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**Biliary Metabolites of Testosterone
and Testosterone Glucosiduronate in the Rat***

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The comparative fate of testosterone and testosterone-17-glucosiduronate in the human was studied by Robel and his coworkers. These authors demonstrated the selective 5β -reduction of testosterone-17-glucosiduronate, whereas testosterone was converted to both 5α - and 5β -metabolites. *In vitro* studies with the male rat liver preparation afforded the consistent results with the *in vivo* metabolism in the human. The incubation with the female rat liver revealed that testosterone-17-glucosiduronate could be reduced to some extent to 5α -metabolites besides 5β -ones.

In order to elucidate these discrepancies between *in vivo* and *in vitro* studies, a mixture of testosterone-4- ^{14}C (^{14}C -T) and testosterone-7- ^3H -17-glucosiduronate (^3H -TGA) was intraperitoneally administered into male and female rats and the biliary metabolites of these steroids were compared.

The present study demonstrates that ^3H -TGA and ^{14}C -T were extensively metabolized in the rat. The majority of the metabolites was rapidly excreted in the bile mainly as monoglucosiduronates and to a minor extent as monosulfates, diconjugates (sulfoglucosiduronates and disulfates) and free steroids. The analysis of the aglycones of the conjugate fractions revealed that the metabolic pattern of TGA was quite different from that of testosterone and that the metabolism of testosterone and TGA were remarkably affected by the sex.

The major portion of the injected TGA was metabolized to 5β -androstane- 3α , 17β -diol irrespective of the sex, appearing principally in the monoglucosiduronate fraction and in small amounts in the diconjugate fraction. In contrast, conversion of testosterone to this metabolite was very minor in the male and almost none in the female. These *in vivo* findings of the selective 5β -reduction of TGA are quite consistent with the *in vivo* metabolism in the human and the *in vitro* metabolism in the rat liver preparation. Considering the results of the present and previous studies, it became quite apparent that TGA was metabolized without hydrolysis of glucuronyl group to 5β -steroids in the rat *in vivo*.

In sharp contrast to the male, the analysis of the female rat bile demonstrated the presence of two 5α -metabolites. Androsterone was excreted as glucosiduronate and was predominantly derived from testosterone. This metabolite constituted the major portion of testosterone metabolites in the female. 5α -Androstane- 3α , 17β -

* 本報告は Steroids, 24, 557 (1974) に発表.

diol was present as a minor metabolite in both monoglucosiduronate and diconjugate fractions with $^3\text{H}/^{14}\text{C}$ ratios higher than the injected dose. The relatively high ^3H content of this metabolite can be clearly interpreted in the light of the previous *in vitro* studies with female rat liver preparations. The incubation with female liver microsomes demonstrated that TGA could be converted to some extent to 5α -androstane- $3\alpha,17\beta$ -diol without hydrolysis of the glucuronyl group, though the conjugate was readily metabolized by the soluble fraction of the liver to afford the corresponding 5β -epimer. The major portion of 5α -androstane- $3\alpha,17\beta$ -diol containing ^3H radioactivity should be produced by the direct metabolism of ^3H -TGA, since the 5α -metabolite pattern of TGA markedly differed from that of testosterone. In fact, androsterone was the major metabolite of testosterone, while the major one derived from TGA was 5α -androstane- $3\alpha,17\beta$ -diol. Thus, these results provide evidence that TGA can be converted directly into the 5α -metabolite as well as the 5β -one *in vivo*.

The production of small amounts of etiocholanolone in the male rat and androsterone in the female, which were derived from ^3H -TGA, indicated the occurrence of the deconjugation and subsequent biotransformation of the minor portion of TGA and its direct metabolites *in vivo*.

There were no substantial differences in the metabolites among the 0-1, 1-2 and 2-24 hr biles. However, evidence was presented that the 2-24 hr bile contained polar steroids (probably hydroxylated ones) derived mainly from ^{14}C -T more than the other bile fractions.

Recently, Schriefers and his coworkers observed a sex-specific aglycone pattern by incubating testosterone with rat liver slices, followed by examination of the glucosiduronate fraction. In the male, testosterone was predominantly converted into C_{19}O_3 -steroids and to a minor extent into 5α - and 5β - C_{19}O_2 -steroids. In the female, on the other hand, the major portion of testosterone was metabolized to androsterone and to a minor extent to C_{19}O_3 - and 5α - C_{19}O_2 -steroids, no 5β -steroids being isolated in the female. These results seem to be compatible with the present *in vivo* studies, except no 5α -metabolites were identified in the male rat bile.

The marked difference in the metabolism between testosterone and its conjugate implies that the catabolic route of testosterone involving the initial conjugation to TGA should be a very minor pathway in the male rat and almost absent in the female. This is supported by the observation that the incubation of testosterone with female rat liver slices resulted in no production of 5β -metabolites in the glucosiduronate fraction.

It is well established that the Δ^4 - 5α -hydrogenase is located in the liver microsomes, whereas the Δ^4 - 5β -hydrogenase is present in the soluble fraction. Recently, Baulieu and his coworkers explained the selective 5β -reduction of TGA in the

human in terms of an anatomical compartmentalization. The differences in solubility of free and conjugated steroids could direct them into different compartments. Thus, the hydrophilic glucosiduronate could not reach the microsomal enzyme and could be readily reduced by the soluble enzyme to give solely 5β -metabolites. While, the lipophilic testosterone can be reduced by both enzymes. However, the present study apparently indicates that TGA can be metabolized by microsomal enzymes of the female rat *in vivo* as well as *in vitro*. Thus, no 5α -reduction of TGA in the human might be ascribable to the lack of or a very weak activity of the Δ^4 - 5α -hydrogenase, which can metabolize TGA or to the special membrane structure (compartment) of the microsomes which might prevent TGA from reaching the enzyme. In order to clarify the mechanism of the 5α -reduction of TGA, however, many problems concerning substrate specificity and multiplicity of the enzymes, precise localization of the enzymes in the organelle, and the membrane transport system should be elucidated.