Substrate Specificity of Human Flavin-containing monooxygenase 1 for Thiocarbamides

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Microsomes isolated from *Spodoptera frugiperda* (Sf)9 cells infected with human FMO1 recombinant baculovirus catalyzed the NADPH- and O2-dependent oxidation of methimazole, thiourea, and phenylthiourea. However there was no detectable activity with 1,3-diphenylthiourea or larger thiocarbamides. Microsomes from control Sf9 cells were devoid of methimazole or thiourea S-oxygenase activity. Trimethylamine up to 1.0 mM had no detectable effect on the oxidation of 10 μM methimazole (Km 5 μM) but 1.0 mM N,N-dimethylaniline or chlorpromazine inhibited the oxidation of 1.0 mM methimazole 50% and 70%, respectively. While products were not isolated, the pronounced inhibition of methimazole S-oxygenation suggests that these amines are alternate substrates for human FMO1. Because 1,3-diphenylthiourea is apparently completely excluded from the catalytic site, these amines drugs are probably approaching the upper size limits of xenobiotics accepted by human FMO1. The substrate specificity of this isoform in humans appears considerably more restricted than that of pig or guinea pig FMO1. Differences in the size of nucleophiles accepted must be considered in attempting to extrapolate the extensive structure-activity studies available for pig FMO1 to this FMO isoform in humans.

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