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Sandia Research on Ion Channels Wins Federal Laboratory Consortium Recognition

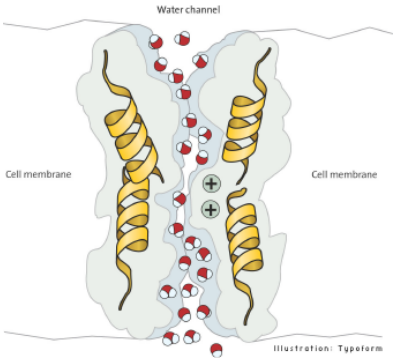
Challenge

All cells must manage their internal and to some extent their external environments. Part of this management involves controlling the concentration of dissolved ions (salts) such as sodium (Na^+), potassium (K^+), and Calcium (Ca^{2+}), all of which are critical for cellular functioning, at concentrations that the cells must regulate. A key methodology for this regulation entails the use of ion channels. These are proteins that span the thickness of the cell's outer membrane (as well as certain internal membranes) and which form molecular pores that are specific to the passage of a certain ion or small molecule (such as water). Under the influence of either receptors for hormones, hormone-like substances, and neurotransmitters, so-called receptor-gated ion channels can shape-shift to open their pore (or "gate"), allowing a specific ion to flow through a membrane. For example, the effects of a hormone like adrenaline (epinephrine) depend, in part, on the triggering of the gate-opening of a channel for calcium (Ca^{2+} ions). The same is true of so-called voltage-gated ion channels, but in their case, the stimulus for gate opening is a change in the voltage across a local area of the cell membrane. The nerve impulse depends on such voltage-gated sodium (Na^+) ion channels.

Because ion channels are key players in biological processes, the pharmaceutical industry has developed drugs that target specific ion channels. For example, to lower blood pressure, a class of drugs known as calcium channel blockers reduces the strength of heart-muscle contraction triggered by the movement (flux) of calcium ion through its channels and into heart-muscle cells.

The challenge in this research was to understand the detailed chemistry that conveys ion-specificity to biological ion channels, as well as the detailed biochemical changes in the protein channel that open its gate allowing ions to flow through. Ultimately, the goals were first, to attempt to produce—via nanoengineering— inorganic mimics of the protein channels, and second, to apply that understanding in selected biological situations.

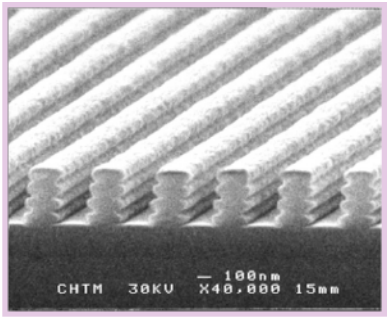
Research



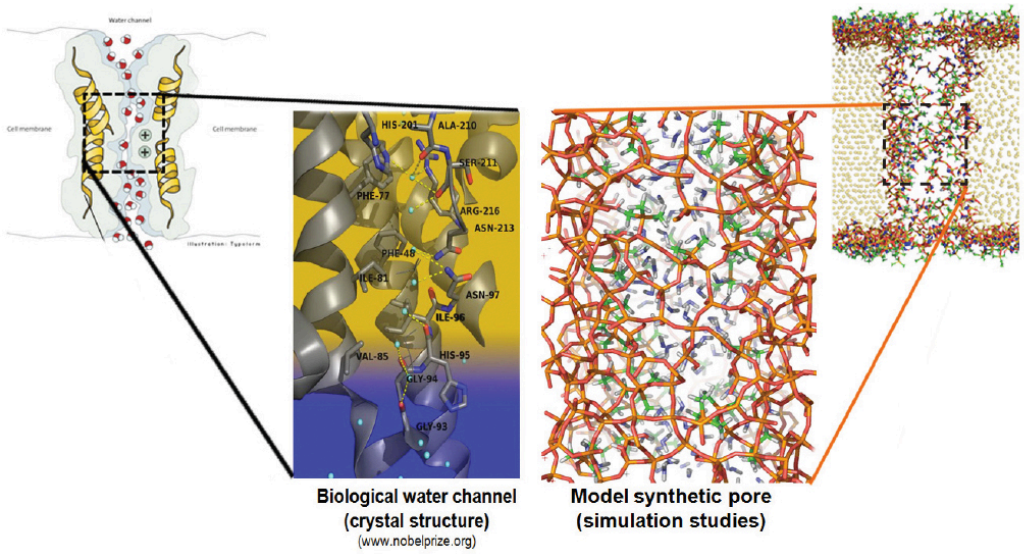
The research initially focused on water channels (aquaporins), whose importance is underscored by the diminishing supplies of fresh water on earth and by the need for new technologies to separate water from dissolved substances, both contaminant toxins and salts (as in the desalination of seawater). At the cellular level, aquaporins accomplish this feat by allowing water to traverse cell membranes while excluding ionic salts.

Drawing of the pore through the cell membrane formed by the structure of an aquaporin protein channel

A combination of sophisticated chemistry and molecular modeling allowed for a more thorough understanding of biological channels and the chemistry that they use in selectively excluding all but the relevant molecule or ion from binding to and traversing their channel. With this understanding in hand, principal investigator Susan Rempe and her collaborators initiated the nanoengineering of inorganic nanochannels in silica, in an attempt to produce new methods of purifying water. This resulted in an R&D100 Award-winning technology that combined the production of parallel nanochannels etched into silica with chemical modification to mimic the chemistry by which biological aquaporins allow passage of water molecules while excluding salts (ions). This technology holds the promise of a whole new class of reverse osmosis "membranes," reducing the energy needed to purify salt water by an order of magnitude. Hence, a careful analysis and modeling of the biological solution to this issue, together with clever synthetic chemistry to replicate and apply it to inorganic silica nanochannels, has been incredibly fruitful. On that basis alone, the Federal Laboratory Consortium Award to Rempe and co-workers is well earned.



Parallel nanochannels etched into silica



Comparison of the biological pore in an aquaporin protein (left) with that of a chemically engineered synthetic pore, a chemically modified silica nanochannel (right).

Rempe next turned to potassium channels, beginning with the chemical basis for allowing the passage of K^+ through the channel while, somewhat counterintuitively, excluding the slightly smaller Na^+. Although there are many varieties of K^+ channel among the different cells of the human body, this research focused on those regulating the innate immune response—the more evolutionarily primitive portion of the immune system that responds quickly and relatively nonspecifically to invasion by bacteria. For example, all bacteria of the gram-negative variety possess a molecule, lipopolysaccharide (LPS), that triggers

this innate response by activating scavenging white blood cells known as macrophages. This immune response includes a component of inflammation (by which blood vessels are "opened up" to the passage of these bacteria-scavenging white blood cells from blood into tissues where bacteria are located). Using a combination of fluorescently labeled probes and electrophysiology, the research identified potassium channels in macrophages that are involved in mediating their activation by bacterial LPS. In addition to providing a new drug target for pharmaceutical intervention in this immune-response component, the work also clarified the relationship between channel structure and activity (its gating of the flux of K^+ through the cell membrane).

Significance

First and foremost, the research demonstrated that a combination of nanoengineering and chemical mimicry of biological protein channels can be fruitful in designing functional devices. By using "evolution's wisdom," such research can improve on the efficiency of man-made technology, in this case in designing more-efficient water-purification technology. In addition, the insight's into structure-function relationships in the complex structural protein convolutions in ion channels and the applications to the immune response offer a fundamental insight into the early immune response, as well as opportunities to constructively manipulate it.

For More Information:
http://www.sciencedirect.com/science/article/pii/S0006349509045020

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