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雌激素对肾缺血再灌注损伤大鼠 Th17/Treg 平衡、氧化应激及肾组织 NF-κB、TGF-β1 表达的影响 *

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摘要 目的：研究雌激素对肾缺血再灌注损伤（RIRI）大鼠 Th17/Treg 平衡、氧化应激及肾组织 NF-κB、TGF-β1 表达的影响。**方法：**取 60 只 SD 大鼠进行实验，随机分作假手术组、模型组以及雌激素组，每组各 20 只。模型组及雌激素组均建立 RIRI 模型，假手术组仅暴露肾脏，不进行肾缺血处理。雌激素组大鼠予以雌激素干预，模型组和假手术组均予以适量的生理盐水干预。分析各组肾功能指标水平以及 Paller 肾小管损伤评分，Th17/Treg 平衡指标水平，氧化应激及肾组织 NF-κB、TGF-β1 表达水平的差异。**结果：**模型组及雌激素组血肌酐（SCr）、尿素氮（BUN）水平以及 Paller 肾小管损伤评分均高于假手术组，且雌激素组上述各项指标水平均低于模型组（均 $P<0.05$）。模型组及雌激素组白细胞介素 -17（IL-17）水平高于假手术组，且雌激素组低于模型组；模型组及雌激素组白细胞介素 -10（IL-10）水平低于假手术组，且雌激素组高于模型组（均 $P<0.05$）。模型组及雌激素组丙二醛（MDA）水平均高于假手术组，且雌激素组低于模型组；模型组及雌激素组超氧化物歧化酶（SOD）水平均低于假手术组，且雌激素组高于模型组（均 $P<0.05$）。模型组及雌激素组肾组织 NF-κB、TGF-β1 表达水平均高于假手术组，且雌激素组低于模型组（均 $P<0.05$）。**结论：**雌激素可有效调节 RIRI 大鼠 Th17/Treg 平衡，减轻氧化应激反应，同时有利于改善肾组织 NF-κB、TGF-β1 表达，缓解其 RIRI。

关键词：肾缺血再灌注损伤；大鼠；雌激素；氧化应激；Th17/Treg 平衡
中图分类号：R-33；R692 **文献标识码：**A **文章编号：**1673-6273（2021）10-1844-05

Effects of Estrogen on Th17/Treg Balance, Oxidative Stress and Expression of NF-κB and TGF-β1 in Renal Tissue of Rats with Renal Ischemia-reperfusion Injury*

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ABSTRACT Objective: To study the effects of estrogen on Th17/Treg balance, oxidative stress and the expression of NF-κB and TGF-β1 in renal tissue of rats with renal ischemia-reperfusion injury (RIRI). **Methods:** 60 SD rats were selected for the experiment, they were randomly divided into sham operation group, model group and estrogen group, with 20 rats in each group. RIRI models were established in both the model group and the estrogen group, while only the kidney was exposed without renal ischemia in the sham operation group. The rats in the estrogen group were treated with estrogen intervention, and the model group and sham operation group were treated with normal saline intervention. The differences of renal function indexes levels, Paller renal tubular injury score, Th17/Treg balance index level, oxidative stress and the expression level of NF-κB and TGF-β1 in renal tissues in each group were analyzed. **Results:** The levels of serum creatinine (SCr), urea nitrogen (BUN) and Paller renal tubular injury score in model group and estrogen group were higher than those in sham group, and the levels of above indexes in estrogen group were lower than those in model group (all $P<0.05$). The level of interleukin-17 (IL-17) in model group and estrogen group were higher than that in sham operation group, and the estrogen group was lower than the model group. The level of interleukin-10 (IL-10) in model group and estrogen group were lower than that in sham operation group, and the estrogen group was higher than the model group (all $P<0.05$). The levels of malondialdehyde (MDA) in model group and estrogen group were higher than those in sham operation group, and estrogen group was lower than model group. The level of

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superoxide gasification enzyme (SOD) in model group and estrogen group was lower than that in sham operation group, and the estrogen group was higher than the model group (all $P<0.05$). The expression levels of NF-κB and TGF-β1 in renal tissues in model group and estrogen group were higher than those in sham operation group, and the estrogen group was lower than the model group (all $P<0.05$). **Conclusions:** Estrogen can effectively regulate Th17/Treg balance in RIRI rats, reduce oxidative stress response, and improve the expression of NF-κB and TGF-β1 in renal tissue, and alleviate RIRI.

Key words: Renal ischemia-reperfusion injury; Rat; Estrogen; Oxidative stress; Th17/Treg balance

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前言

缺血再灌注损伤主要是指机体内缺血一定时长的组织或(和)细胞复流后,损伤程度加剧的现象[1-3]。肾脏是机体内灌注较多的器官之一,肾缺血再灌注损伤(RIRI)极易引起肾脏血管受阻,继而导致血流量减少,进一步引起肾脏微血管损伤的发生,最终促使肾功能的显著降低[4-6]。因此,如何有效减轻或预防RIRI显得尤为重要,一直都是肾损伤保护方面的研究热点。目前,临床上主要是通过肾低温以及热缺血下使用药物保护等手段实现RIRI保护,且后者所受的关注明显更多。雌激素主要源自于卵巢,不仅在生殖系统调控过程中起着至关重要的作用,同时还对多种细胞的生长、分化均有一定的影响[7,8]。有关其在RIRI中作用的研究较少。鉴于此,本文通过研究雌激素对RIRI大鼠Th17/Treg平衡、氧化应激及肾组织NF-κB、TGF-β1表达的影响,以期为临床RIRI的防治提供一定参考。

1 材料与方法

1.1 材料

(1)动物:取60只SD大鼠进行实验,随机分作假手术组、模型组以及雌激素组,每组各20只。所有大鼠体质量为200～250 g,平均(235.22± 10.35)g。均由徐州医科大学实验动物中心提供,动物合格证号:SCXK(苏)2011-002。所有大鼠均放置在医院动物实验中心进行饲养,饲养温度20～25℃,湿度40%～50%,对大鼠的活动、饮食均不进行限制。(2)试剂及仪器:雌激素(购自美国Sigma公司)。大鼠白细胞介素-17(IL-17)以及白细胞介素-10(IL-10)试剂盒均购自武汉伊莱瑞特生物科技股份有限公司。丙二醛(MDA)以及超氧化物歧化酶(SOD)试剂盒购自南京建成生物技术研究所。大鼠单克隆NF-κB、TGF-β1抗体均购自北京中杉金桥有限公司。石蜡切片机(购自北京南北仪器设备有限公司)。电泳仪(购自北京六一生物科技有限公司)。低温冰箱(购自佛山赛如卫科技有限公司)。图像采集分析系统(购自美国GRANT公司)。光学显微镜(购自日本奥林巴斯公司)。BCA蛋白浓度测定试剂盒(购自北京索莱博科技有限公司)。中性树胶(购自厦门海标科技有限公司)。苏木精-伊红染液(购自北京索莱博科技有限公司)。

1.2 研究方法

(1)造模及干预:◎ 造模:首先对所有大鼠实施氯胺酮腹腔注射麻醉,均取仰卧位,并将大鼠固定在操作台上,常规剪除毛发、消毒处理后。选择腹部正中切口进腹,对双侧肾蒂予以分离,避免对输尿管造成损伤。借助无损伤动脉夹实施双侧肾蒂的夹闭,明确肾脏的颜色改变,待肾脏血流被阻断45 min后松开动脉夹,确定复流之后对切口予以缝合。模型组及雌激素组均建立RIRI模型,假手术组仅暴露肾脏,不进行肾缺血处理。◎ 干预:雌激素组大鼠于造模前3 d开始,每日腹腔注射雌激素40 mg/kg/d,假手术组和模型组则于术前3 d开始,每日腹腔注射2 mL生理盐水。(2)生化指标检测:所有大鼠RIRI或暴露肾脏6 h后,以30 mg/L无巴比妥注射麻醉,进行腹主动脉穿刺取血,并将血标本送至检验科以7060型全自动生化分析仪完成血肌酐(SCr)、尿素氮(BUN)水平的检测。(3)肾脏病理学检测:获取所有大鼠肾脏组织,常规固定,包埋,切片处理后行HE染色,之后在光学显微镜下对其病理形态改变进行观察,并由2名经验丰富的病理科医生通过双盲法完成Paller肾小管损伤评分[9]。(4)分别采集所有大鼠的尾静脉血3 mL,以8 cm为离心半径,进行10 min的3000 r/min离心处理。采集血清保存在-80℃冰箱中备用。分别采用酶联免疫吸附法完成IL-17、IL-10以及MDA、SOD的检测,所有操作遵循试剂盒说明书完成。(5)以断头法处死各组大鼠,采集肾组织,以10%中性福尔马林进行固定,常规石蜡切片,脱蜡至水。采用3%过氧化氢清除内源性过氧化物酶活性,并实施微波修复抗原。封闭滴加NF-κB、TGF-β1一抗,室温条件下孵育60 min。以PBS重复冲洗3次,随后滴加二抗,并于室温下孵育30 min。之后进行DAB显色20 min,苏木精复染色,梯度酒精脱水干燥,以二甲苯进行透明,通过中性树胶完成封片处理。结果评价:上述蛋白表达阳性细胞染色为棕黄色和黄色,于高倍镜下随机选择8个视野,以北航计算机图像分析系统测定上述蛋白阳性染色面积并除以统计总面积,即为阳性细胞密度,并以此作为上述蛋白表达水平。

1.3 统计学处理

将SPSS 22.0软件作为数据处理工具。以($\bar{x}\pm s$)实现对计量资料的表示,实施单因素方差分析及LSD-t检验。$P<0.05$表示差异有统计学意义。

2 结果

2.1 各组肾功能指标水平以及肾组织损害程度比较

模型组及雌激素组SCr、BUN水平以及Paller肾小管损伤评分均高于假手术组,且雌激素组上述各项指标水平均低于模型组(均$P<0.05$)。见表1。

2.2 各组Th17/Treg平衡指标比较

模型组及雌激素组IL-17水平高于假手术组,且雌激素组低于模型组;模型组及雌激素组IL-10水平低于假手术组,且雌激素组高于模型组(均$P<0.05$)。见表2。

表 1 各组肾功能指标水平以及 Paller 肾小管损伤评分比较($\bar{x}\pm s$)

Table 1 Comparison of renal function index levels and Paller renal tubular injury score in each group($\bar{x}\pm s$)

Groups	n	SCr(μmol/L)	BUN(mmol/L)	Paller renal tubular injury score(scores)
Sham operation group	20	33.29± 5.24	8.02± 1.35	12.30± 2.45
Model group	20	107.74± 15.96*	25.93± 2.51*	36.94± 3.77*
Estrogen group	20	56.78± 7.33*△	15.38± 1.78*△	20.84± 3.01*△
F	-	14.321	8.940	6.254
P	-	0.000	0.000	0.000

Note: compared with sham operation group, *$P<0.05$; compared with the model group, △ $P<0.05$.

表 2 各组 Th17/Treg 平衡指标评价($\bar{x}\pm s$)

Table 2 Evaluation of Th17/Treg balance indexes in each group($\bar{x}\pm s$)

Groups	n	IL-17(pg/mL)	IL-10(pg/mL)
Sham operation group	20	487.32± 16.38	91.48± 10.55
Model group	20	1132.87± 46.38*	36.97± 3.36*
Estrogen group	20	611.65± 22.10*△	61.53± 5.12*△
F	-	23.693	11.382
P	-	0.000	0.000

Note: compared with sham operation group, *$P<0.05$; compared with the model group, △ $P<0.05$.

2.3 各组氧化应激指标水平比较

模型组及雌激素组 MDA 水平均高于假手术组，且雌激素组低于模型组；模型组及雌激素组 SOD 水平均低于假手术组，且雌激素组高于模型组(均 $P<0.05$)。见表 3。

表 3 各组 MDA 及 SOD 水平比较($\bar{x}\pm s$)

Table 3 Comparison the levels of MDA and SOD in each group($\bar{x}\pm s$)

Groups	n	MDA(nmoL/mg)	SOD(U/mg)
Sham operation group	20	3.52± 1.10	210.83± 16.27
Model group	20	15.84± 2.35*	154.39± 10.59*
Estrogen group	20	11.23± 1.87*△	184.10± 14.37*△
F	-	7.250	16.583
P	-	0.000	0.000

Note: compared with sham operation group, *$P<0.05$; compared with the model group, △ $P<0.05$.

2.4 各组肾组织 NF-κB、TGF-β1 表达水平比较

模型组及雌激素组肾组织 NF-κB、TGF-β1 表达水平均高于假手术组，且雌激素组低于模型组(均 $P<0.05$)。见表 4。

表 4 各组肾组织 NF-κB、TGF-β1 表达水平比较($\bar{x}\pm s$)

Table 4 Comparison of the expression levels of NF-κB and TGF-β1 in renal tissues of each group($\bar{x}\pm s$)

Groups	n	NF-κB	TGF-β1
Sham operation group	20	0.03± 0.01	1.00± 0.00
Model group	20	0.17± 0.04*	1.75± 0.19*
Estrogen group	20	0.08± 0.03*△	1.41± 0.12*△
F	-	4.541	3.987
P	-	0.001	0.023

Note: compared with sham operation group, *$P<0.05$; compared with the model group, △ $P<0.05$.

3 讨论

由于肾脏生理特征的影响，肾脏易在缺血再灌注过程中遭

受损害，其中以肾小管间质的病理表现最为严重，肾脏在发生RIRI后，持续性炎症反应以及肾脏损伤修复反复存在，并形成恶性循环，继而可能引起肾小管萎缩以及进行性纤维化，从而导致肾脏功能下降，最终引起肾脏衰竭[10-12]。随着近年来相关研究的日益深入，不少学者发现RIRI后期会引起肾小管间质纤维化，而肾小管间质纤维化属于复杂的病理过程，同时又是所有慢性肾脏疾病的共同点，是肾脏在损伤的状态下对所有有害刺激所做出的修复性反馈[13-15]。针对肾脏疾病患者若不实施早期有效的控制，随着病情的不断进展会引起肾间质纤维化，最终导致肾衰竭，从而促使患者面临终生透析或肾移植等结局[16-18]。故此，寻求一种有效减轻RIRI的手段具有极其重要的意义。

SCr、BUN均为肾功能状况评价的常用指标，而Paller肾小管损伤评分能够较好地反映肾小管的损伤程度，对这三项指标实施监测能够综合呈现肾功能的总体状况。本研究结果表明，模型组及雌激素组肾功能均较假手术组降低，且雌激素组肾功能优于模型组。提示雌激素可有效改善RIRI大鼠肾功能。究其原因，雌激素属于类固醇激素之一，具有广泛的生物活性，对肾素-血管紧张素系统和肾内外血流动力学具有一定作用，可在一定程度上调节肾小球功能，降低灌注压力，继而发挥保护肾脏功能的作用[19-21]。同时，雌激素可通过刺激血管内皮生长因子表达提升系膜细胞活性，促使细胞外基质合成受阻，且具有调控抗氧化剂合成及脂代谢的功能，有助于减轻肾脏遭受的损害[22-24]。此外，本文显示雌激素组Th17/Treg平衡状况优于模型组，提示雌激素可促进RIRI大鼠Th17/Treg平衡的改善。考虑原因可能是雌激素可发挥一定的抗氧化、抗凋亡作用，抑制炎症因子的分泌以及减少再灌注部位的中性粒细胞浸润，继而发挥RIRI保护作用，减轻全身炎性反应，最终起到了调节Th17/Treg平衡的作用。本研究还发现模型组及雌激素组MDA水平均高于假手术组，且雌激素组低于模型组；模型组及雌激素组SOD水平均低于假手术组，且雌激素组高于模型组，这表明了雌激素的应用可减轻RIRI大鼠氧化应激反应。推测原因为雌激素可有效减轻RIRI，从而避免了大量氧自由基的产生，进一步降低了MDA的产生，促使SOD水平的升高。多项研究表明NF-κB可通过干扰和RIRI有关的多种细胞因子以及黏附分子的表达，并对其生物合成起到调控作用，参与RIRI过程[25-27]。Lu等报道指出，TGF-β广泛分布在机体内多种细胞中，是一种具有多向调控能力的生长因子，且以TGF-β1在人体内活性最强[28]。TGF-β1的过表达已被证实可刺激肾小球系膜细胞以及近曲小管上皮细胞等细胞外基质的合成，进一步参与肾纤维化过程[29,30]。本研究发现：模型组及雌激素组肾组织NF-κB、TGF-β1表达水平均高于假手术组，且雌激素组低于模型组，这提示了雌激素可有效下调肾组织NF-κB、TGF-β1表达水平。考虑原因可能在于：雌激素可促使细胞外基质成分维持在一定范围内，从而发挥抑制肾间质纤维化的作用；此外，雌激素对上皮细胞朝肌成纤维细胞方向的转变具有一定的抑制作用，可明显减少细胞外基质的合成，进一步导致病变肾组织的细胞外基质减少，继而达到抑制肾间质纤维化进展的目的，最终促使上述蛋白表达水平降低[31-33]。

综上所述，雌激素对RIRI大鼠具有一定的保护作用，其主要作用机制可能和下述三点有关：（1）调节Th17/Treg平衡；（2）减轻氧化应激反应；（3）改善肾组织NF-κB、TGF-β1表达水平。

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