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ONTOGENESIS OF STEROID-16α-HYDROXYLASE MULTIPLE FORMS IN THE RAT LIVER: DEVELOPMENT OF THE SEXUAL DIFFERENTIATION AND INTERACTIONS WITH EXOGENOUS LYPOPHILIC COMPOUNDS.

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Steroid hormones are essentially deactivated in the liver. The oxidation reactions involved in their biotransformation are catalyzed by microsomal cytochrome P450-dependent monooxygenases, responsible in other respects for the metabolism of a wide variety of exogenous and endogenous chemicals.

This paper contains information related to steroid-16α-hydroxylase multiplicity in the rodent liver. The male/female ratios, the induction factors and the *in vitro* sensitivity to specific inhibitors vary with the substrate (progesterone, pregnenolone, testosterone and DHEA) in the rat and mouse liver microsomes.

From the competition between different possible exogenous or steroid substrates, it appears that in the rat, 16α-hydroxylase is supported by two different cytochrome P450 forms that are different from the cytochrome P448 and are strictly involved in the metabolism of endogenous steroids: Form I has a high affinity for testosterone; Form II has the highest affinity for pregnenolone. The sex-linked differences in the 16α-hydroxylase activity are based upon variations in the quantitative distributions of Forms I and II. In the mouse liver, we find the same steroid-16α-hydroxylase multiplicity and the same sexual repartition of the two cytochrome P450 forms.

Contrary to what takes place in the rat, the 16α-hydroxylase activities are higher in the female mouse liver.

We followed the ontogenesis of the four steroid-16α-hydroxylases in the rat liver. The enzymatic activity develops at birth. Until the 21st day of life (weaning), sexual differentiation is not apparent. The two cytochrome P450 forms, Forms I and II, are already present but in equal concentrations. There is a strict compartimentation of the endogenous and exogenous compound metabolisms: The steroid-16α-hydroxylases, with the exception of progesterone-16α-hydroxylase, are not inhibited by exogenous chemicals and in particular, by polycyclic hydrocarbons. On the other hand, aryl hydrocarbon hydroxylase is not inhibited by steroids. From the 21st to the 40th day, we observe a transition period with a progressive development of the adult male and female characteristics. The adult status is reached around the 50th day of life in both sexes:

1. The four 16α-hydroxylases are higher in the male than in the female rat liver. They retain their endogenous substrate activity. Form I becomes dominant in the females and Form II in the males.
2. Aryl hydrocarbon hydroxylase becomes sensitive to steroid inhibition *in vitro*. This phenomenon occurs to a greater extent in the male than in the female.