The Effect of Cyclic Nucleotides on Carbachol-Induced Calcium Sensitization in Contraction of α-Toxin Permeabilized Human and Pig Detrusor Smooth Muscle

Introduction and Objective: It has been established that Ca^{2+}-dependent and Ca^{2+} -independent mechanisms are involved in smooth muscle contraction. The functional role of the cyclic adenosine monophosphate (cAMP) or the cyclic guanosine monophosphate (cGMP) pathways in the regulation of the detrusor smooth muscle (DSM) contraction through Ca^{2+} independent mechanism was assessed in α -toxin permeabilized human DSM.
Materials and Methods: The DSM specimens were obtained from human urinary bladder who underwent radical cystectomy due to bladder cancer and pig urinary bladder. The small DSM strips (3 - 4 mm in length and 300 - 400 μm in diameter) were permeabilized with 5,000 U/ml α -toxin for 60 minutes and connected to transducer.
Results: At fixed 1 μM $[Ca^{2+}]_i$, both cAMP and cGMP induced relaxation (Ca^{2+} desensitization) and the relaxation effect of 100 μM cAMP was significantly stronger (human 68.1 ± 4.7 %; pig 85.1 ± 3.5 %) compare to that of 100 μM cGMP (human 42.9 ± 6.5 %; pig 56.0 ± 2.3 %; $P < 0.001$; n = 8; Fig. A.1-3). The application of cAMP but not cGMP significantly attenuated the contraction induced by cumulative addition of Ca^{2+} in both detrusor. The relaxation effect of 100 μM cAMP on contraction induced by 1 μM Ca^{2+} was decreased in muscarinic receptor activation by 10 μM CCh plus 100 μM GTP in both tissues. This decrease was recovered by 1 μM AF-DX-116 and was potentiated by 1 μM Y-27632. No effect of 100 μM cAMP on contraction induced by1 μM Ca^{2+} and 1 μM Calyculin A.
Conclusions: This study demonstrated the predominant role of cAMP pathway in relaxation of human DSM contraction through Ca^{2+}-desensitization by activation of myosine light chain phosphatase. The results of this study confirm the link of M_2 receptor subtype with cAMP pathway and suggest the novel interaction between ROK and cAMP pathways. These findings are useful in the treatment strategy for patients with bladder dysfunction. Further, these results also suggest the pig as a good model for the human in properties of cyclic nucleotides induced-relaxation in detrusor smooth muscle.