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Membrane Permeability of Middle Molecules: A Computational Chemistry Approach

Authors : Sundaram Arulmozhiraja, Kanade Shimizu, Yuta Yamamoto, Satoshi Ichikawa, Maenaka Katsumi, Hiroaki Tokiwa

Abstract : Drug discovery is shifting from small molecule based drugs targeting local active site to middle molecules (MM) targeting large, flat, and groove-shaped binding sites, for example, protein-protein interface because at least half of all targets assumed to be involved in human disease have been classified as “difficult to drug” with traditional small molecules. Hence, MMs such as peptides, natural products, glycans, nucleic acids with various high potent bioactivities become important targets for drug discovery programs in the recent years as they could be used for ‘undruggable” intracellular targets. Cell membrane permeability is one of the key properties of pharmacodynamically active MM drug compounds and so evaluating this property for the potential MMs is crucial. Computational prediction for cell membrane permeability of molecules is very challenging; however, recent advancement in the molecular dynamics simulations help to solve this issue partially. It is expected that MMs with high membrane permeability will enable drug discovery research to expand its borders towards intracellular targets. Further to understand the chemistry behind the permeability of MMs, it is necessary to investigate their conformational changes during the permeation through membrane and for that their interactions with the membrane field should be studied reliably because these interactions involve various non-bonding interactions such as hydrogen bonding, π-stacking, charge-transfer, polarization dispersion, and non-classical weak hydrogen bonding. Therefore, parameters-based classical mechanics calculations are hardly sufficient to investigate these interactions rather, quantum mechanical (QM) calculations are essential. Fragment molecular orbital (FMO) method could be used for such purpose as it performs ab initio QM calculations by dividing the system into fragments. The present work is aimed to study the cell permeability of middle molecules using molecular dynamics simulations and FMO-QM calculations. For this purpose, a natural compound syringolin and its analogues were considered in this study. Molecular simulations were performed using NAMD and Gromacs programs with CHARMM force field. FMO calculations were performed using the PAICS program at the correlated Resolution-of-Identity second-order Moller Plesset (RI-MP2) level with the cc-pVDZ basis set. The simulations clearly show that while syringolin could not permeate the membrane, its selected analogues go through the medium in nano second scale. These correlates well with the existing experimental evidences that these syringolin analogues are membrane-permeable compounds. Further analyses indicate that intramolecular π-stacking interactions in the syringolin analogues influenced their permeability positively. These intramolecular interactions reduce the polarity of these analogues so that they could permeate the lipophilic cell membrane. Conclusively, the cell membrane permeability of various middle molecules with potent bioactivities is efficiently studied using molecular dynamics simulations. Insight of this behavior is thoroughly investigated using FMO-QM calculations. Results obtained in the present study indicate that non-bonding intramolecular interactions such as hydrogen-bonding and π-stacking along with the conformational flexibility of MMs are essential for amicable membrane permeation. These results are interesting and are nice example for this theoretical calculation approach that could be used to study the permeability of other middle molecules. This work was supported by Japan Agency for Medical Research and Development (AMED) under Grant Number 18ae0101047.

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