CVS-03 Inhibition of the unique repolarisation K^+ channel current I_{Kur} by verapamil in human atrial myocytes

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Introduction: Verapamil is widely used as an antiarrhythmic drug in patients with atrial arrhythmias, and its Ca^{2+} antagonistc action is usually believed to be the mechanism. The present study was to determine if anti-atrial arrhythmia was related to the blockade of the unique repolarization K^+ current (I_{Kur}, ultra-rapid delayed rectifier K^+ current).
Method: Whole-cell patch clamp technique was used to determine I_{Kur} and another voltage-gated current, transient outward K^+ current (I_{to1}) in human atrial myocytes.
Results: It was found that verapamil inhibited I_{Kur} in a dose-dependent manner (EC_{50} = 3.74 mM). The effect was fully reversed upon washout of the drug. At test potential of +50 mV, Verapamil at 5 mM decreased I_{Kur} by 40.3 ± 5.1% (2.68 ± 0.21 pA/pF in control and 1.84± 0.17 pA/pF after verapamil, n=8, $p<0.01$). The inhibition of I_{Kur} by verapamil is voltage-independent. In contrast, verapamil (0.1~50 mM) exhibited a slight increase in I_{to1}, but did not show a dose-response fashion. However, verapamil accelerated inactivation of I_{to1}. At 1 mM, the time constant of I_{to1} inactivation was reduced to 51.16± 5.29 from 71.74± 3.3 ms of control (+50 mV, n=8, $p<0.01$). Other kinetics of I_{to1} were not affected by verapamil.
Conclusion: The present study has demonstrated for the first time that verapamil, a well-known calcium blocker, significantly blocks the unique repolarization K^+ current I_{Kur}, and revealed a novel antiarrhythmic mechanism of verapamil.

CVS-04 Effects of genistein on K^+ currents in rat ventricular myocytes

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Introduction: Previous studies showed that genistein modulated ionic channels in a protein tyrosine kinase- (PTK) dependent or independent way upon species and/or channel types. The present study was designed to determine whether transient outward K^+ current (I_{to}), sustained K^+ current (I_{sus}), inward rectifier K^+ current (I_{K1}) were regulated by genistein in rat ventricular myocytes.
Methods: Whole-cell patch technique was applied to record I_{to}, I_{sus}, and I_{K1} in enzymatically dissociated ventricular myocytes from rat hearts. All experiments were conducted at 22~23°C.
Results: Genistein reversibly inhibited I_{to} in a concentration-dependent manner (IC_{50} = 27.8 μM. The compound (50 mM) shifted midpoint of voltage ($V_{0.5}$) for inactivation of I_{to} to -42.5 ±1.0 from –37.6±0.6 mV ($P<0.01$), while the $V_{0.5}$ for I_{to} activation was not significantly altered. In addition, genistein reversibly suppressed I_{sus} with IC_{50} of 17.1 μM. Moreover, the compound at 50 mM reduced I_{K1} at –100 and –50 mV by 40.6±6.2% and 51.4±0.7%, respectively. However, the effects of genistein on I_{to}, I_{Ksus}, and I_{K1} were not affected by the application of phosphotyrosine phophatase inhibitor (sodium orthovanadate, 1 mM). On the other hand, daidzein (100 mM), an inactive analogue of genistein, did not show significant effect on the three K^+ currents. Another type of PTK inhibitor, tyrphostin A23, had no effect on I_{to}, I_{Ksus}, and I_{K1}.
Conclusion: 1) The PTK inhibitor genistein, not tyrphostin A23, reversibly inhibited I_{to}, I_{Ksus}, and I_{K1} in rat ventricular myocytes, and 2) the effects were not affected by the protein tyrosine phosphatase inhibitor orthovanadate. The present study has provided the first information that genistein-induced suppression of I_{to}, I_{Ksus}, and I_{K1} is independent of PTK inhibition.