doi: 10.3978/j.issn.2095-6959.2018.01.001
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2018.01.001

·论著·

姜黄素对肠缺血再灌注继发性肺损伤大鼠 TNF–α 与 IL–6 表达的影响

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[摘　要]　**目的：**观察姜黄素预处理对肠缺血再灌注继发性肺损伤大鼠TNF-α与IL-6表达的影响。**方法：**将30只清洁级大鼠随机分为3组(n=10)：假手术组(S组)，肠缺血再灌注肺损伤模型组(I/R组)，姜黄素预处理组(CUR组)。CUR组大鼠于模型建立前5 d，每天胃饲姜黄素200 mg/kg，S组与I/R组胃饲等容量生理盐水。采用夹闭肠系膜上动脉75 min后恢复灌注的方法制备肠缺血再灌注继发性肺损伤模型。恢复灌注4 h后取肺组织进行肺组织损伤评分、计算肺含水率、检测TNF-α和IL-6表达水平。**结果：**与S组比较，I/R组和CUR组肺组织损伤评分、肺含水率、TNF-α和IL-6表达水平升高(P<0.05)；与I/R组比较，CUR组肺组织损伤评分、肺含水率、TNF-α和IL-6表达水平下降(P<0.05)。**结论：**姜黄素预处理可减轻大鼠肠缺血再灌注继发性肺损伤，其机制可能与抑制肺组织炎症因子TNF-α和IL-6的表达相关。

[关键词]　姜黄素；肺损伤；缺血再灌注；肿瘤坏死因子α；白介素6

Effects of curcumin pretreatment on TNF-α and IL-6 during lung injury induced by intestinal ischemia-reperfusion in rats

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Abstract　**Objective:** To evaluate the effects of curcumin pretreatment on TNF-α and IL-6 during lung injury induced by intestinal ischemia-reperfusion in rats. **Methods:** Thirty female healthy SD rats were divided into three groups randomly (n=10): sham operation group (S group), lung injury inducing by intestinal ischemia-reperfusion group (I/R group), curcumin pretreatment group (CUR group). In CUR group, rats were treated intragastrically with curcumin at a dose of 200 mg/kg for 5 d before operation while rats were treated intragastrically with the same volume of NS in S group and I/R group. Lung injury induced by intestinal ischemia-reperfusion in rats was

收稿日期 (Date of reception)：2017–08–31
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基金项目 (Foundation item)：佛山市卫生和计划生育局医学科研课题 (20160083)。This work was supported by the Medical Scientific Project Foundation of Foshan Department of Health and Family Planning Bureau, China (20160083).

conducted by clamping the superior mesenteric artery for 75 min. The rats were sacrificed after 4-h reperfusion. The lung tissues were obtained for pathological analysis, lung water content evaluation and the determination of TNF-α and IL-6 levels. **Results:** The pathological scores, lung water content, and the levels of TNF-α and IL-6 were significantly increased in group I/R and group CUR as compared with group S (P<0.05). The pathological scores, lung water content, and the levels of TNF-α and IL-6 were significantly decreased in CUR group as compared with group I/R (P<0.05). **Conclusion:** Curcumin pretreatment attenuates the lung injury induced by intestinal ischemia-reperfusion on rats, which might be associated with inhibition of the levels of TNF-α and IL-6 in lung tissue.

Keywords curcumin; lung injury; ischemia reperfusion; TNF-α; IL-6

肠缺血再灌注除引起局部损伤外，还可引起远隔器官损伤，临床上以继发性肺损伤最为常见[1]。肠缺血再灌注可刺激多种炎症细胞活化，触发肺组织炎症反应持续放大而失控。姜黄素具有抗炎、抗凝、抗氧化等多种作用[2]，但姜黄素预处理对肠缺血再灌注继发性肺损伤炎症因子表达的作用目前尚不清楚。本研究拟探讨姜黄素预处理对小肠缺血再灌注继发性肺损伤中TNF-α和IL-6表达的影响。

1 材料与方法

1.1 动物

清洁级雌性SD大鼠30只，体重180~220 g，按基础饲料饲养并适应环境1周，室温保持22~24 ℃，光照明暗比为12:12。

1.2 方法

1.2.1 实验分组及模型建立

采用随机数字表法，将大鼠分为3组(n=10)：假手术组(S组)，肠缺血再灌注肺损伤模型组(I/R组)，姜黄素预处理组(CUR组)。CUR组大鼠于模型建立前5 d，每天胃饲姜黄素(批号：SLBD0850V，美国 Sigma公司)200 mg/kg(采用生理盐水稀释至20 mg/mL)，S组与I/R组胃饲等容量生理盐水。实验开始前12 h禁食，不禁饮，CUR组和I/R组大鼠腹腔注射10%水合氯醛3 mL/kg麻醉，分离肠系膜上动脉，采用无创动脉夹夹闭肠系膜上动脉，75 min后恢复灌注，制备大鼠肠缺血再灌注继发性肺损伤模型。S组大鼠除不夹闭肠系膜上动脉外，其余操作与I/R组和CUR组相同。

1.2.2 标本采集及检测项目

于再灌注4 h时开胸放血处死大鼠，取右上肺行HE染色，根据文献[3]的方法行肺组织损伤评分；取右中肺组织准确称重(湿重)后于85 ℃干燥烘烤箱24 h后再称重(干重)，肺含水率=(湿重−干重)/湿重×100%)；采用ELISA法测定其余肺组织匀浆TNF-α和IL-6表达水平，具体操作步骤参照试剂盒(南京凯基生物科技发展有限公司)方法进行。

1.3 统计学处理

采用SPSS 16.0统计学软件进行分析，率的比较采用卡方检验，正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示，组间比较采用单因素方差分析，P<0.05为差异有统计学意义。

2 结果

S组大鼠肺泡结构完整，未见组织水肿充血及炎症细胞浸润；I/R组大鼠肺泡壁间隔明显变大，大量炎症细胞和明显肺间质水肿；CUR组大鼠肺泡间隔轻度增宽，肺间质轻度水肿，炎性细胞少量浸润(图1)。

与S组比较，I/R组和CUR组大鼠肺组织损伤评分、肺组织含水率、TNF-α和IL-6表达水平升高，差异有统计学意义(P<0.05)；与I/R组比较，CUR组大鼠肺组织损伤评分、肺组织含水率、TNF-α和IL-6表达水平下降，差异有统计学意义(P<0.05；表1)。

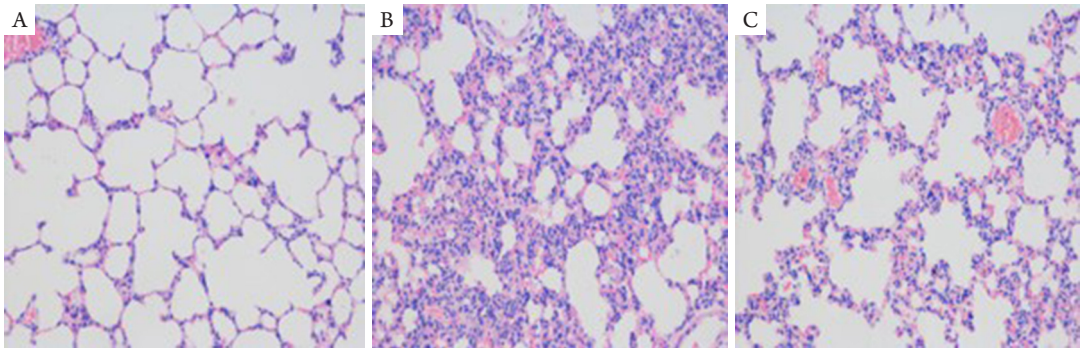

图1 各组大鼠肺组织病理切片(HE，×200)

Figure 1 Pathological morphology of lung tissues for evaluation of lung injury (HE, × 200)

(A)S组；(B)I/R组；(C)CUR组。

(A) S group; (B) I/R group; (C) CUR group.

表1 3组大鼠肺组织损伤评分、肺含水率、TNF-α和IL-6表达水平比较(n=10，$\bar{x} \pm s$)

Table 1 Comparision of the pathological scores, lung water content, the levels of TNF-α and IL-6 of lung tissues in three groups (n=10, $\bar{x} \pm s$)

组别	肺组织损伤评分	肺含水率 /%	TNF-α 表达水平 /(pg·mg^{-1})	IL-6 表达水平 /(pg·mg^{-1})
S 组	1.09 ± 0.56	75.6 ± 2.4	35.7 ± 4.6	46.2 ± 7.1
I/R 组	2.92 ± 0.59*	89.3 ± 2.9*	138.4 ± 13.5*	169.7 ± 16.6*
CUR 组	2.05 ± 0.33*#	83.1 ± 2.2*#	55.3 ± 7.1*#	78.8 ± 10.4*#

与S组比较，*P<0.05；与I/R组比较，#P<0.05。

Compared with S group, *P<0.05; compared with I/R group, #P<0.05.

3 讨论

本实验参照文献[4]，采用夹闭肠系膜上动脉75 min恢复灌注的方法制备大鼠肠缺血再灌注继发性肺损伤模型，结果表明：与S组相比，I/R组大鼠肺组织损伤评分和肺含水率升高，提示本实验肠缺血再灌注继发性肺损伤模型制备成功。

肠缺血后可触发全身炎症反应，过度的炎症反应是引起急性肺损伤的重要原因，其中TNF-α发挥核心作用[5]，TNF-α能激活NF-κB，而后者进一步激活TNF-α，IL-6等多种炎性因子，最终形成瀑布样炎症反应；IL-6可直接增加内皮细胞通透性，促进成熟中性粒细胞的功能性受体介导炎症反应以及氧自由基和蛋白水解酶释放，从而加重肺组织结构损伤。Groeneveld等[6]研究发现：腹主动脉瘤术后患者的缺血再灌注后肺损伤程度和TNF-α，IL-6表达水平的升高显著相关。Zhao等[7]的实验发现大鼠肠缺血再灌注后发生继发性肺损伤且肺组织IL-6表达水平明显升高。本实验结果也提示：I/R组大鼠肺组织病理损伤明显，肺含水率升高并伴有肺组织TNF-α，IL-6表达水平的升高，说明肠缺血再灌注后肺组织产生的炎性因子对肺组织具有继发性损伤作用。

多项研究[8-10]已证实姜黄素对心、神经、肝、肾等器官的缺血再灌注损伤具有保护作用。前期研究[11]也发现姜黄素预处理可通过抑制肠组织TNF-α的表达而减轻大鼠肠缺血再灌注损伤，因此，本实验采用姜黄素200 mg/kg胃饲连续5 d进行预处理观察对肠缺血再灌注肺损伤是否具有保护效应。Kim等[12]发现在大鼠心肌缺血再灌注前给予姜黄素预处理，对心肌具有保护效应，这一保护效应可能与姜黄素预处理抑制TLR-2活性使NF-κB的核转移受限，最终使组织炎性反应减轻相关[13]。此外，Zhang等[14]研究发现姜黄素衍生物C26也可抑制脂多糖诱导的大鼠急性肺损伤后肺组织TNF-α，IL-6的表达水平，其机制可能是通过下调ERK信号通路的磷酸化。Kim等[15]则认为姜黄素可通过促进MAPK的磷酸化，最终使脂多糖诱发的急性肺损伤后升高的TNF-α，IL-6水平下降。本实验

结果也发现：通过给予姜黄素预处理能明显抑制肺组织TNF-α，IL-6的表达水平，并能明显减轻大鼠肠缺血再灌注继发性肺损伤程度，但姜黄素通过何种通路发挥效应仍需进一步研究。

综上所述，姜黄素预处理对肠缺血再灌注继发性肺损伤具有保护效应，抑制肺组织的炎性反应参与这一保护作用，但具体通过何种机制实现仍需进一步研究探讨。

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本文引用： 廖美娟, 赵伟成, 梁幸甜, 贺俭, 刘洪珍, 王靖, 肖蔚. 姜黄素对肠缺血再灌注继发性肺损伤大鼠TNF-α与IL-6表达的影响[J]. 临床与病理杂志, 2018, 38(1): 1-4. doi: 10.3978/j.issn.2095-6959.2018.01.001

Cite this article as: LIAO Meijuan, ZHAO Weicheng, LIANG Xingtian, HE Jian, LIU Hongzhen, WANG Jing, XIAO Wei. Effects of curcumin pretreatment on TNF-α and IL-6 during lung injury induced by intestinal ischemia-reperfusion in rats[J]. Journal of Clinical and Pathological Research, 2018, 38(1): 1-4. doi: 10.3978/j.issn.2095-6959.2018.01.001