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RHO-KINASE INHIBITION RELAXES DETRUSOR FROM NEUROGENIC PATIENTS

Hypothesis / aims of study
Rho-kinases have a central role in the regulation of bladder smooth muscle from human and various animal species. In *vitro* or *in vivo* data from animal models of overactive bladder (OAB) indicate that rho-kinases could be involved in the pathophysiology of OAB. To date, the role of rho-kinases in patients with neurogenic detrusor overactivity has not yet been explored. We aimed to evaluate the effect of Rho-kinase inhibition on detrusor from neurogenic patients pre-contracted with either carbachol or KCl.

Study design, materials and methods
Bladder samples were obtained from 13 different neurogenic patients who underwent partial or total cystectomy. Detrusor strips with or without urothelium were mounted isometrically at a resting tension of 500 mg in a 5 ml organ bath filled with Krebs-HEPES buffer maintained at 37°C and bubbled with 95%O_2-5%CO_2. The strips were equilibrated for 90 minutes. Then, concentration-response curves (CRC) for the rho-kinase inhibitor, Y-27632, (from 10^{-8}M to 3.10^{-5}M) or vehicle were generated on either carbachol (1µM)- or KCl (50 mM)-precontracted detrusor (N=7 in each condition). Results were expressed as a percentage of inhibition of the contractile response to carbachol or KCl. Statistical analysis was performed using two-way ANOVA.

Results
Y-27632 induced a significant concentration-dependent inhibition of carbachol-induced contraction of human detrusor strips without urothelium ($p<0.001$) with a potency of 5.3±0.1 (pD2) and reached a maximal inhibition of -56.1±8.0 % at 3.10^{-5}M. It also significantly inhibited KCl-induced contraction of human detrusor strips without urothelium ($p<0.001$). However, it was less efficient on KCl-induced contraction than on carbachol-induced contraction since the maximal inhibition reached at 3.10^{-5}M was -31.0±4.3% whereas the potency was equivalent. The presence of urothelium did not modify the inhibitory effect of Y-27632 on carbachol as well as on KCl-precontracted detrusor strips.

Interpretation of results
Rho-kinases inhibition decreases detrusor contractions from neurogenic patients. The mechanisms responsible for this inhibition are different depending on whether the contraction is induced by carbachol or KCl, involving different signaling pathways.

Concluding message
This study supports further investigations regarding the potential development of rho-kinase inhibitors for the treatment of OAB.

Specify source of funding or grant	**No**
Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**No**
This study did not require ethics committee approval because	**Only the approval of the patient is required to obtain neurogenic bladder samples**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**