

Interplay of cholesterol, membrane bilayers and the AT1R: A cholesterol consensus motif on AT1R is revealed

Sofia Kiriakidi^{a,c}, Christos Chatzigiannis^b, Christina Papaemmanouil^b, Andreas G. Tzakos^b,
Zoe Cournia^c and Thomas Mavromoustakos^a

^aLaboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Zografou GR-15771, Greece

^bLaboratory of Organic Chemistry and Biochemistry, Department of Chemistry, University of Ioannina, Ioannina GR- 45110, Greece

^cBiomedical Research Foundation, Academy of Athens, 4 Soranou Ephessiou, GR-11527 Athens, Greece
e-mail: sofki@chem.uoa.gr

Hypertension, mediated by the Angiotensin II receptor type 1 (AT1R), is still the major cause of premature death despite the discovery of novel therapeutics, highlighting the importance of an in depth understanding of the drug-AT1R recognition mechanisms coupled with the impact of the membrane environment on the interaction of drugs with AT1R. Herein, we examine the interplay of cholesterol-lipid-candesartan and the AT1R using Molecular Dynamics simulations of a model membrane consisting of 60:40 mol%. DPPC:cholesterol, candesartan and the AT1R, mimicking the physiological cholesterol concentration in sarcolemma membranes. The simulations of the model membrane of 60:40 mol%. DPPC:cholesterol were further validated using DOSY NMR experiments. Interestingly, our results suggest a significant role of cholesterol in the AT1R function imposed through a Cholesterol Consensus Motif (CCM) in the receptor, which could be crucial in the drug binding process. Candesartan diffusion towards AT1R through incorporation into lipid bilayers, appears to be retarded by the presence of cholesterol. However, its direct approach towards AT1R may be facilitated through the mobility induced on the N-terminus by the cholesterol binding on the CCM these novel insights could pave the way towards the development of more potent pharmaceutical agents to combat hypertension more effectively.

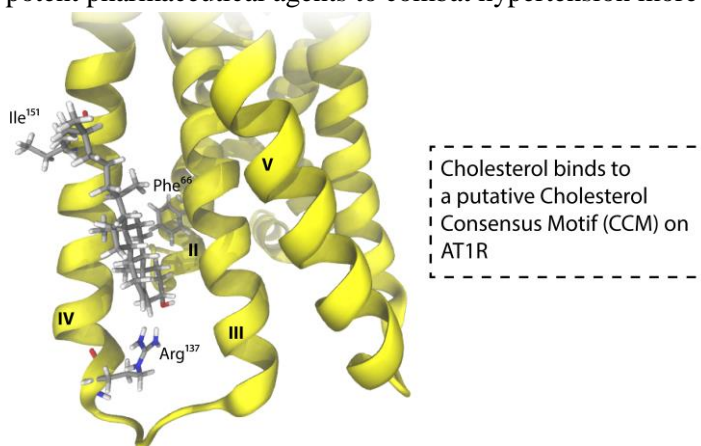


Figure 1: A cholesterol molecule bound to a novel Cholesterol Consensus Motif predicted on AT1R.

References:

1. S. Kiriakidi, C. Chatzigiannis, C. Papaemmanouil, A.G. Tzakos, Z. Cournia, T.Mavromoustakos, Interplay of cholesterol, membrane bilayers and the AT1R: A cholesterol consensus motif on AT1R is revealed, Computational and Structural Biotechnology Journal, vol. 19 pp. 110-120, 2021, doi: <https://doi.org/10.1016/j.csbj.2020.11.042>