Cyanidin-3-*O*-glucoside ameliorates palmitate-induced insulin resistance: modulation of IKK and JNK induced serine IRS-1 phosphorylation

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Insulin plays a key role in the regulation of glucose and lipid homeostasis in adipose tissue, skeletal muscle and liver; in addition to crucial metabolic actions, insulin exerts desirable effects on the maintenance of physiological endothelial hemodynamic function through its ability to stimulate nitric oxide (NO) release through PI3K/Akt axis. It is well established that increased plasma free fatty acids, including pamitic acid (PA), promote lipotoxicity and cause oxidative stress, inflammation, and insulin resistance in endothelium. Under insulin resistant conditions, endothelial dysfunction is characterized by loss of insulin-mediated vasodilator NO production, increased vasocostrictor endothelin-1 (ET-1) and development of prothrombotic state. Several in vitro and in vivo studies suggest that anthocyanins, natural phenols commonly present in food and vegetables from Mediterranean Diet, exert significant cardiovascular health-promoting effects (Speciale et al., 2010); the molecular mechanism involved in their protective effects seems to be mediated by positive regulation of the transcription factor Nrf2, which in turn downregulates NF-kB proinflammatory pathway (Speciale et al., 2013).

The present study examined , at molecular level, the effects of cyanidin-3-O-glucoside (C3G), a widely distributed anthocyanin, on endothelial dysfunction and insulin resistance in human umbilical vein endothelial cells (HUVECs) induced by PA. Our results confirmed that, in PA-exposed HUVECs, insulin resistance was induced by the specific impairment of insulin IRS1/PI3K/Akt signaling pathway and the downstream reduction of (NO) synthase (eNOS) and then of NO release. Furthermore, PA increased vasocostrictor ET-1 mRNA expression in HUVECs contributing to insulin resistance by impairing insulin hemodynamic effects. Interestingly, C3G pretreatment effectively reversed the effects of PA on PI3K/Akt axis. In particular C3G restored eNOS expression, NO release and ET-1 mRNA levels altered by PA. Furthermore, we demonstrated that PA-induced inhibition of PI3K/Akt axis was due to IRS-1 serine phosphorylation mediated by JNK and IKK. In fact, while the phosphorylation of IRS-1 on tyrosine residue is required for insulin-stimulated responses, the phosphorylation of IRS-1 on serine residues terminates the insulin effects. C3G pretreatment was able to restore IRS-1 alteration induced by PA through JNK and IKK downregulation.

These findings suggested that C3G ameliorates endothelial dysfunction implicated in insulin resistance through modulation of IRS-1 phosphorylation.