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Author	渡辺, 宏(Watanabe, Hiroshi) 松井, 道夫(Matsui, Michio)
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Rat Liver Sulfotransferases: Effects of Gonadal Hormones and Other Factors on Enzyme Activities*

Hiroshi K. WATANABE and Michio MATSUI

渡辺　宏，松井道夫

Conjugation of endogenous and exogenous compounds with sulfuric acid is catalyzed by hepatic aryl and hydroxysteroid sulfotransferases (ST), which transfer sulfuric acid from 3′-phosphoadenosine-5′-phosphosulfate (PAPS) to various substrates.

Previous studies from this laboratory showed a remarkable variation in biliary metabolites of androsterone (AD) in Wistar rats. About half of the rats excreted large amounts of steroid glucuronides into bile, while the remaining rats excreted large amounts of steroid sulfates into bile. Subsequent studies revealed the discontinuous variation in hepatic UDP-glucuronyltransferase (GT) activity toward AD, but not toward 4-nitrophenol (NP). The previous study demonstrated that the low level of GT activity did not lead to compensatory stimulation of ST activity in Wistar rats and that sex difference in ST activities became marked after 30 days of age. ST activity toward AD was much higher in adult females than in adult males, whereas higher ST activity toward NP was found in adult males. The present study was designed to clarify the effects of estradiol benzoate (EB), testosterone propionate (TP), progesterone (PG), corticosterone (CS), 3-methylcholanthrene (MC) and phenobarbital (PB) on pubertal development of ST activities toward AD and NP in Wistar rats.

A characteristic feature of ST activity is its regulation by gonadal hormones. ST activity toward AD was much higher in adult females than in adult males. Male low ST activity toward AD was augmented by EB to female high levels, though female high activity was not significantly suppressed by TP. Conversely, ST activity toward NP was higher in adult males. Its high activity was suppressed by EB to female levels, whereas female low ST activity toward NP was increased by TP to male high levels.

Another interesting aspect is the induction of ST activities by PG. Pretreatment with PG exhibited a biphasic effect to elevate low ST activities to high levels: Male ST activity toward AD to feminization and female ST activity toward NP to masculinization. Our puzzling observation that female high ST activity toward AD was not significantly suppressed by TP may be ascribable to the antagonizing effect of endogenous PG against TP. In a previous paper, we reported that adult female ST produced AD sulfate about 15-fold more efficiently than adult male ST, and that males showed 2-3-fold as much ST activity toward NP as females. Thus it appears plausible that endogenous

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PG and its related metabolites may play role in maintaining comparatively high aryl ST activity in females.

Developmental study exhibited a biphasic development of female ST activity toward AD. The enzyme activity increased after birth in parallel in both sexes, attained the highest activity at about 20 days of age, and began to decline afterward. In contrast to males, female ST activity toward AD increased again to high levels after 40 days of age. On the other hand, ST activity toward NP did not show such a prepubertal surge of the enzyme activity, and male ST activity rapidly increased after 30 days of age. Doehler and Wuttke observed highly increased serum estradiol levels between 9 and 21 days of age in male and female rats, and suggested its origin from adrenals. Moreover, suckling infants are exposed to estrogen and PG present in breast milk. Therefore, it is an interesting speculation that the surge of ST activity toward AD during postnatal development to weaning may reflect the effect of estrogen and PG secreted and sucked by immature rats. At puberty, serum concentrations of androgen or estrogen and PG rise in male or female rats respectively, and should bring about their characteristic sex difference in ST activities.

It is well known that PB and MC induce liver microsomal drug-metabolizing enzymes such as monooxygenases and GTs, and liver cytosolic drug-metabolizing enzymes such as glutathione *S*-transferases. Recently we observed that GT activities toward AD and NP were induced by PB and MC in Wistar rats respectively. In contrast to ST, these GT activities were not substantially affected by steroid hormones, except that GT activity toward AD was temporarily suppressed by EB. Unlike these drug-metabolizing enzymes, pretreatment with PB and MC did not significantly induce ST activities toward AD and NP.

Recently four aryl and three hydroxysteroid STs have been separated and purified from rat liver, though these enzymes appear to have comparatively broad substrate specificity. These studies indicate that further study is required to elucidate which enzymes are responsible for sulfation of AD and induction or suppression by steroid hormones.