The strain difference of rats in the metabolism of diazepam

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Abstract

The strain differences in the metabolism of diazepam were examined by using liver microsomes from 9 weeks-old Wistar and Dark-Agouti (DA) rats of both sexes. Liver microsomal diazepam 3-hydroxylation activity was higher in DA rats. Activities of N-desmethylation and 4'-hydroxylation were higher in Wistar than in DA rats.

The sex differences were observed in the diazepam 3-hydroxylation and the N-desmethylation in both strains (male > female). Only Wistar rats had the sex difference in the 4'-hydroxylation (male > female). In Brown Norway (BN) rats, both sexes had significantly higher activity in the diazepam 4'-hydroxylation than that in wistar rats, indicating that BN strain has higher CYP2D activity than other strains of rats.

The age-associated change in the diazepam metabolism of BN rats was investigated in young age indicating that male had higher diazepam 3-hydroxylation, N-desmethylation and 4'-hydroxylation activities than female. These activities of male rats have significantly decrease by aging, except the 3-hydroxylation activity.

Mechanism of Regulation of Cytochrome P450 Expression by Neonatal Imprinting — The Effect of Growth Hormone and The CYP Inducer —

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It is well known that the expression of drug metabolizing enzyme, cytochromes P450 (CYP), is gender-specific in rats after puberty. Expressions of sex-specific CYP isoforms are regulated by sex-specific secretory pattern of growth hormone (GH). The sex-specific GH secretory pattern is imprinted by perinatal serge of testosterone, which occurs in male rats within 1～2 days after birth. In the present study, we examined the effect of the change in the imprinted pattern of GH secretion on CYP expression, and whether expressions of CYP could be imprinted by CYP inducer other than sex hormone.

Rats used in the present study were accidentally produced among strains of transgenic rats carrying human GH (hGH) genes. These rats (low GH rats) do not have pulsatile GH secretory pattern even in adult male, which is specific in normal adult male rats. Moreover, they have characteristics of high plasma insulin levels and severe obesity developed with age.

The relative abundance of CYP forms was obviously female-like (feminized) in the liver of male low GH rats. These feminized expressions patterns have also been observed in other GH