INHIBITION OF HUMAN CYP1-MEDIATED OXIDATIONS BY MAJOR CANNABINOIDS
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Δ⁹-Tetrahydrocannabinol (Δ⁹-THC), cannabidiol (CBD) and cannabinol (CBN), which are major constituents of marijuana, have been reported to inhibit the activity of the drug metabolizing enzymes in rat liver microsomes. However, the inhibitory potential and mechanism of cannabinoids against human cytochrome P450 (CYP) have not been fully evaluated. In addition to the involvement in the bioactivation of procarcinogens, CYP1A enzymes also play an important role in drug metabolism. Thus, the metabolism of CYP1 substrates could be influenced by co-administration of cannabinoids (or marijuana). In the present study, we investigated the effects of three major cannabinoids on 7-ethoxyresorufin O-deethylase (EROD) activity of recombinant human CYP1A1, CYP1A2 and CYP1B1. All cannabinoids used (0.10-25 µM) inhibited the EROD activity (150 nM 7-ethoxyresorufin) of these CYP1 enzymes, with IC₅₀ values ranging from 0.188 to 9.83 µM. The inhibitory effects of Δ⁹-THC were roughly similar among the CYP1 enzymes investigated. CBD was the most potent CYP1A1 inhibitor with an IC₅₀ of 0.537 µM. CBN potently inhibited CYP1A2 and CYP1B1 activities, with IC₅₀ values of 0.188 and 0.278 µM, respectively. Furthermore, the inhibitory effects of three major cannabinoids on the EROD activity of human liver microsomes were similar to those of recombinant CYP1A2. These results suggest that the inhibitory effects of the major cannabinoids depend on human CYP1 isoforms, and that CBN could lead to possible drug-drug interactions with CYP1A2 substrates.

RAT CYTOCHROME P450 2C11 INVOLVED IN OXIDATION OF ANESTHESIC DRUG PROPOFOL AND DEACTIVATED BY PROPOFOL IN LIVER MICROSOMES
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Propofol (2,6-diisopropylphenol) is administered as a bolus for the induction of anesthesia and as an infusion for maintenance of anesthesia or for sedation. One of the major advantages of this drug over other injectable anesthetic agents is the rapid and complete recovery that occurs even after relatively prolonged intravenous infusions. Liver microsomal cytochrome P450 (P450) forms involved in the biotransformation of propofol in rats and the effects of propofol in vivo on P450 levels in rats were investigated. Of six cDNA-expressed rat P450 forms tested, CYP2C11 and CYP2B1 had high catalytic activities from 5 µM and 25 µM propofol concentrations. Rates of propofol metabolism, at a substrate concentration of 20 µM based on the reported human blood concentration, were decreased by intraperitoneal treatment of propofol with male rats, in contrast to a strong induction by phenobarbital. An intravenously administered propofol (10 mg/kg) caused the decrease of total P450 and CYP2C contents and activities of testosterone 16α-hydroxylation and propofol metabolism in liver microsomes from male rats. The suppressive effects were caused by administered propofol (10 mg/kg) in every 4 h on CYP2B activities such as testosterone 16β-hydroxylation or pentoxyresorufin O-depentylation, in addition to the strong suppression of CYP2C function by the single propofol treatment. These results suggest that CYP2C11, presumably deactivated by propofol, has an important role in propofol metabolism in rat liver microsomes. Repeated administration of propofol could markedly decrease the biotransformation of propofol via P450 deactivation.