Animal Models of Partial Ureteral Obstruction (PUO) and Unilateral Ureteral Obstruction (UUO) in Renal Research

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Abstract: Urinary traction infection frequently occurs in the obstructed kidney. The ureters are the long narrow tubes in animals that carry urine from each kidney to the bladder. For human, the ureters are approximately 30 centimeters long. It exits the kidney at the hilum, comes into close contact with common iliac arteries from the aorta. The ureters pass on the lateral abdominal wall and then enters the pelvis where it joins the urinary bladder, passing a short distance into it. Obstructive nephropathy is a serious problem for many patients in the chronic kidney disease. The kidney function declined in obstructive nephropathy is associated with structural derangements, which is reparative in an attempt to overcome the kidney injury caused by the obstruction of urine flow. With sustained obstruction, a permanent loss of renal function may occur. In this problem, renal fibrosis becomes a reactive process. Partial ureteral obstruction (PUO) and unilateral ureteral obstruction (UUO) produce well documented triphasic responses in the renal hemodynamics and renal damage. This is characterized by an early increase in renal blood flow, followed by a decrease toward baseline, and later progressive profound renal ischemia. A lot studies have been performed in rodent models of unilateral urinary tract obstruction.

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Introduction

End-stage renal disease (ESRD) is a big heath problem in the United States and it costs more than $30 billion each year on ESRD therapy in this country. The patients suffering from acute renal failure are even worse. The disease state arising from renal failure is the result of many factors. It is important to reveal the kidney's role in reclamation of metabolic substrates, synthesis of glutathione, free-radical scavenging enzymes, gluconeogenesis, ammoniagenesis, hormones, growth factors, and the production and regulation of multiple cytokines critical to inflammation and immunological. There is considerable drive to develop improved therapies for renal failure. It is estimated that there are over 2 million patients in USA who suffer from end-stage renal disease. About 60,000 patients in the United States are currently on the waiting list for a kidney transplant, and some patients have waited for several years before an appropriate donor can be found (Ma, et al, 2009a). Kidney is derived from the ureteric bud and metanephrogenic mesenchyme (Ma, et al, 2009b). It is important to develop the animal models in the renal research.

The ureters are the long narrow tubes in animals that carry urine from each kidney to the bladder. For human, the ureters are approximately 30 centimeters long. It exits the kidney at the hilum, comes into close contact with common iliac arteries from the aorta. The ureters pass on the lateral abdominal wall and then enters the pelvis where it joins the urinary bladder, passing a short distance into it. Obstructive nephropathy is a serious problem for many patients in the chronic kidney disease. The kidney function declined in obstructive nephropathy is associated with structural derangements, which is reparative in an attempt to overcome the kidney injury caused by the obstruction of urine flow. With sustained obstruction, a permanent loss of renal function may occur. In this problem, renal fibrosis becomes a reactive process. Partial ureteral obstruction (PUO) and unilateral ureteral obstruction (UUO) produce well documented triphasic responses in the renal hemodynamics and renal damage. This is characterized by an early increase in renal blood flow, followed by a decrease toward baseline, and later progressive profound renal ischemia. A lot studies have been performed in rodent models of unilateral urinary tract obstruction (Ma, et al, 2001).

In a mouse model of complete PUO, the angiotensin system regulates about half of the renal interstitial fibrotic response in the obstructed kidney (Fern et al., 1999). At some stage of obstructive nephropathy, pharmacological inhibition of the angiotensin system may not be effective to reduce renal fibrosis and irreversible renal damage would ensue (Klahr and Morrissey, 1998) (Fern et al., 1999; Klahr and Morrissey, 2002).

Interstitial fibrosis is a complex process involving inflammatory cell infiltration, fibroblast

proliferation, epithelial-mesenchymal transition, excessive extracellular matrix accumulation, and reduced matrix degradation (Bohle et al., 1994). This process is a saline feature of progressive renal disease and its extent correlates with renal function deterioration in either glomerular or tubulointerstitial diseases (Bohle et al., 1994; Nath, 1992). In obstructive nephropathy, inflammatory cells appear in the interstitial space shortly after urinary tract obstruction, releasing cytokines and growth factors which stimulate the fibrotic process (Fern et al., 1999; Klahr and Morrissey, 1998). Many studies have shown that inhibition of the renin-angiotensin system or transforming growth factor-β (TGF-β) ameliorates obstruction-induced tubulointerstitial fibrosis, suggesting that angiotensin II and TGF-beta are involved in the development of fibrosis (Guo et al., 2001; Isaka et al., 2000; Klahr and Morrissey, 1998; Miyajima et al., 2000).

Surjury propotols

1. Partial ureteral obstruction (PUO):

The rats are anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and a low midline abdominal incision is made. Right nephrectomy is performed first. The right kidney is mobilized with minimal dissection. Two 2-0 silk ties are placed around the hilar vessels and the right kidney is removed. The left ureter is then traced to its insertion in the bladder, mobilized with minimal dissection to preserve the surrounding neurovasculature and retracted with vessel loops. The psoas muscle is split by blunt dissection to create a space which would accommodate two-thirds of the length of the ureter. The left ureter is moved into that interstice, after which the muscle is reapproximated with three interrupted 5-0 silk sutures. The abdominal wound is then closed with sutures (Figure 1). For the sham operation, the rats underwent the same surgical procedure, including right nephrectomy, but the left ureter is diverted into the psoas muscle. After recovery from anesthesia, the rats are housed individually in metal cages and given buprenorphine hydrochloride (0.02 mg/kg BW, i.m.) to relieve postoperative discomfort. One night before the surgery and clearance experiments, the rats fast but have free access to water.

2. Unilateral ureteral obstruction (UUO):

Rats or mice are anesthetized by i.p. injection, and then shaved on the left side of the abdomen. A vertical incision is made through the skin with a scalpel and the skin is retracted. A second incision is made through the peritoneum and that skin is also retracted to reveal the kidney. Using forceps the kidney is brought to the surface and the ureter is tied with surgical silk, twice, below the kidney. The ligated kidney is placed gently back into its correct anatomical position and sterile saline is added to replenish loss of fluid. The incisions are sutured and mice are caged individually. About 6-days post ligation, the animals are placed in metabolic cages for the collection of urine. Animals are sacrificed 12-hours later and blood and tissues are collected when the sacrificing.

3. Reversal of unilateral ureteral obstruction (R-UUO) injury by mouse model

To induce UUO injury, male C57bl/6J mice (6–8 weeks, 20–25 g) are anaesthetized with 2% inhaled isofluorane. A small left flank incision was made to access the kidney and the ureter is obstructed using a stainless steel B-1V vascular clamp (0.4–1.0 mm). Incisions are sutured and the ureter remain obstructed for 10 days before kidney collection for analysis of obstruction injury, or a second surgery to reverse obstruction and initiate repair. Surgery for R-UUO is as for the induction of UUO with the exception that the vascular clamp is carefully removed from the ureter to allow urine reflow.

Discussion

Complete ureteral obstruction is not a usual cause of human renal disease. PUO and UUO models are useful to examine mechanisms of tubulointerstitial fibrosis in vivo. These models can be induced in either rats or mice and other animals and there is no specific strain dependence. Partial or reversible UUO models are useful techniques in the kidney study. PUO and UUO are good models for the renal research with animals.

Kidney disease is a significant medical problem globally. In the nephrology researches, there are several other models and ways besides PUO and UUO. The following are some examples:

1) Culture renal cells in the research.
2) Glomerular and interstitial injury models
3) Vascular injury models
4) Podocyte-specific genetic models
5) HIV-associated nephropathy transgenic model
6) Alport syndrome mutation model
7) Immune-induced model
8) Non-immune induced model
9) Radiation nephropathy model
10) Puromycin aminonucleoside nephrosis and adriamycin nephropathy
11) Complete ureteral obstruction (CUO)
12) Folic acid nephropathy
13) CyA nephropathy
14) DOCA-salt nephropathy

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References

1. H. Wissel, C. Schulz, P. Koehne, E. Richter, M. Maass, and M. Rüdiger, "*Chlamydophila pneumoniae* induces expression of Toll-like receptor 4 and release of TNF-α and MIP-2 via an NF-κB pathway in rat type II pneumocytes," *Respiratory Research*, vol. 6, article 51, 2005. http://respiratory-research.com/content/6/1/51.
2. John W. Hollingsworth II, Donald N. Cook, David M. Brass, Julia K. L. Walker, Daniel L. Morgan, W. Michael Foster, and David A. Schwartz. The Role of Toll-like Receptor 4 in Environmental Airway Injury in Mice. Am J Respir Crit Care Med Vol 170. pp 126–132, 2004.
3. Ma L, Fogo AB. Role of angiotensin II in glomerular injury. Semin Nephrol. 2001;21(6): 544-53.
4. Wikipedia. http://en.wikipedia.org. 2015.
5. Wikipedia. TLR4. http://en.wikipedia.org/wiki/TLR4. 2014.
6. Bohle A, Strutz F, Muller GA. 1994. On the pathogenesis of chronic renal failure in primary glomerulopathies: a view from the interstitium. Exp Nephrol 2(4):205-210.
7. Fern RJ, Yesko CM, Thornhill BA, Kim HS, Smithies O, Chevalier RL. 1999. Reduced angiotensinogen expression attenuates renal interstitial fibrosis in obstructive nephropathy in mice. J Clin Invest 103(1):39-46.
8. Guo G, Morrissey J, McCracken R, Tolley T, Liapis H, Klahr S. 2001. Contributions of angiotensin II and tumor necrosis factor-alpha to the development of renal fibrosis. Am J Physiol Renal Physiol 280(5):F777-785.
9. Isaka Y, Tsujie M, Ando Y, Nakamura H, Kaneda Y, Imai E, Hori M. 2000. Transforming growth factor-beta 1 antisense oligodeoxynucleotides block interstitial fibrosis in unilateral ureteral obstruction. Kidney Int 58(5):1885-1892.
10. Klahr S, Morrissey J. 2002. Obstructive nephropathy and renal fibrosis. Am J Physiol Renal Physiol 283(5):F861-875.
11. Klahr S, Morrissey JJ. 1998. The role of growth factors, cytokines, and vasoactive compounds in obstructive nephropathy. Semin Nephrol 18(6):622-632.
12. Miyajima A, Chen J, Lawrence C, Ledbetter S, Soslow RA, Stern J, Jha S, Pigato J, Lemer ML, Poppas DP, Vaughan ED, Felsen D. 2000. Antibody to transforming growth factor-beta ameliorates tubular apoptosis in unilateral ureteral obstruction. Kidney Int 58(6):2301-2313.
13. Nath KA. 1992. Tubulointerstitial changes as a major determinant in the progression of renal damage. Am J Kidney Dis 20(1):1-17.
14. Ward, A; Clissold, SP (1987). "Pentoxifylline. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy". *Drugs* 34 (1): 50–97. doi:10.2165/00003495-198734010-00003. PMID 3308412.
15. Adnan Aslan, Güngör Karagüzel, Firat Güngör, Nimet Izgüt-Uysal, Funda Aydin, Mustafa Melikoğlu. The effects of pentoxifylline on renal function and free radical production in unilateral ureteral obstruction. Urological Research .11/2003; 31(5):317-22. DOI:10.1007/s00240-003-0342-1.
16. Shirazi M, Noorafshan A, Farrokhi A. Cent European J Urol. Effects of pentoxifylline on renal structure after urethral obstruction in rat: A stereological study. 2011;64(1):30-3. doi: 10.5173/ceju.2011.01.art6. Epub 2011 Mar 18.
17. U.S. National Library of Medicine. 2008. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000846.
18. Lin, S. L., Chen, R. H., Chen, Y. M., Chiang, W. C., Lai, C. F., Wu, K. D., Tsai, T. J. Pentoxifylline attenuates tubulointerstitial fibrosis by blocking Smad3/4-activated transcription and profibrogenic effects of connective tissue growth factor. J Am Soc Nephrol. 2005;16(9):2702-13.
19. Ma L, Fogo AB. Role of angiotensin II in glomerular injury. Semin Nephrol. 2001;21(6): 544-53.
20. Becker GJ, Perkovic V, Hewitson TD. 2001. Pharmacological intervention in renal fibrosis and vascular sclerosis. J Nephrol 14(5):332-339.
21. Bohle A, Strutz F, Muller GA. 1994. On the pathogenesis of chronic renal failure in primary glomerulopathies: a view from the interstitium. Exp Nephrol 2(4):205-210.
22. Chen YM, Chien CT, Hu-Tsai MI, Wu KD, Tsai CC, Wu MS, Tsai TJ. 1999. Pentoxifylline attenuates experimental mesangial proliferative glomerulonephritis. Kidney Int 56(3):932-943.
23. Chen YM, Ng YY, Lin SL, Chiang WC, Lan HY, Tsai TJ. 2004. Pentoxifylline suppresses renal tumour necrosis factor-alpha and ameliorates experimental crescentic glomerulonephritis in rats. Nephrol Dial Transplant 19(5):1106-1115.

24. Chou SY, Cai H, Pai D, Mansour M, Huynh P. 2003. Regional expression of cyclooxygenase isoforms in the rat kidney in complete unilateral ureteral obstruction. J Urol 170(4 Pt 1):1403-1408.
25. Ducloux D, Bresson-Vautrin C, Chalopin J. 2001. Use of pentoxifylline in membranous nephropathy. Lancet 357(9269):1672-1673.
26. Fern RJ, Yesko CM, Thornhill BA, Kim HS, Smithies O, Chevalier RL. 1999. Reduced angiotensinogen expression attenuates renal interstitial fibrosis in obstructive nephropathy in mice. J Clin Invest 103(1):39-46.
27. Guo G, Morrissey J, McCracken R, Tolley T, Liapis H, Klahr S. 2001. Contributions of angiotensin II and tumor necrosis factor-alpha to the development of renal fibrosis. Am J Physiol Renal Physiol 280(5):F777-785.
28. Hewitson TD, Martic M, Kelynack KJ, Pedagogos E, Becker GJ. 2000. Pentoxifylline reduces in vitro renal myofibroblast proliferation and collagen secretion. Am J Nephrol 20(1):82-88.
29. Isaka Y, Tsujie M, Ando Y, Nakamura H, Kaneda Y, Imai E, Hori M. 2000. Transforming growth factor-beta 1 antisense oligodeoxynucleotides block interstitial fibrosis in unilateral ureteral obstruction. Kidney Int 58(5):1885-1892.
30. Klahr S, Morrissey J. 2002. Obstructive nephropathy and renal fibrosis. Am J Physiol Renal Physiol 283(5):F861-875.
31. Klahr S, Morrissey JJ. 1998. The role of growth factors, cytokines, and vasoactive compounds in obstructive nephropathy. Semin Nephrol 18(6):622-632.
32. Lin SL, Chen RH, Chen YM, Chiang WC, Lai CF, Wu KD, Tsai TJ. 2005. Pentoxifylline attenuates tubulointerstitial fibrosis by blocking Smad3/4-activated transcription and profibrogenic effects of connective tissue growth factor. J Am Soc Nephrol 16(9):2702-2713.
33. Lin SL, Chen YM, Chien CT, Chiang WC, Tsai CC, Tsai TJ. 2002. Pentoxifylline attenuated the renal disease progression in rats with remnant kidney. J Am Soc Nephrol 13(12):2916-2929.
34. Miyajima A, Chen J, Lawrence C, Ledbetter S, Soslow RA, Stern J, Jha S, Pigato J, Lemer ML, Poppas DP, Vaughan ED, Felsen D. 2000. Antibody to transforming growth factor-beta ameliorates tubular apoptosis in unilateral ureteral obstruction. Kidney Int 58(6):2301-2313.
35. Nath KA. 1992. Tubulointerstitial changes as a major determinant in the progression of renal damage. Am J Kidney Dis 20(1):1-17.
36. Navarro JF, Mora C, Muros M, Garcia J. 2005. Additive antiproteinuric effect of pentoxifylline in patients with type 2 diabetes under angiotensin II receptor blockade: a short-term, randomized, controlled trial. J Am Soc Nephrol 16(7):2119-2126.
37. Remuzzi G, Zoja C, Gagliardini E, Corna D, Abbate M, Benigni A. 1999. Combining an antiproteinuric approach with mycophenolate mofetil fully suppresses progressive nephropathy of experimental animals. J Am Soc Nephrol 10(7):1542-1549.
38. Strutz F, Heeg M, Kochsiek T, Siemers G, Zeisberg M, Muller GA. 2000. Effects of pentoxifylline, pentifylline and gamma-interferon on proliferation, differentiation, and matrix synthesis of human renal fibroblasts. Nephrol Dial Transplant 15(10):1535-1546.
39. Vadiei K, Tucker SD, Lopez-Berestein G, Wasan KM. 1996. Nephroprotective mechanism(s) of pentoxifylline: reduction of erythrocyte-mediated vascular congestion and inhibition of nitric oxide release. Pharmacol Toxicol 78(3):174-180.
40. Ward A, Clissold SP. 1987. Pentoxifylline. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. Drugs 34(1):50-97.
41. Ma H, Cherng S, Yang Y. Stem Cell and Renal Disease. Academia Arena, 2009a;1(1):57-61. http://sciencepub.net/academia/0101/08_0553_mahongbao_renalstem.pdf.
42. Ma H, Cherng S, Yang Y. Renal Stem Cell. Journal of American Science. 2009b;5(5):213-222.
43. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3030258/.

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