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论著

抗结核药物异烟肼肝毒性时效关系的代谢组学

廖 艳[2], 彭双清[1], 颜贤忠[3], 张立实[4]

[1]中国人民解放军疾病预防控制所毒理学评价研究中心, 北京 100071

[2]北京中医药大学 基础医学院养生康复系, 北京 100029

[3]国家生物医学分析中心, 北京 100850

[4]四川大学 华西公共卫生学院营养与食品卫生学教研室, 成都 610041

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摘要 摘要：目的
研究异烟肼灌胃后不同时段大鼠尿液的代谢表型改变及其与组织病理学和血浆生化指标变化的相关性，探讨代谢组学在药物毒理学研究中的应用。方法 Wistar大鼠连续经口灌胃0、50、100、200和400mg·kg-1异烟肼3、7、14d, 收集给药前24h及给药期间每天24h的尿液, 测定质子核磁共振（1H NMR）谱，并进行血浆生化指标测定和肝脏组织病理学检查。结果 常规毒性研究方法显示异烟肼在较高剂量、较长给药时间（7d以上）时表现出肝毒性, 并且有较好的时间-效应关系。对大鼠尿液进行代谢组学研究显示各组动物代谢谱各不相同, 随着给药时间的变化, 大鼠尿液1H NMR谱发生一定改变, 代谢谱的改变与常规毒性检测指标相符且更灵敏。与正常对照组比较, 给药组尿样1H NMR谱葡萄糖和牛磺酸显著增加, 2-酮戊二酸和柠檬酸显著降低。结论 大鼠尿液1H NMR代谢轨迹与异烟肼毒性作用时间密切相关, 异烟肼引起的肝毒性与线粒体功能受损、三羧酸循环中能量代谢异常及葡萄糖代谢紊乱有关。代谢组学分析在毒理学研究中有着广泛的应用前景。

关键词 代谢组学 核磁共振技术 模式识别 异烟肼 肝毒性

分类号

Metabonomics Profile of Urine from Rats Administrated with Different Treatment Period of Isoniazid

LIAO Yan[2], PENG Shuang-qing[1], YAN Xian-zhong[3], ZHANG Li-shi[4]

[1]Research and Evaluation Center for Toxicology, Beijing Institute of Disease Control and Prevention, Beijing 100071, China

[2] Department of Rehabilitation, School of Preclinical Medicine, Beijing University of Chinese Medicine, Beijing 100029, China

[3] National Center of Biomedical Analysis, Beijing 100850, China

[4] Department of Nutrition and Food Hygiene, West China School of Public Health, Sichuan University, Chengdu 610041, China

Abstract ABSTRACT:Objective To study the effect of different treatment period of isoniazid (INH) on the metabonomic profile of rat urine and its relationship with traditional toxicity evaluation of blood biochemical indicators and histopathology and to explore the feasibility of metabonomics in the application of drug toxicity. Methods Sixty male Wistar rats were orally administrated with 0, 50, 100, 200, and 400 mg. kg-1 INH for 3, 7, and 14 days, respectively. Rat urine was then collected and its 1H nuclear magnetic resonance (NMR) spectra were acquired. All animals underwent traditional toxicity evaluation. Results Hepatotoxicity was revealed by traditional toxicity evaluation in rats treated with higher dosage and longer treatment of INH. Time-response relationship existed during the treatment. Time-dependent metabonomics changes conformed with the results of traditional toxicity evaluation. The urine metabonomics showed a trajectory bias from those of the controls or pre-administration, and such bias exaggerated along with the prolongation of treatment, indicating a severer toxic injury. Along with the increase of the concentrations of urinary taurine and glucose and the decrease of the concentrations of urinary citrate and 2-oxoglutarate, the 1H NMR spectra of urine in rats treated with INH also changed. Conclusions The metabonomics technique can distinguish the onset and development of toxicity, which helps track and identify biomarkers. The hepatic toxicity induced by INH is related to the injury of mitochondrial function, reduction of energy metabolism in tricarboxylic acid cycle, and perturbations in the metabolism of glucose and lipid. The effect of INH on the rat urine metabonomic profile is related with INH toxicology. Therefore, metabonomics can be

recognized as an ideal technique to explore and evaluate the drug toxicities.

Key words metabonomics nuclear magnetic resonance pattern recognition isoniazid hepatotoxicity

DOI:

通讯作者 彭双清 pengsq@hotmail.com