

论著

细胞内游离钙在辛伐他汀诱导大鼠血管平滑肌细胞凋亡中的作用

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摘要 目的 研究3-羟-3-甲戊二酰辅酶A (HMG-CoA) 还原酶抑制剂辛伐他汀诱导血管平滑肌细胞(VSMC)凋亡的机制。方法 以荧光染料Fura-2/AM负载后荧光分光光度计法检测细胞内游离钙浓度, 以DNA琼脂糖凝胶电泳、流式细胞仪PI/膜联蛋白(annexin)V染色及半胱天冬酶-3激活来检测细胞凋亡。结果 辛伐他汀 $30 \mu\text{mol} \cdot \text{L}^{-1}$ 孵育VSMC后, 细胞内游离钙浓度显著升高, 6 h时达对照的3倍以上 ($P < 0.01$), 维拉帕米 $80 \mu\text{mol} \cdot \text{L}^{-1}$ 与辛伐他汀 $30 \mu\text{mol} \cdot \text{L}^{-1}$ 共同孵育VSMC

6 h后细胞内游离钙浓度为 $(144 \pm 34) \text{nmol} \cdot \text{L}^{-1}$ ($P < 0.01$)。辛伐他汀可诱导细胞凋亡率增高、“DNA梯状”样改变及半胱天冬酶-3的激活, 这些变化均可被维拉帕米所逆转。结论 辛伐他汀通过使细胞外钙大量内流而诱导VSMC凋亡。

关键词 [辛伐他汀](#) [肌, 平滑, 血管](#) [凋亡](#) [钙, 细胞内](#)

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Effect of intracellular free calcium on simvastatin induced vascular smooth muscle cells apoptosis in rats

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Abstract

AIM To investigate the mechanisms involved in simvastatin induced apoptosis in vascular smooth muscle cells(VSMC).

METHODS Cultured VSMC was treated with simvastatin. Intracellular free calcium concentration ($[\text{Ca}^{2+}]_i$) was

measured by fluorescent Ca^{2+} -sensitive probe fura-2 acetoxyethyl ester(Fura-2/AM), apoptotic changes were distinguished by annexin V binding, DNA fragment and caspase-3 activation. **RESULTS** When incubated with $30 \mu\text{mol} \cdot \text{L}^{-1}$ simvastatin, $[\text{Ca}^{2+}]_i$ in VSMC increased with time and reached to $(336 \pm 52) \text{nmol} \cdot \text{L}^{-1}$ at 6 h, more than 3-fold of control ($P < 0.01$, $n=5$). Verapamil ($80 \mu\text{mol} \cdot \text{L}^{-1}$), a membrane voltage-dependent Ca^{2+} channel blocker, inhibited the increase of free calcium concentration induced by simvas

tatin from $(336 \pm 52) \text{nmol} \cdot \text{L}^{-1}$ to $(144 \pm 34) \text{nmol} \cdot \text{L}^{-1}$ ($P < 0.01$). Caspase-3 also activated by simvastatin after 12 h.

Verapamil could efficiently inhibit simvastatin induced caspase-3 activation. Furthermore, $80 \mu\text{mol} \cdot \text{L}^{-1}$ verapamil could decreased simvastatin induced apoptosis rate from $(24.2 \pm 1.7)\%$ to $(7.9 \pm 0.6)\%$ ($P < 0.01$) and also prevented simvastatin induced DNA laddering. **CONCLUSION** Simvastatin could increase $[\text{Ca}^{2+}]_i$ mainly through calcium influx from extracellular solution and then induces apoptosis.

Key words [simvastatin](#) [muscle smooth](#) [vascular apoptosis](#) [calcium cytosolic](#)

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