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Noncovalent interactions between hydroxylated polycyclic aromatic hydrocarbon and DNA: Molecular docking and QSAR study

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) can be hydroxylated by CYP450-oxidases (1A1 and 1B1 mainly) and may cause DNA damage and cancer. However, the mechanism of such interactions has not been fully understood. In this study, an integrated molecular docking and QSAR approach was employed to further investigate the binding interactions between hydroxylated PAHs (HO-PAHs) and calf thymus DNA (CT-DNA). Molecular docking, hydrogen-bonding, hydrophobic and π–π interactions were observed to be characteristic interactions between HO-PAHs and DNA. An optimum QSAR model with good robustness and predictability was developed based on the molecular structural parameters calculated by the density function theory and partial least squares. Additionally, the developed QSAR model indicated that the molecular size, polarizability and electrostatic potential of HO-PAHs were related to the binding affinities to DNA.

Abbreviations: PAHs, polycyclic aromatic hydrocarbons; K_b, binding constants; 1-OHNAP, 1-hydroxynaphthalene; 2-OHFLU, 2-hydroxyfluorene; 9-OHFLU, 9-hydroxyfluorene; 2-OHPHE, 2-hydroxyphenanthrene; 3-OHPHE, 3-hydroxyphenanthrene; 4-OHPHE, 4-hydroxyphenanthrene; 9-OHPHE, 9-hydroxyphenanthrene; 3-OHFLT, 3-hydroxyfluoranthene; 1-OHPYR, 1-hydroxypyrene; 2-OHBcPh, 2-hydroxybenzo[c]phenanthrene; 3-OHBcPh, 3-hydroxybenzo[c]phenanthrene; 4-OHBcPh, 4-hydroxybenzo[c]phenanthrene; 5-OHBcPh, 5-hydroxybenzo[c]phenanthrene; 3-OHBaP, 3-hydroxybenzo[a]pyrene; 4-OHBaP, 4-hydroxybenzo[a]pyrene; 5-OHBaP, 5-hydroxybenzo[a]pyrene; 6-OHBaP, 6-hydroxybenzo[a]pyrene; 7-OHBaP, 7-hydroxybenzo[a]pyrene; 9-OHBaP, 9-hydroxybenzo[a]pyrene; 10-OHBaP, 10-hydroxybenzo[a]pyrene; 12-OHBaP, 12-hydroxybenzo[a]pyrene; 3-OHBkF, 3-hydroxybenzo[k]fluoranthene; 7-OHBbF, 7-hydroxybenzo[b]fluoranthene; 2-OHIPY, 2-hydroxyindeno[1,2,3,-cd]pyrene; $E_{binding}$, binding energy; QSARs, quantitative structure-activity relationships; PLS, partial least squares; R^2, squared correlation coefficient; Q^2_{CUM}, the fraction of the total variation of the dependent variables that can be predicted by all the extracted components; Q^2_{EXT}, external explained variance; SE, standard error.

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1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are classed as persistent organic pollutants (POPs) under the Stockholm Convention. They are a large class of ubiquitous organic pollutants and have received great attention because of their carcinogenic, teratogenic and mutagenic properties (Gallegos et al., 2001; Kumar et al., 2001; Borosky and Laali, 2005; Xue and Warshawsky, 2005). In most cases, PAHs can be hydroxylated by CYP450-oxidases, which is a key step in the activation process to produce the polar biochemically reactive electrophilic species (ultimate carcinogenic metabolites) capable of interacting with cellular macromolecules, particularly nucleic acids and proteins (Zhou et al., 2003). Most recently, hydroxylated PAHs (HO-PAHs) have emerged and are causing increasing concern due to their detection in human hair (Schummer et al., 2009), urine (Campo et al., 2010; Li et al., 2010c), and expired air samples (Li et al., 2010c); these agents have even been found in the bile of deep-sea fish (Escartin and Porte, 1999).

Previous studies have shown that certain HO-PAHs can affect hormone homeostasis, as they act as potent ligands for binding to the aryl hydrocarbon receptor (AhR) and even interact with DNA (Wang et al., 2009a; Wenger et al., 2009; Ohura et al., 2010; Wei et al., 2010). For instance, it was reported that 5 HO-PAHs (2-hydroxychrysene, 2-hydroxyphenanthrene, 1-hydroxypyrene, 2-hydroxynaphthalene and 1-hydroxynaphthalene), which showed structural similarities to 17β-estrodiol, exhibit estrogenic activities (Wenger et al., 2009). Ohura et al. (2010) reported that HO-PAHs showed AhR-ligand binding activities by a recombinant yeast assay system, especially the hydroxylated derivatives of naphthalene. Additionally, a clear morphological change of calf thymus DNA (CT-DNA) from linear type to condensation form was observed after binding with 9-hydroxyfluorene in atomic force microscopy (Wang et al., 2009a). Recently, Wei et al. (2010) also reported that 11 PAHs metabolites predominantly interacted with human p53 DNA by intercalation instead of groove binding. However, the detail mechanisms of DNA binding associated with HO-PAHs remain unclear. Hence, it is of great importance to improve our understanding of the mechanism of interactions between HO-PAHs and DNA.

The formation of DNA adducts is a key step in DNA damage, which could lead to malignancy (Radwan and Ramsdell, 2008). The proven key carcinogenic product, benzo[a]pyrene-r-7,t-8-dihydrodiol-t-9,10-epoxide (BPDE), intercalates rapidly with DNA base pairs to form a complex, which undergoes protonation to yield an intercalated triol carbonium ion intermediate (Geacintov et al., 1981; Meehan et al., 1982). However, the standard samples are limited with respect to making experimental determinations of the binding constants (K_b) of each HO-PAHs to DNA. Therefore, an alternative approach, quantitative structure–activity relationship (QSAR), is suggested by the new EU chemicals legislation REACH (European Commission., 2002), which has been successfully used in acute toxicity studies (Christen et al., 2010; Li et al., 2010b), mixture toxicity (Arrhenius et al., 2004; Neuwoehner et al., 2010), endocrine disrupting activities (Li et al., 2009, 2010a) and photo-induced toxicity (Wang et al., 2009b; Zhang et al., 2010) of organic compounds.

DNA sequences may be changed by the mutagens (Besaratinia and Pfeifer, 2006). Traditional experimental techniques are employed to determine the DNA damage, such as single cell gel electrophoresis (SCGE) (Lee and Steinert, 2003), the micronucleus assay (Grisolia, 2002) and other systems such as the sister-chromatid exchange assay (Tofilon et al., 1985). However, it is difficult to determine the base substitution and the position of mutation only by experimental approaches (Kozack and Loechler, 1999; Joung et al., 2009), which limit the comprehensive understanding of the mechanism of DNA damage. Consequently, further studies are required on the interactions between ligands and DNA by molecular simulation to clarify the mechanism of DNA damage (Kitchen et al., 2004; Moitessier et al., 2008). Molecular simulation, such as molecular docking, has become an important approach to elucidate the interactions between ligands and macromolecular targets, which is a rapid, low-cost detection system which has been successfully used in DNA–ligand interactions (Rabinowitz et al., 2009), xenoestrogen screening (Amadasi et al., 2009) and molecular recognition (Erickson et al., 2004).

In this study, an integrated molecular docking and QSAR approach was employed to investigate the binding interactions between HO-PAHs and CT-DNA. Molecular docking was performed to define a model for the comprehension of the binding interactions between ligands and receptor. By observing the mechanism of interactions, appropriate molecular structural parameters computed by the density function theory (DFT) were adopted to construct QSAR models. These developed QSAR models were externally validated and the applicability domain was depicted. Furthermore, from the developed QSAR models, critical molecular structural features related to DNA-adducts formation were identified.

2. Materials and methods

2.1. Data compilation and the chemical domain

The K_b values of 24 HO-PAHs with CT-DNA were taken from Wang et al. (2009a), and then converted into the form of $\log K_b$ (Table 2). The K_b values were determined by a previously established electrochemical displacement method. More details can be found in the previous study (Wang et al., 2009a).

2.2. Molecular docking

The binding mode for the HO-PAHs to CT-DNA was investigated by CDOCKER, which has been incorporated into Discovery Studio 2.5 (Accelrys Software Inc.) through the Dock Ligands protocol. CDOCKER is an implementation of a docking tool based on CHARMm forcefield that has been proved to be viable. The crystal structure of DNA (PDB entry code: 1DJD) was retrieved from the Brookhaven Protein Database (PDB http://www.rcsb.org/pdb). Hydrogen atoms were added and the crystallographic waters were removed. In CDOCKER,