

M2 RECEPTOR ACTIVATION MODULATES DETRUSOR CONTRACTIONS VIA cAMP INHIBITION.

Hypothesis / aims of study

In many mammalian species, it has been demonstrated that detrusor contraction is mediated by a minority of M3 acetylcholine receptors¹. The more populous M2 receptor is believed to have a regulatory role, which may be mediated by cyclic AMP inhibition, although this has not yet been proven. We hypothesized that there is significant M2 receptor based modulation of detrusor contractions by cAMP. This was tested by measuring the differential force of contractions generated by muscarinic agonists in detrusor tissue: (1) in the absence and then presence of the selective M2 muscarinic antagonist, methoctramine; (2) in the absence and then presence of the adenylyl cyclase activator forskolin which increase cAMP concentration.

Study design, materials and methods

Guinea-pig tissue was obtained from freshly isolated bladders. The urothelium was dissected away and denuded muscle strips were mounted and superfused in an organ bath in a balanced salt solution. The force of contraction generated by varying concentrations of the muscarinic agonists, carbachol and the M2 preferential oxotremorine, were measured in the absence and then presence of the M2 antagonist methoctramine and the adenylyl cyclase activator, forskolin. Data are expressed as mean \pm SD.

Results

Oxotremorine was a significantly more potent agonist than carbachol; $pEC_{50} = 6.39 \pm 0.53$ (n=7) and $pEC_{50} = 5.34 \pm 0.29$ (n=19), respectively ($p < 0.05$). Significant M2 receptor signalling was present when oxotremorine (Fig 1) ($pK_B = 8.57 \pm 0.45$), but not carbachol was used as an agonist. 10 μ M forskolin inhibited oxotremorine contractions indistinguishably from 10nM Methoctramine, dose ratio = 2.38 (95% CI = 1.95-3.23) and dose ratio = 2.93, (95% CI = 1.85-4.01), respectively, n=5 (Fig 2) but, like methoctramine, forskolin had no effect on carbachol induced contractions.

Interpretation of results

These results indicate that there is significant M2 mediated contractility in the guinea-pig detrusor and this is likely to be mediated by cAMP inhibition (Fig 3). M2 activity could only be demonstrated when oxotremorine rather than carbachol was utilised as the agonist.

Concluding message

These findings challenge the current pharmacological strategy of developing M3 selective anticholinergic drugs to control bladder activity. The data suggest that some patients may benefit from inhibition of the M2 receptor in addition to the M3 receptor. Further elucidation of cAMP pathway may lead to novel therapies. The use of a single acetylcholine analogue such as carbachol in some species such as the guinea-pig may lead to the false conclusion that there is no M2 activity present.

References

¹ Journal of Autonomic Pharmacology 21 (5) , 243–248, 2001

Fig 1

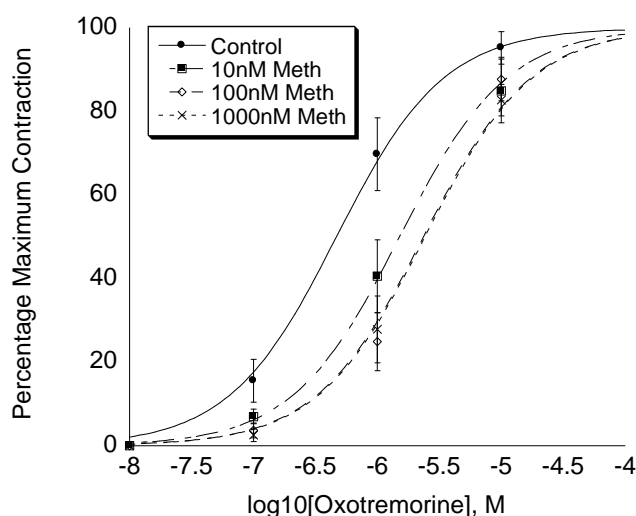


Fig 2

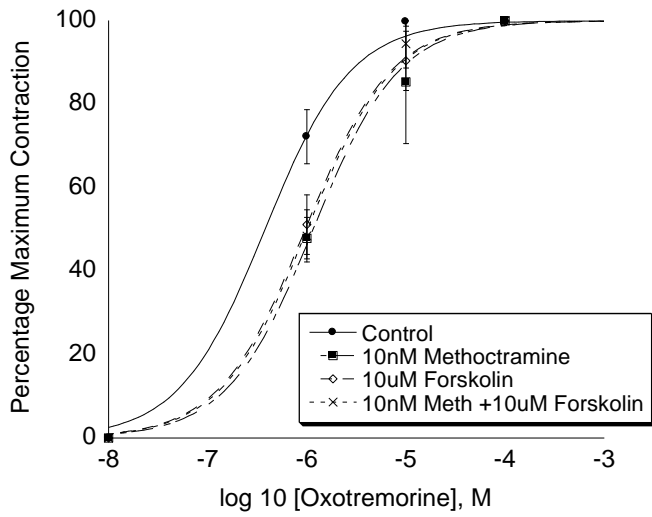
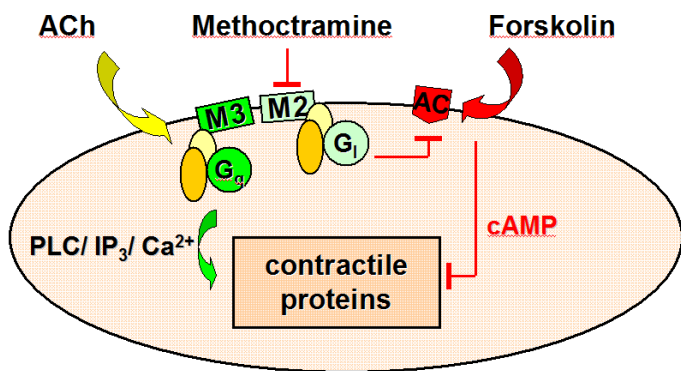


Fig 3



Specify source of funding or grant	Research into Ageing
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	Moorfields and Whittington Research Ethics Committee