Chronic kidney injury and hypertension associate with increased urinary succinate levels

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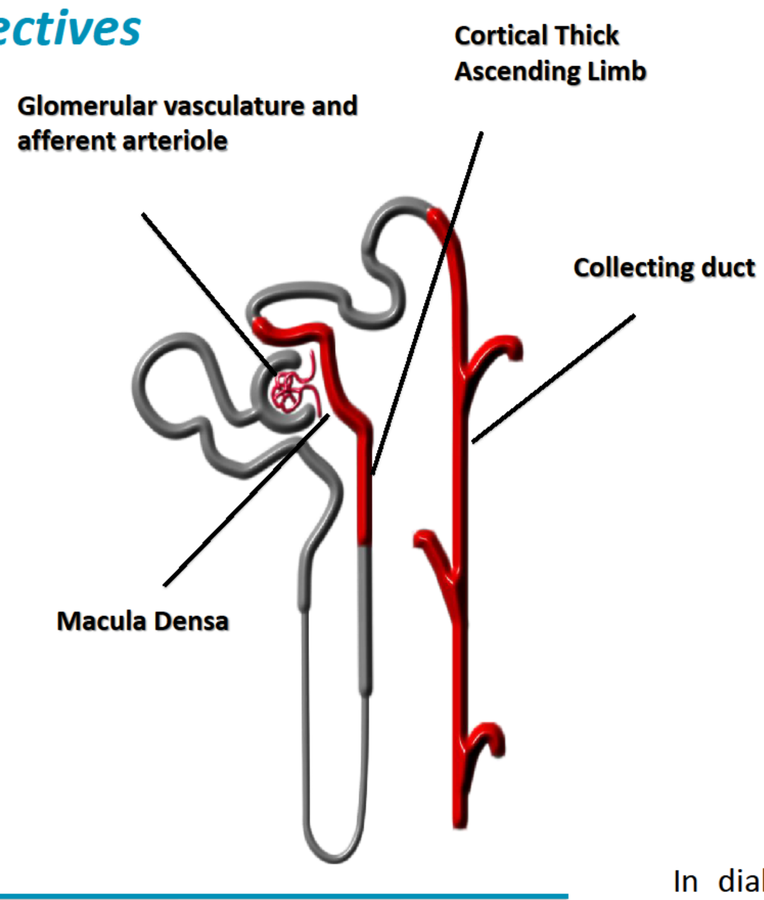
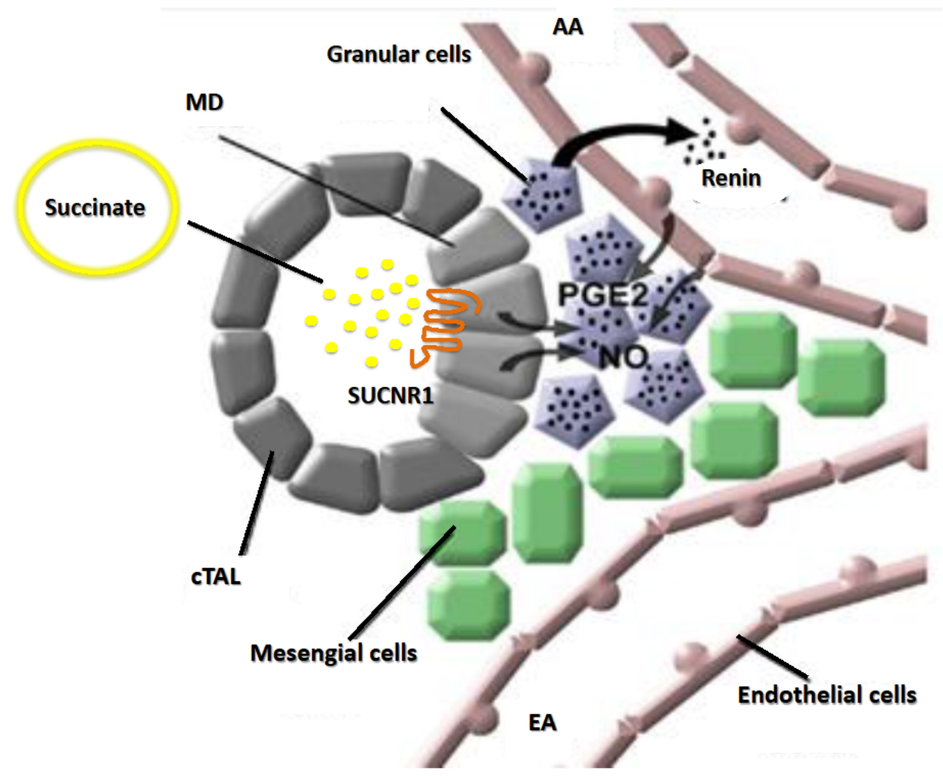
Introduction and objectives

SUCNR1 is expressed in several parts of nephron (red in left panel)1. It contributes to renin release from the Juxtaglomerular apparatus (right panel)2. Succinate receptor activation on macula densa (MD) cells or in endothelial cells of the afferent arteriole (AA) induce the release of prostaglandin E2 (PGE2) and nitric oxide (NO), which trigger the release of renin from granular cells of the juxtaglomerular apparatus (JGA)3.



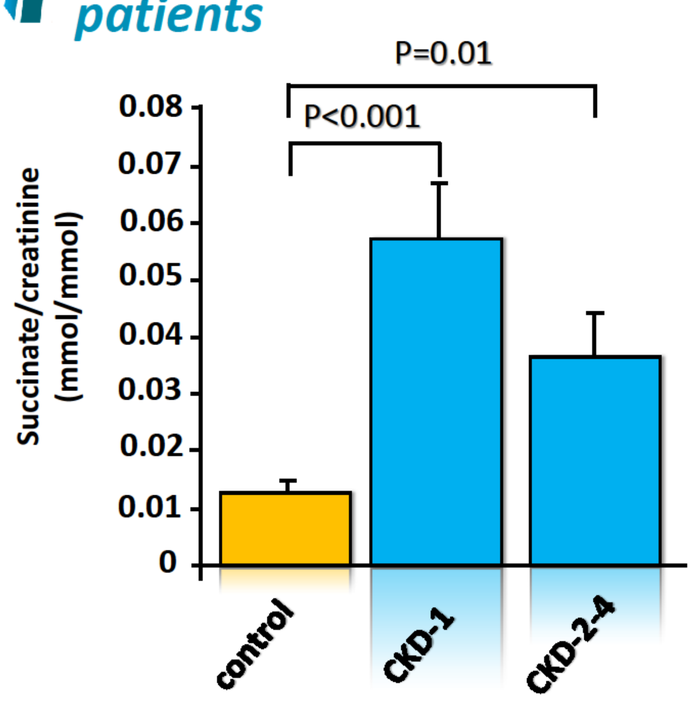


In diabetes mellitus, ischemia/reperfusion injury, or other oxidative stress conditions, functioning of mitochondria is affected, resulting in the release of the Krebs cycle intermediate succinate into the cytoplasm and to the extracellular environment. The renal succinate receptor SUCNR1 senses succinate[4]. As it recently emerged as an activator of RAAS (renin-angiotensin-aldosterone system) and pro-fibrotic events in DM1 (Diabetes mellitus type 1) and hypertension[5], we measured urinary succinate excretion in renal diseases to identify disorders in which SUCNR1 may play a role.

Method

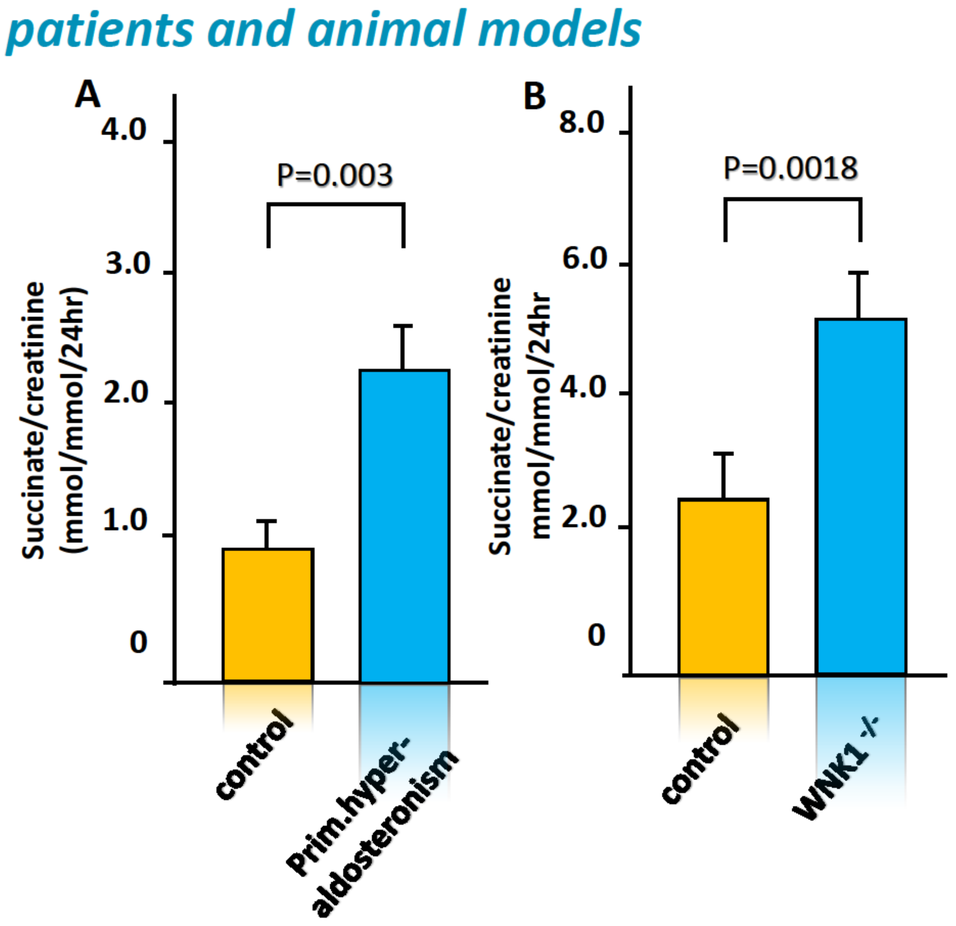
An enzymatic assay optimized for low-volume measurements was used to measure urinary succinate concentration. All the values obtained from the assay were corrected for urinary creatinine levels. P-values <0.05 were considered significant.

Renal succinate release is increased in CKD patients



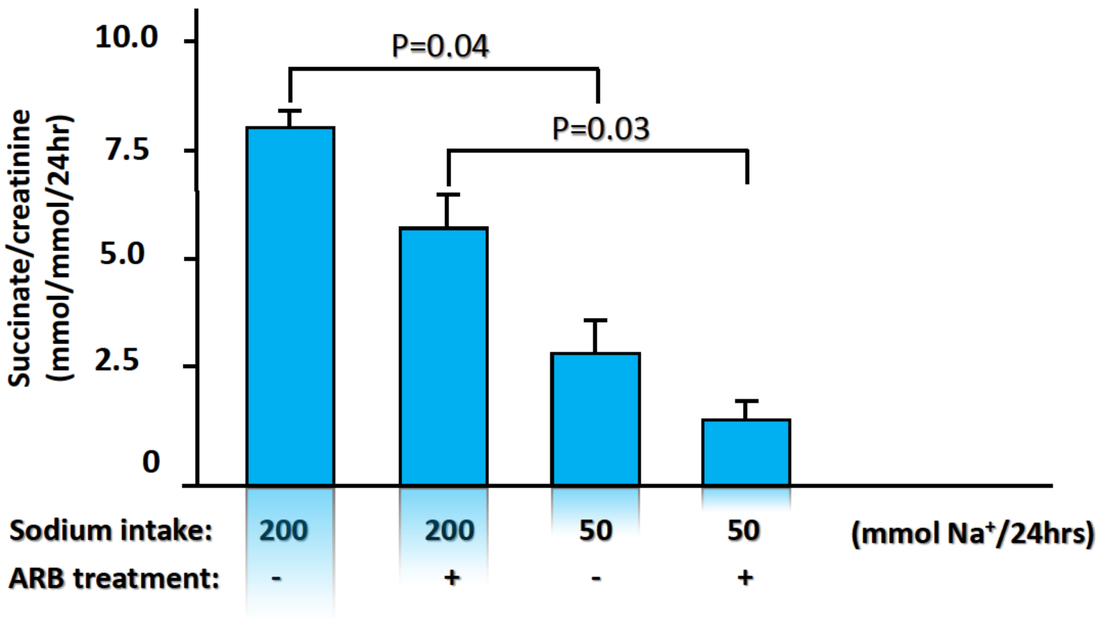
Spot urines of stage 1 (CKD-1; n=10) and stage 2-4 CKD (CKD-2-4; n=10) patients, and of healthy controls (n=12) were analyzed for succinate levels using our microfluid enzymatic assay. Succinate levels were normalized for urinary creatinine levels.

Succinate release is increased in hypertensive patients and animal models



Urinary succinate levels were 1.4 fold higher in primary aldosteronism patients versus controls and 1.7 fold higher in a mouse model of Familial Hyperkalemic Hypertension (FHHt) with WNK1 (WNK lysine deficient protein kinase 1) mutations vs. wild-type littermates.

Urinary succinate excretion in CKD patients correlates with hypertension and proteinuria



In hypertensive CKD patients treated with angiotensin-converting-enzyme (ACE) inhibitors, urinary succinate decreased 3.1 fold following use of Angiotensin receptor blockers (ARBs) and 2.7 fold when subjected to a low-sodium diet. In contrast, subjecting healthy individuals to a high/low sodium diet for 5 days, or adrenalectomized rats infused with aldosteron for 1-5 days did not change urinary succinate levels (data not shown).

Conclusions

I. Renal succinate release is increased in all animal models and patients with affected renal function associated with chronic oxidative stress.
II. With hypertensive CKD patients, urinary succinate levels correlated with the extent of sodium intake, hypertension and proteinuria.
III. As urinary succinate activates SUCNR1, these data indicate to a role for SUCNR1 in activation of the intrarenal RAAS system and/or renal fibrosis as are commonly observed in these chronic renal disorders.

References

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