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论文

eNOS基因转染治疗兔肺动脉高压及肺动脉高压危象

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摘要：

目的 探讨复制缺陷型重组腺病毒载体（AdCMVeNOS）介导内皮型一氧化氮合酶（eNOS）基因转染对左向右分流所致的肺动脉高压及肺动脉高压危象兔的影响。方法 18只肺动脉高压模型兔分成实验组（n=9）和对照组（n=9），实验组气管内滴入AdCMVeNOS病毒转染液（5×109PFU/mL）2mL，对照组滴入生理盐水2mL。4d后结扎左向右分流，同时气管插管吸入10%氧气，检测两组肺动脉收缩压(SPAP)、肺动脉平均压（MPAP）和平均动脉压（MAP）的变化；同时采用硝酸还原酶法测定肺组织一氧化氮（NO）浓度，检测外源性eNOS基因mRNA的表达。结果 实验组肺动脉压较转染前明显下降（P<0.01），而对照组肺动脉压无明显改变，与实验组比较，差异有统计学意义（P<0.05）。缺氧60min后，实验组仅4只兔出现肺动脉高压危象，而对照组全部出现肺动脉高压危象。两组缺氧后均出现氧分压（PaO2）降低，二氧化碳分压（PaCO2）升高， SPAP、MPAP升高，MAP降低。恢复供氧后，实验组各测得值恢复至正常水平，对照组SPAP和MPAP高于基础值，MAP低于基础值(P<0.01)，实验组SPAP、 MPAP和PaCO2的升高幅度以及MAP和PaO2的降低幅度均低于对照组（P<0.01）。免疫组化染色显示实验组肺泡内皮细胞、肺中小血管的平滑肌细胞和内皮细胞的eNOS表达均较对照组明显增加，而且肺组织的NO浓度也明显高于对照组(P<0.001)。琼脂糖凝胶电泳显示，实验组在3.77kb处扩增出特异条带，而对照组在3.77kb处未扩增出特异条带。结论 AdCMVeNOS转染左向右分流所致的兔肺动脉高压动物模型，可有效降低肺动脉压和肺动脉高压危象的发生率。

关键词： 一氧化氮合酶基因；腺病毒载体；肺动脉高压；基因治疗；兔

eNOS gene transfection on pulmonary artery hypertensionand hypertension crisis in rabbits

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Abstract:

Objective Effects of transfection of the endothelial nitric oxide synthase (eNOS) gene were studied in rabbits with pulmonary hypertension induced by left to right shunt or pulmonary hypertension crisis induced by hypoxia . Methods Eighteen pulmonary hypertension rabbits were divided into the experimental group(n=9) and the control group(n=9).In the experimental group,an adenoviral vector encoding eNOS was intratracheally transfected .The same dosage of saline was intratracheally transfected in the control group. The left right shunt was ligated 4 days after transfection, while 10% oxygen was inhaled through endotracheal intubation. Changes of pulmonary artery systolic pressure (SPAP),mean pulmonary artery pressure(MPAP) and mean arterial pressure(MAP) were detected. Concentration of NO and transgene expression mRNA were investigated. Results Compared with that before transfection, pulmonary artery pressure significantly decreased(P<0.01) in the experimental group, while there was no change in the control group. There were significant differences between two groups after transfection. 60min after hypoxia, all rabbits presented pulmonary hypertension crisis in the control group, but only 4 rabbits in the experimental group developed a crisis. Decreased PaO2 and MAP, increased PaCO2, SPAP and MPAP occurred in these two groups after hypoxia. But after the oxygen supply was restored, the variables recovered to normal levels in the experimental group. The variables of SPAP and MPAP were higher than their baseline, and MAP was lower in the control group. Comparing the variables (after vs before hypoxia) between the control group and the experimental group, the increasing extent of SPAP,MPAP and PaCO2 and decreasing extent of MAP, CO and PaO2 in the experimental group were lower than those in the control group . With immunohistochemical staining, expression of the eNOS gene in alveolar endothelial cells, smooth muscle cells and endothelial cells of small pulmonary vessels of the experimental group increased more than that of the control group. The concentration of NO in the experimental group was higher than that in the control group. Agarose gel electrophoresis showed an amplified 3.77kb specific band in the experimental group, but not in the control group. Conclusions Intratracheal adenoviral-mediated eNOS gene transfection can reduce rabbits′ pulmonary hypertension induced by left-to-right shunt and decrease occurrence rate of pulmonary hypertension crisis.

Keywords: Nitric oxide synthase; Adenovirus vector; Pulmonary hypertension; Gene therapy; Rabbit

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