DOCTORAL THESIS

Stereo-selective binding of enantiomeric ligands in PPAR[gamma]: a molecular modeling study

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Date of Award:
2013

Stereo-Selective Binding of Enantiomeric Ligands in PPARγ:

A Molecular Modeling Study

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A thesis submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

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Hong Kong Baptist University

November 2012

Abstract

Peroxisome proliferator-activated receptor γ (PPARγ), the most investigated nuclear receptor (NR) among the three subtypes of PPARs (PPARα, PPARγ and PPARβ/δ), is a ligand-dependent transcription factor that directs gene expression related to adipogenesis and lipid storage. Numerous natural and synthetic molecules have been suggested as PPARγ ligands and classified as full agonist, partial agonist, antagonist and SPPARM depending on their activities. Literatures have reported that ginsenosides Rg3, Rh2 and their end metabolite protopanaxadiol (PPD) have the ability to enhance the insulin secretion and increase PPARγ expression and adipogenesis *in vitro*. However, the recent fluorescence polarization and total internal reflection fluorescence (FR-TIRF) binding-affinity assay demonstrated that the binding affinities of PPD-type ginsenosides increase with the number of sugar moieties on C-3, among the studied ginsenosides, and the bare bone PPD enantiomers exhibit hardly any binding to PPARγ. Since the relevant X-ray crystal structures and/or NMR data are unavailable, the binding modes of PPD-type ginsenosides in PPARγ were investigated by molecular modeling and Essential dynamics analysis (EDA) and reported in this thesis. The docking results indicate that ginsenoside Rg3 bind to PPARγ in a similar manner to that of full agonists. Further molecular dynamics (MD) results indicate that the binding of 20(S)-Rg3 is more probable than that of the 20(R)-enantiomer which agrees with the angiogenesis assay result. Bindings of Rh2 enantiomers are similar to those of Rg3 enantiomers but no stereo-selectivity is found to 20(R/S)-Rh2. However, the bindings of 20(R/S)-PPD in the protein are much weaker relative to those of Rg3 and Rh2 indicating that the sugar on Carbon-3 play an important role in the binding of PPD-type ginsenosides in PPARγ. The binding modes of synthetic halofenic acid (HA)

enantiomers in PPARγ were also investigated by using the same method. The results demonstrate that both the enantiomers have the capability to bind to PPARγ with different orientations in principle and double ligand-binding of HA in the protein is also possible. As a recent experiment reported, 20(R/S)-Rg3 have the capability to activate pregnane X receptor (PXR) stereo-selectively, which is another member of the NR superfamily. The investigation of the binding modes of 20(R/S)-Rg3 in PXR by molecular modeling indicates that the binding of 20(S)-Rg3 enantiomer in PXR is more probable which agrees well with biological experiments.

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