P-101

NITRIC OXIDE 계의 조절은 TWIST-2와 E-CADHERIN을 통해 신장의 KLOTHO 발현을 조절할 수 있다

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The Regulation of The Nitric Oxide System Can Modulate The Klotho Expression in Kidney Via TWIST-2 And E-cadherin

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Aim: The klotho was originally identified as an anti-aging peptide, and was subsequently found to have various biologic actions. Animal experiments clearly showed that renal klotho was lacking in acute kidney injury from a variety of causes including ischemia/reperfusion injury. We investigated whether there was the relationship between NO (nitric oxide) system and klotho expression in kidney, and also investigated TWIST (basic helix-loop-helix transcription factors)-1 and 2, E-cadherin as a possible pathway of such relationship.

Methods: The 10th weeks Sprague-Dawley rats (N=24, 200 g, male) were divided into four groups. Next, we fed low salt diet to control group (N=6), and gave drinking water mixed with L-NAME 1 mg/mL to L-NAME group (N=6), and udenafil 5 mg by subcutaneous injection to Udenafil group (N=6), L-NAME and udenafil to the L-NAME / Udenafil group (N=6) for 4 weeks. On the 28th day, we collected blood and urine samples, and took the kidneys from rats. And then, we measured the level of serum creatinine, urine nitrate/nitrite, urine cGMP by ELISA, and conducted immunohistochemical staining, RT-PCR for klotho, TWIST 1 and 2, E-cadherin.

Results: The serum creatinine and urine nitrate/nitrite level did not show statistical differences between four groups. On the other hand, between control, L-NAME, Udenafil and L-NAME/Udenatil groups, there were significant differences in urine cGMP (2.59±0.88, 1.79±0.99, 1.20±0.52, 0.69±0.59 pmol/well, p=0.0087), klotho mRNA expression (0.98±0.01, 0.30±0.11, 0.68±0.15, 0.54±0.26, p=0.0017), TWIST-2 mRNA expression (1.90±1.65, 139.27±114.87, 10.33±8.42, 20.19±12.25, p=0.0163), and E-cadherin mRNA expression (0.64±0.32, 1.57±0.97, 1.24±1.27, 13.82±3.04, p=0.0029). Therefore, the blocking of NO system decreased klotho expression with TWIST-2 increase, while the induction of NO system increased klotho expression with E-cadherin increase.

Conclusions: This study demonstrates that the regulation of NO system can modulate the klotho expression in kidney via TWIST-2 and E-cadherin pathway.

Key Words: TWIST-2, E-cadherin, Klotho