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论文

大豆苷元在人肝微粒体中的单羟化代谢机制大豆苷元在人肝微粒体中的单羟化代谢机制

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摘要：

目的探讨大豆苷元在人肝微粒中羟基化代谢所涉及的肝细胞色素P450(CYP)同工酶，为研究其在人体内的代谢提供基础。方法通过分析大豆苷元在肝微粒体中和重组CYP酶中形成的单羟化代谢物的酶促动力学,分析其酶学模型，然后用不同CYP同工酶选择性抑制剂或底物进行抑制实验，初步筛选出介导大豆苷元单羟化代谢所涉及的CYP同工酶。结果代谢物的形成动力学符合米氏方程单酶模型。CYP1A2选择性抑制剂呋喃茶碱和CYP1A2单克隆抗体均能明显抑制3种单羟化代谢物的形成。而其他CYP选择性的抑制剂对3种代谢物的形成没有或较小产生抑制作用。用重组酶实验得出相同结果。结论体外肝微粒体研究表明，大豆苷元的单羟基代谢主要由CYP1A2所介导。

关键词： 大豆苷元 人肝微粒体 羟基化代谢 细胞色素P450(CYP1A2)

Mechanism of mono-hydroxylation of daidzein in human liver microsomes

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Abstract:

AimTo identify the cytochrome P450 (CYP) isoform (s) involved in daidzein mono-hydroxylated metabolites using human liver microsomes. MethodsKinetic analysis of the rates of formation of mono-hydroxylated metabolites of daidzein, including 7,8,4′-trihydroxyisoflavone (7,8,4′-THI), 7,3′,4′-trihydroxyisoflavone (7,3′,4′-THI) and 6,7,4′-trihydroxyisoflavone (6,7,4′-THI), was performed using human liver microsomes (HLM) and recombinant enzymes at substrate concentrations ranging from 0.5 to 400 μmol·L^{-1}. Nine selective inhibitors or substrate probes specific for different CYP isoforms were applied for screening the isoform (s) responsible for mono-hydroxylated metabolism of daidzein. ResultsMichaelis-Menten kinetic parameters were best fitted to one-component enzyme kinetic model. The mean K_m(μmol·L^{-1}) and Vmax (μmol·g^{-1}·min^{-1}) values were 27±10 and 4.8±2.1, 54±22 and 2.3±1.0, 51±29 and 2.2±0.8, for the formation rates of 7,8,4′-THI, 7,3′,4′-THI, and 6,7,4′-THI, respectively. Furafylline, the CYP1A2 specific inhibitor, estrogen, and monoclonal antibody raised against human CYP1A2 (MAB-1A2) apparently inhibited the formation of mono-hydroxylated metabolites, The IC_{50} of Fur for the formation of 7,3′,4′-THI, 6,7,4′-THI and 7,8,4′-THI was 1.0, 0.9 and 0.8 mol·L^{-1}, respectively. The IC_{50} of estrogen for the formation of 7,3′,4′-THI, 6,7,4′-THI and 7,8,4′-THI were 51, 60 and 64 mol·L^{-1}, respectively. The IC_{50} of MAB-1A2 for the formation of the mono-hydroxylated products was 1 mol·L^{-1}, but neither other selective inhibitor nor substrate probes, including coumarin (CYP2D6), sulphaphenzole (CYP2C9/10), omeprazole (CYP2C19), quinidine (CYP2D6), diethyldithiocarbamate (CYP2E1), troleandomycin (CYP3A4) and keteconazole (CYP3A4), did so with human liver microsomes. ConclusionThe *in vitro* studies indicated that daidzein mono-hydroxylated products were principally metabolized by CYP1A2 in human.

Keywords: human liver microsome hydroxylation metabolism cytochrome P450 (CYP1A2) daidzein

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