Toxicology and Applied Pharmacology 265 (2012) 300–307

Contents lists available at SciVerse ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

Combined 3D-QSAR, molecular docking and molecular dynamics study on thyroid hormone activity of hydroxylated polybrominated diphenyl ethers to thyroid receptors β

Xiaolin Li [a], Li Ye [b], Xiaoxiang Wang [a], Xinzhou Wang [b], Hongling Liu [a], Yongliang Zhu [b], Hongxia Yu [a,*]

[a] State Key Laboratory of Pollution Control and Resource Reuse, School of the Environment, Nanjing University, Nanjing 210046, PR China
[b] Suzhou NeuPharma Co.,Ltd, Suzhou 215123, PR China

ARTICLE INFO

Article history:
Received 31 May 2012
Revised 27 August 2012
Accepted 28 August 2012
Available online 6 September 2012

Keywords:
Hydroxylated polybrominated diphenyl ethers
Thyroid hormone receptor β
3D-QSAR
Molecular docking
Molecular dynamics

ABSTRACT

Several recent reports suggested that hydroxylated polybrominated diphenyl ethers (HO-PBDEs) may disturb thyroid hormone homeostasis. To illuminate the structural features for thyroid hormone activity of HO-PBDEs and the binding mode between HO-PBDEs and thyroid hormone receptor (TR), the hormone activity of a series of HO-PBDEs to thyroid receptors β was studied based on the combination of 3D-QSAR, molecular docking, and molecular dynamics (MD) methods. The ligand- and receptor-based 3D-QSAR models were obtained using Comparative Molecular Similarity Index Analysis (CoMSIA) method. The optimum CoMSIA model with region focusing yielded satisfactory statistical results: leave-one-out cross-validation correlation coefficient (q^2) was 0.571 and non-cross-validation correlation coefficient (r^2) was 0.951. Furthermore, the results of internal validation such as bootstrapping, leave-many-out cross-validation, and progressive scrambling as well as external validation indicated the rationality and good predictive ability of the best model. In addition, molecular docking elucidated the conformations of compounds and key amino acid residues at the docking pocket, MD simulation further determined the binding process and validated the rationality of docking results.

Introduction

Brominated flame retardants (BFRs) are the cheapest way to reduce the flammability of materials and improve their fire resistance (Rahman et al., 2001). Until now, more than 75 different BFRs have been commercially produced (Covaci et al., 2011). Three commercial polybrominated diphenyl ethers (PBDEs) products, namely PentaBDE, OctaBDE and DecaBDE, have been or still in widespread use as BFRs (de Wit et al., 2010). Therefore, PBDEs have become ubiquitous contaminations and many environmental studies have focused on them (Chen et al., 2011; Johnson-Restrepo and Kannan, 2009).

As endocrine-disrupting chemicals, PBDEs have agonistic and antagonistic activities against estrogen, androgen, and thyroid receptors (Kuriyama et al., 2007; Legler and Brouwer, 2003; Peters et al., 2006). Certain PBDEs (e.g. BDE-47) can be converted to hydroxylated metabolites (HO-PBDEs) by metabolic processes (Hakk and Letcher, 2003), and the latter also show endocrine-disrupting property to a great extent. Some studies have shown that some HO-PBDEs, in particular 6-OH-BDE-47, could competitively bind to human transthyretin (TTR, one of the thyroid hormone transport proteins in plasma for the thyroid hormones T_3 and thyroxine T_4), and displace T_3 and T_4 from TTR, which may lead to a low level of T_3 and T_4 and consequently disturb thyroid hormone homeostasis (Kitamura et al., 2008; Kojima et al., 2009; Meerts et al., 2000). HO-PBDEs have attracted increasing concern (Ueno et al., 2008; Wan et al., 2010; Zhao et al., 2010).

There are two major subtypes of thyroid hormone receptors (TRs), α (TRα) and β (TRβ), which are expressed by different two genes (Malm et al., 2009). Many effects of thyroid hormones on the heart rate and rhythm are mediated through TRα (Johansson et al., 1998), while most actions of thyroid hormones on the liver and other tissues are mainly mediated through activation of TRβ (Forrest and Vennstrom, 2000; Takeda et al., 1992). TRβ is widely distributed in adults, especially in the liver, and its concentrations are generally higher than those of the TRα.

Nowadays, assessment of thyroid hormone activity of chemicals remains a labor-intensive, time-consuming and expensive operation. Thus, it is imperative to develop more efficient and cost-effective alternative methods. As an effective tool for drug design and chemical safety evaluation, quantitative structure–activity relationship (QSAR) method have been applied to discovery and design selective thyroid ligands that interact selectively with TRβ. For instance, based on several series of new synthesized ligands selective for TRβ, a number of QSAR models have been reported: Vedani et al. (2006, 2007)

* Corresponding author. Fax: +86 25 89680356.
E-mail address: hongxiayu01@yahoo.com.cn (H. Yu).

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http://dx.doi.org/10.1016/j.taap.2012.08.030

developed satisfactory 4D-6D QSAR models using Quasar® and Raptor® software; Liu and Gramatica (2007) correlated the descriptors of the aforementioned new synthesized ligands to binding affinity of them to TRβ on the basis of multiple linear regression algorithm; 2D-QSAR model was also established by use of descriptors calculated by CODESSA program and projection pursuit regression method (Ren et al., 2007); 3D-QSAR studies on these ligands were performed combined with a molecular docking approach (Du et al., 2008). These models can identify some critical structural features for high binding affinity of new ligands to TRβ. Recently, Li et al. (2010) have tested hormone activities of a series of OH-PBDEs to TRβ and constructed 2D-QSAR model based on partial least squares algorithm. However, in many cases, the important structural features obtained from 2D-QSAR is not always simple (Hao et al., 2011). Besides, traditional 2D method does not take 3D structural features into account and lacks of spatial information about compounds, therefore, comprehensive molecular structure features that contribute to the thyroid hormone ability of OH-PBDEs are still limited.

3D-QSAR model, especially, the popular Comparative Molecular Similarity Index Analysis (CoMSIA) method takes the 3D conformation property of compounds into consideration, can be helpful in exploring and visualizing useful structural information that influences the hormone activity of compounds. To date there have been no reports for 3D-QSAR studies on hormone activities of OH-PBDEs to TRβ. Therefore, more attention should be paid to further investigations on the structure–activity relationship and the interaction mechanism of OH-PBDEs and TRβ. In the present study, a set of in silico methods including 3D-QSAR, molecular docking and molecular dynamics (MD) simulation have been performed to identify structural features contributing to the thyroid hormone activity and to elucidate the probable binding mode between OH-PBDEs with TRβ. The stability and predictive ability of the developed best model were estimated with internal validation (bootstrapping, 10-fold and 5-fold cross-validation and progressive scrambling) and validated statistically with external validation. The obtained results not only provide some insights into the structural basis for potential thyroid hormone disruption ability of HO-PBDEs but also help understanding interactions between ligands and receptor.

Materials and methods

Data sets

Thyroid hormone activities of 18 HO-PBDEs to human TRβ were taken from the recent literature (Li et al., 2010). The hormone activities of compounds were determined by recombinant two-hybrid yeast assay and corresponding $pREC_{20}$ values ($-\log REC_{20}$, where REC_{20} was the concentration of compound inducing 20% of the maximum effect) were used as dependent variables in the 3D-QSAR analysis. The compounds and corresponding thyroid hormone activity were listed in Table 1. The whole data set was divided into training set (containing 14 compounds) and test sets (containing 4 compounds) in an approximate ratio of 4:1. The training set was used to construct 3D-QSAR models and the test set was used for the model validation. The select of the test set was made on the basis of that they can appropriate represented structural diversity of the whole data set and cover the range of $pREC_{20}$ values. The compounds in the training set and test set were consisted with the ones in the literature (Li et al., 2010).

Molecular docking

To study the binding modes of HO-PBDEs at the active site of TRβ protein and get the optimal conformation used to the development of 3D-QSAR model, molecular docking was performed using Surflex-Dock module in SYBYL® 7.3 software (Tripos, Inc). The 3D structure of each compound in the data set was constructed using the Sketch Molecule module in SYBYL® software. Energy minimizations were performed using Tripos force field with the distance dependent-dielectric function and Powell method with a convergence criterion of 0.001 kcal/mol Å. Partial atomic charges were calculated by the Merck molecular force field 94 (MMFF94) (Halgren, 1996), which made significant approximations in the treatment of important physical interactions and calculated the potential energy more accurate. The crystal structure of thyroid hormone receptor complex with a β-selective ligand (PDB code 1NAX) used in molecular docking was obtained from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/).

The ligands were docked into corresponding protein's binding site with an empirical scoring function and a patented search engine in Surflex-Dock. Prior to initiating the docking simulations, the natural ligand and structural water molecules were removed from the crystal structure and the polar hydrogen atoms were added in standard geometry by using the Biopolymer module implemented in SYBYL® software. Kollman-all atom charges were assigned to protein atoms. The automated docking manner was applied in the present work. In this process, two parameters, i.e., protomol_bloat and protomol_threshold, which determine the volume and extent of the protomol, were specified default values of 1.00 and 0.50, respectively. With other parameters setting default, Surflex-Dock produced the top 10 options of binding conformation for each ligand ranked by total scores. The docking conformation supposed to demonstrate the possible bioactive conformation of ligand was selected based on the following two criteria: (i) the orientation of the conformation of the ligand in a similar with that of the cocrystallized ligands, and (ii) the conformation possessed high docking score. During the docking process, the ligand compounds were considered to be flexible and the receptor protein was regarded as being rigid.

Molecular alignment

Molecular alignment is considered to be one of the most critical steps in 3D-QSAR studies (AbdulHameed et al., 2008), and several alignment rules have been described in the literature (Jiang, 2010; Liu et al., 2010). To derive the best possible 3D-QSAR statistical model, two different alignment rules were employed in this study. The first one was ligand-based alignment. In this process, Compound 16 with highest activity was chosen as the template molecule and the rest of the compounds were aligned to it using of Align Database command in SYBYL® software. The other approach was receptor-based alignment. In this approach, the optimal conformations of all compounds derived from dock analysis were assigned MMFF94 partial

Table 1
Thyroid hormone activities of selected OH-PBDEs.

No.	Compound	$pREC_{20}$ (exp.)	$pREC_{20}$ (pred.)	Residual
1[a]	3′-OH-BDE-7	7.64	7.89	−0.25
2	4′-OH-BDE-17	8.66	8.95	−0.29
3	3′-OH-BDE-28	7.28	7.35	−0.07
4	2′-OH-BDE-28	8.07	7.98	0.09
5	4-OH-BDE-42	9.72	9.34	0.38
6	4′-OH-BDE-49	7.87	7.45	0.42
7	3-OH-BDE-47	8.77	8.96	−0.19
8[a]	5-OH-BDE-47	8.44	8.48	−0.04
9[a]	6-OH-BDE-47	10.43	9.59	0.84
10	4-OH-BDE-90	7.63	7.72	−0.09
11	6-OH-BDE-85	9.77	10.29	−0.52
12[a]	6-OH-BDE-87	9.29	9.11	0.18
13	6-OH-BDE-82	10.44	10.61	−0.17
14	6′-OH-BDE-99	9.62	9.72	−0.10
15	5′-OH-BDE-99	10.34	10.79	−0.45
16	6-OH-BDE-157	12.20	11.82	0.38
17	6-OH-BDE-140	11.31	10.81	0.50
18	3′-OH-BDE-154	10.76	10.63	0.13

[a] Test set.