Contractile activity of the bladder urothelium and lamina propria

By

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ABSTRACT

The normal function of the urinary bladder is to store and void urine in a controlled manner. During the filling stage the bladder exhibits spontaneous non-voiding contractions yet the mechanisms underlying these contractions are unclear. The internal lining of the bladder (urothelium/lamina propria) is an important regulator of bladder function by its involvement in sensory mechanisms and via releasing chemical mediators. In addition, the urothelium/lamina propria also exhibits spontaneous contractions which are mediated by unknown mechanisms. This activity may influence contractions of the bladder and play an important role in bladder function. The present study aimed to investigate the spontaneous contractions of the urothelium/lamina propria to identify receptors which modulate the activity.

In the absence of any neuronal input, strips of urothelium/lamina propria developed spontaneous contractions with a frequency of 3.72 cycles min\(^{-1}\) and an amplitude of 0.65g. The frequency and tension of contractions was increased by stimulation of muscarinic receptors and \(\alpha_1\)-adrenoceptors, and inhibited by \(\beta\)-adrenoceptor stimulation. Each of these receptor systems is a target for clinical therapies used to treat bladder dysfunction, and these results identify the urothelium/lamina propria as a potential site of action for these agents. Using RT-PCR all \(\alpha_1\)- and \(\beta\)-adrenoceptor subtypes were present at the mRNA level in the urothelium/lamina propria, whilst organ bath experiments with receptor subtype selective agonists and antagonists demonstrated that the main functional adrenoceptors in the tissue were the \(\alpha_{1A/L}\)- and \(\beta_2\)-adrenoceptors. Functional experiments also showed that nitric oxide donors decreased the rate of spontaneous contractions and inhibited responses to muscarinic receptor stimulation or electrical field stimulation. However, nitric oxide was not released spontaneously in response to stretch, EFS or muscarinic receptor stimulation. Activation of the nerves innervating the urothelium/lamina propria results in tissue contraction, yet the dominant neurotransmitter released does not activate muscarinic, adrenergic, or purinergic receptors. Upon removal of the urothelium the baseline frequency and tension of spontaneous contractions, and the response to muscarinic and \(\beta\)-adrenergic receptor activation remained unchanged. This identified the lamina propria as the layer responsible for the contractile activity.

In conclusion, the urothelium/lamina propria exhibits spontaneous contractile activity that may influence bladder activity. The rate of contraction was higher in the urothelium/lamina propria compared to the detrusor; however, it is possible that in diseased states of the bladder, these tissues may be more tightly coupled leading to lower urinary tract dysfunction. Therefore, the receptors within the urothelium/lamina propria present novel therapeutic targets for the treatment of bladder disorders.
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DECLARATION

This thesis is submitted to Bond University in fulfilment of the requirements for the degree of Doctor of Philosophy. This thesis represents my own original work towards this research degree and contains no material which has been previously submitted for a degree or diploma at this University or other institution, except where due acknowledgement is made.

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