Секция «Биоинформатика»

Covalent inhibition of butyrylcholinesterase catalytic serine promotes dynamical pocket closure

Научный руководитель – Головин Андрей Викторович

Дианкин Игорь Дмитриевич
Postgraduate
Московский государственный университет имени М.В.Ломоносова, Факультет биоинженерии и биоинформатики, Москва, Россия
E-mail: i.diankin@gmail.com

Igor Diankin1,2, Alexander Zlobin1,2,3, Andrey Golovin1,2,3

1) Faculty of Bioengineering and Bioinformatics, Lomonosov Moscow State University, Moscow, Russia
2) Sirius University of Science and Technology, Sochi, Russia
3) Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Moscow, Russia

Organophosphates (OPs) are highly toxic irreversible inhibitors of acetylcholinesterase. The development of OP hydrolyzing enzyme organophosphatase (OPase) is regarded as a promising strategy to treat OP poisoning. Human butyrylcholinesterase (BChE) is regarded as a promising scaffold for such endeavours [1]. A series of BChE variants were constructed to date exhibiting low activity against model OP paraoxon. However, no large-scale dynamical study was ever conducted on either active or inhibited forms of the enzyme. Here we perform microsecond-scale molecular dynamics simulations on correctly glycosylated butyrylcholinesterase. For the inhibited state we conduct extensive QM-guided parameterization of the catalytic serine - diethyl phosphate adduct. We observe previously undescribed behaviour of the loop Asn68-Trp82 which is highly flexible and can enclose the active site pocket. With the help of metadynamics, we explore the free energy landscape of the process to reveal that enzyme phosphorylation promotes the closure. Our findings reveal features crucial for enzyme reactivation endeavours with oximes as well as potential rational design attempts that explore that flexibility.

The reported study was funded by RFBR, project number 19-34-51043. The research is carried out using the equipment of the shared research facilities of HPC computing resources at Lomonosov Moscow State University [2].

References

1) Lushchekina S.V. et al. Optimization of Cholinesterase-Based Catalytic Bioscavengers Against Organophosphorus Agents // Front. Pharmacol. 2018. Vol. 9. P. 211.
2) Supercomputer Lomonosov-2: Large Scale, Deep Monitoring and Fine Analytics for theUser Community // Supercomputing Frontiers and Innovations. 2019. Vol. 6, No 2