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Author	松井, 道夫(Matsui, Michio) 永井, 総子(Nagai, Fusako) 青柳, 忍(Aoyagi, Shinobu)
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Strain Differences in Rat Liver UDP-Glucuronyltransferase Activity towards Androsterone*

Michio Matsui, Fusako Nagai and Shinobu Aoyagi

松井道夫，永井総子，青柳　忍

Metabolism of androsterone in female and male Wistar rats is characterized by the discontinuous variations in biliary metabolites and hepatic microsomal UDP-glucuronyltransferase (EC 2.4.1.17) activity. Metabolism *in vivo* of androsterone in male Wistar rats suggests the existence of variance of UDP-glucuronyltransferase activity towards the oxygenated metabolites of androsterone as well. With testosterone as substrate, UDP-glucuronyltransferase activity was not so variable. Sprague-Dawley rats, Hartley guinea pigs and CF 1 mice did not exhibit marked diversity towards these substrates. To obtain further information on the properties, substrate specificity and strain differences of UDP-glucuronyltransferase activity, we compared the glucuronidation of androsterone, testosterone, bilirubin, phenolphthalein and 4-nitrophenol by fresh, frozen and Triton X-100 treated microsomal fractions from male Wistar and other strains of rat.

UDP-glucuronyltransferase activities towards five substrates in male Wistar rat liver microsomal fraction

A distinctive feature is the existence of a discontinuous variation in the transferase activity towards androsterone, but not towards the other substrates. Wistar rats can be divided into two groups based on the specific activity. The rats with high transferase activity towards androsterone and those with low transferase activity towards androsterone were found to be in the ratio 1 : 1. The high- to low-specific activity ratios were approx. 9.4 and 9.1 for fresh and frozen microsomal fractions respectively. The corresponding values for the 0.05% Triton X-100 treated microsomal fractions were 19.8 and 15.3 respectively, indicating that treatment with the detergent amplified the diversity between the two groups. UDP-glucuronyltransferase activities towards androsterone and other substrates were stimulated from 3- to 9-fold by treatment of fresh microsomal fraction with Triton X-100 or by freezing microsomal fraction for 4 weeks, whereas treatment of the frozen microsomal fraction with the detergent stimulated glucuronidation only by 1-4 fold. The repeated freezing and thawing of the microsomal fractions at intervals of 1 week revealed that high- and low-activity microsomal fractions provided marked differences in the enzyme activity towards androsterone, but not towards the other substrates. In general, a great increase in the transferase activity was observed up to 2-3 weeks, followed by a gradual decrease in activity, whereas treatment of the frozen micro-

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somal fraction with the detergent afforded the maximal activity at 1 week, which was comparable with that of the detergent-treated fresh microsomal fraction.

UDP-glucuronyltransferase activities towards five substrates in male Donryu, Long Evans, Sprague-Dawley and Wistar King rats

In this study, androsterone and testosterone were incubated with fresh and detergent-treated fresh microsomal fractions, whereas bilirubin, phenolphthalein and 4-nitrophenol were incubated with microsomal fractions frozen for 4 weeks. Of the four rat strains, Donryu and Wistar King rats provided discontinuous variations in their transferase activities towards androsterone, but not towards other substrates. Donryu rats were divided into five high-activity and three low-activity rats. The high- to low-specific activity ratios were about 7.0 and 14.3 for fresh and detergent-treated fresh microsomal fractions respectively. One Donryu rat showed an intermediate activity. Wistar King rats afforded one high-activity and four low-activity rats. The high- to low-specific activity ratios were 6.8 and 18.3 for fresh and detergent-treated fresh microsomal fractions respectively. These high- to low-specific activity ratios were similar to those of Wistar rats. In contrast, Long Evans and Sprague-Dawley rats did not give such a variance.

Discussion

Previous studies from this laboratory showed that male and female Wistar rats gave wide individual differences in hepatic microsomal UDP-glucuronyltransferase activities towards androsterone, but not towards testosterone. The rats with high transferase activity and the rats with low transferase activity were found to be approximately in the ratio 5: 4 and the high- to low-specific activity ratios of fresh and detergent-treated microsomal fractions were about 9 and 16 respectively. Less than 10% of the microsomal fractions showed an intermediate transferase activity. No significant sex-based difference was observed in the kinetic data, except that females gave greater enzyme activity than males. The present study extended our previous findings and demonstrated that Wistar rats did not afford marked variance in the transferase activity towards bilirubin, phenolphthalein and 4-nitrophenol. UDP-glucuronyltransferase is latent, probably buried inside the microsomal vesicle, and can be activated by physical, chemical or enzymic perturbation of the microsomal membrane structure. Freezing the microsomal fraction for 4 weeks activated the transferase towards androsterone and other substrates to an extent comparable with that of the fresh microsomal fraction treated with Triton X-100, whereas the transferase activity of the frozen microsomal fraction was inhibited by the subsequent treatment with the detergent. These results should indicate the complicated mechanism for the enzyme activation. The low activity of the transferase towards androsterone could not be activated by treatment with the detergent or freezing and thawing.

Variability of UDP-glucuronyltransferase activity towards androsterone was found in Donryu and Wistar King rats, but not in Long Evans and Sprague-Dawley rats. Though

Donryu and Wistar King rats afforded similar high and low specific activities to those of Wistar rats, the proportions of high- to low-activity rats were somewhat different. It is noteworthy that wide individual differences exist in the transferase activity towards an endogenous substrate, androsterone, in several normal rat strains.

Recently evidence for the heterogeneity of UDP-glucuronyltransferase has accumulated on the basis of inducibility, age-development, chromatographic separation and substrate specificity of the purified transferase, though androsterone was not among the substrates examined. The purified transferase was phospholipid- or detergent-dependent and its deficiency towards 2-aminophenol in the Gunn strain of rat could be repaired by additon of diethylnitrosamine, suggesting an interaction with the enzyme protein itself or with its linkage to detergent or phospholipid. Thus, the observed low transferase activity towards androsterone in our low-activity microsomal fraction may be due to a defective enzyme and/or abnormal microsomal membrane microenvironment. However, we cannot distinguish between these mechanisms from the present study. Purification of the transferase must be carried out before the mechanism responsible for its regulation can be established.