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7β-hydroxycholesterol is antiapoptotic and induces proliferation in human endothelial cells by a ROS-independent ERK-dependent mechanism

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Atherogenic potential of oxidized low density lipoproteins (oxLDL) has been correlated to their content in 7β-hydroxycholesterol (7βOHC) (Brown and Jessup, 1999). oxLDL have a dual effect on endothelial cell viability, inducing apoptosis at high concentrations and proliferation at low concentrations (Galle *et al,* 2001). Considering that 7βOHC is apoptotic for endothelial cells at concentrations ≥ 20 μg/mL (Lizard *et al*, 1999), a study on the effect of lower concentrations of 7βOHC on human umbilical vein endothelial cells (HUVEC) was undertaken. 7βOHC (1-10 μg/ml) significantly increased viability (+150% after 24 h) of growth factor-deprived HUVEC. This effect was due to an increase in proliferation, determined by [^{3}H]thymidine assay, as well as a reduction in HUVEC apoptosis, suggested by a decrease of caspase-3 activation and annexin V+ staining. 7βOHC protected also against staurosporine treatment. Determination of intracellular ROS with CM-H_2DCFDA showed an increase in ROS production by 7βOHC that was reduced by the NAD(P)H oxidase inhibitor hydralazine, however the antiapoptotic and proliferative effects were independent on ROS. Both antiapoptotic and proliferative effect of 7βOHC were blocked by inhibition of MEK with PD98059 or U0126, nevertheless 7βOHC was unable to induce an increase of ERK phosphorylation. The results show that concentrations of 7βOHC below 20 μg/mL are antiapoptotic and induce proliferation in HUVEC. These effects are ROS-independent and are regulated by the MEK/ERK cascade.

Brown and Jessup (1999) *Atherosclerosis* 142: 1-28.
Galle *et al*. (2001) *Kidney Int*. 59: S120-S123.
Lizard *et al*. (1999) *Arterioscler Thromb Vasc Biol*. 19: 1190-1200.