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Quantitative aspects of L-type Ca^{2+} currents

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ABSTRACT

Ca^{2+} currents in neurons and muscle cells have been classified as being one of 5 types, of which four, L, N, P/Q and R were said to be high threshold and one, T, was designated low threshold. This review focuses on quantitative aspects of L-type currents. L-type channels are now distinguished according to their structure as one of four main subtypes $Ca_v1.1$–$Ca_v1.4$. L-type calcium currents play many fundamental roles in cellular dynamical processes including control of firing rate and pacemaking in neurons and cardiac cells, the activation of transcription factors involved in synaptic plasticity and in immune cells. The half-activation potentials of L-type currents (I_{CaL}) have been ascribed values as low as −50 mV and as high as near 0 mV. The inactivation of I_{CaL} has been found to be both voltage (VDI) and calcium-dependent (CDI) and the latter component may involve calcium-induced calcium release. CDI is often an important aspect of dynamical models of cell electrophysiology. We describe the basic components in modeling I_{CaL} including activation and both voltage and calcium dependent inactivation and the two main approaches to determining the current. We review, by means of tables of values from over 65 representative studies, the various details of the dynamical properties associated with I_{CaL} that have been found experimentally or employed in the last 25 years in deterministic modeling in various nervous system and cardiac cells. Distributions and statistics of several parameters related to activation and inactivation are obtained. There are few reliable complete experimental data on L-type calcium current kinetics for cells at physiological calcium ion concentrations. Neurons are divided approximately into two groups with experimental half-activation potentials that are high, ≈ -18.3 mV, or low, ≈ -36.4 mV, which correspond closely with those for $Ca_v1.2$ and $Ca_v1.3$ channels in physiological solutions. There are very few complete experimental data on time constants of activation, those available suggesting values around 0.5–2 ms. In modeling, a wide range of time constants has been employed. A major problem for quantitative studies due to lack of experimental data has been the use of kinetic parameters from one cell type for others. Inactivation time constants for VDI have been found experimentally with average 65 ms. Examples of calculations of I_{CaL} are made for linear and constant field methods and the effects of CDI are illustrated for single and double pulse protocols and the results compared with experiment. The review ends with a discussion and analysis of experimental subtype ($Ca_v1.1$–$Ca_v1.4$) properties and their roles in normal, including pacemaker, activity, and many pathological states.

Contents

Abbreviations: AHC, auditory hair cells; AM, atrial myocyte; B, Brugada syndrome; BAPTA, 12-bis (2-aminophenoxy) ethane-*N*, *N*, *N′*, *N′*-tetra-acetic acid; BK, big conductance potassium channel; Ca_i or $[Ca^{2+}]_i$, internal calcium ion concentration; Ca_o or $[Ca^{2+}]_o$, external calcium ion concentration; CDI, calcium-dependent inactivation; CH, chromaffin; CICR, calcium-induced calcium release; CNS, central nervous system; CORT, cortical; DA, dopamine; DCN, dorsal cochlear nucleus; DRG, dorsal root ganglion; dors, dorsal; DRN, dorsal raphe nucleus; EGTA, ethylene glycol (*β*-amino-ethyl ether)-*N*, *N*, *N′*, *N′*-tetra-acetic acid; GABA, gamma-aminobutyric acid; HEK, human embryonic kidney; HVA, high-voltage activated; IC, inferior colliculus; KO, knockout; LD, laterodorsal; LVA, low-voltage activated; Mag, magnocellular; MR, medullary respiratory; med, medial; MID, midbrain; MN, motoneuron; N, neuron; NRT, nucleus reticularis thalami; PC, pituitary corticotroph; PF, Purkinje fiber; PM, pacemaker; RF, renal failure; SA, sino-atrial; SE, serotonergic; SH3-GK, src homology 3-guanylate kinase; SK, small conductance potassium channel; SM, skeletal muscle; SMM, smooth muscle; SN, substantia nigra; SNc, substantia nigra pars compacta; SON, supraoptic nucleus; SS, disulphide bond; SYMP, sympathetic; TF, tetralogy of Fallot; TR, thalamic relay; VDI, voltage-dependent inactivation; VM, ventricular myocyte; VWA, Von Willebrand Factor A; WT, wild-type.

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1. Introduction

1.1. Perspective

The passage of ions across cell membranes, and within cells, is of fundamental importance in determining the electrophysiological responses of nerve and muscle cells. Such responses are manifested ultimately in the functioning of the nervous and muscular systems, including organs of crucial biological importance such as the heart and brain. In the late 19th and early 20th centuries, key discoveries were made and biophysical theories proposed concerning such ionic currents, for example by Nernst (1889), Planck (1890) and Bernstein (1902). With new electrophysiological recording techniques, many advances were made in the 1940s and 1950s by, amongst others, in alphabetical order, Eccles, Hodgkin, Huxley and Katz – see Huxley (1959) for a summary. In the 1970s and 1980s, much additional insight was obtained when recordings were made of currents through single ion channels, notably by Neher and Sakmann (Hamill et al., 1981). In the last 20 or so years there has been an enormous number of discoveries concerning the factors which determine ionic current flows in neurons and muscle cells. The present review concerns modeling aspects of the class of calcium currents called L-type, which, as will be seen below, have many consequences beyond electrophysiology.

For graphic but brief historical accounts of calcium current discoveries see Tsien and Barrett (2005) and Dolphin (2006). According to the former review, *"...it is apparent that Ca^{2+} channels have reached the forefront of the field of ion channel research...due to their vital role in cellular signaling, their diversity, and great susceptibility to modulation..."*. Records of the first single channel recording of currents identified as being L-type in neurons were given in (Nowycky et al., 1985), although such calcium currents, designated as mode 2, were previously described in cardiac ventricular cells (Hess et al., 1984). More recent single L-type channel recordings are in Cens et al. (2006), where a comparison of results for Ca^{2+} and Ba^{2+} as charge carrier is shown, and Schröder et al. (1998), where the much greater magnitude of L-type currents in failing heart are compared with those in normal heart.

The principal motivation for the analysis and quantitative modeling of L-type calcium currents is that they occur in most nerve and muscle cells. They often play basic roles in pacemaker activity (see Section 5.2) and more generally in regulating spike frequency by inducing afterhyperpolarization, as for example in the hippocampus by coupling to SK channels (Tanabe et al., 1998; Stocker and Pedarzani, 2000). Wu et al. (2008) showed that L-type Ca^{2+} current in CA1 pyramidal cells, by coupling to delayed rectifier potassium channels ($K_v7.x$), can give rise to long-lasting changes in adaptation.

Comprehensive models of mammalian CNS nerve cells may or may not include a spatial dimension, but in either case the minimum number of distinct current components is usually around 10 and amongst these there should, or will, usually be included several Ca^{2+} currents. If they are included in a model, L-type currents require a careful treatment and our aim here is to attempt to summarize several details of their basic properties and modeling which have been employed for many kinds of nerve and muscle cell. Unfortunately, there is a paucity of reliable and complete experimental data on L-type channel kinetics for most CNS neurons in physiological conditions (see after hyperpolarization Section 4.5).

1.2. Ion channels and neurons

Many protein molecules are embedded in the cell membranes of neurons. Some of these molecules are receptors for the main