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Multiple Forms and a Deficiency of Uridine Diphosphate-glucuronosyltransferses in Wistar Rats*

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Hepatic UDP-glucuronosyltransferase (GT) catalyzes the glucuronidation of endogenous and exogenous compounds, furnishing them water soluble and accelerating their excretion into urine or bile. Glucuronide formation of wide variety of compounds has suggested the existence of multiple forms of GT. At least two or more forms of GT having overlapping substrate specificities have been purified in the rat. The hereditary deficiency of bilirubin GT isoenzyme is known in Gunn rats, a mutant strain of Wistar rats. Previous studies from this laboratory showed discontinuous variation in hepatic GT activity toward androsterone (AD). Classification and breeding experiments revealed dominance of the high-activity phenotype. These results suggest that our colony of Wistar rats with the low-activity phenotype appears to be another example of GT isoenzyme deficiency of genetic origin.

The present paper describes separation and purification of GT active on AD and 4-nitrophenol (NP) from Wistar rats, which had the high-activity and low-activity phenotypes in terms of AD glucuronidation. DEAE-cellulose chromatography separated two GT peaks with different specificities toward AD and NP. Peak I had high NP-GT and low AD-GT activities and was present in both high-activity and low-activity phenotypes. Peak II had high AD-GT and comparatively low NP-GT activities and was found only in rats with the high-activity phenotype. The corresponding peak in the low-activity phenotype had only NP-GT activity. Peak I and peak II were further purified by affinity chromatography on UDP-hexanolamine Sepharose 4B to afford purified enzymes of fraction A and B respectively. Comparison of Km values for AD between microsome-bound and purified enzymes revealed an interesting aspect. The Km value of the microsome-bound enzyme was similar to that of the purified enzyme present in fraction B in rats with the high-activity phenotype. In rats with the low-activity phenotype, the microsome-bound enzyme had the similar Km value to the purified enzyme in fraction A. These results indicate that AD glucuronidation should be mainly catalyzed by GT isoenzymes present in fraction A and B in the low-activity and high-activity phenotypes respectively. If GT isoenzyme is named after a major substrate, AD-GT isoenzyme should be deficient in Wistar rats with the low-activity phenotype. AD glucuronidation in consequence should be catalyzed poorly by NP-GT isoenzyme in these rats.

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Several anthors have reported the purification of two or more forms of GT having partially overlapping substrate specificities. However, there have been several discrepancies between their subunit molecular weights and substrate specificities. Differences in subunit molecular size estimation might be ascribable to the limited accuracy of the SDS-gel technique and to the different detergent systems used to solubilize the microsomal enzymes. On the other hand, differences in substrate specificities might suggest the contamination of other GT isoenzyme or the reconstitution of different GT isoenzyme subunits *in vivo* or during purification procedures.