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EP1 ACTIVATION MODIFIES MUSCARINIC INDUCED CONTRACTIONS

Hypothesis / aims of study

Mechanical and physical stimuli can evoke the release of several substances by the urothelium, for example, prostaglandin E2 (PGE2), nitric oxide, Acetylcholine and adenosine triphosphate (1). PGE2 and Acetylcholine seem to act in a positive feedback on a molecular level (2). PGE2 exerts its effects by binding to one of its four E prostanoid (EP) receptors, classified as EP1-4. Previously, the expression of EP1 in the urinary bladder has been shown in guinea pigs (3) and human (unpublished data). In this study, we hypothesized that EP1 plays a role the positive feedback of PGE2 and Acetylcholine.

Study design, materials and methods

In total, 8 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 aerated Krebs' solution. Subsequently, the bladder was filled to 1,5 ml in 1 hour. In order to investigate the role of EP1 on the positive feedback of acetylcholine and PGE2, repeated stimulations of the urinary bladders have been performed with the muscarinic agonist arecaidine alone or in combination with the EP1 agonist ONO-DI-004. 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. Adding the EP1 receptor agonist prior to the arecaidine stimulation resulted in a significantly decreased frequency of contractions during the 2nd phase. Note, that this effect was present in all bladders, even if it was less prominent in some bladders. No significant changes or trends were observed for the amplitude of the 2nd phase as well as the frequency and amplitude of the initial phase.

Interpretation of results

Adding the EP1 agonist before muscarinic stimulation decreased the frequency of the 2nd phase significantly. Even though only a small effect was detected, it was present in all individuals.

On a molecular level, PGE2 increases the amount of acetylcholine released by the urothelium (2). Previously, we showed that PGE2 was able to enhance muscarinic induced contractions in isolated guinea pig bladders (unpublished data). In this study we showed that activation of EP1 decreased the frequency of muscarinic induced contractions. Hence, EP1 plays a role in modification of muscarinic induced contractions but it shows not to be responsible for the enhancement due to PGE2.

Concluding message

Activation of the EP1 receptor modified muscarinic induced contractions. However, does not appear to be involved in the enhancement of muscarinic induced contractions. Therefore, more research is needed to understand this phenomenon.

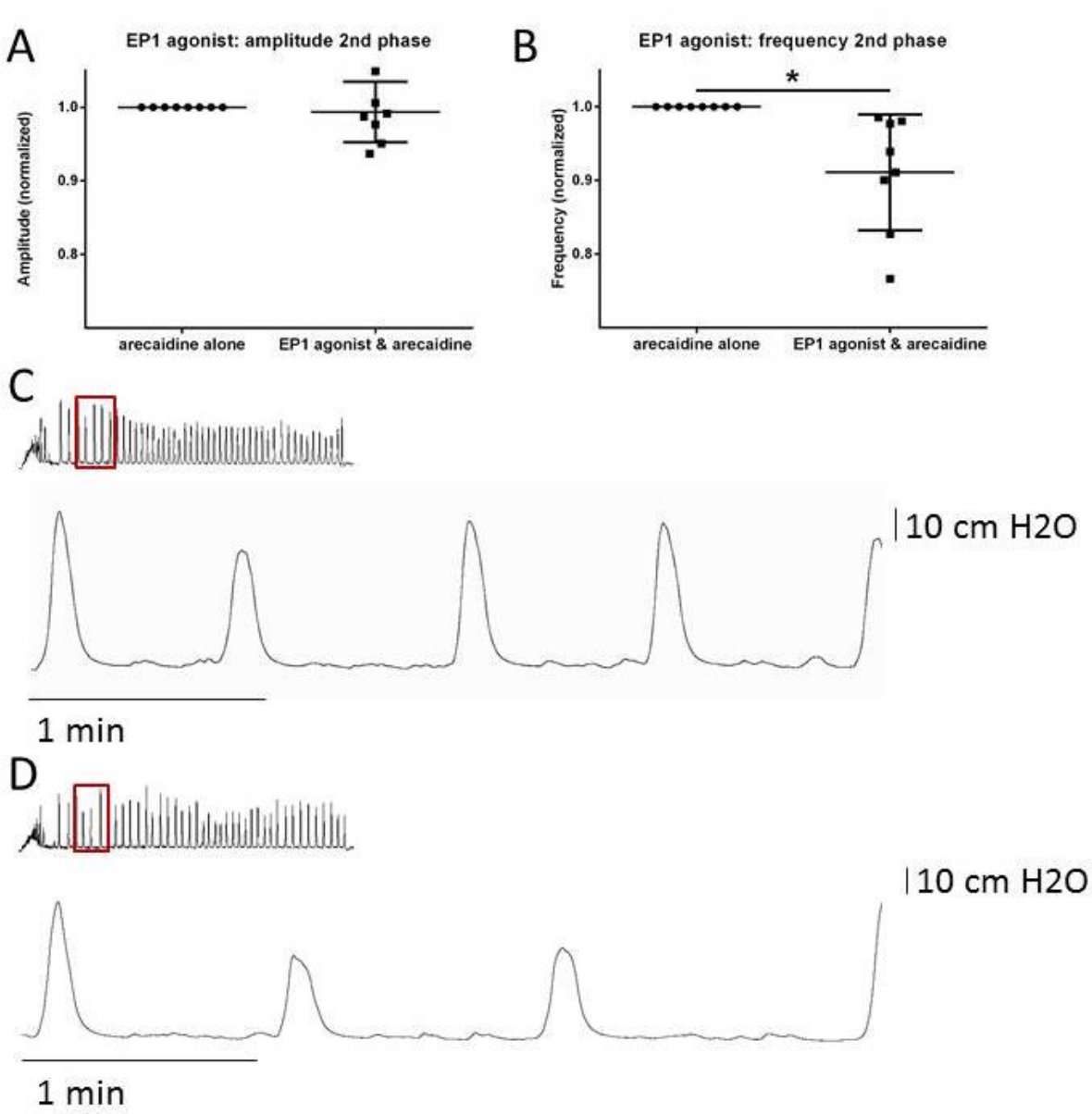

Figure 1. The effect of EP1 activation on muscarinic induced contractions. In Panel A and B the effects of EP1 activation on muscarinic induced contractions are shown. Panel A and B represent quantified data for frequency and amplitude for the 2nd phase of the arecaidine response. Note, that only the frequency of the 2nd phase was reduced significantly. All other parameters were not changed in a significant way. In C and D, raw data sets of the 2nd phase are shown. C represents a typical example of 2nd phase contractions after arecaidine stimulation, D represents a comparable arecaidine response after EP1 activation.

References

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