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Classification and Genetic Expression of Wistar Rats with High and Low Hepatic Microsomal UDP-glucuronosyltransferase Activity towards Androsterone*

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Metabolism of androsterone in male and female Wistar rats is remarkable for the discontinuous variations in metabolites in bile and hepatic microsomal UDP-glucuronosyltransferase (EC 2.4.1.17) activity. Variability of UDP-glucuronosyltransferase activity towards androsterone was found in Donryu and Wistar King rats, but not in Long-Evans and Sprague-Dawley rats. With testosterone, bilirubin, 4-nitrophenol and phenolphthalein as substrates, the transferase activities were not significantly different.

The hereditary deficiency of UDP-glucuronosyltransferase towards bilirubin is well known in Gunn rats, the mutant strain of Wistar rats. Our colony of Wistar rats seemed to be another example of UDP-glucuronosyltransferase insufficiency of genetic origin. The present study was initiated to classify Wistar rats into high-activity and low-activity groups in terms of hepatic UDP-glucuronosyltransferase activity towards androsterone by partial hepatectomy and to determine whether these differences in the transferase activity were under genetic regulation in the offspring derived from the classified high-activity and low-activity rats.

UDP-glucuronosyltransferase is latent, probably buried inside the microsomal vesicle, and can be activated by physical, chemical or enzymic perturbation of microsomal membrane structure. Detergents, Triton X-100 and octaethylene glycol mono-n-dodecyl ether, markedly stimulated the glucuronidation of androsterone and 4-nitrophenol. Octaethylene glycol mono-n-dodecyl ether optimally stimulated the transferase activity 20—30% more than did Triton X-100 and was employed as the activator in this study. An endogenous activator, UDP-*N*-acetylglucosamine, gave approximately 2-fold activation of the transferase activity towards androsterone and 4-nitrophenol. UDP-glucuronosyltransferase is phospholipid- or detergent-dependent, and its apparent deficiency towards 2-aminophenol in Gunn rats could be repaired by addition of diethylnitrosamine or alkyl ketones, suggesting an interaction with the enzyme protein itself or with its linkage to phospholipid or detergent. However, diethylnitrosamine and pentan-2-one showed little effect on our enzyme activity and were unable to abolish the deficiency of the transferase activity towards androsterone. "Androsterone UDP-glucuronosyltransferase" may be defective in the low-activity rats, or the effective activator has not yet been discovered.

UDP-glucuronosyltransferase activities in fresh and detergent-activated microsomal

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fractions obtained by partial hepatectomy showed a discontinuous variation in the transferase activity towards androsterone, but not towards 4-nitrophenol. The high-activity/low-activity specific-activity ratios were approximately 12 : 1 and 19 : 1 for fresh and detergent-activited microsomal fractions respectively. The detergent amplified the marked diversity of androsterone glucuronidation. The hepatectomized rats were decapitated at 4 weeks after operation and the hepatic transferase activities were determined. The results were in good accord with those obtained by partial hepatectomy. Thus partial hepatectomy provides a good means for unequivocal classification of the high- and low-transferase-activity rats.

In order to study the possible role of inheritance in the regulation of UDP-glucuronosyltransferase activity towards androsterone, breeding experiments were performed between the classified high-activity and low-activity rats. The offspring were usually decapitated or hepatectomized at 40—60 days of age and hepatic transferase activity was determined. The similarity of the data for male and female offspring makes sex-linked inheritance of UDP-glucuronosyltransferase unlikely. Therefore the results for male and female offspring were pooled for the purposes of discussion. All (type I or II) or 73% (type III) of the offspring from matings of the high-activity rats showed high enzyme activity. If a trait is inherited in an autosomal dominant fashion, the expected high-activity population of the offspring derived from crosses between homozygotes (genotype *HH*), between homozygotes (*HH*) and heterozygotes (*Hh*) or between heterozygotes (*Hh*) is 100, 100 or 75% respectively. Thus the data are compatible with the Mendelian inheritance and indicate dominance of the high-activity phenotype. All (type IV) or 53% (type V) of the offspring from the crosses between the high-activity and low-activity rats fell into the high-activity group. On the basis of the expected ratios for the offspring, the parent with high transferase activity (type IV) should be normal homozygote (*HH*), whereas the parent with high transferase activity (type V) must be heterozygote (*Hh*). All the offspring (type VI) from matings of the low-activity rats showed low enzyme activity. In conclusion, the present study provides evidence that the genetic expression of the high UDP-glucuronosyltransferase activity towards androsterone is inherited as a single autosomal dominant trait.

Deficiency of UDP-glucuronosyltransferase towards bilirubin is known in humans (Crigler-Najjar syndrome and Gilbert's disease) as well as in Gunn rats, and is characterized as autosomal recessive diseases. In mice, induction of hepatic 4-methylumbelliferone UDP-glucuronosyltransferase by polycyclic aromatic hydrocarbons is genetically regulated in an additive fashion and is probably under the control of the *Ah* locus. Although the molecular mechanisms of the regulation of gene expression are yet to be elucidated, the observed low transferase activity towards androsterone may be due to a defective enzyme or abnormal membrane microenvironment that is under genetic control. To distinguish between these mechanisms, purification of the transferase must be estab-

lished. It is hoped that this animal system will provide useful information on the regulatory mechanism and heterogeneity of UDP-glucuronosyltransferase.