



# HOKKAIDO UNIVERSITY

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### Laboratory of Toxicology

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Toxicology is a field of study which includes 1) the study of chemico-biological interactions causing the disruption of homeostasis of living organisms, and 2) the study of chemico-environmental interactions causing the disruption of the ecological balance of the environment. The disruption of homeostasis of the individual organism may or may not result in the disruption of the ecological balance, but the latter phenomenon always involves the former. Our laboratory aims to study the mechanism of disruption of these biological balances with chemicals to elucidate the way to prevent the disruption. Our current theme include:

1) Search for biomarkers for environmental pollution:

We have been proposing that cytochrome P450, the drug metabolizing enzyme, could be a good biomarker of environmental pollution by certain chemicals. Cytochrome P450 is a collective name of a number of isozymes that are engaging in the metabolic detoxification of chemicals entering into the body. Some of these isozymes are induced by exposure of animals to certain chemicals. We thought that this induction phenomenon can be used to indicate animal's exposure to P450-inducing chemicals in the environment such as PCBs and dioxins. Various animals inhabiting in environments with different degree of pollution were examined for their drug metabolizing enzyme activities and the contents of cytochrome P450 isozymes in the liver of these animals. We are obtaining data indicating that levels of some species of cytochrome P450 in the liver of the animal positively correlate with the degree of accumulation of pollutants in the animal. Test animals include wild rodents to assess

terrestrial pollution, fresh water crabs to assess terrestrial water pollution, and seals and whales to assess marine pollution. We are also looking for other biomarkers which can detect the degree of pollution with chemicals not assessed by P450. Such chemicals include environmental hormones.

2) Effect of environmental chemicals on fetal development:

Numbers of chemicals polluting our environment are carcinogens, teratogens, and environmental hormones. Developing embryos and fetuses are far more sensitive to these chemicals than adults. We are investigating the effect of these chemicals on pregnant mother rats and on their fetuses and their development.

3) Mechanism of generation of reactive oxygen species in Wilson's disease model rats:

Long Evans Cinnamon (LEC) rats accumulate copper in the liver during the course of their growth and develop fulminant hepatitis at 10-20 weeks of age and the survivors from the hepatitis finally develop hepatocellular carcinoma. It has been proposed that reactive oxygen species are generated due to the accumulated copper in the liver of these rats. We found that activities of catalase and glutathione peroxidase, both of which are scavengers of hydrogen peroxide, are markedly reduced in the liver of LEC rats. We also found that hydroxyl radical is generated in the liver S-9 of LEC rats in the presence of hydrogen peroxide and GSH. We propose the hypothesis that the cyclic regeneration of cuprous ions by GSH is responsible for the increased generation of hydroxyl radical from Fenton-type reaction involving hydrogen peroxide and cuprous ions.

4) Study of CYP2D isozymes and their polymorphic expression:

CYP2D isozymes are noted for their polymorphic expressions in several species of animals including in humans and in rats. We showed that the reduced CYP2D activities in DA rats is due to the reduced expression of CYP2D2.

## 5) Study on cancer prevention by cabbage diet :

Cabbages are known to contain indole-3-carbinol, oral doses of which induce CYP1A1, the P450 isozyme capable of metabolically activate polycyclic hydrocarbon carcinogens. Indole-3-carbinol has been shown to prevent chemical carcinogenesis. We are studying to elucidate the mechanism for this apparent paradox.

## 6) Studies on age-associated alterations of drug metabolism :

The largest population of drug consumers is the aged populations in the advanced nations. Aged population is also the group most frequently experiencing drug induced adverse effects. It is of clinical importance to know how drug metabolism alters with aging. We are studying alterations in drug metabolizing enzyme activities and P450 expression levels in aging rats with ages up to 3 years.

## 7) Parkinson's Disease model animals :

Many lines of evidences suggest that Parkinson's Disease may be caused by xenobiotics. We are trying to reproduce Parkinson's Disease symptoms with some success by intra-cranially administering tetraisoquinoline (TIQ) derivatives including dopamine-aldehyde condensation products in rats and mice. The biochemical effects of these compounds are checked using cultured nerve cell lines.

## Recent Publications

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Tasaki, T., Nakamura, A., Itoh, S., Ohashi, K., Yamamoto, Y., Masuda, M., Iwata, H., Kazusaka, A., Kamataki, T., and Fujita, S. : Expression and characterization of dog CYP2D15 using baculovirus expression system. *J. Biochem.* 123 162-168 (1998)