Researchers Find Way to 'See' Water Molecules Hidden Inside Proteins

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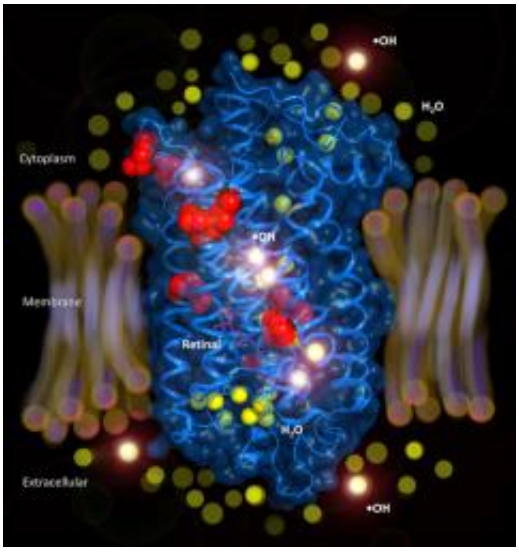

Radiolytic footprinting of the membrane bound G-protein coupled receptor rhodopsin demonstrates the structural activation of bound waters as a function of receptor signaling status. X-rays ionize water molecules inside and outside the membrane protein structure to radicals (-OH, glowing spheres) that react with adjacent amino acid side chains. As the protein changes its structure during signaling, the pattern of reactivity of water within the protein changes reflecting the transmission of the signal through the membrane.

(PhysOrg.com) -- A team of researchers from Case Western Reserve University has discovered a way to look at water molecules hidden deep inside proteins, revealing a network through which information flows when proteins are switched "on."

Their results were published in the August 25, 2009 issue of the Proceedings of the National Academy of Sciences.

The team looked inside rhodopsin, the protein found in the retina at the back of the eye that is responsible for dim light perception. Rhodopsin is a member of a group of proteins called the G-protein coupled receptor (GPCR) superfamily, which physically change shape when turned "on," leading to interactions with other proteins and sending information across cell membranes to regulate many important molecular pathways. Rhodopsin is switched on by light, causing it to change shape and start a series of molecular events that makes night vision possible.

"No one really knows how these molecular pathways send information," said Sayan Gupta, co-author of the study, an instructor at Case Western Reserve University, and an NSLS beamline scientist. "We think that water has an important role and maintains the protein's structure and regulates its dynamics. Now, we have a method to probe the water molecules deep inside proteins using x-rays."

The research team combined two techniques to investigate water's role in the protein's shape shifting: radiolytic protein footprinting and mass spectrometry.

"We focused intense x-rays from the X28C beamline on rhodopsin preparations that were either turned on or off," said Gupta. "This powerful technique creates hydroxyl radicals from the water molecules, which then chemically modify nearby amino acids inside the protein."

The researchers detected the chemical modifications using mass spectrometry and created molecular maps showing where water molecules sit inside the protein when it was off and on. They found that the water molecules rearranged in response to the protein being turned on and interacted with key areas necessary for the protein's function.

"Water's hydrogen bonding allow these proteins a certain plasticity and the ability to take on multiple shapes," said Thomas Angel, co-author of the study and former post-doctoral scholar at Case Western Reserve University.

"Water makes an electrostatic network within these proteins," added Gupta. "The network can break apart, change, and then form a new network, which mediates the flow of information from one side of the protein to the other across the cell membrane."

Genetic mutations within the regions of the protein found to associate with water are known to cause diseases. For example, mutations in these areas of the rhodopsin protein cause a type of genetic night blindness that often leads to complete vision loss.

GPCRs are also the gatekeepers that jumpstart many other biological responses, such as the flight or fight response, mood, and even heart function.

"Water's role in rhodopsin's activation is quite possibly shared by other members of the GPCR superfamily," said Angel. "GPCRs are very important pharmaceutical targets given they create a large signal amplification effect for many different signaling pathways. This superfamily represents an important biomedical target given around 50 percent of pharmaceutical drugs on the market target these proteins. If we know how to turn these proteins and signaling pathways on and off, we can have a large-scale impact on biological response."

More information: T.E. Angel, S. Gupta, B. Jastrzebska, K. Palczewski and M.R. Chance, "Structural waters define a functional channel mediating activation of the GPCR rhodopsin," PNAS, 106 (34), 14367-72 (2009).

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