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This Week's Citation Classic®

Kato R, Oshima T & Tomizawa S. Toxicity and metabolism of drugs in relation to dietary protein. *Jpn. J. Pharmacol.* 18:356-66, 1968.
[Depts. Pharmacology, Natl. Inst. Hygienic Sciences; Sch. Medicine, Keio Univ.; and Coll. Pharmaceutical Sciences, Kitasato Univ., Tokyo, Japan]

The effect of dietary protein content on the drug toxicity and hepatic drug-metabolizing enzymes in rats was investigated. This paper offered a good example for the importance of drug metabolism in the modulation of drug toxicity. [The *SCI*® indicates that this paper has been cited in more than 135 publications.]

Diet, Drugs, and Poisons

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When I wrote my paper in 1968, the *Japanese Journal of Pharmacology* published only four issues a year. It was not well circulated or well cited. However, when I sent the paper in, I was a young scientist, 37 years old, and I strongly wished to enhance the reputation and circulation of the journal. I published eight papers in 1968, one of which is also highly cited in the *Japanese Journal of Pharmacology*.[1] In reality, another reason for the publication of this article in the journal was an economic one—a lack of funds in my grant for buying reprints from foreign countries.

Previously, we had worked on the factors affecting the activities of microsomal drug-metabolizing enzymes in rat liver. We had published several papers on the effect of starvation, hormonal changes, and pathological conditions,[2-4] including another *Citation Classic*.[2] We demonstrated how the change in activity of a drug-metabolizing enzyme affects the intensity of drug action. However, at that time, it was generally assumed that the increases in drug toxicity and in protein deficiency were related to decreases in a defense mechanism of tissues and organs.

Our paper demonstrated clearly that the intensity of drug toxicity is related to the rate of drug metabolism. We showed that low protein or nonprotein diets decreased markedly the content of cytochrome P-450, the in vivo metabolism of pentobarbital, and the oxidations of pentobarbital strychnine, aminopyrine, zoxazolamine, and aniline in rat liver microsomes. Moreover, we demonstrated that mortalities of strychnine, pentobarbital, and zoxazolamine were increased, but mortality of octamethylprophosphamide (OMPA), an organic phosphate insecticide, was markedly decreased. This is because OMPA needs to be activated metabolically by a drug-metabolizing enzyme to produce drug toxicity. Thus, we offered a good example to pharmacologists and toxicologists of the importance of drug metabolism in modulation of drug toxicity. This may be a major reason why an article published in this Japanese journal in 1968 was cited so frequently.

The change of drug-metabolizing enzymes by a variety of factors was sex-related:[3] The effect of protein deficiency was observed in livers of both male and female rats; however, the magnitude of decrease was greater in male rats than in females.

Recently, it has been demonstrated that there are many forms of cytochrome P-450 in rat liver microsomes and that they are regulated individually by hormones and xenobiotics. Many factors affect the expression and content of individual cytochrome P-450 through effects on hormonal organs.[5,6] Thus, understanding the mechanism of change in each cytochrome P-450, under a variety of experimental conditions, has been important in the research on the mechanism and evaluation of drug toxicity.

1. **Kato R & Takanaka A.** Metabolism of drugs in old rats. I. Activities of NADPH-linked electron transport and drug-metabolizing enzyme systems in liver microsomes of old rats. *Jpn. J. Pharmacol.* 18:381-8, 1968. (Cited 110 times.)
2. **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. (Cited 735 times.) [See also: **Kato R.** Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life.* Philadelphia: ISI Press, 1986. p. 170.]
3. ----------. 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 355 times.)
4. **Kato R & Takahashi A.** Thyroid hormone and activities of drug-metabolizing enzymes and electron transport systems of rat liver microsomes. *Mol. Pharmacol.* 4:109-20, 1968. (Cited 90 times.)
5. **Kamataki T, Maeda K, Yamazoe Y, Nagai 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. (Cited 165 times.)
6. **Yamazoe Y, Shimada M, Murayama N & Kato R.** Suppression of levels of phenobarbital-inducible rat liver cytochrome P-450 by pituitary hormone. *J. Biol. Chem.* 262:7423-8, 1987. (Cited 50 times.)

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