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Sub Title	
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Publisher	共立薬科大学
Publication year	1977
Jtitle	共立薬科大学研究年報 (The annual report of the Kyoritsu College of Pharmacy). No.22 (1977.) ,p.133- 134
JaLC DOI	
Abstract	
Notes	抄録
Genre	Technical Report
URL	https://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=AN00062898-00000022-0133

Comparative Fate of Testosterone and Testosterone Sulphate in Female Rats : $C_{19}O_2$ and $C_{19}O_3$ Steroid Metabolites in the Bile*

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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 [^{3}H]-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 androseteone 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-androstan-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,

*本報告は J・Steroid Biochem., **8**, 323 〔1977〕 に発表。

15β, 17β-triol should imply an *in vivo* 15β-hydroxylation of 5α-androstane-3α, 17β-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 5α-androstane-3α, 17β-diol 3, 17-disulphate in both HE and LE rats. Production of 5α-androstane-3α, 17β-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^4-5α- and Δ^4-5β-hydrogenases as well as 3α- and 3β-hydroxysteroid-oxido-reductases. Thus, testosterone sulphate must undergo direct metabolism by liver microsomal Δ^4-5α-hydrogenase and 3α-hydroxysteroid-oxido-reductase to 5α-androstane-3α, 17β-diol 17-sulphate, which must be cosecutively conjugated with sulphuric acid to the 3, 17-disulphate by the sulphotransfease located in the soluble fraction of the liver cell. Gustafsson *et al.* described the 7β-and 15β-hydroxylation of 5α-androstane-3α, 17β-diol 17-sulphate in female rat liver microsomes, whereas 5α-androstane-3β, 17β-diol 3, 17-disulphate and the corresponding 3α-epimer afforded solely the respective 15β-hydroxylated metabolites. 5α-Androstane-3α, 17β-diol 3-sulphate and 17-sulphates of testosterone and 17β-hydroxy-5α-androstan-3-one were not hydroxylated by microsomal enzymes. Based on these observations, the precursor of mono-and disulphates of 5α-androstane-3α, 7β, 17β-triol, unique metabolites of testosterone sulphate, should be 5α-androstane-3α, 17β-diol 17-sulphate. By analogy, 5α-androstane-3α, 17β-diol 3, 17-disulphate (and 17-sulphate) must be converted into 15β-hydroxylated metabolite. Sole production of 17β-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 $C_{19}O_2$ and $C_{19}O_3$ steroid metabolites. Testosterone was predominatly converted into 17-oxo steroids, whereas testosterone sulphate was metabolized to 17β-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.