What Gives an Insulin Hexamer Its Unique Shape and Stability? Role of Ten Confined Water Molecules

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What Gives an Insulin Hexamer Its Unique Shape and Stability? Role of Ten Confined Water Molecules

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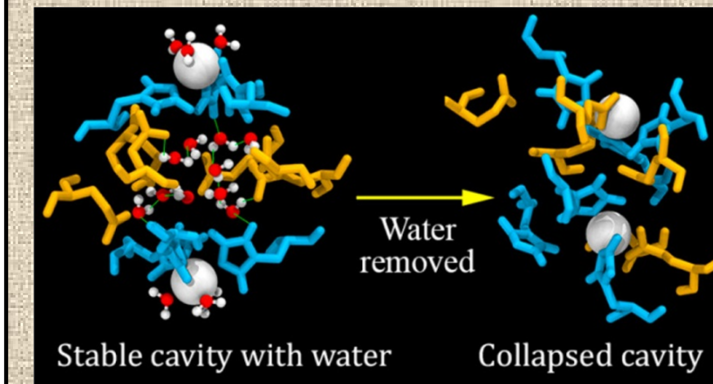

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Insulin falls apart without water

Computer simulations show water holds the insulin hexamer together

By Sam Lemonick

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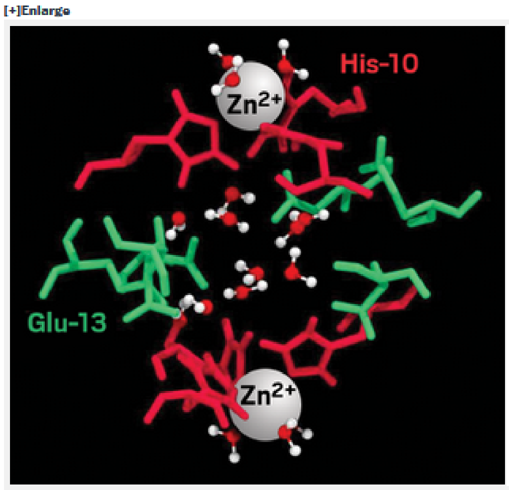
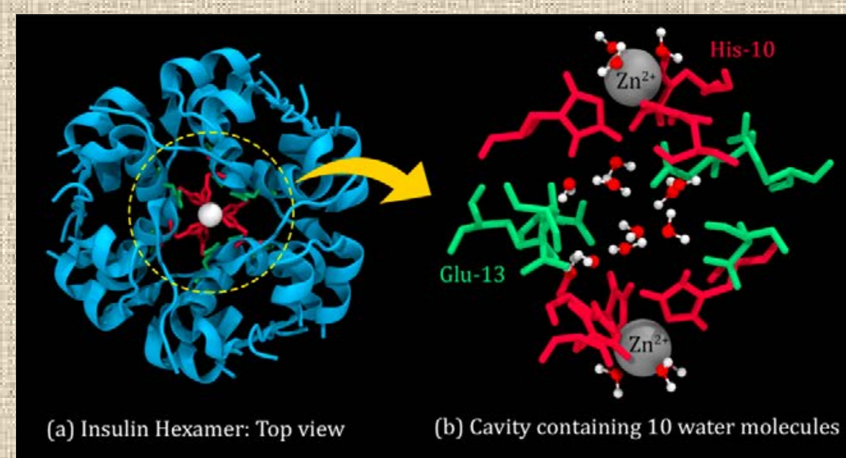


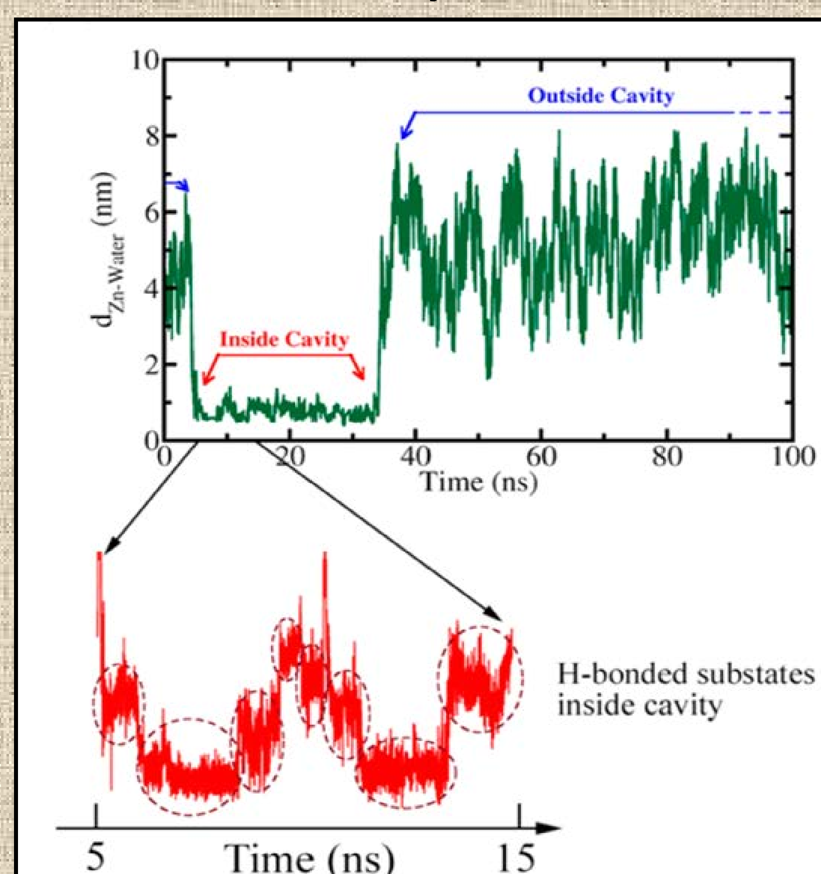
Two zinc cations and ten water molecules stabilize the interior cavity of the insulin hexamer.

Credit: *J. Phys. Chem. B*

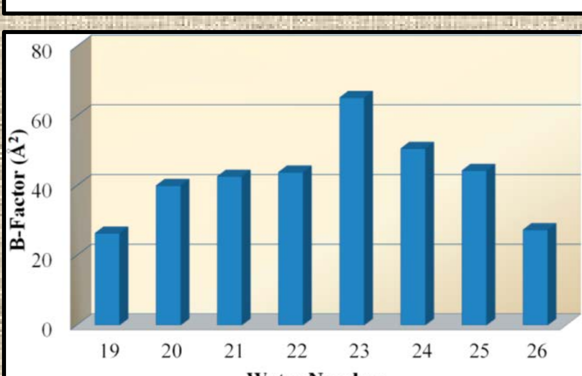
Computer modeling suggests that water molecules play a key role in stabilizing insulin for storage in the body, according to a study (*J. Phys. Chem. B*2018, **DOI: 10.1021/acs.jpcb.8b00453**). Insulin is bioactive as a monomer, but it is stored in the pancreas in groups of six, coordinated around two zinc cations. X-ray crystallography analysis by **Biman Bagchi** and colleagues at the Indian Institute of Science paired with computer simulations revealed that water molecules, about 10 on average, are also present in an interior cavity of the hexamer. So they set out to determine what function, if any, these water molecules play. The group performed atomistic molecular dynamics simulations of the hexamer, zinc cations, and water molecules. They found that three water molecules and three histidine residues coordinate to each of the cations in an octahedral arrangement. Other water molecules enter and leave the cavity, but the simulation showed that these molecules stay fixed nearly in place while inside the hexamer. The study identified an average of 15 hydrogen bond interactions between the 10 water molecules in the cavity, as well as bonds to peptide residues. The group likens the water molecules to a backbone in the hexamer. Next, the researchers simulated the hexamer and zinc cations in the absence of water molecules. That led to new interactions between the cations and peptide residues, and the hexamer cavity collapsed within picoseconds. They did not test the hexamer with other cations, such as calcium, which are seen in nature. Bagchi says this new understanding of water's role could help explain how the hexamer breaks apart to deliver monomeric insulin. It may also help protect insulin in pharmaceuticals against aggregation, which renders it useless. In the body, the hexamer not only serves as a stable way to store insulin, but it also prevents the monomeric form from aggregating.



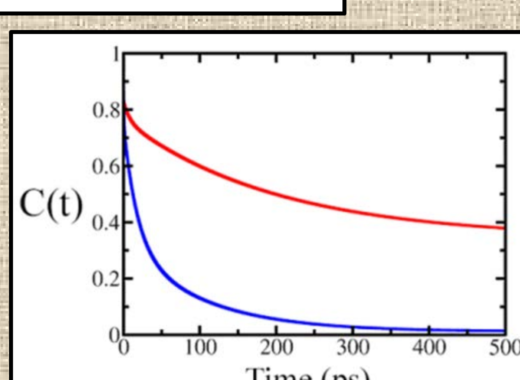
Insulin hexamer Cavity: 10 water molecules



Intermittent entrance and escape of water from cavity



B-factor of cavity water



Slow Hydrogen Bond dynamics inside cavity

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