Nephrology Dialysis Transplantation 30 (Supplement 3): iii3–iii5, 2015
doi:10.1093/ndt/gfv136.1

EXPERIMENTAL AKI

FO006 **CHRONIC NICOTINE EXPOSURE DOWNREGULATES RENAL KLOTHO EXPRESSION AND TRIGGERS DIFFERENT RENAL AND AUTONOMIC RESPONSES ACCORDING TO THE KLOTHO STATUS IN MICE**

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Introduction and Aims: Klotho (Kl) is a single-pass transmembrane and secreted protein that is expressed predominantly by distal kidney tubules and is related to calcium-phosphorus metabolism, regulation of ion channels, intracellular signaling pathways, and longevity. Kl deficiency aggravates acute kidney injury (AKI) and renal fibrosis. Smoking is associated with alterations similar to those related to aging, such as emphysema, vascular disease, and renal failure progression. Nicotine (NIC), a major compound of tobacco and in electronic cigarettes, worsens kidney injury in animal models of AKI, diabetes, nephritis, and subtotal nephrectomy. Here, we investigated renal expression of Kl in a mouse model of chronic NIC exposure and compared wild type (Kl+/+) and Kl deficient mice (Kl+/−) in terms of the effects of that exposure.
Methods: 8- to 12-week old male Kl+/− and Kl+/+ mice received NIC (200 μg/ml) or vehicle (saccharine [SAC] 2%) in drinking water. After 4 weeks, we evaluated plasma levels of cotinine, antidiuretic hormone (ADH), parathyroid hormone (PTH) and aldosterone; mean arterial pressure (MAP); baroreflex sensitivity (BRS), calculated as the ratio of Delta heart rate/Delta MAP; ions in serum and urine; glomerular filtration rate (GFR, fluorescein isothiocyanate-inulin clearance); protein expression of (immunoblotting for) Kl and α7 nicotinic acetylcholine receptor (α7nAChR); and Kl mRNA (qPCR). Data are mean ± SEM.
Results: Plasma levels of cotinine (102.90 ± 5.56 ng/mL) were similar to those seen in human smokers. NIC exposure promoted a significant decline in renal Kl expression of protein (SAC Kl+/+ 100 ± 24.82% vs. NIC Kl+/+ 25.11 ± 4.71%; $p < 0.05$) and mRNA (SAC Kl+/+ 1.15 ±0.26 vs. NIC Kl+/+ 0.69 ± 0.17). After NIC exposure, only Kl+/+ mice showed lower GFR (SAC Kl+/+ 191.7 ± 6.77 vs. NIC Kl+/+ 161.5 ± 5.39 μl/min; $p < 0.05$; SAC Kl+/− 175.2 ± 9.47 vs. NIC Kl+/− 177.2 ± 5.65 μl/min; $p = 0.86$), α7nAChR protein downregulation (SAC Kl+/+ 101.2 ± 4.17% vs. NIC Kl+/+ 72.86 ± 8.0%; $p < 0.05$; SAC Kl+/− 96.86 ± 1.42 vs. NIC Kl+/− 97.14 ± 3.43%; $p = 0.90$), and augmented sympathetic response (BRS: SAC Kl+/+ 2.0 ± 0.62 vs. NIC Kl +/+ 5.50 ± 1.3 vs. SAC Kl+/− 2.77 ± 1.01 vs. NIC Kl+/− 3.88 ± 0.7 bpm/mmHg, $p < 0.05$). However, Kl+/− mice presented higher urea plasma levels (SAC Kl+/+ 52 ± 2.76; SAC Kl+/− 48.38± 2.91; NIC Kl+/+ 57.38 ± 2.56; NIC Kl+/− 60 ± 3.04 mg/dL; $p < 0.05$) and elevated aldosterone levels when exposed to NIC (SAC Kl+/+ 195.1 ± 39.94; SAC Kl+/− 202.3 ± 28.67; NIC Kl+/+ 342.0 ± 50.53; NIC Kl+/− 521.9 ± 80.92 pg/mL; $p < 0.001$). There were no differences among groups in terms of MAP, ions (in plasma or urine), fluid intake, ADH, or PTH.
Conclusions: We can conclude that NIC downregulates Kl expression, and that the expected renal and autonomic responses to NIC exposure are modified in Kl+/− mice. Our results also suggest that nicotine-induced worsening of kidney injury can result from a lack of adequate adaptive responses in Kl deficiency.