

Cyclic AMP이 신장 근위세뇨관 세포에서 caveolin-1과 F-actin에 의한 SGLT 발현과 세포막 이동에 미치는 영향

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Effect of cAMP on SGLT Expression and Trafficking by Caveolin-1 and F-actin in Renal Proximal Tubule Cells

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We determined the mechanisms involved in adenosine 3',5'-cyclic monophosphate (cAMP)-induced expression regulation and membrane trafficking of sodium-dependent glucose cotransporters (SGLTs) in renal proximal tubule cells (PTCs). PTCs were treated with cAMP analogs, including 8-bromoadenosine (8-Br)-cAMP, selective activators of protein kinase A (PKA) or exchange protein directly activated by cAMP (Epac), and forskolin. These analogs resulted in stimulation of SGLT expression and a-MG uptake by PTCs. 8-Br-cAMP-induced PKA and Epac activation increased phosphorylation of extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (MAPK), and nuclear factor kappa B (NF-kB). Furthermore, cAMP-induced SGLT activity was blocked by treatment with Epac specific small interfering RNA (siRNA), PKA inhibitor (PKI), and inhibitors of ERK, p38 MAPK, or NF-kB. Concomitant with cAMP-induced SGLT expression, cAMP stimulated expression of filamentous actin (F-actin) and caveolin-1 (cav-1) in plasma membrane fractions. This effect was blocked by Epac siRNA or PKI. Moreover, cav-1 siRNA decreased SGLT membrane localization suggesting a role for cav-1 in SGLT trafficking. Treatment with cytochalasin D decreased the amount of cav-1 or SGLTs in filamin immunoprecipitates. Furthermore, TRIO and F-actin binding protein (TRIOBP) siRNA for inhibition of F-actin reorganization, cytochalasin D, cav-1 siRNA, or cholesterol disruptor methyl-beta-cyclodextrin abolished the cAMP-induced increase in a-MG uptake. In conclusion, cAMP-induced Epac and PKA activation upregulated a-MG uptake through SGLT expression via ERK/p38 MAPK/NF-kB and SGLT trafficking from an internal pool into the apical membrane with caveolin-1 via actin reorganization in PTCs.

Key Words: Cyclic AMP, SGLT, caveolin-1