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alpha-Lipoic acid induces apoptosis in human colon cancer cells by increasing mitochondrial respiration with a concomitant O₂^{-•}-generation.

Wenzel U, Nickel A, Daniel H.

Molecular Nutrition Unit, Department of Food and Nutrition, Technical University of Munich, Hochfeldweg 2, D-85350, Freising, FRG. uwenzel@wzw.tum.de

Abstract

The antioxidant alpha-lipoic acid (ALA) has been shown to affect a variety of biological processes associated with oxidative stress including cancer. We determined in HT-29 human colon cancer cells whether ALA is able to affect apoptosis, as an important parameter disregulated in tumour development. Exposure of cells to ALA or its reduced form dihydrolipoic acid (DHLA) for 24 h dose dependently increased caspase-3-like activity and was associated with DNA-fragmentation. DHLA but not ALA was able to scavenge cytosolic O₂^{-•} in HT-29 cells whereas both compounds increased O₂^{-•}-generation inside mitochondria. Increased mitochondrial O₂^{-•}-production was preceded by an increased influx of lactate or pyruvate into mitochondria and resulted in the down-regulation of the anti-apoptotic protein bcl-X(L). Mitochondrial O₂^{-•}-generation and apoptosis induced by ALA and DHLA could be prevented by the O₂^{-•}-scavenger benzoquinone. Moreover, when the lactate/pyruvate transporter was inhibited by 5-nitro-2-(3-phenylpropylamino) benzoate, ALA- and DHLA-induced mitochondrial ROS-production and apoptosis were blocked. In contrast to HT-29 cells, no apoptosis was observed in non-transformed human colonocytes in response to ALA or DHLA addition. In conclusion, our study provides evidence that ALA and DHLA can effectively induce apoptosis in human colon cancer cells by a prooxidant mechanism that is initiated by an increased uptake of oxidizable substrates into mitochondria.

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