The Effects of Pilocarpine, a Muscarinic Receptor Agonist, on Contraction of the Urinary Bladder in the Pig and Human

Introduction and Objective: Contraction of urinary bladder is mediated by activation of muscarinic receptors, with M_3-muscarinic receptors predominate. Cholinergic drugs such as bethanechol chloride have been considered to enhance detrusor contractility and promote bladder emptying in patients with underactive bladder. However, the use of cholinergic drugs has not been standardized due to the efficacy and serious side effects. Recently, pilocarpine, a muscarinic receptor agonist has been reported to be effective for the treatment of dryness of eyes or salivation disorders.[1] This study examines the effects of pilocarpine on contraction of porcine and human urinary bladder.
Materials and Methods: Strips of tissues were mounted in 10ml organ baths containing Krebs solution (composition in mM: NaCl 118.4, KCl 4.7, $CaCl_2$ 1.9, $NaHCO_3$ 24.9, $MgSO_4$ 1.15, KH_2PO_4 1.15, glucose 11.7) which was maintained at 37^oC and continuously gassed with 95% O_2 and 5%CO_2. The tissues were subjected to a resting tension of 1 g and allowed to equilibrate for 60 minutes. Cumulative concentration-response curves (CRCs) to pilocarpine were obtained, with Krebs solution containing in the presence of darifenacin, 4-DAMP (M_3 selective antagonist), pirenzepine (M_1 selective antagonist), methoctramine (M_2 selective antagonist), or in the presence of vehicle. These muscarinic receptor antagonists were treated for 30 minutes before the addition of pilocarpine.
Results: Pilocarpine induced contractions of smooth muscle of the detrusor in a concentration-dependent manner, with maximum contraction relative to 80 mM KCl of 134.4% and 78%, respectively, and pEC_{50} values of 5.28 and 5.1, respectively, in the pig and human bladder. Darifenacin, 4-DAMP, pirenzepine, and methoctramine caused surmountable antagonism of responses to pilocarpine, with slopes of Schild plot of 1.37±0.20, 0.80±0.54, 1.05±0.30, and 0.91±0.35, respectively in the pig bladder. The rank order of mean pA_2 values was as follows: 4-DAMP (8.79±0.27) = darifenacin (8.73±0.06) > pirenzepine (6.72±0.12) > methoctramine (6.58±0.16). Darifenacin caused surmountable antagonism of responses to pilocarpine, with slopes of Schild plot of 0.93±0.30 and a pA_2 value of 8.85±0.13 in the human bladder.
Conclusions: Pilocarpine appears to produce contraction of the pig and human bladder through activation of M_3-muscarinic receptor.
REFERENCES
1. JAMA. 2010; 304: 452-60.