Caffeic Acid modulates oxidative stress induced by hyperglycemia in endothelial cells: involvement of Nrf2 pathway

D. Fratantonio[1], A. Speciale[1], A. Azzerboni[4], M. Cristani[1], R. Canali[2], L. Natarelli[2], A. Saija[1,3], F. Virgili[2], F. Cimino[1,3]

[1] Dep. Drug Sciences and Health Products, University of Messina, Messina, Italy; [2] National Research Institute on Food and Nutrition (INRAN), Rome, Italy; [3] Consorzio Interuniversitario Istituto Nazionale di Biostrutture e Biosistemi (INBB), Rome; [4] OU of Obstetrics & Gynecology, Policlinico Universitario 'G. Martino', Messina, Italy

Reactive oxygen species (ROS) play an important role in the pathogenesis of diabetic complications and into development of cardiovascular diseases. Nutritional antioxidants are reported to prevent hyperglycemia induced oxidative stress associated with diabetes (McCord et al, 2005) and recent papers revealed that these compounds are able to induce Nuclear factor erythroid 2-related factor 2 (Nrf2) that in turn upregulates the expression of antioxidant genes. Nrf2 pathway is now considered as the main molecular mechanism involved in the protection of the cells from oxidative damage (Speciale et al, 2011).

In the present study we investigated if caffeic acid (CA), a naturally occurring phenolic compound especially abundant in coffee, possesses protective effects againsthighglucose-induced oxidative stress in Human Umbilical Vein Endothelial Cells (HUVECs). HUVECs were exposed to high glucose (HG; 25 mM) to mimic diabetic conditions and/or treated with CA (10 nM) at the same time for 24h. The current study is aimed at examining the effect of CA on cellular redox status biomarkers such as intracellular glutathione (GSH), superoxide (SOD) levels and Total Antioxidant Status (TAS). Furthermore modulation of Nrf2 expression and Nrf2-targeting antioxidant gene expression (heme oxygenase-1 HO-1) in HUVECs was studied.

High glucose exposure reduced GSH, SOD and TAS intracellular levels. Interestingly, CA treatment restored antioxidant levels in HUVECs exposed to HG. Furthermore we observed that CA was able to induce Nrf2 nuclear translocation and HO-1 gene expression.

Our findings suggest important role of Nrf2 pathway in CA endothelial protection. In conclusion we showed that the coordinate induction of endogenous cytoprotective proteins through activation of the Nrf2 pathway might serve as a new therapeutic approach for prevention or treatment of against oxidative stress induced by HG levels.

Speciale et al.(2011). Curr Mol Med. 11(9):770-89.;

McCord et al. (2005). *Biomedicine & Pharmacotherapy*. 57: 139–142