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| Author(s) | YAMAMOTO, Yukio |
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endoscopic ultrasonic B-mode images.

The third chapter describes endoscopic ultrasonographic evaluation and gray-scale histogram analysis of the pancreatic atrophic lesion after pancreatic duct ligation performed in four normal adult dogs. EUS revealed that the pancreatic ducts were markedly dilated and the pancreas gradually atrophied with a hyperechoic parenchyma. In gray scale histogram analysis of the pancreas, the MD increased gradually until eight weeks, then decreased temporarily. The standard deviation (SD) of the histogram increased markedly and then fluctuated up and down until the fourth week, after which the MD and SD became stable. At four weeks postoper-

atively, collapse of most pancreatic acinar structures was observed and each atrophic lobule was associated with a significantly large amount of interstitial fibrous tissue histopathologically. This was similar to naturally occurring chronic pancreatitis. At 12 weeks postoperatively, most exocrine tissue had decreased and was partly replaced by fibrous and fatty tissue. The changes of MD and SD reflected these histological changes. These findings indicated that EUS is a useful device to image atrophic disorders of the pancreas in dogs. Furthermore, gray-scale histogram analysis provides helpful information for ultrasonic tissue characterization of the pancreas.

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Molecular basis of drug oxidation polymorphism in the Dark Agouti rat : importance of cytochrome P450 2D2

Yukio Yamamoto

*Laboratory of Toxicology,
Department of Environmental Veterinary Sciences,
Graduate School of Veterinary Medicine,
Hokkaido University, Sapporo 060-0818, Japan*

The Dark Agouti (DA) rat has been proposed as a poor metabolizer model for the human debrisoquine 4-hydroxylase polymorphism. Earlier studies suggested that the poor metabolizer phenotype in the DA rat is due to the absence of the expression of CYP2D1 mRNA. Although cytochrome P450 2D1 (CYP2D1) catalyzes debrisoquine 4-hydroxylation, other reports have indicated the involvement of another CYP2D, purified from rat hepatic microsomes and presumed to be CYP2D2, which also exhibits this activity. The levels of CYP2D1 and CYP2D2 mRNAs were markedly lower in DA as compared to Sprague Dawley (SD) rats. Using a baculo-

virus expression system, recombinant CYP2D1 and CYP2D2 from *Spodoptera frugiperda* (Sf9) insect cells were examined and found that both forms catalyze debrisoquine 4-hydroxylase activity. These results suggest that reduced debrisoquine 4-hydroxylase activity in the DA rat is due to the low level expression not only of CYP2D1 but also of CYP2D2.

Interestingly bunitrolol 4-hydroxylation was catalyzed by recombinant CYP2D2, While CYP2D1 was inactive toward to this substrate. Thus the low bunitrolol 4-hydroxylation in DA rats was due to the low level of CYP2D2 expression in this rat strain.

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Xenobiotic metabolizing enzymes as biomarkers for levels of environmental pollution

Mayumi Ishizuka

*Laboratory of Toxicology,
Department of Environmental Veterinary Sciences,
Graduate School of Veterinary Medicine,
Hokkaido University, Sapporo 060-0818, Japan*

Living organisms have several mechanisms of detoxification of xenobiotics for their self-protection. The general pathways of biotransformation follow the conversion of lipophilic xenobiotics into more hydrophilic metabolites. The pathway of xenobiotic biotransformation can be divided into phase I and phase II pathways. The reactions of phase I metabolism include oxidation, reduction and hydrolysis of xenobiotics. In the most of organisms, cytochrome P450 (P450) is the major phase I enzyme. Following the initial oxidative metabolism by phase I enzymes, the xenobiotics are subject to conjugating reactions catalyzed by phase II enzymes. Glutathione S-transferase (GST), UDP-glucuronosyl transferase (UDPGT) and sulfotransferase are the important enzymes catalyzing the phase II metabolism of xenobiotics.

The reactions of xenobiotic metabolism are influenced by numerous endogenous and exogenous factors, which include age, gender, stress, genetic polymorphism, diets, hormone, and exposure to the inducers and inhibitors of xenobiotic metabolizing enzymes. Especially, a number of environmental pollutants are known as inducers of phase I and II enzymes. Therefore, I thought that this induction phenomenon of phase I and II enzymes in organisms by xenobiotics may be useful as a biomarker for monitoring the levels of environmental pollution.

The biomarkers can be defined at biochemical levels as; a toxicant-induced change in gene expression leading to alteration in protein content and enzyme activity that is linked to the amount of environmental contaminants. To use the phase I and II enzymes as biomarkers, it is needed to understand the alteration of activities of xenobiotic metabolism in animals, at the levels of individual enzyme species. Some endogenous and exogenous factors are known to alter the activities of xenobiotic metabolizing enzyme activities.

In the first section of this study, I concern the alteration of xenobiotic metabolizing enzyme activities due in animals to the stressful situations. Following the liver injury, e.g., surgical partial hepatectomy, hepatitis, hepatic infections and carcinoma, the liver is capable of total regeneration. In the first chapter, I demonstrated that the alterations of the levels of 7 hepatic P450 during liver regeneration after liver injury were isozymes selective. The objectives of second chapter were to determine the effects of xenobiotics on activities of phase I and II enzymes. The pesticides affected the activities of many xenobiotic-metabolizing enzymes in rat liver. Furthermore, it was suggested that the induction mechanisms of phase I enzymes by the pesticide may be different from those of phase II enzymes. From the studies of the first section,