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BSA에 의해 유발된 ER stress가 초대배양된 토끼 근위세뇨관세포의 포도당 수송에 미치는 영향

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Effect of Albumin-induced Endoplasmic Reticulum Stress on α-MG uptake in Renal Proximal Tubular Cells

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Proteinuria is linked with progression to renal failure and induces endoplasmic reticulum (ER) stress in renal tubular cells. ER stress initiates unfolded protein response (UPR) as an adaptive mechanism in metabolic demands to regulate cell function and survival. Therefore, this study examined the effect of bovine albumin serum (BSA) overload- induced ER stress on the level of 14C- α - methyl- D- glucopyranoside (α - MG) uptake and its related signaling pathways in primary cultured renal proximal tubule cells (PTCs). 40 mg/ml BSA stimulated the expression of glucose- regulated protein 78 (GRP 78) as a biomarker of ER stress in immunofluorescence study. In addition, BSA increased the level of α- MG uptake in time and dose dependent manners. BSA stimulated the production of cellular reactive oxygen species (ROS) and BSA- induced increases in α- MG uptake which was blocked by antioxidants such as ascorbic acid or N- acetylcystein (NAC). Peroxisome proliferators- activated receptor (PPAR) γ mRNA expression was stimulated by BSA or troglitazone (PPARγ agonist), but was inhibited by GW9662 (PPARγgantagonist). BSA- induced PPARγ activation was inhibited by antioxidants which also blocked the BSA- induced increase of α- MG uptake. In the experiment of BSA- induced ER stress, the expression of GRP 78 and eukaryotic initiation factor 2α (eIF2α) phosphorylation were increased by BSA or troglitazone; the increases were blocked by GW9662 in Western blotting analysis. Moreover, transfection with GRP78 specific small interfering RNA (siRNA) inhibited the BSA- stimulated α- MG uptake. BSA overload also stimulated phosphorylations of c- jun NH2- terminal kinase (JNK) and nuclear factor- kappa B (NF- κB), which were attenuated by GW9662 or GRP78 siRNA. SP600125 (JNK inhibitor) or SN50 (nuclear translocation inhibitor) effectively blocked the α- MG uptake in PTCs exposed to BSA. Finally, consistent with α - MG uptake experiments, the protein expressions of Na+/glucose cotransporters (SGLTs) were increased by BSA or troglitazone; the increases were significantly blocked by antioxidants, GRP78 siRNA, SP600125, or SN50. In conclusion, BSA overload- stimulated PPARγ activation causes ER stress. Primary cultured renal PTCs in ER stress may subsequently lead to increase glucose uptake to the cells by activation of JNK and NF- κB signal pathways.

Key Words : BSA, ER stress, SGLT