PROTECTIVE EFFECTS OF CYANIDIN-3-O-GLUCOSIDE AGAINST PALMITATE-INDUCED INSULIN RESISTANCE IN HUMAN SGBS HYPERTROPHIC ADIPOCYTES

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Introduction: Obesity is a metabolic disorder of multifactorial origin correlated with an elevated morbidity and mortality rates. It predisposes to the metabolic syndrome and is characterized by excess adipose tissue, altered levels of circulating proinflammatory adipokines, imbalances of the adaptive immune system and local and systemic chronic inflammation that can determine the onset of insulin resistance. The relationship between obesity and insulin resistance is based on some endocrine and metabolic adipocytes typical functions. In fact, it has been observed that the increased levels of free fatty acids (FFAs), such as palmitic acid (PA), promote lipotoxicity and determine a state of cellular stress and inflammation with consequent alteration of the insulin signaling pathways with insulin resistance in the adipose tissue. In recent years, epidemiological evidences have shown that anthocyanins, natural phenols commonly present in food and vegetables from Mediterranean Diet, possess not only a high antioxidant and anti-inflammatory activity, but also a marked anti-obesity and insulin sensitizing effect. Therefore, the aim of this work was to evaluate the in vitro potential beneficial effects of cyanidin-3-O-glucoside (C3G), a widely distributed anthocyanin, on insulin resistance induced by high concentrations of PA in human (SGBS) adipocytes, comparing these results with those obtained with murine 3T3-L1cells.

Materials and methods: In all experiments fully differentiated SGBS and 3T3-L1adipocytes were pretreated with different concentrations of C3G (ranging from 1to 20 μM) for 24h and exposed to high concentrations of PA for 24h in order to induce cellular hypertrophy and insulin resistance. In addition, cells were subsequently treated with insulin for 15minutes or 3-6hours for protein and gene expression respectively. The main markers of insulin resistance were evaluated by means of Western blot and Real-time PCR techniques.

Results: To characterize the effect of PA (500 μM) on the insulin signaling at molecular level and to demonstrate the protective effect of C3G in such conditions, we evaluated, in SGBS cells, the mRNA levels of glucose transporter GLUT-1and GLUT-4, hexokinase and adiponectin as markers of insulin sensitivity. The data demonstrated a significant reduction of the gene expression of these markers confirming PA-induced insulin resistance. In the same way the C3G pretreatment, starting from 1μM, dose-dependently restored mRNA levels of the tested genes altered by PA. In addition, these findings were compared to those obtained on 3T3-L1cells. Interestingly, only PA 1mM was able to induce a significant impairment of insulin modulated PI3K/Akt axis in murine adipocytes. Furthermore, the protective effects of C3G pretreatment were dose-dependent but observed at concentrations (5and 10 μM) higher that those effective on in SGBS cells.

Discussions and conclusions: Therefore, these findings demonstrated that C3G ameliorates insulin resistance conditions induced by high concentrations of PA in adipose tissue. The effects observed are supported by the large number of papers reporting that anthocyanins possess a wide range of health-promoting properties targeting specific signal transduction pathways such as PI3K/Akt axis. The results discussed allow us to hypothesize hence a possible application for this natural compound in the prevention and treatment of pathological conditions linked to obesity. However, in human adipocytes, C3G 1μM, which are considered physiologically reachable concentrations, were already effective in improving insulin sensitivity. In addition, human SGBS cells were more sensitive to PA lipotoxicity than murine cells indicating that human cells need to be preferred in in vitro models for obesity research.