中国药理学与毒理学杂志 2011 25 (2): 193-200 ISSN: 1000-3002 CN: 11-1115/R

论著

人支气管上皮细胞5-脂氧合酶介导4-氨基联苯的活化及DNA损伤

朱宏翔[1,2]，胡建安[1]，黄 云[1]，武 越[1]，熊敏如[1]

（1. 中南大学公共卫生学院劳动卫生与环境卫生学系, 湖南 长沙 410078; 2. 湖南省劳动卫生职业病防治所控制评价科, 湖南 长沙 410007）

收稿日期 2010-3-9 **修回日期** **网络版发布日期** 2011-4-8 **接受日期** 2010-12-13

摘要 **目的** 探讨人支气管上皮(HBE)细胞内5-脂氧合酶（5-LOX）对4-氨基联苯（4-ABP）的氧化活化及所致DNA损伤，为LOX作为前致癌物氧化活化的代谢途径提供依据。**方法** ① 体外酶系统实验：4-ABP在含有大豆脂氧合酶（SLO）的体外酶体系中反应，用分光光度法检测体系中反应产物生成。② 细胞实验：4-ABP 100~800 μmol·L^{-1}染毒HBE细胞，MTT法检测HBE细胞存活率；Western印迹法检测5-LOX蛋白表达；单细胞凝胶电泳检测DNA损伤。同时，检测特异性5-LOX抑制剂AA861对5-LOX蛋白表达和多种酶抑制剂对细胞存活率和DNA损伤的影响。**结果** 在过氧化氢参与下，SLO可以协同氧化4-ABP，LOX抑制剂去甲二氢愈创木酸可抑制该协同氧化作用。4-ABP可以使HBE细胞内5-LOX蛋白表达增加，AA861对5-LOX蛋白表达没有影响；4- ABP 400 μmol·L^{-1}可以使HBE细胞产生明显的DNA损伤，彗星细胞的阳性率达47.7%（P<0.01），AA861和萘普生可以抑制该浓度4-ABP所致的DNA损伤，最大保护率分别为58.1%和21.7%。**结论** 4-ABP上调HBE的5-LOX蛋白表达。5-LOX可能通过介导4-ABP协同氧化，导致DNA损伤，这可能是4-ABP致癌的机制之一。

关键词 花生四烯酸盐5 脂氧合酶 氨基联苯化合物 药物协同作用 DNA损伤

分类号 R994.6

Activation of 4-aminobiphenyl mediated by 5-lipoxygenase and DNA damage in human bronchial epithelial cells

ZHU Hong-xiang[1,2], HU Jian-an[1], HUANG Yun[1], WU Yue[1], XIONG Ming-ru[1]

（1. Department of Occupational and Environmental Health, College of Public Health, Central South University, Changsha 410078, China; 2. Department of Control Effect Evaluation,Hunan Provincial Institute for Labor Hygiene and Occupational Diseases, Changsha 410007, China）

Abstract

OBJECTIVE To investigate the effect of 4-aminobiphenyl(4-ABP) on 5-lipoxygenase(5- LOX) protein expression, cytotoxicity and DNA damage in human bronchial epithelial (HBE) cells, and to provide envidence that LOX is a pathway for oxidation and activation of precarcinogens. **METHODS** ① Enzymatic experiment: soybean lipoxygenase (SLO), substrate (4-ABP) and other components reacted in an enzymic system; the product was detected with spectrophotometry. ② Cellular experiment: The effect of 4-ABP on the cellular survival rate was assessed by reduction of tetrazolium dye(MTT) in cultured HBE cells. After HBE cells were exposed to 4-ABP 100-800 μmol·L^{-1} for 4 h, the protein expression of 5-LOX in HEB cells was tested by Western blotting, and DNA damage by single cell gel electrophoresis. Finally the effect of a specific inhibitors of 5-LOX, AA861, on 5- LOX protein expression and DNA damage in the cells was detected. **RESULTS** SLO catalyzed the co-oxidation of 4-ABP in the presence of hydrogen peroxide. Nordihydroguaiaretic acid(NDGA) inhibited the oxidation of 4-ABP by SLO, seemingly in a concentration- dependent manner and with in a special range. 4-ABP induced 5-LOX protein expression, but AA861 was invalid in HBE. 4-ABP caused toxic action and DNA damage in HBE, as the positive rate comet cells was increased to 47.7% by 4-ABP at the concentration of 400 μmol·L^{-1}. Such damage could be significantly inhibited by AA861 and naproxen with a maximum rate of protection of 58.1% and 21.7%, respectively. **CONCLUSION** 4-ABP can regulate 5-LOX protein expression in HBE cells. The co-oxidation of 4-ABP with 5-LOX could induce DNA damage, which could be one of the mechanisms for carcinogenesis of 4-ABP.

Key words arachidonate 5 lipoxygenase aminobiphenyl compounds drug synergism DNA damage

DOI: 10.3867/j.issn.1000-3002.2011.02.013

通讯作者 胡建安 jiananhu@xysm.net