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The Dysfunction of Metabolic Controlling Cell Hydration is a Primary Mechanism for Generation of Aging-Related Nerve Disorders

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Although the vital role of water for living cells is widely accepted, its messenger role in cell signal transduction as well as in the generation of various diseases, including aging-induced increase of the risk of different disorders, still awaits to be elucidated.

The classical membrane theory (the authors of which A. Hodgkin, A. Huxley, J.Eccles in 1963 and B.Kats in 1964 [1] received Nobel Prize in Physiology and Medicine) considered the signal transduction in neurons as an activation of ionic channels in membrane leading to generation of transient ionic currents through the cell surface membrane [1]. Although most of the fundamental predictions of this theory were confirmed by subsequent studies in different laboratories, in particularly by study using *Patch-Clamp* method for recording the elementary electrical events of the membrane, suggested by Nobel Prize winners Erwin Neher and Bert Sakmann [2,3], the nature of physico-chemical mechanisms determining the Membrane Potential (MP) dependent changes of membrane conductance, which is one of the fundamental membrane properties postulated by this theory stays non elucidated. From the viewpoint of these approaches, it is difficult to explain the big number of experimental data on the effects of weak physical and chemical signals on neuromembrane functional activity, the intensity of which is rather far from not only the threshold of ionic channels activation but also from thermal thresholds [4-6].

One of the omissions of membrane theory is that it did not consider the role of water fluxes through the membrane in ionic channels activation and inactivation processes, although the osmotic gradients on cell membrane and its membrane potential-dependent changes as it was postulated by Teorell [7]. It did not consider the variability of active membrane surface during neuronal functional activity, namely the MP-dependent changes of cell volume, which was clearly demonstrated by Isawa et al. [8] in squid axon. These authors have shown that during single Action Potential (AP) the membrane depolarization causes axon swelling, while its hyper polarization leads to axon shrinkage. Later by our work was shown that water fluxes through membrane of squid axon and snail neurons have essential modulation effect on ionic currents during AP: water fluxes have activation and inactivation effects on ionic currents in membrane when they have same and opposite direction, respectively [9].

The next essential omission of membrane conductive theory is that the MP is considered as a sum of Nernst potentials of ionic gradients on the membrane, that it suggested the metabolic energy-driving Na/K pump as "neutral", which does not have a direct contribution in the generation of membrane potential. This postulate was rejected later by a great number of experimental data performed on cells of different species of animals [10]. The idea that the electrogenic character of Na/K pump could have a crucial role in cell volume regulation was suggested by Dean since in 1941 [11]. However because of using non adequate experimental procedures to check this suggestion on the role of Na/K pump, indirect regulation of cell volume was discussable during long period. Only at the end of the past century on fresh isolated brain slices [12] and isolated single neurons of mollusks [13] was experimentally proved the idea of regulatory role of electrogenic Na/K pump. It was shown also that the pump-induced cell volume regulation has a great physiological meaning for metabolic regulation of neuronal membrane functional activity [14]. The number of functionally active protein molecules in neuronal membrane, having enzymatic [15], receptors [9] and ionic channels forming [16] properties, are in functionally active and inactive (reserve) states, depending on active membrane surface (cell hydration). More detailed electron microscopic morphological and biochemical investigation of membrane surface invagination (caveola) have shown the membrane metabolic heterogeneity, having cell-hydration dependent variability [17]. As the activity of intracellular molecules depends on their hydration-induced folding [18], the pump induced regulation of cell hydration has a critical role for intracellular metabolism, including gene expression. At present it is well established that cell swelling triggers cell proliferation, while cell shrinkage promotes the apoptotic patterns [19-21]. The crucial role of cell hydration as a universal and extra-sensitive messenger through which the close-talking between intracellular metabolism and cell bathing medium is realized indicates its high sensitivity to homeopathic concentration ($<10^{-10}$ M) of biologically active substances and non ionizing radiation (infrasound, light, millimeter waves, electromagnetic and static magnetic fields), the intensity of which is less than thermal threshold [6]. It was shown that even light has optical manifestations of the microscopic swelling of axons that accompanies the firing of action potentials in cultured neurons [22].

Despite cell hydration (including the neuronal) is one of the characteristic phenomena for aging, its role in the generation of age-dependent neuronal dysfunction leading to memory loss and the increase of the risk of nerve disorders is not fully understood. It is known that the number of nerve disorders like Parkinsonism, Alzheimer's, multiple sclerosis and other diseases, which are accompanied by memory loss, have the following metabolic characteristics: biphasic changes of neuronal hydration (increase and decrease of cell hydration), cell cytoskeleton deformation, decrease of O_2 uptake, dramatic changes in lipid turnover, an enormous increase of sphyngomyelins in membrane [23-25]. At present the oxidative stress [26], τ phosphorylation [27] and extracellular deposits (senile plaques) of amyloid-β (Aβ) peptide generation are considered to be a key pathogenic mechanism in aging-induced sclerosis and in the increase of nerve disorder generation

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risk [28-30]. The study of oxidative damage in AD and normal aging has shown a strong inverse relationship between neuronal oxidative damage and neuronal size among cases of AD but not controls [31].

Therefore, it is suggested that the elucidation of the nature of cell volume controlling metabolic mechanism(s), dysfunction of which brings to neuronal dehydration in aging, could bring us close in understanding the reason of age-related nerve disorders as well.

It is known that among the number of mechanisms involved in cell volume regulation the Na/K pump has a crucial role in this process, because the Na^+ gradient serves as an energy source for a number of secondary ionic transporters, such as Na^+/Ca^{2+}, Na^+/H^+, Na^+/sugars, amino acids and osmolytes [21,32]. It is known that there are two enzyme systems actively involved in metabolic regulation of cell volume, associated with cation transport across surface membranes: transport ATPases, which are indeed the translocating structure and are fueled by the free energy derived from ATP hydrolysis, and kinases, which may regulate translocation via phosphorylation of the transporter molecules through the phosphorylation of associated regulatory structures. The interaction between these two enzyme systems is realized through the intracellular signaling systems, the dysfunction of which leads to generation of cell pathology, accompanied by corresponding changes of cell hydration. As the Na/K pump is the most ATP-utilizing machine in the cell, it serves as a main regulator of all other ionic pumps and kinases activity. Therefore factors, able to change the balance between the ATP hydrolysis and ATP production system (mitochondria), by changing the Na/K pump activity, could switch on the intracellular signaling systems-induced modulation of cell katabolic and anabolic processes.

Therefore the dysfunction of the Na/K pump–controlling cell hydration, can be considered as a common gate for cell pathology, including nerve disorders and cancer. However the nature of mechanism through which the Na^+/K^+ pump dysfunction leads to apoptosis and proliferation inhibition in excitable cells and enhance proliferation and inhibition of apoptosis in non-excitable cells stays unclear.

The second ionic transporting mechanism in cell membrane, having a crucial role in cell volume regulation is the Na^+/Ca^{2+} exchange [33-36]. It is known that there is a close correlation between the electrogenic Na/K pump and electrogenic Na^+/Ca^{2+} exchange, which have been described since pioneering work by Baker et al. [37]. At present, thanks to great contribution of one of co-authors of this work Prof. Blaustein's group, who discovered and characterized different isoforms of Na/K pump, a close correlation between these two ion transporting mechanisms on the level of different Na/K pump isoforms was shown [38,39].

The protein of Na^++K^+-ATPase (working molecule of Na/K pump) are αβ heterodimmers. The catalytic α subunit, contains the Na^+, K^+, Mg^{2+}-ATP, and ouabain binding sites and is phosphorylated during each pump cycle. β subunit is essential for pump function; it stabilizes the α subunit conformation and chaperones the αβ complex to the cell membrane. There are 4 mammalian α subunit isoforms (α_1 to α_4) which are products of different genes but have ≈ 90% sequence identity, different expression patterns, and different kinetics, and they are differently regulated [38,40-44]. The α_4 subunits were discovered in sperm [45]. It is documented that the low affinity α_1 of Na^+ pump have a "housekeeping" function: they control, primarily, Na^+ in bulk cytosol while the real function of the α_2 and α_3 catalytic isoforms and their functional significance, are uncertain [39,44]. They also have a different localization in cells: α_1 is ubiquitously distributed over the surfaces of cells, while high ouabain affinity isoforms are confined to a reticular distribution within the cellular membrane that paralleled underlying endoplasmic or sarcoplasmic reticulum, with Na^+/Ca^{2+} exchanger protein. It is suggested that α_1 may regulate bulk cytosolic Na^+, whereas α_2 and α_3 may regulate Na^+ and, indirectly, Ca^{2+} in a restricted cytosolic space between the cell membrane and reticulum. The high ouabain affinity Na^+ pumps may thereby modulate reticulum Ca^{2+} content and Ca^{2+} signaling [46]. By the α_2 pump isoform-induced activation of Na^+/Ca^{2+} exchange in reversal mode, leading to increase of blood pressure, was explained by increase of local concentration of Na ions in "junctional" sarcoplasmic/endoplasmic reticulum in result of nanomolar ouabain–induced inactivation of pump [44].

However the individual role of α_3 isoforms of Na/K pump in this process remains unclear. Also is not clear the detailed mechanism of correlation between functions of α_3 pump and Na^+/Ca^{2+} exchange and its functional significance in norm and pathology. By our early works performed on mollusk's isolated nerve ganglia have shown that high affinity ouabain receptors activation leads to elevation ^{22}Na efflux from preliminary ^{22}Na enriched neurons [16], which is due to activation of cAMP dependent Na^+/Ca^{2+} exchange [47]. It is worth to note that in these *in vitro* experiments when initial intracellular Na^+ concentration is higher compared to it in *in vivo* condition, activation effect of 10^{-10}-10^{-7}M ouabain on Na^+/Ca^{2+} exchange in reverse mode is observed, i.e. at level of α_2 and α_3 receptors [48]. While in case of *in vivo* experiments performed on rats, low concentration 10^{-11}-10^{-9}M ouabain has activation effect on Na^+/Ca^{2+} exchange in forward mode, which is accompanied by increase of intracellular cGMP [6].

As the dysfunction of Na/K pump is a common consequence of cell pathology and aging, leading to the accumulation of intracellular Ca ions, the latter, being a strong inhibitor for Na^+/K^+-ATPase, switches on the following metabolic cascade: the ATP accumulation stimulates the intracellular cAMP formation, which leads to the increase of cytoskeleton phosphorylation, while the contraction of Ca ions brings to cell dehydration. Previously it was shown that intracellular cGMP plays a key role in the activation of Ca efflux through Na^+/Ca^{2+} exchange and Ca pump mechanisms [49]. As the cytoplasmic guanylyl cyclase activity, like other proteins, depends on its hydration, it is suggested that the aging-induced inactivation of cGMP formation could serve as a primary mechanism for switching on the pathogenic pathways (Na/K pump weakness, intracellular Ca ions and cAMP accumulation, oxidative stress, Aβ generation, DNA demethylation and damage, etc).

Therefore, it is suggested that for understanding the nature of the mechanism underlying the ground of aging-induced memory loss and the increase of nerve disorder risk, it is extremely important to study the multisided role of osmotic stress on intracellular enzyme activity which is responsible for intracellular Ca homeostasis. This knowledge will greatly influence the strategies designed to decrease the aging-induced risk of neuronal dysfunction. The fact that there is a close correlation between the electrogenic Na/K pump and the electrogenic Na^+/Ca^{2+} exchange, which plays a crucial role in the regulation of intracellular Ca homeostasis, indicate that Ca efflux system is essential in the protection of Na/K pump activity from the pathogenic factor-induced increase of intracellular Ca ions. Since the Na^+/Ca^{2+} exchange

works in stoichiometry of 3Na:1Ca [37,39] it has a strong modulation effect on cell volume [36]. Therefore Na^+/Ca^{2+} exchange has an extremely important role in the cell volume regulation process, namely in excitable tissue, having powerful Na^+/Ca^{2+} exchange systems [36,39]. Its activation in Na influx and Ca efflux regime has hydration, while in reversal mode, i.e. in 3Na efflux and 1Ca influx regime – dehydration effects on cell. Thus the pump inactivation-induced elevation of intracellular cAMP content and intracellular increase of Na ions brings to the activation of Na^+/Ca^{2+} exchange in reversal mode, having a shrinkage effect on cell [47,49]. It is worth to note that because of the higher affinity of intracellular proteins to Ca ions, the dehydration effect of 3Na efflux and 1Ca influx on cell is much more pronounced than Na/K pump effect. However this cAMP dependent Na^+/Ca^{2+} exchange-induced dehydration effect on cell is observable only when the pump is in inactive state [50].

Taking together our recent data on α_3 ouabain receptors-induced activation of Na^+/Ca^{2+} exchange in forward mode which has age-dependent dysfunctional character [51] and that in blood of mammals circulates an endogenous ouabain-like compound in nanomolar concentration leading to release of Ca ions from the intracellular storage [44] allow us to put forward a hypothesis that α_3 isoforms dysfunction-induced intracellular ^{45}Ca elevation could modulate a variety of kinase-mediated pathways, and thereby serve as a primary mechanism for generation of nerve disorders.

The key role of the cyclic nucleotides in metabolic regulation of Na^+/Ca^{2+} exchange is well documented: the increase of intracellular cAMP contents activates potential-dependent Ca^{2+} channel [52] which is accompanied by activation of Na efflux coupling of Ca^{2+} uptake [49], while the increase of intracellular cGMP activates the Na^+/Ca^{2+} exchange in forward mode [53]. It is known that intracellular accumulation of Ca ions binding with calmodulin activates NO -cGMP pathway. Our previous data have shown that the NO-induced elevation of cGMP has activation effect on Na^+/Ca^{2+} exchange in forward mode [54].

As the cytoplasmic guanylyl cyclase activity is highly hydration dependent, it can be suggested that the aging-induced dehydration could inactivate cGMP formation leading to the inhibition of Ca ion extrusion from the cell. The dysfunction of cGMP-dependent the Na^+/Ca^{2+} exchange in excitable cells has been suggested to underlie the ground of age-related cells dehydration, which leads to reduction of cell functional activity.

The reciprocal relation in development between cGMP-dependent Na^+/Ca^{2+} exchange in forward and cAMP-dependent Na^+/Ca^{2+} exchange in reversal mode was shown by our recent works on rats' brain and heart muscle tissue: in young animals the Na^+/Ca^{2+} exchange functioning in forward while in old animals - in reverse mode [51].

The data obtained in the work with rats as well as the earlier data obtained on snail isolated neurons and heart muscle, allow us to consider the aging-induced decrease of cell hydration to be the primary mechanism leading to age-related dysfunctions of different catabolic and anabolic processes.

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