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This Week's Citation Classic™

Kato R & Gillette J R. Effect of starvation on NADPH-dependent enzymes in liver microsomes of male and female rats. *J. Pharmacol. Exp. Ther.* **150**:279-84, 1965. [Lab. Chem. Pharmacol., Natl. Heart Inst., Natl. Insts. Health, Bethesda, MD]

This paper described the presence of androgen-dependent and -independent activities in drug-metabolizing enzymes of rat liver microsomes. The change in the activities by starvation was sex-related and the activities being stimulated by androgen were decreased. [The *SCI*® indicates that this paper has been cited in over 615 publications since 1965.]

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"Before joining the National Institutes of Health (NIH), I worked in the Department of Pharmacology at the University of Milan, Italy, and I was interested in sex differences in the microsomal drug-metabolizing enzyme (DME). At NIH, I worked with J.R. Gillette in B.B. Brodie's lab. At that time, this lab was a mecca for the study of drug metabolism.

"The presence of sex differences in the activity of DME of rat liver had been shown by several investigators. We demonstrated that the magnitude of sex differences depends on the substrate. For example, there were marked sex differences in aminopyrine N-demethylation and hexobarbital hydroxylation, while only a little or no difference was detected in aniline and zoxazolamine hydroxylations. One of my major interests was to clarify factors that modify the activity of DME. However, at that time, most investigators used only male rats. Therefore, we first examined the effect of starvation on DME in male and female rats. We observed clear decreases in hexobarbital hydroxylation and aminopyrine N-demethylation in male rats, but we didn't observe any decrease in aniline and zoxazolamine hydroxylations. Indeed, the aniline hydroxylation in starved male rats was increased. To our surprise, the starvation caused an increase in the activity of DME in all female rats.

"This paper presented the fact that the magnitude of the sex differences in the activity of DME varied markedly with the substrate. Moreover, starvation of male rats impaired the activity of sex-dependent, but not sex-independent, enzymes in male rats and both enzymes in female rats. Castration and androgen-supplement experiments indicated that the impairment occurred only in the enzyme activities being stimulated by androgen, but this stimulation was impaired by starvation and caused marked sex differences in its effect. In the next paper,[1] we reported similar changes in the activity of DME in morphine-or thyroxine-treated, adrenalectomized male and female rats. Therefore, the high rate of citation of this paper may be due to its clear demonstration of the existence of sex-related and -unrelated activities in DME in rat liver and sex-related changes of DME under some abnormal physiological conditions. In addition, this paper was cited for its description of the method for aniline hydroxylation, until the method of Imai *et al.*[2] became more popular.

"All these results have indicated a possible presence of specific forms of cytochrome P-450 in liver microsomes of male rats. Recently, we have purified male- and female-specific cytochrome P-450 (P-450 male and P-450 female) from male and female rats, respectively.[3] The studies on the regulation mechanism of P-450 male will afford new insight to the sex difference of DME. Gillette is now the chief of the Laboratory of Chemical Pharmacology, National Heart, Lung, and Blood Institute, NIH, Bethesda, Maryland."

1. **Kato R & Gillette J R.** Sex differences in the effects of abnormal physiological states on the metabolism of drugs by rat liver microsomes. *J. Pharmacol. Exp. Ther.* **150**:285-91, 1965. (Cited 285 times.)
2. **Imal Y, Ito A & Sato R.** Evidence for biochemically different types of vesicles in the hepatic microsomal fraction. *J. Biochem. Tokyo.* **60**:417-28, 1966. (Cited 400 times.)
3. **Kamatakl T, Maeda K, Yamazoe Y, Nagal T & Kato R.** Sex difference of cytochrome P-450 in the rat. Purification, characterization, and quantitation of constitutive forms of cytochrome P-450 from liver microsomes of male and female rats. *Arch Biochem Biophys.* **225**:758-70, 1983.