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Review

Use of computational modeling approaches in studying the binding interactions of compounds with human estrogen receptors

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ABSTRACT

Estrogens have a whole host of physiological functions in many human organs and systems, including the reproductive, cardiovascular, and central nervous systems. Many naturally-occurring compounds with estrogenic or antiestrogenic activity are present in our environment and food sources. Synthetic estrogens and antiestrogens are also important therapeutic agents. At the molecular level, estrogen receptors (ERs) mediate most of the well-known actions of estrogens. Given recent advances in computational modeling tools, it is now highly practical to use these tools to study the interaction of human ERs with various types of ligands. There are two common categories of modeling techniques: one is the quantitative structure activity relationship (QSAR) analysis, which uses the structural information of the interacting ligands to predict the binding site properties of a macromolecule, and the other one is molecular docking-based computational analysis, which uses the 3-dimensional structural information of both the ligands and the receptor to predict the binding interaction. In this review, we discuss recent results that employed these and other related computational modeling approaches to characterize the binding interaction of various estrogens and antiestrogens with the human ERs. These examples clearly demonstrate that the computational modeling approaches, when used in combination with other experimental methods, are powerful tools that can precisely predict the binding interaction of various estrogenic ligands and their derivatives with the human ERs.

Contents

Abbreviations: CoMFA, comparative molecular field analysis; CoMSIA, comparative molecular similarity indices analysis; E_1, estrone; E_2, 17β-estradiol; EDC, endocrine disrupting chemical; ER, estrogen receptor; H12, Helix 12; LBD, ligand binding domain; OH-PBDE, hydroxylated polybrominated diphenyl ether; OH-PCB, hydroxylated polychlorinated biphenyl; PAH, polycyclic aromatic hydrocarbon; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PFC, perfluorinated compound; QSAR, quantitative structure–activity relationship; RAL, raloxifene; RBA, relative binding affinity; rtER, rainbow trout ER; SERM, selective estrogen receptor modulator; TAM, tamoxifen.

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1. Introduction

Estrogens are a group of vitally important female sex hormones that have many important physiological functions in the body, but they are also well known to be involved in certain pathophysiological and pathogenic processes [1]. The transcriptional actions of estrogens are mediated by the estrogen receptor (ER) α and β [2]. In addition, estrogens can induce rapid signal transduction in certain systems [3]. Alterations in estrogenic hormones and the ER-mediated signaling pathways are involved in the pathogenesis of certain disease states in humans, including abnormalities of the reproductive system [4], carcinogenesis in target organs [5,6], and other abnormal conditions [7–9]. At present, however, only a small fraction of the chemicals which humans are routinely exposed to have been tested for their binding affinity for and activity at the human ERs. Needless to say, it is highly desirable and also crucial to develop time- and cost-effective novel approaches that can predict the estrogenic activity of both endogenous and exogenous compounds.

Given the recent advances in the use of computational modeling approach in biological studies, it becomes increasingly feasible to analyze large numbers of compounds for their potential to interact with the human ERs as well as with other estrogen-binding proteins. Compared to some of the other commonly-used experimental methods (*e.g.*, receptor binding assays, receptor-mediated activity assays, and crystallographic structural studies), computational modeling methods have many distinct advantages, such as high speed, low cost, and high throughput.

In this review article, we will provide a brief overview of the two most widely-used computational approaches for studying the ligand–ER interactions, namely, the classical quantitative structure activity relationship (QSAR) approach and the more contemporary molecular docking-based modeling approach [10]. The QSAR analysis predicts the binding affinity of a new compound for the ERs by comparing its structure against a set of structurally-similar ligands with known binding affinity for the proteins of interest. The molecular docking modeling predicts the binding interaction mode and then calculates the binding energy value ($\Delta E_{binding}$ or $\Delta G_{binding}$) based on the precise structures of both the ligand and the binding site of the protein.

These two methods each have advantages and shortcomings. While the QSAR models sometimes can predict with very high accuracy independent of the receptor structures, this approach relies heavily on the baseline information derived from other structurally-similar ligands with known activity at the receptor of interest (such as receptor binding affinity and/or receptor activation potency). In the absence of sufficient number of known analogs, the predictive ability of the QSAR models usually is very limited. On the other hand, the molecular docking-based computational approach is based on the 3D structures of the binding site of the target protein as well as the ligands, and theoretically this model is far better suited to predict the binding conformation of new ligands with completely different structures.

Next, we will provide an in-depth review of the recent advances in the use of these two computational tools in studying the binding interaction of a variety of chemicals with the human ERs, along with a discussion of our recent results from studying the binding interaction of various endogenous estrogen metabolites, novel non-aromatic steroidal estrogens, and newly-synthesized antiestrogens with the human ERα and ERβ. Jointly, these examples illustrate that the computational modeling approach, in particular the molecular docking analysis, is a rather versatile and reliable approach to predict a chemical's binding mode with ERs, and the results provide unique insights into the 3D structural characteristics of the ligand–ER binding interaction.

2. Overview of the approaches commonly used in computational modeling study

2.1. The QSAR approach

The QSAR model studies the quantitative relationship between the structural descriptors of a chemical and its biological activity. The development of a good QSAR model involves four main steps as summarized below.

2.1.1. Step I. Calculation of the structural descriptors of the small molecules

The calculated descriptors can be molecular features, such as molecular weight, fragment counts, topological descriptors, and geometrical or energy grid descriptors.

The 3D-QSAR is currently the most popular QSAR method. The molecular interaction field is commonly used in 3D-QSAR to calculate the structural descriptors. The interaction energy (steric and electrostatic energies) of that molecule with a probe such as a