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The Cyclic Nucleotides-Dependent Na^+/Ca^{2+} Exchange-Generated Water Efflux from The Cell as A Primary Metabolic Target for Pain Therapy

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From the point of fundamental neuroscience hyper-excitation of nerve ending generates nociceptive signals, which are transmitted to the central nervous system and cause pain. It is known that pain signal generation can be a result of either direct mechanical damage of cell membrane or different cell pathologies. From the perspective of classic membrane theory the hyper-excitation of neuronal membrane is considered as a sustainable membrane depolarization leading to activation of ionic channels for inward ionic currents [1]. This dogma serves as the main barrier for evaluating the cellular mechanism of nociceptive signal generation.

At present, there is a great number of experimental data indicating the non-adequate explanation of membrane theory on the role of cell metabolism in controlling membrane excitability, namely this theory doesn't give a reliable explanation regarding the role of the number of potential-independent metabolic mechanisms through which the dysfunction of intracellular metabolism causes the increase of membrane hyper-excitation (nociceptive signal generation).

By our previous study it has been shown that water fluxes through the membrane has either activation or inactivation effects on ionic channels in the membrane depending on their directions: water fluxes have activation effect on ionic current when the latter has the same direction with water fluxes and it has inactivation effect on it in case their directions are opposite [2-4].

Considering the facts that cell membrane is highly permeable for water and intracellular osmotic pressure exceeds the extracellular one, it is assumed that there must exist metabolically driven water efflux from the cells in order to balance water uptake in cell membrane. Therefore, it becomes clear that the generation of net water influx is able to elevate membrane excitability as a result of impairment of metabolically driven water efflux and increase of osmotic water uptake by neuron. The pain-relieving effect of the factors having dehydration effect on cells, such as hypertonic solution [5], ketamine [6] and magnetic fields [7] has been explained from this point of view.

Our previous study has shown that protein molecules in cell membrane, having enzymes, carriers, receptors and channels-forming properties are functionally active and inactive (reserve) states depending on cell surface (volume) [2-4]. Therefore, the generation of net water influx leading to cell swelling, leads to further increase of membrane excitability by increasing the number of functionally active ionic channels in the membrane. The existence of such a positive feedback between cell swelling and membrane excitation has been shown earlier by our work performed on snail neurons [2].

Thus, the existence of such multistep positive feedback between net water influx and membrane excitability can be considered as a key mechanism for generation of hyper-excitation (nociceptive signal) of neuronal membrane. On the basis of these data, we have suggested that the net water influx through cell membrane is a primary messenger for generation of nociceptive signal, while the activation of net water efflux from the cell is a tool for pain therapy. Therefore, for chronic therapy it is important to have knowledge on the nature of metabolic mechanism the dysfunction of which brings to depression of water efflux from the cells.

The Na^+/K^+ pump, which has a crucial role in metabolic control of cell hydration, generates water efflux from the cells by two pathways: by pushing out more osmotically active particles from the cells than uptaking (due to its stoichiometry of 3Na:2K) and by stimulating intracellular oxidative phosphorylation processes leading to endogenous water release in cytoplasm as Na^+/K^+ pump is a highly ATP utilizing mechanism in cell.

Thus, the activation of electrogenic Na^+/K^+ pump can inhibit membrane excitation by generation of water efflux from the cell bringing to inactivation of inward ionic currents and decrease of the number of functionally active ionic channels in the membrane as a result of cell shrinkage [2,4,8]. Therefore, Na^+/K^+ pump can be considered as a key metabolic mechanism controlling membrane excitability and its dysfunction is a common consequence of any cell pathology that is accompanied by pain generation.

At present, it is established that three types of catalytic isoforms of Na^+/K^+-ATPase (working molecules of Na^+/K^+ pump) are expressed in neuronal membrane, which have different affinities to ouabain (specific inhibitor for Na^+/K^+-ATPase) and different functions. Among these three isoforms, only low affinity isoform (α_1) has Na^+/K^+ pump function, while the isoforms with the highest affinity to ouabain (α_3/α_2) are not directly involved in transporting function of these ions and have only intracellular signaling function [9,10]. Our studies have shown that pM concentrations of ouabain stimulate cGMP-dependent Na^+/Ca^{2+} exchange in forward mode (F Na^+/Ca^{2+} exchange), while its nM concentrations activate cAMP-dependent Na^+/Ca^{2+} exchange in reverse mode (R Na^+/Ca^{2+} exchange) [11]. Moreover, these nucleotides-dependent Na^+/Ca^{2+} exchange is sensitive not only to low ouabain but also to different extremely low concentration of chemical substances [12,13] and physical [14,15] signals with the intensity even less than thermal threshold. Thus, this allows to suggest that the sensitivity of nucleotides-dependent Na^+/Ca^{2+} exchange (i.e. nociceptive signal generation) to different factors has quantum-mechanical character and as it has been shown by our recent work this system is sensitive to EMF-induced water structure changes near the membrane [15].

It is known that Na^+/Ca^{2+} exchange works in stoichiometry of 3Na:1Ca [16]. From this point of view it is followed that the activation of F Na^+/Ca^{2+} exchange could produce cell hydration, while the activation of R Na^+/Ca^{2+} exchange leads to cell shrinkage. However, in our previous study on rats' brain tissues it has been shown that the activation of both Na^+/Ca^{2+} exchange in forward and reverse modes generates water efflux from the neurons which has age-dependent weakening character.

The activation of cGMP-dependent F Na^+/Ca^{2+} exchange activates Na^+/K^+ pump producing net water efflux from the cell by removing the intracellular Ca^{2+} from the cells, which is a strong inhibitor for Na^+/K^+-ATPase [17]. Whereas, the activation of R Na^+/Ca^{2+} exchange, which is accompanied by the increase of intracellular cAMP [18], stimulates water efflux from the cells by activation of Ca^{2+} pump in membrane of endoplasmic reticulum (ER) [19], which in its turn accumulates Ca^{2+} from cytoplasm into ER and stimulates mitochondrial function through junction between ER and mitochondria [20].

Thus, the cyclic nucleotides-dependent Na^+/Ca^{2+} exchange-generated water efflux from the cell is suggested as a primary metabolic target for pain therapy.

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