Araya-Secchi *et al. BMC Genomics* 2011, **12**(Suppl 4):S8
http://www.biomedcentral.com/1471-2164/12/S4/S8

BMC Genomics

PROCEEDINGS **Open Access**

Molecular dynamics study of the archaeal aquaporin AqpM

Raul Araya-Secchi[1,2*], JA Garate [1,3], David S Holmes[2,4], Tomas Perez-Acle[1,4]

From 6th International Conference of the Brazilian Association for Bioinformatics and Computational Biology (X-meeting 2010)
Ouro Preto, Brazil. 15-18 November 2010

Abstract

Background: Aquaporins are a large family of transmembrane channel proteins that are present throughout all domains of life and are implicated in human disorders. These channels, allow the passive but selective movement of water and other small neutral solutes across cell membranes. Aquaporins have been classified into two sub-families: i) strict aquaporins that only allow the passage of water and ii) the less selective aquaglyceroporins that transport water and other neutral solutes, such as glycerol, CO_2 or urea. Recently, the identification and characterization of a number of archaeal and bacterial aquaporins suggested the existence of a third sub-family; one that is neither a strict aquaporin nor an aquaglyceroporin. The function and phylogeny of this third family is still a matter of debate.

Results: Twenty nanosecond molecular dynamics (MD) simulation of a fully hydrated tetramer of AqpM embedded in a lipid bilayer permitted predictions to be made of key biophysical parameters including: single channel osmotic permeability constant (p_f), single channel diffusive permeability constant (p_d), channel radius, potential water occupancy of the channel and water orientation inside the pore. These properties were compared with those of well characterized representatives of the two main aquaporin sub-families. Results show that changes in the amino acid composition of the aromatic/arginine region affect the size and polarity of the selectivity filter (SF) and could help explain the difference in water permeability between aquaporins. In addition, MD simulation results suggest that AqpM combines characteristics of strict aquaporins, such as the narrow SF and channel radius, with those of aquaglyceroporins, such as a more hydrophobic and less polar SF.

Conclusions: MD simulations of AqpM extend previous evidence that this archaeal aquaporin exhibits hybrid features intermediate between the two known aquaporin sub-families, supporting the idea that it may constitute a member of a novel class of aquaporins.

Background

Aquaporins are a large family of transmembrane channel proteins that are present throughout all domains of life and their malfunction has been implicated in several human disorders [1]. Aquaporin channels allow the passive but selective movement of water and other small neutral solutes such as glycerol, CO_2, or urea across cell membranes [1-4].

Structurally, Aquaporins present a homotetrameric organization in which each monomer forms an individual functional pore. The canonical fold of the aquaporin monomer is characterized by a right-handed helical bundle of six transmembrane α-helices (TM1 – TM6) connected by 5 loop regions (loops A to E), in which both amino and carboxyl termini face the cytoplasmic side of the membrane. Loops B and E are formed by a half-membrane spanning helical section (HB and HE respectively) and a non-helical section that

---

* Correspondence: raul@dlab.cl
[1]Computational Biology Laboratory, Centro de Modelamiento Matematico, Facultad de Ciencias Fisicas y Matematicas, Universidad de Chile, Santiago, Chile
Full list of author information is available at the end of the article

RAS is a CONICYT fellow. This work was partially funded by CONICYT (PFB16 and PFB03), Fondecyt 1090451 and supported by the High Performance Computing infrastructure of the National Laboratory for High Performance Computing (NLHPC) &#8220Powered@NLHPC&#8221.
This article has been published as part of *BMC Genomics* Volume 12 Supplement 4, 2011: Proceedings of the 6th International Conference of the Brazilian Association for Bioinformatics and Computational Biology (X-meeting 2010). The full contents of the supplement are available online at http://www.biomedcentral.com/1471-2164/12?issue=S4

Author details

[1]Computational Biology Laboratory, Centro de Modelamiento Matematico, Facultad de Ciencias Fisicas y Matematicas, Universidad de Chile, Santiago, Chile. [2]Facultad de Ciencias Biologicas, Universidad Andres Bello, Santiago, Chile. [3]School of Chemical and Bioprocess Engineering, University College Dublin, Dublin 4, Ireland. [4]Fundacion Ciencia para la Vida, Santiago, Chile.

Authors' contributions

The experimental work was carried out by RAS and JG. DH and TPA conceived the project. The paper was written by RAS with input from TPA and DH. All authors helped interpret the results and read and approved the paper.

Competing interests

The authors declare that they have no competing interests.

Published: 22 December 2011

References

1. Borgnia M, Nielsen S, Engel A, Agre P: **Cellular and molecular biology of the aquaporin water channels.** *Annu Rev Biochem* 1999, **68**:425-458.
2. Preston GM, Carroll TP, Guggino WB, Agre P: **Appearance of water channels in Xenopus oocytes expressing red cell CHIP28 protein.** *Science* 1992, **256(5055)**:385-387.
3. Agre P, Bonhivers M, Borgnia MJ: **The aquaporins, blueprints for cellular plumbing systems.** *J Biol Chem* 1998, **273(24)**:14659-14662.
4. Kruse E, Uehlein N, Kaldenhoff R: **The aquaporins.** *Genome Biol* 2006, **7(2)**:206.
5. Preston GM, Jung JS, Guggino WB, Agre P: **Membrane topology of aquaporin CHIP. Analysis of functional epitope-scanning mutants by vectorial proteolysis.** *J Biol Chem* 1994, **269(3)**:1668-1673.
6. Walz T, Smith BL, Agre P, Engel A: **The three-dimensional structure of human erythrocyte aquaporin CHIP.** *EMBO J* 1994, **13(13)**:2985-2993.
7. Walz T, Hirai T, Murata K, Heymann JB, Mitsuoka K, Fujiyoshi Y, Smith BL, Agre P, Engel A: **The three-dimensional structure of aquaporin-1.** *Nature* 1997, **387(6633)**:624-627.
8. Heymann JB, Engel A: **Aquaporins: Phylogeny, Structure, and Physiology of Water Channels.** *News Physiol Sci* 1999, **14**:187-193.
9. de Groot BL, Heymann JB, Engel A, Mitsuoka K, Fujiyoshi Y, Grubmuller H: **The fold of human aquaporin 1.** *J Mol Biol* 2000, **300(4)**:987-994.
10. Engel A, Fujiyoshi Y, Agre P: **The importance of aquaporin water channel protein structures.** *EMBO J* 2000, **19(5)**:800-806.
11. Stroud RM, Savage D, Miercke LJ, Lee JK, Khademi S, Harries W: **Selectivity and conductance among the glycerol and water conducting aquaporin family of channels.** *FEBS Lett* 2003, **555(1)**:79-84.
12. Gonen T, Walz T: **The structure of aquaporins.** *Q Rev Biophys* 2006, **39(4)**:361-396.
13. Beitz E, Wu B, Holm LM, Schultz JE, Zeuthen T: **Point mutations in the aromatic/arginine region in aquaporin 1 allow passage of urea, glycerol, ammonia, and protons.** *Proc Natl Acad Sci U S A* 2006, **103(2)**:269-274.
14. Froger A, Tallur B, Thomas D, Delamarche C: **Prediction of functional residues in water channels and related proteins.** *Protein Sci* 1998, **7(6)**:1458-1468.
15. Lagree V, Froger A, Deschamps S, Hubert JF, Delamarche C, Bonnec G, Thomas D, Gouranton J, Pellerin I: **Switch from an aquaporin to a glycerol channel by two amino acids substitution.** *J Biol Chem* 1999, **274(11)**:6817-6819.
16. Borgnia MJ, Kozono D, Calamita G, Maloney PC, Agre P: **Functional reconstitution and characterization of AqpZ, the *E. coli* water channel protein.** *J Mol Biol* 1999, **291(5)**:1169-1179.
17. Savage DF, Egea PF, Robles-Colmenares Y, O'Connell JD 3rd, Stroud RM: **Architecture and selectivity in aquaporins: 2.5 a X-ray structure of aquaporin Z.** *PLoS Biol* 2003, **1(3)**:E72.
18. Jung JS, Bhat RV, Preston GM, Guggino WB, Baraban JM, Agre P: **Molecular characterization of an aquaporin cDNA from brain: candidate osmoreceptor and regulator of water balance.** *Proc Natl Acad Sci U S A* 1994, **91(26)**:13052-13056.
19. Froger A, Rolland JP, Bron P, Lagree V, Le Caherec F, Deschamps S, Hubert JF, Pellerin I, Thomas D, Delamarche C: **Functional characterization of a microbial aquaglyceroporin.** *Microbiology* 2001, **147(Pt 5)**:1129-1135.
20. Engel A, Stahlberg H: **Aquaglyceroporins: channel proteins with a conserved core, multiple functions, and variable surfaces.** *Int Rev Cytol* 2002, **215**:75-104.
21. Braun T, Philippsen A, Wirtz S, Borgnia MJ, Agre P, Kuhlbrandt W, Engel A, Stahlberg H: **The 3.7 A projection map of the glycerol facilitator GlpF: a variant of the aquaporin tetramer.** *EMBO Rep* 2000, **1(2)**:183-189.
22. Jensen MO, Tajkhorshid E, Schulten K: **The mechanism of glycerol conduction in aquaglyceroporins.** *Structure* 2001, **9(11)**:1083-1093.
23. Lee JK, Khademi S, Harries W, Savage D, Miercke L, Stroud RM: **Water and glycerol permeation through the glycerol channel GlpF and the aquaporin family.** *J Synchrotron Radiat* 2004, **11(Pt 1)**:86-88.
24. Kozono D, Ding X, Iwasaki I, Meng X, Kamagata Y, Agre P, Kitagawa Y: **Functional expression and characterization of an archaeal aquaporin. AqpM from *Methanothermobacter marburgensis*.** *J Biol Chem* 2003, **278(12)**:10649-10656.
25. Mathai JC, Missner A, Kugler P, Saparov SM, Zeidel ML, Lee JK, Pohl P: **No facilitator required for membrane transport of hydrogen sulfide.** *Proc Natl Acad Sci U S A* 2009, **106(39)**:16633-16638.
26. Lee JK, Kozono D, Remis J, Kitagawa Y, Agre P, Stroud RM: **Structural basis for conductance by the archaeal aquaporin AqpM at 1.68 A.** *Proc Natl Acad Sci U S A* 2005, **102(52)**:18932-18937.
27. Borgnia MJ, Agre P: **Reconstitution and functional comparison of purified GlpF and AqpZ, the glycerol and water channels from *Escherichia coli*.** *Proc Natl Acad Sci U S A* 2001, **98(5)**:2888-2893.
28. Jensen MO, Mouritsen OG: **Single-channel water permeabilities of Escherichia coli aquaporins AqpZ and GlpF.** *Biophys J* 2006, **90(7)**:2270-2284.
29. Zhu F, Tajkhorshid E, Schulten K: **Theory and simulation of water permeation in aquaporin-1.** *Biophys J* 2004, **86(1 Pt 1)**:50-57.
30. Zhu F, Tajkhorshid E, Schulten K: **Collective diffusion model for water permeation through microscopic channels.** *Phys Rev Lett* 2004, **93(22)**:224501.
31. Hashido M, Kidera A, Ikeguchi M: **Water transport in aquaporins: osmotic permeability matrix analysis of molecular dynamics simulations.** *Biophys J* 2007, **93(2)**:373-385.
32. Hashido M, Ikeguchi M, Kidera A: **Comparative simulations of aquaporin family: AQP1, AQPZ, AQP0 and GlpF.** *FEBS Lett* 2005, **579(25)**:5549-5552.
33. Zhu F, Tajkhorshid E, Schulten K: **Pressure-induced water transport in membrane channels studied by molecular dynamics.** *Biophys J* 2002, **83(1)**:154-160.
34. Garate JA, English NJ, MacElroy JMD: **Human aquaporin 4 gating dynamics in dc and ac electric fields: A molecular dynamics study.** *J Chem Phys* 2011, **134(5)**:055110.
35. Jensen MO, Tajkhorshid E, Schulten K: **Electrostatic tuning of permeation and selectivity in aquaporin water channels.** *Biophys J* 2003, **85(5)**:2884-2899.
36. Tajkhorshid Emad, Z F, Schulten Klaus: **Kinetic theory and simulation of single-channel water transport.** Springer, Netherlands;editor 2005:1797-1822.
37. Berezhkovskii A, Hummer G: **Single-file transport of water molecules through a carbon nanotube.** *Phys Rev Lett* 2002, **89(6)**:064503.
38. Zhu F, Schulten K: **Water and proton conduction through carbon nanotubes as models for biological channels.** *Biophys J* 2003, **85(1)**:236-244.
39. Smart OS, Neduvelil JG, Wang X, Wallace BA, Sansom MS: **HOLE: a program for the analysis of the pore dimensions of ion channel structural models.** *J Mol Graph* 1996, **14(6)**:354-360, 376.
40. Tajkhorshid E, Nollert P, Jensen MO, Miercke LJ, O'Connell J, Stroud RM, Schulten K: **Control of the selectivity of the aquaporin water channel family by global orientational tuning.** *Science* 2002, **296(5567)**:525-530.

41. de Groot BL, Frigato T, Helms V, Grubmuller H: **The mechanism of proton exclusion in the aquaporin-1 water channel.** *J Mol Biol* 2003, **333(2)**:279-293.
42. Burykin A, Warshel A: **What really prevents proton transport through aquaporin? Charge self-energy versus proton wire proposals.** *Biophys J* 2003, **85(6)**:3696-3706.
43. Burykin A, Warshel A: **On the origin of the electrostatic barrier for proton transport in aquaporin.** *FEBS Lett* 2004, **570(1-3)**:41-46.
44. Jensen MO, Rothlisberger U, Rovira C: **Hydroxide and proton migration in aquaporins.** *Biophys J* 2005, **89(3)**:1744-1759.
45. Sui H, Han BG, Lee JK, Walian P, Jap BK: **Structural basis of water-specific transport through the AQP1 water channel.** *Nature* 2001, **414(6866)**:872-878.
46. Ho JD, Yeh R, Sandstrom A, Chorny I, Harries WE, Robbins RA, Miercke LJ, Stroud RM: **Crystal structure of human aquaporin 4 at 1.8 A and its mechanism of conductance.** *Proc Natl Acad Sci U S A* 2009, **106(18)**:7437-7442.
47. Russell RB, Barton GJ: **Multiple protein sequence alignment from tertiary structure comparison: assignment of global and residue confidence levels.** *Proteins* 1992, **14(2)**:309-323.
48. Eargle J, Wright D, Luthey-Schulten Z: **Multiple Alignment of protein structures and sequences for VMD.** *Bioinformatics* 2006, **22(4)**:504-506.
49. Jensen MO, Park S, Tajkhorshid E, Schulten K: **Energetics of glycerol conduction through aquaglyceroporin GlpF.** *Proc Natl Acad Sci U S A* 2002, **99(10)**:6731-6736.
50. Hohmann I, Bill RM, Kayingo I, Prior BA: **Microbial MIP channels.** *Trends Microbiol* 2000, **8(1)**:33-38.
51. Tanghe A, Van Dijck P, Thevelein JM: **Why do microorganisms have aquaporins?** *Trends Microbiol* 2006, **14(2)**:78-85.
52. Hill AE, Shachar-Hill B, Shachar-Hill Y: **What are aquaporins for?** *J Membr Biol* 2004, **197(1)**:1-32.
53. Humphrey W, Dalke A, Schulten K: **VMD: visual molecular dynamics.** *J Mol Graph* 1996, **14(1)**:33-38, 27-38.
54. Zhang L, Hermans J: **Hydrophilicity of cavities in proteins.** *Proteins* 1996, **24(4)**:433-438.
55. Phillips JC, Braun R, Wang W, Gumbart J, Tajkhorshid E, Villa E, Chipot C, Skeel RD, Kale L, Schulten K: **Scalable molecular dynamics with NAMD.** *J Comput Chem* 2005, **26(16)**:1781-1802.
56. Mackerell AD, Bashford D, Bellott M, Dunbrack RL, Evanseck JD, Field MJ, Fischer S, Gao J, Guo H, Ha S, *et al*: **All-Atom Empirical Potential for Molecular Modeling and Dynamics Studies of Proteins.** *The Journal of Physical Chemistry B* 1998, **102(18)**:3586-3616.
57. Foloppe N, Mackerell A Jr: **All-atom empirical force field for nucleic acids: I. Parameter optimization based on small molecule and condensed phase macromolecular target data.** *Journal of Computational Chemistry* 2000, **21(2)**:86-104.
58. Feller SE, Mackerell Jr.: **An Improved Empirical Potential Energy Function for Molecular Simulations of Phospholipids.** *J Phys Chem B* 2000, **104(31)**:7510-7515.
59. Darden T, York D, Pedersen L: **Particle mesh Ewald: An N-log(N) method for Ewald sums in large systems.** *The Journal of Chemical Physics* 1993, **98(12)**:10089-10092.
60. Essmann U, Perera L, Berkowitz M, Darden T, Lee H, Pedersen L: **A smooth particle mesh Ewald method.** *The Journal of Chemical Physics* 1995, **103(19)**:8577-8593.
61. Feller S, Zhang Y, Pastor R, Brooks B: **Constant pressure molecular dynamics simulation: The Langevin piston method.** *The Journal of Chemical Physics* 1995, **103(11)**:4613-4621.
62. Pohl P, Saparov SM, Borgnia MJ, Agre P: **Highly selective water channel activity measured by voltage clamp: analysis of planar lipid bilayers reconstituted with purified AqpZ.** *Proc Natl Acad Sci U S A* 2001, **98(17)**:9624-9629.
63. Saparov SM, Tsunoda SP, Pohl P: **Proton exclusion by an aquaglyceroprotein: a voltage clamp study.** *Biol Cell* 2005, **97(7)**:545-550.
64. Zeidel ML, Nielsen S, Smith BL, Ambudkar SV, Maunsbach AB, Agre P: **Ultrastructure, pharmacologic inhibition, and transport selectivity of aquaporin channel-forming integral protein in proteoliposomes.** *Biochemistry* 1994, **33(6)**:1606-1615.
65. Walz T, Smith BL, Zeidel ML, Engel A, Agre P: **Biologically active two-dimensional crystals of aquaporin CHIP.** *J Biol Chem* 1994, **269(3)**:1583-1586.
66. Yang B, Verkman AS: **Water and glycerol permeabilities of aquaporins 1-5 and MIP determined quantitatively by expression of epitope-tagged constructs in Xenopus oocytes.** *J Biol Chem* 1997, **272(26)**:16140-16146.
67. Zeidel ML, Ambudkar SV, Smith BL, Agre P: **Reconstitution of functional water channels in liposomes containing purified red cell CHIP28 protein.** *Biochemistry* 1992, **31(33)**:7436-7440.
68. Tanimura Y, Hiroaki Y, Fujiyoshi Y: **Acetazolamide reversibly inhibits water conduction by aquaporin-4.** *J Struct Biol* 2009, **166(1)**:16-21.

doi:10.1186/1471-2164-12-S4-S8
Cite this article as: Araya-Secchi *et al.*: **Molecular dynamics study of the archaeal aquaporin AqpM.** *BMC Genomics* 2011 **12**(Suppl 4):S8.