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论著

山冈藁吾碱在雌性大鼠肝微粒体内的代谢

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摘要 研究了山冈藁吾碱(clivorine)在雌性大鼠肝微粒体内的代谢. 山冈藁吾碱在雌性大鼠肝微粒体内的主要代谢物为两个非吡咯代谢物M_1和M_2. 与雄性大鼠不同，生成肝毒性的吡咯代谢物为其次要的代谢途径. 文献报道山冈藁吾碱在雄性大鼠肝微粒体内的主要代谢方式是形成相应的吡咯代谢物. 这提示山冈藁吾碱在雌雄大鼠肝微粒体内的主要代谢方式不同. CYP450特异性抑制剂黄胺苯吡唑(CYP2C)，毛果芸香碱(CYP2A1)，二乙基二硫代氨基甲酸钠(CYP2E1)和酮康唑(CYP3A)对M_1和M_2的形成无明显的影响. 黄素单氧化酶的特异性抑制剂甲巯咪唑可以显著地抑制M_2的形成，但对M_1的形成无明显的抑制作用，且M_1在肝微粒体中的形成为NADPH非依赖性，上述结果提示参与M_1和M_2代谢的酶分别为肝微粒体中的水解酶和黄素单氧化酶. 另一方面，毛果芸香碱，黄胺苯吡唑和二乙基二硫代氨基甲酸钠对山冈藁吾碱的吡咯代谢物的形成无明显的影响，而CYP3A的特异性抑制剂酮康唑可以显著地抑制吡咯代谢物的生成，且山冈藁吾碱在重组的大鼠肝CYP2C12，CYP2E1温孵液中无代谢，而在重组的大鼠肝CYP3A1和CYP3A2的温孵液中山冈藁吾碱被代谢成相应的吡咯代谢物. 这提示CYP3A作为主要的CYP450酶参与了山冈藁吾碱的肝毒性吡咯代谢物的形成. 山冈藁吾碱在雌雄大鼠体内的毒性差异可能与其在雌雄大鼠体内的代谢存在差异有关.

关键词 山冈藁吾碱 微粒体, 肝 代谢

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Metabolism of clivorine in female rat liver microsomes

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Abstract

The metabolism of clivorine, an othonecine-type hepatotoxic pyrrolizidine alkaloid, was investigated in female rat liver microsomes. The major *in vitro* metabolites of clivorine found in the incubation mixture are two non-pyrrolic metabolites (M_1 and M_2) and the formation of hepatotoxic pyrrolic metabolites from clivorine is only the minor *in vitro* metabolic pathway of clivorine in female rats. It suggests that the major *in vitro* metabolic pathway of clivorine in female rats is different from that in male rats. Selective CYP450 inhibitors pilocarpine(Pil, CYP2A1), diethyldithiocarbamate (DDC, CYP2E1), sulfaphenazole (Sul, CYP2C) and ketoconazole (Ket, CYP3A) had no significant effects on the formation of M_1 and M_2. Selective flavin-containing monooxygenase(FMO) inhibitor methimazole could inhibit the formation of M_2, but had no inhibitory effect on the formation of M_1 and the formation of M_1 was NADPH independent. The above results suggests that the hydrolase and FMO in microsomes are involved in the formation of M_1 and M_2 respectively. On the other hand, Selective CYP450 inhibitors Pil, DDC, Sul had no significant effects on the formation of pyrrolic metabolites from clivorine, but selective CYP3A inhibitor Ket could significantly inhibited the formation of pyrrolic metabolites of clivorine whereas clivorine was not metabolized by recombinant rat CYP2C12 and CYP2E1, but could be metabolized by recombinant rat CYP3A1 and CYP3A2 to produce its corresponding hepatotoxic pyrrolic metabolites. The above results indicate that rat CYP3A1 and CYP3A2 are the primary CYP450 involved in the formation of hepatotoxic pyrrolic metabolites. The difference in clivorine-induced toxicity can be partly attributed to this metabolic difference in sex.

Key words clivorine microsomes liver metabolism

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