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Dassen E[1], van Koeveringe G [1], van Kerrebroeck P [1]
1. University Hospital Maastricht

INHIBITION OF THE INTRACELLULAR IP3 (INOSITOL-TRI-PHOSPHATE) PATHWAY BLOCKS OXIDATIVE STRESS INDUCED OVERACTIVITY BUT HAS FAR LESS EFFECT ON THE STIMULATED CONTRACTIONS IN DETRUSOR SMOOTH MUSCLE.

Aims of Study

Previous research suggested a role for intracellular calcium stores in the development of 'fast' spontaneous detrusor contractions. Our latest study showed that the inhibition of the IP3 pathway with Xestospongin C led to a significant decrease in rate of force development which was not seen after inhibition of the Ryanodine channel which is responsible for the Calcium Induced Calcium Release (CICR). The effect of Xestospongin C on 'fast' spontaneous contractions was investigated during hypochlorite induced overactivity.

Methods

Urinary bladder muscle strips from pigs were exposed to an oxidative stress solution (hypochlorite 10µM). Hypochlorite induced spontaneous contractions were recorded for 10 minutes. The following 10 minutes the strips were treated in a random order with Xestospongin 4µM, Xestospongin 0,4µM, Ryanodine 80µM and with Krebs as Control. For each treatment 6 muscle strips were used. In all phases of the protocol strips were triggered also with Electrical Field Stimulation (EFS) and Acetylcholine (Ach) 10µM to test vitality. After each treatment we washed out the different substances for 20 minutes in order to see if the strips were still vital. We calculated the number of spontaneous contractions, the rate of force development, and the area under the curve of the spontaneous contractions before and during the treatments.

Results

There was a significant reduction in the number and area under the curve of spontaneous contractions after treatment with Xestospongin C, 4µM (P=0.001) and 0,4µM (P=0.024). The Control group and Ryanodine treatment did not change the number or rate of force development of the spontaneous contractions. After treatment with Xestospongin C 4µM only 1% and in 0,4µM solution 23% of the initial number of spontaneous contractions was seen while 20% of the the amplitude after EFS and Ach triggered contractions was preserved. Rate of force development decreased significantly after EFS and Ach stimulation in both Xestospongin treatment concentrations but not during Ryanodine treatment. After washing out the Control group showed a mean of 90% of initial amplitude after EFS, Ryanodine 80µM 76%, Xestospongin 4µM 86% and in Xestospongin 0,4µM 88% of initial force development was seen. There were no significant differences seen with ACh stimulation.

Conclusions

Modulation of the intracellular excitatory pathways by inhibition of the IP3 pathway, reduced hypochlorite induced spontaneous contractions selectively, while significant amplitudes after EFS and Ach triggered contractions remained. This indicates a new approach to the treatment of detrusor overactivity.