Modulation of adenosine receptor expression in the proximal tubule: a novel adaptive mechanism to regulate renal salt and water metabolism

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ABOUT 180 LITERS OF FILTRATE are produced by the human kidneys every day, with more than 99% of the filtered salt and water being subsequently reabsorbed along the nephron. In view of this high level of renal filtration, even slight alterations in the balance between filtration and reabsorption will result in potentially life-threatening derangements of electrolyte and volume balance. Consequently, the need for tight regulation of glomerular filtration and tubular reabsorption resulted in the evolution of multiple mechanisms that enable the kidney to adapt to changes in requirements for the conservation of salt and water.

Adenosine, similarly to other regulators of renal function (e.g., angiotensin II), is part of a regulatory network that influences both vascular and tubular functions in the kidney. Consequently, adenosine facilitates adaptation of the kidney to varying reabsorptive needs by modulating both glomerular filtration rate (GFR) and tubular reabsorption. The key vascular function of adenosine, involving the control of GFR via the tubuloglomerular feedback mechanism, is well established. Thus A1 adenosine receptor (A1-AR)-deficient mice lack the tubuloglomerular feedback control of GFR (6, 23). In addition to controlling pregglomerular resistance via A1-AR, adenosine influences renal concentrating ability by modulating renal medullary blood flow through activation of A2 receptors (25). With regard to the tubular function of adenosine, experimental evidence suggests that the overall effect of adenosine on tubular reabsorption is stimulatory. Thus both acute nonspecific adenosine receptor antagonism and specific blockade of A1-AR both result in increased natriuresis and diuresis, in part due to reduced proximal tubular reabsorption (2, 3, 5, 24).

Consistent with the antinatriuretic and antidiuretic effects of adenosine being mediated by A1-AR, nonspecific adenosine receptor antagonists like theophylline and caffeine induce natriuresis and diuresis in wild-type mice but have no effect on renal salt and water excretion in A1-AR-deficient mice (20).

What, then, is the effect of a cup of coffee on natriuresis and diuresis in humans? The answer to this question is not as clear as one might think. In studies of short-term application of high doses of caffeine, natriuresis and diuresis were induced in healthy volunteers, but there was little effect when subjects were adapted to chronic caffeine ingestion, suggesting some desensitization mechanisms (1, 4, 5, 13, 19).

The study by Kulick and coworkers (17) now offers important new insights into the involvement of adenosine in long-term adaptation of the kidney to varying reabsorptive needs. Using microdissection and micropuncture techniques, the authors show that chronic exposure of rats to a salt-restricted diet leads to an increased expression of A1-AR in the proximal tubule, accompanied by an enhanced A1-AR-dependent reabsorptive activity. Although regulation of A1AR by changes in chronic salt intake has been shown before (22, 26), this is the first report to indicate that A1-AR expression in the proximal tubule participates in functional adaptive changes in the kidney during salt deficiency. The functional in vivo relevance of A1-AR regulation in the proximal tubule requires the presence of adenosine locally. Although the exact source of adenosine in the proximal tubule is unknown, the presence of concentrating and equilibrative nucleoside transporters (CNTs and ENTs) in the renal cortex suggests that adenosine might be released from the intracellular space (15, 21).

In addition, high levels of ecto-5′-nucleotidase (CD73) are found in the brush border of proximal tubular cells, likely accounting for local extracellular generation of adenosine (9, 18). Kulick et al. (17) show by the use of in vivo micropuncture techniques that addition of adenosine deaminase (which converts adenosine into inosine) to the artificial perfusate inhibits proximal tubule reabsorption, similarly to local A1-AR antagonism. Since adenosine deaminase, when applied to the perfusate, presumably acts in the tubular lumen, its negative effect on reabsorption would be in accordance with local generation of adenosine on the apical aspect of proximal tubular cells and/or release of adenosine from these cells.

Although Kulick et al. do not address the mechanisms of the A1-AR-dependent increase in proximal tubular fluid reabsorption during chronic salt deficiency, Na+/H+ exchanger 3 is a likely candidate to mediate increased Na+ reabsorption, as it is the major Na+ entry pathway in the proximal tubule. In fact, adenosine has been shown to modulate Na+/H+ exchanger 3 activity in vitro (11). If this proves to be the case in vivo, adenosine and angiotensin II would share the same regulatory end point in proximal tubular cells (12, 14, 16). Furthermore, in vitro studies suggest that A1-AR activation may also stimulate proximal tubular Na+/glucose and Na+/phosphate co-transport (7, 2, 10).

According to the traditional view, adaptive changes in the kidney tubular system, e.g., in response to salt restriction, primarily take place in the thick ascending limb of Henle and, even more relevant, in the distal convoluted tubule and the collecting duct. These are the sites where classic hormones like aldosterone and vasopressin modulate renal salt and water reabsorption. The study by Kulick et al. (17), however, reminds us that it is the proximal tubule where the bulk of the filtered load is reabsorbed; consequently, all long-term regulatory mechanisms that affect the proximal tubule could have considerable impact on overall renal reabsorptive capacity.

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