PRESENTATION TITLE: SAFROLE AND HUMAN CYTOCHROME P450: BIOACTIVATION, INHIBITION, AND INDUCTION

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Safrole (4-allyl-1,2-methylenedioxybenzene) is a natural plant constituent, found in sassafras oil and certain other essential oils. In Taiwan, the chewing of betel quid, which had high content of safrole, increased the oral cancer risk. The carcinogenicity of safrole can be mediated through 1'-hydroxysafrole formation, followed by sulfonation to an unstable sulfate that reacts to form DNA adducts. Safrole 1'-hydroxylation (SOH) activities were determined using human liver microsomes and Escherichia coli membranes expressing bicistronic human P450s. SOH was sensitive to the inhibition by a CYP2C9 inhibitor, sulfaphenazole, and CYP2E1 inhibitors, 4-methylpyrazole and diethyldithiocarbamate. The liver microsomal SOH activity showed significant correlations with tolbutamide hydroxylation and chlorzoxazone hydroxylation activities, which were the marker reactions catalyzed by CYP2C9 and CYP2E1, respectively. These results revealed that SOH can be catalyzed by several P450 forms, with the major contributions of CYP2C9 and CYP2E1 to human hepatic SOH. Kinetic analysis revealed that SOH by microsomes, CYP2C9, and CYP2E1 did not show cooperativity. CYP2E1 had an intrinsic clearance greater than CYP2C9. In vitro, safrole was a potent inhibitor of human CYP1A2, CYP2A6, and CYP2E1. With relatively less potency, CYP2D6 and CYP3A4 were also inhibited. Safrole competitively inhibited CYP1A2 activity and non-competitively inhibited CYP2A6 and CYP2E1 activities. In an oral cell line, OECM-1, safrole stimulated cellular expression levels of CYP1A1/2 but not CYP1B1. This induction could be suppressed by arylhydrocarbon receptor antagonist α-naphthoflavone. Arylhydrocarbon receptor may be involved in this CYP1A induction. These results demonstrated the participation of multiple P450 forms in the metabolism and the possible xenobiotic interactions with safrole.

References:

Biography
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