EFFECTS OF PHOSPHODIESTERASE TYPE 5 INHIBITOR AND ALPHA-1A/D ADRENOCEPTOR ANTAGONIST ON BLADDER REMODELING IN RATS WITH SPINAL CORD INJURY

Hypothesis / aims of study
Spinal cord injury (SCI) is often associated with detrusor overactivity and detrusor-sphincter dyssynergia (DSD), which result in inefficient voiding and bladder wall tissue remodeling such as hypertrophy and fibrosis. However, no effective modality for controlling the bladder remodeling is available. Phosphodiesterase type 5 (PDE5) inhibitors and alpha1-adrenoceptor (α1-AR) antagonists, which are used for the treatment of male lower urinary tract symptoms (LUTS) with benign prostatic hyperplasia, are shown to prevent bladder wall fibrosis in animal models with bladder outlet obstruction. In order to clarify whether a PDE5 inhibitor, tadalafil, and an α1A/α1D-AR antagonist, naftopidil, prevents bladder wall remodeling after SCI, we examined the bladder and urethral activity and fibrotic changes with or without tadalafil or naftopidil treatment in SCI rats.

Study design, materials and methods
Forty adult female Sprague-Dawley rats were divided into 4 groups; (1) spinal cord intact, (2) control SCI, (3) tadalafil SCI and (4) naftopidil SCI groups. In SCI groups, rats underwent Th9-10 spinal cord transection followed by oral application of vehicle, tadalafil (2 mg/kg/day) or naftopidil (20 mg/kg/day) for 1, 2 and 4 weeks. Bladder activity was measured via cystometry under an awake condition, and urethral activity was measured via continuous urethral pressure recordings during isovolumetric bladder contractions under urethane anesthesia at 2 and 4 weeks after SCI (n=4 per group). The composition of bladder collagen and elastin were measured at 1, 2 and 4 weeks of SCI (n=4 per group).

Results
In the control SCI group, cystometric analyses showed increases in the number of nonvoiding contractions (NVCs) (1.8 ± 1.0/min and 1.1 ± 0.1/min between voiding cycles at 2 and 4 weeks after SCI, respectively) and residual volume (0.3 ± 0.2 ml and 0.2 ± 0.1 ml at 2 and 4 weeks after SCI, respectively), and a decrease in voiding efficacy (69 ± 0.1% and 73 ± 0.1% at 2 and 4 weeks after SCI, respectively) compared to the spinal intact group. All rats in SCI groups showed the DSD pattern shown by urethral sphincter contraction during isovolumetric bladder contractions in contrast to urethral sphincter relaxation during bladder contractions in the spinal intact group. In addition, there were marked increases in bladder weight (291 ± 113 mg, 308 ± 30 mg and 339 ± 128 mg at 1, 2 and 4 weeks after SCI, respectively), collagen (1.8 ± 0.2 mg/bladder; 78% increase and 2.8 ± 0.3 mg/bladder; 164% increase at 1 and 4 weeks after SCI) and elastin contents (1.8 ± 0.2 mg/bladder; 78% increase and 0.4 ± 0.1 mg/bladder; 261% increase at 1 and 4 weeks after SCI, respectively) in the bladder wall of the control SCI group compared to the spinal cord intact group.

Tadalafil treatment increased bladder contraction interval (10.8 ± 3.8 min; 37% increase at 4 weeks after SCI) and suppressed collagen contents in the bladder wall (1.2 ± 0.1; 29% decrease and 1.7 ± 0.5 mg/bladder; 37% decrease at 1 and 4 weeks after SCI, respectively). Naftopidil treatment decreased residual volume (0.1 ± 0.1 ml; 50% decrease at 2 weeks after SCI), improved voiding efficiency (85 ± 10%; 16% increase at 2 weeks after SCI) compared to the control SCI group and suppressed collagen contents in the bladder wall (1.3 ± 0.4 mg/bladder; 53% decrease at 4 weeks after SCI) compared to the control SCI group.

Interpretation of results
These results indicate that bladder remodeling evidenced by increased collagen contents after SCI is associated with detrusor overactivity with DSD and that tadalafil and naftopidil treatments can reduce these SCI-related changes in the bladder. Detrusor overactivity with impaired voiding and bladder overdistention after SCI might induce vessel compression and suppress the microcirculation in the bladder wall to induce tissue ischemia/hypoxia, leading to fibrotic changes in the bladder and bladder dysfunction. Therefore, suppression of the detrusor overactivity and ischemia/hypoxia condition could be useful to reduce the SCI-induced bladder remodeling. Our results suggest that; (1) PDE5 inhibitor, tadalafil, which can increase the blood flow and...
prevents bladder ischemia, reduces the bladder overload in the storage phase (i.e., detrusor overactivity) to decrease bladder fibrosis in SCI and (2) naftopidil treatment, which can relax the bladder neck and proximal urethra, decreases the urethral resistance increased by DSD and residual urine volume, leading to reductions of the bladder overload during both voiding and storage phases and SCI-induced bladder fibrosis.

Concluding message
Treatment with PDE5 inhibitors or α1A/D-AR antagonists could be effective for neurogenic lower urinary tract dysfunction including bladder remodeling after SCI.

Disclosures
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