Akt down regulation by CYP2C9-induced ROS generation mediate mitochondrial-dependent endothelial cell death elicited by natural antioxidants

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High intake of natural antioxidants (NA) from plant-derived foods and beverages is thought to provide cardiovascular benefit. The endothelium plays a pivotal role in cardiovascular homeostasis and for this reason the molecular events resulting from NA actions on endothelial cells (ECs) are actively investigated. Here we show the direct impact of two NA, coumaric acid and resveratrol, on intracellular reactive oxygen species (ROS) generation and cell physiology in human ECs. While at lower doses both NA promoted antioxidant effects, at moderately high doses NA elicited a dose-dependent pro-oxidant effect, which was followed by apoptosis, cell damage and phospho-Akt (p-Akt) down-regulation. Treatment of ECs with the mitochondrial permeability transition pore (MPTP) inhibitor cyclosporine A (CsA), completely prevented oxidative cell damage strongly indicating mitochondrial involvement in NA-induced ECs impairment. NA-induced pro-oxidant effects were counteracted by sulfaphenazole (SPZ), suggesting a role for Cytochrome P450 (CYP) 2C9 in NA-induced toxicity. SPZ also prevented NA-induced p-Akt down-regulation and mitochondrial membrane potential (MMP) impairment indicating that Akt can work downstream of CYP2C9 in mediating cellular responses to NA. Our study shows in a human vascular model that moderately high-doses of NA can induce mitochondrial-dependent cell damage mediated by CYP2C9 and the Akt pathway.

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