

Introduction to Mini-Reviews on H^+/OH^- Permeability Through Membranes

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Mechanisms for the transport of protons and/or hydroxide (H^+/OH^-) across biological membranes are of fundamental importance to various bioenergetic coupling processes, regulation of intracellular pH, and the creation of localized compartments of acidic (or basic) pH. The means for H^+/OH^- transport always involve highly specialized membrane proteins through which transmembrane H^+/OH^- flow is coupled to some other chemical reaction and/or ionic flow. Purely passive leakage of H^+/OH^- represents counterproductive flow that reduces the efficiency of the biologically directed transport. In this context, it was surprising when Nichols and Deamer (1980) first reported in 1980 that passive H^+/OH^- permeability, or H^+/OH^- conductance, measured near neutral pH in phospholipid vesicles was at least 5 orders of magnitude higher than for other small cations and anions. This finding generated considerable controversy and was pursued by studies from a number of laboratories seeking an explanation for the anomalous H^+/OH^- permeability, using alternative methods and various membrane preparations.

The present series of articles reviews the phenomenon of passive H^+/OH^- leakage, or conductance, in a variety of membrane systems, including phospholipid vesicles, phospholipid bilayers, and biological membranes. Independent of the method or membrane system used, all authors support the original Nichols and Deamer observation: that the absolute magnitude of transmembrane flux of H^+/OH^- is not high, but because of the low concentration of H^+ and OH^- near pH 7, the calculated H^+/OH^- conductance through the phospholipid matrix is anomalously high compared to other small ions. This underscores another characteristic feature, systematically studied by Gutknecht (1984), that H^+/OH^- conductance varies by no more than a factor of 10 over the enormous range of H^+/OH^- concentration from pH 1 to 11. However, while the consensus clearly supports a distinctively high H^+/OH^- conductance of artificial and biological membranes

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that cannot be explained by diffusion through water-filled channels, there is not similar agreement in providing an explanation for the anomaly. In this series, two possible mechanisms are suggested as the authors review the experimental evidence demonstrating the unique characteristics of H^+/OH^- permeability, and test proposed mechanisms for observed behavior.

In the first article, Dave Deamer reviews the unique features of proton permeation across lipid bilayers. He marshalls support for a concept that chains of hydrogen-bonded water molecules ("water wires") within the hydrophobic region of the membrane provide a pathway for protonic conduction. This concept was originally proposed in 1980 by Nichols and Deamer; in the present article, Deamer uses the gramicidin A channel as a model whereby protons may flux via a mechanism of hopping along a continuous chain of water molecules within the spatially restricted channel.

John Nagle's article presents a discussion of the state and form in which water might exist within phospholipid membranes. Three models that employ transient hydrogen-bonded chains of water are identified as a means for translocating protons. These models are distinguished conceptually, and kinetic predictions are given that might be applied to experiments in membranes.

In the article by John Gutknecht, an alternative view is examined, that the high H^+/OH^- conductance values are the result of weakly acidic contaminants that act as proton carriers, or protonophores. Gutknecht uses the planar phospholipid bilayer as a model system for a battery of tests which include predictions from the application of proposed inhibitors or enhancers of H^+/OH^- conductance. He concludes that contaminating protonophores can explain much of the conductive data, but that additional mechanisms, such as "water wires" or "hydrated defects," may be operative as a basal H^+/OH^- conductance.

Walter Perkins and David Cafiso provide a thorough description of H^+/OH^- conductivity measurements in pure phospholipid vesicles using spin probes to measure membrane potentials and calculate net protonic flows across the membrane. They examine the influence of intrinsic physical properties, such as membrane dielectric constant and internal dipole potential, on H^+/OH^- flows across phospholipid vesicles. Consistent with what Gutknecht reported for planar bilayers, the conduction of H^+ or OH^- appears to be positively correlated with changes in membrane dielectric constant. However, results with modulation of membrane dipole potential appeared to be dependent upon the phospholipid system used for measurement, vesicular or planar, and this may have implications toward interpreting the mechanism of H^+/OH^- conductance.

The article by A. S. Verkman reviews methodology and measurements of H^+/OH^- permeability in biological membranes, particularly in epithelial

brush border membrane vesicles. For biological membranes it is necessary to carefully distinguish passive H^+/OH^- leakage from proton flux occurring through one of the protein-mediated processes. In renal proximal tubule brush border vesicles, the characteristics of passive H^+/OH^- permeability are similar to those for pure phospholipid bilayers. However, Verkman contrasts this behavior with that observed in brush border vesicles from human placenta, in which a transmembrane, modulatable protein contributes to passive H^+/OH^- conductance.

References

- Nichols, J. W., and Deamer, D. W. (1980). *Proc. Natl. Acad. Sci.* **78**, 4324–4328.
Gutknecht, J. (1984). *J. Memb. Biol.* **82**, 105–112.