Journal of
Bioequivalence & Bioavailability
ISSN: 0975-0851

Ayrapetyan, J Bioequiv Availab 2016, 8:4
http://dx.doi.org/10.4172/jbb.10000e72

Editorial Open Access

Cell Hydration-induced Changes of Membrane Conductivity as a Marker for Estimation of Biological Effects of Chemical and Physical Factors on Organism

Sinerik Ayrapetyan*

UNESCO Chair-Life Sciences International Postgraduate Educational Center, 31 Acharyan St., Yerevan 0040, Armenia

The Na+/K+ pump generates Na+ gradient on membrane, which serves as an energy source for a number of secondary ionic transporters in membrane, such as Na+/H+, Na+/Ca2+, Na+/sugars, amino acids & other osmolytes [1]. Therefore, the decrease of Na+ gradient is a common consequence of cell pathology and is due to both the impairment of Na+/K+ pump activity and the increase of membrane permeability for Na+ (PNa). It is well established that the impairment of Na+/K+ pump activity in cell pathology is a result of inactivation of Na+/K+-ATPase (working molecules of Na+/K+ pump). However, the metabolic mechanism controlling PNa, which is decreased in cell pathology, has not been fully elucidated yet.

One of the principal discoveries made by the authors (Nobel Prize laureates) of classic membrane theory reveals that there is a negative correlation between Membrane Potential (MP) and membrane permeability for ions [2]. However, the mechanism of MP-dependent changes of membrane permeability has not been clarified.

Later the research group headed by Prof. Tasaki discovered that there was a negative correlation between cell membrane polarization and cell volume [3] but the physiologists did not pay an adequate attention to this discovery for a long time. Only at present, when it has been shown that membrane permeability for water is much higher than for ions [1,4] and that membrane surface determines the quantity of proteins molecules (enzymes, receptors and ionic channels) functioning in membrane [5-7] and water fluxes through membrane activate and inactivate ionic channels in membrane [7], it becomes clear that the discovery of Prof. Tasaki and his coworkers has a great physiological significance. Considering the fact that intracellular osmotic pressure is higher than the extracellular one, it is assumed that intracellular metabolism should generate water efflux in order to balance the osmotic uptake of water by cells. As membrane permeability for water is higher than for ions, it is suggested that the misbalance between water fluxes on membrane should precede ionic fluxes. It is known that during intracellular oxidation processes there is a release of endogenous water molecules in cytoplasm (42 water molecules per one molecule glucose oxidation) which generates water efflux inactivating inward going ionic currents, such as INa [7]. Therefore, it is suggested that the impairment of metabolically driven water efflux, which compensates the osmotically driven water uptake leading to the increase of membrane permeability for PNa, which in its turn decreases Na+ gradient on membrane, can be considered as a primary gate for generation of cell pathology.

Besides membrane hyperpolarization-induced decrease of PNa, electrogenic Na+/K+ pump decreases PNa by means of cell dehydration which in its turn brings to the decrease of active membrane surface and generation of water efflux from the cell [8,9].

It is known that in neuronal and muscle membranes Na+/K+-ATPase has three catalytic isoforms (α1, α2, α3) [10], with different affinities to cardiac glycoside ouabain and functional activities: α1 (with low affinity) and α2 (with middle affinity) isoforms are involved in transportation of Na+ and K+, while α3 (with high affinity) isn't directly involved in transporting Na+ and K+ and has only signaling function [11,12]. Our recent study has shown that the expression of α3 isoform is increased as a result of cell hydration and is decreased by aging. It has also been shown that the expression of α3 isoforms is extra-sensitive to different extremely low concentrations of biologically active substances and physical factors having intensity less than thermal thresholds [13,14]. The activation of α3 isoforms by different weak chemical and physical signals (depending on their quality and intensity) leads to activation of cGMP-dependent Na+/Ca2+ exchange in forward mode (F) or cAMP-dependent Na+/Ca2+ exchange in reverse mode

(R). Furthermore, the threshold of activation of cGMP formation in cell upon the impact of chemical substances is higher that of cAMP formation [15]. We suggest that this can be explained by the fact that probably soluble guanylyl cyclase is more sensitive to factor-induced cell hydration than soluble adenylyl cyclase. Therefore, the activation of cGMP-dependent F Na+/Ca2+ exchange can be considered as a primary reaction to factor-induced water uptake leading to the increase of PNa which is resorted by reactivation of electrogenic Na+/K+ pump that generates water efflux. If cGMP-dependent F Na+/Ca2+ exchange is unable to compensate the factor-induced water uptake, cAMP-dependent R Na+/Ca2+ exchange acts as the second protective mechanism for the compensation of water uptake. It has been shown that in case of low [Ca2+]i cAMP-dependent R Na+/Ca2+ exchange leads to cell hydration by stimulation of endogenous water release, while in case of high [Ca2+]i it leads to cell dehydration [16]. It is worth to note that in both cases cAMP-dependent R Na+/Ca2+ exchange generates water efflux which depresses PNa. However, continuous activation of cAMP-dependent R Na+/Ca2+ exchange can also increase [Ca2+]i which has a multisided poisoning effect on cell. It is known that high [Ca2+]i switches on "Ca2+/Calmodulin-NO-cGMP formation" cascade leading to activation of F Na+/Ca2+ exchange [17,18]. As F Na+/Ca2+ exchange functions in stoichiometry of 3Na:1Ca, its activation increases water uptake (cell hydration) which activates inward going Na+ gradients and shunts membrane potential, i.e., causes cell death. Thus, factor-induced cell hydration due to the release of intracellular water (water efflux leading to PNa decrease) can

***Corresponding author:** Sinerik Ayrapetyan, UNESCO Chair-Life Sciences International Postgraduate Educational Center, 31 Acharyan St., Yerevan 0040, Armenia, Tel: +374 10 624170; Fax: +374 10 624170; E-mail: info@biophys.am

Received June 15, 2016; **Accepted** June 17, 2016; **Published** June 23, 2016

Citation: Ayrapetyan S (2016) Cell Hydration-induced Changes of Membrane Conductivity as a Marker for Estimation of Biological Effects of Chemical and Physical Factors on Organism. J Bioequiv Availab 8: e72. doi:10.4172/jbb.10000e72

be considered as beneficial, while factor-induced cell hydration due to water uptake and increase of PNa can be considered as hazardous. Taking into consideration the above presented data it can be concluded that cell hydration-induced changes of membrane conductivity could serve as a marker for the exact detection of beneficial and harmful effects of any chemical and physical factors on organism.

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