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Oxidized low-density lipoproteins impair endothelial function by inhibiting non-genomic action of thyroid hormone-mediated nitric oxide production in human endothelial cells.

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Abstract

BACKGROUND: Thyroid hormone (TH) plays an important role in the modulation of cardiac function, including contractility and systemic vascular resistance (SVR). 3,5,3'-triiodothyronine (T(3)), the active form of TH, induces the activation of endothelial nitric oxide synthase via PI3K/AKT non-genomic signaling. Hypothyroidism is associated with an increase in SVR and serum low-density lipoproteins (LDL) levels, and accumulation of oxidized LDL (oxLDL) may impair endothelial-dependent vascular relaxation. The aim of this study was to investigate the effects of both native LDL (nLDL) and oxLDL on T(3)-mediated AKT phosphorylation, nitric oxide (NO), and cyclic guanosine monophosphate (cGMP) production in human endothelial cells.

METHODS: Human umbilical vein endothelial cells were exposed to either nLDL or oxLDL for 3 hours and then stimulated with T(3) (10(-7) M) or pretreated with an antioxidant mixture of vitamins E and C for 12 hours before treatment with LDL. An analysis of AKT phosphorylation was performed by Western blot, and NO production was evaluated by using 4,5-diaminofluorescein diacetate. Intracellular production of cGMP was measured by enzymatic immunoassay. LDL oxidation was carried out by incubating LDL with CuSO(4), and α-tocopherol content of LDL was evaluated by high-performance liquid chromatography.

RESULTS: OxLDL impaired T(3)-mediated AKT phosphorylation at serine 473 and significantly decreased the production of both NO (oxLDL+T(3) vs. T(3), 9.79±0.5 AU vs. 80.75±2.8 AU, mean±standard deviation, $p<0.0001$) and cGMP. Furthermore, pretreatment with the antioxidant mixture obviated the inhibitory effect of LDL on T(3) action.

CONCLUSIONS:

The results of this study demonstrate that ***oxLDL may contribute to a blunting of the non-genomic action of T(3)*** *and* ***impair the effect of T(3) on NO and cGMP production in endothelial cells****. These data suggest that oxLDL, apart from inducing the atherosclerotic process,* ***may also promote a mechanism of peripheral resistance to T(3)*** *further amplifying the impact of hypothyroidism on endothelial function by increasing SVR*