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Author	松井, 道夫(Matsui, Michio) 絹山, 優子(Kinuyama, Yuko)
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Comparative Fate of Testosterone and Testosterone Sulphate in Female Rats : $C_{19}O_2$ and $C_{19}O_3$ Steroid Metabolites in the Bile*

MICHIO MATSUI and YUKO KINUYAMA

松井道夫, 絹山優子

In a recent publication, we described that disulphates of 5α -androstane- 3α , 17β -diol and polar hydroxylated steroids constituted the major biliary metabolites of testosterone sulphate in female rats. Gustafsson *et al.* recently reported the 15β -hydroxylation of 5α -androstane- 3α , 17β -diol 3,17-disulphate in female rat liver microsomes. These results strongly suggest the occurrence of 15β -hydroxylated steroids in the biliary metabolites of testosterone sulphate. In the present paper, [^{14}C]-testosterone and [3H]-testosterone sulphate were administered into female rats and the biliary $C_{19}O_2$ and $C_{19}O_3$ steroid metabolites were identified by gas chromatography-mass spectrometry.

There were large variations in testosterone metabolism in female rats. The major metabolic pathway of testosterone in the HE rat was via formation of androsterone glucosiduronate, while the main pathway in the LE rat was via formation of monosulphates of androsterone and 7α - and 11β -hydroxylated androsterones. In a separate paper, we described quite similar variations in androsterone metabolism in female rats. Siiteri *et al.* demonstrated that androsterone glucosiduronate was rapidly excreted unchanged in urine in humans. Thus, we speculated that UDP-glucuronyltransferase enzyme might be very active in the HE rat. The administered androsterone should be predominantly converted into androsterone glucosiduronate and subsequently excreted in the bile. On the other hand, low activity of UDP-glucuronyltransferase or high activity of sulphotransferase in the LE rat might permit further metabolism of androsterone or androsterone sulphate. In previous studies, we demonstrated that the catabolic route of testosterone involving the initial conjugation with sulphuric acid or glucuronic acid should be a very minor pathway in female rats. The present study shows that testosterone metabolites were very similar to those of androsterone. In the HE rat, testosterone should be converted by consecutive action of Δ^4 - 5α -hydrogenase, 3α - and 17β -hydroxysteroid-oxido-reductases to androsterone and subsequently conjugated with glucuronic acid. Thus, variations in testosterone and androsterone metabolism in female rats seem to be regulated by similar biochemical mechanism. 2α , 3α -Dihydroxy- 5α -androstane-17-one was identified in the monoglucosiduronate fraction in both HE and LE rats. To our knowledge, this is the first identification of this steroid as monoglucosiduronate in rat bile. Recently, Gustafsson *et al.* described specific 15β -hydroxylating enzyme active on 5α -androstane- 3α , 17β -diol 3, 17-disulphate in female rat liver microsomes. Isolation of disulphates of 5α -androstane- 3α , 17β -diol and 5α -androstane- 3α ,

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15 β , 17 β -triol should imply an *in vivo* 15 β -hydroxylation of 5 α -androstane-3 α , 17 β -diol 3, 17-disulphate in female rats.

In contrast to testosterone, variations in the metabolite of testosterone sulphate were not so marked. The major biliary metabolite was 5 α -androstane-3 α , 17 β -diol 3, 17-disulphate in both HE and LE rats. Production of 5 α -androstane-3 α , 17 β -diol 3, 17-disulphate was, however, about two times more in the HE rat than in the LE rat. *In vitro* studies with rat liver enzymes demonstrated that testosterone sulphate could be metabolized without hydrolysis of the ester linkage by Δ^4 -5 α - and Δ^4 -5 β -hydrogenases as well as 3 α - and 3 β -hydroxysteroid-oxido-reductases. Thus, testosterone sulphate must undergo direct metabolism by liver microsomal Δ^4 -5 α -hydrogenase and 3 α -hydroxysteroid-oxido-reductase to 5 α -androstane-3 α , 17 β -diol 17-sulphate, which must be cosecursively conjugated with sulphuric acid to the 3, 17-disulphate by the sulphotransferase located in the soluble fraction of the liver cell. Gustafsson *et al.* described the 7 β - and 15 β -hydroxylation of 5 α -androstane-3 α , 17 β -diol 17-sulphate in female rat liver microsomes, whereas 5 α -androstane-3 β , 17 β -diol 3, 17-disulphate and the corresponding 3 α -epimer afforded solely the respective 15 β -hydroxylated metabolites. 5 α -Androstane-3 α , 17 β -diol 3-sulphate and 17-sulphates of testosterone and 17 β -hydroxy-5 α -androstane-3-one were not hydroxylated by microsomal enzymes. Based on these observations, the precursor of mono- and disulphates of 5 α -androstane-3 α , 7 β , 17 β -triol, unique metabolites of testosterone sulphate, should be 5 α -androstane-3 α , 17 β -diol 17-sulphate. By analogy, 5 α -androstane-3 α , 17 β -diol 3, 17-disulphate (and 17-sulphate) must be converted into 15 β -hydroxylated metabolite. Sole production of 17 β -hydroxy steroids indicates little occurrence of hydrolysis of the 17-sulphate group of testosterone sulphate *in vivo*.

From the present study, marked differences in metabolism between testosterone and testosterone sulphate were demonstrated in both C₁₉O₂ and C₁₉O₃ steroid metabolites. Testosterone was predominately converted into 17-oxo steroids, whereas testosterone sulphate was metabolized to 17 β -hydroxy steroids. An investigation of the levels and activities of various enzymes involved in testosterone metabolism may be of interest for obtaining further insight into the regulatory mechanism responsible for large variations in testosterone metabolites.