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RHO-KINASE INHIBITION IMPACTS NEUROGENIC DETRUSOR OVERACTIVITY IN CHRONIC SPINALIZED RATS

Hypothesis / aims of study

Spinal cord injury (SCI) severely disrupts normal bladder function by inducing neurogenic detrusor overactivity (NDO). First line SCI-induced NDO treatments i.e. antimuscarinics often associated with intermittent catheterization are somewhat limited by a mild to moderate clinical efficacy and a significant incidence of side effects. Thus the development of new effective drugs for the treatment of NDO is of crucial importance. Rho-kinase has a central role in the regulation of detrusor smooth muscle contraction since components of the rhoA/rho-kinase signalling pathway are involved in the Ca^{2+}-sensitization of the smooth muscle [1]. 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 [2,3]. Thus, we aimed to evaluate the effects of a rho-kinase inhibitor (Y-27632) on urodynamic parameters in rats with chronic SCI.

Study design, materials and methods

Complete T7-T8 spinal cord transection was performed in 17 female adult Sprague-Dawley rats (250-275g). At 3-4 weeks post-SCI, cystometry was performed in conscious rats to determine the effects of Y-27632 (150 µg/kg, intravenous injection, iv, n=7) and vehicle (saline, iv, n=10) on the following urodynamic parameters: maximal amplitude of micturition pressure (**MP)**; baseline intravesical pressure (**BP)**; delta pressure threshold for inducing micturition (**delta PT)**; intercontraction interval, (**ICI)**; **voided volume**; **amplitude of non-voiding contractions** (NVC) and **the volume threshold** necessary to initiate NVC**.** The effects of Y-27632 or vehicle were observed during a treatment period of 60 min. The results were expressed as percentage of baseline value during the control period i.e before Y-27632 or saline iv injection.

Results

Y-27632 significantly increased voided volume ($p< 0.01$) whereas it did not modify MP, BP, delta PT and ICI. Voided volume reached 117±9% of baseline at 60 min after Y-27632 injection versus 96±4% of baseline for vehicle. The amplitude of NVC was significantly decreased by 43.1% and 17.6% at 30 min and 60 min after Y-27632 administration, respectively when compared to vehicle ($p<0.001$). In addition, Y-27632 significantly increased the volume threshold of NVC ($p< 0.05$). At 30 min and 60 min after Y-27632 injection, it was increased by 117.4 % and by 166.3 % when compared with vehicle.

Interpretation of results

These results indicate that acute Y-27632 treatment exerts an inhibitory effect on NVC characteristic of NDO. This could be due to the fact that inhibition of rho-kinase by Y-27632 has been shown to reduce Ca^{2+}-sensitization of detrusor smooth muscle cells resulting in decreased detrusor contractility [1]. Thus, Y-27632 could exert its effect on NVCs by directly impacting detrusor smooth muscle tone. The rat model of SCI displays not only NDO but also detrusor-sphincter-dyssynergia associated with an inefficient bladder emptying as it is the case in human. Interestingly, Y-27632 significantly increased the voided volume without modifying MP and ICI. A previous study indicates that components of the rhoA/rho-kinase signalling dynamically regulate urethral smooth muscle tone [2]. Thus, the effect of Y-27632 on voided volume could be due to a relaxing effect on the urethra during micturition allowing a better bladder emptying.

Concluding message

The present study demonstrates that inhibition of rho-kinase alters the urodynamic parameters related to NVC and enables a better bladder emptying in the rat model of SCI-induced NDO associated with DSD. This supports the potential development of rho-kinase inhibitors for the treatment of NDO.

References
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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
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