**THE CARDIOPROTECTIVE EFFECT OF ISOSTEVIOL ON ENDOTHELIN-1-INDUCED HYPERTROPHY OF CULTURED NEONATAL RAT CARDIOMYOCYTES**

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Aims: Isosteviol is an active derivative of stevioside and also possessing an anti-hypertensive effect in our previous report. Left ventricular hypertrophy is an independent cardiovascular risk factor related to cardiovascular complications in patients with hypertension. Therefore, a decrease in left ventricular mass is a therapeutic goal in these patients. In the present study, we elucidate the anti-hypertrophy and molecular mechanisms of isosteviol on endothelin-1(ET-1)-induced hypertrophy of neonatal rat cardiomyocytes.

Methods: Cultured neonatal rat cardiomyocytes were stimulated with ET-1, [3H]-leucine incorporation, and the beta-myosin heavy chain promoter activity were measured. We also examined the effects of isosteviol on ET-1-induced intracellular ROS generation and the NADPH oxidase activity. The influence of the stress pathway by isosteviol on the increase of ROS by ET-1 and ET-1-induced extracellular signal-regulated kinase (ERK) phosphorylation also examined. ANOVA was used for statistical analysis, p < 0.05 were considered significant.

Results: Isosteviol inhibited the increase of ET-1-induced of [3H]-leucine incorporation and intracellular ROS levels in a concentration-dependent manner. The increase of ROS and NADPH oxidase activity by ET-1 was significantly inhibited by isosteviol and N-acetylcysteine (anti-oxidant). Isosteviol also inhibited ET-1-induced ERK phosphorylation. These data indicate that isosteviol inhibits ET-1-induced the increase of ROS, NADPH oxidase activity, ERK phosphorylation, [3H]-leucine incorporation and subsequent hypertrophy via its antioxidant ability.

Conclusions: The inhibition of NADPH oxidase activity and ROS level in ET-1 stimulated cardiomyocytes by isosteviol were play an important part in its anti-hypertrophy effect. These results support the therapeutic potential of isosteviol in the prevention of cardiomyocyte hypertrophy.