F-C3

Tankyrase/β-catenin 신호전달에 의한 새로운 항이뇨호르몬-의존성 제 2형 수분통로단백 발현의 조절

경북대학교 의학전문대학원

정현준, 김상엽, 김은정, 권태환

Tankyrases/β-catenin Signaling: A Novel Regulatory Signaling Pathway for Vasopressin-induced AQP2 Expression in Kidney Collecting Duct Cells

Hyun Jun Jung, Sang-Yeob Kim, Eunjung Kim, Tae-Hwan Kwon

Kyungpook National University School of Medicine

Aquaporin-2 (AQP2) is the water channel protein expressed in the kidney collecting ducts, which mediates arginine vasopressin (AVP)-induced water reabsorption. AVP induces translocation of AQP2 from intracellular vesicles to the apical plasma membrane and increases the expression of AQP2 mRNA and protein in the collecting duct principal cells via Gsα-mediated cAMP/PKA signaling pathway. Tankyrases (PARP-5) are the isoforms of poly ADP-ribose polymerases (PARPs). Moreover, β-catenin is a transcriptional regulator of Wnt signaling at the downstream of tankyrases and is degradaded by tankyrase inhibition in the presence of Wnt activation. Thus, tankyrases also affect the transcriptional regulation of Wnt-targeting genes via regulation of TCF/β-catenin complex. We aimed to examine as to whether tankyrase/β-catenin signaling could be a novel signaling pathway for vasopressin-regulated AQP2 expression in kidney collecting duct. RT-PCR and immunoblotting showed that tankyrases are expressed in rat kidney and mouse cortical collecting duct cell line (mpkCCDc14 cells). Inhibition of tankyrases activity by XAV939 significantly decreased the induction of AQP2 expression in response to dDAVP in mpkCCDc14 cells. PARsylation assay using biotin-NAD+ as a substrate of tankyrases exhibited that ADP-ribosylated Gsα expression was increased by dDAVP treatment for 24 h or 48 h, whereas it was not seen in the presence of XAV939 co-treatment. This finding suggested that Gsα is a novel target protein of PARsylation by tankyrases. Time-lapse live-cell FRET imaging analysis, however, revealed that XAV939 did not affect the dDAVP- or forskolin-activated cAMP/PKA levels, which could trigger AQP2 transcription through CRE-dependent transcription. This finding suggested that activation of cAMP/PKA pathways in response to dDAVP was independent of PARsylation of Gsα protein. In silico analysis for transcription factor binding sites demonstrated the TCF/LEF binding sites, which are the binding sites of TCF/β-catenin complex for transcription of Wnt-targeting genes, were present in AQP2 promoter region. Importantly, siRNA-mediated specific knockdown of β-catenin in mpkCCDc14 cells significantly decreased the dDAVP-induced up-regulation of AQP2 in mpkCCDc14 cells. Taken together, tankyrases/β-catenin signaling could be a novel regulatory signaling pathway for vasopressin-regulated AQP2 expression in kidney collecting duct cells.

Key Words: 제2형수분통로단백, 항이뇨호르몬, 신호전달
Aquaporin-2, Vasopressin, Tankyrase/beta-catenin