

Ions are Freed from Electrostatic Restraint by Depolarisation

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Abstract

We recalled the work of Langer in the 1980s showing calcium ions bound to the inner leaflet of cardiac sarcolemma in diastole, which detaches during depolarisation into the cytoplasm. We postulate that this and some unbound calcium ions comprise the calcium that triggers calcium ion release from the sarcoplasmic reticulum, causing contraction. Also during depolarisation, potassium ions are extruded from the sinus node cells into the extracellular fluid. Neither of these actions involve crossing a barrier and therefore do not need channels or “gates”. The ions simply flow down their concentration gradients. Here, an alternative hypothesis is presented, that draws attention to the resting electric field force, equal to the trans-membrane potential, divided by the membrane thickness of about 5nm, an electric field force of the order of 10^7 Vper metre. Depolarisation to a transmembrane potential of zero was demonstrated in sinus node cells; reducing the electric field strength also to zero frees the ions from electric restraint. Freed ions cannot move against their concentration gradient. Sodium is pumped out using up ATP energy; calcium is pumped out of the sarcoplasmic reticulum by a calcium activated ATPase and out of the cell by the sodium-calcium exchange (NCX). Langer thought sarcolemmal calcium was involved in the NCX. We postulate that the potassium ions extruded by cardiac cells during action potentials must be quantitatively equal to those entering the cell during sodium pumping.

INTRODUCTION

If a typical value for the electric potential difference across the membrane of a resting cell is around 70 mV, and its thickness is ~ 5 nm, the corresponding electric field strength is about 10^7 Volts per metre inside the membrane leaflets. This very high value is obtained by dividing the electric potential difference across the membrane by its thickness, the latter being a very small value. The thickness is assumed to be constant. A charged particle in an electric field this high is affected by a force that is independent of its velocity but dependent on its frequency (1). Within the vast literature concerning the membrane that surrounds living cells, there is general agreement that they are mostly lipid bilayers with integral membrane proteins (2) and receptors. The interior of cells used to be thought of as a liquid (cytosol) but is now known to be a gel in which the water is structured (cytoplasm); otherwise we would not have magnetic resonance imaging (MRI). Formerly, our interest has centred on the electrically negative voltage of the cytoplasm. It used to be thought that this negative voltage was created by the ratios of internal to external concentrations of potassium and sodium ions, but this was disproved by Milo & Philips (3) who showed that these ratios were the same in the cells of all the organs of the

body, whereas the cellular internal voltage varies widely, ranging from about -90 millivolts (mV) in heart muscle to -9 mV in red blood cells. Nevertheless, the ionic ratio theory is still widely applied e.g., (1). We think that all the living organisms of nature contain negatively charged particles i.e., *The Electricity of Life*. The particles are by definition (Système Internationale) electrons; electricity is electrons moving. Cells in which no electricity can be detected are dead (4).

METHODS

In searching for a source for the generation of these electrons, we were influenced by the high electric potential of mitochondria of -180 - 220 mV, that is much higher than any other intracellular organelle, e.g., the electric potential of the nucleus is only 15mV different from the cytoplasmic value. Only the mitochondria so far examined have a more negative voltage than the cytoplasm, leading to the hypothesis that they are the generators of electricity in living cells supplying the cytoplasm. This led to the concept of electron density defined as the *probability* of an electron (negatively charged) hitting the measuring electrode (5). Higher electron density will occur if there are more electrons at the site of the electrode tip. It is

calculated as the root mean square ($\sqrt{V^2}$), where V is the measured potential difference. This is always a positive number and the direction of flow of the electrons is from a high electron density site to lower electron density sites (5), e.g., mitochondrion to cytoplasm.

There is an alternative theory about the source of the electrons, namely that they arise from the splitting of water molecules (6). This could yield one or two electrons per oxygen atom. But would it also create oxygen radicals? Oxygen in oxyhaemoglobin could also be a source of electrons, but only a few remain in the red cell as its trans-membrane potential is only -9mV (3), i.e., the cell type with the lowest electron density (3).

RESULTS

Release of Potassium Ions by Depolarisation

We decided not to start with calcium ion consideration because they are tied up with such factors as divalency, a huge inward concentration gradient and

compartmentalisation with sarcoplasmic reticulum. The intracellular calcium ion concentration is extremely low, so that very low concentrations must be used in the perfusate when studying muscle cells with the cell membrane removed (7, 8). For intracellular calcium ion handling to allow contraction, and sodium/calcium exchange (NCX), see reference 9 and 10. For sodium/potassium ion exchange (sodium pumping) see reference 11.

We avoided study of sodium ions because these are thought not to be involved in the pacemaker inward current of sinus node cells.

These problems are avoided in the study of the potassium ion, as it is monovalent and has an outward concentration gradient leading to detection in the extracellular space.

We searched the literature for evidence of potassium ions leaving cells during the cycling of heart cells. The only paper we found was by Kronhaus et al (12) who placed a K^+ sensitive electrode close to the T-tubule of cycling of sinus node cells.

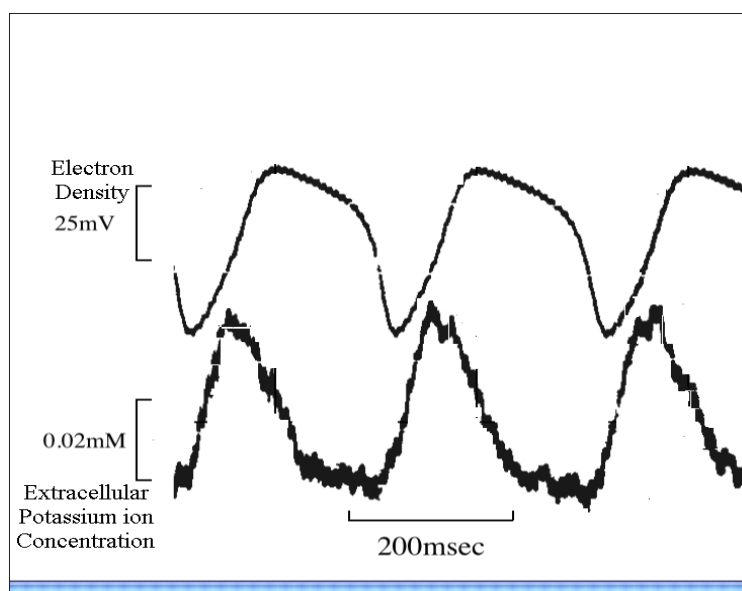


Figure 1. *Spontaneous cycling of sinus node cells. The extracellular K^+ traces are from Kronhaus et al (12) with permission. The electron density curves were calculated by the authors from simultaneous trans-membrane potential data; they indicate depolarisation downward in the traces.*

Our first idea was that the K^+ was exiting the cell through a potassium channel. 80 such channels have been described by McKinnon (13). That made us wonder which one was responsible. We rejected this idea because it seemed to us, looking at Figure 1, that the extrusion of K^+ was triggered by depolarisation. In diastole, the value for electric field strength is of the order of about 10^7 volts per metre, which immobilises all the K^+ (and other cations) in the cell membrane. At the peak of the action potential, the electron density is zero, so the electric field strength will

also be zero. This will release K^+ (and other cations) from immobilisation to become freely permeable. Now the K^+ will move in accordance with its concentration gradient, which is outwards, as seen in the figure. (intracellular $[\text{K}^+]$ is $140\text{--}150\text{mM}$ and extracellular $[\text{K}^+]$ is $3.5\text{--}5\text{mM}$). Outflow of K^+ will cease when repolarisation re-instates the high electric field strength.

We do not have precise measurements of the amount of potassium acquired by the cell during sodium pumping, nor precise enough quantification of the potassium ejected by

depolarisation, but the principle of the steady state would require them to be equal. It appears to be a much smaller quantity than would be required to achieve repolarisation and does not synchronise with repolarisation (Figure 1).

DISCUSSION

When it comes to consideration of calcium ions (Ca^{2+}), the other ion that is removed from the cell between beats, we have to consider the considerable amount of knowledge acquired in the 1980s by Langer (14,15,16). His group showed that Ca^{2+} was bound electrostatically to binding sites on anionic and zwitterionic phospholipids on the inner leaflet of the sarcolemma and detached upon cell depolarisation and participate in the processes leading to contraction. The location in the relaxed heart cell was confirmed by the Borgers group (17,18). Membrane calcium binding responded to proton reduction (16). Weakening of the electric field also allows entry of extracellular Ca^{2+} , i.e., Ca^{2+} entry into the cell, contributing to the Ca^{2+} requiring removal by the NCX, causing, in turn, a rise in intracellular sodium (Na^+) (19) needing sodium pumping and potassium removal (above).

Hypothesis

The potassium ions acquired by calcium dependent living cells during sodium pumping and the potassium ions ejected from such cells during depolarisation, are quantitatively equal, thus achieving a potassium ion steady state.

Ionic Steady State

An important principle is established by Eisner (20) about calcium ion balance. To quote, "in the steady state, Ca influx equals Ca efflux on every beat". Logic would suggest that the same applies to other ions, in order to avoid a general ionic unsteady state during regular cardiac cycling. A change from one steady state to another (e.g., a change of heart rate) would be achieved in a similar way to the change in excitation- contraction, namely the insertion of a transient perturbation (21, 22).

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Cite this article: Mark IM Noble, Angela J Drake-Holland. *Ions are Freed from Electrostatic Restraint by Depolarisation. International Journal of Research in Medical and Clinical Sciences.* 2026; 4(1): 13-16.

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