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Data Article

Barium blockade of the KcsA channel in open and closed conformation datasets

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ABSTRACT

Barium is a potent blocker of the KcsA potassium channel. A strategy using x-ray crystallography and molecular dynamics (MD) simulation has been used to understand this phenomenon as described in Rohaim et al. [1]. Wild type KcsA is purified to homogeneity and crystallized in low and high K^+ conditions. Crystals are grown using the hanging drop vapor diffusion method. To examine barium binding in the selectivity filter of KcsA, the crystals are systemically soaked in various concentrations of barium chloride solution. X-ray crystallography datasets are collected at the Advanced Photon Source. A total of 10 datasets are collected for various barium ion concentrations. Diffraction data are processed using the crystallography pipeline software RAPID. The crystal structures are solved by molecular replacement methods. The structure models are visualized using COOT and refined using REFMAC. Anomalous map coefficients are calculated using the phenix.maps tool in the PHENIX software suite. The datasets are deposited in the Protein Data Bank. The data provides a detailed picture of barium ion interaction with potassium channels. Structural analysis of the KcsA channel reveals two distinct configurations, open- and closed- state. Further MD simulation analysis suggests an energetically fa-

vorable binding mechanism for barium ion in the selectivity filter. The data could be used to interpret functional experiments related to barium blockade for potassium channels. Also, it is valuable for comparison and cross validation with other relevant potassium channel structures.

Specifications Table.

Subject	Biophysics
Specific subject area	Ion channels, X-ray crystallography, molecular dynamics simulation.
Type of data	Tables Structures Graphs
How data were acquired	- Synchrotron beamline NECAT, Argonne Photon Source. - Molecular Dynamics Program: NAMD 2.13 - Force Fields: CHARMM 36 force field and Drude polarizable force field.
Data format	- Deposited as protein structure model in the Protein Data Bank raw data - The tracings of the ions in the selectivity filter are presented in the Microsoft Office files.
Parameters for data collection	KcsA crystals were soaked in 1, 2, 4, 5, 10 mM $BaCl_2$ in the presence of 5 mM KCl. In another experiment crystals were soaked in 0, 1, 5, 10 mM KCl in presence of 5 mM $BaCl_2$. Separately, KcsA was soaked in 5 mM $BaCl_2$ in the absence of KCl. Molecular dynamics simulations were performed using additive CHARMM simulations: Isothermal-isobaric (NPT) conditions at 298 K and 1 atm. The simulations used a time step of 2 fs, and the equilibrated systems were simulated for 100 ns. For the polarizable Drude simulations an additional 100 ns simulations were performed at 310 K with a time step of 1 fs.
Description of data collection	The crystals were flash-frozen in 40% PEG solution. X-ray diffraction datasets were collected at the NECAT 24-ID-C/E and 23-ID-D beamlines at the **Advanced Photon Source.**
Data source location	Institution: Advanced Photon Source. City/Town/Region: Lemont, Illinois Country: USA Institution: Beagle Supercomputer, The Computation Institute, the University of Chicago City/Town/Region: Chicago, Illinois Country: USA Primary data sources: Protein Data Bank accession codes: 6W0A, 6W0B, 6W0C, 6W0D and 6W0E for the open-gate KcsA structures and 6W0F, 6W0G, 6W0H, 6W0I and 6W0J for the closed-gate KcsA structures. The tracings of the ions in the selectivity filter are presented in the Microsoft Office files, i.e. FigureS3_tracing_c36.xslm and FigureS4_tracing_drude.xslm, respectively.
Data accessibility	Repository name: Protein Data Bank Data identification number: 6W0A, 6W0B, 6W0C, 6W0D and 6W0E, 6W0F, 6W0G, 6W0H, 6W0I, 6W0J. raw data https://www.rcsb.org/structure/6W0A https://www.rcsb.org/structure/6W0B https://www.rcsb.org/structure/6W0C https://www.rcsb.org/structure/6W0D https://www.rcsb.org/structure/6W0E https://www.rcsb.org/structure/6W0F https://www.rcsb.org/structure/6W0G https://www.rcsb.org/structure/6W0H https://www.rcsb.org/structure/6W0I https://www.rcsb.org/structure/6W0J Other data in the form of tables and graphs are in the article.

Value of the Data

- The data provides a structural basis for the barium blockade of potassium channels. Moreover, it captures the KcsA channel in both open and closed conformations. Based on the structures, it is shown that barium preferably blocks the open conformation from the intracellular side. Structural and molecular dynamics simulation data indicate that barium could be a conformation specific channel blocker. Altogether, the data provide an insight for the mechanism of barium ion interaction with potassium channels.
- The data provide an interpretation for the functional properties of barium blockade and ionic selectivity in the selectivity filter of KcsA and homologous potassium channels. It can be used as a model for cross correlations and comparisons with novel or existing potassium channel structures. For computational biology, it will be of much interest to study interactions between proteins and heavy metals using the Drude force field.
- The current structure models could be used as a starting point to design non-inactivation KcsA mutants to probe the selectivity of different ionic species in the selectivity filter. The same strategy of data collection could be used to understand the c-type inactivation mechanism in potassium channels. The polarizable force field will be further developed to address interaction between proteins and divalent cations.

1. Data description

X-ray diffraction datasets are collected for each condition (concentration of Ba^{2+}, K^+ and Na^+) yielding ten datasets in total. The first five datasets, shown in Table 1, represent data collection and refinement statistics for the open-gate KcsA structure collected at 1, 2, 4, 5 and 10 mM $BaCl_2$ in the presence of 5 mM KCl. Table 2 shows the data collection and refinement statistics for the closed-gate KcsA channel in 0, 1, 5 and 10 mM KCl in the presence of 5 mM $BaCl_2$, and the last column represents closed-gate KcsA in the presence of 5 mM $BaCl_2$ and 150 mM NaCl. To compare the relevant crystal structures, structure alignments of KcsA soaked crystals are shown in figure S1. Two monomers are shown for clarity, (A) Open-gate structures soaked in 1, 2, 4, 5 or 10 mM $BaCl_2$ in the presence of 5 mM KCl, (B) Closed-gate structures soaked in 0, 1, 2, 5 and 10 mM KCl in the presence of 5 mM $BaCl_2$. The crystallographic B-factors of the backbone are shown in rainbow color ranging from blue (low B-factor) to red (high B-factor). The alignments reveal similar conformations between the open and closed structures. The two distinct conformations are independent of barium concentration. To determine regions of conformational variability, figure S2 is a superposition of the backbone atoms of the open-gate wt KcsA soaked in 1 mM $BaCl_2$/5 mM KCl on the previously identified KcsA structures 1K4C (orange), 1K4D (blue) and 3F7V (grey) structures for TM1 and TM2 (residues 28–118), left, and for the selectivity filter only (residues 75–80), right.

The relative Z-position of cations in the selectivity filter of closed-conductive KcsA and the initial structure for the 100 ns simulations using the CHARMM 36 force field are shown in Figure S3. All coordinates are plots relative to the center of mass of the selectivity filter. The initial ion configuration of the selectivity filter for the simulation is depicted. The traces of Ba^{2+} and K^+ are shown in magenta and green, respectively. The average Z-coordinates of carbonyl oxygens of G79, Y78, G77, V76 and T75, and the hydroxyl oxygen of T75 are shown in red lines to indicate the positions of cation binding sites.

Figure S4 shows the relative Z-position of cations in the selectivity filter of closed-conductive KcsA and the initial structure for the 100 ns simulations using the Drude polarizable force field. All coordinates are plots relative to the center of mass of the selectivity filter. The initial ion configuration of the selectivity filter for the simulation is depicted. The traces of Ba^{2+} and K^+

Table 1

Data collection and refinement statistics of open-gate KcsA.

	KcsA open-gate soaked in 5 mM KCl				
	1.0 mM BaCl$_2$	2.0 mM BaCl$_2$	4.0 mM BaCl$_2$	5.0 mM BaCl$_2$	10.0 mM BaCl$_2$
Wavelength (Å)	0.9792	0.9792	0.9792	0.9792	0.9792
Source	APS 24-ID-E	APS 24I-D-E	APS 24I-D-E	APS 24I-D-E	APS 24-ID-E
Resolution (Å)	49.5–3.2	49.7–3.6	55.1 - 3.5	55.4 - 3.6	50.0 - 3.5
Space group	I 4	I 4	I 4	I 4	I 4
Cell parameters (Å)	156.5, 156.5, 73.9	157.3, 157.3, 74.3	155.9, 155.9, 74.3	156.9, 156.9, 73.6	158.2, 158.2, 74.2
(°)	90.0, 90.0, 90.0	90.0, 90.0, 90.0	90.0, 90.0, 90.0	90.0, 90.0, 90.0	90.0, 90.0, 90.0
Total reflections	88,457	54,744	52,778	57,439	46,708
Unique reflections	14,339	10,574	10,740	10,018	11,509
Multiplicity	6.0 (5.8)	5.2 (4.7)	4.9 (4.8)	5.7 (5.4)	4.1 (4.0)
Completeness (%)	99.1 (96.0)	98.9 (95.6)	98.5 (93.7)	97.9 (91.4)	98.9 (96.5)
Mean I/sigma(I)	8.5 (1.5)	5.3 (1.3)	6.5 (1.1)	7.2 (1.3)	8.7 (1.3)
R-merge	0.18 (1.36)	0.29 (1.62)	0.22 (1.38)	0.26 (1.55)	0.17 (1.09)
R-pim	0.087 (0.61)	0.15 (0.86)	0.12 (0.79)	0.12 (0.75)	0.11 (0.71)
CC1/2	0.99 (0.47)	0.98 (0.33)	0.98 (0.33)	0.99 (0.36)	0.99 (0.36)
Reflections used in refinement	14,333	10,565	10,734	10,014	11,504
R-work/R-free	0.17/0.24	0.18/0.23	0.20/0.24	0.19/0.24	0.19/0.25
RMS bond length (Å)/angle (°)	0.01/1.5	0.01/1.2	0.01/1.1	0.01/1.2	0.01/1.2
Ramachandran favored (%)	89.7	92.8	91.3	91.7	91.5
Allowed (%)	9.2	6.7	8.1	7.5	7.1
Outliers (%)	0.9	0.3	0.5	0.7	1.3

*values in parentheses are for highest-resolution shell.

Table 2

Data collection and refinement statistics of closed-gate KcsA.

	KcsA closed-gate soaked in 5 mM BaCl$_2$				KcsA closed-gate incubated in Ba2+/Na+
	0 mM KCl	1 mM KCl	5 mM KCl	10 mM KCl	
Wavelength (Å)	0.9791	0.9791	0.9791	0.9791	1.033
Source	APS 24-ID-C	APS 24-ID-C	APS 24-ID-C	APS 24-ID-C	APS 23-ID-D
Resolution (Å)	51.0–2.4	54.8–2.6	68.0–2.6	67.9–2.3	68.6–2.5
Space group	I 4	I 4	I 4	I 4	I 4
Cell parameters (Å)	155.0, 155.0, 75.3	155.1, 155.1, 75.3	155.8, 155.8, 75.5	154.2, 154.2, 75.7	156.3, 156.3, 76.3
(°)	90.0, 90.0, 90.0	90.0, 90.0, 90.0	90.0, 90.0, 90.0	90.0, 90.0, 90.0	90.0, 90.0, 90.0
Total reflections	243,853	189,833	252,932	399,672	306,876
Unique reflections	35,112	27,029	28,030	37,609	32,029
Multiplicity	7.0 (7.0)	7.0 (7.0)	9.0 (8.9)	10.6 (9.1)	9.6 (9.9)
Completeness (%)	99.8 (99.9)	97.2 (97.9)	99.9 (99.9)	98.6 (91.8)	99.8 (99.8)
Mean I/sigma(I)	7.6 (1.0)	6.1 (0.9)	5.9 (1.0)	12.0 (1.1)	7.1 (1.7)
R-merge	0.18 (2.66)	0.21 (2.50)	1.03 (7.97)	0.14 (2.42)	0.23 (1.9)
R-pim	0.11 (1.14)	0.12 (1.04)	0.38 (1.37)	0.07 (0.81)	0.08 (0.65)
CC1/2	0.99 (0.12)	0.99 (0.13)	0.84 (0.17)	0.92 (0.29)	0.99 (0.55)
Reflections used in refinement	35,091	27,022	28,019	37,604	32,029
R-work/R-free	0.22/0.24	0.20/0.24	0.19/0.23	0.20/0.23	0.19/0.21
RMS bond length (Å)/angle (°)	0.01/2.2	0.01/1.3	0.01/1.3	0.01/1.2	0.01/1.3
Ramachandran favored (%)	96	96	96.2	95.6	95.4
Allowed (%)	3.9	3.7	3.7	4.1	4.3
Outliers (%)	0	0.1	0	0.1	0.1

*values in parentheses are for highest-resolution shell.

are shown in magenta and green, respectively. The average Z-coordinates of carbonyl oxygens of G79, Y78, G77, V76 and T75, and the hydroxyl oxygen of T75 are shown in red lines to indicate the positions of cation binding sites.

2. Experimental design, materials and methods

KcsA with low KCl concentrations was crystallized in 50 mM Magnesium acetate, 50 mM ammonium acetate pH 5.5 and 25% PEG 400 at 20 °C. After 5 days, crystals were harvested and soaked in cryoprotectant solution containing 40% PEG 400, 5 mM KCl, 145 mM NaCl and $BaCl_2$ (1, 2, 4, 5 or 10 mM) for 1 min at room temperature. This step was repeated 3 times followed by flash-freezing in liquid nitrogen. For KcsA crystallized with NaCl in the absence, the purified peak fraction was collected from the Superdex 200 column and incubated with 5 mM $BaCl_2$ for 10 minutes prior to crystallization. The crystals were flash-frozen in 40% PEG solution. X-ray diffraction datasets were collected at the NECAT 24-ID-C and E, and 23-ID-D beamlines at the Advanced Photon Source. Data was process by the automated pipeline RAPID at Advanced Photon Source (www.lilith.nec.aps.anl.gov/newsite/RAPDMain). Crystal structures were determined by molecular replacement using the structures 1K4C and 1K4D as search models and visualized by COOT [2]. The anomalous difference Fourier maps were calculated using Phenix [3] and contoured at 8σ. The structure refinements were performed using REFMAC [4]. Structure based alignments and figures were performed using PyMOL alignment alogorithms [5]. The RMSD values were calculated using the software LSQKAB in the CCP4 macromolecular crystallography suite [6].

The simulation system was constructed based on the crystal structure of closed-conductive KcsA (PDB ID: 1K4C). The channel was embedded in a bilayer of POPC lipids and solvated in 150 mM KCl using the web based CHARMM-GUI [7]. Most residues were assigned their standard protonation state at pH 7. The residue Glu71 was protonated to form a key hydrogen bond with Asp80 for the normal function of the selectivity filter. The CHARMM force field PARAM36 (C36) for protein [8,9], lipids, and ions [10] was used. Explicit water was described with the TIP3P model [11]. All the simulations were performed under NPT (constant number of particle *N*, pressure *P*, and temperature *T*) conditions at 298 K and 1 atm, and periodic boundary conditions with electrostatic interactions were treated by the particle mesh Ewald method [12] and a real-space cutoff of 12 Å. The simulations used a time step of 2 fs, with bond distances involving hydrogen atoms fixed using the SHAKE algorithm [13]. A dihedral constraint was applied to the dihedral angles of Val76, Gly77 and Tyr78. The barium and potassium cations were located at different sites from S0 to S4 and separated by one or two water molecules in the selectivity filter, and in total 9 ion configurations were simulated with the additive CHARMM36 force field. After minimization and equilibration with harmonic positional restraints on all of the Cα atoms, the equilibrated systems were simulated for 100 ns using NAMD version 2.13 [14]. Then the Drude polarizable force field was used in an additional 100 ns simulation for a set of configurations (as shown in Figure S2) with Ba^{2+}/K^+ occupying S2, S3 and S4; the simulations were performed at 310 K with a time step of 1fs.

Data did not include the use of human subjects.

The work did not involve animal experiments.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have, or could be perceived to have, influenced the work reported in this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dib.2020.106135.

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