Unveiling the molecular mechanism of action of the anti-hypertensive drug irbesartan through 2D NMR Spectroscopy

Eleni Chontzopoulou, Sofia Kiriakidi, Uroš Javornik, Janez Plavec, Andreas Tzakos, Thomas Mavromoustakos

Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Zografou GR-15771, Greece
e-mail: tmavrom@chem.uoa.gr
National Institute of Chemistry, Slovenian NMR Centre, SI-1001 Ljubljana, Slovenia.

Irbesartan is one of the commercially available drugs prescribed for the treatment of hypertension. The drug's mechanism of action includes the antagonism of Angiotensin II in the binding site of AT1Receptor. The binding mode of irbesartan in AT1R's cavity has been thoroughly investigated by research groups worldwide, while the way the drug enters into the active site of the receptor has not been established yet. There are two possible scenarios concerning the way irbesartan enters AT1R. The first one includes the direct drug's incorporation from the aquatic environment of the cell into the trans-membrane receptor AT1R (one-step mechanism), while the other scenario proposes the drug firstly penetrates into the lipid bilayers and then it approaches the active site of the receptor (two-step mechanism). Cyclodextrins are molecules used as drug delivery systems, by encapsulating the hydrophobic drugs in order to increase their bioavailability and pharmacokinetic properties. In this study, irbesartan has been engulfed in a cyclodextrin-carrier and then embedded into the lipid bilayers. The aim of this study is to investigate if irbesartan could interact only with cyclodextrin or it could abandon its carrier and interact directly with the lipid. This is a quite significant insight on the molecular mechanism of action of irbesartan, since the drug's interaction with the lipid bilayers enhances the two-step mechanism of action. Preliminary studies on Irbesartan:2-HP-β-CD complex in DOPC bilayers using 2D NOESY experiments indicate that irbesartan is released from the cyclodextrin and is embedded in the interface of the lipid bilayers.

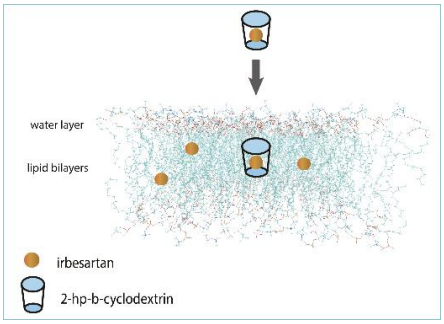

Figure 1: Irbesartan is released by the cyclodextrin-vehicle and interacts directly with the lipid bilayers.

Reference:

1. S. Kiriakidi, C. Chatzigiannis, C. Papaemmanouil, A.G. Tzakos, T. Mavromoustakos, *Biochim. Biophys. Acta Biomembr.* **1862**, 183142 (2020).