

THE PHOSPHODIESTERASE TYPE 4 INHIBITOR, ROLIPRAM, IS MORE EFFICIENT TO RELAX DETRUSOR SMOOTH MUSCLE IN RATS WITH OVERACTIVE BLADDER THAN IN CONTROL RATS

Hypothesis / aims of study

Detrusor smooth muscle relaxation is mainly mediated by the cyclic adenosine monophosphate (cAMP) pathway. Elevation of cAMP levels by phosphodiesterase type 4 inhibition relaxes smooth muscle of various origins. The aim of this study was to evaluate the effect of the PDE4 inhibitor rolipram on detrusor smooth muscle tone in a rat pathological model of overactive bladder (OAB) i.e with partial bladder outlet obstruction (BOO).

Study design, materials and methods

BOO was surgically induced in adult female wistar rats (200 -225 g) (N=7) by placing an extraurethral metal rod (diameter of 1 mm) around the proximal urethra to provide a calibrated loop for a 4.0 silk suture inducing partial BOO. Sham rats (N=8) underwent the same surgical procedure without inserting proximal urethral ligature. After 6 weeks of partial BOO, each rat was anesthetized and the bladder was excised and cut into equal strips. Detrusor strips were mounted isometrically in a 5 ml organ bath filled with Krebs-HEPES buffer maintained at 37°C and bubbled with 95%O₂-5%CO₂. The strips were contracted with carbachol (10⁻⁶M) and allowed to equilibrate during 30 min. The strips were then pre-treated (30 min) with forskolin (FSK), an activator of adenylyl cyclase, at a concentration (3.10⁻⁷M) which does not induce a relaxation by itself, or its vehicle before performing concentration-response curves with rolipram or its vehicle.

Results

In absence of FSK, the cumulative addition of rolipram ranging from 10⁻¹⁰ to 3.10⁻⁵M induced a significant concentration-dependent inhibition of BOO rat detrusor strip contractions elicited by carbachol whereas it had a much lesser effect in sham rat detrusor strips (FSK vehicle + rolipram vehicle vs. FSK vehicle + rolipram : p<0.001 and p<0.05 for BOO and sham rats respectively, two-way ANOVA). Maximal relaxation (R_{max}) of 45.5±2.2% (p<0.05 vs vehicle) was obtained in BOO rats whereas in sham rats, it was only 10.1±5.5% (p=ns vs vehicle). The presence of FSK enhanced significantly the relaxing effect of rolipram both in sham rats (R_{max}=31.8±7.1%) and in BOO rats (R_{max}=66.6±6.5%) (FSK + rolipram vehicle vs. FSK + rolipram: p<0.01 and p<0.001 for sham and BOO rats respectively).

Interpretation of results

These results suggest a change in the control of the cAMP pathway in rats with OAB due to BOO. PDE4 inhibitors would be more efficient to relax detrusor contractions in pathophysiological conditions than in physiological conditions.

Concluding message

The PDE4 inhibitor rolipram is more efficient in relaxing carbachol pre-contracted detrusor strips in rats with partial BOO than in control rats. The elevation of the intracellular cAMP levels by FSK strongly strengthened the relaxant effect exerted by rolipram. PDE4 inhibitors might represent a new pharmacological approach for the treatment of OAB. Nevertheless, further investigations are required to test this hypothesis.

FUNDING: This work was funded by Pelvipharm

ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by French Ministry of Agriculture - Agreement No. 91-86, 7/20/2001