

论文

黄皮酰胺对映体在大鼠肝微粒体中的酶促反应动力学黄皮酰胺对映体在大鼠肝微粒体中的酶促反应动力学

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摘要:

目的研究黄皮酰胺 (clausenamide, Clau) 对映体在大鼠肝微粒体中的酶促反应动力学并比较其立体选择性差异。方法应用反相HPLC法测定Clau对映体在体外代谢系统中的产物, 并用Eadie-Hofstee作图法分析数据、求算酶促反应动力学参数 K_m 和 V_{max} 以及肝代谢速率 V_{max}/K_m 。结果在体外代谢系统中, 左旋黄皮酰胺主要生成7-羟-Clau、5-羟-Clau和4-羟-Clau, 其优势代谢途径为7位羟化; 7位羟化代谢的 V_{max}/K_m 值高于5位和4位。右旋黄皮酰胺的4位羟化反应 K_m 最小、 V_{max} 最大, 因此代谢速率最高, 是左旋体4位羟化的8倍; 而其7-羟-Clau和5-羟-Clau的产生量很小。结论黄皮酰胺对映体在大鼠肝微粒体中的羟化代谢存在明显的底物立体选择性差异。

关键词: 黄皮酰胺 对映体 大鼠肝微粒体 酶促反应动力学 立体选择性

Enzyme kinetics of clausenamide enantiomers in rat liver microsomes

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Abstract:

AimTo investigate the enzyme kinetics of (-)-3S,4r,5r,6S-clausenamide [(-)-Clau] and (+)-3r,4S,5S,6r-clausenamide [(+)-Clau] catalyzed by rat liver microsomes and compare their stereoselective differences. MethodsAn *In Vitro* metabolic system was built by using rat liver microsomes and NADPH-generating system. Clau and its metabolites were determined simultaneously by a reversed-phase high performance liquid chromatography. The kinetic parameters, K_m , V_{max} , and metabolic rate, V_{max}/K_m , were calculated by Eadie-Hofstee plot. ResultsIn the metabolic system, (-)-Clau was found to be mainly metabolized to 7-hydroxy-, 5-hydroxy- and 4-hydroxy-Clau, and 7-hydroxylation was a preferential pathway which exhibited higher V_{max}/K_m value ($0.135 \mu L \cdot \min^{-1} \cdot \text{mg}^{-1}$) than those of 5- and 4-hydroxylation (0.063 and $0.068 \mu L \cdot \min^{-1} \cdot \text{mg}^{-1}$, respectively). For (+)-Clau, it was mainly metabolized to 4-hydroxy-Clau, whereas 7-hydroxy- and 4-hydroxy-Clau were so small that they could not be detected systematically. 4-Hydroxylation of (+)-Clau showed highest V_{max}/K_m value ($0.547 \mu L \cdot \min^{-1} \cdot \text{mg}^{-1}$) among all the metabolites tested, which was 8.0 times higher than that of 4-hydroxylation of its antipode. ConclusionThe data indicated that there were obvious substrate stereoselective differences in the hydroxylation metabolism of (+)- and (-)-Clau, which provided an explanation of the difference of pharmacokinetic characteristics of Clau enantiomers in rats.

Keywords: enantiomer rat liver microsome enzyme kinetics stereoselectivity clausenamide

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