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THE MUSCARINIC RECEPTOR ANTAGONIST PROPIVERINE BINDS TO HUMAN (1-ADRENOCEPTORS AND RELAXES THE HUMAN PROSTATE

Hypothesis / aims of study

There is growing interest in the concomitant use of α_1-adrenoceptor and muscarinic receptor antagonists in the treatment of male lower urinary tract symptoms (LUTS). Propiverine, and some of its metabolites, are muscarinic receptor antagonists and primarily used to treat symptoms of overactive bladder (OAB). Apart from blocking muscarinic receptors, propiverine and some of its metabolites also directly block L-Type Ca^{2+} channels [1]. Here we have explored whether antagonism of α_1-adrenoceptors may additionally contribute to therapeutic effects of propiverine.

Study design, materials and methods

Effects on the tone of human isolated prostate and porcine isolated bladder trigone were assessed by adding propiverine or other drugs to tissue strips pre-contracted with 10 µM of the α_1-adrenoceptor agonist phenylephrine. In porcine bladder trigone, additional phenylephrine concentration-response curves (CRC) were generated in the absence and presence of various concentrations of propiverine. A direct interaction with α_1-adrenoceptors was explored in competition radioligand binding experiments using cloned human α_1-adrenoceptor subtypes expressed in Chinese hamster ovary cells, [^{3}H]-prazosin as the radioligand, and propiverine as well as its metabolites M-5 (2,2-diphenyl-2-propoxy-acetic acid [1-methyl-piperid-4-yl]-ester-N-oxide-trans), M-6 (2,2-diphenyl-2-hydroxy-acetic acid [1-methyl-piperid-4-yl]-ester-N-oxide-trans) and M-14 (2,2-diphenyl-2-propoxy-acetic acid [piperid-4-yl]-ester) were used as competitors. All data are shown as means ± SEM of n experiments.

Results

Propiverine concentration-dependently reduced the tone of human prostate strips which had been pre-contracted with 10 µM phenylephrine. The relaxing potency of propiverine (-logEC_{50} [M]) was 4.8 ± 0.1 (n=4). Under the same conditions, the -logEC_{50} of tamsulosin was 10.5 ± 0.04 (n=5). Similar potencies were calculated when effects of these two drugs were studied in porcine bladder trigone: propiverine 5.0 ± 0.1 (n=5), tamsulosin 11.0 ± 0.04 (n=5). The propiverine metabolite M-14 at concentrations >10 µM also reduced α_1-adrenoceptor-mediated contractions in porcine trigone, while M-5 and M-6 did not.

Table 1 –logEC_{50} [M], negative logarithm of phenylephrine for the half maximum effect during the 1st and 2nd CRC and Eff_{max} [%], maximum contraction during the 2nd CRC expressed in percent of the maximum effect during the 1st CRC (=100%); * p < 0.05 ** p < 0.01 (compared to time-matched control - TMC).

	n	*-logEC_{50} (1st CRC)*	*-logEC_{50} (2nd CRC)*	*Eff_{max}*
TMC	8	5.96 ± 0.18	5.82 ± 0.19	58 ± 9
Propiverine				
10 µM	5	6.22 ± 0.29	5.46 ± 0.38	39 ± 6
30 µM	6	6.02 ± 0.16	5.48 ± 0.28	28 ± 6*
100 µM	6	5.82 ± 0.10	5.90 ± 0.22	9 ± 2**

In a second series of experiments, two subsequent phenylephrine CRCs were generated in porcine trigone, the first in the absence and the second in the presence of inhibitor. In time-matched control (TMC) experiments, the second phenylephrine CRC exhibited the same phenylephrine potency as the first curve but a lowered maximum effect (Eff_{max}; Table 1). Several concentrations of propiverine did not significantly alter the potency of phenylephrine but concentration-dependently and significantly reduced its Eff_{max} when compared to TMC (Table 1).

In radioligand competition binding experiments propiverine exhibited similar affinity for all three α_1-adrenoceptor subtypes (Table 2). Its metabolite M-14 had similar affinity at all three subtypes as its parent compound propiverine, whereas the metabolites M-5 and M-6 did not substantially inhibit radioligand binding to any α_1-adrenoceptor subtypes within the tested concentration range (Table 2).

Table 2: -logK_i [M] values at the three human α_1-adrenoceptor subtypes. Phentolamine was used as an internal control.

Compound	n	α_{1A}	α_{1B}	α_{1D}
Phentolamine	3	8.62 ± 0.19	7.96 ± 0.22	7.87 ± 0.04
Propiverin	3	4.72 ± 0.01	4.94 ± 0.02	4.73 ± 0.02
M-5	3	< 4.00	< 4.00	< 4.00
M-6	3	< 4.00	< 4.00	< 4.00
M-14	3	4.72 ± 0.04	5.02 ± 0.11	4.57 ± 0.06

Interpretation of results

Propiverine concentration-dependently relaxed isolated human prostate and pig bladder trigone strips both pre-contracted with the α_1-adrenoceptor agonist phenylephrine. The latter effect was shared by the propiverine metabolite M-14 but not by the metabolites M-5 or M-6. These data on prostate and trigone muscle tone function do not allow to differentiate whether inhibition of α_1-adrenoceptor-mediated contraction was due to functional antagonism by blocking Ca^{2+} channels or to direct α_1-adrenoceptor-receptor antagonism. Our radioligand binding studies demonstrated affinities for propiverine at all three α_1-adrenoceptor subtypes, which are consistent with the potency to inhibit contraction. This was also mimicked by M-14 but not by M-5 or M-6. Our data suggest that direct antagonism of α_1-adrenoceptors contributes to the observed inhibition of contraction. However, the potency of propiverine to inhibit human prostate and porcine trigone contraction by phenylephrine and its affinity at the human α_1-adrenoceptors are about one order of magnitude lower to its reported affinities at muscarinic receptors [2], but its potency to inhibit muscarinic receptor- or neuronal mediated human detrusor contraction as well as L-type Ca^{2+} channels [2,3] is similar to the observed binding properties to α_1-adrenoceptors.

Concluding message

In contrast to other drugs used for treatment of OAB, propiverine is not only a muscarinic receptor antagonist but also an inhibitor of L-type Ca^{2+} channels [3] and, as shown here, of α_1-adrenoceptors. As all three effects functionally occur in similar concentration ranges, we conclude that direct α_1-adrenoceptor antagonist activity may contribute to the clinical effects of propiverine, particularly in male LUTS.

References

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