



On the Mechanism of the Cardiac L-type Calcium Channel in Cardiac Cells



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Abstract

A hypothesis is presented which suggests that the cardiac L-type calcium channel opens in a stochastic fashion as the calcium channel protein complex moves around in the lipid of the outer leaflet of the sarcolemma. Opening occurs [1] when there is release of calcium ions that are bound in the polarised state to anionic phospholipid of the inner leaflet, the release being a consequence of proton penetration into the sarcolemma upon depolarisation and [2] a calcium channel protein complex moves into the same site on the outer leaflet.

Keywords: Excitation-contraction coupling; Sarcolemmal anionic phospholipid; Stochastic behaviour

Introduction

It is well established that depolarisation of cardiac cells induces an inward current associated with an inward movement of calcium ions (Ca^{2+}), and that this Ca^{2+} triggers release of more Ca^{2+} by interaction with the ryanodine receptors of the sarcoplasmic reticulum (SR), which lie close to the transverse tubules (e.g., [1,2]). This released calcium activates contraction, with subsequent relaxation achieved by active transport into the SR by means of aCa^{2+} activated ATPase, thus causing recirculation of Ca^{2+} (e.g., [3-5]). The intracellular calcium gain by the L-type channels is balanced by an equal and opposite outward movement of Ca^{2+} via the sodium/calcium exchanger (NCX), in order to maintain a Ca^{2+} steady state [6].

While there is a wealth of literature comprising pharmacological effects on this system, the L-type channel is usually depicted as a protein encompassing both leaflets of the sarcolemma through which Ca^{2+} enters the cell. I find this difficult to reconcile with the stochastic nature of L-type channel opening (e.g., [7]) and here develop a different hypothesis.

The principle

The L-type calcium channel is studied by measuring the L-type calcium current, which is an inward current, an electrical measurement. By definition, electricity is electrons moving. An inward current therefore consists of an outward movement of electrons that exceeds the inward movement of positive charges, in this case carried by Ca^{2+} ions. This follows from the fact that an electron is one ten thousandth (10,000th) the mass of a Ca^{2+} . Any channel that enables an inward current will allow an excess

of outward electron flow because electrons have 10,000 times the acceleration of an ion [8] in accordance with Newton's second law (Force, i.e., electromotive force = mass x acceleration).

Development of the hypothesis

The polarised state: A cardiac ventricular cell has a trans-membrane potential of the order of -80mV. Therefore the electrical field force across the double leaflets of the sarcolemma is 10,000volts/mm, sufficient to exclude nearly all charged particles from the inter-lamellar space, including protons, and rendering to the sarcolemma a very high electrical resistance, thus protecting the interior from extracellular electrolyte. Calcium has been demonstrated to be bound to the inner leaflet of the sarcolemma (e.g., [9]), the 2 positive charges of the Ca^{2+} are bound to 2 negative charges of an anionic phospholipid (only found on the inner leaflet in healthy cells) such as phosphatidylserine. The electric field force in a pacemaker cell with an initial trans-membrane potential of -60mV is only 7,500volts/mm, resulting in a lower resistance than the ventricular cell and allowing some electrical penetration of charged particles (dominated by electron outflow, as with all inward currents [8]) - the pacemaker current or funny current (If).

The depolarised state: Depolarisation removes the trans-membrane electric field force, so that protons enter the inter-lamellar space and release Ca^{2+} from its binding to the inner leaflet (the two-site control of the $\text{H}^{+}\text{Ca}^{2+}$ interaction [10]). This Ca^{2+} constitutes part of the trigger Ca^{2+} for Ca^{2+} induced Ca^{2+} release via the ryanodine receptors [11]; the other part comes through the L-type Ca^{2+} channels. The percentage recirculated varies with species and preparation.

The role of the L-type Ca^{2+} protein

There are several proteins that bind different calcium antagonists and other substances, but for the hypothesis, they will be called simply the Ca^{2+} channel protein complex. The plasma membrane is extremely dynamic, with many proteins and receptors “swimming” about in the lipid layer. It is also known that Ca^{2+} “guards” the inner aspect of the L-type Ca^{2+} channel from Ca^{2+} ingress in the polarised condition. The hypothesis contends that the “guard” is that same Ca^{2+} bound to the anionic phospholipid of the inner leaflet when subjected to high trans-membrane electric field force, which “drops off” with the two-site control of the H^+ - Ca^{2+} interaction. If the overlying site on the outer leaflet is occupied by the Ca^{2+} - Ca^{2+} channel protein complex, Ca^{2+} ingress takes place, but not if some other moiety or lipid occupies that site. As the Ca^{2+} channel protein complex is “swimming around” in the outer leaflet lipid in a random manner, the “opening” of the Ca^{2+} channels will occur in a stochastic manner.

Closing of the L-type Ca^{2+} channel

With repolarisation, the cell returns to the stable diastolic state with closed L-type Ca^{2+} channel and field force of 10,000volts/mm. The closure of the channel is both Ca^{2+} and voltage sensitive and also occurs in a stochastic manner [12], i.e., the inactivation of the channel has both voltage and Ca^{2+} dependence. In the present hypothesis, the voltage dependence occurs because of repolarisation by the restoration of intracellular negative charge, i.e., electrons. The Ca^{2+} dependence occurs because Ca^{2+} binds to the inner leaflet of the sarcolemma, the closure and “guarding” function of the channel.

The bioelectric law

It will be apparent that these ideas have occurred with a background basic hypothesis of life called the Bio-electric Law which has gained approval as a possibility in oral presentation [8] but remains unacceptable in the face of established opinions. The essence of that hypothesis is that negative a trans-membrane electrical potential difference means an excess of negative charge (electrons) in the intracellular compartment which is in a gel state. The basic fact of electricity is that it is defined as electrons moving. It is not possible to have electrophysiology without electricity i.e., electronics. Positive currents are excess movements of electrons in the opposite direction. Inward currents are dominantly outflows of electrons that dissipate as heat. In living cells intracellular electrical negativity is restored by mitochondrial electron production.

An evolutionary speculation

As we were not present during early evolution, it is allowable to speculate. At some time organisms incorporated a bacterium-like

organelle that became mitochondria and gave them more energy in the form of the energy rich phosphate system, an evolutionary advantage. They then encountered the problem of excessive Ca^{2+} entry which precipitated as insoluble calcium salts and formed the chalk and limestone of today. The speculation is that an important evolutionary step was the development of the cell membrane, a bilayer of electrical low conductance that is made much lower by the high field force explained above for resting polarised cells. This system protects the intracellular gel from an extracellular Ca^{2+} concentrations in the range 2.2-2.55mM, whereas if one removes the cell membrane one needs a perfusing solution of 1nM Ca^{2+} in order to ensure complete relaxation of the contractile system [13]. The tight control of intracellular Ca^{2+} compensates for the necessity for Ca^{2+} to trigger contraction.

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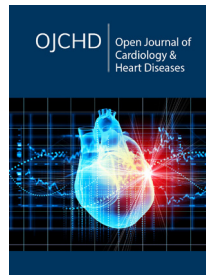
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