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The urothelium and lamina propria as an alternative target for clinical antimuscarinics

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Introduction: Overactive bladder is the most common type of bladder dysfunction and involves spontaneous contractions of the urinary bladder during the filling phase. The first-line pharmaceutical therapies for managing this disorder are antimuscarinics (Moro et al., 2011), which have a primary action of blocking the action of acetylcholine in the urothelium and lamina propria (Nardulli et al., 2012). However, more than 70% of patients who are administered these drugs cease their treatment regimen due to lower than expected treatment benefits or adverse side effects (Vouri et al., 2019). The reason for this is unclear, although this does suggest a varied effectiveness or selectivity of antimuscarinics on urinary bladder tissue. **Aim:** This study aims to find the differences in the abilities to inhibit contractions of the U&LP for commonly prescribed clinical antimuscarinics. **Methods**: Strips of porcine U&LP were mounted in carbogen-gassed Krebs-bicarbonate solution at 37°C. The tissues were paired with carbachol concentration-response curves performed in the absence or presence of clinically used antimuscarinics. The concentration for each antagonist was chosen at which the inhibited contractions reached a significant, but sub-maximal, extent. pEC50 values for each curve were analysed and estimated affinities calculated. Ethical approval was not required for this study as tissues were sourced from the local abattoir after slaughter for the routine commercial provision of food. **Results:** The clinical antimuscarinics producing right parallel shifts from the control in the U&LP (concentration; n value; estimated affinity or pkD; paired Student's two-tailed t-test) included oxybutynin (1µM; 18; 7.08; $p<0.001$), solifenacin (1µM; 11; 6.88; $p<0.001$), darifenacin (100nM; 10; 6.48; $p<0.001$), tolterodine (1µM; 10; 8.00; $p<0.001$), trospium (100nM; 10; 7.63; $p<0.001$) and fesoterodine (100nM; 11; 7.40; $p<0.001$). Propiverine (concentration; n value; paired Student's two-tailed *t*-test) did not produce a shift (1µM; 11; $p=0.50$). **Conclusion:** The data highlights a variance in the effectiveness of each clinically used antimuscarinic to antagonise the response to muscarinic receptor activation of the U&LP.

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