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REVIEW
DERLEME

Animal Models for Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS)

İnterstisyel Sistit/Ağrılı Mesane Sendromu için Hayvan Modelleri

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ABSTRACT
ÖZET

The etiopathogenesis of IC/PBS has not yet been elucidatedt. Several different theories have been proposed for the underlying pathology of IC/PBS. Advancement in addressing this disease has been painfully slow due to lack of understanding of the underlying pathophysiology. A main limitation in IC/PBS research has been the lack of an appropriate animal model. In this review, we focused on the current animal models for IC/PBS disease.

IC/PBS´in etyopatogenezi henüz ayrıntılı bir şekilde açıklanmamıştır. IC/PBS´in altta yatan patolojisi üzerine birkaç farklı teori öne sürülmüştür. Bu hastalıkla ilgili ilerlemeler altta yatan patofizyolojisini anlamadaki eksiklikten dolayı can sıkıcı bir şekilde yavaş olmuştur. IC/PBS araştırmalarında temel kısıtlılık uygun bir hayvan modeli eksikliği olmuştur. Bu derlemede, IC/PBS hastalığı için mevcut hayvan modelleri üzerinde durduk.

Key words: İnterstitial cystitis, painful bladder syndrome, IC animal model

Anahtar kelimeler: İnterstisyel sistit, ağrılı mesane sendromu, IC hayvan modeli

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Animal Models For Interstitial Cystitis/Painful Bladder Syndrome

The International Continence Society has defined IC/PBS as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology" (1). IC is a chronic inflammation of the urinary bladder in the absence of verified infection (2, 3), and presents with the symptoms of frequent and urgent urination along with pain or irritation in the bladder and lower urinary tract (LUT), necessitating the addition of the new terminology painful bladder syndrome (PBS) (3-5). Complete diagnostic criteria for epidemiological studies of IC/PBS have not been established. Earlier diagnostic criteria proposed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDKK) included a cystoscopic finding of glomerulations upon bladder distension or Hunner's ulcer, in addition to bladder pain or urinary urgency, along with several criteria to exclude other diseases (6). However, 10% to 34% of patients with urinary urgency due to bladder pain do not exhibit glomerulations upon bladder distension and only 10% of patients diagnosed with IC present with Hunner's ulcer (7-10).

Depending on the diagnostic criteria used, the prevalence of IC/PBS has been estimated as between 0.03% to 2.0% of adults (11-13). The prevalence of IC/PBS among women is estimated to be 2 to 5 times higher than in men (3, 13). The recent Rand Epidemiology study of IC/PBS in women in the United States identified the prevalence of IC/PBS as 6.5% and 2.7% based on high sensitivity and high specificity diagnostic criteria, respectively, which translates to 3.3 to 7.9 million women suffering from IC/PBS symptoms (14). According to the NIDDK diagnostic criteria, IC/PBS occurs 17 times more frequently in relatives of IC/PBS patients than in the general population in the United States (15). The medical costs have been estimated at more than $100 million per year in the United States (16).

IC/PBS patients suffer considerable morbidity over the course of their lives, especially during their most productive years. Advancement in addressing this disease has been painfully slow due to a lack of understanding of the underlying pathophysiology.

Etiology of IC/PBS

The etiopathogenesis of IC/PBS has not yet been elucidated. Several different theories have been proposed for the underlying pathology of IC/PBS (17), including defects of the barrier glycosaminoglycan layer, infection induced, mast cell activation (18-20) autoimmunity, increased production of antiproliferative factor (21), decreased sialylation and glycosylation of Tam Horsfall Protein (THP) (22), increased TNF-related apoptosis-inducing ligand (TRAIL) receptor 4 (23), elevated transient receptor potential subtype 1 vanilloid receptor in nerve fibers (24), and neuroendocrine and neuroimmune mechanisms (25).

Animal Models For IC/PBS

Numerous animal models for cystitis have been generated in different ways, such as through intravesical administration of chemical irritants or immune stimulants, systemic or environmentally impelled inflammation, a naturally occurring model, and experimentally induced autoimmunity models, which include systemic immunization with bladder homogenate or recombinant uroplakin II protein, and induction of bladder autoimmunity in transgenic URO-OVA mice by ovalbumin (OVA)-specific T cells.

Intravesical Irritant Instillation Models

Instillation of urine from IC patients into the bladder of rabbits resulted in histological inflammatory changes that resembled human IC bladders, but did not yield statistically significant differences in 24-hour urinary frequency and volume (26). Intravesical instillation of acetone solutions induced transient IC in rats, monkeys, and rabbits that included markedly increased voiding frequency and decreased volume per void (27-29). Moreover, intravesical administration of an acidic solution resulted in increased levels of neutrophil chemotactic factors, accumulation of neutrophils, and edema in the bladder of rabbits (30). Intravesical instillation of mustard oil and electrical stimulation of pelvic ganglia activated bladder afferent fibers and produced high levels of plasma extravasation in the bladder of rats (31). Instillation of xylene into the bladder in rats induced inflammation that involved irritation of capsaicin-sensitive sensory nerves in the bladder wall (32).

Intraperitoneal administration of the antineoplastic drug cyclophosphamide has been used extensively for induction of cystitis in animals. It damages the bladder mucosa and causes edema, accumulation of leukocytes in bladder tissue, and hemorrhage (33-35).

Immune Stimulant-Induced Cystitis Models

Intravesical administration of substance P or the bacterial endotoxin LPS resulted in cystitis characterized by neutrophil invasion, hemorrhage and edema in the bladder in two strains of mice (36). Of those responses, only slight hemorrhage was observed in congenic mast cell knockout mice (37). In another model, neurogenic bladder inflammation was induced in rats by injection of pseudorabies virus (PRV) into the abductor caudae dorsalis tail muscle (38). In the equivalent model in mice, PRV induced tumor necrosis factor alpha-dependent mast cell infiltration into the lamina propria along with pelvic pain mediated by histamine (39-42). In addition, the cathelicidin LL-37, an antimicrobial peptide, was used to generate bladder inflammation in mice (43).

Stressful Environmental Stimulus-Induced Cystitis Models

Exposure of animals to various physical and psychological stress factors has been shown to induce cystitis in the bladder. In one study, restraint stress induced activation of mast cells in the bladder, which was attenuated by neonatal depletion of sensory nerve terminals (44). Another group subjected rats to acute cold and restraint stress, which resulted in edema, leukocyte invasion, and mast cell degranulation in the bladder (45). In another study, moderate stress induced by exposing mice to constant illumination for 96 hours resulted in desquamation of superficial and intermediate urothelial cells (46-48).

Naturally Occurring Cat Model for IC/PBS

Idiopathic IC has been observed in domestic cats, with symptoms similar to human IC/PBS such as increased urinary frequency and pain (49). Also similar to human IC/PBS, cats with feline IC exhibit reduced urinary excretion of total and GP-51 glycosaminoglycan, increased bladder wall permeability, and elevated density of neurokinin-1 receptors in the bladder (50-54). In addition, increased substance P immunoreactivity has been found in feline IC and some human IC/PBS studies (52, 54). The major advantage of feline IC is its occurrence in the absence of external stimulants. A disadvantage of this model is its dissimilar gender distribution compared with human IC/PBS, with equal distribution among male and female cats, compared with 2- to 5-fold greater prevalence of human IC/PBS in women (55). Also, the etiology of cystitis development in cats is unknown. Other issues include handling problems that require veterinarian involvement and expensive care in animal facilities (56).

Experimental Autoimmune Cystitis Induced by Immunization with Bladder Homogenate

In different mice strains such as BALB/cAN and SWXJ, experimental autoimmune cystitis (EAC) was generated by immunization with bladder homogenate from syngeneic animals and showed some of the physiopathological features of cystitis (57, 58). The initial EAC model was developed in BALB/cAN mice immunized with a syngeneic bladder homogenate that induced edema, fibrosis, perivascular lymphocytic infiltrations and deposition of mast cells in the detrusor muscle of the bladder (57). Cell-mediated autoimmunity was confirmed in this model by adoptive transfer of spleen cells from bladder homogenate-immunized mice into naïve mice, thereby recapitulating the disease (57). In another study, SWXJ mice that are prone to the generation of autoimmune diseases were immunized with bladder homogenate and developed EAC showing the symptoms of increased urination frequency and decreased volume per void, along with histopathological alterations such as increased infiltration of lymphocytes and mast cells, and thickened lamina propria (59). Bladder homogenate was also obtained from Lewis rats and used to induce EAC in syngeneic animals, demonstrating increased urinary frequency, mast cell accumulation and vascular congestion (60). It was suggested that T helper cells could play a role in the immune response in the bladder to bladder homogenate-induced EAC (61, 62).

EAC Induced by Immunization with Recombinant UPK2 Protein

A potentially more organ specific EAC model was generated by targeting the abundantly expressed urothelial membrane-specific protein uroplakin II (UPK2) (63). SWXJ mice immunized with recombinant murine UPK2 exhibited symptoms of significantly increased urination frequency and decreased volume per void, along with increased infiltration of T cells in the bladder. However, as in the bladder homogenate EAC models, visceral pain was not assessed in this model.

Sensitization to Ovalbumin and URO-OVA Mice

An experimental cystitis model was generated by sensitizing guinea pigs to ovalbumin (OVA) by multiple intraperitoneal injections of the antigen, followed by injection of OVA into the bladder. Those animals exhibited permeability of the urothelium (64-66).

In a parallel study in mice, transurethral instillation of OVA yielded bladder inflammation experimental cystitis in wild type mice, but not in congeneic mast cell deficient mice (67).

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Another EAC model has been created using transgenic URO-OVA mice, which produce a membrane form of OVA, driven by the urothelial-specific uroplakin II gene promoter, as a self antigen on the urothelium. URO-OVA mice are susceptible to induction of bladder inflammation by adoptive transfer of activated OVA-specific CD8+ T cells. In addition, crossbreeding URO-OVA mice with transgenic mice that express an OVA-specific CD8+ T cell receptor (OT-I mice) yielded mice that spontaneously developed autoimmune cystitis (68, 69). However, OVA is not an endogenous antigen of the bladder, and bladder urodynamic changes and pain correlated with the IC/PBS phenotype have not been characterized in this model.

Conclusion

The earlier animal models of IC/PBS were developed through different approaches such as inducing inflammation by transurethral application of irritants or immune stimulants into the urinary bladderand systematic and environmentally caused irritations. Although systemic cyclophosphamide-induced bladder inflammation is a well-described and broadly studied model of chronic cystitis, its pathogenesis does not fit that of human IC/PBS (70). A spontaneous model of IC/PBS described in cats has not been applied extensively in the scientific community due to cost and handling problems (56, 71).

The transgenic URO-OVA mouse model of EAC fabricated a urothelial membrane-specific form of OVA as a self-antigen, and then bladder autoimmune cystitis was generated through the transfer of OVA-specific $CD8^+$ T-cells to this mouse (68, 69). The disadvantage of this model is that OVA is not an endogenous antigen of bladder, and urodynamic assessment of the bladder or bladder dysfunction, as well as pelvic pain associated to IC/PBS phenotype, have not been demonstrated.

The models of autoimmune-mediated cystitis in SWXJ mice generated by immunization with bladder homogenate or the urothelial membrane-specific protein UPK2 faithfully reproduced the urodynamic aspects of human IC/PBS and exhibited inflammatory T cell responses to the targeted bladder tissues (59, 63). The disadvantage of immunization with bladder homogenate is the possible induction of nonspecific and systemic immune reactions along with the bladder-specific responses, due to the inclusion of tissue-nonspecific antigens in the homogenate. The EAC mice immunized with bladder-specific recombinant UPK2 protein exhibited bladder-specific T cell mediated autoimmunity and clear evidence of IC-related bladder dysfunction, as indicated by significantly increased frequency of urination and decreased urine output per void (59, 63). However, this EAC mouse model did not exhibit pelvic pain responses to noxious stimulation with von Frey filaments, thus failing to reproduce one of the major symptoms of human IC/PBS. In view of that, the need remains for an animal model that expresses all of the major phenotypical properties observed in human IC/PBS, namely urinary frequency/urgency and pelvic pain, along with bladder specificity and a high induction rate of the phenotype.

It is evident that IC/PBS influences millions of people. However, no successful therapies have been presented. The present treatment applications merely alleviate the storage or voiding bladder symptoms by different agents and applications. There has been no significant treatment or preventive strategies for IC/PBS for the last several decades. Failure of clinical researches to discover successful therapies for IC/PBS has led the scientific community to develop animal models that could provide a valuable step to jump start translational research in which the clinical studies have been hindered. Thus, it is valuable to develop an animal model that demonstrates all of the major phenotypical features of IC/PBS.

Conflict of Interest
No conflict of interest was declared by the author.

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References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol 2002;187(1): 116-26. [CrossRef]
2. Forrest JB, Vo Q. Observations on the presentation, diagnosis, and treatment of interstitial cystitis in men. Urology 2001; 57(6 Suppl 1): 26-9. [CrossRef]
3. Bogart LM, Berry SH, Clemens JQ. Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. J Urol 2007; 177(2): 450-6. [CrossRef]
4. Hanno PM. Re-imagining interstitial cystitis. The Urologic clinics of North America. 2008; 35(1): 91-9. [CrossRef]
5. Toft BR, Nordling J. Recent developments of intravesical therapy of painful bladder syndrome/interstitial cystitis: a review. Curr Opin Urol 2006;16(4): 268-72. [CrossRef]
6. Hanno P, Levin RM, Monson FC, Teuscher C, Zhou ZZ, Ruggieri M, et al. Diagnosis of interstitial cystitis. The Journal of Urology 1990;143(2): 278-81.
7. Richter B, Hesse U, Hansen AB, Horn T, Mortensen SO, Nordling J. Bladder pain syndrome/interstitial cystitis in a Danish population: a study using the 2008 criteria of the European Society for the Study of Interstitial Cystitis. BJU international 2010; 105(5): 660-7. [CrossRef]
8. Simon LJ, Landis JR, Erickson DR, Nyberg LM, Wein AJ, Foy M, et al. The interstitial cystitis data base study: Concepts and preliminary baseline descriptive statistics. Urology 1997; 49(5A): 64-75. [CrossRef]
9. Koziol JA. Epidemiology of interstitial cystitis. The Urologic clinics of North America. 1994; 21(1): 7-20.
10. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. Urology 1978; 12(4): 381-92. [CrossRef]
11. Curhan GC, Speizer FE, Hunter DJ, Curhan SG, Stampfer MJ. Epidemiology of interstitial cystitis: a population based study. J Urol 1999; 161(2): 549-52. [CrossRef]

12. Clemens JQ, Meenan RT, Rosetti MC, Gao SY, Calhoun EA. Prevalence and incidence of interstitial cystitis in a managed care population. J Urol 2005; 173(1): 98-102. [CrossRef]
13. Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LM, McKinlay JB. Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urology 2007; 177(4): 1390-4. [CrossRef]
14. Berry SH, Elliott MN, Suttorp M, Bogart LM, Stoto MA, Eggers P, et al. Prevalence of Symptoms of Bladder Pain Syndrome/Interstitial Cystitis Among Adult Females in the United States. J Urology 2011; 186(2): 540-4. [CrossRef]
15. Warren JW, Jackson TL, Langenberg P, Meyers DJ, Xu JF. Prevalence of interstitial cystitis in first-degree relatives of patients with interstitial cystitis. Urology 2004; 63(1): 17-21. [CrossRef]
16. Nickel JC. Interstitial cystitis: a chronic pelvic pain syndrome. Med Clin North Am 2004; 88(2): 467-81. [CrossRef]
17. Oberpenning F, van Ophoven A, Hertle L. Interstitial cystitis: an update. Curr Opin Urol 2002; 12(4): 321-32. [CrossRef]
18. Hofmeister MA, He F, Ratliff TL, Mahoney T, Becich MJ. Mast cells and nerve fibers in interstitial cystitis (IC): an algorithm for histologic diagnosis via quantitative image analysis and morphometry (QIAM). Urology 1997; 49(5A Suppl): 41-7.
19. Parsons CL. Prostatitis, interstitial cystitis, chronic pelvic pain, and urethral syndrome share a common pathophysiology: lower urinary dysfunctional epithelium and potassium recycling. Urology 2003; 62(6): 976-82. [CrossRef]
20. Theoharides TC. Panic disorder, interstitial cystitis, and mast cells. J Clin Psychopharmacol 2004; 24(4): 361-4. [CrossRef]
21. Keay S, Zhang CO, Marvel R, Chai T. Antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor: sensitive and specific urine markers for interstitial cystitis. Urology 2001; 57(6 Suppl 1): 104. [CrossRef]
22. Argade SP, Vanichsarn C, Chenoweth M, Parsons CL. Abnormal glycosylation of Tamm-Horsfall protein in patients with interstitial cystitis. BJU Int 2009; 103(8): 1085-9. [CrossRef]
23. Kutlu O, Akkaya E, Koksal IT, Bassorgun IC, Ciftcioglu MA, Sanlioglu S, et al. Importance of TNF-related apoptosis-inducing ligand in pathogenesis of interstitial cystitis. Int Urol Nephrol 2010; 42(2): 393-9. [CrossRef]
24. Mukerji G, Yiangou Y, Agarwal SK, Anand P. Transient receptor potential vanilloid receptor subtype 1 in painful bladder syndrome and its correlation with pain. The Journal of Urology 2006; 176(2): 797-801. [CrossRef]
25. Butrick CW. Interstitial cystitis and chronic pelvic pain: new insights in neuropathology, diagnosis, and treatment. Clin Obstet Gynecol 2003; 46(4): 811-23. [CrossRef]
26. Kohn IJ, Filer-Maerten S, Whitmore KE, Hanno PM, Ruggieri MR. Lack of effect following repeated in vivo exposure of the rabbit urinary bladder to urine from interstitial cystitis patients at low infusion volumes. Neurourol Urodyn 1998; 17(2): 147-52. [CrossRef]
27. Shimizu I, Kawashima K, Hosoki K. Urodynamics in acetone-induced cystitis of anesthetized rats. Neurourol Urodyn 1999; 18(2): 115-27. [CrossRef]
28. Ghoniem GM, Shaaban AM, Clarke MR. Irritable bladder syndrome in an animal model: a continuous monitoring study. Neurourol Urodyn 1995; 14(6): 657-65. [CrossRef]
29. Kato K, Kitada S, Longhurst PA, Wein AJ, Levin RM. Time-course of alterations of bladder function following acetone-induced cystitis. J Urol 1990; 144(5): 1272-6.
30. Elgebaly SA, Allam ME, Walzak MP Jr, Oselinsky D, Gillies C, Yamase H. Urinary neutrophil chemotactic factors in interstitial cystitis patients and a rabbit model of bladder inflammation. J Urol 1992; 147(5): 1382-7.
31. Koltzenburg M, McMahon SB. Plasma extravasation in the rat urinary bladder following mechanical, electrical and chemical stimuli: evidence for a new population of chemosensitive primary sensory afferents. Neurosci Lett 1986; 72(3): 352-6. [CrossRef]
32 Maggi CA, Abelli L, Giuliani S, Santicioli P, Geppetti P, Somma V, et al. The Contribution of Sensory Nerves to Xylene-Induced Cystitis in Rats. Neuroscience 1988; 26(2): 709-23. [CrossRef]
33. Cox PJ, Abel G. Cyclophosphamide cystitis. Studies aimed at its minimization. Biochem Pharmacol. 1979; 15; 28(24): 3499-502.
34. Lanteri-Minet M, Bon K, de Pommery J, Michiels JF, Menetrey D. Cyclophosphamide cystitis as a model of visceral pain in rats: model elaboration and spinal structures involved as revealed by the expression of c-Fos and Krox-24 proteins. Exp Brain Res 1995;105(2): 220-32. [CrossRef]
35. Locher GW, Cooper EH. Repair of rat urinary bladder epithelium following injury by cyclophosphamide. Invest Urol 1970; 8(1):116-23.
36. Jerde TJ, Bjorling DE, Steinberg H, Warner T, Saban R. Determination of mouse bladder inflammatory response to E. coli lipopolysaccharide. Urol Res 2000; 28(4): 269-73. [CrossRef]
37. Bjorling DE, Jerde TJ, Zine MJ, Busser BW, Saban MR, Saban R. Mast cells mediate the severity of experimental cystitis in mice. J Urol 1999; 162(1): 231-6. [CrossRef]
38. Jasmin L, Janni G, Manz HJ, Rabkin SD. Activation of CNS circuits producing a neurogenic cystitis: evidence for centrally induced peripheral inflammation. J Neurosci 1998; 18(23): 10016-29.
39. Rudick CN, Billips BK, Yaggie RE, Schaeffer AJ, Klumpp D. Uti Pelvic Pain Is Independent of Bacterial Colonization, Inflammation, and Type 1 Pili. J Urology 2009; 181(4): 237. [CrossRef]
40. Rudick CN, Bryce PJ, Guichelaar LA, Berry RE, Klumpp DJ. Mast Cell-Derived Histamine Mediates Cystitis Pain. Plos One 2008; 7; 3(5): e2096.
41. Rudick CN, Schaeffer AJ, Klumpp DJ. Pharmacologic attenuation of pelvic pain in a murine model of interstitial cystitis. BMC Urol 2009; 9: 16. [CrossRef]
42. Rudick CN, Schaeffer AJ, Thumbikat P. Experimental autoimmune prostatitis induces chronic pelvic pain. Am J Physiol Regul Integr Comp Physiol 2008; 294(4): R1268-75. [CrossRef]
43. Oottamasathien S, Jia W, McCoard L, Slack S, Zhang J, Skardal A, et al. A murine model of inflammatory bladder disease: cathelicidin peptide induced bladder inflammation and treatment with sulfated polysaccharides. J Urol 2011; 186(4 Suppl): 1684-92. [CrossRef]
44. Spanos C, Pang X, Ligris K, Letourneau R, Alferes L, Alexacos N, et al. Stress-induced bladder mast cell activation: implications for interstitial cystitis. The Journal of urology 1997; 157(2): 669-72. [CrossRef]
45. Ercan F, San T, Cavdar S. The effects of cold-restraint stress on urinary bladder wall compared with interstitial cystitis morphology. Urol Res 1999; 27(6): 454-61. [CrossRef]
46. Elbadawi A. Interstitial cystitis: a critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. Urology 1997; 49(5A Suppl): 14-40.
47. Jezernik K, Medalia O, Aronson M. A comparative study of the desquamation of urothelial cells during gestation and in adults mice following moderate stress or endotoxin treatment. Cell Biol Int 1995; 19(11): 887-93. [CrossRef]
48. Lavelle JP, Meyers SA, Ruiz WG, Buffington CA, Zeidel ML, Apodaca G. Urothelial pathophysiological changes in feline interstitial cystitis: a human model. Am J Physiol Renal Physiol 2000; 278(4): F540-53.
49. Buffington CA, Chew DJ, Kendall MS, Scrivani PV, Thompson SB, Blaisdell JL, et al. Clinical evaluation of cats with nonobstructive urinary tract diseases. J Am Vet Med Assoc 1997; 210(1): 46-50.
50. Moldwin RM. Similarities between interstitial cystitis and male chronic pelvic pain syndrome. Current urology reports 2002; 3(4): 313-8. [CrossRef]
51. Press SM, Moldwin R, Kushner L, Buffington CAT, Schupp-Byrne D. Decreased expression of GP-51 glycosaminoglycan in cats afflicted with feline interstitial cystitis. Journal of Urology 1995; 153(4 Suppl.): 288A.

Erciyes Med J 2013
Article in Press doi: 10.5152/etd.2013.41

52. Caito M, Masty J. The Presence and Distribution of Substance P and Neuron Specific Enolase Immunoreactivity in the Feline Bladder [M s]. Columbus, OH: Ohio State University, Ohio State University; 1995.
53. Gao X, Buffington CA, Au JL. Effect of interstitial cystitis on drug absorption from urinary bladder. J Pharmacol Exp Ther 199; 271(2): 818-23.
54. Buffington CA, Wolfe SA, Jr. High affinity binding sites for [3H]substance P in urinary bladders of cats with interstitial cystitis. The Journal of urology 1998; 160(2): 605-11. [CrossRef]
55. Pontari MA HP, editor. Interstitial cystitis. Philadelphia: WB Saunders; 1995.
56. Westropp JL, Buffington CA. In vivo models of interstitial cystitis. J Urol 2002; 167(2 Pt 1): 694-702. [CrossRef]
57. Bullock AD, Becich MJ, Klutke CG, Ratliff TL. Experimental autoimmune cystitis: a potential murine model for ulcerative interstitial cystitis. J Urol 1992; 148(6): 1951-6.
58. Phull H, Salkini M, Purves T, Funk J, Copeland D, Comiter CV. Angiotensin II plays a role in acute murine experimental autoimmune cystitis. BJU Int 2007; 100(3): 664-7. [CrossRef]
59. Lin YH, Liu G, Kavran M, Altuntas CZ, Gasbarro G, Tuohy VK, et al. Lower urinary tract phenotype of experimental autoimmune cystitis in mouse: a potential animal model for interstitial cystitis. BJU Int 2008; 102(11): 1724-30. [CrossRef]
60. Luber-Narod J, Austin-Ritchie T, Banner B, Hollins C 3rd, Maramag C, Price H, et al. Experimental autoimmune cystitis in the Lewis rat: a potential animal model for interstitial cystitis. Urol Res 1996; 24(6): 367-73. [CrossRef]
61. Ratliff TL, Klutke CG, Hofmeister M, He F, Russell JH, Becich MJ. Role of the immune response in interstitial cystitis. Clin Immunol Immunopathol 1995; 74(3): 209-16. [CrossRef]
62. Ratliff TL, Klutke CG, McDougall EM. The etiology of interstitial cystitis. The Urologic clinics of North America 1994; 21(1): 21-30.
63. Altuntas CZ, Daneshgari F, Sakalar C, Goksoy E, Gulen MF, Kavran M, et al. Autoimmunity to uroplakin II causes cystitis in mice: a novel model of ınterstitial cystitis. Eur Urol 2011 Jun 28. Epub 2011/07/02.
64. Lavelle JP, Apodaca G, Meyers SA, Ruiz WG, Zeidel ML. Disruption of guinea pig urinary bladder permeability barrier in noninfectious cystitis. Am J Physiol-Renal 1998; 274(1): F205-F14.
65. Saban R, Undem BJ, Keith IM, Saban MR, Tengowski MW, Graziano FM, et al. Differential Release of Prostaglandins and Leukotrienes by Sensitized Guinea-Pig Urinary-Bladder Layers Upon Antigen Challenge. J Urology 1994; 152(2): 544-9.
66. Kim YS, Levin RM, Wein AJ, Longhurst PA. Effects of Sensitization on the Permeability of Urothelium in Guinea-Pig Urinary-Bladder. J Urology 1992; 147(1): 270-3.
67. Saban R, Saban MR, Nguyen NB, Hammond TG, Wershil BK. Mast cell regulation of inflammation and gene expression during antigen-induced bladder inflammation in mice. Physiol Genomics 2001; 7(1): 35-43.
68. Liu W, Evanoff DP, Chen X, Luo Y. Urinary bladder epithelium antigen induces CD8(+) T cell tolerance, activation, and autoimmune response. J Immunol 2007; 178(5): 3333.
69. Liu W, Deyoung BR, Chen X, Evanoff DP, Luo Y. RDP58 inhibits T cell-mediated bladder inflammation in an autoimmune cystitis model. J Autoimmun 2008; 30(4): 257-65. [CrossRef]
70. Vera PL, Iczkowski KA, Wang X, Meyer-Siegler KL. Cyclophosphamide-induced cystitis increases bladder CXCR4 expression and CXCR4-macrophage migration inhibitory factor association. PLoS One 2008; 3(12): e3898. [CrossRef]
71. Buffington CA. Comorbidity of interstitial cystitis with other unexplained clinical conditions. J Urol 2004; 172(4 Pt 1): 1242-8. [CrossRef]