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THE ROLE OF PROSTAGLANDINS IN THE MUSCARINIC RESPONSE IN THE ISOLATED NORMAL GUINEA PIG BLADDER

Hypothesis / aims of study

The bladder's sensory mechanism is currently the subject of many studies. One of the main proposed mechanisms is the motor/sensory system, in which autonomic activity leads to afferent activation. This autonomic activity is thought to be mediated through interstitial cells. These cells are suggested to be able to pick up various stimuli in the bladder, including signals from local signalling molecules such as acetylcholine, NO, ATP and Prostaglandins (PG) [1]. The current study aims to investigate the role of PG in the regulation of the stimulatory effect of acetylcholine on autonomic activity.

Study design, materials and methods

The urethra and bladder of 16 male guinea pigs (weight 270–300 g) were removed and placed in an organ bath with Krebs solution. The urethra was cannulated, through which the intravesical pressure was measured continuously. Concentrated drug solutions (COX inhibitor indomethacin, PGE₂ and the muscarinic agonist Arecaidine) were added directly to the organ bath to achieve the required final dilution. The timeline of the experiments is given in Figure 1A.

Results

The response of an isolated bladder to the muscarinic agonist arecaidine is shown in the first part of figure 1A. In order to investigate the role of PG production in this response, the non-specific COX inhibitor indomethacin was applied to the bladders about 10 minutes before stimulation with arecaidine. The results of a typical experiment are shown in figure 1. The reversibility of this effect was checked by adding PGE₂ after the experiments with indomethacin and evaluating the arecaidine response, which showed an increase of the initial burst of autonomic levels even higher than the control.

Interpretation of results

Inhibiting PG production by indomethacin is shown to diminish the initial burst of autonomic activity in the isolated guinea pig bladder, induced by arecaidine. Therefore, PG synthesis and release is able to modulate autonomic activity response towards cholinergic excitation, which suggests an interaction between a cholinergic and prostanoid pathway. The decrease in cholinergic evoked autonomic activity following indomethacin, which was measured in the isolated bladder, suggests an interaction in the motor/sensory system in the bladder wall. This may explain the beneficial effects of COX inhibitors on the overactive bladder.

Concluding message

Our data suggest PG to have an important role in the alternation of autonomic activity through muscarinic receptors. Inhibition of cholinergic activity in the bladder by antimuscarinic drugs is effective in reducing the symptoms of urgency and frequency, without the therapeutic dosage being high enough to act on the muscle [2]. Therefore, we hypothesise that anticholinergics could target the sensory mechanisms operating during the filling phase, with other locally produced substances such as ATP, NO and PG also having a possible role in the regulation of these sensory mechanisms.

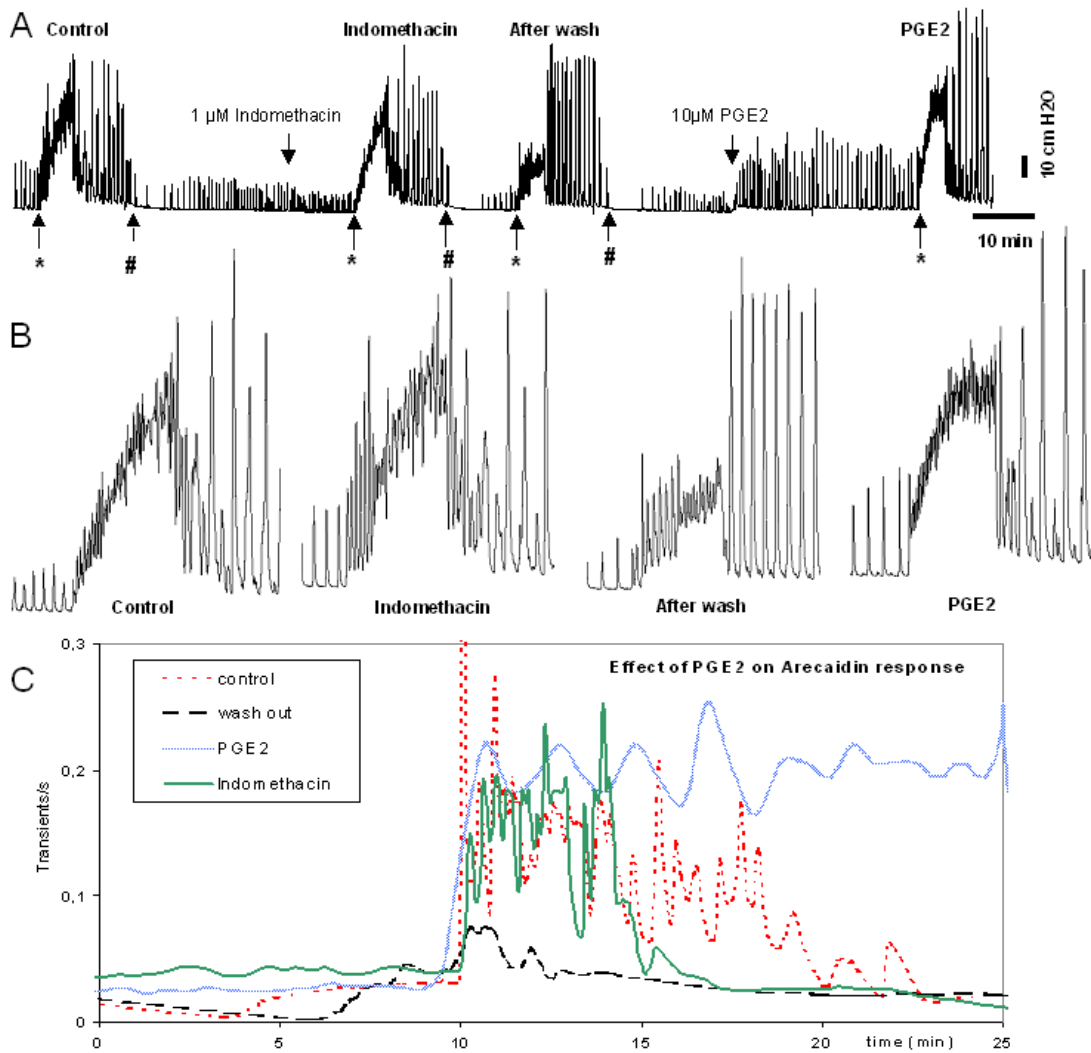


Figure 1. Timeline, Pressure changes and Instantaneous frequency plot of an isolated guinea pig bladder after stimulation with arecaidine

In panel A the timeline of a typical experiment is shown. Arecaidine was used in a concentration of 1 μ M. After the first arecaidine stimulation (indicated with *), the organ bath is washed with Krebs solution to remove the arecaidine (indicated with #). After about 15 minutes indomethacin is added, followed by a second stimulation of arecaidine (*). After washing out the indomethacin (#) and the previously present PG, a third arecaidine stimulation is performed (*) followed by a wash step (#). To check the reversibility, 10 μ M PGE2 is added back in to the organ bath and a last arecaidine stimulation is conducted (*).

Panel B shows an enlargement of each of the arecaidine responses, as shown in Panel A.

In Panel C an instantaneous frequency plot of the isolated guinea pig bladder is shown. The four conditions described in Panel A are summarised.

References

1. J.I. Gillespie The autonomous bladder: a view of the origin of bladder overactivity and sensory urge. *BJU international* 2004, 93(4):478-483.
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Is this a clinical trial?

No

What were the subjects in the study?

ANIMAL

Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?

Yes

Name of ethics committee

Maastricht University Animal Ethical Committee

