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Role of T-type Ca^{2+} channels in the heart

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Abstract

After the first demonstration 30 years ago that Ca^{2+} could permeate through two different channels, the occurrence and role of T-type Ca^{2+} current, I_{CaT} have been the matter of hundreds of publications, including the two 1985' reports in various cardiac tissues and species. Except for its specific biophysical characteristics, I_{CaT} is no longer so easily distinguished from the L-type Ca^{2+} current, I_{CaL}, since it is also sensitive to multiple compounds and various neuromediators including the β-adrenergic agonists. Changes in I_{CaT} occur during development, so that while it is recorded in all embryonic and neonatal cells investigated, I_{CaT} has been reported in adult ventricular cells of only few species in control. However, under various pathological conditions, I_{CaT} is often recorded at some phases of remodelling at least in some localized area and one or more of the three channel proteins, Cav3.1–3.3 are clearly re-expressed under the influence of IGF-1, endothelin, and angiotensin II. I_{CaT} contributes to the control of electrical activity including pacemaker and arrhythmia. Furthermore I_{CaT}, and its low-depolarisation window current, participate in Ca^{2+} entry, so that I_{CaT} has been involved in the release of Ca^{2+} from internal stores, the Ca^{2+}-induced Ca^{2+} release mechanism, although at much lower level than I_{CaL}. I_{CaT} contributes also to Ca^{2+}-dependent hormonal secretion. This review further emphasizes the difficulties encountered in analysing this current.

Keywords: Calcium channels; T-type calcium channels; Heart; Cardiomyocytes; Excitation-contraction coupling; Pacemaker

1. Introduction

Thirty years have passed since the demonstration by Hagiwara et al. [1] that Ca^{2+} could permeate through two different channels in starfish egg cells. Ten years later, almost simultaneously, Bean [2] and Nilius et al. [3] described for the first time in cardiac myocytes (under whole-cell patch-clamp in dog atrium and single channel analysis in guinea-pig ventricular cells, respectively) that in the presence of Ba^{2+} as charge carrier a low-threshold activating, fast-inactivating current coexisted together with a slow-inactivating current having a high activation threshold. The latter, the "classical" Ca^{2+} current corresponds to the "slow inward current" characterized in cardiac tissues more than 15 years before by Reuter [4] and Rougier et al. [5]. The "new" current was called T- ("tiny", "transient") type Ca^{2+} current, I_{CaT}, following the nomenclature established by Tsien's group, while the "classical" Ca^{2+} current was denominated L-type ("long lasting"), I_{CaL}. Again, more than 10 years had to pass before the molecular identity of T-type channels was unveiled. We now know that there are three T-type channel isoforms $Ca_V3.1$–3.3 (α_{1G}, α_{1H} and α_{1I}), two of which ($Ca_V3.1$ and $Ca_V3.2$) are expressed in the heart (see [6]).

2. Occurrence and characteristics of I_{CaT} under control conditions

The two above-mentioned papers [2,3] characterized for the first time in cardiac cells the major differential properties of Ca^{2+} currents flowing through these two channels (Fig. 1). T-type currents activated and inactivated at more negative voltage (−30 mV) than L-type currents; aforesaid.

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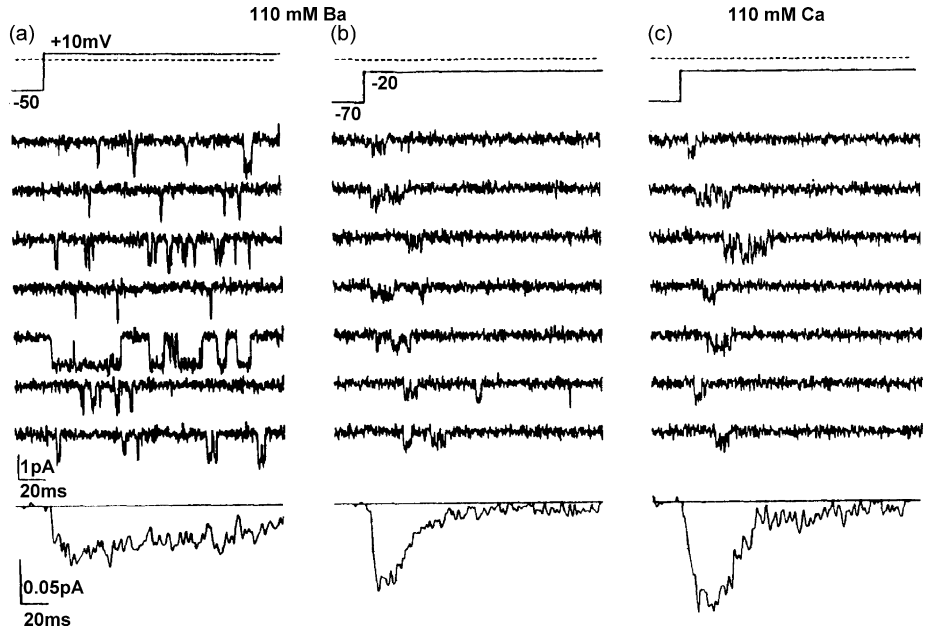

Fig. 1. Cell-attached patch recordings in guinea-pig ventricular cells illustrating the co-existence of two distinct Ca^{2+} channels. The protocols are depicted in the upper panel and the averaged currents in the lower panel. Note that the unitary current amplitude and the averaged time course are very similar with either 110 mM Ba^{2+} or Ca^{2+} as charge carrier. Reproduced with permission [3]: (a) mostly L-type; (b and c) mostly T-type currents.

T-type currents inactivated faster than L-type currents when Ba^{2+} was the charge carrier and single channel conductance was smaller for T-type channels (6–8 pS versus 18–25 pS in isotonic extracellular Ba^{2+} solution). In contrast to L-type Ca^{2+} channels, T-type channels remained functional long after patch excision. As well, these papers showed that T-type channels were less affected by Cd^{2+} than L-type channels (although Co^{2+} blocked both currents to a similar extent) and established the "*insensitivity*" of T-type channels to both agonist and antagonist dihydropyridines and to β-adrenergic receptor activation. From there on, cardiac electrophysiologists have been divided into two populations being "*willing*" or "*reluctant*" to accept, first the existence and second, the pharmacological properties of the T-type Ca^{2+} current in cardiac cells. Since then, I_{CaT} has been recorded in cardiac tissues of a large number of species under control conditions (Table 1). More recently, several interesting studies have suggested that development and various pathological situations favour the occurrence of I_{CaT}.

2.1. Kinetic properties

Kinetic properties of I_{CaT} are reported in earlier chapters of this issue and have already been summarized in a previous review [7]. Here, we will like to focus on some aspects of specific interest for cardiac cell behaviour. In normal cardiac cells, at physiological Ca^{2+} concentrations, the activation threshold for I_{CaT} could be as negative as −70 to −60 mV [8–11]; however, it is more often reported at, or positive to −50 mV. Reports on I_{CaT} density at physiological Ca^{2+} concentrations are quite variable. Peak (at −30 or −20 mV) current densities as low as 0.4–0.7 A/F have been reported in dog [2], frog [12], rat atrial cells [13] and in guinea-pig ventricular myocytes [14,15]. Slightly higher values (1–1.5 A/F) have been reported in frog atrial cells [11], rat developing atrial cells [16], dog ventricle [17,18], ventricular myocytes from hypertrophic cat heart [19] and cat atrial cells [20]. In one report on guinea-pig ventricular myocytes [21], I_{CaT} with a peak density of 1.5 A/F was only detected if extracellular Ca^{2+} was raised from 1.8 to 5.4 mM. Higher I_{CaT} densities of 2–3.3 A/F have been found in rat neonatal cardiomyocytes in culture [22,23], canine Purkinje myocytes [17] and cat atrial latent pacemaker cells [24]. Remarkably high I_{CaT} densities have been reported in postnatal rat cardiomyocytes (8 A/F at 8 days [25], but see comment below), finch ventricular myocytes (6.8 A/F [10]), in hypertrophic rat ventricle (4.8 A/F [26]), hamster ventricular cells (6 A/F [27]) and in embryonic chick ventricle cells (4.2 A/F [28]). The highest value of I_{CaT} density (>15 A/F) was reported by Fermini and Nathan [29] in cultured pacemaker cells from sinoatrial node. Some of these values should, however, be taken with caution in studies that have been done in Na^+-free solutions in the absence of TTX due to a possible contamination with the low-threshold activating TTX-sensitive Ca^{2+} current, which could have densities fully comparable to those of I_{CaT} (see below).

In cardiac cells, the reversal potential of I_{CaT} has not been adequately determined since current–voltage (*I–V*) curves bend down at depolarized potentials without any sign of outward current at high depolarisations. For the purpose of calculation of I_{CaT} activation, it has generally been assumed that the reversal potential of I_{CaT} equals the Ca^{2+} reversal potential [7]. Inadequacies arise from the fact that it is virtually impossible to properly separate I_{CaT} from I_{CaL}: (a)