MOST NEGATIVELY CHARGED SUBFRACTION (L5) INDUCES CARDIOMYOCYTES DAMAGE AND REDUCTION OF CARDIAC ATP-SENSITIVE K+ CHANNELS

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Background: Oxidized LDL has been reported as a prognostic predictor of mortality in chronic congestive heart failure patients and is thought to plays a critical role in atherosclerosis. Previously, it was reported that the naturally occurring ox-LDL, L5, which is the most negative subfraction of LDL could lead to apoptosis of endothelial and vascular muscle cells. However, whether L5 may also affect cardiac myocytes directly or not remains unclear. The present study aims to analyze the impact of L5 on cardiomyocyte viability, apoptosis and function of sarcolemmal KATP channels, and to indentify the underling mechanisms.

Methods: Cultured neonatal rat cardiomyocytes (NRCMs) was subjected to L5. Cell viability, apoptosis, CaM kinase II (CaMKII) activity and phosphorylation, kir6.2 expression and function of KATP channels of NRCMs were determined by MTT assay, caspase 3/7 assay, western blot and patch clamp technique respectively.

Results: In NRCMs, L5 (75μg/mL) significantly enhances caspase 3/7 activity (21031±866.3) and decrease viability (0.189±0.008), comparing to phosphate buffered saline (PBS, 6900±303.5, p<0.01, and 0.312±0.009, p<0.01). L5 also decreases the current density of KATP channel, which elicited by pinacidil (20μM) (L5: -18.12 ± 2.23 pA/pF, vs. baseline: -9.67±2.54 pA/pF, p<0.05, n=5), and recovered by 15-min washout (-15.05±1.77 pA/pF) and further back to baseline after applying glibenclamide (-9.24±1.57 pA/pF), a blocker of KATP channels. Accordingly, Kir6.2 expression on NRCMs was decreased by L5 incubation (0.40,fold of PBS, P<0.05). Furthermore, the expression of phospho-CaMKII (Thr286), constitutively active CaMKII, was increased by L5 (2.9 fold of PBS, P<0.05). Moreover, KN93 (a CaMKII inhibitor) attenuated L5-induced apoptosis (6784 ± 127.4 vs. PBS, p=0.73) and decreased IKATP (-8.27±1.14 pA/pF, p<0.05, n=5).

Conclusion: Increased L5 inhibits the activity of KATP channels and promotes CaMKII activation, which might contribute to L5-induced NRCMs apoptosis.