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EFFECTS OF ALPHA1D/A-ADRENOCEPTOR ANTAGONIST ON URINARY BLADDER IN SPINAL CORD INJURED RATS

Hypothesis / aims of study

Neurogenic lower urinary tract dysfunction (NLUTD) is common in patients with spinal cord injury (SCI) causing the detrusor hyperreflexia and detrusor-sphincter dyssynergia. Alpha$_1$-adrenoceptor (α_1-AR) antagonists have been used for benign prostatic hyperplasia (BPH) and NLUTD patients to reduce the urethral resistance during voiding. However, compared with other α_1-AR antagonist, naftopidil ($\alpha_{1D/A}$-AR antagonist) improves the storage symptoms more effectively in patients with BPH. In this study, therefore, we examined the effect of oral administration of naftopidil on bladder activity to assess the role of α_{1D}-AR on storage function in SCI rats. We also compared the change of bladder activity by the intrathecal injection of naftopidil and silodosin (α_{1A}-AR antagonist) in SCI rats. Additionally, histopathological examination of bladder wall with naftopidil administration was observed in SCI rats.

Study design, materials and methods

Forty-six adult female Sprague-Dawley rats were used in this study. The rats were anesthetized with 2% isoflurane and the spinal cord was completely transected at the lower thoracic level (T9-10) after laminectomy. At 4 weeks after the transaction, we performed three experiments as following;

[1] Oral administration of naftopidil and continuous cystometry (n=14).

The SCI rats were administered 5 mg/day of naftopidil (naftopidil group) or 1 ml of distilled water (control group) by gavage using a fine catheter for 4 weeks. Then SCI rats were anesthetized with 2% isoflurane and the bladder was exposed via a midline abdominal incision. A polyethylene catheter (PE-50) was inserted through the bladder dome to measure residual urine volume and record intravesical pressure. After the operation, SCI rats were placed in a restrainer and the continuous cystometry was performed. Small-amplitude bladder contractions (pressures > 8 cm H_2O) without voiding were indicated non-voiding contractions (NVCs).

[2] Intrathecal injection of silodosin or naftopidil and bladder activity (n=14).

The SCI rats were placed on the restrainer, and naftopidil (0.01–100 μg) or silodosin (0.01–100 μg) was injected intrathecally using a microsyringe. The continuous cystometry was performed, and the changes of bladder activity before and after injections were recorded.

[3] Histopathological examinations of the bladder wall (n=18).

The SCI rats were administered 5 mg/day of naftopidil (naftopidil group) or 1 ml of distilled water (control group) by gavage using a fine catheter for 4 weeks. Then bladder was removed from each rat under isoflurane anesthesia for histopathological examination. Histological sections were stained with Hematoxylin-eosin and Masson's trichrome. The total tissue area and the fibrosis area stained with Masson's trichrome were determined using image-analysis software (Image J version 1.38x, National institutes of Health, Bethesda, MD). The results were expressed as the fibrosis area as a percentage of the tissue section area (%).

Results

On the examination of oral administration of naftopidil on bladder activity, the number of NVCs was significantly (p=0.026) lower in naftopidil group (8.2 ± 3.2) compared with that in the control group (10.6 ± 2.9). Significant changes were not observed in the intravesical baseline pressure, the maximum voiding contraction pressure and the voiding efficacy between 2 groups.

In comparison of bladder activity after intrathecal injection of silodosin or naftopidil, the interval between voiding contractions after intrathecal injection of silodosin (10-100 μg) or naftopidil (0.1-100 μg) was significantly prolonged compared with that before injection (9.2 ± 6.1 min, a 43% increase at 100 μg of silodosin, and 10.7 ± 4.6 min, a 62% increase at 100 μg of naftopidil). The maximal voiding contraction pressure was significantly decreased after intrathecal injection of silodosin (10-100 μg) or naftopidil (1-100 μg) (56.2 ± 9.4 cm H_2O, a 6% decrease at 100 μg of silodosin, and 52.1 ± 8.6 cm H_2O, a 14% decrease at 100 μg of naftopidil). The intravesical baseline pressure did not change by intrathecal injection of each agent. The numbers of NVCs after intrathecal injection of silodosin (10-100 μg) or naftopidil (0.1-100 μg) were significantly decreased (6.2 ± 2.9 per voiding cycle, a 24% decrease at 100 μg of silodosin, and 3.9 ± 4.0 per voiding cycle, a 53% decrease at 100 μg of naftopidil). The voiding efficacy after intrathecal injection of silodosin (1-100 μg) or naftopidil (10-100 μg) was significantly improved (86.0 ± 9.2%, a 8% increase at 100 μg of silodosin, and 86.1 ± 7.7%, a 7% increase at 100 μg of naftopidil). However, there was no significant difference between silodosin and naftopidil groups in each parameter by ANOVA.

Histopathologically, fibrous tissue stained with Masson's trichrome was identified in submucosal layer. The mean percentage of the fibrous area to the total tissue section area in the naftopidil group (21.9 ± 10.0%) was significantly lower than in the control group (48.3 ± 14.7%).

Interpretation of results

In this study, oral administration of naftopidil decreased the number of NVCs in SCI rats. Intrathecal injection of naftopidil or silodosin changed variant parameters of bladder activity including the decrease of the number of NVCs, but there was no significant difference in both groups. These results suggest that both α_{1A}-AR and α_{1D}-AR affect the improvement of neurogenic lower urinary tract dysfunction. However, compared with other α_1-AR antagonist, naftopidil improves the storage symptoms more effectively in patients with BPH, and oral dosage of naftopidil (25-75 mg) is 10 times than silodosin (4-8 mg). Pharmacokinetic analysis showed that naftopidil has high-penetration into the central nervous system. Therefore, it is

suggested that naftopidil affects the spinal cord and decreases the number of NVCs. Moreover, the effect of naftopidil to decrease the NVCs may reduce the load to the bladder wall and decrease the bladder fibrosis.

Concluding message

$\alpha_{1D/A}$-AR antagonist naftopidil improved detrusor hyperreflexia and suppressed fibrosis of bladder wall in SCI rats, suggesting that α_{1D}-AR have an important role in the storage function on detrusor hyperreflexia and naftopidil might be effective for treatment of NLUTD after SCI.

Disclosures

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