ALDOSTERONE ANTAGONISTS - NOVEL ANTIFIBROTIC THERAPY IN CKD PATIENTS

Alexei Bagrov[1], Kaja Metsküla[2], Mai Rosenberg[2]

[1] Padakonn Pharma Ltd., Estonia

[2] Institute of Clinical Medicine, University of Tartu, Estonia

There is no cure for chronic kidney disease (CKD) although current treatment (RAAS blockers, SGLT2i) can slow its progression. Recently an accelerating pace of discovery regarding the cellular/molecular basis for CKD started, including novel biomarkers, amino-terminal type III procollagen peptide (PIIINP), carboxy-terminal type I procollagen peptide (PICP), FGF23, marinobufagenin (MBG). MBG, Na/K-ATPase (NKA) inhibitor is involved in renal sodium transport and implicated in fibrosis and pathogenesis of CKD, and preeclampsia (PE). We demonstrated that MBG induces fibrosis via Fli1, a negative regulator of collagen type-1 synthesis, and MBG-sensitive NKA inhibition is reversed by mineralocorticoid antagonists. CKD and PE were associated with higher plasma MBG levels, a decrease in Fli1 and an increase in collagen-1 in the PE umbilical arteries vs. those from the controls ($p< 0.01$). Rings of arteries from the subjects with PE and rats with CKD exhibited impaired relaxant effect to sodium nitroprusside vs. control vessels. The effects of CKD and PE on Fli1 and collagen-1 were blocked by in vitro treatment of umbilical arteries with 10 μmol/L canrenone.

Therapeutic strategies for antagonism of the effects of MBG involve immunoneutralization of heightened levels with anti-MBG antibodies in PE and CKD. Aldosterone antagonists reduce CTS binding to the NKA and alleviate hypertension and fibrosis in CKD. Our ongoing study tests the hypothesis that CKD patients receiving spironolactone have lower MBG levels.

Novel treatment of CKD involves the use of mineralocorticoid receptor antagonists (KDIGO 2024) but the assessment of increased cardiorenal risk is needed for the rationale of novel clinical trials. MBG represents potential therapeutic target in CKD and PE.