The Functional Role of Phosphodiesterase Enzymes in the Isolated Porcine Urethra

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Objective: Disruptions in pathways that regulate the normal micturition cycle can result in lower urinary tract disorders, including stress urinary incontinence (SUI).[1,2] Phosphodiesterase (PDE) enzymes act by degrading intracellular second messenger molecules, cAMP and cGMP.[3] PDE inhibitors, such as sildenafil (Viagra) and tadalafil (Cialis), normally used for the treatment of erectile dysfunction, have been suggested to relax the urethral smooth muscle from human and animal tissue preparations.[1,2,3] However, these studies have been limited to only investigating the smooth muscle layer. The present study aimed to investigate the functional role of PDE-4 and PDE-5 enzymes in both the urethral smooth muscle and the inner lining of the urethra (mucosal layer) to potentially identify novel treatment targets for SUI management.

Methods: Isolated strips of porcine urethral tissue (7mm x 4mm) were prepared into three groups: mucosa-intact smooth muscle, mucosa-denuded smooth muscle, and mucosal layer only. Tissue strips were mounted in 8mL organ baths containing physiological Krebs-bicarbonate solution, maintained at 37°C, and continuously gassed with 95% O_2 and 5% CO_2. A tension of 1.5-2g was applied, and the tissue strips were allowed to equilibrate for 45 minutes with fresh solution washout every 15 minutes. After a stable pattern of spontaneous contractions was obtained in the urethral mucosa strips, PDE-4 inhibitor, rolipram, or PDE-5 inhibitor, tadalafil, was added cumulatively (0.1 nM – 1 µM). The urethral smooth muscle strips were pre-contracted with phenylephrine (10 µM) before the addition of rolipram or tadalafil. In a separate set of experiments, urethral smooth muscle strips were incubated with the nitric oxide (NO) donor sodium nitroprusside (SNP, 10 µM) for 30 minutes, followed by cumulative addition of tadalafil. One-way ANOVA followed by Dunnett's multiple comparisons test was performed to identify statistically significant differences. A p-value of <0.05 was considered statistically significant.

Results: Rolipram relaxed mucosa-intact strips, significantly greater than the mucosa-denuded strips ($p<0.05$). In contrast, tadalafil relaxed mucosa-denuded strips significantly greater than the mucosa-intact strips ($p<0.05$). In the presence of the nitric oxide (NO) donor sodium nitroprusside (SNP), the relaxant effect of tadalafil in the mucosa-intact strips was enhanced ($p<0.05$). In the presence of SNP, tadalafil was more potent than roflumilast in relaxing mucosa-intact (54% vs 39%) and mucosa-denuded (47% vs 13%) strips. In the urethral mucosal-only strips, rolipram (0.1 nM and above) significantly reduced the frequency of spontaneous contractions ($p<0.05$), but tadalafil did not.

Conclusion: The results from this study contribute to the limited body of knowledge on the role of PDE enzymes in the function of the urethral smooth muscle and mucosal layers. The findings suggest a potential novel crosstalk between cAMP in the urethral mucosa and cGMP in the smooth muscle, similarly seen in the heart. The cAMP pathway predominantly modulates mucosal function, which may cause inhibition of NO production, affecting the cGMP pathway, which is essential for the modulation of smooth muscle contractility. To identify novel treatment targets for individuals with stress urinary incontinence, further understanding of the possible crosstalk and function of the mucosal layer should be further investigated.

References

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