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在线全文

• 中医药·中西医结合 •

电针抑制P2RX7/NLRP3信号通路减轻脓毒症小鼠急性肾损伤*

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【摘要】 目的 探究电针调控嘌呤能受体P2X7（P2X7 purinergic receptor, P2RX7）/ NLR家族Pyrin域蛋白3（NLR family pyrin domain containing 3, NLRP3）信号通路对脓毒症急性肾损伤（sepsis associated acute kidney injury, SA-AKI）的保护效应及机制。**方法** 将6～8周龄C57BL/6J健康雄性小鼠随机分为空白组、模型组、电针组、P2RX7拮抗+模型组、P2RX7拮抗+模型+电针组；采用腹腔注射脂多糖（lipopolysaccharide, LPS）建立SA-AKI模型，LPS注射前1 h腹腔注射P2RX7拮抗剂A438079；LPS注射1.5 h后给予电针干预（10 Hz, 0.5 mA, 30 min）；造模后24 h内评估小鼠生存率，血液生化测定血清肌酐（serum creatinine, Scr）含量、ELISA检测血清及肾脏IL-1β和IL-18含量；HE染色观察肾脏组织病理学变化；实时荧光PCR和免疫荧光检测肾脏P2RX7、NLRP3表达水平。**结果** 与NS组小鼠存活率相比较，24 h内LPS组存活率降低至30%（P<0.05），而EA可将LPS小鼠存活率提升15%，但与LPS组相比较差异无统计学意义（P>0.05）；电针治疗可改善小鼠肾脏组织病理损伤，降低SA-AKI的Scr水平（P<0.05），以及血清中炎症因子IL-1β和IL-18的含量（均P<0.000 1）；电针减少肾脏组织中IL-1β（P<0.000 1）、IL-18（P<0.001）和P2RX7、NLRP3（均P<0.05）的表达水平。**结论** 电针改善SA-AKI的作用机制可能与抑制P2RX7/NLRP3信号通路、减轻全身炎症反应有关。

【关键词】 脓毒症 急性肾损伤 电针 P2RX7 NLRP3

Electroacupuncture Alleviates Acute Kidney Injury in Septic Mice By Inhibiting the P2RX7/NLRP3 Signaling Pathway

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[Abstract] Objective To investigate the protective effects and mechanisms of electroacupuncture on the P2X7 purinergic receptor/NLRP3 signaling pathway in sepsis-associated acute kidney injury (SA-AKI). **Methods** Healthy male C57BL/6J mice, 6-8 weeks old, were randomly assigned to the following groups: control, model, electroacupuncture, P2RX7 antagonist + model, and P2RX7 antagonist + model + electroacupuncture. The SA-AKI model was established by intraperitoneal injection of lipopolysaccharide (LPS). The P2RX7 antagonist A438079 was administered intraperitoneally 1 hour before LPS injection. Electroacupuncture (10 Hz, 0.5 mA, 30 min) was performed 1.5 hours after LPS injection. Mouse survival rates were assessed within 24 hours after modeling. Serum creatinine (Scr) levels were measured by blood biochemistry, IL-1β and IL-18 levels in serum and kidney tissues were measured with ELISA. Renal histopathological changes were observed by HE staining. Real-time fluorescent PCR and immunofluorescence assays were used to assess renal P2RX7 and NLRP3 expression levels. **Results** The 24-hour survival rate in the electroacupuncture group was 45%, a 15% improvement over the model group. Electroacupuncture treatment reduced renal histopathological damage, lowered Scr levels in SA-AKI (P < 0.05), and decreased serum inflammatory mediators IL-1β and IL-18 (both P < 0.000 1). Electroacupuncture also reduced renal tissue expression levels of IL-1β (P < 0.000 1), IL-18 (P < 0.001), P2RX7, and NLRP3 (both P < 0.05). **Conclusion** The mechanism by which electroacupuncture ameliorates SA-AKI may involve inhibition of the P2RX7/NLRP3 signaling pathway and attenuation of systemic inflammatory responses.

[Key words] Sepsis Acute kidney injury Electroacupuncture P2RX7 NLRP3

脓毒症是由全身性感染引起的临床复杂综合征，其特征为系统性炎症和多器官损伤[1]。作为急性肾损伤（acute kidney injury, AKI）的主要因素，脓毒症约占AKI住院患者的45%～70%[2]，且由脓毒症引发的相关急性肾损伤（sepsis-associated acute kidney injury, SA-AKI）死亡率高达70%[3-4]，成为临床治疗的重要挑战。SA-AKI病理机

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制涉及病原体相关分子模式和损伤相关分子模式激活免疫细胞(如巨噬细胞、中性粒细胞等),导致大量的促炎细胞因子失控性地释放,如抗肿瘤坏死因子α(tumor necrosis factor α, TNF-α)、白细胞介素(interleukin, IL)1β、IL-6等,最终引发全身性炎症和多器官损[5]。

研究发现,电针可能通过多种途径调控炎症反应,从而改善SA-AKI。如电针刺激脓毒症小鼠"足三里"可激活坐骨神经和迷走神经,调节肾上腺髓质中的多巴胺产生,从而抑制全身性炎症反应[6]。另有研究表明,电针可通过迷走神经-肾上腺抗炎通路降低促炎细胞因子水平[7],并提高脓毒症大鼠的存活率[8-9]。此外,嘌呤能受体P2X7(P2X7 purinergic receptor, P2RX7)/NLR家族Pyrin域蛋白3(NLR family pyrin domain containing 3, NLRP3)信号通路可能参与了电针的抗炎作用[10],但其在SA-AKI中的具体机制尚不明确。

在炎症或组织损伤时,细胞外三磷酸腺苷(extracellular adenosine triphosphate, eATP)水平升高,激活P2RX7(一种非选择性的阳离子通道)[11],P2RX7的激活可触发NLRP3炎症小体的激活,进而促进IL-1β和IL-18的成熟与释放,这一过程可能是SA-AKI的关键病理机制之一[12-13]。NLRP3炎症小体为先天性免疫系统的重要组分,在脓毒症等炎症性疾病中发挥重要作用[14]。研究表明,AKI可引起肾脏 P2RX7表达上调,从而导致肾小管炎症、中性粒细胞浸润及肾间质成纤维细胞死亡,加剧肾脏损伤[15-16]。研究发现, P2RX7拮抗剂能有效改善肾小管损伤,缓解肾脏损伤的病理进程[17-18]。以上研究提示,靶向抑制P2RX7可能是治疗AKI的新策略。目前有关电针通过P2RX7/NLRP3信号通路改善SA-AKI的研究较少。因此,本研究拟探讨电针是否通过抑制P2RX7/NLRP3信号通路减轻炎症反应,从而为SA-AKI的治疗提供新依据。

1　材料与方法

1.1　实验材料

1.1.1　实验动物

选用6 ~ 8周龄清洁级健康C57BL/6J雄性小鼠,体质量20 ~ 25 g,购于成都达硕实验动物有限公司,许可证号:SCXK(川)2022-0030。本研究所有动物实验均按照美国国立卫生研究院(NIH)《实验动物护理和使用指南》进行,并经成都中医药大学实验动物伦理委员会批准(审查号2018-24)。

1.1.2　主要试剂及仪器

酶联免疫吸附试验(enzyme linked immunosorbent assay, ELISA)试剂盒购于江苏晶美生物,反转录试剂盒和实时荧光定量PCR试剂盒购于成都福际生物,脂多糖(lipopolysaccharide, LPS)、P2RX7 抗体均购于Sigma, A-438079购于Selleck, NLRP3抗体购于ImmunoWay, antibody-mouse IgG(H+L)购于北京博奥森, Antibody-rabbit IgG(H+L)购于武汉伊莱瑞特, 0.25 mm×13 mm针灸针(江苏华佗),BS-460全自动生化分析仪(深圳迈瑞),Bioer 9600 FQD-96C实时荧光定量PCR仪(杭州博日),PanoBrain全自动玻片扫描仪(Meca Scientific) 。

1.2　方法

1.2.1　实验分组及模型建立

小鼠适应性饲养1周后,随机分为空白组(NS组)、模型组(LPS组)、电针组(EA组)、P2RX7拮抗+模型组(A-438079+LPS组)、P2RX7拮抗+模型+电针组(A-438079+LPS+EA组)。参考既往研究报道并结合我们前期预实验中各组小鼠死亡率探测结果,设定样本量如下:空白组10只,模型组30只,其余各组20只。模型组、电针组、P2RX7拮抗+模型组和P2RX7拮抗+模型+电针组均采用一次性腹腔注射0.1 mL LPS溶液(3 mg/mL),空白组则注射等体积生理盐水。

1.2.2　P2RX7拮抗剂注射

将P2RX7拮抗剂A-438079用纯化水配成15 mg/kg浓度的溶液。A438079+LPS组和A438079+LPS+EA组于小鼠造模前1 h进行腹腔注射,注射体积为0.2 mL/只。

1.2.3　电针干预

小鼠腹腔注射LPS 1.5 h后进行电针干预。选取小鼠双侧"足三里"穴(膝关节后下方,在腓骨小头下约3 mm,胫骨外侧约2 mm处的肌沟中)进行电针。使用一次性针灸针双侧"足三里"直刺3 mm,连接韩氏电针仪,参数设置为连续波、频率10 Hz、强度0.5 mA,留针30 min,以后肢肌肉轻微跳动为度。

1.2.4　样本采集与指标检测

LPS注射24 h后,进行眼眶静脉血采集,全血室温静置30 min后,3 000 r/min离心20 min,分离血清用于IL-1β、IL-18的ELISA检测和Scr的生化检测。取血后,迅速切取肾脏组织,—80 ℃保存用于采用肾脏组织IL-1β、IL-18的ELISA检测和*P2RX7*、*NLRP3* mRNA检测。未被取血小鼠经生理盐水和体积分数为4%多聚甲醛心脏灌流后,取肾组织于体积分数为4%多聚甲醛固定24 h,经常规脱水、包埋、切片后,分别进行苏木精-伊红染色(hematoxylin-eosin staining, HE)观察肾组织病理学变化和免疫荧光染色检测肾组织P2RX7、NLRP3蛋白表达水平。

1.2.5 实时定量PCR（RT-qPCR）检测肾组织*P2RX7*和*NLRP3* mRNA含量

根据Animal Total RNA Isolation Kit试剂盒说明书提取小鼠肾脏组织中总RNA并逆转录为cDNA。在实时定量PCR仪上进行RT-qPCR，扩增条件：95 ℃ 3min，95 ℃ 10 s，60 ℃ 30 s，40个循环。以*GAPDH*为内参，通过$2^{-\Delta\Delta Ct}$方法计算mRNA表达水平。引物由成都福际生物技术有限公司设计合成。*P2RX7*：F(5'-3') gacaaacaaagtcacccggat，R(5'-3') cgctcaccaaagcaaagctaat；*NLRP3*：F(5'-3') attacccgcccgagaaag，R(5'-3')tcgcagcaaagatccacaca；*GAPDH*：F(5'-3')cagtggcaaagtggagattgttg，R(5'-3') tcgctcctggaagatggtgat。

1.2.6 免疫荧光检测肾组织P2X7和NLRP3蛋白表达水平

肾组织石蜡包埋并切片，蜡块切片经脱蜡修复，PBS冲洗3次，P2RX7、NLRP3一抗(1∶100)4 ℃孵育过夜；PBS洗3次，Cy3、AF488荧光二抗(1∶200)，37 ℃孵育1 h，PBST洗3次；用含DAPI的抗荧光淬灭封片剂封片，全自动切片扫描仪采集图像。

1.2.7 统计学方法

所有实验数据以$\bar{x}\pm s$表示，采用SPSS 26.0和GraphPad Prism 10.1.2进行统计分析和作图。使用SPSS软件进行正态性分析。若数据满足正态性和方差齐性，则使用单因素方差分析(One-Way ANOVA)对多组数据进行整体比较，并采用Tukey多重比较进行事后分析。若数据不符合正态分布，则采用非参数检验。使用Kaplan-Meier生存分析比较各组间生存率的差异。$P<0.05$为差异有统计学意义。

2 结果

2.1 电针提高脓毒症急性肾损伤小鼠的存活率

LPS造模后采用Kaplan Meier方法分析小鼠的生存率(图1)。结果显示，NS组小鼠存活率为100%，LPS组存活率降低至30%($P<0.05$)，EA组将存活率提升至45%，但与LPS组差异无统计学意义($P>0.05$)。

2.2 电针缓解脓毒症急性肾损伤小鼠炎症反应

如图2所示，与NS组相比较，LPS组小鼠在造模后24 h血清中IL-1β和IL-18水平均明显升高(均$P<0.000\,1$)，表明脓毒症小鼠建模成功；与LPS组相比较，EA组小鼠血清中IL-1β和IL-18水平均明显降低(均$P<0.000\,1$)，提示电针治疗可有效抑制脓毒症小鼠的炎症反应。

2.3 电针改善脓毒症小鼠急性肾病理损伤

小鼠肾脏组织HE染色结果显示，NS组小鼠肾脏组织结构完整，未见明显病理学改变；LPS组小鼠肾脏呈现典型的急性损伤病理特征，包括肾小管上皮细胞明显肿胀/坏死、肾小球结构紊乱、间质大量中性粒细胞及淋巴细胞浸润；而EA组小鼠肾脏病理损伤有明显改善，肾小管肿胀程度减轻，肾小球结构清晰度恢复，间质炎性细胞浸润减少(图3)。结果提示电针治疗可减轻脓毒症诱导的肾脏组织病理损伤。

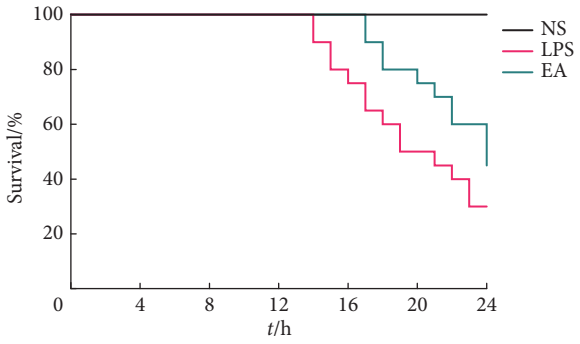

图 1 电针提高脓毒症急性肾损伤小鼠的存活率

Fig 1 Electroacupuncture improves survival rate in SA-AKI mice

NS: normal saline; LPS: lipopolysaccharide; EA: electroacupuncture. $n=20$.

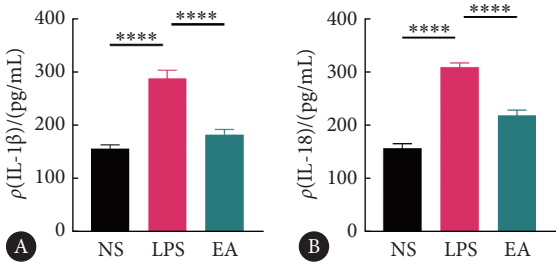

图 2 电针降低脓毒症急性肾损伤小鼠血清中炎症因子含量

Fig 2 Electroacupuncture reduces serum inflammatory cytokine levels in SA-AKI mice

A, The concentration of IL-1β in serum; B, the concentration of IL-18 in serum. $n=6$, $^{****}P<0.000\,1$.

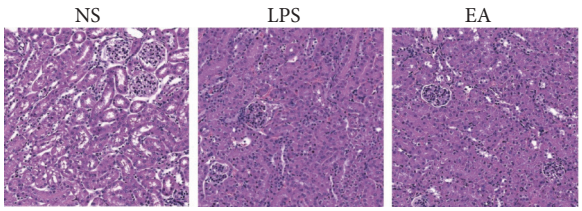

图 3 电针减轻脓毒症急性肾损伤小鼠的肾脏病理学改变（HE ×200）

Fig 3 Electroacupuncture alleviates renal pathological changes in SA-AKI mice (HE, original magnification × 200)

2.4 电针降低SA-AKI肾脏损伤标志物及肾脏组织炎症因子表达

由图4可见，与NS组相比较，LPS组血清中Scr浓度较高($P<0.001$)，而EA组血清中Scr浓度明显低于LPS组($P<0.05$，图4A)；与NS组相比较，LPS组肾脏组织中IL-1β、IL-18的含量均明显增加($P<0.000\,1$)，而EA组肾脏组

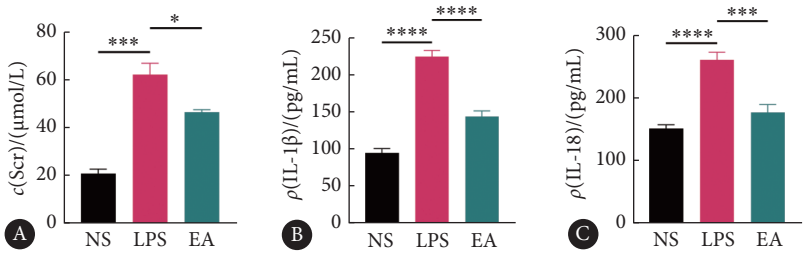

图 4 电针降低脓毒症急性肾损伤小鼠血清肌酐及肾脏炎症因子水平

Fig 4 Electroacupuncture reduces serum creatinine and kidney inflammatory cytokine levels in SA-AKI mice

A, Scr level; B, IL-1β concentration in mouse kidney tissue; C, IL-18 concentration in mouse kidney tissue. $n = 6$. $^{*}P < 0.05$, $^{***}P < 0.001$, $^{****}P < 0.000\,1$.

织中IL-1β、IL-18含量低于LPS组($P< 0.05$, 图4B、4C)。结果提示, 电针治疗可明显改善脓毒症急性肾损伤小鼠的肾功能损伤, 并抑制肾脏局部炎症反应。

2.5 电针抑制P2RX7和NLRP3炎症小体通路的激活

RT-qPCR检测肾脏组织中*P2RX7*和*NLRP3* mRNA表达水平结果见图5A, LPS组小鼠肾脏组织中*P2RX7*和*NLRP3* mRNA表达水平明显高于NS组(均$P< 0.000\,1$); 与LPS组相比较, EA组*P2RX7*和*NLRP3* mRNA的表达均明显降低(均$P< 0.01$)。采用免疫荧光对肾脏组织中P2RX7和NLRP3蛋白表达水平检测同样发现, LPS组小鼠的肾脏组织P2RX7和NLRP3蛋白表达水平较NS组升高(均$P< 0.001$); EA组P2RX7和NLRP3蛋白表达水平较LPS组降低(均$P< 0.01$, 图5B、5C)。结果表明, 电针治疗可抑制P2RX7/NLRP3炎症小体通路的激活。

2.6 电针通过抑制P2RX7/NLRP3信号通路的激活减轻SA-AKI

为阐明电针治疗SA-AKI的作用机制, 本研究采用P2RX7拮抗剂(A-438079)进行验证。结果发现, EA组($P< 0.05$)和A-438079+LPS组($P< 0.001$)血清Scr水平较LPS组降低, 而A-438079+LPS+EA组血清Scr水平较A-438079+LPS组进一步下降($P< 0.05$); EA组小鼠肾脏组织中IL-1β($P< 0.01$)和IL-18($P< 0.000\,1$)表达较LPS组均降低, A-438079+LPS+EA组小鼠肾脏中IL-1β和IL-18的表达较A-438079+LPS组下降更明显($P< 0.05$, 图6A ~ 6C); RT-qPCR结果显示, A-438079+LPS组P2RX7($P< 0.000\,1$)和NLRP3($P< 0.05$)mRNA表达水平较LPS组下调, A-438079+LPS+EA组较A-438079+LPS组进一步抑制*P2RX7*和*NLRP3* mRNA表达(均$P< 0.001$, 图6D、6E)。以上结果显示, EA可抑制 P2RX7激活、协同增强P2RX7拮抗剂的抗炎效应, 并通过P2RX7/NLRP3信号通路改善SA-AKI。

3 讨论

脓毒症是导致急性肾损伤的首要病因, SA-AKI患者死亡率较单纯脓毒症患者增加1.5 ~ 2倍[19-20]。本研究采用腹腔注射LPS的方法成功建立SA-AKI小鼠模型。模型验证结果显示, 小鼠表现出呼吸急促、对刺激反应减弱, 肾脏HE染色显示明显的组织间质水肿和炎性细胞浸润, 血清肌酐和炎症因子水平(IL-1β、IL-18)升高等典型脓毒症

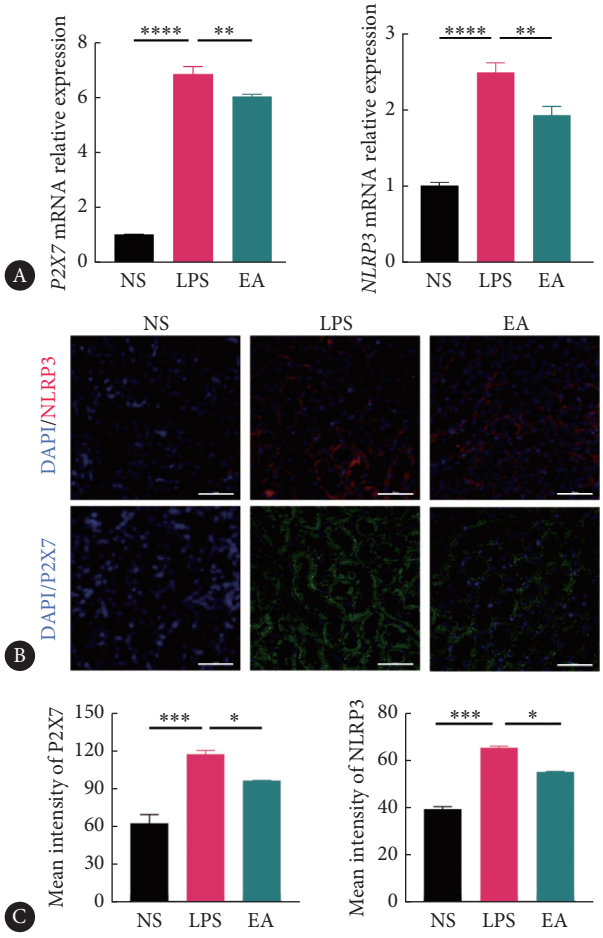

图 5 电针抑制脓毒症小鼠肾脏中P2RX7和NLRP3表达水平

Fig 5 Electroacupuncture inhibits P2RX7 and NLRP3 expression levels in kidney tissue of SA-AKI mice

A, Expression of *P2RX7* and *NLRP3* mRNA ($n = 6$); B, representative immunofluorescence images of P2RX7 and NLRP3 expression (scale bar = 50 μm); C, statistical analysis of mean immunofluorescence intensity for P2RX7 and NLRP3 ($n = 3$). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.000\,1$.

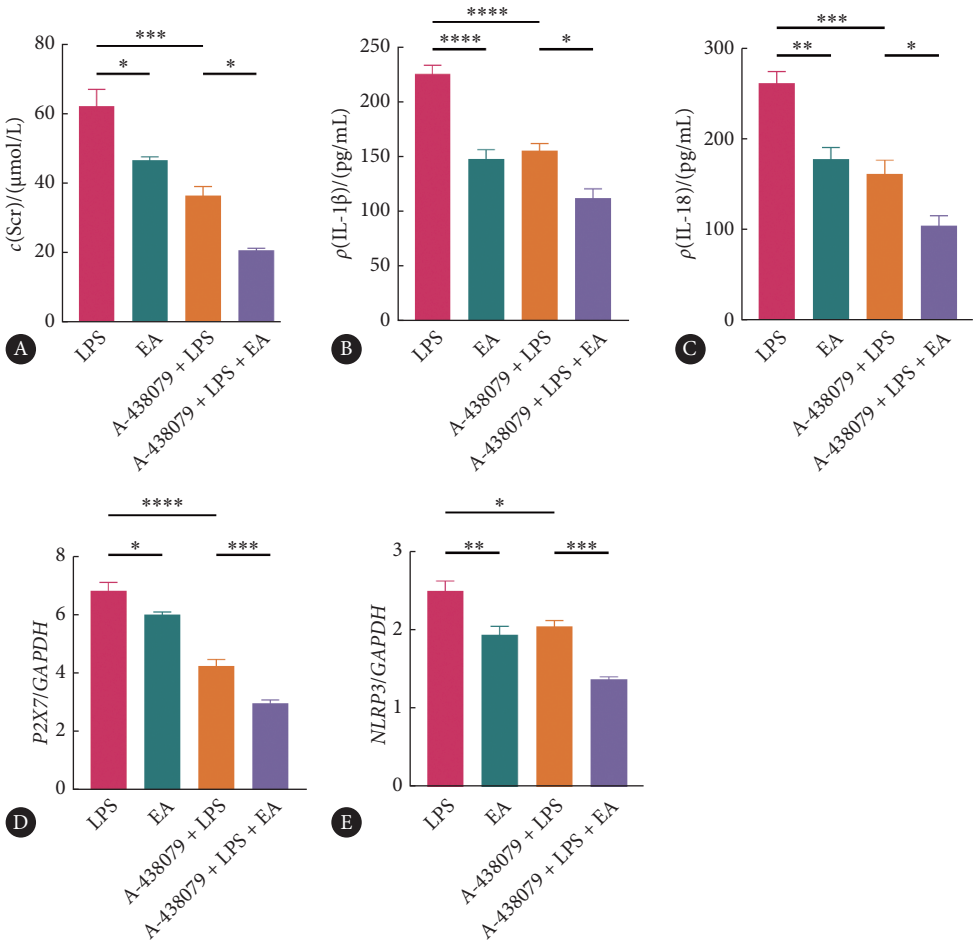

图 6 电针通过抑制P2RX7/NLRP3信号通路激活减轻SA-AKI

Fig 6 Electroacupuncture alleviates SA-AKI by inhibiting activation of the P2RX7/NLRP3 signaling pathway

A, Scr expression levels; B, IL-1β expression levels in mouse kidney tissue; C, IL-18 expression levels in mouse kidney tissue; D, *P2RX7* mRNA expression levels; E, *NLRP3* mRNA expression levels. $n = 6$. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

特征。上述结果表明SA-AKI小鼠模型构建成功。

既往研究表明，电针刺激“足三里”穴可激活迷走神经-脾脏反射通路和迷走神经-肾上腺轴发挥抗炎作用，对脓毒症小鼠具有保护作用[21]。本研究结果显示，电针干预使SA-AKI小鼠24 h存活率从30%提升至45%，降低小鼠血清Scr和促炎细胞因子水平(IL-1β、IL-18)，并改善小鼠肾脏组织结构损伤。 P2RX7广泛表达于巨噬细胞、肥大细胞、淋巴细胞和树突状细胞等免疫系统细胞，在抗炎中发挥重要作用，为治疗炎症性疾病的重要治疗靶点[22-23]。

临床研究表明[24]，脓毒症患者外周血多种免疫细胞P2RX7表达明显升高。动物研究显示[25-28]，阻断P2RX7的表达有助于减轻脓毒症发生和发展过程炎症反应及心、肝脏、肾脏和肺等多器官损伤。激活的P2RX7可介导Na^{+}和Ca^{2+}内流及K^{+}外流[29]，从而激活磷脂酶D[30]、丝裂原活化蛋白激酶途径(MAPK)[31]、NF-κB[32]及NLRP3炎症小体[33]等多条炎症调节通路。eATP可激活P2RX7诱导NLRP3炎症小体的组装及caspase-1的活化，从而增强促炎因子IL-1β和IL-18的成熟和释放[23]。这一过程不仅在免疫防御中起重要作用，也在多种炎症性疾病和组织损伤中发挥关键作用。研究表明[34]，脓毒症引起的多个器官细胞焦亡现象与NLRP3炎症小体介导的细胞焦亡途径有着密切的联系，提示NLRP3炎症小体在脓毒症病理过程发挥重要作用。在脓毒症动物模型中，NLRP3缺陷可提高动物的生存率[35]。本研究结果显示，在LPS诱导的脓毒症模型中，*P2RX7*、*NLRP3*的mRNA及蛋白表达量均大幅度升高。而P2RX7拮抗剂A-438079可进一步降低脓毒症模型小鼠血清肌酐水平以及肾脏组织中促炎细胞因子(IL-1β和IL-18)以及NLRP3的表达量。提示阻断P2RX7的表达对脓毒症诱导的急性肾损伤具有保护作用。

本研究结果同样显示，电针治疗可抑制LPS诱导的脓毒症模型P2RX7和NLRP3表达。与单独使用A-438079相比，A-438079联合电针治疗可进一步降低Scr水平以及肾脏中IL-1β、IL-18、P2RX7和NLRP3的表达。这表明电针增强了A-438079对P2RX7/NLRP3信号通路激活的抑制效

果, 进而更有效地缓解了肾组织损伤。提示电针可能通过抑制P2RX7/NLRP3信号通路的激活缓解脓毒症诱导的AKI。

综上所述, 本研究证实电针可通过抑制P2RX7/NLRP3信号通路激活, 有效减轻SA-AKI的全身性炎症反应和肾损伤, 提高脓毒症急性肾损伤模型小鼠的生存率, 但其作用机制仍需深入探讨。本研究也存在局限性, 首先, 在本研究中使用的 P2RX7拮抗剂并非肾脏靶向性, 因此难以区分肾脏特异性效应, 后续研究可采用 P2RX7条件性敲除小鼠模型, 特异性地敲除肾脏 P2RX7进行验证, 从而更精准地评估 P2RX7在肾脏中的作用。其次, 本研究未深入探讨P2RX7/NLRP3信号通路下游分子的变化, 因此无法完全阐明其具体机制。未来研究应结合多组学分析, 以更全面阐明电针的肾脏保护机制, 为SA-AKI治疗提供新策略。

*　　*　　*

作者贡献声明　王苗苗负责数据审编、正式分析、调查研究、研究方法、研究项目管理和初稿写作, 赵晓晓负责数据审编、调查研究、研究项目管理和验证, 侯帅负责数据审编、调查研究和研究项目管理, 肖欣怡负责调查研究和研究项目管理, 尹海燕负责论文构思、数据审编、经费获取、研究方法、监督指导和审读与编辑写作。所有作者已经同意将文章提交本刊, 且对将要发表的版本进行最终定稿, 并同意对工作的所有方面负责。

Author Contribution　WANG Miaomiao is responsible for data curation, formal analysis, investigation, methodology, project administration, and writing--original draft. ZHAO Xiaoxiao is responsible for data curation, investigation, project administration, and validation. HOU Shuai is responsible for data curation, investigation, and project administration. XIAO Xinyi is responsible for investigation and project administration. YIN Haiyan is responsible for conceptualization, data curation, funding acquisition, methodology, supervision, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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