Strain differences in age-associated change in Testosterone 6β-hydroxylation in Wistar and Dark Agouti rats

Yutaka Maeda

Laboratory of Toxicology,
Department of Environmental Veterinary Sciences,
School of Veterinary Medicine,
Hokkaido University, Sapporo 060, Japan

This study examines strain differences in testosterone (T)-hydroxylations between Wistar and Dark Agouti (DA) rats of both genders. The DA rat, an animal model, is a poor metabolizer of such drugs as debrisoquine, which are metabolized by cytochrome P450 (CYP) 2D. T-16α- and 2α- hydroxylations, which are mediated by CYP2C11, were catalyzed at similar rates by the microsomes of both strains. In contrast, the liver microsomes from mature male DA rats catalyzed T-6β-hydroxylation, CYP3A mediated activity, at higher rates (~2-fold) than did Wistar rat liver microsomes. There was no difference between immature male DA and Wistar rats for T-6β-hydroxylation, indicating that the activity in the male DA rat increases with maturation. Polyclonal antibodies raised against rat liver microsomal CYP3A2 and a CYP3A inhibitor, troleandomycin (TAO), effectively inhibited T-6β-hydroxylation by liver microsomes from both strains of rats. The level of T-6β-hydroxylation activity correlated well with the amount of CYP3A protein in the microsomes in mature as well as in immature male and female Wistar and DA rats. Northern blot analysis repeatedly indicated that the cellular contents of CYP3A2 mRNA were slightly (~20%) higher in the livers of mature DA rats than in there of mature Wistar rats. Three results indicate that the increased levels of CYP3A are responsible for the increased T-6β-hydroxylation activity and protein in the DA rat.

Regio- and stereoselective propranolol metabolism by 3 forms of purified cytochrome P450 from rat liver and the effect of cytochrome b5 on these metabolisms

Sativa Marumo

Laboratory of Toxicology,
Department of Environmental Veterinary Sciences,
School of Veterinary Medicine,
Hokkaido University, Sapporo 060, Japan

Regio- and stereoselectivity of the cytochrome P450-mediated propranolol metabolism (4-, 5-, 7-hydroxylation and N-desisopropylation) were studied using purified cytochrome P450 species (P450 2D1, P450 3MC1 and P450 3MC2).

With each purified cytochrome P450 species, the regioselectivity was distinct and different between the two optical isomers used as substrates. The stereo-selectivity was different depending on the position of propranolol to be metabolized. The regio- and stereoselectiv-