Cyanidin-3-O-glucoside protects endothelial cells from Palmitic acid-induced oxidative stress by activating Nrf2 pathway

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Circulating levels of free fatty acids are commonly elevated in patients with metabolic syndrome such as obesity and diabetes, representing one of the main risk factors for endothelial dysfunction in thesediseases. In addition to having an important role in the activation of inflammatory pathways, fatty acids, like palmitic acid, are also implicated in the activation of oxidative stress, not only by uncoupling oxidative phosphorylation and increasing the generation of oxygen species but also by impairing endogenous antioxidant defenses. In this study, we investigated whether Cyanidin-3-O-glucoside (C3G), largely present in human diet and probably the best-known and investigated anthocyanin, recognized as a potent intracellular antioxidant (Speciale et al., 2010), may act as a modulator of gene regulation and signal transduction pathways against palmitate (PA)-induced inflammation and oxidative stress (Kim et al., 2010) in Human Umbelical Vein Endothelial Cells (HUVECs). In particular the effects of C3G on cellular adaptive response, that seems to be regulated through an increase in the translocation of the transcription factor Nrf2 into the nucleus, was studied in order to investigate the molecular mechanism of C3G protective effects.

At this aim, HUVECs were pretreated with C3G (40 μM) for 24h, and then incubated with 100 μM Palmitic Acid (PA) for 3h. Pretreatment with C3G appeared able to prevent at intracellular levels the increase in oxidative stress biomarkers and to improve antioxidant systems (glutathione, Superoxide Dismutase, Total antioxidant status). Furthermore, C3G showed to inhibit both leukocyte adhesion to the endothelial cells and gene expression of adhesion molecules (VCAM-1 and E-selectin) induced by PA exposure. Interestingly, C3G was also able to increase Nrf2 nuclear levels and HO-1 and NQO-1 genes, that are know to be trascriptionally modulated by Nrf2, so supporting a key role of this pathway against PA-induced intracellular oxidative stress.

This study demonstrates that C3G is able to protect HUVECs against oxidative alterations induced by PA, playing an important role in the prevention of diseases associated with oxidative stress. Moreover, the activation of one of the most important adaptive stress response pathways, the Nrf2 pathway, a redox-sensitive regulatory network, support the hypothesis that anthocyanins posses activities and roles that are totally independent on their putative antioxidant capacity but are able to interact with cell functions at different levels.

Kim et al. (2010). *Journal of Endocrinology.* 207, 35–44

Speciale et al.(2010). *J Agric Food Chem*. 24, 12048-54