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Structural basis for glycerol conductance and selectivity of human aquaporin 7

Content

Lipid metabolism of triglycerides in adipocytes serves as our main source for storing and retrieving energy. The triglycerides are broken down into glycerol and free fatty acids in lipolysis, and glycerol exit the cell via the aquaglyceroporin aquaporin 7 (AQP7) to be available for gluconeogenesis. In this study we investigated the glycerol conductance and selectivity of AQP7 by solving the structure of human AQP7 using x-ray crystallography to 1.9 Å resolution in the presence of glycerol, and carrying out molecular dynamics simulations of glycerol and water passage. Glycerol molecules were observed in the AQP7 structure both with the hydroxyl groups facing the hydrophilic side of the pore, which is also seen in other aquaglyceroporin structures, and also facing the hydrophobic side, unique for AQP7. These observations support a conducting mechanism in which rotation of the glycerol molecule serves to break hydrogen bonds that releases glycerol from more tightly bound positions and thus facilitating its transition along the pore. In molecular dynamics simulations, the lack of complete unbinding and spontaneous binding of glycerol at the millisecond timescale and a 2-4 times lower water permeability in the presence of glycerol suggest a high glycerol affinity and that high water permeation is hindered by glycerol. AQP7 is an interesting target for drug development as AQP7-deficiency in mice is linked to obesity and diabetes, and increased adipocyte lipolysis and subsequent glycerol release is observed in tumor microenvironments. Our observations provide a framework for understanding the mechanism of glycerol transport over the plasma membrane in adipocytes.

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