Rho-kinase inhibition impacts neurogenic detrusor overactivity in chronic spinalized rats

Broquères-You D¹, Behr-Roussel D¹, Oger S¹, Compagnie S¹, Caisey S¹, Denys P², Chartier-Kastler E³, Giuliano F¹, ²

(1) Pelvipharm, Gil Sur Yvette, (2) Raymond Poincare Hospital, Dept. of Neurological Rehabilitation, Garches, France (3) Pitié Salpêtrière Hospital, Dept. of Urology, Paris

OBJECTIVES

- Spinal cord injury (SCI) severely disrupts normal bladder function by inducing neurogenic detrusor overactivity (NDO). First line SCI-induced NDO treatments i.e. anticholinergics are often associated with intolerable side effects and are poorly effective in some cases. Modulation of the RhoA/ROK signaling pathways represents a promising therapeutic approach for SCI-induced NDO.

- Rho-kinase has a central role in the regulation of detrusor smooth muscle contraction since components of the rhoA/rho-kinase signaling pathway are involved in the Ca²⁺ sensitization of the smooth muscle. Moreover, in vitro and in vivo data from animal models of overactive bladder (OAB) indicate that Rho-kinases are involved in pathophysiological mechanisms responsible for OAB.

Thus, we aimed to evaluate the effects of a Rho-kinase inhibitor (Y-27632) on urodynamic parameters in rats with chronic SCI.

MATERIALS & METHODS

Animals

A total of 17 female adult Sprague-Dawley rats weighing 250-275 g were used in this study.

Complete spinal cord transection

Rats were anesthetized using isoflurane (2.0-2.5 %). A dorsal midline incision was first made to expose the dorsal part of the spinal cord. The overlying muscle and skin were sutured. In order to prevent urinary tract infection (UTI), the animals were treated with antibiotics. Postoperatively, the animals were given a single subcutaneous injection of cefovecin (20 mg/kg) and netilmicin (20 mg/kg) iv injection.

Cystometry experiment on conscious rats was performed in metabolic cage at 48 hours after catheter implantation. In this study, intravesical pressure recording and bladder perfusion (50 µl/min) with room temperature sterile saline. In addition, voided volume was continuously collected and directly measured by means of a weighing device (Sartorius BP2215). Three replicable micturition cycles were recorded before any drug administration used as baseline values. Then, the effects of Y-27632 (150 µg/kg, iv, m-7) and vehicle (saline, iv, m, 10) were evaluated during a treatment period of 60 minutes.

Data Analysis

Urodynamic parameters were analysed: maximal amplitude of micturition pressure (MP); baseline intravesical pressure (BP); delta pressure threshold for inducing micturition (delta PT); intercontraction interval (ICI); voided volume; frequency of NVC and volume threshold to elicit non-voiding contractions (%). All the data were expressed as mean±SEM for N experiments corresponding to N animals. Statistical comparison of urodynamic parameters were performed with a two-way analysis of variance (ANOVA) statistical analysis test followed by Bonferroni post-test with GraphPad Prism4.03 software. P < 0.05 was considered statistically significant.

RESULTS

Effect of Y-27632 or vehicle on the micturition reflex in conscious SCI rats

Y-27632 (150 µg/kg) decreased the amplitude of non-voiding contractions and increase the volume threshold necessary to elicit non-voiding contractions. It did not modify the frequency of non-voiding contractions.

Effect of Y-27632 on urodynamic parameters related to non-voiding contractions in conscious SCI rats

Y-27632 (150 µg/kg) did not modify maximal pressure, baseline pressure, pressure threshold to elicit voiding contractions and the intercontraction interval between two micturitions. In contrast, it increased the voided volume.

CONCLUSIONS

- The present study demonstrates that inhibition of rho-kinase alters the urodynamic parameters related to non-voiding contractions and enables a better bladder emptying in the rat model of SCI-induced neurogenic detrusor overactivity.
- Rho-kinases may be involved in the regulation of bladder afferent nerve activity since the initiation of non-voiding contractions is closely linked to bladder afferent nerve activity.
- Rho-kinase inhibitors thus appear as a putative but very attractive therapeutic possibility for the treatment of OAB.