Title	Variability of androsterone metabolism in male wistar rats
Sub Title	
Author	松井, 道夫(Matsui, Michio) 青柳, 忍(Aoyagi, Shinobu)
Publisher	共立薬科大学
Publication year	1979
Jtitle	共立薬科大学研究年報 (The annual report of the Kyoritsu College of Pharmacy). No.24 (1979.) ,p.81- 82
Abstract	
Notes	抄録
Genre	Technical Report
URL	http://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=AN00062898-00000024-0081

Variability of Androsterone Metabolism in Male Wistar Rats*

MICHIO MATSUI and SHINOBU AOYAGI

松井道夫，青柳　忍

Some remarkable features characterize the metabolism of androsterone in female Wistar rats, i.e. discontinuous variations in biliary metabolites and hepatic UDP-glucuronyltransferase activity. These observations together with recent findings on the metabolism of androsterone glucuronide and androsterone sulfate indicate that the hepatic UDP-glucuronyltransferase must be principally responsible for the diversity of the *in vivo* metabolism of androsterone in female rats. Experiments with male Wistar rat liver demonstrated the existence of variations in transferase activity toward androsterone similar to those of female rats. These results indicate clearly the variability of androsterone metabolism in male rats. In the present paper, [^{3}H]androsterone and [^{3}H]androsterone glucuronide were administered intraperitoneally into male Wistar rats, and the biliary metabolites were isolated and identified by gas chromatography-mass spectrometry.

The results of the present study demonstrate that androsterone was metabolized extensively to oxygenated steroids in male Wistar rats. Furthermore, wide individual differences were observed in biotransformation and biliary excretion. It was found that half of the rats (HE rats) excreted large amounts of steroid monoglucuronides rapidly into bile, whereas the remaining rats (LE rats) excreted various steroid conjugates slowly into bile. In marked contrast, the injected androsterone glucuronide was excreted rapidly into bile and behaved like a metabolic end-product, as was found in female Wistar rats and humans. There has been accumulating evidence that steroid glucuronides are excreted in rat bile more rapidly than steroid sulfates.

In a previous paper, we described the marked variations in biliary metabolites of androsterone in female Wistar rats. About half of the rats excreted mainly androsterone glucuronide into bile, while the remaining rats excreted predominantly the monosulfates of $C_{19}O_2$ and $C_{19}O_3$ steroids in the bile. Subsequent *in vitro* studies with male and female Wistar rats revealed the discontinuous variations in hepatic microsomal UDP-glucuronyltransferase activities toward androsterone but not toward testosterone, females showing greater enzyme activity than males. The rat with a high level of the transferase activity (HG) and the rat with a low level of the transferase activity (LG) were found approximately in the ratio 5: 4 and the HG to LG specific activity ratio was about 9, irrespective of the sex. Thus, the variability of the UDP-glucuronyltransferase activity should be principally responsible for the large variations in the *in vivo* metabolism of androsterone in female rats. On the other hand, androsterone was metabolized mainly to polyoxygenated steroid

* 本報告は *Biochem. Pharmacol.*, **28**, 1023 (1979) に発表。

monoglucuronides in male HE rats. Gas chromatography-mass spectromety analysis of the trimethylsilyl derivatives of androsterone metabolites revealed the occurrence of several monooxo-trihydroxy and tetrahydroxy steroids. Since we identified 2- and 16-oxygenated $C_{19}O_3$ steroids as androsterone metabolites, we synthesized three 2,3,16,17-tetraoxygenated steroids by introduction of a 16-hydroxy group into 2α,3α-dihydroxy-5α-androstan-17-one. In the HE rats, androsterone was metabolized to the monoglucuronides of androsterone, 2α,3α-dihydroxy-5α-androstan-17-one, 3β,17β-dihydroxy-5α-androstan-16-one, 5α-androstane-3α,16α,17β-triol, 2α,3α,16α-trihydroxy-5α-androstan-17-one, 2α,3α,17β-trihydroxy-5α-androstan-16-one, and 5α-androstane-2α,3α,16α,17β-tetrol. In the LE rats, 5α-androstane-3α,16α,17β-triol and 3β,17β-dihydroxy-5α-androstan-16-one were isolated as the monosulfate and the disulfate respectively. In addition, 5α-androstane-3β,16α,17β-triol was identified in the mono- and disulfate fractions. Low recovery of androsterone in the monoglucuronide fraction might reflect the increased hydroxylase activities in male rats, leading to a type of metabolite different from that in female rats. However, these results imply that the variation of UDP-glucuronyltransferase should exist not only for androsterone but for the oxygenated metabolites of androsterone.

The relationship between the UDP-glucuronyltransferase activity *in vitro* and the glucuronidation *in vivo* is not clear. The glucuronidation *in vivo* can be affected by several factors such as UDP-glucuronic acid, β-glucuronidase, and other metabolizing enzymes besides UDP-glucuronyltransferase. The situation is complicated by the fact that UDP-glucuronyltransferase is latent and probably inside the microsomal vesicle. The enzyme can be activated by physical, chemical, or enzymatic perturbation of the membrane structure. Comparative studies indicate that UDP-glucuronyltransferase may be operating largely in a constrained form *in vivo*. From comparative studies on the glucuronidation of 1-naphthol in perfused liver and hepatic UDP-glucuronyltransferase, Bock *et al.* reported that the markedly decreased UDP-glucuronyltransferase in Gunn rats does not lead to impaired glucuronide formation in perfused livers, due probably to compensatory activation of the latent enzyme. In contrast to this, our female Wistar rats showed good correlation between glucuronidations *in vivo* and *in vitro*. This may be ascribable to the striking differences in UDP-glucuronyltransferase activities toward androsterone of HE and LE rats. In fact, activation of the latent enzyme with Triton X-100 amplified the diversity between HG and LG microsomes. To extend our findings, it is of interest to investigate the specificity of "androsterone UDP-glucuronyltransferase" in male rats. Work is now under progress in our laboratory to study the nature and extent of the variability of hepatic UDP-glucuronyltransferase in rats of the Wistar and other strains.