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EFFECTS OF TOLTERODINE ON VOLUME INDUCED SPONTANEOUS ACTIVITY IN THE ISOLATED BLADDER.

Hypothesis / aims of study

The isolated guinea pig bladder generates spontaneous, co-ordinated activity resulting in transient rises in intravesical pressure. Increasing intravesical volume increases transient frequency and rapid decrease leads to quiescence followed by gradual return in activity [1]. Our aim was to examine the effect of tolterodine upon both spontaneous activity and this quiescent period ("Inhibitory phase").

Study design, materials and methods

Bladders were isolated from female guinea pigs (n=4), cannulated per urethra and placed in Tyrodes solution. 100nM arecaidine was added directly to the bathing solution to "augment" activity. Intravesical volume was altered by 2000µl via the urethral cannula taking 10 seconds for each incremental increase or decrease in volume. Each bladder had a typical baseline volume of 800µl. Effects of the doses 0, 10, 30, 100nM of tolterodine upon changes in the frequency of spontaneous activity, both immediately after volume increase and once it has achieved steady state, were assessed. The time for the frequency of spontaneous activity during the inhibitory phase to return to 66.6% of its initial pre-volume increase level (Tau phase) was also assessed.

Results

Little difference was seen with 10nM tolterodine. However, at higher doses the frequencies both initially following volume increase and at steady state were reduced. More noticeable was the increase in the period of quiescence following volume decrease. An analysis of all records is demonstrated in figure 1. Little significant difference was seen in the presence of 10nM tolterodine. Though, at 30 and 100nM significant increases were seen in the mean duration of the inhibitory phase. Significant reductions were also seen in the mean frequency following volume increase (IF_{max}) and at steady state (F_{ss}). The change in mean underlying pressure, upon which transient contractions are superimposed (P_{shift}), from baseline to steady state remains insignificant at the tested doses of tolterodine.

Interpretation of results

The inhibition of phasic activity within the isolated bladder seen following a reduction in volume suggests the presence of local volume/ stretch related inhibitory mechanisms within the bladder wall. It has been previously suggested that anticholinergic medications act upon a system distinct from the micturition contraction involved in the regulation of sensation, with further suggestion that mechanisms involved in the regulation of phasic activity may be a therapeutic target. The data from these experiments further supports this idea with effects seen on both spontaneous and volume induced activity. The most noticeable effect of tolterodine is on the inhibitory phase. At doses >30nM the inhibitory phase is significantly prolonged, becoming 3 times longer in the presence of 100nM. Although the physiological relevance of the inhibitory phase is not understood, clinically, it may serve to reduce afferent discharge, and therefore sensation, during micturition that would otherwise be uncomfortable or even painful. It has been previously suggested that the initiation of the inhibitory phase and co-ordination of the return of activity may be related to certain structures within the bladder; consisting of the urothelium, interstitial cells or sub-urothelial ganglia. The action of tolterodine suggests a direct muscarinic component in the regulation of the inhibitory phase with further speculation that the muscarinic receptors involved are situated on one, or a combination of these structures.

Concluding message

It is conceivable that clinically anti-cholinergics act peripherally upon the mechanisms involved in the generation of phasic activity in addition to those involved in the regulation of volume induced activity. Data from previous studies have supported distinct muscarinic involvement in the generation and regulation of phasic activity with clinical data supporting the idea of anti-cholinergics directly affecting a sensory system. This data further supports an additional effect of anti-cholinergics upon activity induced by changes in volume, the most noticeable being that seen upon the period of quiescence following volume reduction, termed the 'inhibitory phase'. Although the mechanisms behind this activity is not known these observations represent potentially useful therapeutic targets upon which anti-cholinergics may be acting, in addition to highlighting systems involved in the integrated physiology of the bladder.

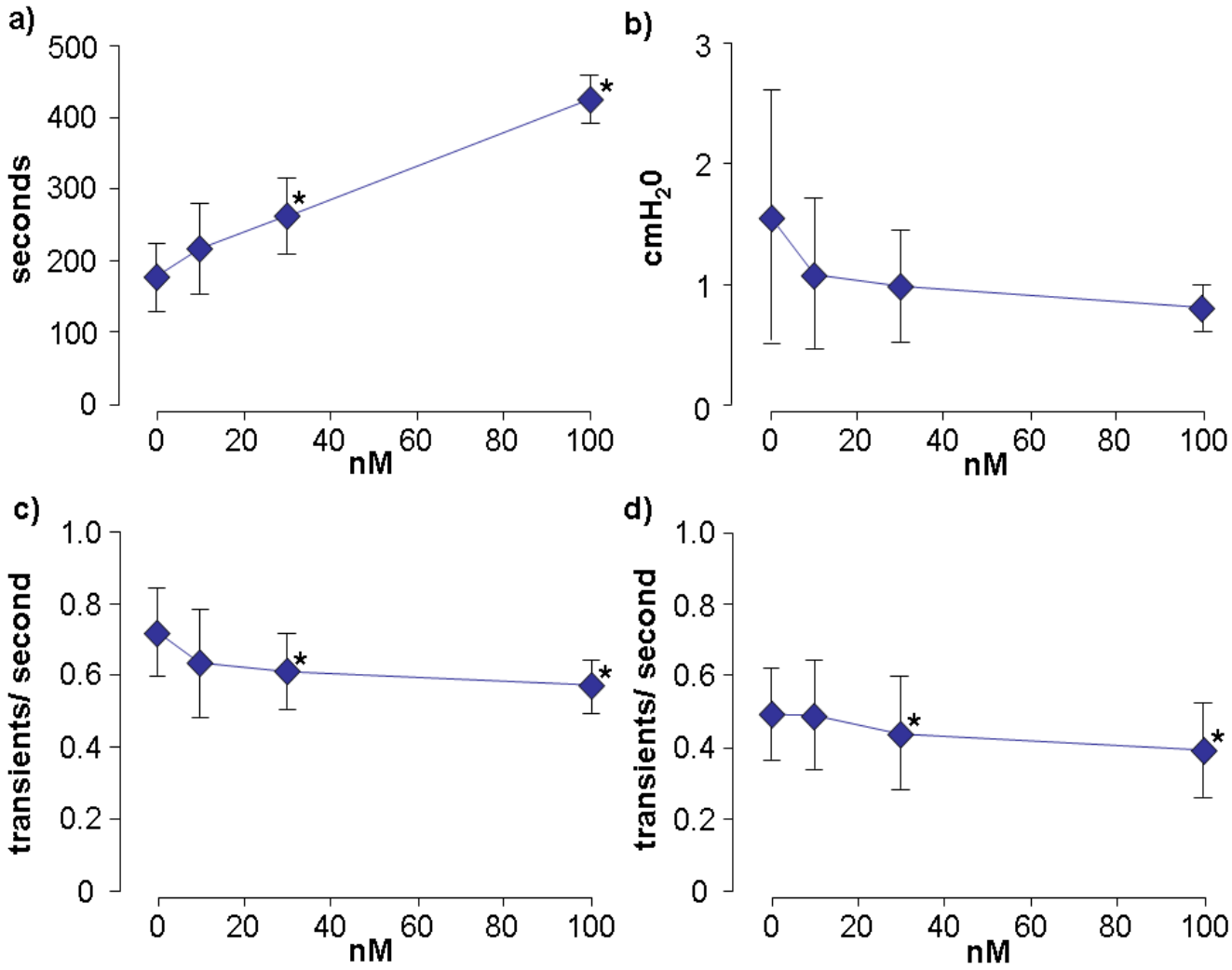

Figure 1. Data collected from 4 bladders illustrating the effects of increasing doses of tolterodine upon the volume response. a) effects on the tau value of the inhibitory phase. Ordinate, tau value (seconds). b) represents change in underlying pressure (P_{shift}). Ordinate, pressure (cmH_2O). c) and d) illustrate the effects of tolterodine upon frequency following volume increase (IF_{init}) and at steady state (F_{ss}) respectively. Ordinates, frequency (transients/ second). For all panels the abscissa represents the dose of tolterodine added to the preparation (nM). Data points are shown as mean values $\pm$ 1 s.d. (n=4). A significant difference between doses and the control, (0nM), is indicated (*), ($p<0.05$, student t-test).

References

1. 1. Finney SM, Stewart LH, Gillespie JI. Intrinsic properties of volume induced responses in the isolated bladder: a further characterisation. BJU Int 2008 Nov; 102(9): 1154-61.

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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	**Animals killed in accordance with schedule 1 of Home Office regulations, UK.**