

New directions in photo-pharmacology

Control of a mechanosensitive potassium ion channel with photolipids

O. Klaja, A. N. Bondar, *Department of Physics, Freie Universität Berlin, Theoretical Molecular Biophysics Group*

In Short

- In order to reduce unwanted side-effects of drugs high spatio-temporal precision can be achieved by using light-activated medicinal compounds
- Contribute to development of new photo-lipids to control opening of TRAAK ion channel
- Characterize, how photo-switchable lipids modulate activity of TRAAK potassium ion channel

TRAAK is a member of the family of the two-pore domain ion channels, which open when tension is applied to the membrane [1]. These ion channels help control the resting potential in neurons after action potential bursts, and are a target for the development of new therapeutics for treating pain and neurological disorders. In collaboration with Prof. Dirk Trauner (University of New York, USA) we work on understanding how the photo-switchable lipid FAAzo4 can be used to control the opening and closing of the TRAAK mechanosensitive ion channel.

In order to study how photo-switchable lipids modulate potassium ion channel activation [2], we developed CHARMM force field parameters for the photo-switchable lipid FAAzo-4 which has never been studied by means of theoretical approach. We have simulated and characterized properties of membranes containing FAAzo-4 (Fig. 1). The location of photo lipids in membranes is currently unknown. Our simulations provide, for the first time, a molecular picture of how photo-lipids sit in membranes, and of how lipid bilayers adjust to the presence of photo-switchable lipids. We anticipate that results of our research will assist the design and interpretation of new photo-lipids.

Relative to a pure POPC membrane, addition of trans-FAAzo4 increases the membrane thickness by about 1 Å, and it decreases the area per lipid. In the presence of cis-FAAzo4, the membrane thickness and the area per lipid are largely the same as for pure POPC. Analysis of SCD for POPC lipids suggest that somewhat enhanced fluidity of the membrane containing cis-FAAzo4, and decreased for trans-FAAzo4-containing membranes. We will study photo-switchable lipids which are distinguished by a length of side-chains regulating depth of azobenzene group in a membrane.

Photo-switching of membranes containing FAAzo-4 results in increased pressure in the region where TRAAK expands while switching to active conformation. Our preliminary results suggest that TRAAK will close upon photo-switching [2]. We will continue to study the effects of photo-switchable membranes on conformational dynamics of TRAAK. We will study interactions of charged residues with surrounding lipids and inter-protein salt-bridges. Furthermore, we aim to characterize the allosteric mechanism of TRAAK activation.

WWW

<https://www.physik.fu-berlin.de/en/einrichtungen/ag/ag-bondar/index.html>

More Information

- [1] S. G. Brohawn, E. B. Campbell, and R. Mackinnon *Nature* **516**, 126-130 (2014). doi: 10.1038/nature14013
- [2] J. A. Frank et al., *Nat. Commun.* **6**, 7118 (2015). doi:10.1038/ncomms8118

Funding

Research supported in part by funding from the DFG Priority Program SPP 1926 Next Generation Optogenetics: Tool development and application', from the Excellence Initiative of the German Research Foundation provided via the Freie Universität Berlin, and from the Center for Research Strategy of the Freie Universität Berlin.

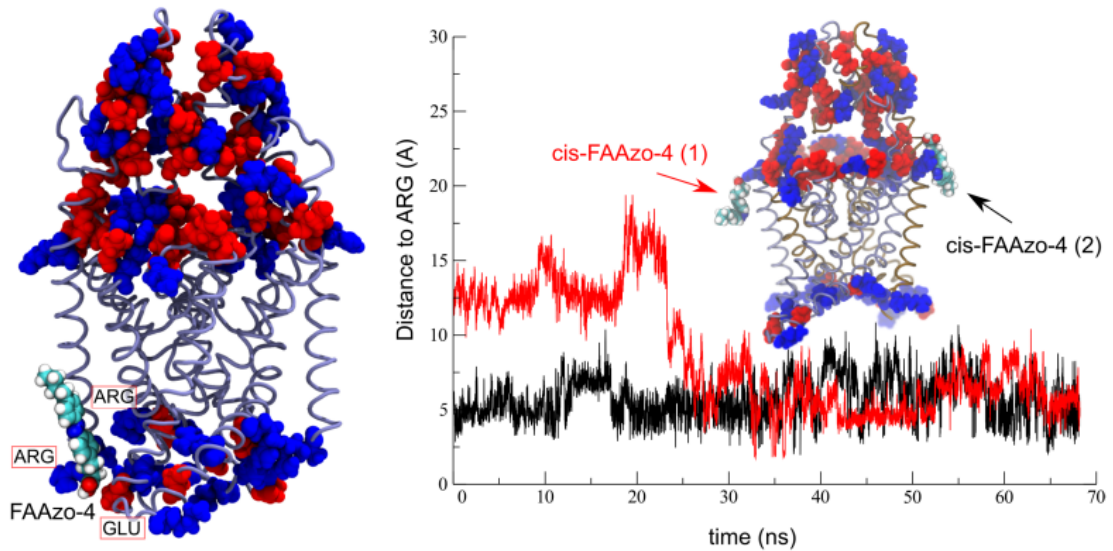


Figure 1: Figure 1. Binding of photo-switchable lipids to TRAAK. (Left) *trans*-FAAzo4 binds in the lower helical bundle of TRAAK close to TM2/TM3 tip. (Right) *Cis*-FAAzo4 binds to the arginines at the same site for both chains of protein. Blue sphere represent atoms of negatively charged aminoacids, red spheres are positively charged aminoacids.

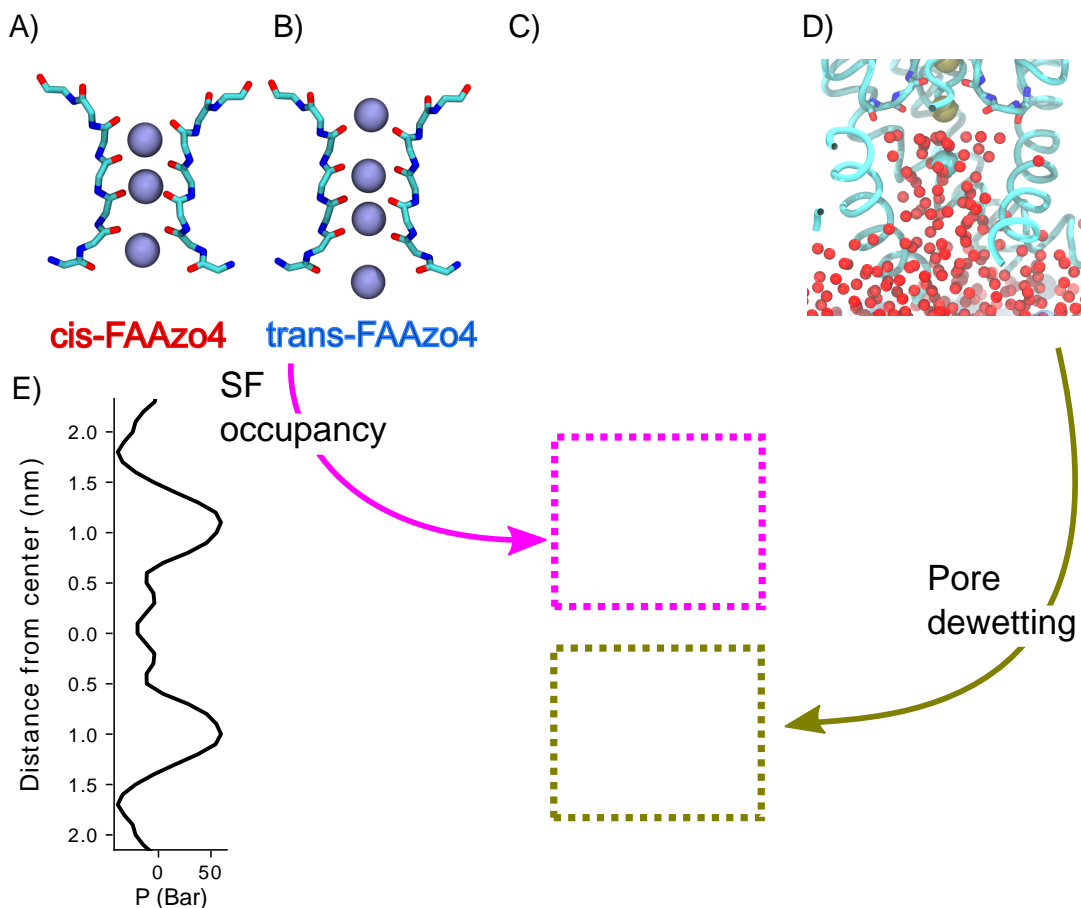


Figure 2: Figure 2. Structural and dynamical changes in TRAAK in a FAAzo4/POPC membrane. (A-B) Sites occupied in the SF by potassium ions in simulation with *cis*-FAAzo4 (panel A) vs. *trans*-FAAzo4 (panel B). (C) Structural changes of TRAAK. Red structure represents simulation with *cis*-FAAzo4 molecules, blue structure is taken from simulation of *trans*-FAAzo4. (D) Water pore in lower helical bundle of TRAAK. (E) Difference in lateral pressure profile due to photo-switching of a FAAzo-4/POPC membrane.