# $Ca^{2+}$-ions and activation of the inward currents in mammalian ventricular myocardium.

H. Windisch and H.A. Tritthart

Universitäts-Institut für Med. Physik und Biophysik, Universität Graz, A-8010 Graz, Austria

A well established experimental technique to study the slow inward current in cardiac ventricular fibres is inactivation of the fast Na-system by membrane depolarization produced by increasing the external $K_o^+$-concentration. The resulting slow membrane responses in $K^+$-enriched solutions have been shown to increase with raised extracellular $Ca_o^{2+}$- concentration as expected for the slow $Ca^{2+}$-inward current: in addition we found a simultaneous $Ca^{2+}$-induced recovery of the depressed fast Na-system. In guinea pig papillary muscles, action potentials were recorded at a low rate of stimulation (1/min). Maximum rate of rise ($\dot{V}max$) and membrane potential (V) were measured at two different $Ca_o^{2+}$-concentrations during stepwise depolarization through $K_o^+$-increase. Plotting the steady state values of $\dot{V}max$ against the membrane potential two curves, one for normal (2.5 mM) and one for high (8mM) $Ca_o^{2+}$ were obtained. The curves were S-shaped and could be fitted by the equation $\dot{V}max = \dot{V}_s/(1 + \exp((V_v-V)/s))^2$. $\dot{V}_s$, the saturation value of $\dot{V}max$, was 297 V/s at normal $Ca_o^{2+}$-concentration and 264 V/s at 8 mM $Ca_o^{2+}$. $V_v$, the membrane potential at a $\dot{V}max$ of 1/4 of $\dot{V}_s$ was 57.95 mV and 54.18 mV, and the slope factor s was 3.74 and 4.32 respectively. The square of the values within the brackets has been used because it gave a better fit of the results. Using normalized curves of non-squared values ($V_s$ = 1) increase of $Ca_o^{2+}$ (from 2.5 to 8 mM) shifted the curve by 3.4 mV in the depolarizing direction (values taken at $\dot{V}_s/2$). However, the slopes of the curves were still slightly different even after normalisation. Similar $Ca_o^{2+}$-induced decrease of the maximum value and of the steepness of the curve of inactivation have been described by Shoukimas (1) for the giant axon of loligo pealei. At membrane potentials more negative than -65 mV, $Ca_o^{2+}$-increase consistently reduced $\dot{V}max$ leading to a reduced $V_{s_2}$. At membrane potentials less negative than -65 mV, however, $Ca_o^{2+}$-increase led to higher values of $\dot{V}max$. This enhancement of Vmax was related to the initial part of the rising phase and was also seen at membrane potentials sufficiently low for complete Na-inactivation. At these low membrane potentials, the differentiation of the rising phase often yielded two peaks. The first peak was probably due to the fast $Na^+$-inward current and showed a linear correlation with the $Ca_o^{2+}$-concentration.But the second peak of $\dot{V}max$ showed a linear correlation only to the logarithm of the $Ca_o^{2+}$-concentration and therefore most likely reflected the $Ca^{2+}$-inward current. These findings indicate a dual effect of $Ca_o^{2+}$-increase on slow responses: a strong reactivation of the fast Na-system and an enhancement of the slow, $Ca^{2+}$-mediated inward current.

1. Shoukimas, J.J. (1978) J.Membrane Biol. 38, 271 - 289.