# Pravastatin Attenuates Ceramide-Induced Cytotoxicity in Mouse Cerebral Endothelial Cells with HIF-1 Activation and VEGF Upregulation.

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## Abstract

Ceramide is a pro-apoptotic lipid messenger that induces oxidative stress and may mediate apoptosis in cerebral endothelial cells (CECs) induced by TNF-alpha/cycloheximide, lipopolysaccharide, oxidized LDL, IL-1, and amyloid peptide. Exposure of CECs to C2 ceramide for 12 h caused cell death in a concentration-dependent manner, with a LC50 of 30 microM. Statins are inhibitors of 3-hydroxyl-3-methyl coenzyme A reductase which is the rate-limiting enzyme for cholesterol biosynthesis. Pretreatment with pravastatin at 20 microM for 16 h substantially attenuated ceramide cytotoxicity in mouse CECs. Increases in vascular endothelial growth factor (VEGF) expression were detected within 1-3 h after pravastatin treatment. This pravastatin action was accompanied by the activation of hypoxia-inducible factor-1 (HIF-1), a transcription factor known to activate VEGF expression. These results raise the possibility that pravastatin may protect CECs against ceramide-induced death via the HIF-VEGF cascade.