# Endothelium Modulates Contractile Response to Simvastatin in Rat Aorta

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Z. Naturforsch. **55c,** 121–124 (2000); received July 22/September 10/1999

HMG-CoA Reductase, Simvastatin, Endothelium, Rat Aorta

Simvastatin is an inhibitor of HMG-CoA reductase used in the treatment of hypercholesterolemia. In the present study simvastatin-induced contraction was observed in rat aortic thoracic rings, this effect increased when the endothelium was removed and when NO synthase was blocked by L-NOARG ($3 \times 10^{-5}$ M). The contractile effect of simvastatin on intact aortic rings diminished when cyclo-oxygenase was inhibited with indomethacin ($10^{-5}$ M). Also in the presence of endothelium, pretreatment with mevalonate (1 mM), the product of HMG-CoA reductase activity, significantly inhibited the contraction. In other experiments carried out on endothelium-removed preparations and in medium containing the calcium antagonist, diltiazem ($10^{-5}$ and $10^{-6}$ M), the contraction dose-response curves were significantly reduced and the same happened in the presence of the inhibitor of sarcoplasmic reticulum Ca-$^{2+}$–ATPase, cyclopiazonic acid (CPA) ($3 \times 10^{-6}$ M).

The results suggest that simvastatin might increase intracellular calcium concentration. This effect could lead to an activation of NO synthase and cyclooxygenase pathways in endothelial cells and to contraction in vascular smooth muscle cells. This rise in $Ca^{2+}$ concentration could be due to an inhibition of isoprenoid synthesis prevented by mevalonate.