Dipyridamole Decreases Glomerular Filtration in the Sodium-Depleted Dog
Evidence for Mediation by Intrarenal Adenosine

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SUMMARY. To determine the renal effects of inhibiting the uptake and subsequent metabolism of endogenous adenosine, dipyridamole, a nucleoside transport inhibitor, was infused intrarenally into anesthetized dogs. Dipyridamole (24 µg/kg per min) inhibited the cellular extraction of [14C]adenosine (72 ± 3% vs. 9 ± 3%) and elevated the excretion of endogenous adenosine (0.60 ± 0.08 to 1.70 ± 0.21 nmol/min, *P* < 0.05). The action of exogenous adenosine to decrease glomerular filtration rate is known to be enhanced by sodium depletion, and is minimal or absent in sodium-loaded animals. To ascertain whether dietary sodium intake alters the renal effects of elevated endogenous adenosine, dipyridamole was infused into sodium-depleted and sodium-loaded dogs. In the sodium-depleted dogs (n = 9), dipyridamole infusion decreased the glomerular filtration rate by 59 ± 7% (20 ± 1 to 8 ± 2 ml/min, *P* < 0.05) which returned to control levels within 30 minutes after stopping infusion of dipyridamole. Renal vascular resistance was unchanged during dipyridamole infusion. In the sodium-loaded dogs (n = 5), dipyridamole had no effect on glomerular filtration rate (22 ± 4 vs. 25 ± 3 ml/min) or renal vascular resistance. In a separate series of sodium-depleted dogs (n = 8), the dipyridamole-induced decrease in glomerular filtration rate was completely reversed or inhibited by theophylline, an adenosine receptor antagonist. These experiments demonstrate that inhibition of cellular uptake of adenosine elevates adenosine levels, that dipyridamole decreases glomerular filtration rate in sodium-depleted but not sodium-loaded dogs, and that the decrease in glomerular filtration rate is inhibited by theophylline. We conclude that the decrease in glomerular filtration rate during dipyridamole administration is mediated by increased endogenous adenosine. (Circ Res 56: 242-251, 1985)

WORK in several laboratories has raised the possibility that intrarenally produced adenosine plays a role in the intrinsic control of glomerular filtration rate (GFR) and renin release (Spielman and Thompson, 1982). It has been postulated that extracellular adenosine, produced from cellular 5'-adenosine monophosphate (5'-AMP), presumably, but not necessarily, as a product of the adenosine triphosphate (ATP) hydrolysis associated with active transepithelial transport, acts to alter renal function. Stated simply, increased active solute reabsorption, secondary to an increased GFR, would increase adenosine production which would, in turn, act to constrict the afferent arteriole and dilate the efferent arteriole (Osswald et al., 1978b) and thereby reduce glomerular capillary hydrostatic pressure and GFR. Evidence in support of this hypothesis has come from studies that have evaluated the renal action of exogenously administered adenosine (Osswald et al., 1975; Spielman et al., 1980) or, in a few cases, with the use of methylxanthines as adenosine antagonists (Osswald et al., 1980; Gerkens et al., 1983). For the most part, however, only circumstantial evidence has been obtained that supports a role for endogenously produced adenosine in the control of renal function. A more direct assessment of the actions of intrarenal adenosine would be to elevate endogenous levels of adenosine, through pharmacological or physiological perturbations, while monitoring renal function.

In a variety of nonrenal tissues, extracellular adenosine has been reported to enter cells by facilitated diffusion through a nucleoside uptake mechanism, where it is deaminated and phosphorylated to inosine and 5'-AMP (Arch and Newsholme, 1978). This nucleoside uptake mechanism is inhibitable by a variety of pharmacological agents (Paterson, 1979). The hypothesis tested in this study was that inhibition of cellular uptake of adenosine increases the extracellular levels of adenosine, which in turn alters renal function. The present investigation was thus undertaken (1) to identify the presence of a renal uptake mechanism for adenosine, (2) to determine whether its inhibition leads to the elevation of extracellular adenosine, and (3) to determine whether the elevation of endogenous levels of adenosine by inhibition of cellular uptake results in changes in renal function that mimic the effects of exogenously administered adenosine.

Methods

Preparation

Experiments were performed on dogs of either sex, weighing 12-20 kg. The animals were allowed free access
to water and were deprived of food 24 hours before the experiment. On the day of the experiment, the animals were anesthetized with sodium pentobarbital (30 mg/kg, iv) and maintained with periodic small doses as needed. The trachea was exposed and cannulated, and each animal was mechanically ventilated with a Harvard respirator. Minute volumes were initially selected from the nomogram of Kleinman and Radford (1964). Body temperature was monitored with a rectal temperature probe and maintained at 37°C by a circulating water-heating pad and a radiant heat lamp, when necessary. Catheters (PE 240) were placed in the femoral arteries for measurement of blood pressure (Statham strain gauge, P23Db, Hewlett-Packard recorder, 7754B) and for blood sampling, and in the femoral veins for systemic infusions and anesthetic administration.

A retroperitoneal flank incision was made to expose the left renal artery for placement of a noncannulating electromagnetic flow probe (Zepeda Instruments). The flow probe was calibrated by renal artery cannulation at the end of each experiment. A small curved infusion needle (22-gauge) was placed into the renal artery distal to the flow probe. The patency of the needle was maintained with a constant infusion at a rate of 1.38 ml/min. Another small curved needle (20-gauge) was placed in the renal vein for sampling of the renal venous effluent. The dogs were then placed in a metal frame which held them in a position approximating their normal standing posture. After the completion of all surgical procedures, at least 1 hour was allowed for attainment of steady state, as determined by the stability of blood pressure, renal blood flow, and blood gas measurements.

Analytical

Inulin concentrations in plasma and urine were determined by the anthrone method described by Davidson and Sackner (1963). Plasma and urine sodium and potassium concentrations were determined by flame photometry.

One and one-half milliliter aliquots of plasma and urine taken during each clearance period were processed and analyzed for adenosine as follows. The blood samples (3-4 ml) were immediately diluted in 300 μl of a solution containing 32 μM dipryridamole and 3μM erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA), an inhibitor of adenosine deaminase. The blood samples were then centrifuged and a 1.5-ml plasma aliquot was removed and placed in 60 μl of 70% perchloric acid. Similarly, 1.5-ml aliquots of urine were placed in 60 μl perchloric acid. All samples were then centrifuged at 10,000 g for 30 minutes to remove the protein precipitate. A 1.2-ml aliquot of the perchloric acid extract was removed and neutralized with a concentrated solution of potassium carbonate (7 M). The potassium perchlorate precipitate was removed by centrifugation and a 200-μl aliquot of the neutralized acid extract was used for high-pressure liquid chromatography (HPLC) analysis of adenosine. Four control tubes were prepared from a single arterial or venous blood sample and processed with each sample set. Two tubes received known amounts of adenosine, and the third was used to measure endogenous levels. In the final tube, the collecting solution was replaced with 2–5 units of adenosine deaminase activity in saline. The adenosine values of these tubes were used to ensure the identity of the adenosine peak and to calculate the recovery of adenosine for each experiment.

The neutralized acid extract was injected (WATERS-WISP) onto a C18 reverse-phase column (Beckman Ultrasphere ODS) and eluted using an isocratic (9–12% of a 70% solution, balance was 4 mM K2HPO4) elution (1.15 ml/min). A fraction (±2.5 min) of the eluate containing adenosine, as determined by the retention time of standards (and verified by the recovery tubes), was collected using a timer (ChronTrol), valve (The Lee Co. #LFAA1201418A), and fraction collector (Eldex Universal) system. The adenosine fraction was concentrated to dryness under reduced pressure using a vortex evaporator (Buchler Instruments). The samples were resuspended in 1 ml of water and the adenosine converted to inosine by the addition of 0.5 unit of adenosine deaminase and incubated for 15 minutes at room temperature. The adenosine deaminase was inactivated by the addition of 1 ml of HPLC grade methanol, and the samples were once again concentrated to dryness under reduced pressure, reconstituted in a small volume (typically 220–250 μl), and a 200-μl aliquot was injected on a C18 reverse-phase column and eluted as described above. We quantified the inosine peak by measuring the area under the curve (WATERS data module) and relating this to standards run under the same condition. Recoveries for all experiments were 100 ± 7%, and individual values were not corrected for recovery.

Indicator Dilution Curves

The [U-14C]-adenosine (278 mCi/mmol) was obtained from Amersham. The 9-β-D-arabinofuranosyl-adenine-2-[3H] (ara-A) (32.6 Ci/mmol) was obtained from ICN. The ara-A was converted to 9-β-D-arabinofuranosyl hypoxanthine-[2-3H] (ara-H) by treatment with adenosine deaminase (Sigma Chemical) and subsequent purification on a HPLC reverse phase column. Injectate containing [3H]ara-H (2 μCi/ml) and [14C]adenosine (0.34 μCi/ml) was made up in 1.5 ml of normal saline. The bolus was quantified by diluting 100 μl of the injectate with 900 μl saline and counted for radioactivity. Bolus injections (2–4 sec) of 1 ml were made directly into the renal artery cannula while a constant infusion rate of 1.38 ml/min was maintained to flush the cannula. Immediately before initiation of the bolus injection, sampling was begun from both ureters and the renal vein. Before each injection, renal vein plasma and urine samples were obtained for determination of blank activity. Urine samples were collected for an average of 30 seconds (range 15–60 sec) to obtain approximately 1 ml of urine per sample depending on urine flow. Contiguous 10-second withdrawals via the renal vein catheter (average 20 ml/min) were made starting with the injection and lasting 2 minutes after completion of the injection. All samples were corrected for the blank values immediately before the injection, and results were normalized as the plasma or urine concentration (% of injectate/ml).

Urine samples (0.7–1.2 ml) for radioactivity determinations were collected directly into preweighed scintillation vials. After sample collection, the volume was determined gravimetrically. In a few cases where the sample volume was less than 0.7 ml, 0.5 ml of saline was added after volume determination.

Statistical

Statistical analysis was performed by analysis of variance using the Student-Newman-Keuls test for multiple comparisons and by Student's paired t-test when appropriate. A P value of <0.05 was considered statistically significant. All data are presented as mean ± 1 SEM.
Experimental

Group I—Effect of Dipyridamole on the Renal Uptake of Adenosine and the Concentration of Adenosine in Plasma and Urine (n = 5)

To determine whether renal adenosine uptake is blocked by dipyridamole, we employed a single-injection, multiple-tracer, indicator-dilution technique. The uptake of adenosine was compared with that of a nonmetabolized analog of adenosine, 9-β-D-arabinofuranosyl hypoxanthine (ara-H), used as an extracellular reference. A group of dogs maintained on a normal laboratory diet were prepared as described above, with the following additions. A right flank incision was made to expose the right ureter, which was cannulated with PE 240 tubing. The incision was then closed to prevent excess fluid loss. After the surgical preparation, the animals were given a saline volume expansion of 5% of body weight to initiate a brisk urine flow. An intravenous infusion of saline (4-5 ml/min) was given to maintain urine flow rate at approximately 2 ml/min. After at least 60 minutes had been allowed for stabilization of the animal preparation, renal adenosine uptake studies were performed, and samples for adenosine concentration were taken, as described above, during a control period, and after 45 minutes of dipyridamole infusion into the renal artery at 24 μg/kg per min.

Group II—Effect of an Adenosine Uptake Inhibitor, Dipyridamole, on Renal Function in Dogs Maintained on a Low-Sodium Intake (Group Ila, n = 9) or a High-Sodium Intake (Group Ib, n = 5)

To determine whether the elevation of endogenous adenosine by inhibition of cellular uptake produced renal effects similar to those resulting from the intrarenal infusion of exogenous adenosine, we studied renal function before, during, and after the intrarenal infusion of dipyridamole. Because the effects of exogenous adenosine on renal function are enhanced by sodium depletion and attenuated or blocked by sodium loading (Osswald et al., 1978a), dogs were divided into two groups and either sodium-depleted or sodium-loaded to determine whether renal effects of elevation of endogenous adenosine by inhibition of uptake are also influenced by dietary sodium intake.

One group of dogs (group Ila) was given 100 mg of furosemide (iv) on the first day of the dietary regimen, and maintained on a low-sodium diet (<2 mEq/day) for 10-14 days before the experiment. Dogs were allowed water ad libitum. On the day of the experiment, animals were prepared as described above. During the experiment, dextrose (5.5% in water) was infused (1.38 ml/min) into the renal artery for the control period. Urine was collected for two or three 15-minute clearance periods, and midpoint systemic arterial and renal venous blood samples were taken. This procedure was repeated during the infusion of dipyridamole (24 μg/kg per min in 5.5% dextrose) and again during dextrose infusion for the recovery period. A period of 30 minutes was allowed after the onset and termination of the dipyridamole infusion before beginning the dipyridamole and recovery clearance periods, respectively.

Another group of dogs (group Ib) was given 15 mg deoxycorticosterone acetate each day and fed the same low-sodium food as the previous group to which had been added 200 mEq sodium (as NaCl). This dietary regimen was continued for 10-14 days. The experimental procedure for group Ib dogs was identical to the procedure outlined above for group Ila except that saline (0.9%) was used in place of dextrose for the control and recovery periods and was used as vehicle for the dipyridamole.

In both groups, bolus injections of adenosine (5 and 10 nmol) were given into the renal artery during the control and dipyridamole periods to test for enhancement of the renal vasoconstriction to exogenous adenosine by dipyridamole.

Group III—Effect of Dipyridamole on Renal Function in the Sodium-Depleted Dog, during Constant Renal Perfusion Pressure (n = 5)

To determine whether the renal actions of dipyridamole in the low-sodium dog (group Ila) were a consequence of the fall in arterial blood pressure, another group of dogs was sodium-depleted and prepared as described above, except that a clamp was placed around the abdominal aorta cephalad to the left renal artery. Two clearance periods were conducted during the infusion of 5.5% dextrose at the animals’ ambient blood pressure. The aortic clamp was then tightened to lower the renal perfusion pressure (RPP) to 100 mm Hg, which is in the autoregulatory range and was near the average mean arterial pressure (MAP) of the dogs in group Ila during steady state dipyridamole infusion. The dextrose infusion was continued, and clearance periods were conducted. Maintaining RPP at 100 mm Hg, dipyridamole was infused and clearance periods were conducted after 30 minutes of equilibration. The dipyridamole was replaced by dextrose, and RPP was maintained at 100 mm Hg for the recovery clearance periods.

Group IV—Effect of an Adenosine Antagonist, Theophylline, on the Dipyridamole-Induced Changes in Renal Function in the Sodium-Depleted Dog (n = 8)

To determine whether the renal effects of dipyridamole could be inhibited or reversed by an adenosine antagonist, a group of dogs (group IV) was sodium-depleted and prepared as described above. In five dogs (group IVa) dextrose was infused (2.76 ml/min) into the renal artery and control urine and blood samples were collected. The dipyridamole infusion was then started (24 μg/kg per min, 1.38 ml/min) while the dextrose continued (1.38 ml/min). After a 30-minute equilibration period, blood and urine samples were collected. The dextrose infusion was replaced by theophylline (5 μmol/min) while the dipyridamole continued, and another equilibration period was allowed before samples were collected again. In a group of three dogs (group IVb), the above procedure was followed, except that the theophylline and dipyridamole periods were reversed. Theophylline (5 μmol/min) was infused during a dextrose infusion for the second set of samples, and then the dextrose was replaced by dipyridamole (24 μg/kg per min).

In both groups, bolus injections of adenosine (5 and 10 nmol) were given into the renal artery to test for enhancement and attenuation of the renal vasoconstriction by dipyridamole and theophylline, respectively.

Results

Group I—Effects of Dipyridamole on the Renal Uptake of Adenosine and the Concentration of Adenosine in Plasma and Urine

The cumulative venous recovery of labeled adenosine and ara-H was 15.6 ± 2.7 and 50.5 ± 7.6%,
respectively, during control. In the presence of dipyridamole, the recovery of adenosine increased to 48.1 ± 8.9% (P < 0.05 compared to control) and was not different from the venous recovery of ara-H (56.4 ± 10.5%, NS) during dipyridamole. The ratio of adenosine to ara-H in the first eluting samples averaged 0.28 ± 0.03 compared to 0.91 ± 0.03 during dipyridamole (P < 0.05), indicating that the cellular uptake of adenosine was inhibited in the presence of dipyridamole. Representative dilution curves for the venous effluent before and during dipyridamole are shown in Figure 1.

The control urinary excretions following injection of labeled adenosine and ara-H were 10.8 ± 1.2 and 19.8 ± 1.7% of the amount injected. Excretion of the adenosine label was increased in the presence of dipyridamole to 15.2 ± 2.2% and was not different from ara-H excretion (20.1 ± 2.5%, NS). The adenosine:ara-H ratio in the early eluting samples was 0.57 ± 0.03 in control and increased to 0.82 ± 0.01 during dipyridamole (P < 0.05). These results, similar to those obtained with renal venous plasma, indicate that this level of dipyridamole blocked the cellular uptake of tracer adenosine. Representative dilution curves for the urinary effluent before and during dipyridamole are shown in Figure 2.

The renal venous concentration of endogenous adenosine increased from 48 ± 9 nM in control to 108 ± 25 nM during dipyridamole. The urinary excretion of endogenous adenosine increased from 595 ± 77 pmol/min to 1695 ± 207 pmol/min during dipyridamole (P < 0.05). The concentration of endogenous adenosine in arterial blood also increased during dipyridamole, however, due to the variability of the response (in two of the five dogs studied, arterial adenosine decreased) this increase was not statistically significant (73 ± 26 vs. 165 ± 59 nM, NS).

**Group II—Effects of an Adenosine Uptake Inhibitor, Dipyridamole, on Renal Function in Dogs Maintained on a Low-Sodium or a High-Sodium Intake**

The intrarenal infusion of dipyridamole caused a decrease in GFR in the dogs maintained on the low-sodium diet but produced no significant change in GFR when infused into the dogs that had been maintained on the high-sodium diet (Fig. 3; Table I). GFR was decreased in the low-sodium dogs (group Ia) by an average of 58.6% (19.8 ± 1.1 vs. 8.2 ± 1.5 ml/min, P < 0.05), and returned to control levels in the recovery period (20.3 ± 1.1 ml/min). In the high-sodium dogs (group Ib), the average GFR during the infusion of dipyridamole was not significantly different from the control GFR (22.3 ± 3.9 vs. 25.1 ± 3.4 ml/min, NS). The intrarenal infusion of dipyridamole in the low-sodium dogs consistently produced a small and transient increase in renal blood flow at the onset of the infusion, which waned, and during the steady state was lower than the control blood flow (145 ± 10 vs. 117 ± 10 ml/min, P < 0.05). Steady state blood flow during the infusion of dipyridamole was also somewhat lower in the high-sodium dogs, albeit, not significantly (178 ± 24 vs. 157 ± 18 ml/min, NS).

The intrarenal infusion of dipyridamole had no effect on the renal perfusion pressure in the dogs maintained on the high-sodium diet. In contrast, the infusion of dipyridamole resulted in a fall of renal perfusion pressure in the low-sodium dogs (121 ± 5 to 101 ± 6 mm Hg, P < 0.05). Renal vascular resistance (RVR) was not significantly different in...
either group of dogs during the infusion of dipyridamole. Filtration fraction (FF) decreased significantly in the sodium-depleted dogs (0.28 ± 0.03 vs. 0.13 ± 0.02, P < 0.05) during the infusion of dipyridamole, but was not significantly different in the sodium-loaded dogs.

Fractional excretion of sodium and the plasma concentrations of sodium and potassium were not significantly different from control values during the infusion of dipyridamole.

In group IIa dogs (low-sodium), injections of 5 and 10 nmol of adenosine resulted in 45 ± 8 and 56 ± 10% decreases in renal blood flow (RBF) during the infusion of dextrose; during the infusion of dipyridamole, the decreases in RBF in response to 5 and 10 nmol adenosine were significantly greater (66 ± 11 and 74 ± 11%, respectively; P < 0.05). In the high-sodium group, RBF decreased by 14 ± 3

### TABLE 1

<table>
<thead>
<tr>
<th>Group</th>
<th>GFR (ml/min)</th>
<th>RBF (ml/min)</th>
<th>RPP (mm Hg)</th>
<th>FF</th>
<th>RVR (mm Hg/mill per ml)</th>
<th>FE_{Na} (%)</th>
<th>Plasma Na⁺ (mEq/liter)</th>
<th>Plasma K⁺ (mEq/liter)</th>
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<tbody>
<tr>
<td>IIA: sodium-depleted (n = 9)</td>
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<tr>
<td>Control</td>
<td>19.8 ± 1.1</td>
<td>145 ± 10</td>
<td>121 ± 5</td>
<td>0.28 ± 0.03</td>
<td>0.91 ± 0.10</td>
<td>0.23 ± 0.15</td>
<td>134.4 ± 1.0</td>
<td>3.34 ± 0.10</td>
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<tr>
<td>Dipyridamole</td>
<td>8.2 ± 1.51</td>
<td>117 ± 10†</td>
<td>101 ± 6†</td>
<td>0.13 ± 0.02 †</td>
<td>0.95 ± 0.14</td>
<td>0.15 ± 0.05</td>
<td>130.7 ± 1.9</td>
<td>3.57 ± 0.12</td>
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<tr>
<td>Recovery</td>
<td>20.3 ± 1.1</td>
<td>135 ± 17</td>
<td>117 ± 5</td>
<td>0.27 ± 0.03</td>
<td>0.93 ± 0.13</td>
<td>0.44 ± 0.05</td>
<td>121.4 ± 3.1</td>
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<tr>
<td>Control</td>
<td>22.3 ± 3.9</td>
<td>178 ± 24</td>
<td>102 ± 8</td>
<td>0.24 ± 0.03</td>
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<td>25.1 ± 3.4</td>
<td>157 ± 18</td>
<td>99 ± 9</td>
<td>0.29 ± 0.03</td>
<td>0.69 ± 0.12</td>
<td>2.09 ± 0.50</td>
<td>159.3 ± 3.9</td>
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<td>Recovery</td>
<td>27.3 ± 3.4</td>
<td>133 ± 19†</td>
<td>123 ± 11†</td>
<td>0.39 ± 0.07</td>
<td>1.02 ± 0.15</td>
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<td>Initial</td>
<td>25.7 ± 3.4</td>
<td>165 ± 27</td>
<td>133 ± 3</td>
<td>0.30 ± 0.05</td>
<td>0.89 ± 0.13</td>
<td>0.77 ± 0.54</td>
<td>139.5 ± 3.4</td>
<td>3.65 ± 0.35</td>
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<tr>
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<td>24.4 ± 4.1</td>
<td>163 ± 34</td>
<td>100</td>
<td>0.32 ± 0.06</td>
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<td>130.9 ± 3.6</td>
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<tr>
<td>Recovery</td>
<td>24.1 ± 3.4</td>
<td>181 ± 42</td>
<td>100</td>
<td>0.31 ± 0.07</td>
<td>0.74 ± 0.21</td>
<td>0.10 ± 0.03</td>
<td>128.2 ± 3.5</td>
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<tr>
<td>Control</td>
<td>21.9 ± 1.0</td>
<td>154 ± 14</td>
<td>124 ± 8</td>
<td>0.29 ± 0.04</td>
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<td>7.9 ± 2.5†</td>
<td>119 ± 15†</td>
<td>99 ± 8†</td>
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<td>0.86 ± 0.07</td>
<td>0.18 ± 0.06</td>
<td>132.5 ± 3.4</td>
<td>3.41 ± 0.11</td>
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<td>Dipy/Teo</td>
<td>25.7 ± 1.9</td>
<td>157 ± 11</td>
<td>112 ± 7</td>
<td>0.31 ± 0.03</td>
<td>0.72 ± 0.07</td>
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<tr>
<td>Control</td>
<td>31.3 ± 5.2</td>
<td>165 ± 7</td>
<td>117 ± 6</td>
<td>0.38 ± 0.08</td>
<td>0.71 ± 0.05</td>
<td>0.28 ± 0.08</td>
<td>135.5 ± 3.7</td>
<td>3.44 ± 0.25</td>
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<td>Theophylline</td>
<td>30.6 ± 4.9</td>
<td>175 ± 15</td>
<td>107 ± 3</td>
<td>0.36 ± 0.08</td>
<td>0.61 ± 0.04</td>
<td>0.74 ± 0.10</td>
<td>125.5 ± 3.6</td>
<td>3.39 ± 0.18</td>
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<tr>
<td>Theo/Dipy</td>
<td>25.5 ± 3.5</td>
<td>174 ± 23</td>
<td>96 ± 6†</td>
<td>0.29 ± 0.05</td>
<td>0.57 ± 0.06</td>
<td>0.74 ± 0.05</td>
<td>125.9 ± 3.6</td>
<td>3.74 ± 0.24</td>
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GFR = glomerular filtration rate; RBF = renal blood flow; RPP = renal perfusion pressure; FF = filtration fraction; RVR = renal vascular resistance; FE_{Na} and FE_{K} = fractional excretion of sodium and potassium, respectively.

* FE_{Na}, n = 3.
† FE_{Na}, plasma Na⁺, and plasma K⁺, n = 3.
‡ P < 0.05.
and 25 ± 8% during the control saline infusion and by 28 ± 5% (P < 0.05) in response to 5 nmol adenosine and 39 ± 6% (NS) in response to 10 nmol adenosine during the dipyridamole infusion.

In some preliminary experiments, dipyridamole was infused into the femoral vein. With systemic administration, the effects on renal function were the same as that seen in the intrarenal infusion.

Group III—Effect of Dipyridamole on Renal Function during Constant Renal Perfusion Pressure

An initial clearance period was performed in each animal at its ambient arterial pressure. The average initial RPP for five dogs was 133 ± 3 mm Hg. Initial GFR was 25.7 ± 3.4 ml/min, and RBF was 165 ± 27 ml/min. Filtration fraction was 0.30 ± 0.05 and fractional sodium excretion was 0.77 ± 0.54% (Fig. 4).

There was no effect of decreasing renal perfusion pressure (RPP) to 100 mm Hg on GFR (25.7 ± 3.4 vs. 24.4 ± 4.1, ml/min, NS) or RBF (165 ± 27 vs. 163 ± 34 ml/min, NS). Filtration fraction and vascular resistance remained constant as well (Table 1). With the fall in RPP fractional excretion of sodium decreased significantly from 0.77 ± 0.54 to 0.16 ± 0.09% (P < 0.05).

With RPP maintained at 100 mm Hg, dipyridamole infusion resulted in a fall in GFR from 24.4 ± 4.1 to 15.0 ± 3.6 ml/min (P < 0.05). There was no change in RBF with dipyridamole infusion (167 ± 43 ml/min, NS); consequently, filtration fraction decreased from 0.32 ± 0.06 to 0.22 ± 0.06 (P < 0.05). Vascular resistance and fractional sodium excretion did not change significantly from the previous period.

During the recovery period, (i.e., 30 minutes after stopping dipyridamole infusion), GFR and filtration fraction both returned to their respective control values (GFR: 24.1 ± 3.4 ml/min; FF: 0.31 ± 0.07). There was no significant change in RBF, vascular resistance, or fractional sodium excretion.

Group IV—The Effect of Theophylline on the Renal Actions of Dipyridamole

The intrarenal infusion of dipyridamole in group IV resulted in changes similar to those described for group II dogs (Table 1; Fig. 5). GFR decreased from 21.9 ± 1.0 to 7.9 ± 2.5 ml/min (P < 0.05); likewise, RBF decreased from the control level of 154 ± 14 ml/min to 119 ± 15 ml/min (P < 0.05). Filtration fraction also decreased from 0.29 ± 0.04 to 0.12 ± 0.03 (P < 0.05). As with group II, MAP decreased during the dipyridamole infusion from 124 ± 8 to 99 ± 8 mm Hg (P < 0.05). Injections of adenosine during the control dextrose infusion resulted in decreases in RBF of 35 ± 10 and 42 ± 11% for 5 and 10 nmol adenosine, respectively. In response to the same doses during the dipyridamole infusion, the decreases in RBF were significantly greater (51 ± 14% and 60 ± 12%; P < 0.05). The concomitant infusion of theophylline resulted in the reversal of all of these effects (Fig. 5). GFR increased to 25.7 ± 1.9 ml/min and RBF increased to 157 ± 11 ml/min. Neither increase was significantly different from the respective control values. The filtration fraction returned to the control level (0.31 ± 0.03) during theophylline infusion as well. Renal perfusion pressure increased from 99 ± 8 to 112 ± 7 mm Hg, a value which was not statistically different than the control value of 124 ± 8 mm Hg. The decreases in RBF in response to adenosine injections were 31 ± 15 and 43 ± 20% during the theophylline infusion, and were not significantly different than the control responses.

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In an additional three dogs, theophylline was infused prior to dipyridamole to determine if the effects of dipyridamole on renal function could be inhibited by the presence of theophylline. Theophylline infusion alone did not significantly change GFR from the control level (31.3 ± 5.2 vs. 30.6 ± 4.9 ml/min, NS). Likewise, RBF did not change in the steady state (165 ± 7 vs. 175 ± 15 ml/min, NS), although there was an initial tendency of blood flow to increase immediately after the theophylline infusion was begun. Renal perfusion pressure was also not affected by theophylline (117 ± 6 vs. 107 ± 3 mm Hg, NS). Fractional sodium excretion increased from 0.28 ± 0.08 to 0.74 ± 0.10% (P < 0.05). Theophylline infusion did not affect renal vascular resistance or filtration fraction (Table 1). The infusion of theophylline attenuated the decreases in RBF to adenosine injections as compared to control. Injections of adenosine (5 and 10 nmol) during the dextrose infusion resulted in 44 ± 3% and 52 ± 6% decreases in RBF. During the theophylline infusion, the decreases in RBF in response to adenosine were significantly less (19 ± 5% and 33 ± 3%, P < 0.05).

In the presence of theophylline, the infusion of dipyridamole did not significantly affect GFR (30.6 ± 4.9 vs. 25.5 ± 3.5 ml/min, NS) or RBF (175 ± 15 vs. 174 ± 23 ml/min, NS). Filtration fraction did not change from the value during theophylline infusion alone (0.36 ± 0.08 vs. 0.29 ± 0.05, NS). Likewise, dipyridamole infusion in the presence of theophylline had no effect on renal perfusion pressure (107 ± 3 vs. 96 ± 6 mm Hg, NS); however, this was significantly different from the control value of 117 ± 6 mm Hg (P < 0.05). Vascular resistance and fractional sodium excretion were not changed with the infusion of dipyridamole (Table 1). Adenosine injections (5 and 10 nmol) during the theophylline/dipyridamole infusion resulted in 33 ± 17 and 47 ± 21% decreases of RBF which were not significantly different than the control responses.

**Discussion**

The reported actions of adenosine—namely, the production of a marked fall in GFR (Tagawa and Vander, 1970), alteration of cortical distribution of blood flow (Spielman et al., 1980), a decrease in renin release (Tagawa and Vander, 1970)—form the basis of the hypothesis that intrarenally produced adenosine, as the active extracellular metabolite of the ATP hydrolysis associated with transepithelial transport, is the mediator of the intrinsic regulation of renal function. However, the majority of the previous studies have involved the use of exogenous adenosine, and, whereas these studies provide important support for the role of adenosine as a regulator of renal function—alone, this evidence can be considered as merely suggestive. The use of dipyridamole, a nucleoside uptake blocker, in the present study more directly allows for the investigation of the role that endogenous adenosine may play in the regulation of renal function. The hypothesis tested in the present study was that inhibition of the cellular uptake of adenosine increases the extracellular level of endogenous adenosine, which, in turn, alters renal function. We therefore sought to determine the effect of dipyridamole on (1) the renal uptake of adenosine, (2) the plasma and urinary levels of adenosine, and (3) renal function.

For any substance to have a role as a regulatory intercellular mediator, it must have a system for inactivation, through uptake and/or metabolism. Nucleoside uptake is known to occur by facilitated diffusion in a variety of cell types (Berlin and Oliver, 1975), and is inhibitable pharmacologically (Paton et al., 1975). Dipyridamole has been shown to block the uptake of adenosine by a number of cell types, including erythrocytes, platelets, and myocardial cells (Feigl, 1983). In the present study, to determine whether renal adenosine uptake is blocked by dipyridamole, we employed a single-injection, multiple-tracer, indicator-dilution technique. This technique involves the simultaneous injection of radio-labeled adenosine, together with a radio-labeled reference, in this case a non-transported, non-metabolized analog of adenosine, ara-H, and collection of serial samples of the urinary and renal venous effluents. Comparison of the tracer adenosine to the reference in urine and renal venous blood yields important information about the renal handling of adenosine (Thompson et al., in press). Based on knowledge of adenosine transport in other tissues, we hypothesized that injected adenosine can leave the vascular compartment by simple diffusion into the interstitial space, as well as by facilitated diffusion into cells via the nucleoside carrier, whereas the reference, ara-H, can leave the vascular compartment only by simple diffusion. Thus, the difference in the recovery of tracer adenosine and the recovery of the reference was taken as the uptake and metabolism of adenosine by cells (Thompson et al., in press). The difference between the recovery of adenosine and that of the reference is virtually abolished during the infusion of dipyridamole (Figs. 1 and 2), and indicates that the cellular uptake of adenosine is blocked. This inhibition of the cellular uptake is apparent in both the renal venous and urinary effluents, leading to the conclusion that the kidney possesses a dipyridamole-sensitive cellular uptake mechanism for adenosine in both the vascular and tubular compartments.

Once in the cell, adenosine is metabolized to inosine or 5'-AMP by adenosine deaminase or adenosine kinase, respectively. Because adenosine metabolism is primarily intracellular (Berne and Rubio, 1974) and its physiological actions are primarily extracellular (Arch and Newsholme, 1978), exogenous administration of adenosine during pharmacological inhibition of the cellular uptake is generally expected to result in increased extracellular levels.
and, hence, increase its biological activity. In the heart, dipyridamole enhances the coronary vasodilation produced by adenosine (Feigl, 1983). Likewise, the renal vasoconstriction produced by the intrarenal injection of adenosine is augmented in the presence of dipyridamole (Sakai et al., 1981). In the present study, bolus injections of adenosine produced transient vasoconstrictions which were enhanced during the infusion of dipyridamole.

The knowledge that dipyridamole blocks the uptake and potentiates the action of exogenously administered adenosine has led investigators to use dipyridamole to enhance events suspected to be mediated by elevated levels of endogenous adenosine (Feigl, 1983). However, because the mechanism by which intracellular adenosine exits the cell remains to be defined, and because the dipyridamole-inhibitable, facilitated diffusion is presumably a bidirectional process (Plagemann and Wohlhueter, 1980), release, as well as cellular uptake, may be inhibited in the presence of dipyridamole. Thus, it is important to ascertain whether blocking cellular uptake is actually associated with levels of adenosine.

In general, it can be assumed that the concentration of adenosine in venous blood and urine can be used as an indication of the concentration of adenosine in the extracellular fluid. Measurements of adenosine in the plasma and urine before and during the administration of dipyridamole indicate that extracellular adenosine levels are indeed elevated by dipyridamole. The concentration of adenosine in arterial blood also increased during dipyridamole, and this is presumably due to the effect of dipyridamole on adenosine uptake in other tissues, a finding not surprising in light of the fall in arterial blood pressure. The increases in venous and urinary adenosine concentration were not, however, dependent on an increase in extrarenal adenosine levels, since the rise in venous and urinary adenosine was also seen in two of the five experiments in which the arterial levels were decreased or unchanged. In addition, the arterial concentration of adenosine was increased, on the average, to slightly more than 100 nM, and the changes in renal function that occurred would require, in an infusion of exogenous adenosine, a concentration of 5 μM, or 50 times the concentration observed with the dipyridamole infusion, suggesting that the functional changes were probably elicited by increases in intrarenal adenosine levels.

Having established that (1) cellular uptake of adenosine is blocked by dipyridamole in the kidney, and (2) adenosine levels are elevated during the administration of dipyridamole, we then sought to determine the effects of elevated endogenous adenosine on renal function. The renal actions of adenosine are influenced by the dietary sodium intake of the animal (Osswald et al., 1978a). That is, the intrarenal infusion of adenosine results in a decrease in GFR in sodium-depleted rats and dogs, but has relatively little, if any, effect when infused into sodium-loaded animals. Likewise, the effect of exogenous adenosine to produce a redistribution of renal cortical blood flow is influenced by the dietary sodium intake of the animal (Spielman et al., 1980). The mechanism responsible for these differences in response to adenosine is unknown at present, although the enhanced renin-angiotensin system and increased renal nerve activity present in the sodium-depleted animal are possibilities. Several recent studies have been aimed at clarifying the role of angiotensin in the renal actions of adenosine. The reduction in RBF following a brief occlusion of the renal artery—which is thought to be mediated by adenosine—as well as the decrease in RBF in response to an injection of adenosine, has been attenuated by high concentrations of the angiotensin II antagonist [Sar^1, Ile^7] AII (Spielman and Osswald, 1979), suggesting an adenosine-AII interaction. However, measurements of renal lymph AII, used as an indication of interstitial AII levels, have shown that intrarenal AII did not increase, but actually decreased, during an adenosine infusion (Spielman, 1984). Therefore, whereas an adenosine-AII interaction appears to exist, it may be more complicated than has been postulated previously.

To determine the renal effects of elevated endogenous adenosine and the influence of sodium intake on these actions, we studied the effects of dipyridamole administration in sodium-depleted and sodium-loaded dogs, thereby comparing the renal effects of endogenous to exogenous adenosine. Animals maintained on a diet low in sodium were found to have a reversible fall in the GFR in response to the dipyridamole infusion, whereas GFR did not change upon infusion of dipyridamole in the sodium-loaded dogs.

In addition to the fall in GFR, renal blood flow was also reduced during the dipyridamole infusion in the sodium-depleted dog. There was, however, no calculated change in the renal vascular resistance as mean arterial blood pressure was concomitantly reduced. The filtration fraction was markedly reduced during the dipyridamole infusion, indicating that the fall in GFR was proportionally greater than the fall in renal plasma flow. No hemodynamic changes were observed during the infusion of dipyridamole in the sodium-loaded dogs. These effects are similar in many ways to the effects of the intrarenal infusion of adenosine, but the fall in the arterial blood pressure, an effect not seen during the infusion of adenosine, makes the comparison somewhat complicated.

To compare the effects of dipyridamole to the effects of exogenous adenosine more directly, and to determine what contribution the fall in arterial pressure had on the decrease in GFR, we infused dipyridamole into another series of sodium-depleted animals in which renal perfusion pressure was held.
constant. When renal perfusion pressure was held constant at 100 mm Hg, dipyridamole infusion still produced a marked fall in GFR (~38%), indicating that the effect of dipyridamole is, for the most part, independent of the fall in arterial pressure. It should be noted here that, whereas mean arterial pressure fell during the dipyridamole infusion and was a major contributing factor to the decrease in RBF, systemic pressure did not fall below the autoregulatory range of the kidney and should not have been expected to result in a decrease in RBF. These findings suggest that dipyridamole, or endogenous adenosine, may cause an impairment of autoregulation in sodium-depleted animals. The mechanism by which this interference might occur is unknown, and may be of sufficient importance to merit further investigation.

The ability of theophylline to antagonize the actions of adenosine is well documented. In the kidney, theophylline has been shown to act as a competitive inhibitor of adenosine’s actions to produce a vasoconstriction (Osswald, 1975), decrease GFR, and inhibit renin secretion (Spielman, 1984). Furthermore, this action of theophylline has been shown to occur at doses well below those required for an inhibitory effect on cyclic nucleotide phosphodiesterase (Spielman, 1984). To ascertain whether the decrease in GFR resulting from dipyridamole infusion in the sodium-depleted dog was mediated by elevated adenosine levels, theophylline was infused before and after the dipyridamole infusion. Theophylline was able to reverse, as well as inhibit, the dipyridamole-induced decrease in GFR, suggesting that elevated endogenous adenosine was responsible for the fall in GFR.

In summary, we found that, in the anesthetized dog, dipyridamole blocked the cellular uptake of adenosine, elevated the extracellular concentration of adenosine, and decreased GFR in the sodium-depleted but not the sodium-loaded dog, and the effect on GFR was blocked by the adenosine antagonist, theophylline. Elevation of endogenous adenosine by inhibition of cellular uptake resulted in a fall in GFR in the sodium-depleted animal, a condition known to enhance the actions of adenosine. Although the intent of this investigation was to evaluate the renal effects of elevated endogenous adenosine through pharmacological inhibition of its cellular uptake, the marked effect of dipyridamole to decrease GFR in the sodium-depleted animal raises important issues concerning the clinical use of dipyridamole in situations where extracellular fluid volume is reduced. These findings indicate that, given an appropriate physiological or pathophysiological situation (e.g., sodium-depletion), elevated levels of endogenous adenosine have the capability of altering GFR. Whereas the present findings are consistent with a role for intrarenally produced adenosine in the regulation of renal function, it remains to be determined whether endogenous adenosine elevated by circumstances other than pharmacological (i.e., physiological or pathophysiological) will result in similar changes in renal function.

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