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论著

阿托伐他汀抑制RhoA/Rho激酶活性逆转低氧性肺动脉高压大鼠肺动脉高压和肺血管重构

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摘要：

目的：探讨阿托伐他汀是否通过抑制肺动脉RhoA/Rho激酶通路的激活而逆转低氧所致的大鼠肺动脉高压及肺血管重构。方法：32只成年雄性Westar大鼠随机分成4组：A组为正常对照组；B，C，D组建立常压低氧性肺动脉高压大鼠模型，自低氧干预第1天起C组每日给予1 mg/mL阿托伐他汀溶液10 mg/kg灌胃,D组以生理盐水10 mL/kg灌胃。模型建成时右心导管测定肺动脉平均压（mPAP）；肺组织病理切片对肺小血管周围炎性细胞浸润和肺血管结构改变进行评分，采用病例图像分析系统测定肺小动脉管壁厚度占外径的百分比（WT%）和管壁面积占血管总面积的百分比（WA%）,评价肺血管重构的严重程度；Western印迹检测肺动脉组织蛋白中RhoA的表达，Rho激酶的调节亚单位MYPT 1磷酸化水平。结果：低氧干预B组大鼠mPAP，右室肥大指数［RV/(LV+S)］，WT%，WA%分别为（29.6±1.1）mmHg，（39.0±0.7）%，(35.6±2.4)%，（56.5±5.1）%，较正常对照A组［（16.8±0.7）mmHg，（29.4±0.5）%，(22.3±1.2)%，(36.6±2.3)%］增高，差异均有统计学意义（P<0.05）；经阿托伐他汀干预C组大鼠mPAP，RV/(LV+S)，WT%，WA%分别为（25.3±3.2）mmHg，(36.3±2.1)%，(29.2±3.2)%，(48.1±2.7) %，较正常对照A组高（P<0.05），同时较低氧干预B组低（P<0.05）；生理盐水对照D组上述指标均与低氧干预C组无明显差别。Western 印迹结果显示：在B组大鼠肺动脉组织中RhoA，磷酸化MYPT 1表达明显较A组大鼠上调，C组大鼠则较B组大鼠有明显减低。结论：阿托伐他汀能显著降低低氧性肺动脉高压大鼠的mPAP，改善肺血管的重构，其作用机制可能与阿托伐他汀抑制肺动脉中RhoA/Rho激酶活性有关。

关键词： 低氧性肺动脉高压；阿托伐他汀；RhoA/Rho激酶

Atorvastatin attenuates hypoxic pulmonary hypertension in rats by inhibiting RhoA/Rho kinase pathway

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Abstract:

ObjectiveTo investigate whether atorvastatin treatment can improve the symptoms of hypoxia induced pulmonary hypertension in rats by inhibiting RhoA/Rho kinase pathway. MethodsA total of 32 Westar rats was divided into 4 groups: normoxic controls (Group A), hypoxic controls (Group B), hypoxia plus atorvastatin ［10 mg/（kg·d）］ group(Group C), and hypoxia plus the vehicle of atorvastatin (Group D). Rats for hypoxia treatment were maintained under the condition of 10% FiO2 6 h/d for 4 weeks. At the end of 4 weeks, rats were anesthetized and the mean pulmonary arterial pressure (mPAP) was measured by right heart catheterization. The ratios of arteriole wall thickness to vascular external diameter (WT%), and vascular area to total vascular area (WA%) were measured by a computerized image analyzer. RhoA and phos MYPT 1 expression in the pulmonary artery were determined by Western blot. ResultsComparing with Group A, the mPAP ［(29.6±1.1）mmHg vs （16.8±0.7）mmHg］, RV/(LV+S) ［(39.0±0.7）%vs （29.4±0.5）%］, WT% ［（35.6±2.4)% vs (22.3±1.2)%］ and WA% ［(56.5±5.1)% vs (36.6±2.3)%］ in Group B were all significantly increased (P<0.05). Comparing with Group B, the mPAP ［（25.3±3.2)mmHg］, RV/(LV+S) ［(36.3±2.1)%］, WT% ［(29.2±3.2)%］ and WA% ［(48.1±2.7)%］ in Group C were signifcantly decreased. The vehicle of atorvastatin had no such effect. The expression of RhoA and phos MYPT 1 in the pulmonary artery was increased in Group B, but it was decreased in Group C. ConclusionRhoA/Rho kinase pathway plays an important role in the development of hypoxic pulmonary hypertension. Atorvastatin can improve the symptoms of hypoxic pulmonary hypertension by inhibiting RhoA/Rho kinase activity.

Keywords: hypoxic pulmonary hypertension;atorvastatin;RhoA/Rho kinase

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