学位論文内容の要旨

博士の専攻分野の名称：博士（獣医学）　　氏名：Aksorn Saengtienchai

学位論文題名

Characterization and interspecies diversity of xenobiotic metabolism: a study of phase I oxidation and phase II conjugation reactions（異物代謝酵素の酵素学的特徴と多様性: 第 I 相反応と第 II 相抱合反応）

The species differences with regards to the capacity to metabolize and eliminate drugs and other xenobiotics from the body are typically substantial, complicating the effective use of drugs, as well as minimizing the ability to predict the adverse consequences of xenobiotics. The key factor to determine the species differences are the xenobiotic metabolizing enzymes. It has been reported that the xenobiotic metabolism is divided into phase-I and II reactions. In phase-I reaction, the main enzymes are the cytochromes P450 (CYP). Phase-II enzymes also play an important role in the metabolism of phase-I metabolites to more water-soluble forms. In particularly mammals, glucuronidation and sulfation extremely contribute to metabolisms of various xenobiotics. In the present study, I aim to evaluate the interspecies differences of both phase-I and phase-II reaction by using warfarin and pyrene as a model compounds.

Warfarin, the anticoagulant drug, was used as a model to study the characterization of phase-I, CYP and non-CYP reaction, in rats and chickens. I found that the metabolic activity of warfarin was drastically higher in chicken microsomes and cytosol fractions than that of rats. Also I found that there was the interspecies difference in the stereoselectivity of warfarin between rats and chickens.

To estimate the interspecies differences of phase-II reaction from various mammalian species, I constructed the method to analyze urinary metabolites of pyrene that is one of the typical polycyclic aromatic hydrocarbons (PAHs). Based on the constructed method, urinary pyrene metabolites from 16 mammalian species with non-experimentally exposed condition were analyzed. The results indicated that glucuronide conjugations were mainly eliminated via urine in various mammals, except cats and ferrets. Interestingly, sulfate conjugate was detected in pig urine, although pig is well known species that have low aryl-sulfotransferase (SULT) activity. Based on the kinetic analysis, high *Vmax/Km* of SULT was found in pig, which is higher than that of rats.

To summarize the study, I constructed the novel method to characterize interspecies differences, and clear interspecies differences of xenobiotics metabolism of both phase-I and phase-II were observed.