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Effect of Steroid Hormones and Xenobiotics on the Pubertal Development of UDP-Glucuronosyltransferase Activities towards Androsterone and 4-Nitrophenol in Wistar Rats*

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Glucuronidation is an important pathway in the detoxification of endogenous and exogenous compounds. Hepatic microsomal UDP-glucuronosyltransferase (GT) catalyses the transfer of glucuronic acid from UDP-glucuronic acid to various compounds. GT activities are negligible in early-foetal liver, develop perinatally, and are affected by endogenous and exogenous compounds. In rat liver, GT activities are classified into late-foetal and neonatal groups on the basis of their developmental period from low to high values. The activities are also classified into two groups on the basis of their inducibility by 3-methylcholanthrene (GT_1) and phenobarbital (GT_2).

Previous studies from our laboratory showed discontinuous variation in hepatic GT activity towards androsterone in Wistar rats, the high-activity to low-activity ratios being approx. 16 : 1. Classification and breeding experiments revealed dominance of the high-activity phenotype. Developmental study demonstrated that androsterone GT activity surged rapidly after 30 days of age in rats with the high-activity phenotype. Wistar rats with the low-activity phenotype did not show any pubertal surge of the enzyme activity. In contrast, such a striking individual difference was not found in 4-nitrophenol GT activity. There were no obvious sex difference in GT activities towards androsterone and 4-nitrophenol.

The present experiments were primarily designed to elucidate the effects of oestradiol benzoate, testosterone propionate, progesterone, corticosterone, 3-methylcholanthrene and phenobarbital on the pubertal development of GT activities towards androsterone and 4-nitrophenol in Wistar rats. The study includes age-dependent effects of oestradiol benzoate and phenobarbital, and effects of breast milk, on GT activities.

An interesting aspect of androsterone GT activity is its temporary suppression by pretreatment with oestradiol benzoate. This suppression was marked in 40-day-old rats with the high-activity phenotype, but disappeared when the enzyme activity was measured at 3 weeks after the oestrogen treatment or when the oestrogen was administered to older rats. The temporary suppression of GT activity by oestrogen may designate another type of functional heterogeneity of GT activity. In a previous paper, we reported that androsterone GT activity began to surge rapidly after 30 days

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of age in rats with the high-activity phenotype, the adult enzyme activity being attained at about 60 days of age. Females showed slower development than males, but reached the high male activities at around 60 days of age. It is known that gonadal hormones normally affect hepatic enzymes after around 30 days of age (puberty) in rats. Thus slower development of female androsterone GT activity appears to be due to temporary suppression by physiological oestrogen. Moreover, it is of interest to speculate that comparatively slow development of androsterone GT activity, as compared with other activities in the neonatal cluster, might arise from an inhibitory effect of oestrogens present in breast milk. The high-activity and low-activity phenotype in Wistar rats can be imprinted prenatally or postnatally. To determine whether rat's breast milk had any imprinting effect on androsterone GT activity, newborn rats from parent with the low-activity or high-activity phenotype were nursed by foster-mothers with the opposite phenotype. The results indicate that breast milk did not alter the genetically determined expression of androsterone GT activity.

Another age-dependent effect on androsterone GT activity was found by phenobarbital treatment in rats with the high-activity phenotype. The induction rate of androsterone GT activity was the highest in 40-day-old rats. Enhancement of the enzyme activity by phenobarbital was detected only in the detergent activated microsomal fractions. This increased latency may be due to hypertrophy of liver endoplasmic reticulum, by which GT enzymes are buried presumably deeper inside the membrane. Inducibility by phenobarbital and non-inducibility by 3-methylcholanthrene, together with the post-natal development of the enzyme activity, establish the GT_2 nature of androsterone GT activity.

DEAE-cellulose column chromatography of solubilized androsterone GT demonstrated the existence of two peaks of GT active on androsterone. Peak-I GT was found in rats with the high-activity and low-activity phenotypes and corresponded to low androsterone GT activity, whereas peak-II GT was found only in rats with the high-activity phenotype and had high androsterone GT activity. Falany and Tephly purified rat liver androsterone GT isoenzyme to apparent homogeneity by using chromatofocusing and affinity chromatography. The GT isoenzyme reacted with androsterone and ethiocholanolone, but showed no activities towards 4-nitrophenol, 1-naphthol, 4-methylumbelliferone, oestrone, oestradiol, testosterone and morphine. Interestingly, our colony of Wistar rats with the low-activity phenotype showed markedly decreased GT activity towards androsterone, but not towards 4-nitrophenol, phenolphthalein, bilirubin and testosterone. Important consequences of these findings may be that androsterone GT isoenzyme should be deficient in Wistar rats with the low-activity phenotype, and that androsterone glucuronidation in consequence should be catalysed poorly by other GT isoenzyme(s) in these rats. The deficiency of bilirubin GT isoenzyme is known in Gunn rats. Our colony of Wistar rats appears to be another example of GT isoenzyme deficiency.