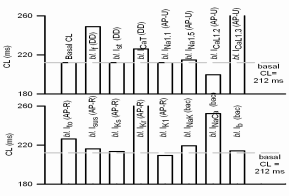
Functional Roles of Ionic Currents in A Mouse Sino-atrial Node Cell Model

S Kharche, M Lei, H Zhang

University of Manchester, UK

Introduction: Functional roles of ion currents in a mouse sino-atrial node (SAN) cell model were simulated by ion current block.

Methods: In the Mangoni et al. mouse SAN model, ionic currents were blocked to study their roles in pacemaking. $[Ca^{2+}]_i$ was buffered simulating effects of ryadonine. Effects of these simulations were quantified as alterations in cell action potential (AP) characteristics, *i.e.*, cycle length (CL), AP duration at 90% repolarisation (APD_{90}), maximum diastolic potential (MDP), and maximal upstroke velocity (dV/dt_{max}).



CL changes due to various ion channel blocking.

Results: Table 1 summaries AP basal properties. Phase plane analysis shows the diastolic depolarization (DD) is regulated by hyperpolarization activated (I_f), sustained inward (I_{st}), and T-type Ca^{2+} (I_{CaT}) currents. AP upstroke is regulated by the fast Na^+ ($I_{Na1.1}$ and $I_{Na1.5}$) and the L-type Ca^{2+} currents ($I_{CaL1.2}$ and $I_{CaL1.3}$). AP repolarisation is regulated by the transient outward (I_{to}), sustained outward (I_{sus}), rapidly and slowly activating delayed rectifying (I_{Kr} and I_{Ks} respectively) and the inward rectifier (I_{K1}) currents. The Na^+-K^+ pump (I_{NaK}) and Na^+-Ca^{2+} exchanger (I_{NaCa}) are background currents. As shown in Figure, I_f blocking increased CL by 17.4%. I_{CaT} block caused a 6% CL increase. Blocking $I_{CaL1.3}$ or I_{Kr} arrested pacemaking. Blocking I_{NaCa} caused an 18% CL reduction. Reducing $[Ca^{2+}]_i$ (0.1 μM to 0.001 μM) increased CL by 5.1%. A small 20% increase of $[Ca^{2+}]_i$ arrested pacemaking.

Conclusions: I_{st}, $I_{Na1.1}$, $I_{Na1.5}$ are not functional in the pacemaking. I_{NaCa} and I_{NaK} are functionally background currents rather than regulators of intracellular ionic concentrations. The model has limited predicative potential and requires further development.

Table 1. Experimental range and model AP features.

	CL (ms)	APD_{90} (ms)	MDP (mV)	dV/dt_{max} (V/s)	TOP (mV)
Exp. range	106 ~ 232	45.8 ~ 107.1	-70 ~ -52	8.2 ~ 45.2	-54.6 ~ -40
Model	212.31	121.1	-66.87	5.31	-47.3