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EPO 对肾脏缺血再灌注损伤大鼠肺内氧化应激状态的影响 *

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摘要 目的: 探讨促红细胞生成素 (erythropoietin,EPO) 对大鼠肾脏再灌注损伤模型肺内氧化应激状态的影响。**方法:** 清洁级 Sprague-Dawly(SD)大鼠 36 只适应性喂养 1 周后,随机分为 3 组,即假手术组(A 组)、肾脏再灌注损伤组(B 组)和 EPO 预处理组(C 组),每组 12 只。A 组大鼠只打开腹腔,游离双侧肾蒂但不夹闭;B 组与 C 组都建立了大鼠肾脏再灌注损伤模型,且 C 组在夹闭肾蒂前 2 h 腹腔注射人重组 EPO(5000 U/kg)。术后 24 h,处死大鼠,检测肺内氧化应激水平。**结果:** A 组大鼠精神状态良好,肾小管结构正常,未见明显上皮细胞肿胀、脱落,肺泡结构基本完整,肺泡间隔未增厚,有少量炎性细胞浸润;B 组鼠毛耸立,无光泽,饮水量减少,肾小管结构破坏消失,肾小管扩张,可见大量蛋白管型,肺泡结构破坏,肺泡腔缩窄,肺泡间隔增厚,组织水肿,大量炎性细胞浸润;C 组大鼠精神状态有所恢复,一般状况尚可,肾小管损伤较 B 组轻似,肾小管坏死区域有所减少,坏死偶见,肺泡壁轻度破坏,结构较为清晰,可见少量炎性细胞浸润。B 组与 C 组大鼠的血尿素氮(blood urea nitrogen, BUN)与血肌酐(serum creatinine, Scr)水平、肺组织血红素氧合酶(heme oxygenase, HO)-1 与丙二醛(malondialdehyde, MDA)水平都显著高于 A 组,C 组以上指标均显著低于 B 组 ($P<0.05$)。B 组超氧化物歧化酶 (superoxide dismutase, SOD) 和谷胱甘肽过氧化物酶 (glutathione peroxidase, GSH-Px)的水平均显著高于 A 组(均 $P<0.05$),而 C 组 SOD 和 GSH-Px 的水平均显著高于 B 组(均 $P<0.05$),A 组与 C 组间对比无显著差异。**结论:** EPO 用于大鼠肾脏再灌注损伤模型能缓解肺内氧化应激状态,促进肾功能及肺组织恢复,发挥肾脏保护作用。

关键词: 促红细胞生成素;大鼠;肾脏再灌注损伤;肺内氧化应激

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Effects of EPO on Oxidative Stress in Lung of Rats with Renal Ischemia-reperfusion Injury*

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ABSTRACT Objective: To investigate the effects of erythropoietin (EPO) on oxidative stress in the lung of rats with renal reperfusion injury. **Methods:** 36 healthy Sprague-Dawly (SD) rats were randomly divided into 3 groups: sham operation group (group A), renal reperfusion injury group (group B) and EPO pretreatment group (group C), there were 12 rats in each group. Rats in group A were only opened the abdominal cavity, free bilateral renal pedicle but not clamped; group B and group C were established rat kidney reperfusion injury model, and group C were injected intraperitoneally with human recombinant EPO (5000 U/kg) at 2 hours before clamping the renal pedicle. All the rats were sacrificed 24 hours after surgery and were to detect the level of oxidative stress in the lung. **Results:** The rats in group A were in good mental state, normal tubular structure and there were no obvious swelling and shedding of epithelial cells, the alveolar structure was basically intact, the alveolar space was not thickened, and there was a small amount of inflammatory cell infiltration. The rats in group B were hairy, dull, water consumption decreased, renal tubular structure disappeared, renal tubules dilated, and there large number of protein casts were observed, and alveolar structure destruction, alveolar cavity narrowing, alveolar septum thickening, tissue edema, massive inflammatory cell infiltration were observed. The mental state of the rats in group C were recovered, the general condition were acceptable, the tubular damage was lighter than that of group B, the area of renal tubular necrosis were reduced, and necrosis were occasionally seen, the alveolar wall was slightly damaged, the structure was clear, and a small amount of inflammatory cell infiltration was observed. The levels of blood urea nitrogen (BUN) and serum creatinine (Scr), the levels of heme oxygenase(HO)-1 and malondialdehyde (MDA) in lung tissue in group B and group C were significantly higher than those in group A, and group C were significantly lower than group B ($P<0.05$). The levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in group B were significantly higher than those in group A ($P<0.05$), while the levels of SOD and GSH-Px in group C was significantly higher than those in group B ($P<0.05$). There was no significant difference between group A and group C. **Conclusion:** The

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application of EPO in the rat kidney reperfusion injury model can alleviate the oxidative stress in the lungs and promote the recovery of renal function and lung tissue, thus exerting renal protection.

Key words: Erythropoietin; Rat; Renal reperfusion injury; Intrapulmonary oxidative stress

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前言

缺血再灌注损伤[1,2]是指由于血液再灌注后机体器官的缺血性损伤反而会更加严重的现象。因肾脏属于高灌注器官，肾血流量在机体发生感染性休克、烧伤和出血的时候会很大程度降低，随着血流恢复灌注会使肾功能损伤持续加重，这种现象即为肾脏缺血再灌注损伤。它是临床上缺血性急性肾衰竭发生的主要因素之一，同时也是能够影响机体肾移植手术是否成功的关键因素。其发病原因主要涉及有脓毒败血症、外科手术、心血管疾病和创伤等过程中病理生理过程和过程中重要损伤环节。此病有着非常多样和复杂的病理机制，主要包含自由基释放异常、细胞凋亡、能量代谢障碍、氧化应激、炎症反应等[3,4]。一旦患者不幸患有此病则其发生死亡的风险是很高的。即使能够存活但是还会发生严重程度不一的肾功能损伤，这对患者的预后不利。所以，如何避免和缓解此病造成的严重肾功能受损，更好保护肾脏组织免受侵害将成为人们关注和持续进行研究的方向。此外，已有研究报道肾缺血再灌注不仅导致原位器官受损，还可通过诱发细胞凋亡、促炎症反应等累及远隔脏器如肺、肝和心脏等受损。在缺血再灌注过程中，机体产生的过多氧自由基可通过氧化应激作用破坏蛋白质、脂质及 DNA，对细胞的结构和功能产生不利的影响。肺氧化应激的严重程度与肾缺血再灌注损伤的发生密切相关，而缓解肺氧化应激也可使机体肾功能损伤得以改善[5]。促红细胞生成素(erythropoietin, EPO)基因位置在 7 号染色体长臂 22 区，有 4 个糖基化位点[6]；EPO 蛋白为一种含唾液酸的酸性蛋白且属于糖蛋白类激素，能够刺激骨髓造血功能，作用于机体发挥着营养神经和保护神经的功效[7,8]。同时 EPO 还能促进机体脑组织对缺血缺氧环境的耐受力和抗细胞凋亡、抗氧化、抗炎等等众多作用[9,10]。研究证实 EPO 作用于肾脏是通过自分泌或着旁分泌的方式参与肾脏修复和损伤过程中[11]。本文通过设定大鼠肾脏再灌注损伤模型，探究了 EPO 对此种大鼠肺内氧化应激状态的影响作用，希望为肾脏再灌注损伤和 EPO 后续临床研究提供参考。

1 资料与方法

1.1 实验材料

清洁级 Sprague-Dawly(SD)大鼠 36 只(购自北京维通利华实验动物技术有限公司，批号 20914422)，养于 20-25 ℃室内铁笼中，雄性，体重 200-220 g。人重组 EPO(10000 IU/ 瓶)购自沈阳三生制药公司；ELISA 试剂盒购自上海生工公司。

1.2 分组与造模

SD 大鼠随机分为 3 组，各 12 只。A 组：假手术组、B 组：肾脏再灌注损伤组、C 组：EPO 预处理组。A 组大鼠打开腹腔，游离双侧肾蒂但不夹闭；B 组与 C 组大鼠肾脏再灌注损伤模型被建立，C 组大鼠肾蒂夹闭前 2 h 通过 i.p. 5000 U/kg EPO。

模型建立方法：术前禁食 8 h，不禁水；氯胺酮麻醉(i.p. 80 mg/kg)，大鼠以仰卧姿势被固定在手术板上，75%酒精涂擦消毒，腹部备皮。上腹部正中位置进行切口，逐层切开皮肤、腹部肌肉及腹膜；露左侧肾蒂，左肾脂肪囊内游离左肾，予无创微血管夹夹闭。缺血 30 min 后暴露右肾蒂，结扎右输尿管及右肾动静脉后移除右肾。在人重组 EPO 处理中，在缺血后 45 min 通过左肾静脉注射人重组 EP0。缺血 45 min 后将撤掉血管夹，观察待肾脏颜色恢复红润状态则再灌注良好，造模成功，关腹，单笼饲养，自由食水。

1.3 观察指标

(1)观察大鼠饮食、精神状态、鼠毛变化等情况。(2)大鼠在肾脏缺血再灌注 24 h 后，用 10 %的水合氯醛 i.p.麻醉大鼠，统一摘除左侧眼球，留取全血 3-4 mL，静置 30 min 后离心分离上层血清，检测血清中血尿素氮(blood urea nitrogen, BUN)与血肌酐(serum creatinine, Scr)水平。(3)同时取大鼠的肺与肾脏组织标本，吸干血迹，随后浸入 4 %甲醛中，肺组织进行研磨，采用 ELISA 法检测肺组织氧化应激指标血红素氧合酶(heme oxygenase, HO)-1、丙二醛(malondialdehyde, MDA)、超氧化物歧化酶(superoxide dismutase, SOD)、谷胱甘肽过氧化物酶(glutathione peroxidase, GSH-Px)水平。肾组织进行 HE 切片染色，在肾脏皮髓交界处，随机选取 5 个高倍视野(× 200)，每个视野随机选取 20 个肾小管，观察大鼠的肾脏病变情况。取右肺中叶组织进行 HE 切片染色，随机选取 5 个高倍视野(× 200)，观察大鼠的肺组织病变情况。

1.4 统计方法

选择 SPSS 20.00，计量资料($\bar{x}\pm s$)实施 t 检验，三组间对比为 one-way 分析，检验水准为α=0.05。

2 结果

2.1 大鼠一般情况

A 组：大鼠精神状态良好，鼠毛光泽度尚可，反应无异常出现。

B 组：鼠毛耸立，无光泽，饮水量减少，进食少，精神萎靡，畏寒蜷缩。

C 组：大鼠精神状态有所恢复，一般状况尚可，不过依然存在饮水量、进食量减少情况。

2.2 血清 BUN 与 Scr 水平对比

B 组与 C 组大鼠的血清 BUN 与 Scr 都显著高于 A 组，C 组低于 B 组(均 *P<0.05*)。见表 1。

2.3 肺组织氧化应激相关指标水平对比

B、C 组大鼠肺组织中 HO-1 与 MDA 水平都显著高于 A 组，且 C 组显著低于 B 组(均 *P<0.05*)。B 组 SOD 和 GSH-Px 的水平均显著高于 A 组(均 *P<0.05*)，而 C 组 SOD 和 GSH-Px 的水平均显著高于 B 组(均 *P<0.05*)，A 组与 C 组间对比无显著差

表 1 三组大鼠血清 BUN 与 Scr 水平对比 ($\bar{x}\pm s$)

Table 1 Comparison of serum BUN and Scr levels in three groups of rats ($\bar{x}\pm s$)

Groups	n	BUN(μmol/L)	Scr(μmol/L)
Group A	12	7.64± 1.55	75.55± 2.04
Group B	12	38.99± 2.01[a]	387.00± 18.49a
Group C	12	25.03± 13.02[ab]	243.00± 14.20[ab]
F		12.033	24.024
P		0.000	0.000

Note: compared with the group A, [a]*P<0.05*; compared with the group B, [b]*P<0.05*.

表 2 三组大鼠肺组织氧化应激相关指标水平对比($\bar{x}\pm s$)

Table 2 Comparison of levels of oxidative stress related indicators in lung tissue of three groups of rats ($\bar{x}\pm s$)

Groups	n	HO-1(pg/mL)	MDA(nmol/mL)	SOD(ng/mg)	GSH-Px(mg/mg)
Group A	12	85.20± 2.82	3.67± 0.45	6.13± 1.08	21.57± 2.46
Group B	12	276.87± 22.10[a]	9.87± 1.49[a]	3.42± 0.86 [a]	14.62± 2.03[a]
Group C	12	176.02± 19.29[ab]	6.72± 1.22[ab]	5.38± 1.05[b]	19.95± 2.09 [b]
F		13.044	8.934	23.438	32.742
P		0.000	0.001	0.000	0.000

Note: Same as Table 1.

异。见表 2。

2.4 肾组织病理学对比

A 组:肾小管结构正常,上皮细胞未出现明显肿胀、脱落现象,不伴有肾实质出血,细胞核大小适中,肾小管管腔内未见颗粒样管型、蛋白管型。B 组:肾小管结构破坏消失,肾小管扩张,可见大量蛋白管型,上皮细胞肿胀、脱落,细胞核溶解,伴有肾实质和间质的出血。C 组:损伤较 B 组轻似,肾小管坏死区域有所减少,坏死偶见,但依然存在组织坏死、脱失。

2.5 肺组织病理学对比

A 组:肺泡结构基本完整,肺泡腔清晰可见,肺泡的间隔也未增厚,仅有少量炎性细胞浸润。B 组:肺泡结构破坏,肺泡腔缩窄, 肺泡间隔增厚,组织水肿,大量炎性细胞浸润。 C 组:肺泡壁轻度破坏,结构较为清晰,可见少量炎性细胞浸润。

3 讨论

肾脏是人体内重要的排泄和内分泌器官,可维持机体内环境的稳定,也可排泄机体大部分的代谢废物[12]。因此,肾脏对维持整个机体内环境的平衡至关重要。有研究表明:当肾脏功能受损时,其邻近和远端器官如心、肺、肝、肠和脑等的功能也会严重受损。肾脏再灌注损伤是指多种原因导致血液中断或不足使肾脏缺血,恢复血流灌注时肾脏结构破坏、功能障碍和反而加重的现象[13]。该病多见于感染、休克、肾移植、肾切除术等患者,在早期尽量恢复其肾脏组织的血流再灌注,可以减少缺血引起的肾脏损伤,改善机体的预后[14]。

EPO 是一种多功能营养因子及神经保护因子,EPO 在胚胎早期由肝脏生成,然后逐渐向肾脏转移,由皮质管周围的间质细胞合成[15]。人重组 EPO 具有与天然 EPO 相同的生物学活,是用重组 DNA 技术生产的含有与天然分离的 EPO 完全相同氨基酸序列的糖蛋白。EPO 能通过多种途径减轻移植肾的缺血再灌注损伤,其能减少因氧张力诱导的细胞凋亡,对大鼠肾脏缺血再灌注损伤起明显保护作用[16]。本研究显示 B 组与 C 组大鼠的血清 BUN 与 Scr 都显著高于 A 组,C 组显著低于 B 组,对比差异都有统计学意义。血清 BUN 与 Scr 是临床上用于评估肾功能的常用指标, 肾功能在肾脏缺血再灌注损伤后受到严重的影响,可导致血清 BUN 与 Scr 水平增高。EPO 均能显著改善肾脏缺血再灌注损伤后的肾功能,降低血清 BUN 与 Scr 水平[17]。

肾脏再灌注损伤的发生机制比较复杂, 可由多种因素、通过多个层次、多种机制、多种途径介导组织损伤,其中其中肺组织的氧化应激作用已成为当前研究的主导观点[18]。肾脏功能和结构受到损害的主要原因为肺组织中会过量释放出氧自由基,组织含氧量在缺血期会明显减少,导致减弱组织抵抗氧化的能力。而随后的再灌注现象中,血液中富含氧,大量电子受体被供给导致组织中蛋白质和脂质过氧化,从而使组织功能、结构受到侵害[19]。MDA 是一种脂质过氧化稳定代谢产物,检测 MDA 水平能够指示肾组织中氧自由基的含量和脂质过氧化反应的程度;HO-1 是一种重要的抗氧化蛋白,在生理状况下,在部分肺上皮细胞中出现 HO-1 少量表达,氧化应激状态下可呈现高表达状况[20]。SOD 为体内抗氧化酶系的重要成员,负责清除机体释放的自由基,其代表机体清除自由基的能力;GSH-Px 为临床评估机体抗过氧化能力的指标之一,可清除机体代谢过程中产生的过氧化物和羟自由基; 在氧化应激状态下 SOD 和 GSH-Px 均呈低表达状态[21]。本研究显示 HO-1 和 MDA 在 B、C 两组大鼠肺组织中的含量是显著高于 A 组大鼠肺组织中含量,同时两者在 C 组大鼠肺组织中的含量是低于 B 组大鼠肺组织中含量的。B 组 SOD 和 GSH-Px 的水平均显著高于 A 组, 而 C 组 SOD 和 GSH-Px 的水平均显著高于 B 组。由此可见,EPO 可抑制大鼠肾脏缺血再灌注损伤时体内肺组织氧化应

激反应,减轻肾脏缺血再灌注损伤损伤,从而发挥对肾脏的保护作用。基础研究也表明 EPO 可提高肾脏损伤后的氧张力,可以抑制自由基介导的脂质过氧化过程,使组织修复并恢复肾脏功能[22]。

已有研究证实缺血前药物预处理可对肾脏缺血再灌注损伤起到一定的保护作用[23-25]。本研究组织形态学观察发现肾脏缺血再灌注损伤可引起肾小管上皮细胞坏死,大量肾小管管腔被细胞碎屑,蛋白管型等堵塞,而坏死组织还会造成继发性的氧化应激反应,进一步加重肾脏缺血再灌注损伤,从而导致肾功能下降[26-28]。此外,对肺组织的病理学观察显示,肾脏缺血再灌注损伤可导致肺泡结构破坏,肺泡腔缩窄,肺泡间隔增厚,组织水肿,大量炎性细胞浸润,进一步证实肾脏缺血再灌注损伤可累积远隔脏器损伤,导致肺组织病变。EPO 可减轻肾脏组织学损伤,保留更多有功能的肾单位,减少肾小管结构的破坏,并可降低肺泡结构损伤及炎性细胞浸润,以此对肾脏缺血再灌注损伤起到保护作用[29,30]。本研究也有一定的不足,EPO 的具体作用机制仍有待于进一步研究。

综上所述,EPO 在大鼠肾脏再灌注损伤模型中的应用能缓解肺内氧化应激状态,促进肾功能及肺组织恢复,从而发挥肾脏保护作用。

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(下转第 4237 页)

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