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Identification of CYP2D6 and CYP3A4 Involved in the Metabolism of Haloperidol: Substrate Concentration Dependency

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Recent microsomal incubation studies have shown that CYP3A4, but not CYP2D6, is mainly responsible for metabolism of haloperidol. The present study was carried out to identified the cytochrome P450 isoforms involved in the metabolism of haloperidol according to substrate concentration. In vitro studies were performed the enzymes responsible for the metabolism of haloperidol using human liver microsomes and recombinant human cytochrome P450 isoforms. Recombinant CYP2D6, CYP3A4, and CYP3A5 were identified to catalyze the metabolism of haloperidol to 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-pyridinium (HPP+) and 4-(4-chloeophenyl)-4-hydroxypiperidine (CPHP). The metabolic activities of haloperidol of 13 human liver microsomes were significantly correleated with dextromethoephan O-demethylation at low dose concentration, and testosterone 6β-hydroxylation and midazolam 1-hydroxylation were correlated with high dose level haloperidol metabolism. Our results suggest the involvement of CYP3A4 in the metabolism of haloperidol at high doses of haloperidol, while CYP2D6 contributes at lower doses (therapeutic dose levels).

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