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Differential Effects of *d,l*-Sotalol and *d*-Sotalol on Isoproterenol-Increased Delayed Rectifier Outward Potassium Current in Guinea Pig Single Ventricular Myocytes. Influence of Temperature

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In this study we compared the effects of *d,l*-sotalol and *d*-sotalol on the delayed rectifier outward potassium current (I_K) in the absence and presence of isoproterenol in isolated guinea pig single ventricular myocytes. We also studied the modulation of the preventive activities of *d,l*-sotalol on the isoproterenol-induced increase of I_K by different temperatures. Electrophysiological effects were studied using the whole-cell configuration of the patch-clamp technique.

Time-dependent delayed rectifier K^+ currents I_K (I_{Kr} and I_{Ks}) were measured in response to 300 ms (a time to mimic the cardiac action potential) depolarizing pulses from a holding potential of -40 mV in three experimental protocols [control, isoproterenol (10^{-9} -10^{-6} M), and isoproterenol (10^{-9}-10^{-6} M) plus either *d,l*-sotalol (10^{-4} M) or *d*-sotalol (10^{-4} M)]. $I_{K\,tail}$ currents were measured upon repolarization to -40 mV. The experiments were carried out at approximately 37°C. To study the effect of temperature on I_K , the temperature of the bath solution was varied between 22°C and 37°C.

The magnitude of the I_K current increased with the flow rate of the perfusion solution. Thus, we chose a constant flow rate (1.5 ml/min) during all the experiments. Isoproterenol significantly increased I_K and $I_{K\,tail}$ in a concentration- and temperature-dependent manner. At 37°C, I_K was significantly amplified in the presence of isoproterenol (10^{-9} - 10^{-6} M) plus *d*-sotalol (10^{-4} M). At 10^{-8} M isoproterenol, I_K was increased by 92.7±17.1 % before and 54.3±13.4 % after *d*-sotalol ($P < 0.05$). In contrast, *d,l*-sotalol strongly suppressed the effect of isoproterenol on I_K, and compared to control, I_K was decreased by 35.6±8.1% at 10^{-8} M isoproterenol ($P < 0.05$). At 10^{-6} M isoproterenol, *d,l*-sotalol prevented partially the isoproterenol-induced increase of I_K. But at a temperature of 22°C, *d,l*-sotalol (10^{-4} M) counteracted completely the increase of I_K by 10^{-6} M isoproterenol and in comparison with the control, I_K was decreased by 30.6±6.7 % ($P < 0.05$).

We conclude that the β-adrenergic blocking property of *d,l*-sotalol, but not of *d*-sotalol maintains the delayed rectifier K^+ outward current block in the presence of isoproterenol in guinea pig myocytes. This may result in a superior antiarrhythmic efficacy compared to *d*-sotalol. This effect of *d,l*-sotalol in the presence of isoproterenol results from its β-adrenergic blocking properties, its contribution on I_{Ks} and its class III contribution on I_{Kr}. The effect of isoproterenol on I_K is also temperature-dependent. The temperature shifts the

preventive activities of *d,l*-sotalol on the isoproterenol-induced enhancement of I_K toward low values reducing its efficacy in patients with increased body temperature.