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Improvement of Solubility of Poorly Water-soluble Drugs Using Lipocalin-type Prostaglandin D Synthase

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Extended Abstract

Lipocalin-type prostaglandin D synthase (L-PGDS) is a member of the lipocalin superfamily, which is composed of a group of secretory transporter proteins for small lipophilic molecules. L-PGDS can bind to a large range of lipophilic ligands, which differ in molecular size (M_r: 250–800) and physico-chemical properties. Using the binding capabilities of L-PGDS, we have proposed that the drug delivery system (DDS) of L-PGDS as a delivery vehicle could facilitate the pharmaceutical and clinical developments of poorly water-soluble compounds. The purpose of this study is to comprehensively investigate an effect of L-PGDS in improving the solubility of poorly water-soluble drugs. We carried out *in silico* docking simulations of L-PGDS for various approved drugs and investigational new drugs, and an improvement of solubility of the drugs with L-PGDS was estimated by solubility measurement and isothermal titration calorimetry (ITC) measurement.

A library of three-dimensional chemical structure (7,178 kinds of approved drugs and investigational new drugs) was obtained from ZINC database. Docking of each drug to the crystal structure of L-PGDS (PDB code: 3O2Y) was performed with AutoDock Vina. The predicted binding energies for the docked drugs ranged from –47.1 to –9.6 kJ/mol. Among them, we picked up four drugs such as telmisartan, nilotinib, lapatinib, and MCC-555, which possessed high binding affinities against L-PGDS. Telmisartan and nilotinib dissolved in PBS up to 13.3 μM and 11.9 μM, respectively, while lapatinib and MCC-555 were insoluble in PBS. However, in the presence of 1 mM L-PGDS, the solubility of these drugs drastically increased to 1,540 μM for telmisartan, 85.4 μM for nilotinib, 574 μM for lapatinib, and 707 μM for MCC-555, indicating clearly that L-PGDS improved the solubility of the drugs. Further, in order to elucidate the thermodynamic parameters for binding L-PGDS with telmisartan, we carried out ITC measurement in PBS at 25 ºC. By the reverse titration of L-PGDS to telmisartan, we detected exothermic reactions, indicating favorable enthalpy changes on binding reactions. L-PGDS formed a 1:2 complex with telmisartan, and the dissociation constants for binding were calculated to be 0.35 μM for the high-affinity site and 1.29 μM for the low-affinity site. The Gibbs energy change (ΔG), enthalpy change (ΔH), and entropy term ($-T\Delta S$) for the binding to high-affinity site were –36.9 kJ/mol, –31.8 kJ/mol, and –5.0 kJ/mol, respectively, while the values of ΔG, ΔH, and $-T\Delta S$ for the binding to low-affinity site were –33.6 kJ/mol, –34.5 kJ/mol, and 0.8 kJ/mol, respectively. Also, we are going to determine thermodynamic parameters for binding L-PGDS with the other drugs.

In conclusion, the combination strategies of *in silico* screening, solubility measurement and ITC measurement are highly useful to discover poorly water-soluble drugs available for DDS using L-PGDS and to characterize physico-chemical properties of binding L-PGDS with the drugs.