Pharmacokinetic interaction of green tea extracts and simvastatin: Inhibition of cytochrome P450 enzymes by green tea catechins

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【Background and purpose】Food components and drugs may interact in several ways leading to consequences for health. Some well-known examples of clinically relevant food-drug interaction are those of green vegetables and oral anticoagulants, St. John's wort and antiretroviral drugs or grapefruit juice and statins. Food components may, indeed, augment or reduce the efficacy of drugs and/or reduce their tolerability through diverse mechanisms of interaction. It is well-known that green tea catechins have many beneficial properties such as chemopreventive, antiatherogenic and antioxidant actions. However, currently, Werba et al. reported a case of statin muscle intolerance that was probably triggered by consumption of green tea (Ann Intern Med, 149: 286-287, 2008). Based on the clinical finding, our recent study showed that single and repeated oral administration of green tea extract (GTE) in rats increased significantly the AUC and C_{max} but not $t_{1/2}$ of simvastatin (SIM). Further, in these GTE-pretreated rats, the AUC, C_{max} and $t_{1/2}$ of simvastatin acid, an active metabolite of SIM, showed a tendency of increase as observed in the case of SIM. The aim of current study was to evaluate the *in vitro* inhibitory effects of green tea catechins on the activities of several human cytochrome P450 (CYP) enzymes. 【Methods】The green tea catechins investigated were epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate, and catechin composition (green tea extract, GTE, total catechins 86.4%, w/w). Bupropion hydroxylation (CYP2B6), amodiaquine *N*-deethylation (CYP2C8), (*S*)-mephenytoin 4'-hydroxylation (CYP2C19) and midazolam 1'-hydroxylation (CYP3A) were used as probe reactions in pooled human liver and intestinal microsomes. 【Results and Discussion】Each catechin and GTE was shown to inhibit CYP-catalyzed metabolism in mixed-type or non-competitive manners. Apparent IC_{50} values of GTE were 139.4 μg/mL, 39.5 μg/mL, 54.4 μg/mL and more than 200 μg/mL, respectively, for CYP2B6, CYP2C8, CYP2C19 and CYP3A. Among the components of GTE, the inhibitory effects of gallate-type catechins tended to be greater than those of non-gallate-type catechins. These results suggested that green tea catechins were more potent inhibitors of CYP2C8 and CYP2C19 than CYP2B6 and CYP3A. 【Conclusion】Consumptions of green tea catechins may affect the CYP activity in the intestine and/or liver, resulting in the significant interaction with clinically used drugs.