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七氟醚预处理介导 AMPK α 1 通路对大鼠心肌缺血再灌注损伤的保护作用 *

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摘要 目的: 探讨七氟醚预处理介导腺苷酸环化激酶 (AMP-activated protein kinase, AMPK) α 1 通路对大鼠心肌缺血再灌注损伤 (myocardial ischemia-reperfusion injury, MIRI) 的保护作用。**方法:** 将清洁级雄性 SD 大鼠 60 只随机平分为三组: 模型组、地佐辛组与七氟醚组, 三组均建立 MIRI 模型。地佐辛组与模型组都在建模前 24 h 腹腔注射地佐辛 40 μ g/kg 与等剂量生理盐水, 七氟醚组吸入 2.5 % 七氟醚 15 min。**结果:** 所有大鼠在建模过程中均存活, 无大鼠因严重并发症而舍弃。地佐辛组与七氟醚组再灌注后 24 h 与 48 h 的左心室收缩压、左心室舒张末期压、心肌梗死面积百分比、血清去甲肾上腺素含量、心脏组织 AMPK α 1 和皮质激素调节激酶 -1 (glucocorticoid-regulated kinase-1, GK1) 蛋白相对表达水平都低于模型组 ($P < 0.05$), 七氟醚组低于地佐辛组 ($P < 0.05$)。**结论:** 七氟醚预处理可通过抑制大鼠 MIRI 的 AMPK α 1 通路的激活和血清去甲肾上腺素释放, 从而减少大鼠心肌梗死面积, 并进一步促进心功能恢复正常。

关键词: 七氟醚; 预处理; 心肌缺血再灌注损伤; 腺苷酸环化激酶 α 1; 去甲肾上腺素的释放; 心肌梗死

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Sevoflurane Preconditioning Mediates the Protective Effect of AMPK α 1 Pathway on Myocardial Ischemia-reperfusion Injury in Rats*

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ABSTRACT Objective: To investigate the protective effect of sevoflurane preconditioning-mediated adenylate cyclic kinase (AMP-activated protein kinase, AMPK) α 1 pathway on myocardial ischemia-reperfusion injury in rats. **Methods:** Sixty clean-grade male SD rats were randomly divided into three groups-model group, dezocine group and sevoflurane group. All three groups established myocardial ischemia-reperfusion injury models. Both the dezocine group and the model group were intraperitoneally injected with 40 μ g/kg of dezocine and the same dose of normal saline 24 hours before modeling, and the sevoflurane group were inhaled with 2.5 % sevoflurane for 15 minutes. **Results:** All rats were survived in the modeling process, and there were no rats were abandoned due to severe complications. The LVSP, LVEDP, percentage of myocardial infarction area, serum norepinephrine content, cardiac tissue relative expression level of glucocorticoid-regulated kinase-1 (GK1) and AMPK α 1 protein at 24 h and 48 h after reperfusion in the dezocine group and sevoflurane group were lower than the model group ($P < 0.05$), and the sevoflurane group were lower than the dezocine group ($P < 0.05$). **Conclusion:** Sevoflurane pretreatment can reduce the myocardial infarct size in rats and further promote the return of normal cardiac function by inhibiting the activation of AMPK α 1 pathway in MIRI and the release of serum norepinephrine in rats.

Key words: Sevoflurane; Preconditioning; Myocardial ischemia-reperfusion injury; Adenylate cyclase α 1; Norepinephrine release; Myocardial infarction

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前言

随着医学技术的提高, 心肌缺血疾病的死亡率逐年下降, 但是很多患者在治疗过程中可能会出现 MIRI, 出现继发性心肌损伤的问题, 从而严重影响患者的康复^[1,2]。MIRI 的发病机制比较复杂, 涉及到多种细胞因子与基因表达的异常^[3-5]。AMPK

容易被代谢压力减少激活, 激活的 AMPK 可发生磷酸化修饰, 从而通过调控雷帕霉素靶蛋白 (mTOR) 与糖皮质激素调节激酶 -1 (glucocorticoid-regulated kinase-1, GK1) 表达, 参与细胞内各种生物学行为的调节^[6]。在低氧环境下 AMPK 可以诱导低氧诱导因子 -1 α 和血管内皮生长因子表达促进肿瘤血管生成, 进而促进肿瘤的增殖与侵袭^[7]。七氟醚 (sevoflurane, SEVO) 是目前在

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临床上广泛应用于心脏手术,七氟醚预处理后可从一定程度上改善心肌损伤,对线粒体功能具有保护作用,能减少机体心肌梗死面积和死亡率。基础研究表明七氟醚对心肌细胞存在保护作用,有利于对细胞凋亡进行抑制^[8-10]。本文具体探讨了七氟醚预处理介导 AMPK α 1 通路对大鼠 MIRI 的保护作用,以明确其预处理的作用效果与机制。

1 材料与方法

1.1 试剂和仪器

清洁级雄性 SD 大鼠 60 只(内蒙古双奇药业股份有限公司),体重 400-500 g。于清洁动物实验室饲养,操作过程符合动物伦理要求,每笼 4 只大鼠,实验室温度 20~28 °C,相对湿度 50~60 %,通风良好,环境安静,实验期间自由进食饮水,12 h:12 h 照明。七氟醚购自上海恒瑞医药有限公司(国药准字 H20070172),地佐辛购自国药准字 H20080329,扬子江药业集团有限公司,-80 °C 超低温冰箱(中国美的)、Olympus 光学显微镜(日本奥林巴斯),去甲肾上腺素试剂盒(Cusabio 公司);抗 AMPK α 1 抗体、抗 GK1 抗体、抗 β -actin 抗体都购自美国 Sigma 公司。

1.2 心肌缺血再灌注损伤模型的建立

将所有大鼠随机平分为三组:模型组、地佐辛组与七氟醚组,三组都建立 MIRI 模型。地佐辛组与模型组都在建模前 24 h 腹腔注射地佐辛 40 μ g/kg 与等剂量生理盐水,七氟醚组吸入 2.5 %七氟醚 15 min。

在建模过程中,将大鼠麻醉后,实施正压呼吸机辅助通气。于第 5 肋间进行左胸廓切开术以暴露心脏,用丙烯缝线结扎左

前降支冠状动脉,左心室前壁苍白且心电图 ST 段升高表明缺血成功。持续缺血 30 min 后,松开扎线恢复心脏再灌注 2 h。

1.3 观察指标

(1)在再灌注后 24 h 与 48 h 三组各取 8 只大鼠进行实验,分离大鼠右颈总动脉,将含 0.1 %肝素钠的导管插入左心室,监测大鼠左心室血流动力学的变化,重点记录左心室收缩压(LVSP)、左心室舒张末期压(LVEDP)等指标。(2)在再灌注后 24 h 与 48 h 将 2 mL 1.0 %伊文思蓝经主动脉注入左心室染色,然后处死大鼠后取出离体心脏,置于 1.0 %的 2,3,5-三苯基氯化四氮唑溶液中,观察、测定并计算心肌梗死面积百分比。(3)取处死大鼠的心脏血 1.0 mL 左右,不抗凝,静置 30 min 后低温离心 10 min(3000 rpm),取上层血清,采用酶联免疫吸附测定法(ELISA)检测去甲肾上腺素含量。(4)取大鼠心脏组织制成匀浆,提取总蛋白后,应用 Western 方法检测各组心脏组织 AMPK α 1、GK1 蛋白的相对表达水平。

1.4 统计方法

选择 SPSS22.00 软件进行数据分析,计量数据采用均数 $\pm$ 标准差表示,两两对比为 t 检验,多组间对比为方差分析,检验水准为 $\alpha=0.05$ 。

2 结果

2.1 左心室血流动力学情况对比

所有大鼠在建模过程中都存活,也无大鼠因严重并发症而舍弃。地佐辛组与七氟醚组再灌注后 24 h 与 48 h 的左心室收缩压与左心室舒张末期压都低于模型组($P<0.05$),七氟醚组低于地佐辛组($P<0.05$)。见表 1。

表 1 三组再灌注后不同时间点的左心室血流动力学情况对比(mmHg,均数 $\pm$ 标准差)

Table 1 Comparison of left ventricular hemodynamics at different time points after reperfusion in three groups (mmHg,mean $\pm$ standard deviation)

Groups	n	24 h after reperfusion		48 h after reperfusion	
		Left ventricular systolic pressure	Left ventricular end-diastolic pressure	Left ventricular systolic pressure	Left ventricular end-diastolic pressure
Model group	8	156.22 $\pm$ 13.28	14.09 $\pm$ 0.33	156.87 $\pm$ 15.63	14.11 $\pm$ 0.35
Dezocine group	8	144.09 $\pm$ 12.58 [#]	12.75 $\pm$ 0.12 [#]	143.98 $\pm$ 12.52 [#]	12.56 $\pm$ 1.57 [#]
Sevoflurane group	8	132.98 $\pm$ 12.87 ^{**}	11.09 $\pm$ 1.33 ^{**}	130.65 $\pm$ 14.02 ^{**}	11.65 $\pm$ 2.17 ^{**}
F		18.013	7.822	18.743	7.532
P		<0.001	<0.001	<0.001	<0.001

Note: Compared with the model group, [#] $P<0.05$; compared with the dezocine group, ^{*} $P<0.05$. The same below.

2.2 心肌梗死面积百分比对比

地佐辛组与七氟醚组再灌注后 24 h 与 48 h 的心肌梗死面积百分比都低于模型组($P<0.05$),七氟醚组低于地佐辛组($P<0.05$)。见表 2。

2.3 血清去甲肾上腺素含量对比

地佐辛组与七氟醚组再灌注后 24 h 与 48 h 的血清去甲肾上腺素含量低于模型组($P<0.05$),七氟醚组低于地佐辛组($P<0.05$)。见表 3。

2.4 AMPK α 1、GK1 蛋白相对表达水平变化对比

地佐辛组与七氟醚组再灌注后 24 h 与 48 h 的心脏组织 AMPK α 1、GK1 蛋白相对表达水平低于模型组($P<0.05$),七氟醚组低于地佐辛组($P<0.05$)。见表 4。

3 讨论

心肌缺血为临床上常见的致残与致死性疾病,其中 MIRI 的发生也较为常见,严重影响患者的康复^[11,12]。特别是 MIRI 后可致脑组织出现氧化应激反应,一旦氧化应激过重,便会导致心肌组织损害。七氟醚是心脏手术的常用麻醉剂,在临床上的应用具有很高的安全性^[13,14]。本研究显示所有大鼠在建模过程中都存活,也无大鼠因严重并发症而舍弃;地佐辛组与七氟醚组再灌注后 24 h 与 48 h 的左心室收缩压与左心室舒张末期压都低于模型组($P<0.05$),七氟醚组低于地佐辛组($P<0.05$);地佐辛组与七氟醚组再灌注后 24 h 与 48 h 的心肌梗死面积百分比都低于模型组($P<0.05$),七氟醚组低于地佐辛组($P<0.05$),表明

表 2 三组再灌注后不同时间点的心肌梗死面积百分比对比(% ,均数± 标准差)

Table 2 The percentage of myocardial infarction area at different time points after reperfusion in the three groups (% , mean ± standard deviation)

Groups	n	24 h after reperfusion	48 h after reperfusion
Model group	8	21.46± 2.18	21.75± 1.78
Dezocine group	8	15.20± 1.55 [#]	15.38± 2.15 [#]
Sevoflurane group	8	12.98± 2.47 ^{**}	12.56± 3.18 ^{**}
F		8.933	9.144
P		<0.001	<0.001

表 3 三组再灌注后不同时间点的血清去甲肾上腺素含量对比(pg/ml,均数± 标准差)

Table 3 Comparison of serum norepinephrine levels at different time points after reperfusion among the three groups (pg/ml, mean ± standard deviation)

Groups	n	24 h after reperfusion	48 h after reperfusion
Model group	8	178.89± 32.32	177.34± 29.88
Dezocine group	8	153.09± 22.18 [#]	153.09± 30.66 [#]
Sevoflurane group	8	115.60± 30.52 ^{**}	114.78± 28.99 ^{**}
F		28.913	28.114
P		<0.001	<0.001

表 4 三组再灌注后不同时间点的 AMPKα1、GK1 蛋白相对表达水平变化对比(均数± 标准差)

Table 4 Comparison of the relative expression levels of AMPKα1 and GK1 proteins at different time points after reperfusion in the three groups (mean ± standard deviation)

Groups	n	24 h after reperfusion		48 h after reperfusion	
		AMPKα1	GK1	AMPKα1	GK1
Model group	8	6.22± 0.44	6.26± 0.34	6.22± 0.41	6.29± 0.76
Dezocine group	8	3.87± 0.33 [#]	3.29± 0.29 [#]	3.81± 0.33 [#]	3.32± 0.18 [#]
Sevoflurane group	8	1.77± 0.32 ^{**}	0.92± 0.12 ^{**}	1.67± 0.09 ^{**}	0.94± 0.05 ^{**}
F		35.022	39.280	35.661	39.774
P		<0.001	<0.001	<0.001	<0.001

七氟醚预处理能减轻大鼠 MIRI,结合相关研究分析:该药物在稳定血流动力学、抑制自主神经反射等方面具有优势,并能减轻血流动力学紊乱、心律增快等不适症状^[15,16]。另外,其对呼吸功能的抑制作用比较轻,降低大鼠 MIRI 后心肌组织内谷氨酸含量,增加 γ-氨基丁酸含量,发挥其心肌保护作用^[17,18]。

缺血再灌注引起的心肌损伤是冠状动脉疾病的主要病理表现,目前仍不存在保护心脏免受 MIRI 影响的有效治疗方法,因此,有必要发现或开发预防心肌再灌注损伤的新策略,以改善冠状动脉疾病患者的临床结局^[19]。七氟醚的临床药理应用结果显示:其具有用量小、术中血流动力学影响小以及术后苏醒快等特点,具有良好的抗凋亡功能,能抑制心肌细胞凋亡,从而保护心肌功能^[20,21]。本研究显示地佐辛组与七氟醚组再灌注后 24 h 与 48 h 的血清去甲肾上腺素含量低于模型组,七氟醚组低于地佐辛组,结合 Huang XT 等^[22]研究分析,MIRI 患者的心肌组织可受到伤害,可直接影响去甲肾上腺素的分泌,七氟醚能抑制 AMPK 活性导致突触活动减少,从而促进去甲肾上腺素的释放。

AMPKα1 是评价心肌损伤的标志物,其含量越高,表明心肌组织损伤越严重^[23]。GK1 为一种 PI3K 依赖性丝/苏氨酸蛋白激酶,激活该蛋白表达可促使肿瘤细胞的转移与侵袭^[24]。

AMPKα1/GK1 信号途径可调控促 CRF-1 的表达,进一步调控血清糖皮质激素浓度,从而使 GK1 被激活,可增强细胞增殖能力^[25]。有研究显示恶性肿瘤患者 GK1 表达增多与患者的不良预后密切相关,降低 GK1 的表达能使 EMT 标志蛋白 E-cadherin 上调,从而抑制肿瘤的侵袭和转移^[26-28]。七氟醚具有抗氧化自由基功能,它能改善心肌组织微循环,增加局部血流;其也具有高选择性和高效性,从而产生抗焦虑、镇静、镇痛等作用^[29-31]。本研究显示地佐辛组与七氟醚组再灌注后 24 h 与 48 h 的心脏组织 AMPKα1、GK1 蛋白相对表达水平低于模型组,七氟醚组低于地佐辛组,表明七氟醚预处理能抑制大鼠 MIRI 的 AMPKα1 通路的激活,与上述研究结果一致。不过本研究也存在一定的不足,七氟醚的剂量与保护作用的量效关系也需要进一步研究,且还需要进行细胞学分析。

总之,七氟醚预处理可通过抑制大鼠 MIRI 的 AMPKα1 通路的激活和血清去甲肾上腺素释放,从而减少大鼠心肌梗死面积,并进一步促进心功能恢复正常。

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