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Developmental Alteration of Hepatic UDP-glucuronosyltransferase and Sulphotransferase towards Androsterone and 4-Nitrophenol in Wistar Rats*

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Glucuronidation and sulphation play an important role in the detoxification of endogenous and exogenous compounds. Hepatic microsomal UDP-glucuronosyltransferase (EC 2.4.1.17) catalyses the transfer of glucuronic acid from UDP-glucuronic acid to various compounds, and hepatic cytosolic aryl (EC 2.8.2.1) and hydroxysteroid (EC 2.8.2.2) sulphotransferases transfer H_2SO_4 from adenosine 3′-phosphate 5′-sulphatophosphate to various substrates. Recent studies from this laboratory showed a marked variation in biliary metabolites of androsterone in Wistr rats. About half of the rats excreted large amounts of steroid monoglucuronides into bile, whereas the remaining rats excreted mainly steroid mono- and disulphates into bile. Subsequent studies *in vitro* revealed the discontinuous variation in hepatic UDP-glucuronosyltransferase activity towards androsterone but not towards testosterone, bilirubin, 4-nitrophenol and phenolphthalein in Wistar rats. The genetic expression of high UDP-glucuronosyltransferase activity towards androsterone is inherited as a single autosomal dominant trait.

It is known that activities of hepatic UDP-glucuronosyltransferase and sulphotransferases change through perinatal development. There is also accumulating evidence that sulphotransferase activities vary with age and sex.

To study the regulatory mechanism of androsterone metabolism, we performed a comparative study on the postnatal development of UDP-glucuronosyltransferase and sulphotransferase activities towards androsterone. For purposes of comparison, UDP-glucuronosyltransferase and sulphotransferase activities towards 4-nitrophenol as well as cytochrome P-450 contents were also determined.

A striking feature of androsterone metabolism is the discontinuous variation in hepatic UDP-glucuronosyltransferase activity in adult male and female rats. Wistar rats could be classified into the high-activity and low-activity groups in terms of the transferase activity towards androsterone. Such a pronounced difference was not found in the hepatic UDP-glucuronosyltransferase activity towards 4-nitrophenol, sulphotransferase activity towards androsterone and 4-nitrophenol, and cytochrome P-450 contents. However, a marked sex-besed difference in the sulphotransferase activity towards androsterone and 4-nitrophenol was observed in adult male and female rats.

We have established the classiffication of Wistar rats with high and low hepatic UDP-

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glucuronosyltransferase activity towards androsterone by partial hepatectomy and breedings of the hepatectomized rats, which enabled us to study the development of UDP-glucuronosyltransferase activity towards androsterone. The transferase activity was markedly enhanced after 30 days of age in the high-activity group, whereas the transferase activity remained low throughout in the low-activity group. UDP-glucuronosyltransferase activity is classified into late-foetal and neonatal groups on the basis of the developmental period of the enzyme activity from low to high values. Thus the high transferase activity towards androsterone may belong to the neonatal group, though the transferase activity rapidly surged after weaning. Our preliminary purification experiments on DEAE-cellulose suggest the existence of two peaks of UDP-glucuronosyltransferase active on androsterone. Peak I showed low transferase activity and was found in both high-activity and low-activity groups, whereas peak II had high transferase activity and was present only in the high-activity group. Further study under progress may clarify this apparent multiplicity. In contrast with androsterone glucuronidation, the transferase activity towards 4-nitrophenol did not give such variation and was found to be of the late-foetal nature as reported previously.

A pronounced feature of the sulphotransferase activity was a sex-based difference and this difference was marked after 30 days of age. The transferase towards androsterone showed about 15-fold greater activity in adult females than in adult males, whereas 2-3-fold higher sulphation activity towards 4-nitrophenol was found in adult males. The highest transferase activity towards androsterone was attained at about 20 days of age in both sexes. Subsequently the transferase activity markedly decreased in males. In females, the transferase activity began to decrease likewise after weaning, but increased again to a high level after 40 days of age. These results suggest a biphasic pattern of development of sulphotransferase activity towards androsterone in female rats. It is known that sulphotransferase are under hormonal regulation. Sulfotransferase activity towards cortisol is regulated by gonadal and adrenal hormones. Another interesting aspect is the multiplicity of sulphotransferases. Recently three hydroxysteroid sulphotransferase have been separated and purified from female rat livers. Thus further study is required to clarify the regulatory factors, property and multiplicity of our sulphotransferase(s) active on androsterone. In contrast with androsterone sulphation, males developed high sulphotransferase activity towards 4-nitrophenol at 30—40 days of age, whereas females did not show such a surge in the enzyme activity. Recently, four aryl sulphotransferase have been separated and purified from male rat livers. However, all the purified transferase sulphurylated 4-nitrophenol and had broad substrate specificity.

Glucuronidation and sulphation are competing conjugation reactions. The present study shows that the low level of the UDP-glucuronosyltransferase activity did not lead to compensatory stimulation of the sulphotransferase activity. This developmental study demonstrates that Wistar rats with several combinations of high and low activities of

hepatic UDP-glucuronosyltransferase and sulphotransferase towards androsterone are available as a function of age and sex. Further study with this animal model is required to obtain insight into the regulatory mechanism of drug metabolism.