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New insight into adenosine receptor control of salt and fluid homeostasis

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The control of salt homeostasis is essential in complex organisms with closed circulatory system and the kidney regulates this salt balance by modulating the connection between renal glomeruli and tubules.[1] Indeed, the glomeruli respond to changes in salt delivery to the tubules through the tubuloglomerular feedback (TGF), whereas tubules respond to changes in Glomerular Filtration Rate (GFR) in the glomeruli with the glomerulotubular balance (GTB). The TGF-GTB system contributes to the kidney's ability to regulate renal microcirculation, fluid homeostasis and blood pressure. It compensates for approximately 66% of an outside disturbance such as changes in salt and fluid intake.[1]

In the TGF, changes of salt concentration in the tubular fluid at the end of the thick ascending limb of loop of Henle are sensed by the macula densa cells and result in inverse change in GFR.[2,3] As a consequence of the TGF, salt and fluid delivery to the distal nephron is kept within certain limits, facilitating the adjustments of re-absorption along the late part of the nephron. The mechanism by which the macular densa converts the luminal salt and fluid signal into the signaling of one or more autocrine mediator(s) has been under debate until recent findings on the indispensable role of adenosine in mediating the underlined mechanism.[4]

GTB refers to the ability of the proximal tubule segment of the kidney to adjust salt and fluid transport in proportion to variations of the GFR. An involvement of changes merely of the net re-absorption pressure in the peritubular capillary has failed to fully explain GTB. Recent models favor mechanisms underlying balanced tubular re-absorption that include both peritubular capillary effects and luminal factors which directly modulate proximal tubular transport.[5–7] Specifically, changes in renal Na^+-H^+ exchanger-3 (NHE3) activity, which is of major importance for the maintenance of the trans-tubular Na^+ re-absorption homeostasis and acid-base balance in the proximal tubule, were found to associate with flow-dependent transport. NHE3 activity was enhanced with an increase in luminal flow rate[8] and NHE3 kinetic parameters stratified according to decreased, normal, and increased GFR.[9] Consistent with NHE3 being involved in the control of GTB are studies in NHE3-deficient mice, where it was shown that GTB is significantly reduced.[10] The cellular signals from torque to NHE3 remain to be delineated. Nevertheless, one recurring theme in descriptions of transport regulation has been the targeting of both luminal and peritubular membranes in a coordinated fashion by one (or more) hormones.

Adenosine is a purine nucleoside produced locally in normoxic kidneys. It acts via activation of specific G protein-coupled adenosine receptor subtypes (A1, A2A, A2B and A3).[4] Interestingly, the renal content of adenosine is increased of several folds within few minutes of renal ischemia. This increase in adenosine concentration is completely blocked by inhibition of salt transport indicating that adenosine generation and release is dependent on salt re-absorption and on a compromise balance between energy supply and expenditure, e.g. when salt-re-absorption, hence transport work, is increased[11] or when oxygen supply and ATP content is limited such as during ischemia.[12–14]

Osswald and coworkers first proposed that local generation of adenosine, as a consequence of increased salt transport, may elicit TGF-induced afferent arteriole vasoconstriction.[15] Studies have revealed that mice deficient of adenosine receptor 1 (A1R) lack the TGF,[16,17] confirming what was first suggested by Osswald and colleagues.[15] The proposed model of adenosine action foresees that an increase in concentration-dependent update of salt and potassium by the Na^+-K^+-$2Cl^-$ co-transporter leads to an enhanced hydrolysis of ATP in part due to the activity of the basolateral Na^+-K^+-ATPase, which would result in a transport dependent intra- and extracellular generation of adenosine. Extracellular adenosine via activation of A1R would trigger an increase in intracellular calcium concentration in the smooth muscle cells and vasoconstriction of the afferent arteriole.[4]

We propose that in addition and in parallel of being a key mediator of TGF, adenosine is that fundamental humoral signal that controls GTB. Our proposition is based on several evidences. ARs are expressed on both luminal and peritubular membranes in the kidney[4] and GTB is suppressed in A1R deficient mice.[18] Adenosine is released by renal endothelial cells in response to changes in blood flow and ARs expressed on endothelial cells control vascular tone. Adenosine, via ARs expressed in renal tubules,[19,20] directly regulates salt and fluid transport, in addition to and independent from their hemodynamic effects. Furthermore, we found that A1R activation exerts a bimodal effect on NHE3 activity: a low concentration of A1R agonists stimulates NHE3 activity, while a high concentration of A1R agonists inactivates NHE3 activity. A1R antagonists block both effects.[21,22] Our hypothesis is that the adenosine released by both endothelial and epithelial cells cooperatively controls salt and fluid re-absorption in response to change in GFR. On one hand, adenosine receptors in the endothelium would affect net re-absorption pressure in the peritubular capillary possibly by modulating the capillary vascular tone. On the other hand, adenosine receptors in the epithelium would modulate directly salt and fluid re-absorption by regulation of NHE3 activity. Interestingly, the dual effect induced by adenosine receptor activation on NHE3 activity might be the mechanism by which adenosine switches from a phase of increased to a phase of decreased salt and fluid re-absorption. This dual effect is depended on adenosine

concentration and, hence, Na^+-transport work and is medicated by A1R activation. In summary, A1R-dependent adenosine action via regulation of TGF-GTB system is a key signaling mechanism in the control of renal salt and fluid handling. Modulation of A1R activation might be fundamental in restoring compromised extracellular body fluid volume and composition, blood volume and pressure.

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Conflict of interest

The author declares no conflict of interest.

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