

Non-Neurogenic and Neurogenic Voiding Dysfunction
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**CHRONIC CYSTITIS WITH URINARY FREQUENCY INDUCED BY
CONTINUOUS HYPERPERMEABILITY OF UROTHELIAL LAYER IN RATS**

*Yukio Hayashi**, Pittsburgh, PA; *Atsumi Tamura, Masahito Kawatani, Akita, Japan;*
Hiroko Matsuyoshi, Shiro Hiragata, Michael B Chancellor, William C de Groat, Naoki
Yoshimura, Pittsburgh, PA

Introduction and Objective: The urothelium is normally impermeable and resistant to hostile urine environment. However, it is postulated that reduced permeability in the urothelial layer is an important etiology of painful bladder syndrome including interstitial cystitis that is characterized by urinary frequency, urgency, and suprapubic pain, although the direct linkage is not fully elucidated. Thus, in this study, we examined whether continuous increases in urothelial permeability result in chronic cystitis with bladder dysfunction in rats. **Methods:** To induce bladder hyperpermeability in female Sprague-Dawley rats, 0.5 ml protamine sulfate (PS; 10, 30, or 100 mg/ml in PBS) was intravesically injected every 2 days, and kept in bladder during 30 min under halothane anesthesia. Seven days after the first treatment with PS, continuous cystometry (0.04 ml/min) was performed in urethane-anesthetized rats in order to evaluate bladder function. After cystometry, plasma extravasation was evaluated by measuring the tissue concentration of Evans Blue that was administered intravenously (50 mg/kg) 15 min prior to removal of the bladder. Hematoxyline-eosin (H.E.) staining of bladder tissue was also performed in order to evaluate tissue inflammation. **Results:** PS dose-dependently decreased intercontraction intervals (ICI) in cystometry without affecting other parameters of intravesical pressure (basal, threshold or maximal). ICI after 30 and 100 mg/ml PS treatment was significantly reduced compared with that of vehicle-treated rats. Although ICI was not significantly changed in 10 mg/ml PS-treated rats compared with vehicle-treated rats, following intravesical infusion of 300 mM KCl reduced ICI in these PS (10 mg/ml)-treated animals. Plasma extravasation was enhanced dose-dependently after PS treatment. H.E. staining study also showed that numerous inflammatory cells were infiltrated in the suburothelial layer in PS-treated rats. **Conclusions:** These results indicate that continuous urothelial hyperpermeability elicited by repeated PS treatments can induce chronic bladder inflammation, resulting in urinary frequency in rats. Thus, this PS-treated rat model could be useful for studying the mechanism inducing chronic cystitis and bladder dysfunction due to increased urothelial permeability, which is considered to be a pathogenesis of painful bladder syndrome including interstitial cystitis. **Source of Funding:** DK57267, DK68557, P01 HD39768 and Juanita Gregg Foundation