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Enantiospecific effects of sibutramine enantiomers on cytochrome P450 inhibition *in vitro*

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Objective: The aim of this study was to investigate the enantioselective differences of sibutramine enantiomers in the inhibition of human CYP enzymes *in vitro*

Methods: Using a cocktail assay, the effects of sibutramine enantiomers (R/S- form) and 4-(4-chlorobenzyl) pyridine (CBP) on the 9 CYP isoform specific marker reactions were screened in human liver microsomes. According to USFDA guidelines, phenacetin (50 μM), coumarin (5 μM), bupropion (50 μM), rosiglitazone (1 μM), tolbutamide (100 μM), omeprazole (20 μM), dextrophan (5 μM), chlorzoxazone (50 μM) and midazolam (5 μM) were chosen as substrates of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A, respectively. Cocktails, test compounds and NADPH re-generating system were incubated 15 min after 5 pre-incubation with human liver microsomes (HLMs) *in vitro* for competitive screening. The respective metabolites of the nine substrates and internal standard chlorpropamide (200 ng/mL) were measured by LC-MS/MS system.

Results: CBP showed more potent inhibitory effect on CYP2B6 with IC50 values of 0.014 μM than sibutramine enantiomers (7.07 μM for R-form and 2.43 μM for S-form) based on bupropion-dependent inhibition. However, CBP also potently inhibited other CYPs except CYP3A4. In addition, R-sibutramine less slightly inhibited dextromethorphan-mediated CYP2D6 activities relative to S-sibutramine, and the IC50 value was more than 50 μM for R-sibutramine and 24.21 μM for S-sibutramine, respectively.

Conclusion: Based on these data, R-sibutramine was selective and potent inhibitor for CYP2B6 *in vitro* and S-sibutramine potently inhibited CYP2B6 and slight inhibited CYP2D6 when human liver microsomes were used as the enzyme source. Thus, the present findings signified that R-isomer of sibutramine is a potent stereoselective inhibitor of CYP2B6, whereas, inhibition for other CYPs was substantially negligible.

Biography

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