

Exactly When Do Potassium Ions Appear in Extracellular Fluid Bathing Sino-Atrial Cells

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Abstract

This study was an attempt to postulate a different mechanism for repolarisation of sino-atrial cells by re-study of published data of sinus node cell cycling. Potassium ion (K^+) appearance in the extracellular compartment measured by K^+ -sensitive electrode during spontaneous cycling of sinus node cells was found in the historic manuscript (1). The extracellular K^+ appearance had timing suggesting triggering by, rather than causing, repolarisation (determined from the newly calculated electron density trace). The K^+ efflux continued after the cessation of repolarisation, suggesting that the K^+ efflux was not the mechanism of repolarisation. Alternatively, it is suggested that K^+ is released by the action potential from its diastolic fixation in the cell membrane, and then diffuses along its strong outwardly directed concentration gradient.

INTRODUCTION

Eisner (2) has shown that there is a steady state for calcium ion balance (Ca^{2+}) for the basic reason that cells cannot burst with calcium and die, unless there is an equal loss of Ca^{2+} to the cell exterior. This has to be true for other ions such as sodium (Na^+) and potassium (K^+), that participate in cellular activity. The other basic principle is that one can only move from one steady state ionic to another under neurohumoral influence, using the principle of “transient perturbation” (3).

When one considers the case of K^+ , one is aware that the situation is illustrated by the fact that repetitive activity of muscle cells involves repetitive intake into the cell of Na^+ , as beautifully demonstrated by the Boyett et al, (1987). The Na^+ has to be “got rid of” in order to maintain the ionic steady state. This is achieved by the membrane $Na^+K^+ATPase$ or “sodium pump”, which gets rid of 3 Na^+ out for 2 K^+ in. But now the cell has to get rid of unwanted K^+ . The present study suggests that this is more easily achieved during depolarisation because the outward concentration allows K^+ to diffuse out when not restrained electrically.

Following activation, the cell does not need the acquired K^+ from the sodium pump. The Eisner principle of ionic steady state requirement might come into play again; one might need a K^+ pump! Not so, as, without restrain, cells

are high in K^+ concentration, and Na^+ in low concentration compared with extracellular concentrations.

METHODS

The intracellular voltage data of Kronhaus, Spear, Moore and Kline (1), with permission, was converted to electron density by calculating the corresponding mean square root values. The timing of the relevant events was explored by geometric analysis of these derived traces and of the extracellular K^+ concentration traces, recorded from a K^+ sensitive electrode with tip positioned by the T-tubules.

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RESULTS

It was shown that the appearance of K^+ , in the extracellular fluid of cycling sino-atrial pacemaker cells continued

beyond the end of maximum repolarisation as indicated by the maximum of the electron density trace after the action potential (Figure 1).

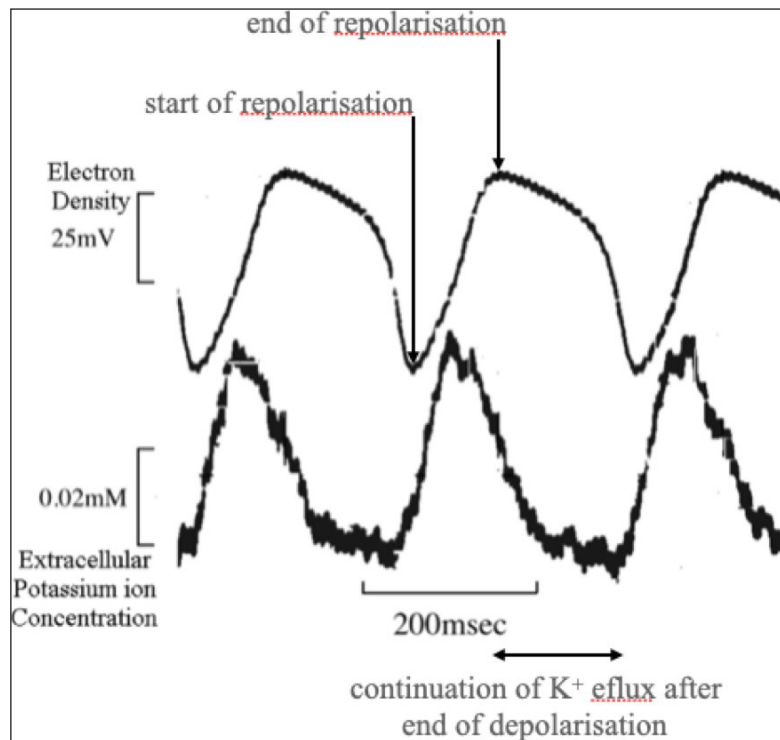


Figure 1. Upper trace: electron density during sino-atrial pacemaker cell cycling. Lower trace: simultaneous record of extracellular K^+ cycling. Vertical downward arrows indicate start and end of repolarisation. Double arrow indicates the duration of K^+ efflux after the end of repolarisation, i.e., no residual depolarisation and the beginning of diastole

DISCUSSION

There is a difference of opinion about the source the trans-membrane electric potential of heart cells Noble (5), i.e., (distribution of membrane ions versus mitochondrial production of electrons). However, whichever theory one adopts, there appears to be no doubt that the cell membrane in diastole (rest) of the sino-atrial pacemaker cells is subject to an electric field derived from the measured trans-membrane electric potential of -60mV and the cell membrane thickness of 5 nm.

This follows from the general rule, namely that a typical value for the electric potential difference across the membrane of any 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 Taghian; Narrmoneva; and Kogani (6). 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 (5nm). 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 Taghian T, Narrmoneva DA, Kogani AB (6).

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 (Levental & Lyman, 7) and receptors. We therefore turned to the works of Chen's group, experts on electric field effects. They showed "electric field-induced functional reductions in the K^+ channels mainly resulted from supra-membrane potential- mediated electro-formational changes". Reactions of the cell membrane to electrical interventions are described by Chen W, Hon Y, ChenY, Astumian D. (8), who also extensively reviewed the studies of its electrical field. In our opinion, their applied electric shocks above the physiological range may have limited relevance to the the effect of electric field changes that take place during the cycling of trans-membrane potential in the physiological situation. We also adopted the concept of electrons, i.e., electric particles (electron movement = electricity according to the Systeme Internationale). Electron density is defined as the *probability* of an electron (negatively charged) hitting the measuring electrode

Scudder (9). 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 electric 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 Scudder, (9).

The obvious criticism of the present study is in the use of this derived definition (electron density) might be its stochastic nature (probability) as an index of concentration, but the source of the electric potential used for the derivation is the electron content of the space explored. An additional criticism was raised by Kronhaus, Spear, Moore and Kline (1) who originated the traces of electric potential and extracellular K^+ . They had doubts about how close to the tubular cell membrane they could position their K^+ electrode tip.

The corresponding changes in electron density are presented in Figure 1, which shows depolarisation in the downward direction (loss of electricity during the sharp downward deflection is the action potential caused mainly by electron outflow). The diastolic changes follow the sharp upward deflection of repolarisation. It is interesting that the reason for the threshold to commence action potential firing is not clear from the literature. We could contribute the suggestion that the electric field strength that declines as the transmembrane voltage declines (electrical leakage through a high, but not high enough electrical resistance) until it is too weak to paralyse ion movement, i.e., during diastole, the electric field reaches a value that can no longer immobilise ions such as sodium (Na^+) and calcium (Ca^{2+}) which, when freed from electric restraint would flow in accordance with their concentration gradients; these are both inward and would contribute to the rapid loss of negative charge. Inward movement of both ions are thought to contribute to the up-stroke of the action potential of heart cells Morad and Tung (10). The rise of intracellular Na^+ is related to the number of beats in Purkinje cells (Boyett, Hart, Levi, Robert, 1987). As far as the energy for the total depolarisation is concerned, We like the concept of Veech, Kashiwaya and King (11), that the resting membrane potential of cells are measures of electrical work, not of ionic currents.

There is much evidence of Ca^{2+} binding to the inner sarcoplasmic leaflet in diastole Langer (12, 13 & 14), and Borgers, et al (15), Borgers M, Thone F, Ver Donck L. (16), that are consistent with the concept of ionic immobilisation by the electric field. I decided not to start the analysis with calcium ion considerations because they are tied up with such factors as divalency, a huge inward concentration

gradient and compartmentalisation with sarcoplasmic reticulum Eisner et al (2). The intracellular cytoplasmic 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 Fabiato A, Fabiato F (17), Keentish et al (18). For intracellular calcium ion handling to allow contraction, and sodium/calcium exchange (NCX), see with Primeau et al (19). With the behaviour of potassium ions (K^+) in the sino-atrial cycling, these problems are avoided as it is monovalent and has an outward concentration gradient leading to detection in the extracellular space. Since the plasma membrane at rest has a much greater permeability for K^+ , the resting membrane potential (-70 to -80 mV) is much closer to the equilibrium potential of K^+ (-90 mV) than it is for Na^+ (+65 mV). Permeability is therefore much faster than that for sodium and we were looking for the fastest effect of changes in the electric field.

My first idea was that the K^+ was exiting the cell through a potassium channel. Such channels have been described by with Primeau et al (19). That made us wonder which one was responsible. I rejected this idea because it seemed, looking at Figure 1, that the timing of the outflow of K^+ was not compatible with the timing of the electrical waves.

I expected that release of K^+ from the electrical restraint exerted by the field would occur at the same time as that for Na^+ and Ca^{2+} , i.e., at the threshold electron density for the initiation of the action potential. In Figure 1, the commencement of appearance of extracellular K^+ occurs approximately 28 msec after the time of the threshold. A delay is inevitably caused by the time required for K^+ to cross the cell membrane and diffuse to the electrode tip. I made the time from the nadir of the electrical trace to the peak of extracellular K^+ trace approximately 32 msec. By subtraction, we come to an estimate for the time of release of K^+ of 4 msec. Is this small enough to deduce that the K^+ is released at the threshold potential of the sinus node?

Another interesting measurement derived from Figure 1 is that K^+ continues to flow into the extracellular space for 69 msec after the time of completion of repolarisation. These measurements were sufficient to convince us that repolarisation is not a K^+ dependent process, and that repolarisation is not a large outflow of K^+ . (Our opinion is that repolarisation is a flow of electricity from mitochondria (at electron density 200 mV) to the cytoplasm at zero mV. 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.

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 [Arloch (3), Noble (21)]. Such changes could result from receptor-induced decreased electric resistance of the cell membrane in the case of tachycardia (shortening time to threshold potential) and increased electric resistance in the case of bradycardia (lengthening the time to threshold potential).

Hypothesis

The potassium ions (K^+) acquired by calcium dependent living cells during sodium pumping and the K^+ ejected from such cells by depolarisation, are quantitatively equal, thus achieving a K^+ steady state. The release of K^+ to the exterior is triggered at the threshold trans-membrane potential that triggers the action potential. It is postulated that this is a release of ions from the electrical restraint of the electric field at a critical value during the diminishing strength of the electric field during diastole.

CONCLUSION.

K^+ extrusion is not synchronised with repolarisation but continues past the timing of the end of repolarisation.

DECLARATIONS

Ethical Approval

not applicable

Funding

None. not applicable

Some data obtained from Kronhaus KD, Spear, JF, Moore EN, Kline RP. Sinus node extracellular potassium transients following vagal stimulation. *Nature* 1978;;275(5678):322-324. doi: 10.1038/275322a0. with permission from Dr Spear, see Figure legend.

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