REGIOSELECTIVE DIFFERENCES IN CAFFEINE METABOLISM IN WISTAR AND DARK-AGOUTI RATS.
—A New Polymorphism—

Keiichi MORITA

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

The metabolism of caffeine was examined by using liver microsomes from Dark-Agouti (DA) rats known as a poor-metabolizer animal model for debrisoquine 4-hydroxylation and Wistar rats of both sexes. In adult rats, significant strain (DA male >Wistar male) and sex (male>female) differences were observed in C–8 hydroxylation, but not in the N-demethylation. By contrast, immature male rats of DA and Wistar strains showed the same activity level of C–8 hydroxylation. Kinetic studies using liver microsomes revealed that adult rats of both strains had similar Km values, but the Vmax values in male DA rats were significantly higher than those of male Wistar rats. We presumed that adult male DA rats had high levels of P450 isoform(s) responsible for the C–8 hydroxylation in their liver microsomes. Troleandomycin (TAO), a known CYP3A inhibitor, effectively reduced the rat microsomal C–8 hydroxylation in a concentration-dependent manner. An anti-rat CYP3A2 antibody effectively inhibited the microsomal C–8 hydroxylation, whereas this antibody did not affect N-demethylation. These results suggest that C–8 hydroxylation is mediated largely by an isoform(s) of the CYP3A subfamily in rat liver microsomes. Treatment of rats with CYP3A inducers caused a marked increase in C–8 hydroxylase activity. The results of western blotting analysis using anti-CYP3A2 anti-serum showed that the staining density of the protein band in DA rat liver microsomes was stronger than that in Wistar rats. We found a marked sex-dependent strain difference in C–8 hydroxylation between the Wistar and DA strains of rats.