

DESENSITISATION OF URETHRAL SMOOTH MUSCLE: INTERACTION BETWEEN ADRENOCEPTOR AND MUSCARINIC RECEPTOR MEDIATED PATHWAYS.

Hypothesis / aims of study

Alpha₁-adrenoceptor agonists have been suggested as a possible treatment for urinary stress incontinence, but no compound acting via this mechanism has yet been developed to the clinical stage. One possible explanation for this lack of success in drug development is desensitisation of the urethral smooth muscle by the agonist itself. Previous studies have shown that incubation with an α₁-adrenoceptor agonist induces desensitisation of the porcine urethra (1). The urethra is dually innervated by both the sympathetic and parasympathetic divisions of the autonomic nervous system, and interaction of these two facets has been shown previously at the presynaptic level (2). Postsynaptic interaction between the parasympathetic and sympathetic nervous system is yet to be reported in the urethra.

Aim of study: To investigate the effect of prior incubation with an adrenoceptor agonist on muscarinic receptor-mediated contractile responses of the porcine urethra, and vice versa.

Study design, materials and methods

Porcine urethra circular smooth muscle strips (with or without urothelium) were mounted in organ baths at 37°C in Krebs-bicarbonate solution. Contractile responses to the muscarinic receptor agonist carbachol, and adrenoceptor agonist noradrenaline, were obtained following a 15 minutes exposure to either noradrenaline (7μM, EC₅₀ concentration) or carbachol (4μM, EC₅₀ concentration) and a 30 minute wash period. Tissues were also incubated with corticosterone (1μM), desipramine (1μM) and propranolol (1μM), to block type I and II reuptake and β-adrenoceptor activation by noradrenaline respectively, and thus target urethral α_{1A/L} adrenoceptor receptors. Furthermore, separate experiments were carried out in the presence or absence of indomethacin (10μM) and TTX (1μM) to block prostaglandin production and nerve mediated effects respectively.

Results

In urethral smooth muscle (no urothelium) maximum responses to carbachol were significantly reduced, by 46.3±11.0% (Figure 1A), following pre-incubation with noradrenaline (mean±SEM, n=8-10; p<0.05 vs control). In addition, pre-incubation with carbachol significantly reduced maximum responses of urethral smooth muscle to noradrenaline, by 35.6±10.0% (P<0.05) (Figure 1B). The amount of desensitisation caused by the two agonists was not significantly different. In urethral tissues with intact urothelium, pre-incubation with noradrenaline significantly reduced subsequent responses to carbachol by 42.9±14.1% (P<0.05) (Figure 1C), similar to that seen in muscle only strips. However, no desensitisation was observed in noradrenaline-induced contractions of intact strips pre-incubated with carbachol (Figure 1D). This did not change in the presence of indomethacin (10μM) or TTX (1μM). All smooth muscle strips without urothelium achieved greater contractile responses to agonists compared to their counterparts with urothelium.

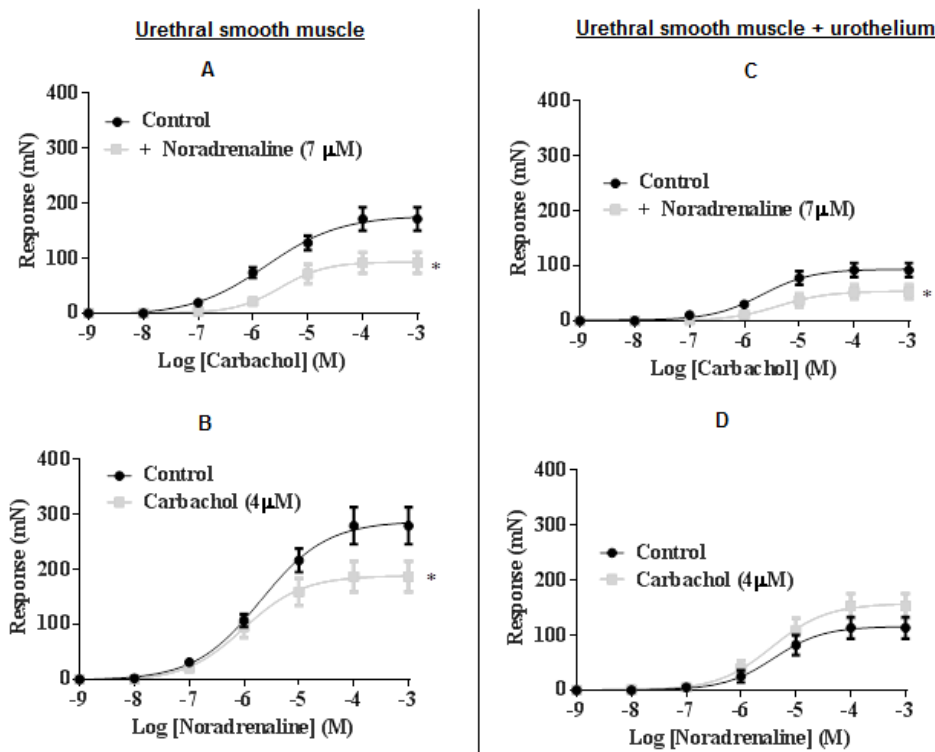


Figure 1: Responses of urethral smooth (A-B) and smooth muscle with urothelium (C-D) to carbachol after pre-incubation with noradrenaline and vice versa. (Mean±SEM, n=8;10 * p<0.05, vs control).

Interpretation of results

In urethral smooth muscle, the sympathetic and parasympathetic facets of the autonomic nervous system appear to interact at the postsynaptic level, with desensitisation of contractile responses. Stimulation of alpha _{1A/L} receptors in the urethral smooth muscle leads to desensitisation of muscarinic receptor-mediated contractions, whilst stimulation of muscarinic receptors leads to desensitisation of alpha _{1A/L} receptor-mediated contractions. The amount of desensitisation of the response was similar in each case.

Alpha _{1A/L} receptor-mediated desensitisation of carbachol contractions does not appear to involve the urothelium, with a similar amount of desensitisation in intact & denuded tissues.

This suggests that desensitisation is due to interaction of the pathways at the level of the smooth muscle intracellular pathways. Conversely, cholinergic-mediated desensitisation of alpha _{1A/L} receptor-mediated contractions is not observed when the urothelium is present. A possible explanation is that stimulation of muscarinic receptors in the urothelium may act to counter desensitisation, possibly by release of a substance that enhances contractions. This requires further investigation, but the mechanism does not appear to involve prostaglandins or to be a nerve-mediated effect.

Concluding message

These data demonstrate interaction between the adrenergic and the muscarinic pathways in urethral smooth muscle at the post-synaptic level. Stimulation of alpha _{1A/L} adrenoceptors desensitises muscarinic receptor-mediated contractions and vice versa.

References

1. Bagot et al. (2005) Eur. Urol supplement 4(3) p207, 820.
2. Mattiasson et al. (1984) J Auton Pharmacol. 4(4):241-9

Disclosures

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Subjects: ANIMAL **Species:** Pig (large white) **Ethics Committee:** Bond University Ethical Committee