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Opening Address to the Symposium "Water Channel Proteins: from their Discovery in 1985 in Romania to the 2003 Nobel Prize in Chemistry and their Implications in Molecular Medicine Systems"

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ABSTRACT

The symposium will give an overview of the field of water channel proteins (WCPs). Firstly, a historical perspective of the development of this field, from the discovery of the first such protein in the red blood cell membrane to recently identified WCPs will be presented. Secondly, a description of the way in which solving the three dimensional structure of some WCPs lead to a better understanding of their function in molecular terms. Thirdly, recently identified roles of WCPs in selected systems (red blood cells, lens fibers, corneal endothelium, kidney proximal tubules, insect upper malpighian tubules, cardiac muscle) will be discussed. The methods (including original ones) and the interesting results obtained will be illustrated by studies on rabbit kidney proximal tubules, by expression of water channels in *Xenopus* oocytes, by freeze-fracture-labeling of AQP0, by applying electron and X-ray crystallography in studies of AQP0 and AQP1, by a mathematical model of electrolyte and fluid transport across corneal endothelium, or by the use of monoclonal antibodies for immunological detection of cell membrane WCPs on animal and plant tissues. Finally, as selected examples of the pathological implications of WCPs the membrane defects affecting water permeability in epilepsy and Duchenne muscular dystrophy will be described.

Keywords: water channel proteins, aquaporins, red blood cells, kidney, corneal endothelium, cardiac muscle, monoclonal antibodies, fluid transport, epilepsy, Duchenne muscular dystrophy.

1.THE FIRST OBJECTIVE OF THE SYMPOSIUM

The symposium of the development, evolution, of will give an overview of of one of the hottest fields of cell and molecular biology namely that of water channel proteins (WCPs) and will discuss their structure-function relationships with medical applications This will be achieved by choosing several objectives. The first objective will be to provide a historical perspective of the field, as reviewed in ref [1]. The milestones in WCP discovery will be presented: the idea of hydrophilic pores in the red blood (RBC) membrane for passage of water and ions [2, 3], the inhibitory action of mercurials on water flow through aqueous channels (pores) [4], the first experiments aimed at associating water channels with specific membrane proteins using radioactive-sulfhydryl labeling methods [5,6] suggesting that band 3 (according to the nomenclature of Fairbanks et al. [7]) is involved in water transport, discovery of the first water channel protein in the RBC membrane [8,9]. The protein (also found in the kidney) was purified by chance by the group of Agre [10], who later found its water transport property [11]. This WCP was called initially CHIP28 and later [12] aquaporin 1 (AQP1). The development of the field will include presentation of some of the recently identified members of the WCP superfamily (an example being the Rp-MIP from insect upper malpighian tubules).

2. OTHER OBJECTIVES OF THE SYMPOSIUM

The second objective will be to describe how the present knowledge of the high resolution three dimensional structure of some WCPs lead to a better understanding of their function in molecular terms, such as comparative studies of aquaporin 0 (AQP0) and AQP1 structure and water transport properties. These studies indicate that the dynamic movements of the key residues establishing the narrowest regions of the channel, believed to prevent waters from moving through the channel are sufficient to allow water permeation across these regions. Original hypotheses such as the "indirect sodium-water coupling" hypothesis of cell volume regulation in cardiac muscle and others will also be presented.

The third objective will be to present known or recently identified structural and physiological roles of WCPs in selected systems (cells, tissues and organs). Examples of such systems include red blood cells, lens fibers, corneal endothelium, kidney proximal tubules, insect upper malpighian tubules, cardiac muscle. In order to achieve the understanding of the physiological roles of WCPs in these systems a variety of methods have been used.

Among those that will be discussed are: comparative nuclear magnetic resonance measurements of water transport across the membrane of red blood cells from various animal species, original methods to measure the very high water permeability of rabbit kidney proximal tubules, expression of water channels in *Xenopus* oocytes, freeze-fracture-labeling, a method whereby the individual AQP0 channels are labeled with antibody gold complexes, structures of AQP0 and AQP1 determined by electron and x-ray crystallography, a mathematical model of electrolyte and fluid transport across corneal endothelium (allowing to compare predictions of translayer fluid transport by two competing theories, electro-osmosis and local osmosis), the use of monoclonal antibodies for immunological detection of cell membrane WCPs on mammalian, non mammalian, and plant tissues (e.g. monoclonal anti-AQP1 and anti-AQP4 antibodies as tools both in examinations on formaldehyde fixed and paraffin embedded tissue samples)

Closely linked to the methodological approach is also the presentation of original hypotheses such as the "indirect sodium-water coupling" hypothesis of cell volume regulation in cardiac muscle and others.

Finally, an objective linked with all those mentioned above, will be to present selected examples of the pathological implications of WCPs. Again, the historical perspective will be combined with present knowledge. As an example the membrane defects affecting water permeability in epilepsy and Duchenne muscular dystrophy will be described from their first discovery to the recent understanding of the involvement of AQP4 in the cellular and molecular mechanisms of these diseases.

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