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Visualizing Proton Conductance in the Gramicidin Channel

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In this month's *Biophysical Journal*, Pomes and Roux (1996) provide a molecular dynamics simulation of protonic conductance along a single strand of hydrogen-bonded water in the gramicidin channel. This result complements an earlier report by Sagnella and Voth (1996) and is significant because protons do not depend on diffusion alone to move through aqueous media. Instead a proton can hop along chains of hydrogen-bonded water molecules, so that the measured ionic mobility of protons in water is several times higher than that of sodium or potassium ions. Proton conduction by hopping along water chains was first proposed by Hladky and Haydon (1972) to explain the anomalously high proton conductance through the gramicidin channel, which is approximately 15 times that of potassium ions.

Although proton conductance through the gramicidin channel is intrinsically interesting, it may also provide a useful model system for biological systems of more general interest. The term "proton wire" was coined by Nagle and Morowitz (1978) to describe possible proton conductance pathways in proteins in which hydrogen-bonded side chains of amino acids could provide pathways for protons. Although a proton wire composed purely of amino acid side chains has not yet been discovered, there are now a number of proposed protonic conductance processes in which water molecules are likely to be involved. For instance, proton conductance along water chains in proteins has been proposed for bacteriorhodopsin and bacterial reaction centers (see Pomes and Roux, this issue, for references) and the F_1Fo ATP synthase (Schulten and Schulten, 1985; Akeson and Deamer, 1992). It is here that the new molecular dynamics simulations will be most useful in guiding further research. Pomes and Roux show that protons in the channel are present as $O_2H_5^+$, rather than OH_3^+. Furthermore, a proton strongly orients the water in the channel and moves within the water by a semi-collective transfer mechanism, rather than by random diffusion or a highly coordinated process. Proton translocation is limited by the hydrogen bonds between water molecules and polar groups on the sides of the channels. If the hydrogen bonding forces are turned off in the simulation, proton mobility increases dramatically. Taken together, these results provide a new conceptual framework to investigate mechanisms by which proteins conduct protons as part of their function.

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Slow Inactivation of Sodium Channels: More Than Just a Laboratory Curiosity

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Sodium currents are usually regarded as fast transients. In response to depolarization, channels open but then rapidly close within a millisecond to an inactive state. Repolarization of the membrane is necessary to reprime channels for subsequent depolarization-induced opening. The recovery from inactivation is voltage dependent and, after brief depolarizations, occurs within 10 ms or so at the resting potential of excitable cells (−70 to −90 mV). This orchestrated sequence of rapid voltage-dependent changes in sodium channel conformation produces many of the salient features of an action potential: fast upstroke of the depolarizing phase (activation), termination of depolarization (inactivation), and the refractory period (recovery from inactivation), as originally described so elegantly by Hodgkin and Huxley.

In addition to these rapid gating transitions, sodium channels undergo very slow voltage-dependent shifts in availability for opening, on a time scale of seconds to minutes. In this issue of the *Biophysical Journal*, Cummins and Sigworth (1996) show that slow inactivation is impaired in a mutant form of the skeletal muscle sodium channel that causes the hereditary muscle disorder hyperkalemic periodic paralysis (HyperPP). This result may be the key to a previously unanswered question about the mechanism of the prolonged episodes of weakness in HyperPP (Ruff, 1994) and provides the first direct evidence for a potential physiological role of slow inactivation.

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