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Genetic Deficiency of Androsterone UDP-Glucuronosyltransferase Activity in Wistar Rats is due to the Loss of Enzyme Protein*

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Hepatic microsomal UDP-glucuronosyltransferase (GT) catalyzes the glucuronidation of endogenous and exogenous compounds.

The hereditary deficiency of bilirubin GT isoenzyme is known in Gunn rats, a mutant strain of Wistar rats. Previous studies from our laboratory showed discontinuous variation in rat liver GT activity towards androsterone, but not towards bilirubin, testosterone, 4-nitrophenol, and phenolphthalein. Subsequent studies demonstrated that the genetic expression of the high-activity phenotype is inherited as a single autosomal dominant trait. Comparison of the purified enzyme obtained by DEAE-cellulose and UDP-hexanolamine affinity chromatography revealed the defective nature of the androsterone GT isoenzyme in the low-activity phenotype.

In the present study, we employed chromatofocusing and UDP-hexanolamine affinity chromatography. In rats with the high-activity phenotype, androsterone GT was eluted at about pH 7.4 and had a subunit Mr of 52000, whereas testosterone GT was eluted at about pH 8.4 and had a subunit Mr of 50000. The transferase that conjugates both androsterone and testosterone was eluted at about pH 8.0 and had subunit Mr values of 50000 and 52000. In rats with the low-activity phenotype, androsterone GT was absent, whereas testosterone GT was eluted at around pH 8.5, with a subunit Mr of 50000.

Comparison of Km values for androsterone or testosterone between microsome-bound and purified enzymes displayed comparatively consistent results in the high-activity rats. The microsome-bound enzyme provided the apparent Km values of 20—33 and 133—192 μM for androsterone and testosterone respectively. The purifed androsterone GT obtained by DEAE-cellulose and UDP-hexanolamine chromatography gave an apparent Km of 20 μM for androsterone. These data appear to be compatible with the present study, which displayed the apparent Km values of 5—8 and 110—120 μM for androsterone and testosterone in the purifed enzymes respectively.

An interesting aspect of the chromatographic profile in the low-activity phenotype is the absence of testosterone GT activity eluted at around pH 8.0 as well as the defect of androsterone GTs. Before purification, the microsome-bound enzyme did not show any significant difference in testosterone GT activity between the high-activity and low-activity phenotypes. These data appear to indicate that the GT isoenzyme eluted at about

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pH 8.0 might be yielded by aggregation or reconstitution of androsterone and testosterone GT isoenzymes *in vivo* or during purification, still maintaining their ability for glucuronidation. This hypothesis clearly explains why the single peak of testosterone GT activity was observed in the low-activity phenotype. Another possibility may be that rats with the low-activity phenotype have at least one other defective GT which is capable of conjugating androsterone and testosterone. However, further study is required to clarify these aberrant chromatographic profiles.