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Predicting anti-androgenic activity of bisphenols using molecular docking and quantitative structure-activity relationships

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HIGHLIGHTS

- The underlying antagonistic mechanism of bisphenols on human androgen receptor (hAR) was deciphered.
- A QSAR model was developed to predict the anti-androgenic activity of bisphenols.
- The data gap for other bisphenols on their anti-androgenic activity was filled.

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ABSTRACT

Both *in vivo* and *in vitro* assay indicated that bisphenols can inhibit the androgen receptor. However, the underlying antagonistic mechanism is unclear. In this study, molecular docking was employed to probe the interaction mechanism between bisphenols and human androgen receptor (hAR). The binding pattern of ligands in hAR crystal structures was also analyzed. Results show that hydrogen bonding and hydrophobic interactions are the dominant interactions between the ligands and hAR. The critical amino acid residues involved in forming hydrogen bonding between bisphenols and hAR is Asn 705 and Gln 711. Furthermore, appropriate molecular structural descriptors were selected to characterize the non-bonded interactions. Stepwise multiple linear regressions (MLR) analysis was employed to develop quantitative structure-activity relationship (QSAR) models for predicting the anti-androgenic activity of bisphenols. Based on the QSAR development and validation guideline issued by OECD, the goodness-of-fit, robustness and predictive ability of constructed QSAR model were assessed. The model application domain was characterized by the Euclidean distance and Williams plot. The mechanisms of the constructed model were also interpreted based on the selected molecular descriptors i.e. the number of hydroxyl groups (*nROH*), the most positive values of the molecular surface potential ($V_{s,max}$) and the lowest unoccupied molecular orbital energy (E_{LUMO}). Finally, based on the model developed, the data gap for other twenty-six bisphenols on their anti-androgenic activity was filled. The predicted results indicated that the anti-androgenic activity of seven bisphenols was higher than that of bisphenol A.

1. Introductions

Increasing concern over bisphenol A (BPA) as an endocrine-disrupting chemical (EDC) and its possible effects on human health have prompted the removal of BPA from consumer products (European Commission, 2011; Health Canada, 2010). As a result, the uses of BPA structural analogues have been gradually increasing. Those BPA structural analogues usually consist of two phenolic rings joined by a bridging alkyl moiety or other chemical structure and are designated bisphenols. The bisphenols have been used as base chemical in the manufacturing of fire-resistant polymers, polycarbonate plastics, resin lining of food and beverage cans, dentistry sealants, and thermo-sensitive coatings for paper

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materials (Delfosse et al., 2012). With the increasing use of the bisphenols, they has frequently detected in indoor air, dust, surface water, drinking water, influents, effluents, sediments, foods and biota up to now (Liao et al., 2012a, 2012b, Liao and Kannan, 2013; Yang et al., 2013b; Song et al., 2014; Wang et al., 2015; Zhang et al., 2016). As the molecular structures of bisphenols are similar to BPA, whether they also could disturb the endocrine system of organism is expressed increasing concern.

To date, both the *in vitro* assays and *in vivo* assays results indicated that bisphenols shown distinct disrupting activities with the different hormone signaling pathway (Rivas et al., 2002; Coleman et al., 2003; Kitamura et al., 2005; Riu et al., 2011; Li et al., 2012; Ji et al., 2013; Naderi et al., 2014; Rosenmai et al., 2014; Shi et al., 2015; Rochester and Bolden, 2015). Activating and/or inhibiting the receptors and synthetases activity of steroid hormone signaling pathway is the critical pathway for bisphenols to disturb the endocrine system (Rochester and Bolden, 2015). For example, Kitamura et al. (2005) comparatively examined the endocrine-disrupting activities of BPA and 19 bisphenols by means of different *in vitro* reporter assays. Their tested results indicated that most bisphenols exhibited estrogenic activity and anti-androgenic activity. While only four bisphenols exhibited thyroid hormonal activity. Recently, Ji et al. (2013) and Shi et al. (2015) investigated the effect of bisphenol S (bis-(4-hydroxyphenyl)sulfone; BPS) and bisphenol AF (1,3-trifluoro-2,2- bis-(4-hydroxyphenyl)propane, BPAF) on the steroid hormone signaling pathway of zebrafish, respectively. Their results indicated that BPS and BPAF exposure could modify the histology of zebrafish testis/ovary and influence the homeostasis of steroid hormone (testosterone and estradiol). Activating estrogen receptor and/or inhibiting the androgen receptor may be the dominant reason for the observed phenomena. Clarifying the interaction mechanism between bisphenols and estrogen receptor and androgen receptor is of vital importance to help in understanding the toxicity mechanism and prioritizing chemicals for further testing.

Thus far, almost all of the previous studies were focus on probing the interaction mechanism between bisphenols and estrogen receptor (ER). For example, Coleman et al. (2003) developed CoMFA (Comparative molecular field analysis) models, CoMSIA (Comparative molecular similarity indices analysis) models, and HQSAR (Hologram quantitative structure activity relationship) models to predict the estrogenic activity of bisphenols. Recently, Delfosse et al. (2012) analyzed the binding pattern between three bisphenols and ER. Zhuang et al. (2014) probed the molecular recognition process of seven halogenated BPAs toward ERα by molecular modeling. Ng et al. (2015) performed molecular dynamics simulations to understand the mechanisms between bisphenols and ER, and developed a predictive model by employing molecular docking. However, the disrupting mechanisms of bisphenols interaction with androgen receptor (AR) have not yet examined up to now. It was the purposes of the present study that molecular docking integrated with quantitative structure-activity relationship (QSAR) modeling methods will be employed to modeling the anti-androgenic activity of bisphenols. Then, the data gaps for other bisphenols on their anti-androgenic activity will also be filled based on the developed model.

2. Materials and methods

2.1. Overall study design

This study contained four components. The relationship of the four components was depicted in Fig. 1. Part one was obtained the anti-androgenic activity data of Bisphenols. Part two was probed the mechanism of antiandrogen action by employing molecular docking method. On the basis of the results from the molecular docking, appropriate molecular descriptors will be selected to describe the critical interactions between the bisphenols and human AR (hAR). Then, a predictive model will be constructed and evaluated. Finally, based on the model developed, the data gap for other bisphenols without experimental data will be filled on their anti-androgenic activity.

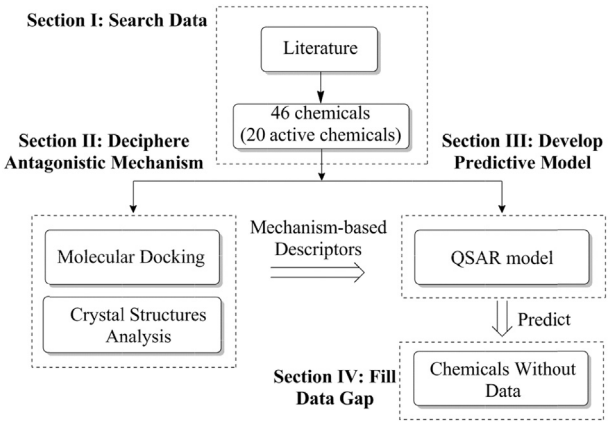

Fig. 1. Overall study design: the relationship of different parts.

2.2. Data sets

The experimental data sets were obtained from the study of Kitamura and co-workers (Kitamura et al., 2005). The data sets contain 20 Bisphenols (Data set I) (Table 1). The tested toxicity effects of these Bisphenols were anti-androgenic activity, which were tested by NIH3T3 cells carrying ARE-luciferase reporter gene. The androgen receptor antagonistic effect was expressed as (IC_{50}), which represent a chemical inhibited the 50% androgenic activity of dihydrotestosterone. The original data sets were randomly divided into a training set (3/4) and a validation set (1/4). The training set was employed to develop QSAR models, and the validation set was used to evaluate the predictive ability of the model. Except for the 20 Bisphenols, another 26 Bisphenols without available antagonistic activity information were also collected. Their anti-agonistic activity data will be filled by our developed model. The molecular structures of all the Bisphenols were listed in Table S1 of the Supplementary material.

For QSAR analysis, the logarithm of relative potency (log*RP*) was adopted. The log*RP* of a tested compound was defined as following:

$$\log RP = \log \frac{IC_{50,\mathrm{FT}}}{IC_{50,\mathrm{BPAs}}} \quad (1)$$

where $IC_{50,\mathrm{FT}}$ and $IC_{50,\mathrm{BPAs}}$ were the androgen receptor anti-agonistic effect concentration of flutamide and bisphenols, respectively.

2.3. Molecular modeling

Molecular modeling was employed to analyze the binding patterns of bisphenols in the hAR ligand binding sites. On the basis of the optimized structures from molecular docking, binding pattern analysis was performed. All the calculations except for the hydrophobic interaction analysis were performed with Discovery Studio 2.5.5 (Accelrys Software Inc). The hydrophobic interaction was characterized by the LigPlus program (Laskowski and Swindells, 2011).