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Atrial-ventricular differences in voltage-gated Na^+ currents of rabbit cardiomyocytes

Atrial fibrillation (AF) is the most common clinical arrhythmia. Voltage-gated Na^+ channel blockers (NCB) are amongst the most effective antiarrhythmic drugs for AF but carry significant risk of ventricular tachyarrhythmia. It has been suggested that differences in Na^+ channel characteristics between atrial and ventricular cells can be exploited to develop atrial-selective antiarrhythmic drugs. Ranolazine, an antianginal drug, is an NCB that possesses antiarrhythmic properties and has been suggested to show atrial selectivity the basis for which remains unclear. In this study, atrial-ventricular differences in the voltage-gated Na^+ current (I_{Na}) and its block by ranolazine were investigated. I_{Na} was recorded from rabbit left atrial and right ventricular myocytes at room temperature using the whole-cell patch clamp technique. Recording solutions contained low equimolar Na^+ (10 mM) and nifedipine (20 μM) was used to block Ca^{2+} currents. I_{Na}-voltage relations and steady-state voltage-dependent inactivation curves were obtained from a holding potential (V_{hold}) of -120 mV. I_{Na} conductance density was greater in atrial than in ventricular cells (2.0±0.1 vs 1.1±0.1 nS/pF; P<0.0001). The voltage for half-maximal ($V_{1/2,\ act}$) activation for atrial and ventricular myocytes respectively was -46.9±0.7 mV (n=19) and -39.4±1.2 mV (n=15; P<0.0001) and the $V_{1/2,\ inact}$ inactivation was -102.1±0.4 mV and -90.4±0.2 mV (P<0.0001) respectively. The use-dependence of I_{Na} block by ranolazine (30 μM) was investigated using trains of 40 depolarising pulses at various diastolic intervals (DI; 110, 60 & 40 ms) from different V_{hold} (-120, -110 & -100 mV) in atrial and ventricular myocytes. While both cell types exhibited block that was both use- and voltage-dependent, ranolazine was effective at more negative voltages in atrial than in ventricular cells. In summary, I_{Na} of rabbit cardiomyocytes show atrial-ventricular differences in voltage-dependent activation and inactivation and in ranolazine block consistent with an atrial-selective antiarrhythmic action.