

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

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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 (α 1, α 2, α 3) [10], with different affinities to cardiac glycoside ouabain and functional activities: α 1 (with low affinity) and α 2 (with middle affinity) isoforms are involved

in transportation of Na⁺ and K⁺, while α 3 (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 α 3 isoform is increased as a result of cell hydration and is decreased by aging. It has also been shown that the expression of α 3 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 α 3 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 than 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

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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.

References

- Hoffmann EK, Sørensen BH, Sauter DP, Lambert IH (2015) Role of volume-regulated and calcium-activated anion channels in cell volume homeostasis, cancer and drug resistance. *Channels (Austin)* 9: 380-396.
- Hodgkin AL (1964) The conduction of the nervous impulse. Liverpool University Press.
- Iwasa K, Tasaki I, Gibbons RC (1980) Mechanical changes in crab nerve fibers during action potentials. *Science* 210: 338-339.
- Borgnia M, Nielsen S, Engel A, Agre P (1999) Cellular and molecular biology of the aquaporin water channels. *Annu Rev Biochem* 68: 425-458.
- Ayrapetyan SN, Suleymanyan MA, Saghyan AA, Dadalyan SS (1984) Autoregulation of the electrogenic sodium pump. *Cell Mol Neurobiol* 4: 367-383.
- Ayrapetyan SN, Arvanov VL, Maginyan SB, Azatyan KV (1985) Further study of the correlation between Na-pump activity and membrane chemosensitivity. *Cell Mol Neurobiol* 5: 231-243.
- Ayrapetyan SN, Rychkov GY, Suleymanyan MA (1988) Effects of water flow on transmembrane ionic currents in neurons of *Helix pomatia* and in squid giant axons. *Comp Biochem Physiol A Comp Physiol* 89: 179-186.
- Ayrapetyan SN, Sulejmanyman MA (1979) On the pump-induced cell volume changes. *Comp Biochem Physiol Part A Comp Pharmacology* 64: 571-575.
- Carpenter DO, Fejtli M, Ayrapetyan S, Szarowski DH, Turner JN (1992) Dynamic changes in neuronal volume resulting from osmotic and sodium transport manipulations. *Acta Biol Hung* 43: 39-48.
- Juhaszova M, Blaustein MP (1997) Na⁺ pump low and high ouabain affinity alpha subunit isoforms are differently distributed in cells. *Proc Natl Acad Sci U S A* 94: 1800-1805.
- Xie Z, Askari A (2002) Na⁺/K⁺-ATPase as a signal transducer. *Eur J Biochem* 269: 2434-2439.
- Wu J, Akkuratov EE, Bai Y, Gaskill CM, Askari A, et al. (2013) Cell signaling associated with Na⁺/K⁺-ATPase: activation of phosphatidylinositide 3-kinase I/Akt by ouabain is independent of Src. *Biochemistry* 52: 9059-9067.
- Ayrapetyan S (2013) Na⁺/K⁺ pump $\alpha 3$ isoform is a universal membrane sensor for weak environmental signals. *J Bioequiv Availab* 5: 31-40.
- Ayrapetyan S, Baghdasaryan N, Mikayelyan Y, Barseghyan S, Martirosyan V, et al. (2015) Cell hydration as a marker for nonionizing radiation. In: Markov M (ed.), *Electromagnetic Fields in Biology and Medicine*. (2nd edn.), CRC Press, USA.
- Azatyan KV, Karapetyan IC, Ayrapetyan SN (1994) Effect of Acetylcholine of low doses on ⁴⁵Ca²⁺ influx into the *Helix Pomatia* neurons. *Biol Mem Harwood Academic Publishers GmbH* 7: 301-304.
- Nikoghosyan A, Heqimyan A, Ayrapetyan S (2015) Primary mechanism responsible for age-dependent neuronal dehydration. *International Journal of Basic and Applied Sciences* 5: 5-14.
- Azatian KV, White AR, Walker RJ, Ayrapetyan SN (1998) Cellular and molecular mechanisms of nitric oxide-induced heart muscle relaxation. *Gen Pharmac* 30: 543-553.
- Brini M, Carafoli E (2009) Calcium pumps in health and disease. *Physiol Rev* 89: 1341-1378.