molecular dynamics simulation of CYP2D6 and CYP2C19

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CYP2D6 and CYP2C19 affects metabolization of some drugs, and examination of its mechanism of action is important for understanding drug metabolism. CYPs is expressed not only in the liver but also in the small intestine, and is known to affect the first pass effect. Enzymatic reactions are altered depending upon pH, temperature, and other internal conditions of the body, resulting different the liver or small intestine, though difficult to be evaluated. In the previous study, we have reported the possibility that CYP2D6 isolated from the human liver and small intestine may have different activities. In the present study, we used molecular dynamics calculations to investigate the effects of environmental conditions on the activity and stability of CYP2D6 and 2C19 such as pH around the protein.

AMBER16 was used for molecular dynamics simulation of CYP2D6 and 2C19, and the wild type protein registered in Protein Data Bank was used as the initial structure (PDB ID 3qm4, 4gqs). In CYP2D6, there are 13 His residues, and His376 is in the proximity of heme iron. When periodic boundary condition were used with these residues differing in the side chain dissociation state (pH6.5, 7.5) to evaluate structural changes in the active center.

When His was dissociated, changes in the crystal structure were observed for His416, His477, and His478 residues exposed on the surface of CYP2D6; the side chain moved by 1.8 Å. On the other hand, when His376 in the vicinity of the active center was dissociated, the side chain of His376 itself was twisted, resulting in the maximum deviation of about 1 Å with about 60° distortion from the crystal structure.

However, virtually no changes from the crystal structure occurred with respect to the heme group. The concluded that structural differences between pH 6.5 and pH 7.5 have little effect on the CYP2D6 activity and stability.