576

Lagou M[1], Gillespie J[1], Drake M[1]
1. University of Newcastle

RESPONSE TO MUSCARINIC STIMULATION IN THE ISOLATED WHOLE MOUSE BLADDER VARIES WITH FILLING VOLUME.

Hypothesis / aims of study

Complex autonomous activity is a recognised feature of the isolated whole rodent bladder, taking the form of localised modular contractions, stretches and propagating contraction waves [1]. Such activity has been postulated to provide a basis for generation of increased afferent return, since localised deformation of the bladder wall is likely to stimulate sensory nerve endings [2]. Previous work has shown that muscarinic agonists strongly enhance autonomous activity in the isolated whole bladder, generating a complex response in the intravesical pressure trace consisting of a shift in the baseline pressure and superimposed phasic pressure fluctuations. In the current study we evaluated how filling volume affects the autonomous activity of the isolated whole mouse bladder, in the presence of various muscarinic agonists and antagonists.

Study design, materials and methods

The urinary bladder and urethra were microsurgically removed *post mortem* from female C57bl mice (age 3-4 months, n=17). A glass cannula was secured at the bladder neck, and connected via a 3-way tap to a pressure transducer. A graduated syringe was used to control intravesical volume. The bladder was placed in a 30ml organ bath containing Tyrode's saline bubbled with 95% oxygen, 5% carbon dioxide under physiological conditions of pH and temperature. Intravesical pressure was recorded with Newcastle Photometric Systems hardware and software. Drugs employed were the muscarinic agonist arecaidine, and selective muscarinic antagonists. Appropriate volumes of concentrated drug solutions were placed directly into the organ bath to achieve the required final dilution.

Results

Arecaidine elicited a compound pressure response comprising a baseline shift in intravesical pressure and superimposed phasic fluctuations. Effect of bladder distension on the pressure response generated by exposure to 100nM arecaidine varied according to intravesical volume. At low volumes, a small increase in volume increased the baseline pressure shift elicited by arecaidine, with little effect on the phasic fluctuations. At filling volumes of 80-100 microlitres, the baseline pressure shift elicited by arecaidine was more-or-less constant, but there was a substantial enhancement of the phasic fluctuations (see figure). A selective muscarinic M2-receptor antagonist reduced the amplitude of the phasic fluctuations without influencing the baseline shift, except at very high concentrations (possibly representing a non-specific action). A differential effect of a selective muscarinic M3-receptor antagonist was seen. At very low concentrations it reduced the amplitude of the phasic fluctuations, while at slightly higher concentrations it reduced the baseline shift, eliminating all contractile response to arecaidine at concentrations of 300nM.

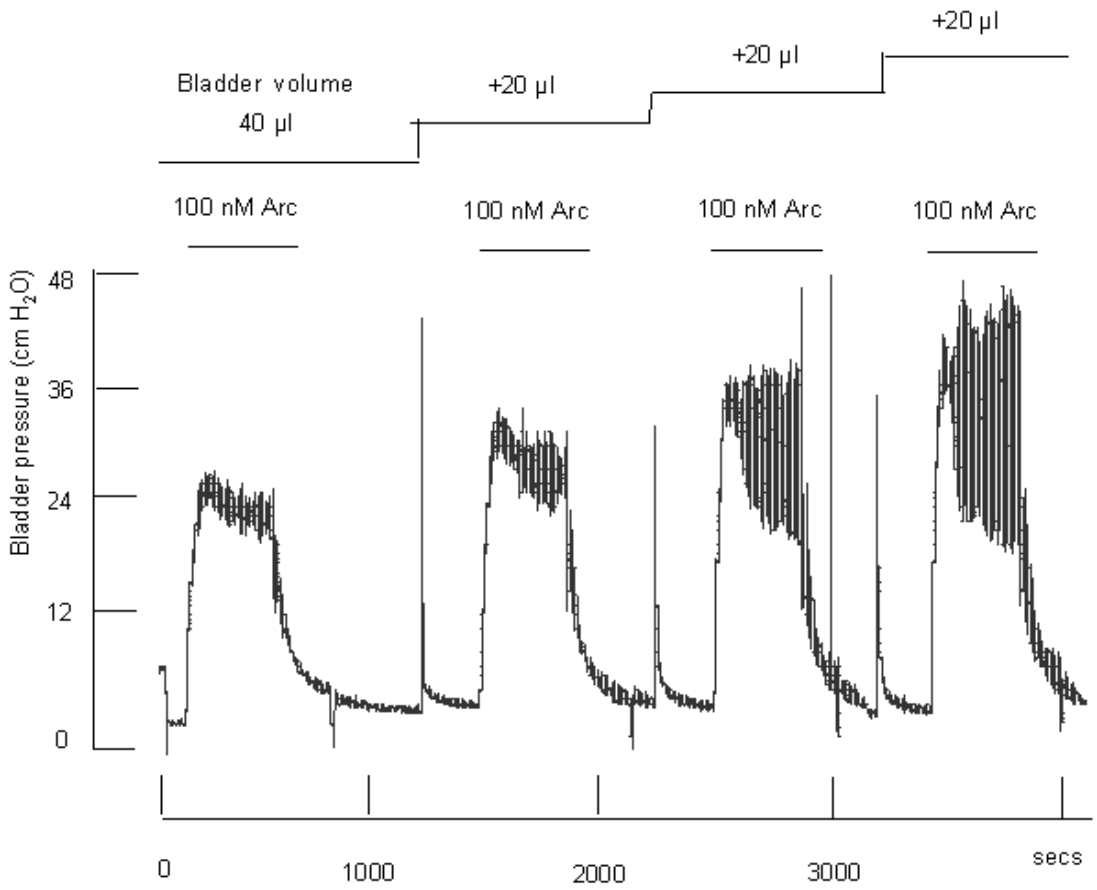

Figure *pressure trace generated by 4 applications of 100nM arecaidine (Arc); the agonist was present as denoted by the horizontal bars. Between each application, intravesical volume was increased by 20 microlitres. At low volumes, the baseline pressure shift elicited by arecaidine increased with increased volume. At higher volumes, the extra baseline pressure shift was minimal, but there was a disproportionate increase in the superimposed phasic fluctuations.*

Interpretation of results

Muscarinic agonist stimulation elicits a baseline pressure shift and phasic pressure fluctuations. The former varies with volume only at low intravesical volumes, the latter varies with volume mainly at high intravesical volumes. The baseline shift is reduced by M3-receptor antagonist, and seems most likely to be a result of activation of M3-receptors on the smooth muscle of the bladder. The pressure fluctuations are influenced by M2- and M3-receptor antagonists. This is consistent with reports of M2-receptor phenomena expressed only in the presence of prior M3-receptor activation [3]. The mechanical deformation seen with the high amplitude fluctuations is likely to stimulate afferent nerves in the bladder wall, causing a substantial increase in sensory return at high filling volume. This provides a theoretical justification for use of M2-receptor antagonists in treatment of overactive bladder.

Concluding message

The bladder shows compound responses to cholinergic stimulation which varies with filling volume. The phasic component at high filling volume may be a physiological mechanism for increasing sensory return; it is inhibited by both M2- and M3-receptor antagonists.

References

[1] Autonomous activity in the isolated guinea pig bladder. Exp Physiol. 2003 Jan;88(1):19-30

[2] Model of peripheral autonomous modules and a myovesical plexus in normal and overactive bladder function. Lancet. 2001 Aug 4;358(9279):401-3.

[3] Contractile role of M2 and M3 muscarinic receptors in gastrointestinal, airway and urinary bladder smooth muscle. Life Sci. 2003 Dec 5;74(2-3):355-66.

FUNDING: Research into Ageing