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Binding mechanism of triclocarban with human serum albumin: Effect on the conformation and activity of the model transport protein

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ABSTRACT

Triclocarban (TCC) is an antibacterial agent in antibacterial personal care products. Human serum albumin (HSA) is the transport protein with the ligand binding properties. The current study was undertaken to identify the binding mechanism of TCC with HSA by using biophysical methods. The fluorescence and UV–vis spectral results showed that the fluorescence quenching of HSA by TCC was static quenching by the formation of HSA-TCC complex. The binding constants were obtained by molecular modeling and fluorescence quenching, and the results indicated the existence of strong interaction between HSA and TCC with binding constant $K_b \sim 10^5$ L/mol. TCC can enter into the binding pocket of domain II of HSA by mainly hydrophobic and hydrogen bonds forces. The conformations of TCC and HSA are all changed during the binding interaction of them. We hope that this work will provide some useful information for understanding the activity and mechanism of antibacterial agent with the transport protein.

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1. Introduction

Triclocarban (TCC, Fig. 1, A) is first identified as an antibacterial agent and is widely employed as an active ingredient in antibacterial personal care products, such as bar soap, toothpaste, deodorant, and cleansing lotions [1,2]. The popularity of products containing TCC continues, drawing people's great attention including its toxicity, bioaccumulation potential, endocrine effects, and potential for antibacterial resistance development [3]. The U.S. Environmental Protection Agency classified TCC as a high production volume chemical requiring environmental risk assessment [4]. Human exposure to TCC has been associated with methemoglobinemia [5]. Recent findings from Hammock's group indicated that TCC had significant biological effects on mammalian targets [6]. At high concentrations, TCC might act as an endocrine disruptor [7]. TCC is a potent inhibitor of the enzyme soluble epoxide hydrolase (sEH) and can covalently bind to proteins by oxidative metabolism [8]. In addition, TCC could serve as a potential biomarker for human exposure to TCC [9]. Because of the widespread use of TCC, the potential adverse health effects of TCC on humans are being constantly discovered. Therefore, a need exists to identify the binding mechanism of TCC with the model transport protein, human serum albumin (HSA) (Fig. 1, B).

The disposition of toxic compounds is often affected by their binding with HSA, which is the most abundant in human blood bloodstream and presents at a concentration of ~50 mg/mL [10,11]. Being one of the most abundant proteins in the blood plasma, HSA is known as the "silent receptor" to bind with many drugs and toxicants [12–14] because of its tertiary structure consisting of three homologous domains (I, II, and III), and each domain contains two subdomains A and B [15]. Two major drug binding sites (Site I and II) are situated within subdomain IIA and IIIA of HSA (Fig. 1 B) [16]. Owing to the effects of many drugs or toxicants binding interactions with HSA on their distributions, bound/free concentrations, and metabolisms in the circulation, interactions of them with HSA is consistently the hotspots in the research of pharmacology and environmental toxicology [10,17–21]. Zhang et al. have studied the binding interactions of some benzophenone UV stabilizers with HSA by using spectroscopy and molecular dynamics simulations, which indicated that the degradation products of UV stabilizers have higher binding affinities to HSA, suggesting higher potencies in causing adverse effects on human health [19,20]. Liu et al. have selected HSA as protein model to analysis the binding mechanism of it with CdTe quantum dots, chrysoidine, and 4-aminoantipyrine and to deep insight into the toxic effects of them on the activity and confirmation of protein [22–24]. However, to the best of our knowledge the binding interaction of TCC with HSA has not been investigated. Moreover, the structure, stability, and physicochemical properties of HSA in the presence of TCC have not been explored earlier.

In the present work, we have investigated the binding interaction of TCC with HSA and its effect on the structure and activity of HSA by using

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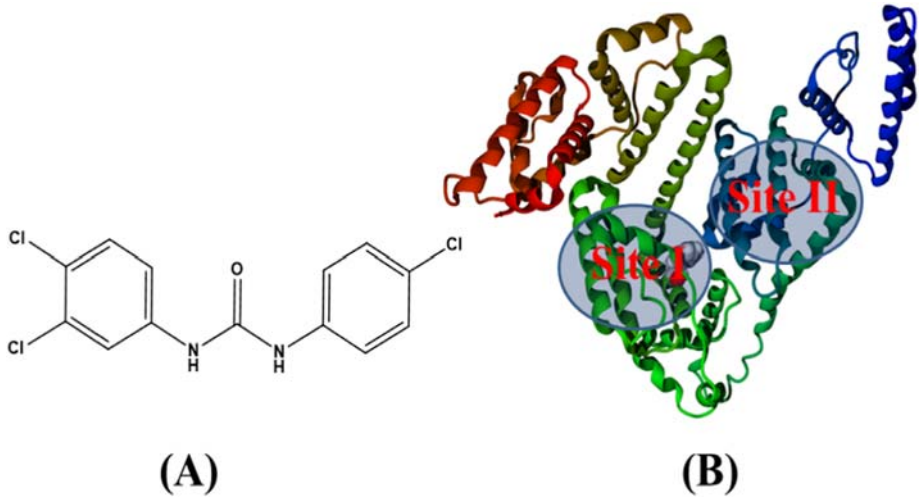

Fig. 1. Molecular structure of TCC (A) and HSA (B).

fluorescence, UV — vis absorption, and circular dichroism (CD) spectroscopy. Molecular docking method was used to explore the binding location of TCC within the HSA. In addition, the esterase-like activity of HSA in the absence and presence of TCC was assayed by measuring the hydrolysis of *p*-nitrophenyl acetate. Ultimately, the findings of this study will provide the molecular level detail on interaction between TCC and the model transport protein in human blood in order to overall assess the contribution to toxic responses made by TCC.

2. Materials and methods

2.1. Chemical reagents

HSA(A1887, fatty acid and globulin free, MW ~66.5 kDa) and TCC (purity, >99%) were purchased from Sigma Chemical Co. (St. Louis, MO) and Shanghai Aladdin biochemical reagent Limited by Share Ltd., respectively. 8-anilino-1-naphthalenesulfonic acid (ANS) (purity, >97%), bilirubin(purity, >98%), and 4-nitrophenyyl acetate(purity, >98%) were purchased from Sigma Chemical Co. (St. Louis, MO), Other reagents were of analytical grade. All the experimental used water was ultra-purified distilled water.

2.2. Methods

2.2.1. UV–vis absorption spectroscopy

UV–vis absorption spectra of HSA, TCC, and HSA-TCC system were registered with a SPECORD S600 spectrophotometer (Jena, Germany) at room temperature. The esterase-like activity of HSA in the absence and presence TCC were also recorded on a SPECORD S600 spectrophotometer. *p*-Nitrophenyl acetate was used as the substrate that was resolved into *p*-nitrophenol with a molar extinction coefficient $\varepsilon =$ 17,700 L/(mol cm) at 405 nm [25].

2.2.2. Fluorescence spectroscopy

The steady-state fluorescence spectra of HSA were recorded with a LS-55B Spectrofluorometer (Perkin-Elmer, USA) in a 1 cm optical path fluorescence quartz cell. The scan range of steady-state fluorescence spectra was set from 300 to 500 nm by setting the excitation wavelength at 280 nm with increments of 5 nm. The displacement of ANS from HSA was analyzed by using the fluorescence spectral method. The fluorescence spectra of ANS in HSA were measured by exciting at 370 nm with emission wavelength range from 400 to 600 nm.

2.2.3. CD spectropolarimetry

CD spectra of HSA in the absence and presence of TCC were acquired by a Chirascan spectrometer (Applied Photophyysics Ltd., Leatherhead, Surrey, UK) using a quartz cell of 1 mm path length. Scans speed was set at 50 nm/min with a slit width of 1 mm. The different content including a-helix, β-sheet, β-turn, and random coil of protein have been estimated by using he program CD spectra deconvolution program (CDNN). In addition, the scanning range of bilirubin-HSA system was 300–550 nm using a quartz cell of 10 mm path length. Scans speed was set at 50 nm/min with a slit width of 1 mm.

2.2.4. Molecular modeling

The geometry of TCC was optimized by using Gaussian 09 at Density Functional (DFT) B3LYP/6-311^{++} G (d, p) level [26]. In addition, the computed absorption spectra, computed excitation energies and electronic transition configurations of TCC before binding with HSA were obtained at Time Dependent DFT(TD-DFT) B3LYP/6-311^{++} G (d, p) level. In addition, the molecular orbital plots of TCC after binding with HSA was also obtained by using energy calculation at Gaussian 09 DFT B3LYP/6-311++G (d, p) level. The 3D structure of HSA (PDB ID 3LU7) was obtained from the website of Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank [27,28]. Then AutoDock 4.2.3 and AutoDock tools v 1.5.4 were used to model the binding interaction of TCC with HSA [29]. The compound that bound with the original HSA and water molecules were removed and polar hydrogen atoms were added. In addition, Kollman united atom type charges were calculated and added, and salvation parameters were also added by using AutoDock tools v 1.5.4. In order to find the possible binding sites of TCC in HSA, a grid volume with 126 × 126 × 126 grid points was selected to cover all surface of HSA. The number of genetic algorithm (GA) runs were set at 100, the population size was set at 150, the maximum number of evals, generations, top individuals were set at 150, 2,500,000, 27,000, and 1, respectively. In addition, the number of generations for picking worst individual was set at 10, and all other parameters were default settings parameters. At last, the docked model with the lowest docking energy was selected to present the binding mode of TCC with HSA by using the Molegro Molecular Viewer software [30].

3. Results and discussion

3.1. DFT calculation of TCC

Herein, DFT calculation was carried out to obtain the computed absorption spectra and isodensity plots orbital for the Highest Occupied

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