Natriuretic and Diuretic Actions of a Highly Selective Adenosine A1 Receptor Antagonist

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Abstract. The natriuretic and diuretic action of a highly selective adenosine A1 receptor (A1AdoR) antagonist, 1,3-dipropyl-8-[2-(5,6-epoxy)norbornyl]xanthine (CVT-124), was investigated in anesthetized rats. CVT-124 (0.1 to 1 mg/kg) caused dose-dependent increases in urine flow and fractional and absolute sodium excretion of by six- to 10-fold and, at 0.1 mg/kg, increased the GFR (1.6 ± 0.1 to 2.5 ± 0.2 ml/min; P < 0.01). There were no changes in BP or heart rate. CVT-124 reduced absolute proximal reabsorption (26 ± 3 to 20 ± 2 nl/min; P < 0.05) despite unchanged proximally measured, single-nephron GFR (SNGFR) (42 ± 5 to 44 ± 4 nl/min; NS) and thereby decreased fractional proximal reabsorption (60 ± 3 to 46 ± 4%; P < 0.05). Despite increasing distal tubular fluid flow rate (5.4 ± 0.7 to 9.7 ± 0.9 nl/min; P < 0.001), it reduced the proximal-distal difference in SNGFR (before: 9.4 ± 1.0 nl/min; vehicle: 8.3 ± 0.6 nl/min; P < 0.05) despite unchanged proximally measured, single-nephron GFR (SNGFR) (42 ± 5 to 44 ± 4 nl/min; NS) and thereby decreased fractional proximal reabsorption (60 ± 3 to 46 ± 4%; P < 0.05). Despite increasing distal tubular fluid flow rate (5.4 ± 0.7 to 9.7 ± 0.9 nl/min; P < 0.001), it reduced the proximal-distal difference in SNGFR (before: 9.4 ± 1.0 nl/min; vehicle: 8.3 ± 0.6 nl/min; P < 0.05).

Received December 31, 1997. Accepted October 5, 1998.

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1046-6673/1004-0714$03.00/0
Journal of the American Society of Nephrology
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Adenosine (Ado) is produced in the kidney, where it regulates GFR, tubular reabsorption, and renin secretion (1–5). However, it exerts selective, and often antagonistic, effects on cell function mediated through a family of adenosine receptors.

The A1 adenosine receptor (A1AdoR) subtype is linked to inhibition of cAMP generation. It is implicated in contractile responses of the afferent arteriole (6) and enhanced distal tubular fluid reabsorption by highly selective A1 AdoR antagonists. In the rat, it has a 400- to 1800-fold greater affinity for A1 than A2 receptors (11,13). This is a significant improvement over a conventional A1AdoR antagonist such as 8-cyclopentyl-1,3-dipropylxanthine (CPX), which has a selectivity of approximately 70-fold (11). The significant A2AdoR antagonist activity of some previous drugs has limited their utility as pharmacologic probes of A1 AdoR action and as drugs for use in humans as diuretics or renal protective agents. Thus, any blockade of A2Ado receptors could reduce the GFR and sodium excretion (U Na V) and also may cause unwanted cardiac stimulation and increases in BP (14).

The first aim of this study was to explore the proximal actions of CVT-124 in the anesthetized rat. Direct micropuncture methods have not been applied previously to study sites of inhibition of tubular fluid reabsorption by highly selective A1AdoR antagonists. This is important because previous studies of the effects of A1AdoR blockade on tubular NaCl and fluid reabsorption have shown site-specific effects: increased NaCl reabsorption in the medullary thick ascending limb (15) and short loops of Henle (16), but decreased NaCl or water reabsorption in the collecting ducts (1,17). Clearance studies in rats (18) and humans (2,3,19) suggest that A1AdoR antagonists may impair reabsorption in the proximal tubules, where we have recently located high-affinity A1 AdoR binding sites (12).
However, direct assessment of proximal reabsorption with renal micropuncture techniques during $A_1$AdoR blockade has not been undertaken.

The efficacy of proximally active diuretics such as carbonic anhydrase inhibitors has been limited because of activation of the tubuloglomerular feedback (TGF) response that leads to vasoconstriction of the afferent arteriole and a reduction in the single-nephron GFR (SNGFR) during increased delivery of tubular fluid to the macula densa segment (20). TGF responses are blocked by microperfusion of the relatively $A_1$AdoR-specific antagonists 1,3-dipropyl-8-cyclopentylxanthine (CPX) (21) or 1,3-dipropyl-8-sulfenylxanthine (PSPX) (22) into the lumen of the macula densa segment. However, the precise mechanism of $A_1$AdoR in transmission of TGF signals remains controversial, and the role of blockade of TGF in the renal hemodynamic responses to $A_1$AdoR blockade has not been investigated. The degree to which SNGFR is influenced by TGF can be assessed from differences in proximally measured SNGFR (with macula densa delivery interrupted) and distally measured SNGFR (with macula densa and TGF function intact). Thus, a second aim of this study was to characterize the role of TGF in changes of SNGFR during $A_1$AdoR blockade by contrasting proximal and distal measurements of SNGFR during intravenous infusion of CVT-124.

Materials and Methods

Studies were undertaken on male Sprague Dawley rats weighing 150 to 250 g. They were fed a standard laboratory chow (Ralston-Purina Co., St. Louis, MO) with a sodium content of 0.3 g · 100 g$^{-1}$. Rats were allowed food and water ad libitum. On the day of study, they were anesthetized with a thiobarbiturate (Inactin, 100 mg/kg intraperitoneally; Research Biochemicals, Natick, MA).

For studies of whole-kidney clearance and micropuncture, rats were anesthetized and prepared as described previously (23). A tracheostomy was performed for spontaneous ventilation. Rats were maintained on a servo-controlled rodent operating table at 37°C. A femoral artery was cannulated for measurement of mean arterial pressure and heart rate, and both femoral veins were cannulated for intravenous infusions. One transmitted a maintenance solution of 0.3% NaCl at 37°C, and prepared for micropuncture as described previously (23). The bladder was catheterized through a midline incision. The left femoral artery was cannulated for measurement of mean arterial pressure and heart rate, and both femoral veins were cannulated for intravenous infusions. One transmitted a maintenance solution of 0.3% NaCl at 37°C, and prepared for micropuncture as described previously (23). For free-flow micropuncture studies, the last surface convolution of a proximal tubule (PT) and the first convolution of a distal tubule (DT) were selected, after intravenous injections of 50 μl of FD&C dye. They were punctured in random order with glass micropipettes (outer diameter 8 to 12 μm). Timed (2 to 5 min) samples of fluid were withdrawn upstream from an oil block. The sample was transferred into a constant-bore capillary tube whose length was measured with a micrometer to calculate the tubular fluid volume. Thereafter, the sample was ejected into scintillation fluid and the $[^3]$H activity was counted. Paired samples of late proximal (LP) and early distal (ED) fluid were obtained in each period.

Rats of group 1 ($n = 10$) and group 2 ($n = 11$) served to define the dose–response effects for CVT-124, or its vehicle, on renal clearance parameters. Forty-five minutes after completion of surgery, there was a basal period of 45 min during which renal clearance was measured with blood (200 μl) sampled at the midpoint. Blood samples were replaced with equal volumes of 0.6% bovine serum albumin in 0.154 M NaCl solution. Thereafter, rats of group 1 received a bolus injection of vehicle (Veh: 0.3 ml of a 3% solution of polyethylene glycol-400 plus 2% ethanol in 0.154 M NaCl solution), followed, at 30-min intervals, by CVT-124 at 0.1, 0.3, 0.5, and 1 mg/kg. Rats of group 2 received intravenous bolus injections of 0.3 ml of the CVT-124 vehicle, following the same course as for group 1. An infusion of 0.154 M NaCl was administered intravenously during periods 2 to 5 at a rate adjusted at 10-min intervals to equal the change in urine flow rate, compared to the basal period. The clearance periods commenced 10 min after CVT-124 or vehicle.

The effects of vehicle or CVT-124 on proximal reabsorption, distal tubular fluid delivery, and SNGFR were assessed from two or three paired precisely timed samples of tubular fluid drawn from the LP and ED tubules of different nephrons. The aim is to quantify the effects of intravenous CVT-124 on absolute and fractional reabsorption of fluid independent of any effects on TGF. Rats of group 3 ($n = 8$) received vehicle, and rats of group 4 ($n = 9$) received intravenous CVT-124 (0.5 mg/kg). Tubular fluid samples were drawn during the basal period and 15 min after administration of vehicle or CVT. After 15 min, additional fluid samples were drawn from the LP and ED tubules.

The SNGFR was calculated from the product of the tubular fluid flow rate ($TF_V$) and tubular fluid:plasma $[^3]$H-inulin ratio. The absolute proximal reabsorption (APR) was calculated from the difference between the SNGFR and the $TF_V$, both measured at the LP. The fractional proximal fluid reabsorption ($FR_{prox}$) was calculated from the APR factored by the SNGFR. Paired comparisons of SNGFR measured from the LP and ED were made during the basal and experimental periods.

Rats of groups 5 and 6 served to determine the effects of intravenous CVT-124 on the maximal TGF responses. Rats were prepared as described previously (23). The TGF response was assessed in superficial nephrons from the change in proximal stop flow pressure (PSF; an index of glomerular capillary pressure). For measurement of PSF, a wax block was inserted at the midpoint of a superficial PT to block the tubular lumen. An ultramicropipette (outer diameter 1 to 2 μm) was inserted upstream from the block. It was connected to a servo-null pressure recorder (Instruments for Physiologic Science, La Jolla, CA). A perfusion micropipette (outer diameter 10 μm) was inserted downstream. It was filled with artificial tubular fluid (ATF) whose composition matched end proximal tubular fluid (23). The PSF was recorded during loop perfusion with ATF at 0 and 40 nl/min (a maximum stimulus). The difference between these values was recorded as the maximum TGF response. Group 5 ($n = 6$) was a vehicle control. Measurements of maximal TGF responses were made before (basal) and 15 to 45 min after intravenous administration of 0.3 ml of vehicle. Group 6 ($n = 6$) was studied similarly before and 15 to 45 min after intravenous administration of 0.3 ml of CVT-124 (0.5 mg/kg). Data obtained from one to three nephrons in each period were averaged.

Chemical Methods

The sodium concentration of plasma and urine was measured with an automated ion-selective electrode method (ELISE; Beckman, Columbia, MD).

Statistical Analyses

The data are presented as mean ± SEM. Results were assessed by ANOVA followed, where appropriate, by post hoc Dunnett $t$ test to
assess between-group differences. Statistical significance was taken at $P < 0.05$.

**Results**

The mean arterial pressure and heart rate during the basal periods averaged $116 \pm 3$ mmHg and $371 \pm 5$ min$^{-1}$, respectively, and were not changed by vehicle or CVT-124 in any protocol.

**Groups 1 and 2**

CVT-124, given to rats of group 1 ($n = 10$), increased the GFR by $50\%$ at the lowest dosage (Figure 1A). At higher doses, this effect on GFR waned somewhat. In contrast, it caused a log-linear increase in diuresis of $10\times$ over the dose range tested (Figure 1B). Absolute and fractional excretion of Na$^+$ increased dose dependently with CVT-124 (Figure 1, C and D). During time-controls with the vehicle (group 2; $n = 11$), there were no significant changes.

**Groups 3 and 4**

Micropuncture values for proximal fluid reabsorption and distal fluid delivery are summarized in Table 1. For reasons that are not clear, the values for SNGFR and APR tended to be

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*Figure 1. Mean ± SEM values for dose–response relationship for effects of CVT-124 on single-kidney values for GFR (A), urine flow rate (B), absolute sodium excretion (C), and fractional sodium excretion (D). Data are shown for rats receiving CVT-124 ($\bigcirc$; $n = 10$) or equivalent volumes of vehicle ($\bullet$). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.005$, compared to vehicle.*
higher in the basal state in group 4. It is apparent that there were no changes in the vehicle and time controls of group 3 for proximal tubule fluid reabsorption, but there was a small decrease in tubular fluid delivery to the ED. In contrast, during infusion of CVT-124 in group 4, the APR declined significantly by 22%, accompanied by a reduction in FR prox. The tubular fluid flow rate at the ED was increased by 80 ± 14% by CVT-124.

The SNGFR recorded from the late LP (macula densa delivery interrupted) was significantly (P, 0.05) greater than from the ED (macula densa delivery intact) in the basal and experimental periods in groups 3 and 4 (Table 1). This suggests that the macula densa contributed a signal to reduce distal-measured SNGFR in each condition. For group 3 (vehicle), there were no differences between the basal and experimental periods for values for SNGFR measured from the LP or ED (Table 1). For group 4, the SNGFR measured from the LP was not significantly changed during infusion of CVT-124. However, the SNGFR measured from the ED was increased by 19%. This resulted in a significant blunting of the LP-ED SNGFR differences during CVT infusion in group 4.

Groups 5 and 6
For groups 5 and 6, the PSF measured during zero LH perfusion averaged 38.6 ± 1.4 mmHg and was not significantly different for either group during period 1 (basal) or period 2 (experimental). Therefore, data are presented as changes in PSF during LH perfusion with ATF at 40 nl/min, compared to zero loop perfusion.

As shown in Figure 2A, the maximal PSF response to loop perfusion with ATF at 40 nl/min was stable in group 5 (vehicle control) but, as shown in Figure 2B, was decreased significantly (P < 0.01) by 19 ± 3%, from 8.6 ± 0.9 to 6.2 ± 0.7 mmHg during intravenous infusion of CVT-124 at 0.5 mg/kg in group 6.

Discussion
This study confirms that a potent, highly selective A1 AdoR antagonist causes marked diuresis and natriuresis (2–4,11). The A1 AdoR antagonist was found to have a unique profile of nephron action that entails a combined inhibition of tubular fluid reabsorption in the proximal tubule and inhibition of TGF

Table 1. Free-flow micropuncture data for tubular fluid flow rate (TFv) and single-nephron GFR (SNGFR) at the late proximal (LP) and early distal (ED) tubules, absolute proximal reabsorption (APR) of fluid, and fractional proximal reabsorption (FRprox): effects of vehicle or CVT-124

<table>
<thead>
<tr>
<th>Group and Period</th>
<th>LP TFv (nl/min)</th>
<th>LP SNGFR (nl/min)</th>
<th>APR (nl/min)</th>
<th>FRprox (%)</th>
<th>ED TFv (nl/min)</th>
<th>ED SNGFR (nl/min)</th>
<th>LP-ED SNGFR (nl/min)</th>
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<tbody>
<tr>
<td>Group 3 (n = 8)</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>basal</td>
<td>17.4 ± 1.8</td>
<td>34.4 ± 1.8</td>
<td>18.3 ± 1.2</td>
<td>56.0 ± 4.0</td>
<td>7.5 ± 0.3</td>
<td>27.7 ± 2.0</td>
<td>6.1 ± 1.2</td>
</tr>
<tr>
<td>vehicle</td>
<td>15.2 ± 1.7</td>
<td>33.7 ± 1.9</td>
<td>18.5 ± 1.3</td>
<td>54.1 ± 3.3</td>
<td>5.9 ± 0.5</td>
<td>25.7 ± 1.4</td>
<td>7.3 ± 1.0</td>
</tr>
<tr>
<td>difference (P value)</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td></td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Group 4 (n = 9)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>basal</td>
<td>17.8 ± 2.4</td>
<td>42.1 ± 5.0</td>
<td>26.1 ± 3.2</td>
<td>60.1 ± 2.6</td>
<td>5.4 ± 0.7</td>
<td>33.3 ± 4.2</td>
<td>9.4 ± 1.0</td>
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<td>CVT-124</td>
<td>25.6 ± 3.9</td>
<td>44.4 ± 3.8</td>
<td>20.4 ± 2.0</td>
<td>46.2 ± 3.8</td>
<td>9.7 ± 0.9</td>
<td>39.7 ± 3.2</td>
<td>4.6 ± 1.5</td>
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<tr>
<td>difference (P value)</td>
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<td>&lt;0.05</td>
<td></td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>changes with CVT-124 compared to changes with vehicle (P value)</td>
<td>&lt;0.01</td>
<td></td>
<td>&lt;0.05</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* All values are shown as mean ± SEM in the basal state and after vehicle or CVT-124 (0.5 mg/kg). Data were assessed by ANOVA.
that would otherwise be activated by the enhanced delivery of filtrate to the macula densa segment. The reduction in APR, without a change in SNGFR measured simultaneously at the LP, suggests that A1AdoR blockade can uncouple glomerular filtration and tubular reabsorption. Glomerulotubular balance normally maintains a constant fractional proximal reabsorption during increases in SNGFR (24). This is the first direct demonstration with micropuncture techniques that A1AdoR inhibition inhibits proximal tubular fluid reabsorption and disrupts glomerulotubular balance in vivo. The finding that intravenous CVT-124 increases whole-kidney GFR and SNGFR measured from the distal tube and blunts the inhibitory effect of the macula densa on SNGFR, despite increasing distal tubule fluid delivery, indicates that it disrupts TGF responses. This was confirmed by direct measurements of maximal TGF responses.

The distribution of A1AdoR in the kidney has been determined using radioligand binding or gene expression. High-affinity binding sites for A1AdoR are located on collecting duct cells (5), proximal tubule brush border membranes (8,12), glomeruli, medulla (8), and microvessels (9). Sites of A1AdoR gene expression include collecting ducts, juxtaglomerular apparatus (7,10), glomeruli, thick ascending limb of the loop of Henle, and proximal tubule (10). These findings are consistent with our functional studies that have identified the PT and likely the afferent arteriole and/or glomerulus as sites of action of A1AdoR antagonists on proximal reabsorption and TGF.

Studies of A1AdoR using in vitro preparations have shown that they can regulate proximal tubule cell function. Cultured opossum kidney cells are a continuous cell line that resembles the proximal tubule. They exhibit sodium-coupled phosphate and glucose transport systems that are inhibited by adenosine (25). A selective A1AdoR antagonist can inhibit sodium-coupled phosphate uptake into cultured rat proximal tubule cells (26). An A1AdoR antagonist added to the bathing solution of isolated perfused rabbit proximal convoluted tubules inhibits basolateral bicarbonate conductance. Interestingly, both enhancement of the degradation of adenosine by addition of adenosine deaminase or inhibition of cellular release of adenosine by addition of S-[4-nitrobenzyl]-6-thioinosine mimic the effects of A1AdoR antagonists (27). These observations suggest a hypothesis that could explain our finding that A1AdoR in the proximal tubule can couple APR to SNGFR. An increase in SNGFR and proximal tubular fluid delivery stimulates luminal Na+ entry via exchange for H+, phosphate, glucose, etc. (reviewed in reference (24)). The resulting increase in intracellular [Na+] stimulates basolateral Na+K+-ATPase and adenosine release. Adenosine could facilitate base exit via the basolateral Na+/HCO3- cotransporter (27), thereby maintaining a stable cellular [H+]i which is required to sustain the increased rates of Na+ reabsorption via luminal Na+/H+ countertransport. This hypothesis has not been tested directly.

Studies in human subjects are also consistent with an important role for impaired proximal reabsorption in the diuretic and natriuretic response to A1AdoR blockade. CVT-124 given to normal volunteers causes dose-dependent diuresis and natriuresis (19). The A1AdoR antagonist FK-453, whether given to healthy subjects (2) or those with essential hypertension (3), increases excretion not only of NaCl but also of bicarbonate, urate, phosphate, and lithium. This is consistent with inhibition of proximal reabsorption. Lithium clearance can be an uncertain marker in the presence of diuretic drugs (28), but the present findings show directly that A1AdoR tonically stimulates proximal tubule fluid reabsorption and uncouples it from changes in GFR.

A1AdoR blockade with intravenous CVT-124 increases tubular fluid flow rate and enhances delivery of filtrate to the early distal tubule of the superficial nephrons. Carbonic anhydrase inhibition also impairs proximal reabsorption and increases distal delivery of filtrate, yet the two inhibitors have directionally opposite effects on whole-kidney GFR. SNGFR measured at the distal tubule, and macula densa regulation of SNGFR. In the rat, inhibition of carbonic anhydrase by benzolamide reduces whole-kidney GFR and renal blood flow sharply in parallel with a reduction in the distal measurement of SNGFR, whereas the proximal measurement of SNGFR is preserved. Tucker and Blantz (20) concluded that during benzolamide, the TGF response was intact and responded to the increased distal delivery of filtrate by reducing SNGFR. In contrast, during CVT-124, our results show that the TGF is sufficiently blunted to prevent the macula densa from reducing the SNGFR, despite the increase in distal tubular fluid delivery. Of interest, proximally measured SNGFR was not altered by either benzolamide (20) or CVT-124 (Table 1). This demonstrates that the differential effects of these two classes of drugs on GFR are attributable to differential effects on TGF rather than to direct microvascular actions.

In a previous study, Munger and Jackson (4) found no proximal-distal SNGFR differences in the basal state and therefore no effects of A1AdoR blockade. In their study, the vehicle-treated animals had a greater than threefold increase in sodium excretion, and A1AdoR blockade did not alter whole-kidney GFR or SNGFR measured from the distal tubule. It seems likely that the natriuretic response to the vehicle in this prior study prevented, in some way, the operation of TGF. Regardless, it is interesting that in a situation in which the macula densa was not operative in controlling glomerular hemodynamics, A1AdoR blockade did not alter whole-kidney GFR (4), consistent with our conclusion that the explanation for the decrease in whole-kidney GFR with CVT-124 is blockade of TGF.

A number of previous studies support the role for adenosine in transmission of TGF signals (21,22,29). Osswald and colleagues (29), using less selective pharmacologic probes, concluded that adenosine, produced in response to increased metabolic activity of renal tubules during enhanced reabsorption of NaCl at the macula densa, causes vasoconstriction of the afferent arteriole. Our data do not address directly the controversy of whether adenosine regulates TGF via actions on the macula densa (22) or afferent arteriole (21).

CVT-124 was an effective and dose-dependent diuretic and natriuretic agent (Figure 1). At the lowest dose tested, it increased the GFR. However, the major factor responsible for the natriuresis was a reduced rate of tubular Na+ reabsorption. This is shown by dose-dependent increases in fractional Na+.
excretion despite a maximal increase in GFR at the lowest dose. At the highest dose tested, the $\frac{FE_{\text{Na}}}{GFR}$ exceeded 4%. This places the diuretic efficacy of CVT-124 as lower than loop diuretics but similar to or greater than thiazide or potassium-retaining diuretics. Indeed, CVT-124 is a potent diuretic when administered intravenously to humans (19). Conventional diuretic drugs have highly selective sites of action in the nephron. Their ability to induce NaCl loss is limited by post-diuretic NaCl retention. This is ascribed to a decrease in GFR and an enhanced NaCl reabsorption at nephron segments downstream from the site of diuretic action. In contrast, A$_1$AdoR antagonists not only block tubular reabsorption in the proximal tubule but also in the downstream collecting ducts (1,17). Indeed, a purely proximal diuretic would have limited clinical utility because of excessive flow-dependent K$^+$ secretion in the distal nephron. In contrast, in preliminary studies, CVT-124 does not induce kaliuresis in humans (19), presumably because it also inhibits Na$^+$ and fluid reabsorption, and K$^+$ secretion in the collecting ducts (1,17). Moreover, by blocking TGF, A$_1$AdoR antagonists should also counter the fall in GFR during diuretic-induced volume depletion. These data suggest unique properties of A$_1$AdoR antagonists that may give them some special advantages as diuretic agents. This remains to be explored in clinical studies.

In summary, results of these studies show that A$_1$AdoR blockade inhibits tubular fluid reabsorption in the proximal tubule and prevents TGF-mediated reductions in GFR. This spectrum of actions of enhanced GFR due to blockade of TGF-induced afferent arteriolar vasoconstriction, impaired proximal (and likely distal) reabsorption, and uncoupling of SNGFR and APR characterizes a novel class of diuretic agent.

Acknowledgments

This study was supported by Grants DK 49870 and DK 36079 from the National Institute of Diabetes and Digestive and Kidney Diseases and by funds from the George E. Schreiner Chair of Nephrology.

We are grateful to Marly Davidson for preparing the manuscript.

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