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. 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.

Study design, materials and methods
Complete T7-T8 spinal cord transaction 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 168.3 % 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. 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. 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
2. Rajasekaran et al, Neurourol Urodyn 2005

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What were the subjects in the study?  ANIMAL
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?  Yes