様式 7

論　文　内　容　要　旨

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学位論文題目	分子動力学法及び密度汎関数法を用いた CYP2D6 における チオリダジンの代謝機構に関する研究		

Cytochrome P450s (CYPs) is now known to exist in multiple forms and to play important roles in the oxidation of endogenous substrates such as androgens and estrogens for biofunctional control (Sasahara K et al., *J. Neurosci.* (2007)) as well as tremendous range of drugs (Sasahara K et al., *Drug. Metab. Dispos.* (2015)). In fact, CYPs are involved in the catalysis of approximately 75% of drug metabolism reactions, suggesting CYPs are most important drug-metabolizing enzymes. Therefore it is important to clarify the metabolic profiles and mechanism of drugs. CYP2D6 is second most responsible for the CYP-mediated metabolism. Thioridazine (THD) is one of the phenothiazine-type antipsychotics, which exhibit dopamine D_2 antagonistic activity. THD shows characteristic metabolic profiles compared to other phenothiazine-type antipsychotics such as chlorpromazine. The sulfur atom attached to the phenothiazine ring is preferentially oxidized mainly by CYP2D6, i.e. the 2-sulfoxide is a major metabolite, and interestingly this metabolite shows more potent activity against dopamine D_2 receptors than THD. On the other hand, the formation of this metabolite causes many serious problems for its clinical use. Recently, Wang et al. revealed the crystallographic structure of THD with CYP2D6. In the current study, *in vitro* metabolic profiles of THD with CYP2D6 as well as other CYP isozymes were experimentally examined using LC-UV-MS/MS under experimental concentrations closer to the effective blood ones. At the same time, the binding and reaction mechanisms at the atomic and electronic levels were computationally examined based on the assumption as to whether or not the different crystallographic binding poses correspond to the different metabolites. The binding and oxidative reaction steps in the whole metabolic process were investigated using molecular dynamics (MD) and density functional theory (DFT) calculations, respectively. The observed metabolites and crystallographic binding poses can be related to each other by means of MD and DFT calculations. The results presented here will act as links between crystallographic, dynamic, and kinetic pictures, and the observed metabolism of THD with CYP2D6. The current study demonstrated the essential importance of the orientation of the substrate in the reaction center of CYP2D6 for the metabolic reaction (from Sasahara K et al., *Bioorg. Med. Chem.* (2015)).

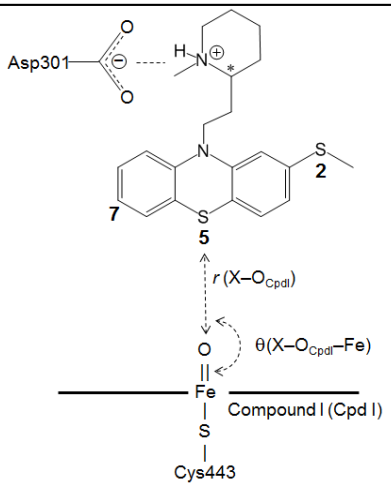

Figure 1. THD, Compound I, and Asp301. *: asymmetric carbon

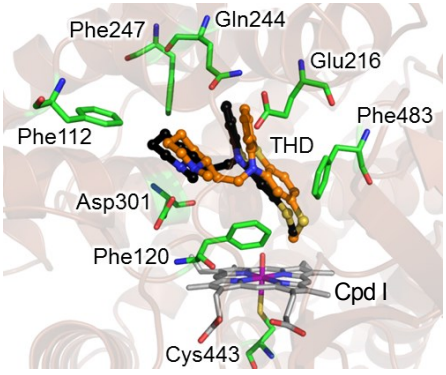

Figure 2. Calculated equilibrium binding poses (orange) together with crystallographic ones (dark).