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血红素加氧酶 -1 对急性重症胰腺炎相关肺损伤 TLR4/NF-κB 通路的影响 *

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摘要 目的:探讨血红素加氧酶 -1(HO-1)对急性重症胰腺炎相关肺损伤(PALI)Toll 样受体 -4(TLR4)/ 核因子 -κB(NF-κB)信号传导通路的影响。**方法:**32 只 SD 大鼠随机分为 Sham 组、PALI 组、HO-1 促进剂组、HO-1 抑制剂组,每组 8 只。PALI 组经胆胰管注入牛磺胆酸钠制备急性重症胰腺炎(ANP)动物模型。Sham 组胆胰管内不注入牛磺胆酸钠,其余操作同 PALI 组。HO-1 促进剂组于造模后 30 min 经腹腔注射牛血晶素 75 μg/kg;HO-1 抑制剂组于造模后 30 min 经腹腔注射锌 - 原卟啉 20 μmol/kg。PALI 组和 Sham 组均于造模后 30 min 经腹腔注射等量生理盐水。各组大鼠术后 24 h,进行肺损伤学评分,统计肺湿 / 干重比值。检测大鼠术后 24 h 血清淀粉酶、TNF-α、IL-6、NGAL 水平。检测大鼠术后 24 h 肺组织中 TLR4、NF-κB p65 蛋白表达。**结果:**PALI 组肺损伤学评分、肺湿 / 干重比值、淀粉酶、TNF-α、IL-6、NGAL、TLR4、NF-κB p65 明显高于 Sham 组;HO-1 促进剂组肺损伤学评分、肺湿 / 干重比值、淀粉酶、TNF-α、IL-6、NGAL、TLR4、NF-κB p65 明显低于 PALI 组;HO-1 抑制剂组肺损伤学评分、肺湿 / 干重比值、淀粉酶、TNF-α、IL-6、NGAL、TLR4、NF-κB p65 明显高于 PALI 组;差异均有统计学意义(P<0.05)。**结论:**HO-1 能够通过抑制 TLR4/NF-κB 信号通路的激活,下调 TNF-α、IL-6、NGAL 等炎症因子的释放,从而发挥减轻急性重症胰腺炎相关肺损伤的作用。

关键词:急性重症胰腺炎;急性肺损伤;Toll 样受体 -4/ 核因子 -κB 信号通路;血红素加氧酶 -1

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Effect of HO-1 on TLR4/ NF-κB Pathway in Acute Necrotizing Pancreatitis-associated Acute Lung Injury*

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ABSTRACT Objective: To explore the effect of Heme oxygenase -1 (HO-1) on TLR4/ NF-κB pathway in acute necrotizing pancreatitis-associated acute lung injury. **Methods:** 32 SD rats were randomly divided into Sham group, PALI group, HO-1 promoter group and HO-1 inhibitor group, with 8 rats in each group. ANP animal model was prepared by injecting sodium taurocholate into biliopancreatic duct in PALI group. Sodium taurocholate was not injected into biliopancreatic tube in Sham group, and the other operations were the same as PALI group. The HO-1 promoter group was intraperitoneally injected with bovine hemagglutinin 75 μg/kg 30 min after modeling. The HO-1 inhibitor group was intraperitoneally injected with zinc-protoporphyrin 20 μmol/kg 30 min after modeling. The PALI group and Sham group were intraperitoneally injected with the same amount of normal saline 30 min after modeling. Lung injury scores were performed 24 h after surgery, and lung wet/dry weight ratio was calculated. Serum amylase, TNF-α, IL-6 and NGAL levels were detected 24 h after operation. The expressions of TLR4 and NF-κB p65 in the lung tissues of rats at 24 h after surgery were measured. **Results:** Lung injury scores, lung wet/dry weight ratio, amylase, TNF-α, IL-6, NGAL, TLR4 and NF-κB p65 were significantly higher in PALI group than Sham group. The lung injury scores, lung wet/dry weight ratio, amylase, TNF-α, IL-6, NGAL, TLR4 and NF-κB p65 were significantly lower in the HO-1 promoter group than those in the PALI group. Lung injury scores, lung wet/dry weight ratio, amylase, TNF-α, IL-6, NGAL, TLR4 and NF-κB p65 p65 were significantly higher in the HO-1 inhibitor group than in the PALI group. All the differences were statistically significant (P<0.05). **Conclusions:** HO-1 can reduce the release of inflammatory factors such as TNF-α, IL-6 and NGAL by inhibiting the activation of the TLR4/NF-κB signaling pathway, thereby reducing lung injury associated with acute severe pancreatitis.

Key words: Acute severe pancreatitis; Acute lung injury; TLR4/NF-κB; Heme oxygenase -1

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前言

急性重症胰腺炎(acute necrotizing pancreatitis,ANP)是临床常见急腹症,死亡率较高,可达 20%-40%。急性重症胰腺炎患者的早期死亡高峰在 1-2 周左右,主要死于全身炎症反应综合征(systemic inflammatory response Syndrome,SIRS)导致的多器官功能障碍综合征 (multiple organ dysfunction syndrome,MODS),其中急性肺损伤是急性重症胰腺炎的常见并发症之一,有可能进展为急性呼吸窘迫综合征,威胁患者的生命[1-5]。Toll 样受体 -4(Toll like receptor-4,TLR4)/ 核因子 -κB(nuclear factor kappa B,NF-κB)信号传导通路在急性重症胰腺炎早期促发的炎症反应和器官损伤中发挥重要的介导作用[6-9]。目前,如何减轻急性重症胰腺炎相关肺损伤的程度,以及关于急性重症胰腺炎相关肺损伤 (acute necrotizing pancreatitis-associated acute lung injury,PALI) 发生机制的研究仍然是医学界的重要课题[9-12]。

血红素加氧酶 -1(heme oxygenase-1,HO-1)是血红素降解的起始酶和限速酶,能够在血红素的代谢过程中,促进血红素形成胆绿素等产物,发挥抗炎症反应及抗凋亡、抗氧化的功能[13]。有研究发现,HO-1 的过表达能够改善急性重症胰腺炎的肝脏病变及肝肾功能[14],但关于其在急性肺损伤中影响机制尚不完全清楚。本研究运用 HO-1 对 PALI 大鼠模型进行干预,探讨其对 TLR4/NF-κB 信号通路的影响,旨在为临床 PALI 的治疗提供依据。

1 材料与方法

1.1 实验动物及分组

32 只 SD 大鼠(SCXK(陕)2018-001),雄性,清洁级,体重 200-300 g,饲养于西安交通大学动物实验中心,在安静、温暖(18-25℃)、避强光、昼夜光照节律的实验室饲养 1 周后供本研究实验所用,自由饮水和摄食。为每只 SD 大鼠编号,按照随机数字表法分为 Sham 组(假手术组)、PALI 组、HO-1 促进剂组、HO-1 抑制剂组,每组 8 只。本实验中所有动物实验,均参照《实验动物管理条例》进行,符合动物伦理学标准,并通过西安交通大学医学部伦理学委员会批准。

1.2 方法

1.2.1 ANP 动物模型制备 PALI 组,动物术前 12 h 禁食,不禁水。术前腹腔内注射 10%水合氯醛 3-4 mL/kg 麻醉,达到满意麻醉状态后腹部备皮,剑突下 2 cm 腹正中开腹,找到十二指肠及胆胰管,阻断胆总管出肝门处,静脉留置针穿刺胆胰管开口处的十二指肠对侧壁,进入十二指肠肠腔,退出针芯,进入套管,按 1 mL/kg 体重的剂量缓慢(0.1 mL/min)注射 4%牛磺胆酸钠(购于美国 Sigma-Aldrich 公司);注射完毕应用血管钳夹闭胆总管入十二指肠处 5 min,肉眼可见充血、水肿时提示造模成功,随后缝合、关腹[15-17]。所有实验操作在无菌操作下完成。

Sham 组(假手术组),胆胰管内不注入牛磺胆酸钠,其余操作同 PALI 组。

HO-1 促进剂组,于造模后 30 min 经腹腔注射牛血晶素 75 μg/kg。

HO-1 抑制剂组,于造模后 30 min 经腹腔注射锌 - 原卟啉 20 μmol/kg。

PALI 组和 Sham 组均于造模后 30 min 经腹腔注射等量生理盐水。

1.2.2 标本采集 各组大鼠分别于术后 24 h 采用腹主动脉抽血法处死。采集血液后抗凝,离心,采集血清。取胰腺和肺组织。(1)大鼠术后 24 h 肺损伤学评分、肺湿 / 干重比值: 取右肺上叶进行常规病理检查,参考 Osman 肺脏组织学评分标准进行肺损伤评分[18],评分范围 0～9 分,分数越高表明肺组织水肿、肺泡组织炎细胞浸润、组织出血的程度越严重。取左肺称重,电热干燥箱烘烤(60℃,48 h),称干重。计算肺组织湿 / 干重比值 = (肺湿重 - 肺干重)/ 肺干重。(2) 大鼠术后 24 h 血清淀粉酶、TNF-α、IL-6、NGAL 水平检测: 采用全自动生化分析仪检测血清淀粉酶含量(检测试剂盒购于美国 Sigma 公司)。应用 ELISA 法检测血清中肿瘤坏死因子 -α(TNF-α)、白介素 -6(IL-6)、中性粒细胞明胶酶相关载脂蛋白(NGAL)含量(检测试剂盒购于北京中杉金桥生物有限公司)。(3) 大鼠术后 24 h 肺组织中 TLR4、NF-κB p65 蛋白表达检测:取 10 g 右肺中叶,匀浆,常规进行 Western-blot 检测。TLR4、NF-κB p65 蛋白一抗及二抗均购于美国 Sigma 公司,实验结束后经图像分析软件进行分析,以平均灰度值表示 TLR4、NF-κB p65 蛋白的相对含量。

1.3 统计学方法

采用 SPSS 21.0 统计学软件进行数据分析。正态计量数据用 "$\bar{x} \pm s$" 表示,多组独立,正态,方差齐资料组间比较采用单因素方差分析,两两比较采用LSD-t法。P<0.05 为差异有统计学意义。

2 结果

2.1 各组大鼠术后 24 h 肺损伤学评分、肺湿 / 干重比值比较

单因素方差分析结果显示,各组大鼠术后 24 h 肺损伤学评分、肺湿 / 干重比值均存在明显统计学差异(P<0.05)。PALI 组肺损伤学评分、肺湿 / 干重比值明显高于 Sham 组;HO-1 促进剂组肺损伤学评分、肺湿 / 干重比值明显低于 PALI 组;HO-1 抑制剂组肺损伤学评分、肺湿 / 干重比值明显高于 PALI 组;差异均有统计学意义(P<0.05)。见表 1。

2.2 各组大鼠术后 24h 血清淀粉酶、TNF-α、IL-6、NGAL 水平比较

单因素重复测量方差分析结果显示,各组大鼠术后 24 h 血清淀粉酶、TNF-α、IL-6、NGAL 水平存在明显统计学差异(P<0.05)。PALI 组淀粉酶、TNF-α、IL-6、NGAL 水平明显高于 Sham 组;HO-1 促进剂组淀粉酶、TNF-α、IL-6、NGAL 水平明显低于 PALI 组;HO-1 抑制剂组淀粉酶、TNF-α、IL-6、NGAL 水平明显高于 PALI 组;差异均有统计学意义(P<0.05)。见表2。

2.3 各组大鼠术后 24 h TLR4、NF-κB p65 表达水平比较

各组大鼠术后 24 h 肺组织中 TLR4、NF-κB p65 表达水平均存在明显统计学差异 (P<0.05)。PALI 组 TLR4、NF-κB p65 表达水平明显高于 Sham 组;HO-1 促进剂组 TLR4、NF-κB p65 表达水平明显低于 PALI 组;HO-1 抑制剂组 TLR4、NF-κB p65 表达水平明显高于 PALI 组;差异均有统计学意义(P<0.05)。见表 3。图 1。

表 1 各组大鼠术后 24h 肺损伤学评分、肺湿 / 干重比值比较($\bar{x}\pm s$)

Table 1 Comparison of lung injury scores and lung wet/dry weight ratio 24 hours after operation in rats of each groups($\bar{x}\pm s$)

Groups	Amount(n)	Lung injury scores	Lung wet/dry weight ratio
Sham Group	8	0.13± 0.35	2.56± 0.23
PALI Group	8	5.50± 1.07※	4.65± 0.48※
HO-1 promoter Group	8	2.75± 0.71※#	3.59± 0.36※#
HO-1 inhibitor Group	8	6.38± 0.74※#	5.22± 0.43※#
F	-	110.636	73.968
P	-	<0.001	<0.001

Note: ※, compared with the Sham group, $P<0.05$; #, compared with the PALI group, $P<0.05$.

表 2 各组大鼠术后 24 h 血清淀粉酶、TNF-α、IL-6、NGAL 水平比较($\bar{x}\pm s$)

Table 2 Comparison of serum amylase, TNF-α, IL-6 and NGAL levels at 24 hours after operation in rats of each groups($\bar{x}\pm s$)

Groups	Amount(n)	Serum amylase (U/L)	TNF-α (pg/mL)	IL-6 (pg/mL)	NGAL (ng/mL)
Sham Group	8	244.98± 10.14	19.56± 2.86	48.22± 5.73	81.67± 9.33
PALI Group	8	2299.06± 36.73※	936.63± 71.93※	196.39± 8.03※	1189.00± 63.19※
HO-1 promoter Group	8	1846.76± 75.07※#	244.55± 16.21※#	123.62± 12.40※#	831.37± 43.28※#
HO-1 inhibitor Group	8	2621.96± 63.13※#	1299.28± 91.87※#	240.26± 8.56※#	1457.85± 90.75※#
F	-	3213.969	816.648	701.158	803.48
P	-	<0.001	<0.001	<0.001	<0.001

Note: ※, compared with the Sham group, $P<0.05$; #, compared with the PALI group, $P<0.05$.

表 3 各组大鼠术后 24 h TLR4、NF-κB p65 表达水平比较($\bar{x}\pm s$)

Table 3 Comparison of TLR4 and NF-κB p65 expression levels at 24 hours after operation in rats of each groups($\bar{x}\pm s$)

Groups	Amount(n)	TLR4	NF-κB p65
Sham Group	8	881.31± 73.60	588.84± 38.19
PALI Group	8	2384.04± 67.51※	1448.20± 56.59※
HO-1 promoter Group	8	1756.90± 132.00※#	818.45± 47.04※#
HO-1 inhibitor Group	8	2859.02± 95.02※#	1823.16± 63.10※#
F	-	641.979	948.47
P	-	<0.001	<0.001

Note: ※, compared with the Sham group, $P<0.05$; #, compared with the PALI group, $P<0.05$.

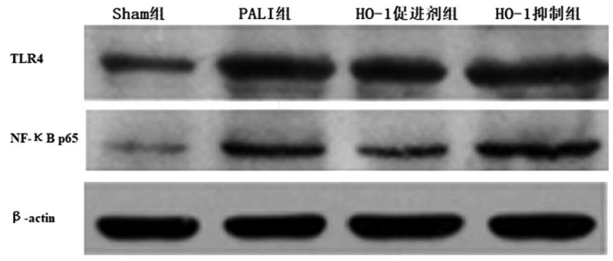

图 1 各组大鼠术后肺组织中 TLR4、NF-κB p65 蛋白的表达

Fig.1 Expression of TLR4 and NF-κB p65 protein in lung tissue of rats after operation

3 讨论

PALI 的病理生理学改变包括肺组织微血管通透性增加，渗出液进入肺泡导致肺顺应性降低，从而引起的低氧血症。体内肠源性内毒素（LPS）水平的增加是急性重症胰腺炎发生肺损伤的主要诱因[19]。高水平的 LPS 能够通过与相应的受体结合，激活相关信号传导通路，导致体内炎症细胞分泌高水平的炎性细胞因子，促发炎症反应和肺损伤[20]。Toll 受体家族（TLRs）为 LPS 的主要受体，TLR4 在 LPS 炎症信号的传导中发挥重要作用[21-24]。有研究表明，TLR4/NF-κB 途径在急性重症胰腺炎早期促发的炎症反应和器官损伤中发挥重要的介导作用[25-28]。本研究结果显示，PALI 组 TLR4、NF-κB p65 表达水平明显高于 Sham 组，说明急性重症胰腺炎相关肺损伤时，内毒素对 TLR4 的刺激，可导致 NF-κB p65 活化。

本研究中，PALI 大鼠经 HO-1 促进剂处理后，肺损伤学评分和肺湿 / 干重比值均明显降低。而 PALI 大鼠经 HO-1 抑制剂处理后，肺损伤学评分和肺湿 / 干重比值均明显升高。说明HO-1 的过表达能改善急性重症胰腺炎大鼠肺组织的病变程度。

血清淀粉酶活性测定主要用于急性胰腺炎的诊断[29]。TNF-α、IL-6 等促炎因子在急性重症胰腺炎的发病中发挥核心

作用，也是诱发最终多器官功能障碍的重要致病因素[30,31]。中性粒细胞明胶酶相关载脂蛋白（NGAL）最初是在激活中性粒细胞中被发现的一种小分子量分泌性蛋白，有研究证实，NGAL与急性重症胰腺炎大鼠病情的严重程度密切相关，急性重症胰腺炎大鼠血清中 NGAL 的表达量高于轻症急性胰腺炎[32]。NGAL 与炎症、免疫应答、趋化作用、信号转导等过程相关，具有消炎、抗炎抑制细胞死亡的作用[33]。本研究发现，PALI 大鼠血清中 TNF-α、IL-6、NGAL 水平明显高于 Sham 组，说明 TNF-α、IL-6、NGAL 等炎性细胞因子参与了 PALI 的发生发展过程。HO-1 促进剂组淀粉酶、TNF-α、IL-6、NGAL、TLR4、NF-κB p65 水平明显低于 PALI 组；HO-1 抑制剂组淀粉酶、TNF-α、IL-6、NGAL、TLR4、NF-κB p65 水平明显高于 PALI 组。说明经过 HO-1 的干预，能够对急性重症胰腺炎体内的炎症程度发挥抑制作用，与降低内毒素对 TLR4 的刺激，从而抑制 NF-κB p65 活化有关。

总之，在急性重症胰腺炎相关肺损伤的发生发展过程中，TLR4/NF-κB 信号传导途径发挥了重要作用，HO-1 能够通过抑制该信号通路的激活，下调 TNF-α、IL-6、NGAL 等炎症因子的释放，从而发挥减轻急性重症胰腺炎相关肺损伤的作用。

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