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The net water uptake by excitable cells is a primary mechanism for pain signal generation

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Abstract

From the biophysical point of view pain signal can be considered as an abnormal (hyper) excitation of neuronal and muscle membranes, which is transmitted into central nervous system (CNS) and generates pain sensation. Since pain can be generated by different phenomena, starting from mechanical damage to the breakdown of different metabolic pathways, there must be a common cellular mechanism through which various physical, chemical and metabolic factors generate abnormal excitation of cell membrane. It is known that pain sensation can be changed upon the effect of extremely weak chemical and physical signals, having intensity even less than thermal threshold and non-linear dose-dependent character. Therefore, such a cellular target must have a quantum-mechanical nature.

From the biophysical point of view pain signal can be considered as an abnormal (hyper) excitation of neuronal and muscle membranes, which is transmitted into central nervous system (CNS) and generates pain sensation. Hence, the bioequivalence of the water by the cells in the body determines the phenomenon. Since pain can be generated by different phenomena, starting from mechanical damage to the breakdown of different metabolic pathways, there must be a common cellular mechanism through which various physical, chemical and metabolic factors generate abnormal excitation of cell membrane. It is known that pain sensation can be changed upon the effect of extremely weak chemical and physical signals, having intensity even less than thermal threshold and non-linear dose-dependent character. Therefore, such a cellular target must have a quantum-mechanical nature. Previously we have suggested that cell hydration is a fundamental cell parameter which has quantum-mechanical sensitivity and determines cell functional activity, including membrane excitability [1-3]. The cell hydration-induced control of its functional activity is realized by surface dependent-changes of the number of functionally active proteins (enzymes, receptors and channels) in the membrane and hydration-induced regulation of intracellular macromolecules' activity through folding-unfolding mechanism [4-7]. Moreover, it has been shown that the metabolic control of cell membrane excitability has a crucial role in trans-membrane water fluxes-induced activation and inactivation of ionic channels. The water fluxes have activation effect on ionic currents having the same directions and inactivation effect on the currents with opposite directions [6,8]. As intracellular osmotic pressure exceeds the extracellular one, water efflux from the cells has a metabolic nature and it has been suggested that the metabolic generation of water efflux from the cell is a pathway through which the low permeability of membrane for inward Na^+ and Ca^{2+} currents is controlled [6,9]. Therefore, the impairment of metabolically generated water efflux from the cells, bringing to the activation of net water influx, which in its turn leads to membrane permeability for Na^+ and Ca^{2+}, is a common consequence of any pathology. On the basis of these data previously we have suggested that pain sensation is a result of overhydration-induced hyper excitation of neuronal and muscle membranes [10]. According to this hypothesis the activation of water efflux from the neuronal and muscle cells could have pain-relieving effect. Therefore, the evaluation of the nature of the metabolic mechanism responsible for generation of water efflux from the cells seems extremely important from the point of effective pain therapy.

It is known that water efflux can be generated by electrogenic ion transporting process pushing out more osmotic active particles from the cells than up taking as well as by releasing water molecules in cytoplasm during intracellular oxidative process. In these two aspects the Na^+/K^+ pump has a crucial role in metabolic regulation of cell volume: from one side Na^+/K^+ pump functioning in stoichiometry of $3Na^+:2K^+$ pushes out more osmotic particles that uptakes, from the other side Na^+/K^+ pump, being the highest ATP utilizing machine, stimulates the intracellular metabolism leading to water molecule release in cytoplasm [11,12].

It is known that Na^+/K^+-ATPase in nerve and muscle membranes has three catalytic isoforms having different affinities to ouabain. The isoforms with low affinity to ouabain (a1-agonist >10-7M) have Na^+/K^+-pump function, while the middle (a2-agonist nM) and the highest (a3-agonist pM) affinity isoforms have only intracellular signaling function regulating $[Ca^{2+}]$ i through Na^+/Ca^{2+} exchange localized in cell membrane [13,14]. Traditionally, the correlation between Na^+/K^+ pump and Na^+/Ca^{2+} exchange is explained by pump-induced changes of the Na^+ gradient on the membrane [13,15,16]. However, by our earlier work it has been shown that ouabain at nM and pM concentrations can have activation effects on Na^+/Ca^{2+} exchange in reverse (R) and forward (F) modes, respectively without having direct effect on Na^+/K^+ pump activity [4,17]. It has been shown that the activation of R Na^+/Ca^{2+} exchange is accompanied by the increase of intracellular cAMP contents, while the activation of F Na^+/Ca^{2+} exchange by the increase of intracellular cGMP contents [17,18]. The role of cyclic nucleotides in controlling $[Ca^{2+}]$ i and in regulation of Na^+/Ca^{2+} exchange was thoroughly described in the excellent review by Brini and Carafoli [19].

By our study it has also been shown that both R and F modes of Na^+/Ca^{2+} exchange serve as common sensors not only for low concentrations of ouabain but also for other weak chemical and physical signals such

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as synaptical transmitters, their agonists and antagonists as well as for ionizing and non-ionizing radiation [20-25]. Meanwhile, cGMP-dependent F Na^+/Ca^{2+} exchange is more sensitive to aging and different factors than cAMP-dependent R Na^+/Ca^{2+} exchange [26-28]. It has been shown that the increase of lipid fluidity (~40%) by the involvement of non-metabolized decanoic fatty acid in neuronal membrane leads to cell swelling, which is accompanied by the increase of intracellular cGMP contents without changing intracellular cAMP level [3,29,30]. These data allow us to consider that the water uptake-induced elevation of cGMP is a primary metabolic response to water uptake. The study of the feedback effect of cGMP-dependent Na^+/Ca^{2+} exchange on cell hydration has shown that though Na^+/Ca^{2+} exchange functions in stoichiometry of $3Na^+$:$1Ca^{2+}$, the F Na^+/Ca^{2+} exchange has dehydration effect on brain tissue in young (healthy) animals, while in older (non-healthy) animals it has hydration effect. More detailed investigation of the nature of F Na^+/Ca^{2+} exchange on brain tissue dehydration has shown that in healthy animals the cGMP-dependent F Na^+/Ca^{2+}-induced cell dehydration is due to activation of Na^+/K^+ pump in result of $[Ca^{2+}]$ i decrease [15,18,27]. Thus, F Na^+/Ca^{2+} exchange activation has pain-relieving effect as on one hand it leads to inhibition of membrane excitability by activation of Na^+/K^+ pump through generation of water efflux from the cells and by membrane hyperpolarization, on the other hand it depresses synaptical signal transmission by decreasing $[Ca^{2+}]$ i [6,31-33]. In case of high $[Ca^{2+}]$ i (cell pathology) when the power of F Na^+/Ca^{2+} exchange is not enough to activate Na^+/K^+ pump, it leads to activation of water influx-induced generation of abnormal membrane discharge which stimulates high $[Ca^{2+}]$ i-induced activation of synaptical activity into CNS and generates pain sensation. Therefore, it is suggested that the inward water fluxes through the membrane serve as cellular primary mechanism for generation of pain signals.

This suggestion can be supported by the data on pain-relieving effect of hypertonic solution and the effects of the factors activating cGMP-dependent Na^+/Ca^{2+} exchange such as static magnetic field, NO donors (SNAP), mechanical vibration with infrasound frequency [22,25,34-36].

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