

INFLUENCE OF URETHANE ANAESTHESIA ON THE EFFECT OF RESINIFERATOXIN TREATMENT ON DETRUSOR OVERACTIVITY IN RATS WITH SPINAL CORD INJURY

Hypothesis / aims of study

It has been reported that systemic treatment with capsaicin (CAP) inhibits non-voiding contractions (NVCs), which may represent detrusor overactivity (DO), in rats with spinal cord injury (SCI) under anaesthesia with urethane, probably by desensitization of CAP-sensitive C-fibers (1, 2). However, urethane-anaesthesia itself may affect nervous system innervating lower urinary tract (LUT), which may modify the effect of CAP or resiniferatoxin (RTX). In the present study, we investigated the effect of RTX-treatment on cystometric parameters in the same SCI rats in both conscious and urethane-anesthetized conditions and evaluated the influence of urethane-anaesthesia on the effect of RTX on LUT function in SCI rats.

Study design, materials and methods

Female Sprague-Dawley rats were used. Under isoflurane anaesthesia, SCI was created by transection of the spinal cord at the T9-T10 level through a laminectomy. Four weeks after the transection, a polyethylene catheter (PE-50) was implanted into the bladder through the dome for cystometry (CMG) under anaesthesia with pentobarbital sodium (40 mg/kg intraperitoneally). One day after the catheter-implantation, animals were placed individually into transparent observation chamber. After 5 min adaptation period, base-line eye-wipe test was performed by applying CAP solution (0.001 mg/eye) on the eye-surface and then counting the number of eye wipes for 1.5 min. The tested eye was rinsed with 0.9 % saline and swabbed after CAP application. Then, under isoflurane anaesthesia, animals were placed in a restraint cage (Ballman Cage) and allowed to recover from anaesthesia for CMG measurements. CMG was repeated 4 times with saline instillation at a rate of 12 ml/hr and the fourth measurement served as the base 1 value in a conscious condition. On the next day, RTX (0.3 mg/kg) or vehicle was injected subcutaneously (s. c.) under isoflurane anaesthesia. One day after the RTX or vehicle injection, secondary eye-wipe test and CMG measurements in a conscious condition were performed in the same way. Then the restrained animals were administered with urethane (1.5 g/kg s. c.), and CMG measurements were repeated 4 times every 1hr after the urethane-administration (Figure 1). NVCs were determined as the bladder contractions whose amplitude was more than 3 cmH₂O observed during filling.

Results

In the RTX treated group, 2 of 9 animals failed to show desensitisation judged by the eye-wipe test were excluded for further investigations. The animals that had too small bladder capacity (< 0.6ml) or no NVCs on the base-line CMG (base 1) were also excluded. Finally, 10 SCI animals were used for further investigations (N=5 for vehicle-treated, N=5 for RTX-treated). After the RTX-treatment in a conscious condition, urinary retention was observed in 3 out of 5 animals; the voided volume significantly decreased and the residual urine and the bladder capacity increased. In addition, the number of NVCs significantly decreased although their amplitude did not change significantly (Figures 2A and 3). On the other hand, no parameters changed significantly after the vehicle-treatment (Figures 2 B and 3). After the urethane-injection, all of the animals treated with RTX developed urinary retention. The amplitude of NVCs significantly decreased, whereas the number of NVCs did not change significantly in the RTX-treated group (Figures 2A and 4). No CMG parameters significantly changed after the urethane-injection in the vehicle-treated group (Figures 2B and 4).

Interpretation of results

The results of the present study suggest that desensitization of CAP-sensitive nerves by systemic RTX-treatment suppresses the micturition reflex, and decreases the number of NVCs in SCI rats in a conscious condition, and also that urethane-anaesthesia further inhibits the micturition reflex and NVCs, especially the amplitude of NVCs.

Concluding message

The present results indicate that the suppressive effect of RTX on non-voiding contractions as well as voiding contractions in SCI rats can be enhanced by urethane-anaesthesia. Such suppressive effect of urethane-anaesthesia itself should be taken into consideration when we evaluate a drug-effect on LUT function in rats, especially with SCI.

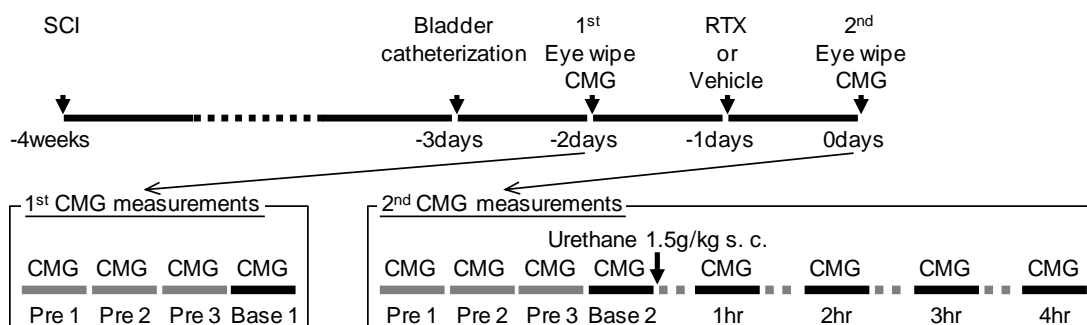


Figure 1. Time schedule of the experiments

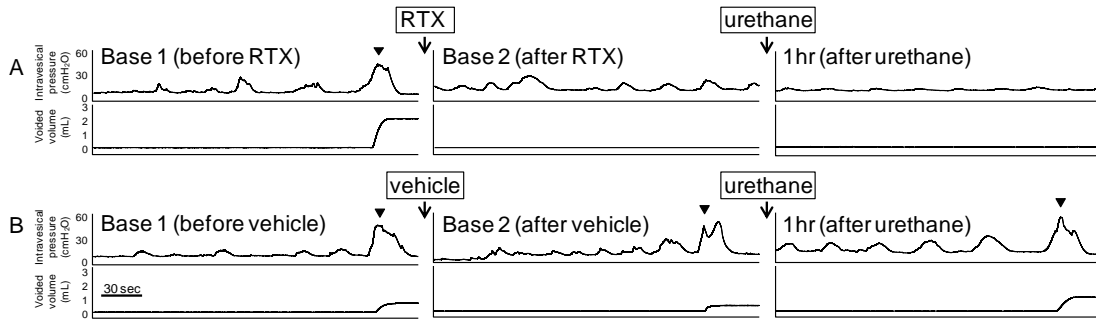


Figure 2. Representative trace of CMG measurements at Base 1, 2 in a conscious condition and 1hr after urethane injection in a SCI rat treated with RTX (A) or vehicle (B). Arrow heads indicate initiation of micturition.

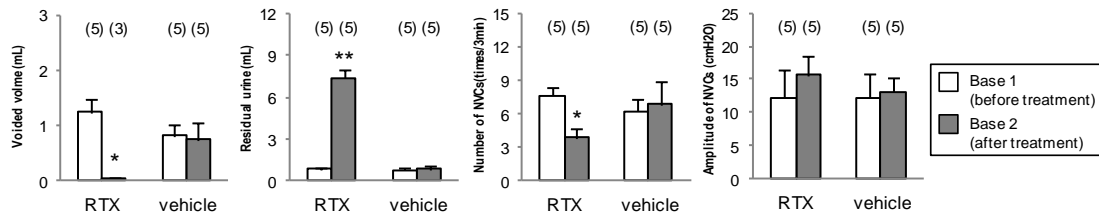


Figure 3. Effect of RTX or vehicle on cystometric parameters in conscious SCI rats. Values are mean \pm S. E. M. * P <0.05, ** P <0.01: significantly different from Base 1 (paired Student's t -test). The values in parenthesis show the number of rats used.

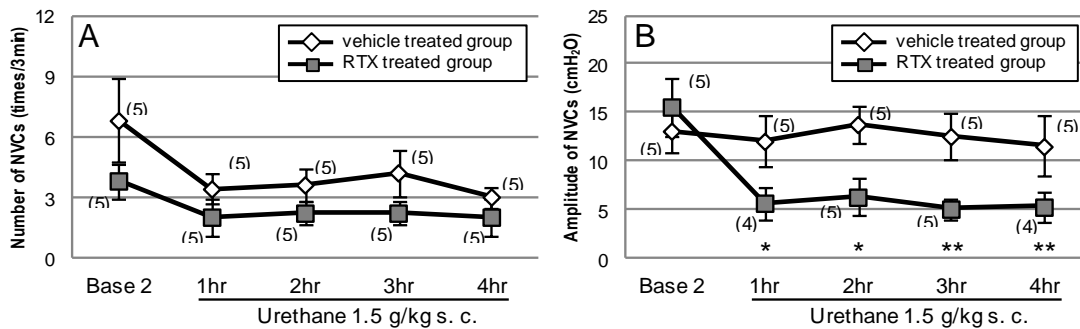


Figure 4. Time dependent changes of NVCs in SCI rats after urethane injection. Values are mean \pm S. E. M. * P <0.05, ** P <0.01: significantly different from Base 2 (one-way ANOVA followed by Dunnett's test). The values in parenthesis show the number of rats evaluated.

References

- Cheng CL, Ma CP, de Groat WC. Effect of capsaicin on micturition and associated reflexes in chronic spinal rats. Brain Res. 1995;678(1-2):40-8.
- Cheng CL, de Groat WC. The role of capsaicin-sensitive afferent fibers in the lower urinary tract dysfunction induced by chronic spinal cord injury in rats. Exp Neurol. 2004;187(2):445-54.

Disclosures

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