Abstract:

Human umbilical vein endothelial cells (HUVECs) were established as in vitro models for the modulation of endothelial function and cell viability by statins. Emphasis was placed on the biphasic effects of the drugs on nitric oxide (NO) bioavailability and cytotoxicity, as well as drug interference with the interaction of endothelial NO synthase (eNOS) with caveolin-1 (Cav-1). Incubation of HUVECs with fluvastatin, lovastatin or cerivastatin for 24 h caused an approximately 3-fold upregulation of eNOS expression that was associated with increased eNOS activity and accumulation of cGMP. Cerivastatin exhibited the highest potency with an EC50 of 13.8 +/- 2 nM after 24 h, while having no effect after only 30 min. The effects of statins on eNOS expression were similar in control and Cav-1 knockdown cells, but the increase in eNOS activity was less pronounced in Cav-1-deficient cells. Statin-triggered cytotoxicity occurred at approximately 10-fold higher drug concentrations (maximal toxicity at 1-10 microM), was sensitive to mevalonate, and was significantly enhanced in the presence of NG-nitro-L-arginine. The overexpression of eNOS induced by clinically relevant concentrations of statins may contribute to the beneficial vascular effects of the drugs in patients. Stimulation of NO synthesis and cytotoxicity appear to share a common initial mechanism but involve distinct downstream signaling cascades that exhibit differential sensitivity to HMG-CoA reductase.
inhibition.

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