T-TYPE CALCIUM CHANNELS IN CARDIAC MUSCLE: NEWS IN KINETICS AND MODULATION

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Introduction

It is widely accepted that two types of Ca ++ channels exist in heart muscle (Bean 1985, Nilius et al. 1985, for a review see Bean 1989). T-type Ca ++ channels (or "low threshold activated", Carbone and Lux 1984) are one class of channels in heart muscle that are characterized by the following properties: activation at membrane potentials as negative as -50 mV, fast inactivation, tiny single channel conductance, slow deactivation, insensitivity to dihydropyridine calcium agonists or antagonists. The physiological role of this channel is still under discussion. It seems that T-type Ca ++ channels are involved in triggering of spontaneous electrical activity (Nilius 1986, Coulter et al. 1989, White et al. 1989), control of humoral secretion in some cells (DeRiemer and Sakmann 1986, Cohen et al. 1989, Suzukii et al. 1990), cell growth and cell differentiation as well as oncogenic transformation (Caffrey et al. 1987, Chen et al. 1988, Kawano and DeHaan 1989, Xu and Best 1990). In heart muscle, functional significance is still puzzling. Another problem seems to be the quite inhomogeneous expression of T-type Ca ++ channels in heart muscle (no "T" in frog ventricle, ferret ventricle, rabbit ventricle, rat ventricle; "T" present in frog atrium, guinea pig atrium and ventricle,
rabbit atrium, rat atrium, human atrium, chick ventricle, dog atrium). The higher incidence in the sino-atrial system hints to a possible function that does not play a role in the working myocardium. Here, some novel properties of T-type Ca\(^{++}\) channels in heart are reported that may help to complete the molecular characterization of this type of voltage gated Ca\(^{++}\) channel.

**Methods**

All experiments were performed on single ventricular cells enzymatically isolated from guinea pig hearts (method described by Mitra and Morad 1985). For electrophysiological measurements cells were incubated in a solution that contained (mM): 140 K aspartate, 2 MgCl\(_2\), 10 EGTA, 2 ATP, 10 Hepes titrated with KOH at pH 7.2. Pipette solution contained (mM): 110 CaCl\(_2\), 10 Hepes titrated to pH 7. Ca\(^{++}\) has been shown to permeate T-type Ca channels better than Ba\(^{++}\), whereas it is strongly the opposite for L-type Ca\(^{++}\) channels (Droogmans and Nilius 1989). The pipette solution used is very convenient for discrimination between T and L in single channel experiments. Details of current measurements are described in detail elsewhere (Droogmans and Nilius 1989). In short: 150 ms voltage steps were used, filtered at 2 kHz with an 8-pole Bessel filter, and digitized at 150 \(\mu\)s using a 12-bit AD converter. Each trace contained 1024 samples.

**RESULTS**

**T-type Ca channels have subconductance states**

Figure 1 shows a typical example for T-type Ca channels at two different potentials. Openings almost appear in one burst per depolarisation. Longlasting bursts can be detected at -40 mV (left). The sometimes rather long first latency should be noted. The resulting averaged current is slowly inactivating.