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신장에서의 노화 관련 Nrf2-Keap1 signal 시스템의 변화

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Age-related Nrf2-Keap1 Signaling System Change in the Kidney

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Background: Aging is a multifactorial process characterized by a progressive decline in physiological function. Decreased kidney function is associated with cardiovascular disease and mortality. Therefore, increasing our insight into kidney aging by understanding the anatomic, physiologic, and pathologic changes of aging in the kidney is important to prevent disastrous outcomes in elderly people.
Methods: Male 2-, 12-, and 24-month-old C57/BL6 mice were used in this study. We measured histological change, oxidative stress, aging-related protein expression in the kidneys.
Results: 24-month-old mice displayed increased albuminuria (16.5±1.1 ng/24hr vs. 41.5±8.4 ng/24hr, 65.5±10.4 ng/24hr; $p<0.05$ vs. 2M). Creatinine clearance decreased with aging, although this was not statistically significant (0.39±0.04 ml/min vs. 0.21±0.05 ml/min; $p>0.05$ vs. 12M). There were increases in mesangial volume (10.1±1.19% vs. 17.2±2%, 36.3±3.58%) and tubulointerstitial fibrosis (0.83±0.11% vs. 0.87±0.07%, 15.9±1.99%) in 24-month-old mice ($p<0.01$). There were also increases in F4/80 expression (0.11±0.06% vs. 0.4±0.11%, 2.5±0.52%; $p<0.01$) and in apoptosis detected by TUNEL (positive mesangial cells, 0.27±0.09% vs. 0.53±0.12%, 2.6±0.63%; glomerulus and cortical tubular areas, 0.27±0.09% vs. 0.53±0.12%, 2.8±0.67%.01). Urine isoprostane (7.4±0.3% vs. 19.4±0.78 %, 21.9±1.9%) excretion increased with aging and SOD1 (1±0.09 fold vs. 0.78±0.07 fold, 0.69±0.01 fold) and SOD2 (1±0.21 fold vs. 0.73±0.03 fold, 0.56±0.09 fold) were decreased in 24-month-old mice. Expression of Nrf2 in total protein (1±0.2 fold vs. 1.02±0.12 fold, 1.31±0.24 fold) was not decreased in 24-month-old mice. However, Nrf2 expression in nuclear (1±0.44 fold vs. 1.94±0.7 fold, 1.61±0.46 fold; $p<0.05$ vs. 24M) and in nuclear/total protein ratio (1±0.82 fold vs. 1.83±0.6 fold, 1.08±0.38 fold; $p<0.05$ vs. 24M) were decreased in 24-month-old mice. Keap1 expression (1±0.16 fold vs. 0.93±0.12 fold, 1.15±0.35 fold) was increased in 24-month-old mice compared with other groups. HO-1 (1±0.08 fold vs. 9.39±0.81 fold, 8.87±0.51 fold) and NQO-1 (1±0.01 fold vs. 1.18±0.19 fold, 1.04±0.24 fold) were decreased in 24-month-old mice compared with 12-month-old mice.
Conclusions: Nrf2 suppression and Keap1 activation with aging could induce oxidative stress, leading to decrease in antioxidant gene expression such as HO-1 and NQQ-1.

Key Words: 신장, 노화
Kidney, Aging, Nrf2