

## Lipid Fluidity as an Essential Therapeutic Tool for Cell Pathology

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### Editorial

It is known that the decrease of Na<sup>+</sup> gradients on cell membrane is a common consequence of cell pathology. According to the classical membrane theory, low permeability of cell membrane for Na<sup>+</sup> and high permeability for K<sup>+</sup> are the main reasons for asymmetric distribution of inorganic ions between intra- and extra-cellular mediums and generation of Membrane Potential (MP) [1]. However, this theory is unable to explain the mechanism of the metabolic control of semi-permeable properties of cell membrane for inorganic ions, which are disturbed in cell pathology. Our previous work, performed on squid axons and snail neurons, has shown that water efflux from the cells has inactivation effect on inward Na<sup>+</sup> and Ca<sup>2+</sup> currents and activation effect on outward K<sup>+</sup> currents, while the water uptake has opposite effect on them [2].

The facts that intracellular osmotic pressure exceeds the extracellular one and cell membrane permeability for water is much higher (more than ten times) than for ions [3,4], allow us to assume that intracellular metabolism should generate water efflux from the cell in order to balance the osmotic uptake of water by cells. Therefore, we have suggested that metabolically generated water efflux from the cells is the main mechanism through which the metabolic control of membrane permeability for inorganic ions is realized [5].

The metabolically generated water efflux from the cell takes place by two mechanisms: a) Ion transporting system which pushes out more osmotic active particles from the cells than uptakes it; and b) Intracellular oxidative processes leading to the release of water molecules in cytoplasm (one molecule glucose oxidation generates 42 H<sub>2</sub>O).

Among the metabolic mechanisms generating water efflux from the cell, Na<sup>+</sup>/K<sup>+</sup> pump has a crucial role. On one side, Na<sup>+</sup>/K<sup>+</sup> pump decreases intracellular osmolarity due to its 3Na<sup>+</sup>: 2K<sup>+</sup> stoichiometry, on the other side it stimulates the release of H<sub>2</sub>O in cytoplasm as a result of activation of intracellular phosphorylation processes.

Osmotic water uptake by cells takes place through: a) Membrane lipids; b) Water aqua pores [3]; and c) Ionic channels [2,6].

Water efflux through lipid phases of the membrane depends on lipid fluidity. The latter is increased by cell swelling, heating, involvement of unsaturated fatty acids in lipids as well as by the factors having elevation effect on both intracellular Ca<sup>2+</sup>-induced activation of lipase activity and β-oxidation of fatty acids [7,8]. As Na<sup>+</sup>/K<sup>+</sup> pump regulates all the mentioned cell parameters [9], the Na<sup>+</sup>/K<sup>+</sup> pump-induced membrane fluidity decrease serves as one of the pathways through which Na<sup>+</sup>/K<sup>+</sup> pump counteracts osmotic water uptake by cells and decreases cell membrane permeability for Na<sup>+</sup> and Ca<sup>2+</sup>.

It is known that the activation of cell metabolism leads to formation of unsaturated fatty acids in membrane through the activation of β-oxidation of fatty acids, including fatty acids with short carbon chain (fewer than 10 carbon atoms). By our previous study it has been shown that the application of non-metabolized 2-decenoic acid (DA), which increases membrane fluidity by 40% [10], leads to neuronal swelling and blocks Na<sup>+</sup> channels due to the increase of water fluxes through the lipids, in this way weakening water uptake-induced activation effect on Na<sup>+</sup> channels [11]. It has also been shown that the elevation of membrane lipid fluidity by this mechanism brings to potential-

independent inhibition of bursting activity (Epileptiform discharge) of neurons [10] and depresses synaptic transmitters-induced membrane activity and Na<sup>+</sup>/Ca<sup>2+</sup> exchange in membrane. Therefore, based on the aforementioned data, it can be concluded that the increase of membrane fluidity could serve as a universal hallmark for cell pathology, including cancer, and the factors, which depress membrane fluidity, could have therapeutic effect and serve as a focal point for physiotherapeutic and chemotherapeutic treatments of different diseases [12,13].

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