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Variations in Biliary Metabolites of Androsterone in Female Rats*

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In previous papers dealing with the biliary metabolites of testosterone and testosterone conjugates in the rat, we reported that androsterone was the major metabolite of testosterone in the female. However, little is known about the *in vivo* metabolism of androsterone in the rat. In the present investigation,[^{3}H]-androsterone was administered intraperitoneally into female rats and the biliary metabolites were isolated and identified by gas chromatography-mass spectrometry.

The present study demonstrates that the major portion of androsterone metabolites was rapidly excreted in the bile. Some interesting features characterize the metabolism of androsterone in female rats, *i.e.*, large variations in the biotransfomation and biliary excretion. Rats provided a considerably constant bile flow, but variation was observed in the biliary excretion rate of the metabolites. Rats could be classified into two groups based on the excretion rate of the radioactivity in the bile. One group (the HE rat) excreted about 44% of the radioactivity during the first hour and approximately 96% of the injected dose was found in the bile during 24 h. In contrast, another group (the LE rat) eliminated only 9% of the radioactivity in the first hour, about 61% of the dose appearing in the bile during 24 h. A relationship evidently existed between the rate of biliary excretion of steroids and the biliary conjugates. The HE rat excreted large amounts of glucuronides in bile, whereas monosulphates were the predominant conjugate in the LE rat. Analysis of the free steroids after hydrolysis revealed the marked difference between two groups. The free steroids were separated by t.l.c. and separated metabolites were trimethylsilylated and analyzed by GC and GC-MS. The identified metabolites had relative retention times and mass spectra identical with those of the respective reference steroids. Androsterone was the major steroid identified in the glucuronide fraction of the HE rat. In addition to this, small amounts of 3α, 7α-dihydroxy-5α-androstan-17-one monoglucuronide and monosulphates of 3α,7α-, 3α, 11β-, and 3α,15α-dihydroxy-5α-androstan-17-ones and androsterone were identified. Major metabolites in the LE rat were monosulphates of 3α,7α-, 3α, 11β-, and 3α,15α-dihydroxy-5α-androstan-17-ones and androsterone. As minor metabolites, androsterone and 3α, 17β-dihydroxy-5α-androstan-16-one were isolated in the monoglucuronide and diconjugate fractions of the LE rat, respectively. Very small amounts of 5α-androstane-3α, 17β-diol were identified in the diconjugate fraction of both HE and LE rats. Gustafsson *et al.* reported the isolation of these metabolites from the pooled faeces of germfree rats and the bile of female rats doesd with [^{14}C]-pregnenolone. Thus, these metabolites seem to be

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present as normal constituents in rat bile, but the quantities of these steroids present in the 0-24 h control bile were under the limit of our analytical method.

Androsterone is metabolized by several different pathways of biotransformations such as hydroxylation at C-7, C-11, C-15 and C-16, reduction of 17-keto group, and conjugation with glucuronic acid and sulphuric acid. The rate at which each reaction proceeds, and its relative importance, may be affected by genetic and physiological factors, resulting in changes in the pattern of metabolism. Siiteri *et al.* administered [^{3}H] labelled androsterone glucuronide to humans and found that this conjugate was rapidly excreted in urine without undergoing further metabolism. It is of interest to speculate that UDP-glucuronyltransferase enzyme might be very active in the HE rat. Thus, the injected androsterone should be rapidly conjugated with glucuronic acid and eliminated in the bile. On the other hand, low activity of UDP-glucuronyltransferase or high activity of sulphotransferase in the LE rat might result in the further metabolism of androsterone or androsterone sulphate. A similar variation was observed in the metabolism of [^{14}C] -testosterone in female rats. When the major portion of the radioactivity was rapidly eliminated in the bile, the predominant biliary metabolite of testosterone was androsterone glucuronide. Comparative studies on the metabolism of androsterone glucuronide and androsterone sulphate in female rats will be the subject of a future communication.