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Torimoto K. [1], Kim D. [2], Kim J. H. [1], Yoshiyama M. [3], de Groat W. [4], Chancellor M. [1], Fraser M. [1]
1. Department of Urology, University of Pittsburgh, 2. Department of Urology,Taegu Catholic University, 3. Department of Neurology, Chiba University, 4. Department of Pharmacology, University of Pittsburgh

INTRAVESICAL RESINIFERATOXIN REVEALS THE NATURE OF BLADDER EXTERNAL URETHRAL SPHINCTER REFLEXES IN NORMAL AND SPINAL CORD INJURED RATS.

Aims of Study

Many patients with spinal cord injury (SCI) exhibit detrusor hyperreflexia (DH) compounded with incomplete voiding due to detrusor sphincter dyssynergia (DSD). At least in the case of the former, C-fiber sensitisation has been implicated. If maintained abnormal chronic C-fiber hyperactivity is responsible for DH, then reduction of C-fiber activity should alleviate DH. Moreover, recent evidence suggests that desensitisation of C-fibers reduces voiding pressure in SCI [1]. Such findings suggest that vanilloid agonists might be useful for alleviating DSD. Local administration of a C-fiber neurotoxin by bladder instillation would seem an attractive strategy for controlling both DH and DSD, and indeed several clinical trials with capsaicin (CAP) have been undertaken.[1,2] Resiniferatoxin (RTX) has similar physicochemical properties to CAP, but with 1,000X greater potency. The fortuitous property of RTX in 10% EtOH to cause rapid desensitization with minimal irritation, unlike the effective doses of CAP with its tissue-toxic vehicle (30% EtOH), may hold the key to solving the problem of bladder irritation/damage following CAP therapy when dealing with patient populations.[3] In order to test the efficacy of RTX on desensitizing C-fibers in the lower urinary tract following SCI, thereby reducing both DH and DSD, instillation of RTX was performed during continuous cystometry in normal and SCI rats.

Methods

Normal and 2-3 week chronic spinalized female Sprague-Dawley rats (250-300g) were anesthetized with urethane (1.2 g/kg s.c.). Urodynamic studies were performed using either transurethral cystometry (TU-CM) or a novel 3way-Catheter System (3CS) consisting of a transvesical catheter for anterograde urethral perfusion pressure recording (UPP), one for isolated bladder infusion and pressure recording, and a third as a vent for voiding. Fine wire electrodes were placed percutaneously into the pelvic floor for external urethral sphincter electromyography (EUS-EMG). After a control period, RTX at concentrations of 1, 10, 100 nmol and 1 μmol, or 1 μmol alone, in 10% ethanol/saline was infused into the bladder for periods of 30 minutes for each dose.

Results

During cumulative dose-response TU-CM studies in normal rats, both maximum intravesical pressure (Pves, max) and bladder contraction frequency (BF) significantly increased while EUS-EMG activity decreased significantly. Normal rats by 3CS did not demonstrate significant increases in either Pves, max or BF, but did exhibit significant decreases in EUS-EMG activity and a significant reduction in the micturition-associated nadir of UPP. Similarly, chronic spinalized rats by 3CS showed little evidence of excitation following RTX, with a decrease in Pves, max and no change in BF. EUS-EMG activity in chronic spinalized rats decreased significantly following RTX, as were dyssynergic UPP contractions.

Conclusions

The present results using 3CS demonstrate that intravesically instilled RTX in both normal and SCI rats resulted in little evidence of bladder excitation. Rather, they suggest that the apparent excitation during TU-CM may be due to changes in outlet function. Both the normal and SCI rat show rapid desensitization of EUS-EMG activity, providing direct evidence that C-fibers are necessary for the bladder EUS reflex. Intravesical RTX instillation would, therefore, appear a promising treatment for conditions involving DH and/or DSD.

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