A Recipe for Salt and Blood Pressure Regulation

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Salt has been used as a food preservative and part of the human diet for thousands of years. Consequently, human dietary sodium chloride intake is significantly higher than that needed to sustain life. Fortunately, kidneys function to regulate sodium chloride excretion to maintain proper levels of sodium chloride and extracellular volume when dietary salt intake changes. If the kidneys are properly functioning, then an increase in dietary salt intake results in increased sodium chloride excretion (natriuresis), and extracellular fluid volume remains unchanged. On the other hand, if the kidneys do not function properly to excrete sodium chloride, then extracellular fluid volume expansion occurs, and an elevation in blood pressure is required to bring extracellular fluid volume and plasma sodium back to homeostatic levels.

The report by Liclican et al1 in this issue of Hypertension provides convincing evidence that a properly functioning axis that includes adenosine2A (A2A) receptors and epoxyeicosatrienoic acids (EETs) is required for the kidneys to respond to increased dietary salt intake.

A2A Receptors and EETs: Dietary Salt and Blood Pressure

A balance between salt intake and salt excretion is maintained by a coordinated effort that relies heavily on proper kidney function. When dietary salt intake is increased, there are neural, hormonal, and paracrine factors, as well as the proper function of renal blood vessels and tubular epithelial cell transporters, working in unison to excrete the excess salt. EETs have been demonstrated to be an essential component of this coordinated renal natriuretic response. High dietary salt has been demonstrated to increase renal cytochrome P450 2C (CYP2C) enzymes that are responsible for generating EETs.1–4 Pharmacological inhibition or genetic manipulation to decrease CYP2C enzymes results in dietary high salt–induced elevations in blood pressure.1–4 Likewise, salt-sensitive animal models of hypertension demonstrate an inability to increase renal CYP2C expression in response to a high-salt diet.1–4

The findings by Liclican et al1 in this issue of Hypertension further demonstrate in Dahl salt-resistant (SR) rats that increasing dietary salt increased EET levels in the renal cortex and medulla. Additional evidence is presented that A2A receptor activation is required for the increase in renal EET levels in response to high dietary salt intake. When the A2A receptor antagonist ZM241385 was administered to Dahl SR rats, renal EETs did not increase, and blood pressure did increase in response to high dietary salt. These findings are in agreement with previous studies conducted by this group demonstrating that Dahl SR but not Dahl salt-sensitive rats had an increase in renal cortical and medulla CYP2C and adenosine A2A receptor expression in response to a high-salt diet.5 This previous study also demonstrated that the Dahl salt-sensitive rats did not increase renal EETs in response to a nonselective adenosine analogue.5 Therefore, an axis of A2A receptors to EETs is required for the kidneys to properly respond to increased dietary salt intake.

The exact mechanism responsible for A2A receptor regulation and activation in response to a high-salt diet responsible for the natriuresis remains speculative. There is clear evidence that increased renal expression of the A2A receptors is required for the natriuresis in response to increased dietary salt.1,5 What is less clear is whether increases in renal adenosine levels are necessary for the kidney to increase sodium excretion. Urinary purine levels increase in Dahl SR but not in Dahl salt-sensitive rats in response to high dietary salt.5 Then again, urinary purine levels and plasma adenosine levels are elevated in Dahl salt-sensitive compared with Dahl SR rats.5 Thus, renal A2A receptor activation is required, but it is still not clear whether increased adenosine levels are necessary for the natriuretic response in the Dahl SR rat.

A2A receptor activation and subsequent EET actions at the renal vascular and tubular levels could operate in concert to produce increased sodium excretion (Figure). One aspect thought to be necessary for increased sodium excretion in response to dietary salt is an increase in renal blood flow. Renal preglomerular microvessel dilation occurs in response to A2A receptor activation or EETs.6 Recent studies also demonstrated that synthesized EETs are necessary for the renal vasodilation to adenosine and A2A receptor activation.6–8 On the basis of these findings, one can postulate that the increased renal CYP2C expression observed does not require A2A receptor activation but is required for natriuresis in response to a high-salt diet. Interestingly, adenosine-mediated dilation in the cerebral circulation has been linked to adenosine2A receptor activation and the synthesis and release of EETs.9 The possible contribu-
tion of the adenosine$_{2B}$, as well as other adenosine receptors, to renal hemodynamics in response to a high-salt diet remains unknown.

Another aspect that is necessary for increased sodium excretion in response to dietary salt is decreased tubular sodium reabsorption. Interestingly, A$_{2A}$ receptors and EETs could interact on tubular sodium transport to contribute to natriuresis. CYP2C protein expression in the rat cortical collecting duct and thick ascending limb increases and decreases in response to corresponding changes in dietary sodium.$^{10}$ In addition, patch-clamp experiments conducted in rat cortical collecting duct cells have demonstrated that 11,12-EET inhibits epithelial sodium channel activity.$^{10,11}$ However, adenosine activation of the adenosine$_1$ but not the A$_{2A}$ receptors was linked to the ability of EETs to inhibit cortical collecting duct epithelial sodium channel activity.$^{11}$ Thus, the contributions of the adenosine$_1$ receptors and 11,12-EET inhibition of the epithelial sodium channel to the natriuretic response to high dietary salt require further investigation.

**Perspectives**

The report by Liclican et al$^1$ provides evidence that the A$_{2A}$ receptor-EET axis is required for the kidneys to maintain proper sodium balance and blood pressure in the face of elevated dietary salt. If this axis is not properly functioning, then an elevated blood pressure is required to maintain sodium balance. The questions that remain are whether increased renal adenosine levels are required for this response, the specific renal tubular and vascular mechanisms responsible, and whether other adenosine receptors participate in the natriuretic response. These questions are critical, because the potential use of adenosine receptor–based therapies for the treatment of infection, autoimmunity, ischemia, and neurodegenerative diseases is moving toward clinical use in humans.$^{12}$ The findings of the study by Liclican et al$^1$ in this issue of *Hypertension* make A$_{2A}$ receptors and EETs stronger candidates as therapeutic targets for salt-sensitive hypertension.

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**References**


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