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论著

15-HETE与ERK1/2在大鼠缺氧性肺动脉收缩中的作用

吕昌莲[1,2],张家宁[2],叶宏[3],李一经[1△],朱大岭[2,4]

1东北农业大学兽医学， 黑龙江 哈尔滨 150030;哈尔滨医科大学 2 药学院， 3 公卫学院，黑龙江 哈尔滨 150086;4 黑龙江省生物医药工程重点实验室-省部共建国家重点实验培育基地， 黑龙江 哈尔滨 150081

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摘要 目的:为揭示缺氧性肺血管收缩机制,探讨细胞外信号调节激酶1/2 (ERK1/2)是否参与15-羟基二十碳四烯酸（15-HETE）收缩缺氧大鼠肺动脉的过程以及15-HETE对 ERK1/2活性的影响。 方法: 将大鼠置于氧气分数为12.0%的低氧箱中连续9 d形成缺氧模型。完整取出心肺，在显微镜下分离直径0.8-1.0 mm肺动脉剪为3 mm长的动脉环在组织浴槽内进行张力研究。比较15-HETE给药前后肺动脉环张力变化；用ERK1/2上游激酶抑制剂U0126孵育肺动脉环，比较U0126孵育前后15-HETE对缺氧性肺动脉环的收缩作用；机械法去除动脉环内皮，再比较U0126孵育前后15-HETE的收缩作用。酶法分离培养大鼠肺动脉平滑肌细胞。Western blotting方法检测15-HETE作用时间（5-90 min）及浓度（10^{-9}-10^{-6} mol/L）对 ERK1/2 的表达及活性的影响。 结果: 15-HETE对缺氧大鼠肺动脉环有收缩作用，呈浓度-效应关系，与正常对照组比较差异显著（P<0.05）；内皮完整和内皮去除的肺动脉环，U0126孵育前后，15-HETE的缩血管作用都受到抑制，差异显著（均为P<0.05）。Western bloting结果显示，15-HETE明显增强肺动脉血管平滑肌细胞ERK1/2的活性，随时间延长而降低，随浓度增加而增加，但对ERK1/2的蛋白表达无影响。 结论:15-HETE能上调大鼠肺动脉血管平滑肌细胞ERK1/2的活性，提示ERK1/2的活化是15-HETE收缩慢性缺氧大鼠肺动脉的一个重要环节。

关键词 缺氧 花生四烯酸类 肺动脉 血管收缩 有丝分裂素激活蛋白激酶类 大鼠

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Effects of 15-HETE and ERK1/2 on pulmonary artery constriction in chronic hypoxic rats

LV Chang-lian[1,2],ZHANG Jia-ning[2],YE Hong[3],LI Yi-jing[1],ZHU Da-ling[2,4]

1Veterinary Medicine Department, Northeast Agricultural University, Harbin 150030, China;2 College of Pharmacy, 3 Public Health College, Harbin Medical University, Harbin 150086, China;4 Key Laboratory of Biopharmaceutical Engineering of Heilongjiang Province, Harbin 150081, China

Abstract

<FONT face=Verdana>AIM:The aim of the present study was to investigate whether the extracellular signal regulated kinase-1/2 (ERK1/2) pathway was involved in 15-hydroxyeicosatetraenoic acid (15-HETE)-induced chronic hypoxic pulmonary artery (PA) constriction and whether ERK1/2 activity was influenced by 15-HETE, for clarifying the mechanism of hypoxic pulmonary vasoconstriction (HPV).
METHODS:Rats were placed in hypoxic box with fractional inspired oxygen (FiO2) 0.12 for 9 days to make hypoxic models, while those lived in FiO₂ 0.21 served as normal controls. Heart and lungs were taken out from chest and PA in diameter of 1-1.5 mm was isolated and cut into rings with 3 mm long for tension studies in organ baths. The ring tensions before and after adding 15-HETE were compared. Influences of ERK1/2 upstream kinase inhibitor U0126 as well as endothelium integrity on 15-HETE-induced HPV were observed. Expression and
 activity of ERK1/2 in cultured rat pulmonary artery smooth muscle cells (PASMCs
) treated with 15-HETE for different times and concentrations were examined by Western blotting. RESULTS:15-HETE significantly constricted PA rings from hypoxic
 rats, and the response of the hypoxic rings were significantly greater than tha
t of normoxic ones (P<0.05). U0126 significantly reduced vasoconstriction i
nduced by 15-HETE both in endothelium-intact and -denuded rings (both were P
<0.05). Western blotting results showed 15-HETE enhanced activity of ERK1/2 in
PASMCs, increasing with concentration and decreasing with time. CONCLUSION:15-HETE upregulates activity

of ERK1/2 in PASMCs of rats. The activation of ERK1/2 is an important step in 15-HETE- induced HPV in rats.</FONT>

Key words Anoxia Arachidonic acids Pulmonary artery Vasoconstriction Mitogen-activated protein kinases Rats

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通讯作者 李一经