Review of: "Proton Mechanisms of Neurotransmission and Calcium Signalling for Impulse Initiation, Development, and Propagation"

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Potential competing interests: No potential competing interests to declare.

Giuliano Molinari's presented work on "Proton Mechanisms of Neurotransmission and Calcium Signaling for Impulse Initiation, Development, and Propagation" has all the scientific qualities to be published, as it concerns the enormous importance of the transfer of hydrogen ions across the membrane in the life processes of biologically important structures. Protons' action on the biological membrane is accompanied by:

- protons are involved in the energetic supply of the cell or of subcellular structures;
- alteration of the physicochemical characterization of the interphase of the living cell or subcellular structure, such as mitochondria, synaptosomes, etc.;
- transfer of information through ion channels and binding to specific receptors.

The author of the manuscript also talks about the possibility of protons to mediate the processes in the brain affecting its higher function, cognition. In this case, according to my opinion, their action also depends on other environmental factors that can affect the membrane of the nerve cells, the factors changing the “pH” of the nerve cell's surrounding medium, including the physical factors: light, elevated temperature due to some inflammatory processes, low energy fields, as well as constant magnetic fields.

Scientific developments in recent years speak about the state of brain activity and functional activity of mitochondria. The transfer of protons actually determines the main function of the mitochondria, which is to produce the macroergic compound ATP, which is used as a "universal currency of exchange" for the energetic needs of the living cell. Namely, in the oxidation processes occurring in the mitochondria, hydrogen is removed from the substrates of biological oxidation and carried to the components of the respiratory chain located in the inner mitochondrial membrane. The hydrogen atom splits into protons and electrons, which are transmitted along the respiratory chain to oxygen, and water is produced. Protons are "pumped" through so-called "proton pumps" on the other side of the membrane. As a result, polarization occurs, and a membrane potential develops. The energy released by the removal of this potential with the participation of the ATP-synthase enzyme complex is accumulated in the form of the macroergic compound ATP. ATP leaves the mitochondria by being carried across the inner membrane with the assistance of a specific protein carrier. From the mitochondria, ATP is transferred to other departments of the cell and releases energy necessary for important processes such as biosynthesis, mechanical and osmotic work, muscle contraction, nerve impulse generation, active transport, transmission of genetic information, etc. The conduction of protons along the surface of a phospholipid-water interface is considerably faster than

the proton conduction in the bulk phase [*Teissié, J., Prats, M., Soucaille, P., Tocanne, J.F. Evidence for conduction of protons along the interface between water and polar lipid bilayer. Proc. Natl. acad. Sci. USA, 82, 3217, 1985; Gabriel, B., Teissié, J. Proton long-range migration along protein monolayers and its consequences on membrane coupling. Proc. Natl. acad. Sci. USA, 93, 14521, 1996*]. According to Teissié and colleagues, the enhanced lateral proton movement occurs along a hydrogen-bonded network on the membrane surface in accordance with the mechanism previously proposed by Onsager [*Onsager, L. The motion of ions: principles and concepts. Science. 166, 1359, 1969*] for proton conduction in ice crystals and by Nagle and Morowitz [*Nagle, J.F., Morowitz, H.J. Molecular mechanisms for proton transport in membranes. Proc. Natl. acad. Sci. USA, 75, 298, 1978*] for proton translocation in membranes. As a result, protons move considerably faster on the membrane surface on the membrane surface than expected by classical diffusion. A similar mechanism was used to explain proton diffusion in the bulk phase, which is considerably faster than the diffusion of ions of comparable size in the same medium due to a “hop-and-turn” mechanism. The other reason could be the increased surface concentrations of protons as compared to the bulk concentrations caused by a negative surface potential. The negative surface potential is due to the net surface charges of the phospholipid polar head-groups. Nature usually solves problems by recruiting and mobilizing every possible molecular interaction [*Hong, F.T. Molecular Electronic Switches in Photobiology, 134, 2004, CRS Handbook of Organic Photochemistry and Photobiology, 2nd edition, Press LLC; Hong, F.T. The enigma of creative problem solving, in Molecular Electronics: Bio-sensors and Bio-computers, Barsanti, L., Evangelista, V., Gualtieri, P., Passarelli, V., Vesti, S. (Eds.), Kluwer, Dordrecht, 2003, p. 457*].

Using the properties of the protons and their conduction through the proton channels, it becomes possible to bring them into the state of "switch on" under the influence of physical factors in the environment around the cell. Whether it is possible for the properties of protons to reach the property of the brain, which is "fault tolerant" to the characteristics of artificial intelligence, can be proved by scientific research. Numerous scientific results in this field can build on the deterministic procedure for information processing and be of assistance to information technology.