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The Electrolyte Distribution Puzzle, Electric Potential and Role of Quantum Mechanics in Living Cells

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Abstract

Examination of published data showed that, although the distribution of potassium ions between extracellular and intracellular compartments of a number of living cells in the same organism was constant, there was a wide variation in transmembrane electric potential. e.g., heart ventricle cell at about -90mV and the red blood cell at -9mV, i.e., there is no correlation between distribution of intracellular potaassium ions and trans-membrane electric potential. The sodium pump appeared to be activated only by increased intracellular sodium ion concentration above the predetermined normal value. Examination of the electric potential of intracellular organelles revealed that the highest were found in mitochondria at -180mV - 220mV. Therefore the source of electricity, i.e., electrons moving, in living cells,, is postulated to be intracellular mitochondria. Depolarisation is postulated to be a trans-cell-membrane outflow of electrons. Repolarisation is postulated to be an intracellular flow of electrons from mitochondria to the cytoplasm. Electron flows depend on potential difference and intervening electric impedance.

Keywords: *electrophysiology, electrons, potassium ion, sodium ion, electric impedance*

Introduction

Living cells are characterised by a trans-membrane potential that is negative in the interior [11, 13, 14]. Text books, internet information files, etc., and research papers usually state that trans-membrane ion transport causes a trans-membrane potential difference, this difference depends on the resulting difference between the potassium ion (K^+) concentrations of the intracellular and extracellular compartments: these are claimed to be maintained by the membrane sodium pump(Na^+/K^+ATPase).

In a long career as a physiological physician, I frequently measured plasma electrolyte concentrations and even total body sodium (Na^+) in patient care and research. I never considered the role of intracellular ion concentrations while at the same time producing results in electrophysiology relevant to excitation/contraction coupling in the heart. Derivation of the ECG required knowledge of the intracellular voltages of the heart, but I paid little attention to the cause of these negative electric potentials. However the data of Anderson [1] seemed to be worth further thought; his data shows that the total electric charge of intracellular positive ions equals the total intracellular electric charge of negative ions, so there is no imbalance there to explain the electrical negativity of the intracellular compartment.

20 years of retirement and further interest in cardiology led me to explore the original work of Nernst to find that he only worked out the factors affecting a change in trans-membrane potential of cells, not the absolute value.

Nernst

His equation was:

$Ecell = E0 - (RT/nF)lnQ$, where

Ecell= cell potential under non-standard conditions.

E0= cell potential under standard conditions. in which there is a negative trans-membrane potential. i.e., a net excess of intracellular negative electrical charges

R = gas constant which is 8.31 (volt-coulomb)/molK).

T = temperature in Kelvins.

F = Faraday's constant, 96500 coulombs/mol.

Q = Reaction quotient, which is the equilibrium expression with initial concentrations rather than equilibrium concentrations.

n = number of moles of electrons exchanged in the change from *E0*to *Ecell*.

i.e., an equation to evaluate the difference in electric potential between *Ecell and E0*

An example of such a change is depolarisation of cells (loss of negative electric charge) as occurs, for instance in activation of heart cells or nerve cells.

And yet the textbooks quote the Nernst equation as one for the absolute value of E_m:

$$E_m = \frac{RT}{F} \ln \left(\frac{r P_{K^+} [K^+]_{out} + P_{Na^+} [Na^+]_{out}}{r P_{K^+} [K^+]_{in} + P_{Na^+} [Na^+]_{in}} \right)$$

E_m = the membrane potential (in volts, equivalent to joules per coulomb),

Pion = The permeability for that ion (in meters per second),

$[ion]_{out}$ = the extracellular concentration of that ion.

$[ion]_{in}$ = the intracellular concentration of that ion in the same units as $[ion]_{out}$(absolute units don't matter, as the ion concentration terms become a dimensionless ratio).

R = the ideal gas constant (joules per kelvin per mole).

T = the temperature in kelvins,

F = Faraday's constant (coulombs per mole).

r = the absolute value of the transport ratio (1.5 in the case of the Na+/K+ATPase (sodium pump).

In effect, according to this (which is not actually by Nernst), the variable that determines E_m is the difference in potassium ion (K^+) concentration between the extracellular and intracellular compartments. This contrasts with the original Nernst equation in which the variable that determines a difference in trans-membrane potential is the number of electrons involved in that change. Electrons orbit the nucleus of atoms and ions which have 10,000 times the mass of an electron. I therefore stated my idea that depolarisation was cellular loss of electrons and that repolarisation was electron regeneration [25]; this challenge is currently regarded as heretical [36], but I consider that a longer explanation of the objections is worthy of an article rather than a short letter [25, 26]. In addition, articles by Bailey, e.g., [2] have brought the notice of physiologists and physicians to the importance of quantum mechanics in the understanding of intracellular function. Electrons, being sub-atomic particles, are subject to quantum rules, not Newtonian ones.

Membrane Theory

With the membrane theory, that assumes the second equation above, the difference between the potassium ion (K^+) concentrations of the intracellular and extracellular compartments are maintained by the membrane sodium pump (Na^+/K^+ATPase). Re-establishment of the internal and external ion concentrations after a perturbation is also attributed to the to themembrane sodium pump, which is is directly energy (ATP) dependent, whereas an 'exchanger' e.g., the Na^+/Ca^{2+}exchanger - see below, uses energy of the electrochemical gradient for transport, i.e., indirectly energy dependent.

Source of Cellular Electricity

An explanation is required for the dynamic changes in trans-membrane potentials when cells are activated, but this requires an examination of the question, "What is the source of electricity in living organisms?" (Electric potentials are recorded all over the body in medical investigations). This question does not seem to be addressed by texts, which are derived from Hodgkin and Huxley [13], and that state that depolarisation results from an inflow of sodium ions (Na^+) and repolarisation results from an outflow of potassium ions (K^+), i.e., ions carry electric charge, so flow of ions creates an electric current. But so could flow of charged sub-atomic particles in accordance with quantum mechanics. Magnetic resonance studies have established that the cell interior is a gel allowing electric current, not an aqueous solution (cytoplasm, not cytosol).

The source of electricity in cells was explored by finding data on the electric potential of various cell organelles.

Table1. *Variation of electric potential between organelles*

organelle	electric potential (mV)	reference
lysosoome	19	17
endoplasmic reticulum	0	19
nucleus	cytoplasmic - 15	22
mitochondrion	-180 to -220	28

Mitochondria are known to release electrons from NADH and $FADH_2$during oxidative phosphorylation. Tian, Sun, Dong & Kin [35] noted that this is subject to shuttling with the nucleolus, tunneling being a process available to sub-atomic particles, such as electrons which follow quantum rules. The higher negative electric potential of mitochondria suggests a higher electron density (excess electrons other than those in the atoms and ions) compared with cytoplasm (Table 1) and other organelles, raising the possibility of electron flow from mitochondria to other cellular components that have lower electron density. Such flow has been demonstrated in organic chemistry [32].

I concluded that the source of electricity in living cells was probably the mitochondria.

Cell Ionic Concentrations

Increasing doubts about membrane theory led to an exploration of cell ionic concentrations.

Table2. *Cell ionic concentrations in mM except for Ca2+ in nM. From the table of Milo & Philips [24]*

ion	mammalian heart or RBC	Blood Plasma
K^+	100	4
Na^+	10	100-200
Mg^{2+}	10(bound) 0.5(free)	1
Ca^{2+}	10-100nM	2
C^{l-}	5-100	100

In Table 2, note that the distribution of ions is the same in heart and red blood cells, but whereas heart has a trans-membrane electric potential of -90mV, the red blood cell (RBC) has a trans-membrane potential of only -9mV. The mature red blood cell (the simplest cell in the body) has lost its sodium pump during maturation [10]. The highest estimate of red blood cell sodium concentration is 11.4±3.1 mM [31]. This must be compared with the extracellular sodium concentration of 145mM. The intracellular potassium concentration of the red blood cell is 80-120mM [29] compared to 3.5- 5 mM concentration in plasma. So the red blood cell can achieve a normal low intracellular sodium concentration and high intracellular potassium concentration without a sodium pump (or a very weak one in immature cells, [10]). The conclusion is that sodium pumping by the Na^+/K^+ATPase is not the cause of most of the the low intracellular Na^+ and high intracellular K^+ that is entered into the $[K^+]$ out and $[K+]_{in}$ in the second equation above and therefore is not a determinant of intracellular negative potentials.

The statement that the distribution of ion concentrations results from the action of the sodium pump is also falsified by the finding that distribution of potassium ions is genetically determined [33].

Variation of trans-membrane potential between cell types

The fact of such a huge difference in transmembrane potential between red blood cells (-9mV) and heart ventricle (-90mV) led to an exploration of variation of trans-membrane potential between other cell types all of which, within a given body, have the same K^+ distribution between extracellular and intracellular compartments.

Table3. *Variation in trans-membrane potential between tissues with the same K+ distribution*

tissue	Trans-membrane electric potential (mV)
heart ventrcle	-85
skeletal muscle	-80
vascular endothelium	-80
nerve	-80
adrenal cortex	-70
leukocyte	-65
salivary gland acinar cell	-65
sinus node cell	-60
vascular smooth muscle cell	-60
platelet	-56
brown fat cell	-54
retinal cell	-40
pancreatic aacinar cell	-39
liver	-37
fat cell	-34
pancreatic islet cell	-22
red blood cell	-9

The conclusion is that the variation in trans-membrane potential is not caused by different $[K^+]out/[K^+]in$ ratios, which are similar in all these cells.

The Complication of Intracellular Functions Requiring Ca2+

There is an implication in the reasoning so far that cells, e.g., the red cell, achieve their normal K^+ distribution without a sodium pump, but not-so-simple cells do have sodium pumps. What are they for? My suggestion is that those cells that require a rise in intracellular calcium ion (Ca^{2+}) to obtain their particular functional role, e.g., all types of muscle, require a mechanism to get rid of the Ca^{2+} once the function has been accomplished. The Na^+/Ca^{2+} exchanger, which exchanges $3Na^+$ in, to one Ca^{2+} out (thus causing some depolarisation) fulfills this requirement but leads to an increase in intracellular Na^+ concentration. This Na^+ has to be got rid of in turn and the Na^+/K^+ATPase sodium pump fulfills this requirement. A very good example of this is seen in the study by Boyett et al [6] in the Purkinje fiber of the heart ventricle. Doubling the frequency of contractions, thus greatly increasing the amount of Ca^{2+} entering the cells, thus also increasing the activity of the Na^+/Ca^{2+} exchanger, they observed an increase in intracellular Na^+, measured by ion selective electrode, and a small (about 10mV) increase in intracellular negative potential caused by the sodium pump ($3Na^+$ out for $2K^+$ in). This correction process achieved by increased sodium pumping took about 10 minutes to complete. This can be interpreted as an electrogenic consequence of Na^+/K^+ATPase activity to deal with the *increased* intracellular sodium concentration above normal.

The conclusion is that the basic resting intracellular negative electrical potential is not caused by the sodium pump, the pump acting as a corrective in cells subject to an increased intracellular sodium load, due to other factors determined by the cell's particular function.

The Dynamics of Changes in Trans-Membrane Potential Upon Cell Activation

The function of many cells requires activation by depolarisation, i.e., loss of the internal electric negativity. A return to the initial more negative potential is the process of repolarisation.

The dominant description to be found in texts stems from the magnificent work of Hodgkin& Katz [13] and Hodgkin & Huxley [14] (my heroes that I knew as a young doctor). They studied the giant axon of the squid. From my present viewpoint, the preparation was rather unphysiological, as they amputated the

axon from the cell body, sucked out the intracellular gel and mitochondria (without which a cell cannot live), replaced them with physiological solution and inserted an electrode inside the lumen. They could then pass electric currents into and out of the axon across the cell membrane by applying appropriate electrical potential differences. They found that inward current was dependent on the presence of sodium ions (Na^+) in the extracellular fluid and outward current was dependent on the presence of potassium ions (K^+) in the intracellular fluid. Unfortunately, from my present viewpoint, this has been interpreted as depolarisation being due to an inward current carried by Na^+ and repolarisation is due to an outward current carried by K^+. One objection to this is that what we really want to know is how depolarisation occurs in the intact cell. The idea that these currents flowed through specific channels led to a burst of activity by physiologists using the patch clamp technique. In this, a piece of cell membrane is placed in the apparatus and various "gates" displayed which are claimed to represent channel openings and closings. So many of these have been recorded that their total surface area exceeds the known actual surface area of the intact cell. Moreover such gates have been recorded in membranes lacking channels [21]. As cell membranes do not generate electricity, the voltages and currents have to be applied from the experimental apparatus and therefore fail to simulate the natural depolarisation and repolarisation of intact cells.

Another objection to the Na^+_{in} and K^+_{out} statement is that if the cycle is very repetitive (e.g., trains of nerve impulses), the cell will become overloaded with Na^+ and become depleted of K^+, as the sodium pump activation is too slow to cope with the necessary rapid correction of this imbalance and does not respond to excess extracellular K^+, only to excess intracellular Na^+.

Depolarisation

I thought another alternative explanation of depolarisation was appropriate in consideration of the possible speed of depolarisation. The heart ventricular muscle cell depolarises at a velocity of 430volts/sec [5]. I judge this to be much faster than can be achieved by Na^+ inflow, Na^+ having 10,000 times the mass of an electron. The extremely fast depolarisation can be appreciated also in Draper&Weidmann's [9] records of heart ventricle action potentials. Also, these records show that after a brief fast little repolarisation, there is a voltage reflection of a slow inward current that is known to be inflow of calcium ions (Ca^{2+}) [4, 16] through a genuine ion channel, the Ca^{2+}channel, and it will be observed that this deflection reaches a peak in about 50 ms. This is also apparent from the actual traces of slow inward current, e.g., [4]. As the sodium ion is very similar in mass to to Ca^{2+}, one would expect the speed of Na^+ through a postulated Na^+ channel to reach its peak in a similar time (about 50ms), but depolarisation takes 1millisecond in heart ventricle. A peak of Na^+ concentration was not observed, with an intracellular sodium sensitive electrode, during peak depolarisation in Purkinje fibres [6].

The clue to a possibly solution came from published studies of the changes in intracellular potential and trans-membrane currents of the cells of the sinus node, the pacemaker of the heart. There is an electric current between action potentials (between heart beats - diastole), which in the conventional polarity is inward, but a current conventionally regarded as positive is, by definition, a flow of electrons (negatively charged) in the opposite direction. No measurements have been made that this current is dependent on, or carried, by, one or more positively charged ions, yet the original authors still thought that unknown positively charged ion(s) carried the current through an ion channel and named it the "funny current, If" [8], a name still used in current texts! There is nothing funny or mysterious about it; it is simply an electric current. like any other electric current consisting of a flow of electrons dependent on the electrical potential difference and the intervening impedance (Ohm's Law in the case of a pure resistance). The trans-membrane potential on these cells gradually drifts from -60mV (after repolarisation of the preceding action potential) to -40mV when there is sudden drop in impedance so that a much faster outflow of electrons generates the next action potential.

The importance of impedance drop causing depolarisations was tested in the Purkinje fibers of the heart ventricle, which also have a pacemaker current, although much slower than that of the sino-atrial node cell. Weidman (1951) assessed the impedance throughout the electric cycle by applying constant small amplitude current pulses and recording the resulting voltage responses (resistance = voltage/current). It transpired that during the rapid upstroke of the action potential (which is similar to that of the

main ventricular muscle), the impedance dropped to a value indistinguishable from zero in his recording, thus accounting for the extremely rapid outflow of electrons at that point in time. There was an immediate return, during the action potential plateau, to the highest impedence value. This continued until completion of repolarisation and then dropped to a slight lower value during the diastolic pacemaker depolarisation.

There is plenty of reason to suppose that the depolarisations of cells is the result of a reduction of electrical impedance (that includes resistant, capacitive and inductive impedances, and semi-conduction). Nerve cell synapses pass depolarisations of one nerve ending to another nerve or a muscle cell by means of chemical neurotransmitters, e.g., serotonin, or acetylcholine. In the case of the sinus node cell disussed above, acetylcholine released from vagal nerve endings increases the impedance (via the activation of cell membrane acetylcholine receptors) during diastole, so that the pacemaker current is slowed, it takes longer to reach the -40mV threshold for the firing of the next action potential, leading to a reduction in heart rate. Or, if there is nor-adrenalin release from sympathetic nerve endings or an increase in circulating adrenaline concentration, there is a decrease in impedance (via cell membrane adrenoreceptors) during diastole, leading to a speeding up of the pacemaker current, shortening the duration before the firing of the next action potential, and the heart rate is therefore increased.

Before leaving discussion of the sinus node cell, one needs an explanation of the greater drop in impedance to cause the faster electron outflow of the upstroke of the action potential that is the actual trigger for the excitation and contraction of the heart. This action potential has been shown to be Ca^{2+} dependent by Hagawara, Irisawa & Kameyama [12]. One possibility is that the electric field force (trans-membrane potential divided by membrane thickness of 5-8 nanometers), at a trans-membrane potential of -40 mV, is insufficient to continue the binding of Ca^{2+} to the inner leaflet of the cell membrane [20], in contrast to the continued binding at more negative potentials such as -60mV. If so, this detachment of Ca^{2+} from the inner cell membrane might herald the larger decrease in impedance, the opening of the Ca^{2+} channel (Ca^{2+} entry augmenting the depolarisation), and the Ca^{2+} dependence of the action potential [12].

In tissues that exhibit travelling waves of depolarisation, i.e., conducting tissue, like nerve axons, cardiac and skeletal muscle, the depolarisations are extremely rapid, such as 430volts/sec [5], which have all the characteristics of short circuits, confirmed in the records of Draper&Weidmann [9], and the drop to near zero impedance at "the spike" seen in Weidmann's records [38]. In these cases, the drop in impedance that allows such rapid outpouring of electrons is unlikely to be due mainly to chemical mediation, but due to the trans-membrane potential at any given location along the fiber being short-circuited by the depolarisation in the immediately proximate point in the fiber.

Vascular smooth muscle is of interest because, unlike nerve, cardiac muscle or skeletal muscle, the need for continuous contraction (tone), to maintain the required resistance to blood flow, the cell trans-membrane potential varies from -60mV to less negative values, resulting in variation in Ca^{2+}delivery to the contractile filaments of actomyosin. This is another example of the depolarisation being controlled by external chemical delivery, in that nor-adrenaline released from sympathetic nerve endings reduces the impedance of the cell membrane, allowing greater electron outflow, depolarisation and contraction.

In non-conductive tissues, such as pancreatic Islets of Langerhans ß cells, there is a continuous S shaped relationship between trans-membrane electrical potential difference and blood dextrose concentration involved in the control of insulin secretion [7]. This might also be explained by an effect of ∂-glucose upon cell membrane impedance.

Repolarisation

The rate of repolarisation, particularly in nerve action potentials is much faster than can be accounted for by the efflux rate of K^{+}as measured by Hodgkin and Keynes [15]. By contrast the postulate of repolarisation by mitochondrial derived electrons is the fastest that can be imagined. In all living cells, my proposal postulates that repolarisation occurs due to a flow of electrons from the mitochondria to the cytoplasm. The principle is that as depolarisation lowers the cytoplasmic electric potential, that increases the potential difference between the mitochondria and the cytoplasm, and current flows at a rate determined by the electrical potential difference and the intervening intracellular impedance.

The nerve axons mostly do not have other functions than that of conduction by cable theory which determines conduction velocity, not action potential repolarisation speed. In the present context, the fact of most interest is the duration of a nerve action potential of within 1 millisecond (1ms). Thus, after the conducted depolarisation, there is very swift resumption of the negative internal potential that follows, I suggest, from the distribution of mitochondria within axons [34]. The high speed of repolarisation in nerves is unlikely to be achievable by K^+ out flow, which, in view of the variability of neural activity, would likely lead to ionic imbalance.

In skeletal muscle there are also trains of action potentials generated by release of acetylcholine at the motor neuron nerve endings. The spikes are also of very short duration but longer than in nerve, namely 2 to 5 ms. The variation in the trains causes smooth and graded changes in force of contraction, achieved through summation of responses to successive stimuli and recruitment of motor units. (The function of electric depolarisations is to release internal Ca^{2+}which reacts with act myosin filaments to cause contraction). Repolarisation by mitochondrial-generation of electrons is rapid, to allow high frequency trains of impulses. Mitochondria are appropriately distributed within the cell [37].

In cardiac ventricular muscle, an initial rapid repolarisation is followed by the slow inward Ca^{2+}current, the release of $Ca^{2+}$from the terminal cysternae and the Na^+/Ca^{2+}inward current which removes 1 $C^{a2+}{}_{out}$ for $3Na^+{}_{in}$. This amounts to a greater increase in intracellular positive charge ($Ca^{2+}$and Na^+) and a delay of about 400 ms to complete repolarisation by mitochondria-derived electrons. The result is the long characteristic action potential of cardiac ventricle as recorded by Draper & Weidman [9].

In smooth muscle, nitric oxide produced from endothelial cells causes repolarisation and relaxation [30]. An important vascular function, particularly in arteries and arterioles is dilatation in response to increased blood flow to the peripheral organ supplied, e.g., exercise of downstream skeletal muscle. The endothelial cells between the vascular smooth muscle cells and the vessel lumen have been shown to depolarise from -70mV to -63mV in response increased blood flow [3]. The so-called flow mediated dilatation (FMD) is nitric oxide (NO) dependent, the NO being produced by the endothelial cells [23]. In this tissue, acetylcholine (ACh, a potent vasodilator) released from parasympathetic nerve endings seems to increase cell membrane impedance causing an increased intracellular electric potential (less depolarisation but so-called hyperpolarisation) and relaxation [18]. Nor adrenaline from sympathetic nerve endings and circulating adrenaline have the opposite effect (decreased impedance, more depolarisation and vasoconstriction).

In comparing different muscle types, mitochondrial density (and citrate synthesis activity) falls progressively from cardiac to skeletal to smooth muscles [27], a progression that may indicate differences in energy consumption and electrical activity. The oxidative phosphorylation capacity per mitochondria is similar between the three types [27]. Molecular density of other tissues has not been studied in detail in this review, but intracellular electric potential, mitochondrial density, and metabolic rates seem to differ similarly between the different tissues.

Conclusions

1. There is valid evidence that the distribution of intracellular ions is not dependent on the membrane sodium pump, but may be genetically determined.
2. There is no correlation between distribution of intracellular ions and trans-membrane electric potential.
3. The source of electricity, i.e., electrons moving, is postulated to be intracellular mitochondria.
4. Depolarisation is postulated to be a trans-membrane outflow of electrons.
5. Repolarisation is postulated to be an intracellular flow of electrons from mitochondria to the cytoplasm.

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