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CARDIAC ION CHANNEL EFFECTS OF PROPIVERINE

Hypothesis / aims of study

Propiverine is an antimuscarinic drug used for the therapy of overactive bladder.[1] Beside its antagonistic properties on muscarinic receptors it possesses other mechanisms of action, including reduction of Ca^{2+} influx via L-type Ca^{2+} channels in detrusor smooth muscle cells.[2] In recent years the medical community has become increasingly aware of QT interval lengthening effects of drugs intended for non-cardiac indications.[3] Many drugs enhance the risk of ventricular arrhythmia by prolonging the QT interval due to inhibition of the cardiac rapidly activating inward rectifier potassium current (I_{Kr}). The aim of this study was to examine the electrophysiological effects of the spasmolytic drug propiverine on different cardiac ion channels, since block of outward currents can be compensated by concomitant block of inward currents (increase of repolarization reserve). In addition, action potentials were measured in order to estimate the net effect of all currents.

Study design, materials and methods

Ionic currents were measured in HEK-293 cells stably transfected with human ether-a-go-go-related gene (HERG) K^+ channels or in freshly isolated human atrial and guinea-pig ventricular cardiomyocytes using the whole-cell patch clamp technique. Action potentials were recorded from right ventricular papillary muscles of human and guinea pig hearts or from dog Purkinje fibres.

Results

Propiverine blocked in a concentration-dependent manner HERG channels expressed in HEK-293 cells as well as native I_{Kr} current in ventricular myocytes of guinea-pig, the respective -logIC_{50} [M] values were 5.00 and 5.74. At high concentrations (100 µM), propiverine suppressed I_{Ks} (Figure 1).

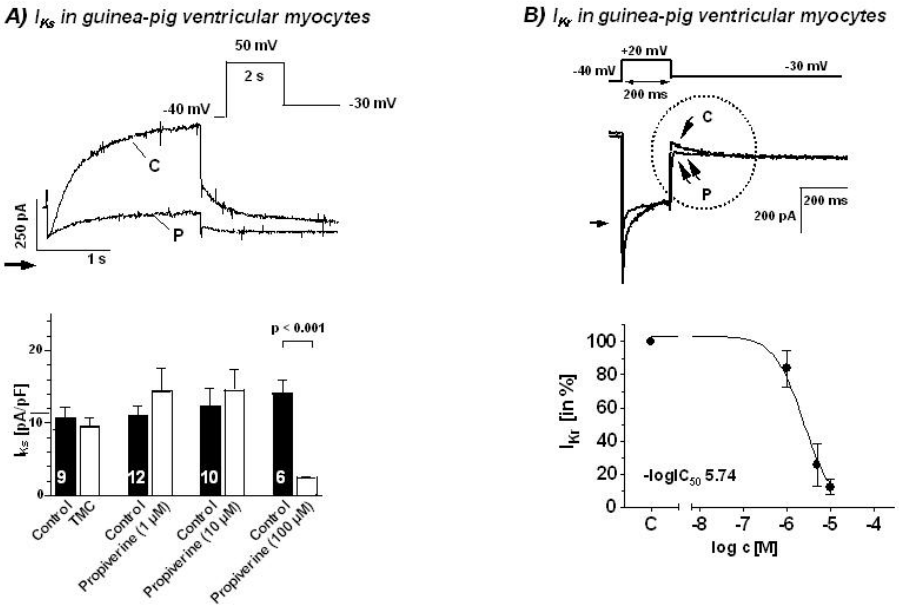

Fig. 1: Concentration-dependent effect of propiverine on I_s and I_{kr} in guinea-pig ventricular myocytes. C – control current, P – after exposure to 100 µM (A) or 10 µM (B) propiverine. Data as mean ± S.E.M. from n investigated cells.

Transient outward currents in human atrial myocytes were not affected. In guinea-pig ventricular myocytes, propiverine blocked L-type Ca^{2+} current ($I_{Ca,L}$), -logIC_{50} [M] was 4.46, it also reduced $I_{Ca,L}$ in human atrial myocytes with a -logIC_{50} [M] of 4.39 (Fig. 2). Sensitivity of propiverine towards cardiac Ca^{2+} channels was one order of magnitude lower than in detrusor smooth muscle cells. Despite block of I_{Kr}, action potential duration was not prolonged in guinea-pig and human ventricular tissue but decreased progressively until excitation failed altogether (Fig. 2). Similar effects were observed in dog Purkinje fibers.

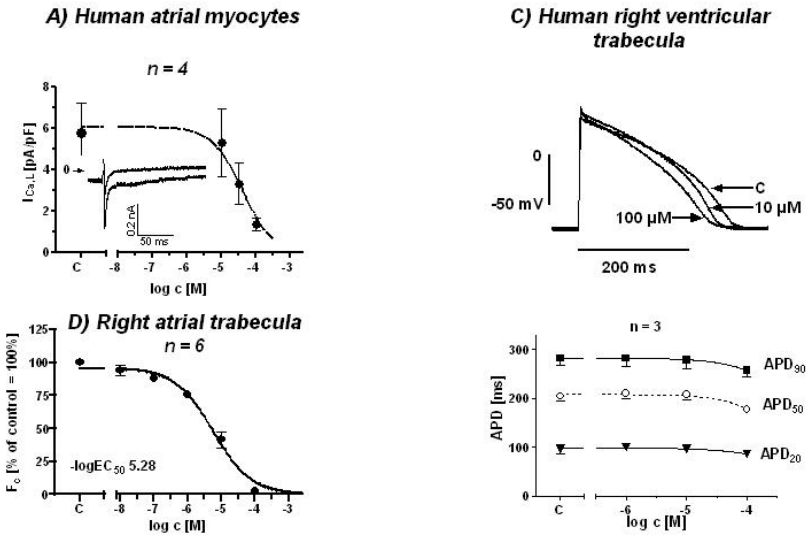

Fig. 2: Concentration-dependent effect of propiverine on (A) $I_{Ca,L}$ in human atrial myocytes, (B) on force of contraction in human right atrial trabecula and (C) on action potential in human right ventricular trabecula. Data as mean ± S.E.M. from n investigated cells or tissue preparations.

Interpretation of results

In terms of therapeutic plasma levels, 17- to 42-fold higher propiverine concentrations are required for block of HERG channels in the expression system, but only 3- to 7-fold for block of native I_{Kr} current. This may appear a small cardiac safety factor compared with the value of 30-fold that was recently suggested. Propiverine also blocked I_{Ks}, however this effect is expected even to enhance APD prolongation due to I_{Kr} block, yet APD was in fact shortened. Therefore, lack of APD-prolonging effect of propiverine in our experiments (and lack of QT-prolongation in clinical experience) could be due to compensation of HERG channel block by propiverine because of the drug's concomitant blocking effect on $I_{Ca,L.}$

The low sensitivity of cardiac Ca^{2+} channels towards propiverine may even be of advantage, since block of $I_{Ca,L}$ in the myocardium is well known to cause unwanted negative inotropic effects. It was shown before, that inhibition of $I_{Ca,L}$ by propiverine in detrusor smooth muscle cells and relaxation of detrusor contractility occurs in about one order of magnitude lower concentrations[2] than block of $I_{Ca,L}$ in cardiac cells suggesting that propiverine may exhibit some organ selectivity which is absent in classical calcium channel blockers as for instance in the dihydropyridine derivative nifedipine.

Concluding message

In summary, we proposed that the concomitant block by propiverine of HERG and Ca^{2+} channels lead to a compensation of the respective effects on APD. This dual effect may explain the cardiac safety of propiverine in the clinical setting. We propose that lack of torsadogenic risk of propiverine is related to enhancement of repolarization reserve by block of $I_{Ca,L}$. Propiverine may exhibit some organ selectivity blocking $I_{Ca,L}$ in the urinary bladder.

References

[1] World J Urol (2001) 19; 324-335.
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HUMAN SUBJECTS: This study was approved by the University Clinics Ethical Committee and followed the Declaration of Helsinki Informed consent was obtained from the patients.