

THE ROLE OF THE PROSTAGLANDIN SYSTEM IN MUSCARINIC INDUCED CONTRACTIONS OF THE GUINEA PIG URINARY BLADDER

Hypothesis / aims of study

Mechanical and physical stimuli can evoke release of several substances by the urothelium, for example, prostaglandin E2 (PGE2), nitric oxide, Acetylcholine and adenosine triphosphate (1). It has been shown, that the different systems interact with each other and that PGE2 and Acetylcholine seem to act in a positive feedback on molecular level (2). Therefore, the aim of our study was to investigate the role of PGE2 on muscarinic induced contractions.

Study design, materials and methods

In total, 18 male guinea pigs were sacrificed and the urinary bladder and proximal urethra were dissected immediately, catheterized and transferred to a heated organ bath (40 mL, 33–36°C) containing constantly gassed Krebs' solution. Subsequently, the bladder was filled to 1,5 ml in 1 hour. In order to investigate the effect of PGE2 on muscarinic induced contractions, repeated stimulations of the urinary bladders have been performed with the muscarinic agonist arecaidine alone or in combination with PGE2. Furthermore, the cox-1 and -2 inhibitor, Acetylsalicylic acid, has been added before stimulation with arecaidine to evaluate the effect of endogenous PGE2 on muscarinic induced contractions. To confirm that the effect was due to absence of endogenous PGE2, exogenous PGE2 was added afterwards. Arecaidine responses were compared within each guinea pig bladder to prevent bias by inter-individual differences. Changes in intravesical pressure were recorded using a BIOPAC data acquisition system.

Results

In general, the arecaidine response could be divided into two phases. The initial phase was characterized by an irregular rise in pressure, low/mediate amplitude and high frequency contractions, and lasted for approximately 2 minutes. Afterwards, regular contractions developed. These phasic contractions were characterized by a higher amplitude and lower frequency compared to the contractions of the initial phase.

After PGE2 stimulation, two different patterns of arecaidine response were recognized. Some bladders showed an initial tonic increase in pressure followed by the low frequency phasic contractions, whereas others started with high frequency phasic contractions followed by similar low frequency contractions. Figures 1 A and B show typical examples of these two patterns.

Adding Acetylsalicylic acid before stimulation with arecaidine resulted in a diminished rise in tonic pressure during the initial phase of the arecaidine response. This effect could be reversed by adding PGE2 after inhibiting both cox enzymes by Acetylsalicylic acid and before stimulation with arecaidine. Figure 1 C shows a typical example of how the rise in pressure during the initial phase of the arecaidine response changes due to inhibition of cox-1 and cox-2.

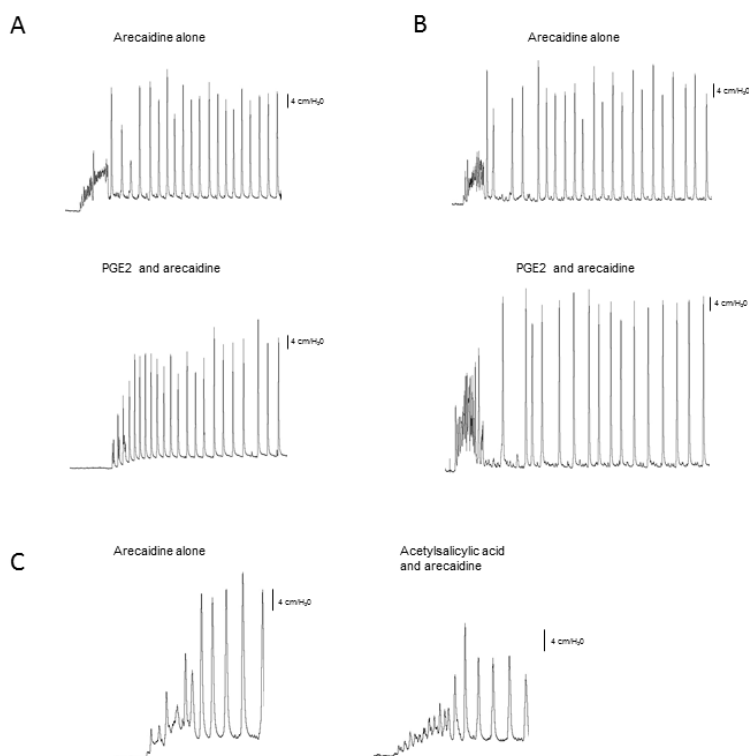


Figure 1. Different patterns (see text for a detailed description) of the arecaidine response in combination with PGE2 or Acetylsalicylic acid.

Interpretation of results

Adding PGE2 before muscarinic stimulations had a reinforcing effect on both observed response patterns to arecaidine. Therefore, PGE2 could be seen as a possible candidate to amplify muscarinic signals within the urinary bladder. Inhibition of the PGE2 producing enzymes cox-1 and cox-2 had an effect on muscarinic induced contractions. Probably, arecaidine could activate directly or indirectly those enzymes, resulting in the production of PGE2, which have been shown to strengthen the response to arecaidine stimulation. This hypothesis is supported by the work of Nile *et al.*, that showed such an interaction within the urothelium (2). In that study, it was shown that the muscarinic agonist arecaidine and PGE2 were indeed able to induce production or release of each other.

Furthermore, stimulation with PGE2 after adding Acetylsalicylic acid indicated the reversability of this effect.

Concluding message

This study provides evidence that the Acetylcholine and Prostaglandin systems in the urinary bladder act in a positive feedback loop and are therefore candidates to play an important role in amplification of the signals transduced from the urothelium to the detrusor muscle. The location of the different steps in the cascade and the targets for modulation of this process need to be determined in the near future.

References

1. Birder LA. More than just a barrier: urothelium as a drug target for urinary bladder pain. *Am J Physiol Renal Physiol.* 2005 Sep;289(3):F489-95.
2. Nile CJ, Gillespie JI. Interactions between cholinergic and prostaglandin signaling elements in the urothelium: role for muscarinic type 2 receptors. *Urology.* 2012 Jan;79(1):240 e17-23.

Disclosures

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