in vivo, or when relaxin was administered to AT2R-knockout mice. While heterodimer complexes were formed between RXFP1 and AT2Rs independent of ligand binding, relaxin did not directly bind to AT2Rs but signaled through RXFP1-AT2R heterodimers to induce its antifibrotic actions. These findings highlight a hitherto unrecognized interaction that may be targeted to control fibrosis progression.

Dikmen, B., H. Yagmurdur, et al. "Preventive effects of propofol and ketamine on renal injury in unilateral ureteral obstruction." J Anesth. 2010 Feb;24(1):73-80. doi: 10.1007/s00540-009-0861-1.

Propofol as an anesthetic agent may attenuate NO-induced renal tubular cell apoptosis by downregulating the expression of iNOS in an animal model of unilateral UO.

Ebrahimi, B., Z. Li, et al. "Addition of endothelial progenitor cells to renal revascularization restores medullary tubular oxygen consumption in swine renal artery stenosis." Am J Physiol Renal Physiol. 2012 Jun 1;302(11):F1478-85. doi: 10.1152/ajprenal.00563.2011. Epub 2012 Mar 14.

Endothelial progenitor cells (EPC) delivery, in addition to percutaneous transluminal renal angioplasty (PTRA), restores medullary oxygen-dependent tubular function, despite impaired medullary blood and oxygen supply. These results support further development of cell-based therapy as an adjunct to revascularization of renal artery stenosis (RAS).

Eskild-Jensen, A., K. Thomsen, et al. "Glomerular and tubular function during AT1 receptor blockade in pigs with neonatal induced partial ureteropelvic obstruction." Am J Physiol Renal Physiol. 2007 Mar;292(3):F921-9. Epub 2006 Nov 28.

The counterbalance between AT1 receptor-mediated vasoconstriction and NO-mediated vasodilatation which maintain GFR in normal young porcine kidneys is changed by neonatal induced chronic PUUO. This may have diagnostic potential in children with suspected congenital obstruction.

Felsen, D., D. Schulsinger, et al. "Renal hemodynamic and ureteral pressure changes in response to ureteral obstruction: the role of nitric oxide." J Urol. 2003 Jan;169(1):373-6.

Arginine infusion 18 hours after unilateral ureteral obstruction led to increases in renal blood flow and ureteral pressure that were not seen in control animals. These results suggest that the nitric oxide system of the kidney is activated in unilateral ureteral

obstruction. Since the addition of arginine is accompanied by an increase in renal blood flow and ureteral pressure, it further suggests that a lack of availability of substrate for NOS may explain the decrease in renal blood flow and ureteral pressure in obstruction. Providing substrate may be a way of maintaining renal blood flow in unilateral ureteral obstruction.

Fitzgerald, J., S. Y. Chou, et al. "Regional expression of inducible nitric oxide synthase in the kidney in dogs with unilateral ureteral obstruction." J Urol. 2001 Oct;166(4):1524-9.

Unilateral ureteral obstruction enhances nitric oxide synthase expression in the medulla but not in the cortex. This increased expression in the medulla may be the result of increased medullary hypoxia in unilateral ureteral obstruction, possibly contributing to medullary hyperemia after unilateral ureteral obstruction release.

Glynne, P. A., J. Picot, et al. "Coexpressed nitric oxide synthase and apical beta(1) integrins influence tubule cell adhesion after cytokine-induced injury." J Am Soc Nephrol. 2001 Nov;12(11):2370-83.

These studies provide a mechanism by which inflammatory cytokines induce PTEC damage in sepsis, in the absence of hypotension and ischemia. Future therapeutic strategies aimed at specific iNOS inhibition might inhibit PTEC shedding after cytokine-induced injury and delay the onset of acute renal failure in sepsis.

Grau, V., O. Stehling, et al. "Accumulating monocytes in the vasculature of rat renal allografts: phenotype, cytokine, inducible no synthase, and tissue factor mRNA expression." Transplantation. 2001 Jan 15;71(1):37-46.

The large numbers of activated monocytes accumulate inside allograft vessels. As they express genes the products of which might damage the allograft by inducing cell death or thrombosis, we speculate that they directly participate in allograft destruction.

Gueler, F., S. Rong, et al. "Postischemic acute renal failure is reduced by short-term statin treatment in a rat model." J Am Soc Nephrol. 2002 Sep;13(9):2288-98.

The hydroxy-3-methylglutaryl coenzyme A reductase inhibition protects renal tissue from the effects of ischemia-reperfusion injury and thus reduces the severity of ARF. The chain of events may involve anti-inflammatory effects, with inhibition of mitogen-activated protein kinase activation and the redox-sensitive transcription factors nuclear factor-kappaB and activator protein-1.

Hanatani, S., Y. Izumiya, et al. "Akt1-mediated fast/glycolytic skeletal muscle growth attenuates renal damage in experimental kidney disease." J Am Soc Nephrol. 2014 Dec;25(12):2800-11. doi: 10.1681/ASN.2013091025. Epub 2014 Jul 10.

Akt1-mediated muscle growth reduces renal damage in a model of obstructive kidney disease. This improvement appears to be mediated by an increase in eNOS signaling in the kidney. Our data support the concept that loss of muscle mass during kidney disease can contribute to renal failure, and maintaining muscle mass may improve clinical outcome.

Hegarty, N. J., L. S. Young, et al. "Nitric oxide in unilateral ureteral obstruction: effect on regional renal blood flow." Kidney Int. 2001 Mar;59(3):1059-65.

NO plays a vasodilatory role even in the hypoperfusion of prolonged UO. The administration of exogenous nitrates has a restorative effect on blood flow, suggesting therapeutic potential in UO.

Hewitson, T. D., M. G. Tait, et al. "Dipyridamole inhibits in vitro renal fibroblast proliferation and collagen synthesis." J Lab Clin Med. 2002 Sep;140(3):199-208.

The results of this study demonstrate that at clinically relevant concentrations, dipyridamole inhibits profibrotic activities of renal fibroblasts. Effects on mitogenesis are mediated through a cyclic guanosine monophosphate-protein kinase G effector pathway.

Hochberg, D., C. W. Johnson, et al. "Interstitial fibrosis of unilateral ureteral obstruction is exacerbated in kidneys of mice lacking the gene for inducible nitric oxide synthase." Lab Invest. 2000 Nov;80(11):1721-8.

NO produced via the inducible NOS normally serves a protective function in UUO.

Ito, K., H. Yoshii, et al. "Adrenomedullin increases renal nitric oxide production and ameliorates renal injury in mice with unilateral ureteral obstruction." J Urol. 2010 Apr;183(4):1630-5. doi: 10.1016/j.juro.2009.12.002. Epub 2010 Feb 20.

Adrenomedullin increased renal nitric oxide, and suppressed tubular apoptosis, interstitial fibrosis and inflammatory cell infiltration in mice with unilateral ureteral obstruction. The renoprotective peptide adrenomedullin may be useful for that condition.

Kim, J. and B. J. Padanilam "Loss of poly(ADP-ribose) polymerase 1 attenuates renal fibrosis and inflammation during unilateral ureteral obstruction."

Am J Physiol Renal Physiol. 2011 Aug;301(2):F450-9. doi: 10.1152/ajprenal.00059.2011. Epub 2011 May 25.

PARP1 induces necrotic cell death and contributes to inflammatory signaling pathways that trigger fibrogenesis in obstructive nephropathy.

Kipari, T., J. F. Cailhier, et al. "Nitric oxide is an important mediator of renal tubular epithelial cell death in vitro and in murine experimental hydronephrosis." Am J Pathol. 2006 Aug;169(2):388-99.

The nitric oxide is a key mediator of macrophage-directed tubular cell apoptosis in vitro and in vivo and also modulates tubulointerstitial fibrosis.

Knerr, I., K. Dittrich, et al. "Alteration of neuronal and endothelial nitric oxide synthase and neuropeptide Y in congenital ureteropelvic junction obstruction." Urol Res. 2001 Apr;29(2):134-40.

The alterations in NOS gene expression and NPY innervation in tissue specimens of patients with congenital ureteropelvic junction obstruction.

Lo, T. H., K. Y. Tseng, et al. "TREM-1 regulates macrophage polarization in ureteral obstruction." Kidney Int. 2014 Dec;86(6):1174-86. doi: 10.1038/ki.2014.205. Epub 2014 Jun 11.

Chronic kidney disease (CKD) is an emerging worldwide public health problem. Inflammatory cell infiltration and activation during the early stages in injured kidneys is a common pathologic feature of CKD.

Manucha, W. and P. G. Valles "Cytoprotective role of nitric oxide associated with Hsp70 expression in neonatal obstructive nephropathy." Nitric Oxide. 2008 May;18(3):204-15. doi: 10.1016/j.niox.2008.01.005. Epub 2008 Feb 1.

Nitric oxide (NO) has emerged as an important endogenous inhibitor of apoptosis. The NO can produce resistance to obstruction-induced cell death by mitochondrial apoptotic pathway, through the induction of Hsp70 expression, in neonatal unilateral ureteral obstruction.

Mazzei, L., I. M. Garcia, et al. "WT-1 mRNA expression is modulated by nitric oxide availability and Hsp70 interaction after neonatal unilateral ureteral obstruction." Biocell. 2010 Dec;34(3):121-32.

Wilms tumor gene 1 (wt-1), a key regulator of mesenchymal-epithelial transformation, is downregulated during congenital obstructive nephropathy, leading to apoptosis. The rosuvastatin may modulate WT-1 mRNA expression through renal nitric oxide bioavailability, preventing neonatal obstruction-induced apoptosis associated with Hsp70 interaction.

Miyajima, A., J. Chen, et al. "Interaction of nitric oxide and transforming growth factor-beta1 induced by angiotensin II and mechanical stretch in rat renal tubular epithelial cells." J Urol. 2000 Nov;164(5):1729-34.

Changes in intrarenal pressure accompanying unilateral ureteral obstruction can result in tubular mechanical stretch and mediator release from renal tubules. The nitric oxide is an intermediate in angiotensin II stimulated TGF-beta1 expression but not in stretch induced TGF-beta expression, and that TGF-beta1 is a negative regulator of nitric oxide in rat renal epithelial cells. The complex interaction of these cytokines may be a target for intervention in the fibrotic and apoptotic processes in the obstructed kidney.

Miyajima, A., J. Chen, et al. "Role of nitric oxide in renal tubular apoptosis of unilateral ureteral obstruction." Kidney Int. 2001 Apr;59(4):1290-303.

The obstructed kidney in unilateral ureteral obstruction (UUO) is characterized by renal atrophy and tissue loss, which is mediated by renal tubular apoptosis. The mechanical stretch is related to renal tubular apoptosis and that NO plays a protective role in this system in UUO.

Moosavi, S. M., Z. Bagheri, et al. "Pre- or post-treatment with aminoguanidine attenuates a renal distal acidification defect induced by acute ureteral obstruction in rats." Can J Physiol Pharmacol. 2013 Nov;91(11):920-8. doi: 10.1139/cjpp-2013-0059. Epub 2013 Jun 20.

Acute unilateral ureteral obstruction (UUO) impairs distal nephron acid secretion and stimulates expression of inducible nitric oxide synthase (iNOS) in post-obstructed kidney (POK). The in vivo application of a selective iNOS inhibitor partially improved the acute UUO-induced distal nephron acidification defect, while post-treatment but not pre-treatment with aminoguanidine ameliorated decrements of glomerular filtration, sodium reabsorption, and urine-concentrating ability.

Moridaira, K., H. Yanagisawa, et al. "Enhanced expression of vsmNOS mRNA in glomeruli from rats with unilateral ureteral obstruction." Kidney Int. 2000 Apr;57(4):1502-11.

An increase in vsmNOS mRNA expression in glomeruli of the CLK and OK from rats with UUO may be mediated by increased action of endogenous angiotensin II that occurs after the onset of ureteral obstruction.

Morisada, N., M. Nomura, et al. "Complete disruption of all nitric oxide synthase genes causes markedly accelerated renal lesion formation following unilateral ureteral obstruction in mice in vivo." J Pharmacol Sci. 2010;114(4):379-89. Epub 2010 Nov 9.

The role of nitric oxide (NO) derived from all three NO synthases (NOSs) in renal lesion formation remains to be fully elucidated. We addressed this point in mice lacking all NOSs.

Nishida, M., Y. Okumura, et al. "The role of apelin on the alleviative effect of Angiotensin receptor blocker in unilateral ureteral obstruction-induced renal fibrosis." Nephron Extra. 2012 Jan;2(1):39-47. doi: 10.1159/000337091. Epub 2012 Mar 7.

Therough the apelin/APJ/Akt/eNOS pathway may, at least in part, contribute to the alleviative effect of losartan in UUO-induced renal fibrosis.

Ozbek, E., Y. O. Ilbey, et al. "Melatonin attenuates unilateral ureteral obstruction-induced renal injury by reducing oxidative stress, iNOS, MAPK, and NF-kB expression." J Endourol. 2009 Jul;23(7):1165-73. doi: 10.1089/end.2009.0035.

PURPOSE: To investigate whether melatonin (MLT) treatment has any protective effect on unilateral ureteral obstruction (UUO)-induced kidney injury in rats. MLT may prevent UUO-induced kidney damage in rats by reducing oxidative stress. The mechanism for this is likely mediated via reduction in the expression of iNOS, p38-MAPK, and NF-kB, since MLT reduces the activation of these pathways.

Rivera-Huizar, S., A. R. Rincon-Sanchez, et al. "Renal dysfunction as a consequence of acute liver damage by bile duct ligation in cirrhotic rats." Exp Toxicol Pathol. 2006 Nov;58(2-3):185-95. Epub 2006 Jul 7.

Renal failure is a common complication in patients with alcohol-induced cirrhosis who undergo a superimposed severe alcoholic hepatitis.

Stern, J. M., J. Chen, et al. "Effect of UUO on D1aR expression reveals a link among dopamine, transforming growth factor-beta, and nitric oxide." Am J Physiol Renal Physiol. 2004 Mar;286(3):F509-15. Epub 2003 Nov 11.

Dopamine (DA) modulates the release of cytokines, which are involved in the fibrotic and apoptotic sequelae of UUO, and that these effects are independent of DA's known vasoactive properties.

Sun, D., Y. Wang, et al. "Effects of nitric oxide on renal interstitial fibrosis in rats with unilateral ureteral obstruction." Life Sci. 2012 Jun 14;90(23-24):900-9. doi: 10.1016/j.lfs.2012.04.018. Epub 2012 Apr 30.

The administration of L-Arg promoted the synthesis of NO and significantly elevated the expressions of VEGF, eNOS and PTC density with the conspicuous loss of HIF-1alpha and TGF-beta1 expressions and ultimately ameliorated renal fibrosis, which was markedly aggravated by L-NAME administration.

Valles, P. G., L. Pascual, et al. "Role of endogenous nitric oxide in unilateral ureteropelvic junction obstruction in children." Kidney Int. 2003 Mar;63(3):1104-15.

In kidneys from children with UPJ obstruction an increased activity and expression of iNOS in medulla and cNOS-dependent eNOS in cortex were demonstrated. A role of cNOS in modulating GFR and interstitial fibrosis can be suggested. Prolonged UPJ obstruction would lead to a worsened prognosis on renal injury.

Vaughan, E. D., Jr., D. Marion, et al. "Pathophysiology of unilateral ureteral obstruction: studies from Charlottesville to New York." J Urol. 2004 Dec;172(6 Pt 2):2563-9.

Strategies for inhibiting fibrosis include antibody to TGF-beta, use of antisense oligonucleotides to TGF-beta, use of drugs that inhibit other pro-fibrotic mediators or gene therapy to inhibit fibrosis.

Zebger-Gong, H., J. Kampmann, et al. "Decreased transplant arteriosclerosis in endothelial nitric oxide synthase-deficient mice." Transplantation. 2010 Mar 15;89(5):518-26. doi: 10.1097/TP.0b013e3181c7dce4.

Upregulation of inducible NOS and nNOS isoforms may be beneficial in preventing allograft arteriosclerosis in the early posttransplant period.

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