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Role of macula densa adenosine triphosphate (ATP) in tubuloglomerular feedback

YiLin Ren, Jeffrey L. Garvin, Ruisheng Liu, and Oscar A. Carretero

Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit, Michigan

Role of macula densa adenosine triphosphate (ATP) in tubuloglomerular feedback.

Background. Recent studies have shown that adenosine triphosphate (ATP) is liberated from macula densa cells in response to increased tubular NaCl in vitro. We tested the hypothesis that increased NaCl in the macula densa stimulates the release of ATP, resulting in extracellular formation of adenosine which is involved in signal transmission of the tubuloglomerular feedback response.

Methods. Rabbit afferent arterioles and attached macula densas were simultaneously microperfused in vitro. Tubuloglomerular feedback was induced by increasing macula densa Na/Cl from 11/10 to 81/80 mmol/L and was measured before and after treatment.

Results. We first tested whether hydrolysis of ATP is required for tubuloglomerular feedback. When we enhanced conversion of ATP to adenosine by adding hexokinase or apyrase to the bath and arteriole lumen, the tubuloglomerular feedback response was augmented. During the control period, tubuloglomerular feedback decreased arteriole diameter by 2.2 ± 0.2 μm. In the presence of hexokinase, tubuloglomerular feedback decreased diameter by 3.4 ± 0.3 μm ($N = 8$) ($P < 0.05$, with vs. without hexokinase). In the apyrase group, tubuloglomerular feedback decreased diameter by 2.7 ± 0.4 μm during the control period. When apyrase was added, tubuloglomerular feedback decreased diameter by 4.7 ± 0.4 μm ($N = 8$) ($P < 0.05$, with vs. without apyrase). When hydrolysis of adenosine monophosphate (AMP) to adenosine was blocked by supplementing the bath with 100 μmol/L α,β-methylene adenosine 5′-diphosphate (MADP), an inhibitor of 5′-nucleotidase, tubuloglomerular feedback response was blocked and diameter remained unchanged. We next studied whether ATP released from the macula densa binds to P_2 receptors and activates the tubuloglomerular feedback response. The P_2 purinergic receptor inhibitor suramin was added to both arteriole lumen and bath. During the control period, tubuloglomerular feedback decreased diameter by 3.7 ± 0.5 μm. Suramin (100 μmol/L) did not significantly inhibit tubuloglomerular feedback, since in the presence of suramin diameter decreased by 3.8 ± 0.3 μm ($N = 7$). Finally, we added the adenosine A_1 receptor inhibitor FK838 to both bath and lumen and found that it completely blocked high NaCl-induced tubuloglomerular feedback.

Conclusion. We concluded that ATP released from the macula densa is broken down to form AMP in the extracellular space. AMP in turn is degraded by ecto-5′-nucleotidases to adenosine, which mediates signal transmission of the tubuloglomerular feedback response.

Key words: ATP, adenosine, tubuloglomerular feedback.

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Recent studies have shown that adenosine triphosphate (ATP) is liberated from macula densa cells in response to increased tubular NaCl delivery in vitro [1]. Additionally, ATP levels in the interstitium of the renal cortex are increased by maneuvers that cause a tubuloglomerular feedback response [2]. Extracellular ATP may exert its biologic effects directly via its P_2 purinergic receptor, or indirectly via hydrolysis by ectonucleotidases, forming adenosine which binds to adenosine receptors. Regardless of the ultimate source, adenosine has been implicated as integral to the tubuloglomerular feedback response. Peritubular infusions of theophylline, which competes with adenosine for A_1 receptors, attenuated the tubuloglomerular feedback–induced fall in single-nephron glomerular filtration rate (SNGFR) and stop-flow pressure (SFP) [3, 4]. In corollary experiments, dipyridamole, an inhibitor of adenosine uptake that increases interstitial adenosine concentrations, potentiated tubuloglomerular feedback [3]. We have shown that A_1 antagonists block tubuloglomerular feedback [5]. Other maneuvers that reduced extracellular adenosine concentrations, such as infusions of adenosine deaminase, also attenuated tubuloglomerular feedback activity, whereas infusion of an adenosine deaminase inhibitor enhanced tubuloglomerular feedback [6]. However, P_2 purinergic receptors have been found in the renal vasculature. This raised another possibility, that ATP is released from macula densa cells and evokes tubuloglomerular feedback–dependent preglomerular vasoconstriction directly. It is not clear whether the ATP released from the macula densa is broken down to adenosine and participates in the tubuloglomerular feedback response, or whether it binds to ATP receptors and stimulates tubuloglomerular feedback.

The present studies were performed to test the hypothesis that ATP released from the macula densa in response to increased NaCl is primarily broken down to form extracellular adenosine which contributes to signal transmission of the tubuloglomerular feedback response. Three approaches were utilized to evaluate this hypothesis: (*1*) enhancement of hydrolysis of ATP to adenosine diphosphate (ADP) and adenosine, (*2*) prevention of adenosine formation by 5′-nucleotidase, and (*3*) blockade of the ATP class of purinergic receptor P_2 or adenosine A_1 receptors.

METHODS

Afferent arterioles with macula densa attached were isolated and microperfused as described previously [7–9]. Briefly, young male New Zealand white rabbits (1.5 to 2.0 kg) were fed standard rabbit chow (Ralston Purina, St. Louis, MO, USA) and given tap water ad libitum. They were anesthetized with sodium pentobarbital (40 mg/kg, intravenously) and given an injection of heparin (500 U, intravenously). The kidneys were sliced along the corticomedullary axis, and slices were placed in ice-cold minimum essential medium (MEM) (Gibco, Grand Island, NY, USA) containing 5% bovine serum albumin (BSA; Intergen, Burlington, MA, USA). A single superficial afferent arteriole and its intact glomerulus from each rabbit were microdissected together with adherent tubular segments consisting of portions of the thick ascending limb, macula densa, and early distal tubule. Samples were transferred to a temperature-regulated chamber mounted on an inverted microscope (Olympus IMT-2, Tokyo, Japan) with Hoffmann modulation. Both the afferent arteriole and the end of either the distal tubule or thick ascending limb were cannulated with an array of glass pipettes as described previously [8]. Intraluminal pressure of the afferent arteriole was measured by Landis' technique, using a fine pipette introduced into the lumen through the perfusion pipette. The afferent arteriole was perfused with MEM supplemented with 5% BSA and (in mmol/L) 5 $NaHCO_3$, 10 NaCl, 10 HEPES, and 10 NaOH. Intraluminal pressure was maintained at 60 mm Hg throughout the experiment. The macula densa was perfused with physiologic saline consisting of (in mmol/L) 10 HEPES, 1.0 $CaCO_3$, 0.5 K_2HPO_4, 4.0 $KHCO_3$, 1.2 $MgSO_4$, 5.5 glucose, 0.5 Na acetate, 0.5 Na lactate, and either 80 (high NaCl) or 10 NaCl (low NaCl). MEM was gassed with air and physiologic saline was oxygenated with 100% O_2. The pH of each solution was 7.4. The bath was similar to the arteriolar perfusate except that it contained 0.15% BSA, and was exchanged continuously at a rate of 1 mL/min. Microdissection and cannulation were completed within 90 minutes at 8°C, after which the bath was gradually warmed to 37°C for the rest of the experiment. Once the temperature was stable, a 30-minute equilibration period was allowed before taking any measurements. Images were displayed at magnifications up to 1980× and recorded with a video system. Afferent arteriole diameter was measured with a MetaMorph image analysis system (Universal Imaging, West Chester, PA, USA).

Experimental protocols

Time control. First we conducted time control experiments showing that during two consecutive tubuloglomerular feedback responses the afferent arteriole reacted in a similar fashion. After a 30-minute equilibration period, NaCl concentrations of the macula densa perfusate were increased from low to high. Five minutes later, the macula densa perfusate was switched back to low NaCl and a second tubuloglomerular feedback response was induced by increasing the macula densa perfusate to high NaCl.

Effect of enhanced hydrolysis of ATP on afferent arteriole constriction induced by high NaCl at the macula densa. To determine whether an increase in hydrolysis of ATP released from the macula densa potentiates the tubuloglomerular feedback response, we added ATPases to the bath to facilitate hydrolysis of ATP and thereby increase adenosine formation. The macula densa was first perfused with low-NaCl solution for 5 minutes, and then the perfusate was changed to high NaCl. Five minutes later, the macula densa perfusate was switched back to low NaCl and hexokinase (20 U/mL) or apyrase (5 U/mL), which hydrolyzes ATP to adenosine, was added to the bath and arteriole lumen. Following a 20-minute equilibration period, the macula densa perfusate was changed to high NaCl. These concentrations of ATPases have been reported to effectively increase ATP hydrolysis [10, 11].

Effect of 5′-nucleotidase blockade on afferent arteriole constriction induced by high NaCl at the macula densa. To determine whether tubuloglomerular feedback requires adenosine, we examined the maximum response of the afferent arteriole to increased NaCl at the macula densa before and after inhibiting the exoenzyme 5′-nucleotidase, which converts adenosine monophosphate (AMP) to adenosine. The experiments were performed as described above. The macula densa was first perfused with low-NaCl solution for 5 minutes, and then the perfusate was changed to high NaCl. Five minutes later, the macula densa perfusate was switched back to low NaCl and α,β-methylene adenosine diphosphate (MADP) (10^{-4} mol/L), an inhibitor of 5′-nucleotidase, was added to the bath. Following a 20-minute equilibration period, the macula densa perfusate was changed to high NaCl.

Effect of adenosine A_1 receptor blockade on afferent arteriole constriction induced by high NaCl at the macula densa. To determine whether the tubuloglomerular feedback response relies on stimulation of adenosine A_1

receptors, we measured tubuloglomerular feedback before and after blocking these receptors. The experiments were performed as described above. The macula densa was first perfused with low-NaCl solution for 5 minutes, and then the perfusate was changed to high NaCl. Five minutes later, the macula densa perfusate was switched back to low NaCl and an adenosine A_1 receptor blocker, FK838 (10^{-6} mol/L), was added to the arteriole lumen and bath. We previously reported that FK838 at this concentration completely blocked the vasoconstrictor action of exogenous adenosine (10^{-6} mol/L) on the afferent arteriole [5].

Effect of P_2 receptor blockade on afferent arteriole constriction induced by high NaCl at the macula densa. To determine whether ATP released from the macula densa binds to another cell type and activates the tubuloglomerular feedback response, we examined tubuloglomerular feedback response before and after blocking the P_2 receptors. The experiments were performed as described above, except that a P_2 receptor blocker, suramin (10^{-4} mol/L), was added to the arteriole lumen and bath. This concentration of suramin has been shown to completely block ATP-induced increases in intracellular calcium in an isolated perfused macula densa preparation [12].

Statistics

Values are expressed as mean ± SEM. A paired *t* test was used to examine whether the diameter at a given concentration differed from control. $P < 0.05$ was considered significant using Bonferroni's correction for multiple comparisons.

RESULTS

Time control

In time controls, afferent arteriole diameter decreased from 17.7 ± 0.7 μm to 14.2 ± 1.4 μm when the solution perfusing the macula densa was first changed from low to high NaCl. When we repeated the process, diameter decreased from 17.7 ± 1.0 μm to 14.9 ± 1.0 μm. The two consecutive tubuloglomerular feedback responses were not significantly different ($N = 5$).

Effect of enhanced hydrolysis of ATP on afferent arteriole constriction induced by high NaCl at the macula densa

In the first series of experiments, we added an ATPase to the bath to facilitate hydrolysis of ATP after it is released from the macula densa, thereby increasing adenosine formation. We first enhanced conversion of ATP to ADP and adenosine by adding hexokinase (20 U/mL) to the bath. When the macula densa perfusate was changed from low to high NaCl, tubuloglomerular feedback decreased afferent arteriole diameter by 2.2 ± 0.2 μm (from 18.5 ± 1.0 μm to 16.3 ± 0.9 μm) ($N = 8$). When the solution was changed to low NaCl, diameter returned to 18.8 ± 1.0 μm. Adding hexokinase (20 U/mL) to the bath did not alter afferent arteriole diameter when the macula densa was perfused with low NaCl (18.8 ± 1.0 μm vs. 17.8 ± 1.0 μm), but augmented constriction when the macula densa perfusate was changed to high NaCl. Diameter decreased by 3.4 ± 0.3 μm (from 17.8 ± 1.0 μm to 14.1 ± 1.0 μm) ($P < 0.05$, with vs. without hexokinase) (Fig. 1). To confirm this, we suffused the bath and afferent arteriole lumen with apyrase (5 U/mL), which also facilitates hydrolysis of ATP to ADP and adenosine. When NaCl was increased from low to high, TGF decreased arteriole diameter by 2.7 ± 0.4 μm (from 20.0 ± 0.7 μm to 17.3 ± 0.5 μm). Adding apyrase to the bath and lumen significantly enhanced the tubuloglomerular feedback response. Diameter decreased by 4.7 ± 0.4 μm (from 19.4 ± 0.7 μm to 14.7 ± 0.5 μm) ($N = 8$) ($P < 0.05$, with vs. without apyrase) (Fig. 2).

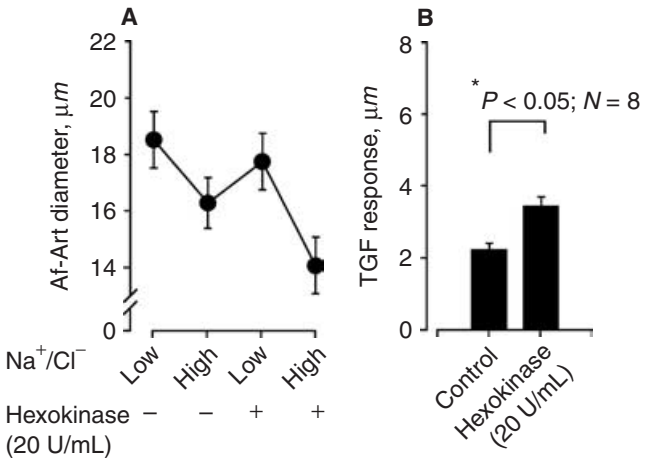

Fig. 1. Effect on tubuloglomerular feedback (TGF) caused by adding hexokinase to the bath to enhance conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and adenosine. (*A*) Afferent arteriole (Af-Art) constriction induced by increased NaCl at the macula densa. (*B*) Tubuloglomerular feedback response. Increased conversion of ATP to adenosine enhanced tubuloglomerular feedback, suggesting that ATP released from the macula densa was hydrolyzed to adenosine which participated in the tubuloglomerular feedback response. $^*P <$ 0.05, with vs. without hexokinase ($N = 8$).

Effect of 5′-nucleotidase blockade on afferent arteriole constriction induced by high NaCl at the macula densa

Next, we investigated whether adenosine formation is essential for the tubuloglomerular feedback response. The 5′-nucleotidase blocker MADP was added to the bath. As shown in Figure 3, when the macula densa perfusate was changed from low to high NaCl, tubuloglomerular feedback decreased afferent arteriole diameter by 3.4 ± 0.5 μm (from 19.7 ± 1.1 μm to 16.4 ± 1.5 μm). When the luminal solution was switched back to

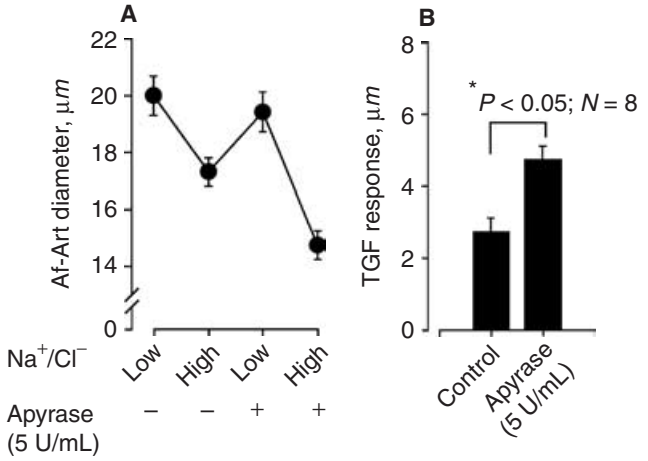

Fig. 2. Effect on tubuloglomerular feedback (TGF) caused by adding apyrase to the bath and lumen to enhance conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and adenosine. (*A*) Afferent arteriole (Af-Art) constriction induced by increased NaCl at the macula densa. (*B*) Tubuloglomerular feedback response. Increased conversion of ATP to adenosine significantly augmented tubuloglomerular feedback. $^*P < 0.05$, with vs. without apyrase ($N = 8$).

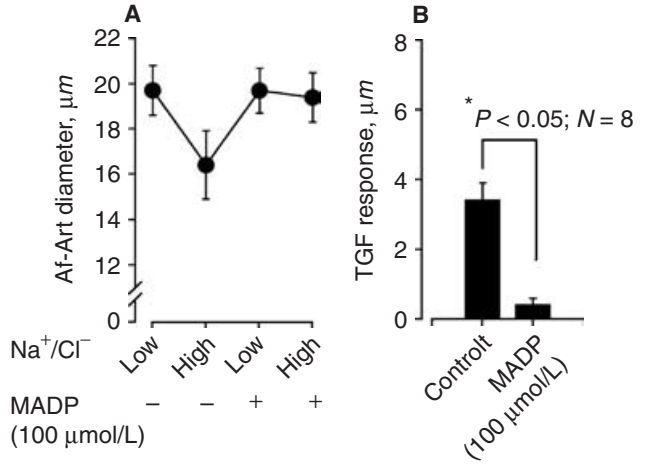

Fig. 3. Effect on tubuloglomerular feedback (TGF) caused by adding α,β-methylene adenosine 5′-diphosphate (MADP) to the bath to block 5′-nucleotidase. (*A*) Afferent arteriole (Af-Art) constriction induced by increased NaCl at the macula densa. (*B*) Tubuloglomerular feedback response. In the presence of MADP, tubuloglomerular feedback was eliminated, suggesting that formation of adenosine is essential for the tubuloglomerular feedback response. $^*P < 0.05$, with vs. without MADP ($N = 8$).

low NaCl, diameter returned to baseline. When MADP at 10^{-4} mol/L was added to the low-NaCl macula densa perfusate, it did not alter afferent arteriole diameter (19.9 ± 1.0 μm vs. 19.7 ± 1.0 μm). When the macula densa perfusate was changed to high NaCl in the presence of MADP, which blocks adenosine formation, the tubuloglomerular feedback response was completely suppressed and afferent arteriole diameter remained unchanged (from 19.7 ± 1.04 μm to 19.4 ± 1.1 μm) ($N = 8$) ($P < 0.05$, with vs. without MADP).

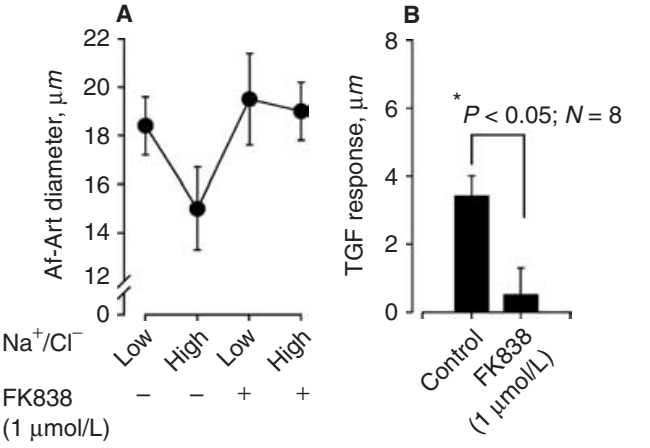

Fig. 4. Effect of FK838, an adenosine A_1 receptor antagonist, on afferent arteriole constriction induced by high NaCl at the macula densa. (*A*) Afferent arteriole (Af-Art) constriction induced by increased NaCl at the macula densa. (*B*) Tubuloglomerular feedback response. Treatment with FK838 had no effect on basal diameter but completely blocked the constriction induced by high NaCl at the macula densa. $^*P < 0.05$, with vs. without FK838 ($N = 8$).

Effect of adenosine A_1 receptor blockade on afferent arteriole constriction induced by high NaCl at the macula densa

We next investigated whether tubuloglomerular feedback relies on activation of the adenosine A_1 receptor. For this, we examined the maximum response of the afferent arteriole to increased NaCl concentrations at the macula densa before and after blocking the adenosine A_1 receptor. During the control period, when NaCl was increased from low to high, tubuloglomerular feedback decreased arteriole diameter by 3.2 ± 0.5 μm (from 18.3 ± 0.9 μm to 15.1 ± 1.3 μm). Adding FK838 to the bath and afferent arteriole lumen completely abolished the tubuloglomerular feedback response. When macula densa NaCl was changed from low to high, afferent arteriole diameter remained unchanged (19.4 ± 1.4 μm vs. 19.0 ± 0.9 μm) ($N = 8$) ($P < 0.05$, with *vs.* without FK838) (Fig. 4). To test the possibility that the inhibitory effect of FK838 on tubuloglomerular feedback involves blockade of both the adenosine A_1 receptor and the P_2 purinergic receptor, we perfused the afferent arteriole alone and studied its response to exogenous ATP in the presence of FK838. We first generated a dose-response curve with ATP as a control, then added FK838 (10^{-6} mol/L) to the bath and arteriole lumen and generated a second ATP dose-response curve. Figure 5 illustrates the afferent arteriole response to ATP in the absence or presence of FK838. ATP constricted the afferent arteriole in a dose-dependent manner. One and 10 μmol/L ATP reduced arteriole diameter from 20.1 ± 0.7 μm to 17.4 ± 1.0 μm and 16.2 ± 0.9 μm, respectively. When arterioles were treated with FK838, ATP-induced constriction remained unchanged.

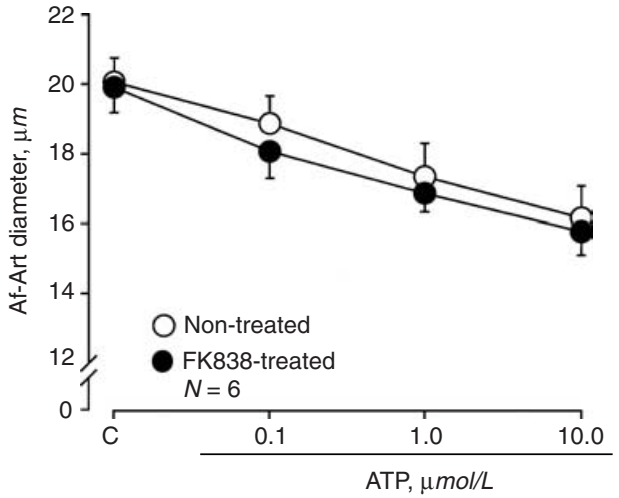

Fig. 5. Effect of FK838 on afferent arteriole response to exogenous adenosine triphosphate (ATP). We first generated a dose-response curve with ATP as a control (○). Then we added 10^{-6} mol/L FK838 to the bath and afferent arteriole lumen and generated a second ATP dose-response curve (●). FK838 did not alter the afferent arteriole (Af-Art) response to ATP, suggesting that FK838 at this concentration does not block the P_2 receptor ($N = 6$).

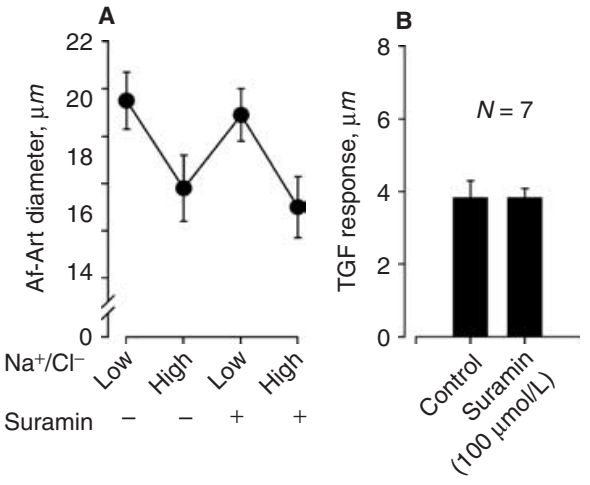

Fig. 6. Effect of suramin, a P_2 receptor antagonist, on afferent arteriole constriction induced by high NaCl at the macula densa. (*A*) Afferent arteriole (Af-Art) constriction induced by increased NaCl at the macula densa. (*B*) Tubuloglomerular feedback response. Treatment with suramin did not alter the tubuloglomerular feedback response, suggesting that activation of P_2 receptors may not play an important role in tubuloglomerular feedback ($N = 7$).

Effect of P_2 receptor blockade on afferent arteriole constriction induced by high NaCl at the macula densa

We next examined the effect of suramin, a P_2 purinergic receptor blocker, on the tubuloglomerular feedback response. During the control period, when NaCl was increased from low to high, tubuloglomerular feedback decreased afferent arteriole diameter by 3.8 ± 0.5 μm (from 19.5 ± 1.2 μm to 15.8 ± 1.4 μm). Adding suramin to the bath and arteriole lumen did not alter the tubuloglomerular feedback response. When macula densa NaCl was changed from low to high, tubuloglomerular feedback decreased arteriole diameter by 3.8 ± 0.3 μm, the same as control (from 18.9 ± 1.1 μm to 15.0 ± 1.3 μm) ($N = 7$) (Fig. 6).

DISCUSSION

Our findings suggest that ATP released from the macula densa in response to increased NaCl is rapidly metabolized to ADP, AMP, and ultimately adenosine by the cell surface ectonucleotidases involved in the tubuloglomerular feedback response. This is supported by the fact that when we prevented adenosine formation with MADP, which blocks 5′-nucleotidase, the tubuloglomerular feedback response was abolished; and conversely, when we enhanced ATP hydrolysis with hexokinase or apyrase and thereby increased adenosine formation, the tubuloglomerular feedback response was augmented. Moreover, blocking the adenosine A_1 receptor with FK838 inhibited tubuloglomerular feedback, whereas suramin, which blocks the P_2 receptor, did not influence the tubuloglomerular feedback response.

Macula densa cells are thought to be richly endowed with small mitochondria distributed along the basal and lateral aspects [13, 14] and exhibit relatively low Na^+-K^+-ATPase activity [15], supporting the concept that they possess substantial ATP-generating capacity. Recent in vitro studies have shown that macula densa cells release ATP in response to increased tubular NaCl delivery [1], and ATP is increased in the cortical interstitium by maneuvers that cause tubuloglomerular feedback [2]. Extracellular hydrolysis of nucleotides is catalyzed by several classes of membrane-bound enzymes called ectonucleotidases. Biochemically, these enzymes are characterized by their ability to hydrolyze purine and the pyrimidines nucleoside di- and triphosphate. These enzymes are widely expressed in many tissues, including the kidney, and hydrolysis of ATP can be a rapid process with half-degradation times of well under 1 minute. The final step in the conversion of interstitial adenine nucleotides to adenosine is catalyzed by the action of ecto-5′-nucleotidase. This enzyme is widely distributed in the kidney and expressed in all nephron segments, including macula densa cells. It is also expressed by fibroblasts and mesangial cells [16–18]. To clarify whether the ATP released from the macula densa is broken down to form the adenosine involved in the tubuloglomerular feedback response, we used a 5′-nucleotidase blocker or ATPases to either inhibit 5′-nucleotidase or increase hydrolysis of ATP and thereby alter the formation of adenosine. Our results demonstrated that blocking 5′-nucleotidase with MADP, which prevents formation of adenosine,

abolished the tubuloglomerular feedback response, whereas enhancing the conversion of ATP to ADP and AMP, which increases the formation of adenosine, augmented the tubuloglomerular feedback response. This suggests that ATP released from the macula densa must be hydrolyzed to adenosine in order to effect a tubuloglomerular feedback response. Taking together the demonstration of regulated release of ATP by macula densa cells and the evidence for adenosine dependence of tubuloglomerular feedback, we may assume that ATP is metabolized to adenosine via ADP and AMP within the confines of the juxtaglomerular interstitium. Consistent with our studies, Thomson et al [19] demonstrated that tubuloglomerular feedback efficiency and range were both significantly reduced by blocking 5′-nucleotidase.

Because adenosine is a major metabolic end product and is known to elicit vasoactive effects, it has been viewed as one possible paracrine factor that transmits signals from the macula densa to mediate the tubuloglomerular feedback response. In situ hybridization has shown a high density of A_1 receptor mRNA in the terminal segment of the afferent arteriole [20, 21]. Several studies using a variety of techniques have examined the direct effect of adenosine on the resistance of renal glomerular arterioles. There is general agreement that the adenosine A_1 receptor mediates vasoconstriction in the afferent arteriole [21, 22]. On the other hand, abundant evidence indicates that extracellular ATP exerts its biologic effects by activating members of the P_2 class of purinoceptors. Autoradiography showing binding of the P_2X ligand in the interlobular arteries and afferent arteriole supports the preglomerular localization of P_2X receptors [23]. In isolated perfused rabbit afferent arterioles, ATP added to the bath caused vasoconstriction that was probably mediated by P_2X receptors, because β,γ-methylene ATP had the same effect [21]. To test whether the tubuloglomerular feedback response relies on adenosine A_1 or purinergic P_2 receptors, we tested both an A_1 receptor antagonist (FK838) and a P_2 receptor antagonist (suramin). Blocking the adenosine A_1 receptor with FK838 abolished the tubuloglomerular feedback response whereas blocking the purinergic P_2 receptor with suramin did not, suggesting that activation of the A_1 receptor by adenosine is a necessary component of the tubuloglomerular feedback pathway, but activation of the P_2 receptor may not play a very important role in tubuloglomerular feedback. Microperfusion studies in A_1 receptor knockout mice clearly showed complete absence of tubuloglomerular feedback responses, with no detectable drop in stop-flow pressure after increased distal fluid delivery [24, 25], in agreement with the original suggestion made by Osswald et al [3] and our present studies where adenosine was a mediator rather than a modulator of the tubuloglomerular feedback mechanism.

In our in vitro studies, which directly addressed the tubuloglomerular feedback response, we found that addition of a P_2 receptor antagonist to the bath and afferent arteriole lumen did not alter the tubuloglomerular feedback response. In contrast to our results, others have reported that P_2 receptors mediate tubuloglomerular feedback; however, they examined afferent arterioles from rats and P_2X_1 knockout mice using the juxtamedullary nephron technique [26]. While the reason for this discrepancy is not clear, it may be related to the different species used and/or systemic neurohormonal influences. Another possibility is the different location of the afferent arteriole(s) studied. Regulation of the tubuloglomerular feedback mechanism may differ in renal cortex vs. juxtamedullary nephrons due to different responsiveness of superficial cortex vs. juxtamedullary afferent arterioles to neurohormonal factors. Vasoconstriction caused by adenosine is reportedly higher in superficial cortex compared to juxtamedullary afferent arterioles [21, 22]. Furthermore, afferent arterioles exhibit a higher sensitivity to luminal angiotensin II in renal cortex but not juxtamedullary nephrons [27].

CONCLUSION

ATP released from the macula densa is broken down to form AMP in the extracellular space. AMP in turn is degraded by ecto-5′-nucleotidases to adenosine, which mediates signal transmission of the tubuloglomerular feedback response.

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Reprint requests to YiLin Ren, M.D., Hypertension and Vascular Research Division, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202.
E-mail: yren1@hfhs.org

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