【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (New multidisciplinary fields)

Title of Project : Clarification of factors governing sensitivity of disruption of intracellular receptor-xenobiotic metabolizing enzyme signaling pathways by chemical substances

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Research Area : New multidisciplinary fields

Keywords : Toxicology, Sensitivity, Risk assessment

【Purpose and Background of the Research】

Influence of the environmental pollution by chemical substances has been pointed out as a cause of population decrease, mass mortality and teratogenesis of wildlife, but appropriate risk assessment in many wild species has not yet been carried out. The foremost reason for the limited number of risk evaluation studies on wild animals is the difficulty in collecting the samples (tissue and cell), unlike the case of laboratory animals. As the evaluation tests of hazardous chemicals on wild animals is ethically and technically difficult, results derived from model animals are alternatively extrapolated for the evaluation, and consequently the hazardous properties of chemicals are not definitely evaluated. The reason is that the susceptibility to chemicals is greatly different among species and strains. The differences in genes coding intracellular receptors (IRs) and xenobiotic metabolizing enzymes (XMEs) are postulated as a factor to explain the differences in susceptibility. However, until now, mostly the sequences and functions of IRs and XMEs have been clarified only in human and rodents, but very much lacking in wildlife. The lack of comparative approach targeting a variety of species makes it difficult to understand the molecular mechanisms underlying the susceptibility to chemical substances. The grand design of this study is to uncover the molecular mechanisms underlying the susceptibility to chemical substances in terms of the disruption of intracellular receptor-XME signal transduction system induced by chemicals in various species.

【Research Methods】

Focusing on IRs and cytochrome P450s, members of XMEs, construction of highly-developed assay systems and comprehensive analysis of interactions with chemicals will be attempted. Following four issues will be addressed in this research.

A) Comprehensive analysis of chemicals interacting with IRs
B) Comprehensive analysis of CYP-dependent metabolic pathways and metabolites of chemicals
C) Clarification of intrinsic factors of IRs and CYPs governing sensitivity to chemicals
D) Searching for factors other than IRs and CYPs governing sensitivity to chemicals

【Expected Research Achievements and Scientific Significance】

In order to assess the risk that is specific for each species, comparative studies on genetic information and function of IRs and CYPs in key species representing phylogenetically or ecologically relevant groups are indispensable. However, there are few studies with such a perspective. The originality of this research proposal is to evaluate the differences in sensitivity to chemical substances from the ligand profile of IRs, and substrate specificity and metabolic capacity of CYPs in various species including wildlife. The preeminent scientific significance of this proposal is enabling the evaluation of risk and hazardous properties of chemicals without a need for taking out the tissues of wildlife, if the genes of IRs and CYPs are available. In addition, the expected research results will provide a basic knowledge to elucidate the molecular evolutionary process of the intracellular signal transduction systems for the recognition of low molecular weight substances. Furthermore, methodology to be established will be a model to normalize and standardize the ecotoxicological tests on chemical substances.

【Publications Relevant to the Project】

Lee, J.S., Kim, E.Y., Iwata, H. (2009) Dioxin activation of CYP1A5 promoter/enhancer regions from two avian species, common cormorant and chicken: association with aryl hydrocarbon receptor 1 and 2 isoforms. *Toxicology and Applied Pharmacology,* 234, 1-13.

【Term of Project】 FY2009-2013
【Budget Allocation】 168, 900 Thousand Yen

【 Homepage Address and Other Contact Information】

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