We investigated the involvement of CYP1A2 in the pharmacokinetics and metabolism of caffeine using mice lacking its expression (CYP1A2 -/-). The half-life of caffeine elimination from blood was seven times longer in the CYP1A2 -/- than wild-type mice. The clearance was concomitantly eight times slower. No parameter that could affect the pharmacokinetics differed between CYP1A2-/- and wild-type mice such as creatinine for kidney function; alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and bilirubin for liver function; or albumin for protein binding. Other P450s CYP2A, 2B, 2C, 2E1, and 3A were also unchanged in the knockout animals. Caffeine 3-demethylated metabolites thought previously to be characteristic of CYP1A2 (especially 1-methylxanthine and 1-methylurate) were also found in the urines of the CYP1A2-/--animals, although at 40% of the level found in wild-type mice. These data indicate that the clearance of caffeine in wild-type mice is primarily determined by CYP1A2.
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